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NATURAL PRODUCTS: FROM CHEMISTRY TO PHARMACOLOGY (C HO, SECTION EDITOR)

Bioactive Molecules of Endophytic Fungi and Their Potential in Anticancer Drug Development

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Abstract

Purpose of Review Endophytes such as bacteria, fungi and actinomycetes are play significant role in the production of bioactive metabolites and plant defence mechanisms. These endophytes develop asymptomatically in the inner tissues and cells of the host plant without causing any symptoms. But studies are ongoing on endophytic fungi, since many of the mycoflora endophytes are unstudied as well as widespread and highly diverse. Endophytic fungi are a large source of different types of metabolites that can be used for the treatment of various types of diseases and manufacture of drugs in the pharmaceutical industries. Recent studies have shown that endophytic fungi, through their alternative biochemical pathway in the host, and produce some anticancer compounds.

Recent Findings The production of novel anticancer compounds by endophytic fungi can help to reduce the amount of anticancer compounds extracted from plants and also help to reduce the loss of plant biodiversity. As per observation, every plant examined to date has a flora of at least one endophyte and, in the case of woody plants, more than a hundred species of endophytic fungi may be present in different parts of the plant. Endophytic fungi are the best producer of many bioactive anticancer compounds, such as taxol, podophyllotoxin, camptothecin and their derivatives.

Summary The present review focuses on biosynthesis of anticancer bioactive compounds from endophytic fungi. Furthermore, it explains the mechanism of action of the anticancer compounds and their application.

Keywords Endophytes · Anticancer · Taxol · Podophyllotoxin · Camptothecin · Vincristine and Vinblastine

Introduction

Today, cancer is one of the deadliest diseases in the world, and the number of cancer patients is increasing every year. The death rate due to cancer is therefore challenging and calls for new strategies and approaches to explore natural sources for the production of novel and effective bioactive metabolites that may be an antagonistic to cancer. From a variety of natural sources, recent research has shown that some new chemotherapy active compounds can provide first-hand anticancer derivatives and their classes with a unique cancer treatment potential. If we talk about the endophytic fungi as a natural source, then these have huge potential for the production of chemotherapeutic compounds such as taxol, podophyllotoxin, camptothecin and vinca alkaloids can be used as analogues for cancer treatment. The endophyte inhabits the internal parts of the host plant so that the chemistry of the host plant is highly affected by the production of metabolites by these microorganisms. As a result, during the co-evolution of the microorganism with the host plant, the properties were developed to produce natural bioactive metabolites similar to their host in which they survived. Ongoing studies suggest that the ability of most medicinal plants to produce bioactive pharmaceutical compounds is due to the presence of these microorganisms [1–7].

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Endophytic Fungi: a Source of Natural Anticancer Bioactive Metabolite

Cancer is a major disease affecting more than six million people worldwide every year. The surge in anticancer drugs is therefore inclined, and natural sources, such as plants, animals and microorganisms, provide alternatives bioactive metabolites to cancer treatment. Bioactive compounds isolated from endophytic fungi may be used for cancer treatment. The ongoing work on the preparation of pharmaceutical compounds from endophytic fungi provides an alternative for the development of such drugs that could be reliable, economical and environmentally friendly. Bioactive anticancer compounds synthesised by endophytic fungi use alternative pathways [8].

Taxol

An anticancer bioactive compound taxol is a diterpenoid isolated from the Pacific Yew Tree of *Taxus brevifolia*. It is widely used in the treatment of cancer and tissue proliferating diseases in humans. But this cytotoxic bioactive compound taxol isolated from the plant extract is costly and not easily available. Various studies have indicated an alternative route for the production of this novel compound from endophytic fungi *Taxomyces andreanae*, isolated from the inner bark of the yew plant. When the effect of the bioactive compound isolated from *Taxomyces andreanae* is observed in cancer cells, it has shown a potential cytotoxic effect against cancerous proliferative cells, and later screening and characterization is performed, and the isolated bioactive compound is called paclitaxel [9, 10]. After the discovery of the taxol from the yew plant, different species of the *Taxus* and non-taxis species have been observed by the research community for the production of the taxol like *Taxus sumatrana, Taxus baccata, Taxus Canadensis, Taxus floridana, Torreya grandifolia, Taxus chinensis, Taxus cuspidata, Cardiospermum halicacabum, Hibiscus rosa-sinensis, Taxus yunnanensis, Terminalia arjuna, Taxus mairei, Ginkgo biloba* and *Wollemia nobilis* [11, 12]. Due to increase in the demand for taxol, chemists and biotechnologists are developing semi-synthetic pathway for its production through a precursor known as 10-deacetylbaccatin III.

Taxol production from endophytic fungi is not stable because there is a decline in production after some generation, so that several other parameters are optimised to enhance taxol production [12–14]. Mirjalili et al. [15] isolated the 25 different endophytic fungi from the inner bark of *Taxus baccata* and four out of 25 were PCR positive for this gene. After, several analyses of the fungal strain *Stemphylium* sp. was observed for the production of taxols [16]. Isolated endophytic fungi from *Taxus wallichiana* var. *mayrei* are also observed for the taxol synthesis [17]. The anticancer compound taxol is also produced by a variety of endophytic fungi such as *Colletotrichum gloeosporioides, Glomerella cingulata, Nigrospora sphaerica, Pestalotiopsis guepinii, Alternaria alternata* and *Fusarium solani* isolated from different host plants [18]. Similarly, an endophytic fungi *Lasiodiplodia theobromae* isolated from *Morinda citrifolia* also showed the active production of taxol [19].

Mechanism of Action of Taxol

Taxol acts as an antineoplastic agent with unique properties to promote and stabilise the polymerization of microtubules and helps to prevent depolymerization.

The mitotic arrest initiated by the taxon is due to the activation of the spindle assembly checkpoint proteins, an important event in the cell cycle that inhibits chromosome segregation. The abnormal persistence of the microtubules causes interference with mitotic spindle assembly and chromosome separation, which leads to mitotic arrest and causes cell death [20–22]. As kinetochores remain attached, paclitaxel plays an important role in the mitotic arrest of the cell (Fig. 1). Molecular sequencing and available molecular data reveal the presence of two genes 10-deacetylbaccatin III-10-O-acetyltransferase (DBAT) and C-13 phenylpropanoid side chain-CoA acyltransferase (BAPT) play a vital role in the biosynthesis of taxol.

Taxol has also been extensively studied for its antiangiogenesis activity, which is the most important feature of cancer cells. From a decade onwards, various evidences related to both activities support the taxol as an anticancer bioactive compound. The first evidence related to cell inhibition of angiogenesis was seen in vascular endothelial growth factor (VEGF) tumours obtained from the transgenic murine Met-1 breast cancer model and paclitaxel helps to suppress the expression of VEGF in the murine Met-1 strain [24, 25]. Immune histochemical expression of CD31, VEGFmRNA and VEGF also decreases in human transplanted oral squamous cell carcinoma model and in lung tumour xenograft [26, 27]. Some studies use the taxol against the cancer in combination with other molecules like cyclooxygenase (COX) to find out the antiangiogenesis and cell apoptosis in SKOV-3 (human ovarian carcinoma cell xenograft bearing mice). The effect of molecules on the model was continued for 28 days and the level of mRNA in the vascular endothelial growth factor (VEGF) was determined by RT-PCR, and the microvessel density and apoptotic indexation were determined by immune histochemistry and terminal deoxynucleotidyl transferase–mediated deoxyuridine triphosphate nick end labelling (TUNEL) method [28]. The proliferation, differentiation and migration of human endothelial venous cells were 10-100 times more sensitive to paclitaxel compared to tumour cells [29]. In addition, similar results have been obtained in the proliferation, migration and

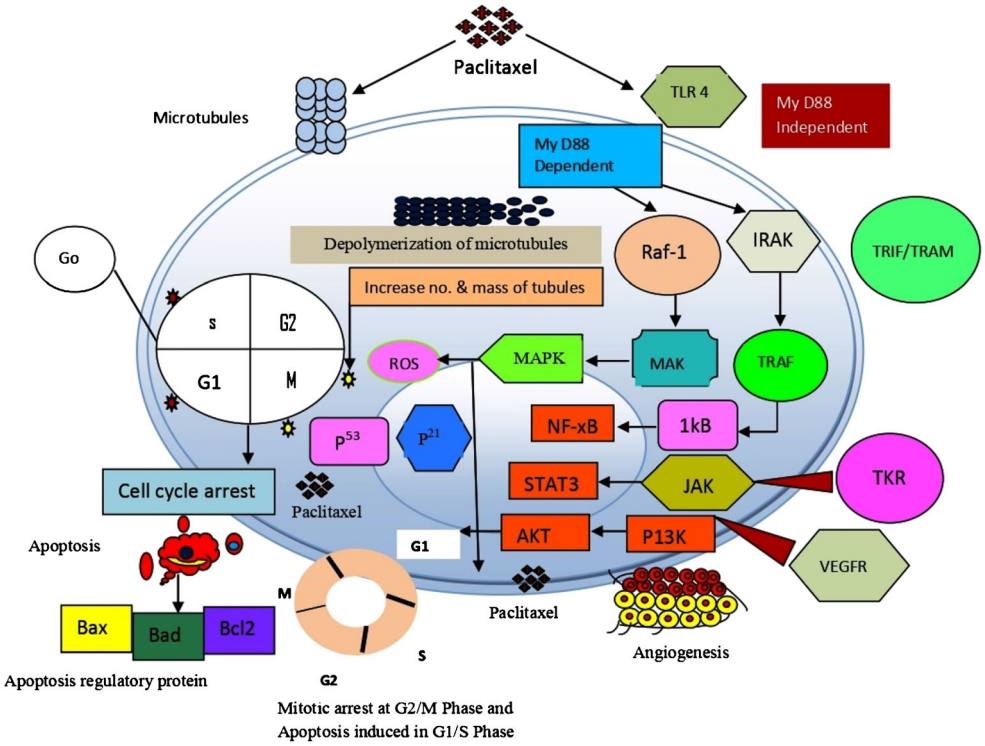

Fig. 1 Mechanism of action of paclitaxel [23]

differentiation of human cultured umbilical endothelial venous cells and in the capillary germination of rat aortic ring explants, showing that endothelial cells are 10–100 times more sensitive to paclitaxel than tumour cells. Pasquier and colleagues [30] explain the dose concentration of cytostatic impact of paclitaxel on human endothelial cell proliferation. The cytotoxic effect generally involved signalling networks such as microtubule network disturbance, G2-M arrest, increased Bax/Bcl-2 ratio and mitochondrial permeability to cause cancer tumour cell damage and apoptosis. The cytotoxic effect of paclitaxel is characterized by strictly proliferating inhibition of the microtubule complex organisation without any alteration, arrest of G2-M, and apoptotic initiation [30]. Wang et al. [31] discuss that the antimetastatic and antiangiogenesis effects of taxol on *in vivo* melanoma by giving continuous 3-week 5 mg/kg taxol dose for pulmonary mice have inhibited the formation of metastases in the model, caused apoptosis and melanoma genesis in the melanoma cells, inhibited angiogenesis and decreased expression of VEGF. Taxol administration increased the expression of E-cadherin and Suppressor gene nm23

In many other studies, the anticancer bioactive compound paclitaxel has increased the over-expression of a potent endothelial-specific thrombospondin-1 inhibitor (TSP-1). The continued low-dose administration of anticancer molecules to the rat vivo malignant prostate cancer model (Dunning AT-1) stimulates the expression of TSP-1 that inhibits tumour growth. The lower concentrations also support the plasma level of TSP-1 in the mice model and strongly support the hypothesis that the low concentration of paclitaxel induces TSP-1 [32–35]. In case of combined effect of inhibition of taxol with alendronate, a bisphosphate molecule injected intravenously in SCID mice has been observed. Pre-injection of alendronate to mice causes bone metastases to be partially blocked by human PC-3ML cells and causes tumour formation in some soft and peritoneum tissues. But the combination of both molecules blocked the growth of PC-3L tumours in the bone marrow and soft tissue on a regular basis and increased the survival rate [36]. In another study, the antimetastatic effect of taxol on the PC-3 human prostatic tumour variant (PC-ML) and immune-fluorescence observation revealed that taxol develops an abnormal microtubule bundle in dose-dependent treatment. Slot blotting and gelatinase studies found that taxol doses of 50 to 250mg/M2/day inhibited the secretion of Mr 72,000 and Mr 92,000 type IV collagenases and Mr 57,000 gelatinase, and blocked the total protein synthesis without any effect on protein turnover. Paclitaxel was also observed for the pro-metastatic effect of TLR4 expressed tumour in cancer cells. Activation of TLR4 by paclitaxel increased the expression of the inflammatory moderator and these pro-inflammatory changes promote the initiation and mobilisation of Lyg6C+ and Lyg6G+ myeloid progenitor cells into tumours. Activation of positive TLR-4 tumour cells by paclitaxel encouraged de novo generation of intratumoural lymphatic vessels that were extremely lenient to attack the malignant cell. The above finding strongly supports

the possibility of activating the inflammatory route that promotes angiogenesis, metastases and lymphogenesis in the treatment of TLR-4 expressing paclitaxel tumours [37].

Podophyllotoxin

Podophyllotoxin lignin, an important precursor to the development of anticancer drugs, is also used in inflammatory diseases. Aryltetralin lactone podophyllotoxin is widely used in the preparation of anticancer drugs such as etoposide, etophos and teniposide. The isolation of anticancer drugs from endophytic fungi opens a new way for the development of anticancer drugs. Podophyllotoxin substitutes for etoposide and teniposide, which plays an important inhibiting role during DNA replication by interacting with the enzyme topoisomerase II and adversely affecting the enzyme, inhibiting its activity (Fig. 2). This bioactive compound has also been shown to increase the level of topoisomerase II which leads to increased DNA cleavage. The anticancer compound etoposide does not prevent the catalytic activity of the topoisomerase II enzyme, but it is toxic to topoisomerase II, which leads to increased DNA duplex cleavage and causes permanent break of the double-stranded DNA. Due to the change in genetic makeup through recombination, translocation, deletion and insertion, the cell death occurs [38–42]. The bioactive compound extracted from the endophytic fungi *Phialocephala fortunii* isolated from *Podophyllum pelatum* L. has been shown to have a cytotoxic effect on the cell, and the bioactive molecule isolated was identified as podophyllotoxin [43]. *Podophyllum emodi* Wall is the major source of podophyllotoxin and *Podophyllum peltatum* too. But these plants are growing slowly and this affects the production of anticancer compounds. Due to their rigorous use, these plants are becoming significantly endangered at the present time. At this date, the synthetic approach to the compound is not acceptable at the commercial stage. However, some of their semi-synthetic constituents are very active, including the etoposide, teniposide, and etoposide phosphate inhibitors of topoisomerase II [44, 45].

The most important etoposide derivative has been widely used throughout the world for cancer treatment over the last two decades. The endophytic fungus *Fusarium solani* is also isolated from the root of *Podophyllum hexandrum* is also capable for production of podophyllotoxin [46]. The podophyllotoxin was also isolated from two fungal strain *Podophyllum peltatum* associated endophyte *Phialocephala fortinii* [43].

Several other scientists have also reported the isolation of podophyllotoxin from fungi with the non-host plant-like fungal strain *Alternaria* sp. associated with *Sabina vulgaris*, *Fusarium oxysporum* of the Himalayan medicinal plant *Juniperus recurva* and *Aspergillus fumigatus* associated with *Juniperus communis* L. Horstmann's [47, 48]. In the endophytic fungi analysis the *Fusarium* sp. isolated from *Dysosma versipellis* produces endogenous podophyllotoxin [49]. Huang et al. [50] isolated six endophytic fungi from the rhizomes of *S. headroom*, the strain TW5 was able to produce anticancer podophyllotoxin and was morphologically identified as *Mucor fragilis* Fresen. Antineoplastic activity of podophyllotoxin against metastatic lung cancer has been reported [51]. Podophyllotoxin has been reported to demonstrate its antineoplastic properties by preventing tubulin assembly into microtubules and thereby inducing apoptosis [51, 52]. The antimitotic activity of podophyllotoxin and its mechanism of action are similar with an alkaloid, colchicines [53, 54]. The mechanism of this effect is by stopping the

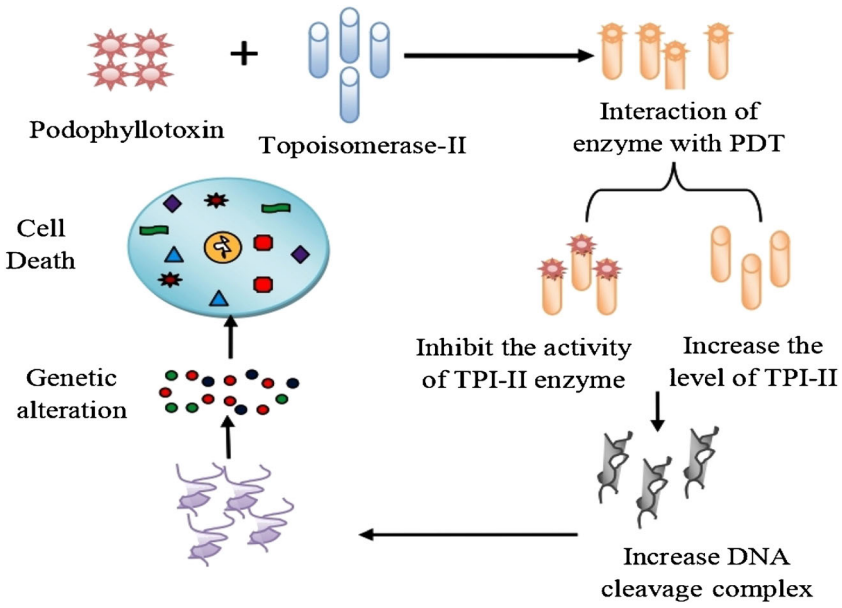

Fig. 2 Mechanism of action of podophyllotoxin

polymerization of tubulin, which could induce cell cycle arrest at mitosis and disrupt the formation of mitotic spindle microtubules [54]. It arrests the cell cycle at the early metaphase stage, which results in the death of epithelial cells. The reports suggested that podophyllotoxin prevents microtubule polymerization leading to mitotic arrest by the accumulation of mitosis-related proteins, BIRC5 and aurora B [55, 56]. Podophyllotoxin on binding to tubulin disrupts the imbalance between the assembly and disassembly of microtubules resulting in mitotic arrest [57]. The active sites for podophyllotoxin and colchicine are similar which leads to competitive binding to tubulin-like stegnacin and combretastatin [58, 59]. Unlike taxoids and epothilones, which stabilise microtubules, podophyllotoxin binding to tubulins inhibits formation and destabilises microtubules. Another mode of action of etoposide and podophyllotoxin is its inhibitory effect on topoisomerase II by inhibiting DNA strand breakage [51, 60, 61]. Etoposide, teniposide and etopophos, which are semi-synthetic products of podophyllotoxin, have been shown to have an inhibitory effect on DNA topoisomerase II, which inhibits DNA re-linking [62–64]. Etoposide being cell cycle specific having prime activity in late S phase and G2 [65].

The compound 4′-O-demethyl-4-deoxypodophyllotoxin-4′-yl 4-((6-(2-(5-fluorouracil-yl) acetamido) hexyl) amino)-4-oxobutanoate has been shown to induce cell cycle arrest in the G2/M phase by regulating levels of cdc2, cyclinB1 and p-cdc2 in A549 cells [66]. Podophyllotoxin derivative, tris substituted aniline-4′-O-demethyl-podophyllotoxin, has been reported to possess antitumour cell growth and DNA topooisomerase inhibitory properties. It also showed growth inhibitory properties against tumour cell lines, including subclones that are resistant to etoposide. It is ten times more potent than etoposide in cell death and inhibition of topoisomerase II. Podophyllotoxin is shown to bind with cell proteins and functions by increasing the incorporation of amino acids into proteins, impairing purine synthesis and limiting the incorporation of purine into RNA [55, 67]. Podophyllotoxin initiates a pro-apoptotic endoplasmic reticulum stress signalling pathway in cancer cell. Podophyllotoxin at 2 mg/kg injected intraperitoneally inhibits the growth of tumour cells P-815, P-1537 and L-121 antineoplastic activity is similar to paclitaxel [68]. In HepG2 cells, 4β-(1,3,4-oxadiazole-2-amino-5-methyl)-4-deoxypodophyllotoxin (OAMDP) induces mitochondrial regulatory apoptosis proteins containing pro-apoptotic proteins, cytochrome c and apoptosis-inducing factor. Release of cytochrome from mitochondria to cytosol indicates apoptotic cells at an early stage which then activates caspase, caspase being a marker in early apoptotic cells. Thus, OAMDP induces HepG2 cells in apoptosis [69].

Podophyllotoxin acetate (PA) demonstrated to inhibit γ-ionizing radiation (IR)-induced migration/invasion in A549 cells (a non–small cell lung cancer (NSCLC) cell line). IR has been shown to increase the invasion and migration of A549 cells which decreased with treatment of 10 nM podophyllotoxin actetate. PA is also reported to act by impeding expressions/activities of matrix metalloprotease (MMP2), MMP-9 and vimentin, suggesting that epithelial-mesenchymal transition (EMT) has been inhibited by PA. The pathway involved in increased invasiveness and migration through IR induction is mediated by activation of EFGR-AKT, wherein PA blocked the same effect. Furthermore, P38 and p44/42 ERk were also involved in IR-induced invasion/migration synergistically inhibitors of MAPK with PA reduced this effect. Whereas in IR-induced invasiness/migration, transcription of cyclic AMP response element binding protein-1 (CREB-1) and signal transducer and activator of transcription 3 (STAT3) were increased as well as increase in epithelial-mesenchymal transition. On treatment with PA transcription factors was downregulated thereby blocking IR-induced invasion and migration [70].

Camptothecin

Camptothecin is an important cancer medication and is commonly prepared from plants. However, the endophytic fungi attracted the attention of the scientific community to the ability to produce a wide range of bioactive anticancer compounds, such as camptothecin, because these microbes contain the same metabolite as the host. Camptothecin (CPT) is the third-largest drug used for the treatment of cancer and mostly isolated from the *Camptotheca acuminata* and *Nothapodytes foetida*. The camptothecin is a pentacyclic pyrroloquinoline alkaloid and is used in the preparation of anticancer drugs in the form of irinotecan and topotecan [10].

In nature, the camptothecin is present in the form of 20-S camptothecin and the other enantiomeric form of this drug is 20-R camptothecin, which is found in an inactive state. On the international market, the total demand for camptothecin is around 3000 kg/year, but the production rate worldwide is about 600 kg which can not satisfy the requirements of the pharmaceutical industry to manufacture enough anticancer drugs [71, 72]. In the beginning, the mechanism of action of camptothecin on cancer cell is believed to have a cytotoxic effect on the cell that prevents the synthesis of RNA and DNA. But further studies have revealed that the camptothecin and its derivatives interact with the enzyme topoisomerase-1 cleavage complex and stabilise the enzyme (Fig. 3). After the stabilisation of the enzyme, there is an initiation of apoptotic event series that will occurr which finally leads to the death of the cell [73].

In 2007, ninety four endophytic fungi were isolated from *Camptotheca accuminata* and these 16 strains displayed cytotoxicity to Vero or PC3 cells. The endophytic fungi *Fusarium solani* demonstrated maximum cytotoxic activity against the cancer cell and camptothecin was found to be generated

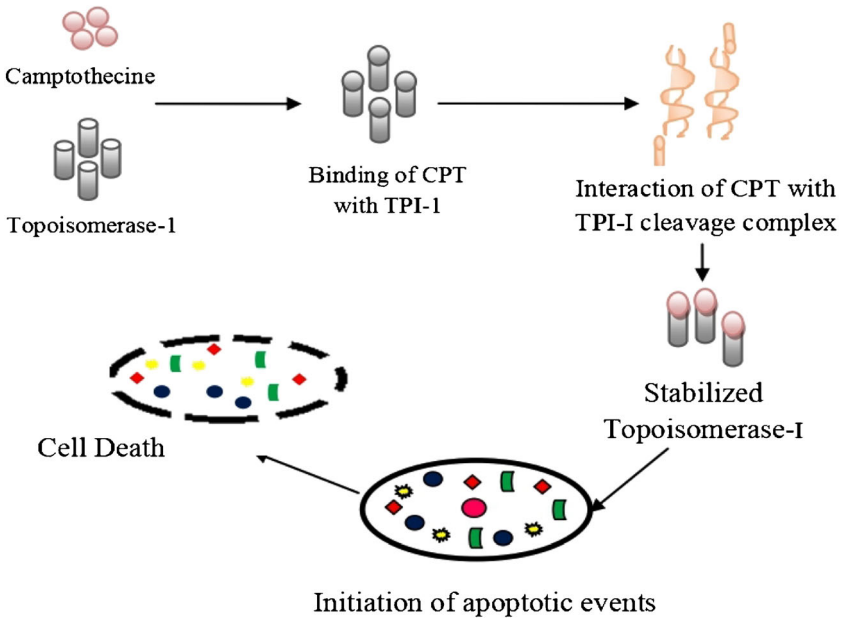

Fig. 3 Mechanism of camptothecin on cancer cell

through TLC, HPLC and EI-MS analysis [74]. Pu et al. [75] isolated two *Aspergillus* sp. strains and *Trichoderma atroviride* (endophytic fungi) from *Camptotheca acuminata* and all of these fungi developed camptothecin in the fermentation broth. The total yields provided by these microbes were 7.93, 42.92 and 197.82 μl/L. Camptothecin was also found to be produced by *Aspergillus niger*, detected by high-performance liquid chromatography and isolated from the *Piper betel*. Cytotoxic activity on the colon cancer cell line is also observed [76]. Endophytic fungi isolated from the bark of *Camptotheca acuminata* have also been known for the development of camptothecin [77].

Researchers are developing novel methodologies and approaches for the production of camptothecin from different types of endophytic fungi. In an attempt, *Entrophospora infrequens*, an endophytic and fungus, isolated from the inner bark of *Nothapodytes foetida* grown on different nutrient combinations either alone or in the combination of different nitrogen and carbon sources for optimise of its condition for maximum production of camptothecin [78]. In another study, the endophytic fungi of *Penicillium* sp. for the development of camptothecin, isolated from *Camptotheca acuminata* Decne, were also observed. CPTs are documented to bind to the topoisomerase I and DNA complex resulting in DNA strand break aggregation after replication leading to cell death during the S phase of the cell cycle [79]. The previous researches on U87 glioma cells showed that continuous exposure of CPT and etoposide leads to synergistic cytotoxic and DNA damaging effect but is dependent on state of cellular protein tyrosine phosphorylation [80]. CPT being a toxin of DNA topoisomerase I (Top1) is considered to be the key compound for antitumour production [81]. CPT is a DNA Top1 toxin, an enzyme involved in major biological functions of DNA, such as replication, transcription, recombination and repair of DNA [79, 82, 83] [84–86]. CPT and its analogues majorly target on Top1 by forming non-covalent bonds between Top1 and DNA strands complex. This complex in turn results in irreversible DNA strand breaks and thereby preventing recombination of DNA double helix leading to cytotoxicity. Previous studies revealed that CPT sensitivity to cancer cell lines is directly linked to Top1 concentration, meaning the cells having high levels of Top1 are hypersensitive to CPT induced cell death [79, 87].

Numerous studies have shown that the concentration of Top1 enzyme in cancer cells is higher than in normal cells and this enzyme has significance in the replication of cancer cells [88]. In colon carcinoma cell lines HT-29 and SW-620, CPT and its analogue VP-16 had additive cytotoxicity. CPT and VP-16 induced cytotoxicity and protein-linked DNA breaks (PLDB) were supra-additive in U87 glioma cell lines, whereas CPT and genistein had additive effects [80]. In a review, CPT and HCPT showed induced apoptotic pathways *in vitro* and *in vivo* in human breast cancer cells MCF-7 and MD-MB-468. HCPT and CPT induced cell death is dose-dependent and time-dependent DNA fragmentation analyses by terminal deoxynucleotidyl transferase–mediated nick end labelling (TUNEL) assay. They showed that MDA-MB-468 cells were more receptive to CPT and HCPT than MCF-7 cells. HCPT induced apoptosis in MDA-MB-468 cells more effectively than CPT whereas, in MCF-7 cells, CPT showed more effects than HCPT. In MCF-7 cells, p53 and p21 levels and WAF1/CIP1 protein were increased in dose- and time-dependent manner. Whereas the levels of p21 WAF1/CIP1 protein increased in MDA-MB-468 cells during treatment with HCPT or CPT, but no substantial improvement in the levels of mutated p53 protein was observed. However,

increased p53 levels in MCF-7 cells for treatment with CPT have been inhibited by pre-incubation with aphidicolin DNA break-inhibitor, but no inhibition has been seen in elevated p21WAF1/CIP1 protein levels. Although in MCF-7 and MDA-MB-468 HCPT- and CPT-treated cells, the transcription of p21WAF1/CIP1 increased in a dose-dependent manner as demonstrated by Northern Blot study. They concluded that HCPT and CPT therapy showed elevated levels of p21WAF1/CIP1 protein and mRNA, which in turn induced p53-dependent and independent pathway apoptosis in human breast cancer cells [89].

Vincristine and Vinblastine

The natural sources of these bioactive compounds are the leaves of vinca plants only but the growth rate of this plant is very low and it requires a huge amount of leaves for their extraction. Therefore, the extraction of vincristine and vinblastine from the plants are laborious, time-consuming and expensive. Hence, there is a need for a cost-effective and sustainable method for the production of the anticancer bioactive compounds from natural sources. In the present scenario, there is a keen interest in endophytic fungi from different host plant after the discovery of paclitaxel-producing fungi which may also be capable to produce the vincristine and vinblastine chemotherapeutic compounds. The novel bioactive compounds vincristine and vinblastine play an important role in the treatment of different types of cancer as well as in Hodgkin's and leukaemia disease [90, 91].

Vinca alkaloid compounds bind to microtubules and inhibit cell proliferation (Fig. 4). Vincristine and its derivatives or associated compounds prevent beta-tubulin polymerization by binding to it. The cell association with vinca alkaloid induces the p53 tumour protein and the 1a (p21) CDK (cyclin-dependent kinase) inhibitor to alter the function of protein kinase. This protein kinase phosphorylates and inactivates Bcl2. Phosphorylated Bcl2 loses its ability to form heterodimer with BAX and loss of BLC2 function due to increased activity of P53 and p21, which triggers apoptosis. The cell that was exposed to the vinca alkaloid loses its ability to expand in the mitotic process due to the poor development of the mitotic spindle, which contributes to apoptosis of the cell [84].

Vincristine and vinblastine are terpenoid indole alkaloids derived from the bonding of vindoline and catharanthine monomers and are excellent anticancer drugs [85, 92, 93]. Vincristine's main mechanism of action is to interfere with the development of microtubules and mitotic spindle dynamics disrupting intracellular transport and reducing tumour blood flow, with the latter possibly arising from antiangiogenesis [86, 92]. Antiangiogenesis compound is categorized into either direct inhibitors in the rising vasculature that target endothelial cells, or indirect inhibitors that block angiogenesis inducer activity [94]. The endophytic fungi *Alternaria* sp. and *Fusarium oxysporum* isolated from *Catharanthus roseus* have the ability to produce vinblastine [95] and vincristine [96] respectively. Kumar et al. [85] isolated endophytic fungi *F. oxysporum* of the Indian *C. roseus* plant which produced the anticancer compounds vincristine and vinblastine at 67 mg/L and 76 mg/L respectively. The endophytic fungus *Curvularia verruculosa* has been isolated from the leaves of *C. roseus* which produced vinblastine. *In vitro* cytotoxic activity of the fungal vinblastine was regulated against HeLa cells; IC_{50} of 8.5 μg/mL was observed [97]. The endophytic fungus *Talaromyces radicus* from *C. roseus* contained 670 μg/L of vincristine and 70 μg/L of vinblastine. Vincristine was partially purified and tested for cytotoxicity in HeLa, MCF7, A549, U251, and A431 cells. The cure of vincristine resulted in the dose-dependent growth inhibition in HeLa, MCF7, A549, U251 and A431 with IC_{50} values of 4.2, 4.5, 5.5, 5.5 and 5.8μg/mL, respectively. The normal cells HEK293, however, were not significantly impacted [98, 99]. Similarly, an endophytic fungus *Nigrospora sphaerica* isolated from *Catharanthus roseus* have been observed for the production of vinblastine and are characterized by liquid chromatography and mass spectroscopy, later tested against the breast cancer cell lines MDA-MB 231 [100].

Other Anticancer Secondary Metabolites Isolated From Endophytic Fungi

The discovery of the novel antibiotic penicillin was a landmark in the pharmaceutical industry in the development of antibiotics. Similarly, the discovery of endophytic fungi bioactive anticancer compound taxol offers a novel path to the development of anticancer drugs. In recent times, a large

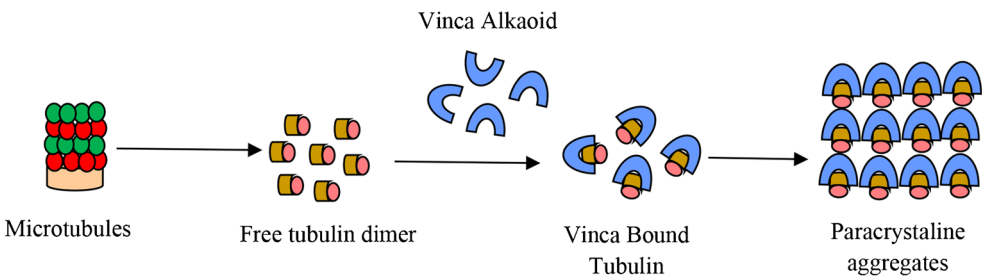

Fig. 4 Mechanism of action of vinca alkaloid

Table 1 Cytotoxicity and other activity of another anticancer compound from endophytic fungi

Endophytic fungi	Host plant	Isolated anticancer compound	IC_{50} value	Cell line	Activity	Reference
Phomopsis sp.	*Excoecaria agallocha*	2-(7'-Hydroxyoxooctyl)-3-hydroxy-5-methoxy-benzene acetic acid ethyl ester	25 μg/mL 30 μg/mL	HEp-2 cells HepG2 cells	Cytotoxicity	[114]
Phomopsis sp.	*Tectona grandis*	Phomoxanthones A Phomoxanthones B	0.99 μg/mL 4.1 μg/mL	KB cells KB cells	Cytotoxicity	[115]
Pestalotiopsis sp.	*Rhizophora mucronata*	Pestalotiopsone F	-	Murine cancer cell line L5178Y	Cytotoxicity	[116]
Eutypella sp.	*Etlingera littoralis*	Eutypellin A	12 μM 84 μM 38 μM 88 μM	KB cells MCF-7 cells NCI-H187 cells Vero cells	Cytotoxicity	[117]
Xylaria sp.	*Licuala spinosa*	Eremophilanolides	3.8–21 μM	KB, MCF-7 and NCI-H187 cancer cell lines	Cytotoxicity	[118]
Dothiorella sp.	*Aegiceras corniculatum*	Dothiorelons F and G	2 g/mL	Raji cancer cell line	Cytotoxicity	[119]
Lasiodiplodia sp.	*Excoecaria agallocha*	Ethyl-2,4-dihydroxy-6-(80-hydroxynonyl)-benzoate	0.13 μM 12.50 μM 1.92 μM 3.31 μM 39.74 μM	DA-MB-435 HepG2 HCT-116 A549 Leukaemia THP1	Cytotoxicity	[120]
Claviceps purpurea	*Mimosops elengi* (bakul)	Ergoflavin	1.90±1 μM 1.20±3 μM	Human TNF-α IL-6	-	[121]
Fungus isolate KLAR 5	*Knema laurina* Warb.	Trichothecolone	12.90 μM 10.06 μM 11.31 μM	Human epidermoid carcinoma (KB) cells Human breast cancer (BC-1) cells Human small cell lung cancer (NCI-H187) cells	Cytotoxicity	[122]
Fusarium equiseti	*Salicornia bigelovii* Torr.	Ergosterol peroxide	64.5 μM 52.4 μM 77.56 μM	MCF-7 cells MDA-MB-231 cells Caco-2 cancer cells	Cytotoxicity	[123]
Rhytidhysteron rufulum AS21B	*Azima sarmentosa*	Rhytidenone G	17.98 μM 7.3 μM	Human cancer cell lines Ramos lymphoma and drug-resistant NSCLC H1975	Cytotoxicity	[48]
		4,8-Dihydroxy-3,4-dihydronaphthalen-1(2H)-one	23.1 μM 50 μM	Ramos cell NSCLC H1975 cell	Antitumour	
Sporothrix sp.	*Kandelia candel*	Sporothrin B Sporothrin C Diaporthin	20 μg/mL 23 μg/mL 23 μg/mL	HepG2 (human liver cancer cell) cell lines	Antitumour	[124]
Aspergillus niger MA-132	*Avicennia marina*	Nigerapyrones E	8 μM 48 μM 43 μM	W1990 cell lines MDA-MB-231 cell lines A549 cell lines	Cytotoxicity	[125]
Penicillium citrinum	*Bruguiera sexangula*	Penibenzophenone B	15.7 μg/mL	Human A549 cell lines	Cytotoxicity	[126]
Eupenicillium sp.	*Glochidion ferdinandi*	Trichodermamide C	0.68 μg/mL 4.28 μg/mL	Human colorectal carcinoma HCT116 cell Lung carcinoma A549 cell	Cytotoxicity	[127]
Penicillium sp.	*Hopea hainanensis*	Monomethylsulochrin	30.0 μg/mL 30.0 μg/mL	KB cell HepG2 cell	Cytotoxicity	[128]
Diaporthe sp.	*Rhizophora stylosa*	Epi-isochromophilone II	4.4 μM 3.9 μM 3.0 μM	Renal carcinoma cell lines, ACHN cells OS-RC-2 cells 786-O cells	Cytotoxicity	[110]
Preussia sp.	*Aquilaria sinensis*	Spiropreussione A	2.4 μM 3.0 μM	A2780 cells BEL-7404 cells	Cytotoxicity	[129]

Table 1 (continued)

Endophytic fungi	Host plant	Isolated anticancer compound	IC_{50} value	Cell line	Activity	Reference
Penicillium janthinellum	*Sonneratia caseolaris*	Trichodermamides B	8.0 μM 1.8 μM 1.9 μM 1.6 μM	K562 HL-60 HO-8910 MGC80	Cytotoxicity	[130]
Penicillium brocae MA-231	*Avicennia marina*	Brocazine G	664 nM 661 nM	A2780 cell lines A2780 CisR human ovarian cancer cell lines	Cytotoxicity Antimicrobial	[131]
Phomopsis sp.	*Excoecaria agallocha*	Xanthone O-glycoside, 3-O-(6-O--L-arabinopyranosyl)-D–glucopyranosyl-1, 4-dimethoxyxanthone	9 μM/mL 16 μM/mL	HEp-2 cells HepG2 cells	Cytotoxicity	[107]
Penicillium expansum XG8D (unidentified)	*Excoecaria agallocha* *Xylocarpus granatum*	Expansols A Merulin A Merulin C	15.7 μM 4.98 μg/mL 1.57 μg/mL	HL-60 cell line BT474 cell lines	Cytotoxicity Cytotoxicity	[132] [133]
Diaporthe phaseolorum SKS019	*Acanthus ilicifolius*	5-Deoxybostrycoidin Fusaristatin A	5.32 μM 6.57 μM 8.15μM	MDA-MB-435 cell lines NCI-H460 human cancer cell lines MDA-MB-435	Cytotoxicity	[134]
Phomopsis amygdale	*Corylus avellana*	4-Butoxy-6-(1-hydroxypentyl)-5, 6-dihydro-2H-pyran-2-one	132.23 μg/mL 82.18 μg/m 24.26 μg/mL 13.84 μg/mL	PC-3 (human prostate adenocarcinoma-bone/CRL-1435TM) HT-29 (human colon adenocarcinoma) MDA-MB-231 (human breast adenocarcinoma) Abnormal cell line HEK293 (human embryonic kidney 293)	Cytotoxicity	[135]
Penicillium brefeldianum	*Pinellia ternata*	N-Demethylmelearoride A	36.6 μM/L	HepG2 cells	Cytotoxicity	[136]
Alternaria tenuissima	*Erythrophleum fordii* Oliver	Tenuissimasatin	1.78 μM/L	Human colon cancer cell HCT-8	Cytotoxicity	[137]
Phomopsis sp.	*Musa acuminata*	Oblongolide Y	48 μM	BC cell line	Cytotoxicity	[138]
Phomopsis sp.	*Xylocarpus granatum*	Phomopsichalasin G	7.5 μM, 8.6 μM, 6.4 μM, 3.4 μM, and 7.1 μM	HCT-8 cancer cell lines HCT-8/T cancer cell lines A549 cancer cell lines MDA-MB-231 cancer cell lines A2780 cancer cell lines	Anticancer	[108]
Trichoderma sp.	*Xylocarpus granatum*	(9R,10R)-dihydro-harzianone	30.1 μM/L 30.7 μM/L	HeLa cell lines MCF-7 cell lines	Cytotoxicity	[139]
Penicillium sp.	*Bruguiera gymnorrhiza*	Meleagrin	9.7 μM 8.3 μM	HL60 cell lines A549 tumour cell lines	Cytotoxicity	[140]
Nigrospora sp.	*Pongamia pinnata*	2,3-didehydro-19a-hydroxy-14-epicochlioquinone B	4 μM 5 μM 7 μM	MCF-7 cell lines SW1990 cell lines SMMC7721 tumour cell lines	-	[141]
Fusarium sp.	*Kandelia candel*	Beauvericin	5.76 ±0.55 μM 5.34 ±0.09 μM	KB cells KBv200 cells	Apoptosis induced	[142]
Aspergillus flocculus	*Markhamia platycalyx*	Cis-4-hydroxymellein, 5-hydroxymellein, diorcinol, botryoisocoumarin A and mellein	30 μM	Chronic myelogenous leukaemia cell line K562	Cytotoxicity	[143]

number of medicinal plants have been identified for endophytic fungi and their anticancer activity. Endophytic fungi are a possible source of new metabolites for cancer treatment. Several bioactive anticancer compounds derived from these microbes can be used against cancer cells. Apart from the anticancer metabolites mentioned above, several other compounds are also isolated from endophytic fungi that display strong cytotoxicity activity against cancer cells. The ethyl solvent–derived metabolite of endophytic fungi isolated from the *Cymbopogon flexuose* collected from the Kemmannugundi regions of Karnataka showed anticancer activity against the breast lungs and colorectal cancer cell lines [101]. The endophytic fungi *T. involucrata,* namely *Penicillium citrinum*, *P. citrinum* CGJ-C2, *Cladosporium* sp. and *Cryptendoxyla hypophloia* isolated from *Tragia involucrata* Linn. The ethyl extract of the *Penicillium citrinum* showed the antioxidant as well as anticancer activity against breast cancer cell line and human leukaemia cell line [102]. Majoumouo et al. [103] isolated an endophytic fungus from *Terminalia catappa* and observed its cytotoxicity against human cervical cancer cells. An endophytic fungi *Chaetomium* sp. isolated from *Adenophora axillifora* and alkaloid derivatives cytoglobosin from endophytic fungi *Chaetomium globosum* were observed for anticancer activity against the lungs and tumour cell line [104].

Some derivatives and compounds contain nitrogen and heterocyclic rings such as9-deacetoxyfumigaclavine C, citriquinochroman, chaetoglobosin U and aspochalasins D which were extracted from the different types of endophytic fungi and observed for anticancer activity against the various cancer cell lines [105]. In other studies, the coumarin derivatives such as furanocoumarin, 5-methyl-8-(3-methylbut-2-enyl) furano-coumarin, and arundinone B, polyoxygenated benzofuran-3 (2H)-one purified from endophytic fungi *Microsphaeropsis arundinis* and *Penicillium* sp., showed effective anticancer activity against CA cell lines T24 and A549 CA cells [106]. The marine endophytic fungi *Phomopsis* sp. (ZH76) isolated from the stem of *Exoecaria agallocha* produced a xanthone compound 3-O-(6-O-α-l-arabinopyranosyl)-β-d–glucopyranosyl-1,4-dimethoxyxanthone showed an inhibitory growth against the HEp-2 and HepG2 cells cell line [107].

Similarly, the fungal strain *Phomopsis* sp. isolated from *Acanthus llicifolius was* observed as a source of phomoxanthones, dicerandrol A [108], dicerandrol B [99], dicerandrol C [109], diacetylphomoxanthone B [107] and penexanthone A [110]. These compounds display potential cytotoxic activity against MDA-MB-435, HCT-116, Calu-3 and Huh7 cell lines. The xenthene derivatives ergoflavin isolated from the *Aspergillus* sp., *Penicillium oxalicum*, *Pyrenochaeta terrestris, Claviceps purpurea* and *Phoma terrestris* have also been detected for their anticancer activity against various cancer cell line like renal ACHN, pancreatic Panc, colorectal and lung Calu1 cell lines [111]. The fungal extract of *Fusarium* sp., *Aspergillus fumigates* and *Aspergillus terrus* showed the cytotoxic effects against the Hela cervix and HepG2 cancer cell line [112, 113]. Some of the other anticancer compounds isolated from the different sources of endophytic fungi are given in the below Table 1.

Conclusion

Endophytic fungi are a special group of microorganisms that produce secondary metabolic compounds and have gained the scientific community's attention for their potential applications. There is no question that endophytic fungi have significant role to play in the development of a novel secondary metabolite that can be widely used in agriculture and pharmaceutical industries. Based on this review, we conclude that endophytic fungi are the novel source of bioactive anticancer compounds such as taxol, podophyllotoxin and camptothecin. Future research on insulation and strain enhancement of endophytic fungi for the development of anticancer compounds will open a new direction for pharmaceutical research. Much of the ongoing work on endophytic fungi is limited to laboratory level, so a human intervention study is also required to classify possible anticancer compounds. The discovery of more novel bioactive anticancer compounds that form endophytic fungi would also have the potential for cancer therapy.

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Compliance with Ethical Standard

Conflict of Interest No conflict of interest associated with this work.

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