Am J Cancer Res 2022;12(7):2897-2919
www.ajcr.us /ISSN:2156-6976/ajcr0143617

Review Article

Exploring the anticancer activities of novel bioactive compounds derived from endophytic fungi: mechanisms of action, current challenges and future perspectives

Rubina Kousar[1*], Muhammad Naeem[2*], Mohamad Ikhwan Jamaludin[3], Ammara Arshad[4], Aisyah Nazirah Shamsuri[5], Nelofar Ansari[6], Samreen Akhtar[7], Abu Hazafa[8], Jalal Uddin[9], Ajmal Khan[10], Ahmed Al-Harrasi[10]

[1]Collage of Life Science, Department of Biological Sciences and Technology, China Medical University, Taichung 406040, Taiwan; [2]College of Life Science, Hebei Normal University, Shijiazhuang 050024, Hebei, China; [3]Bioinspired Device and Tissue Engineering Research Group, School of Biomedical Engineering and Health Sciences, Faculty of Engineering, Universiti Teknologi Malaysia, Johor Bahru 81310, Johor, Malaysia; [4]Department of Nutrition Sciences, School of Health Sciences, University of Management & Technology Lahore, Pakistan; [5]Johor Pharmaceutical Services Division, Hospital Permai Lama, Jalan Persiaran Permai, Johor Bahru 81200, Johor, Malaysia; [6]Department of Botany, University of Balochistan, Quetta, Pakistan; [7]Department of Zoology, University of Sargodha, Pakistan; [8]Department of Biochemistry, Faculty of Sciences, University of Agriculture, Faisalabad 38040, Pakistan; [9]Department of Pharmaceutical Chemistry, College of Pharmacy, King Khalid University, Abha 62529, Saudi Arabia; [10]Natural and Medical Sciences Research Center, University of Nizwa, PO Box 33, 616 Birkat Al Mauz, Nizwa, Oman. [*]Equal contributors and co-first authors.

Received April 18, 2022; Accepted June 1, 2022; Epub July 15, 2022; Published July 30, 2022

Abstract: Cancer is the second leading cause of death all around the world. The natural compounds derived from the endophytic flora of fungi are possible solutions to cancer treatment because they are safe for health, cost-effective, biocompatible and have fewer toxicity issues. The active ingredients in endophytic fungi that are responsible for anti-cancer activities are alkaloids, terpenoids, glycosides, saponin, peptides, steroids, phenols, quinones, and flavonoids. This review highlights the anti-cancer activities of entophytic fungus against human papillary thyroid carcinoma (IHH4), human pancreatic (PANC-1), ovarian (OVCAR-3), hepatic (HepG2), lung (A-549), human lymphoma (U937), human skin carcinoma (A431), breast (MCF-7), and Kaposi's sarcoma. The emerging evidence suggested that bioactive compounds isolated from endophytic fungi showed their anti-cancer activities by revealing the disturbance of the microtubule network caused by increased levels of Bax and Bcl-2 proteins that triggers cell cycle arrest at the G2-M phase, by inhibiting the DNA replication via binding with topoisomerase II, by regulating the activity of extracellular signal-regulated kinase and NF-kB, by evaluating the levels of p21, p27, and cyclins B/D1/E that led to cell death by apoptosis and cell cycle arrest. This review will assist readers in better comprehending bioactive chemicals and the beneficial interaction between the fungal endophytes and medicinal plants.

Keywords: Endophyte fungi, cancer, treatment, apoptosis, cell cycle arrest, anti-tumor, bioactive compounds, signalling pathways

Introduction

Cancer is the second leading cause of death all around the world and has become a global health concern in the twenty-first century due to high incidence rate. Approximately, 15 million people die every year due to the persistence of malignant cells, and the number of cases significantly increases day by day [1]. It is the most obvious obstacle to improving cancer therapy in medical systems-conventional methods for the treatment of cancer, includes radiation, surgery, and chemotherapy [2]. Currently, a variety of chemotherapeutic drugs have been used for cancer treatment, still causing serious side effects on different organs, including the lungs, liver, and kidneys. Increasing the emergence of multidrug resistance also increases the risk of cancer development progression [3]. The increasing rate of cancer can be tackled with promising novel natural compounds from endophytic flora of fungi that are safe for health,

biocompatible, have fewer toxicity issues, and are less resistant as compared to conventional anti-cancer agents. These natural compounds are alternatives options to chemotherapeutic drugs and possible solutions to cancer treatment. These natural compounds exhibit anticancer nature and could use for controlling a variety of cancers. Due to their high abundance, they can be used as therapeutic agents to prevent cancer development progression [4-6].

Endophytic fungi have drawn special attention because they are an excellent source of bioactive compounds. Endophytic fungi are easy to culture in the fermentation media and consistently secrete the secondary metabolites. Endophytes are the symbiotic group of microorganisms, usually fungi and bacteria that colonize into the different tissues of their respective host. Endophytic fungi are the most important group among all microorganisms. They secreted out the large variety of bioactive-compounds such as paclitaxel, podophyllotoxin, camptothecin, vinblastine, hypericin and diosgenin that are isolated from *Thielavia subthermophila, Seimatoantlerium nepalense, Catharanthus roseus, Sinopodophyllum hexandrum, Dysosma veitchii, Rhizopus oryzae (94Y-01), Chaetomella raphigera, Aspergillus fumigatus, Rhizopus oryzae* and *Seimatoantl erium nepalense,* targeting cancer and different diseases, thus being used for therapeutic purposes [7-15]. A large variety of other novel cytotoxic compounds have been isolated from fungal endophytes. However, their mode of action against cancer is still unclear and needs to explore at a cellular and molecular level [7, 16]. These novel compounds are preferred to conventional chemical drugs due to their safe action on different tissues, biocompatible, high bioavailability, and high biodiversity. Their biochemical nature is greatly reflected as flavonoids, quinones, alkaloids, and lactones. These secondary metabolites showed their action against different cancer cell lines and are considered as more reliable therapeutic option for cancer therapy [8].

The present review highlights the anti-cancerous activity of some endophytic fungi isolated bioactive compounds. We also reported the biodiversity, recent developments in clinical studies, current challenges, and future directions of endophytic fungi in the present review for a better understanding. This article indicated endophytic growth's exploration, advancement, and progress with the anti-cancer movement. The current review additionally gives a decent establishment to logical researchers who might want to work in the field of bioactive mixes from endophytic microorganisms.

Biodiversity of fungal endophytes

Large diversity of microorganisms such as archaea, bacteria, and fungus helpful for screening for bioactive compounds [17]. Ascomycota, basidiomycota, mucoromycota, and oomycota are some of the fungi that have been shown to be endophytic in diverse crops. More than half of all endophytic fungi are found in Ascomycota, followed by Basidiomycotes. The phylum Oomycota has the fewest known fungus species. According to a study on the variety of endophytic fungi from differentplants, the most common genera are *Aspergillus*, *Fusarium*, *Penicillium*, and *Piriformospora* [18]. Some niche-specific fungal strains have also been reported, such as *Penicillium brevicompactum* and *Penicillium glabrum* from barley (*Hordeum vulgare*); *Chaetomium, Cryptococcus, Berkleasmium,* and *Gibberella zeae* were derived from maize (*Zea mays*) while *Diaporthe phaseolorum, Gibberella moniliformis, Diaporthe helianthi, Leptospora rubella, Didymella bryoniae,* and *Guignardia vaccinii* were isolated from soybean wheat (*Triticum aestivum*) [17, 19].

Various medicinal plants have been used to isolate endophytic fungi. Bioactive compounds derived from these endophytic fungus are of economic importance. Fungal endophytes are colonized older sections of the endemic plant *Cordemoya integrifolia*, such as leaves and petioles, more often than younger leaves. *Pestalotiopsis* sp. and *Penicillium* are the most common fungal endophytes [20]. Different fungal endophytes found in Thai medicinal plants have been shown to produce bioactive compounds. Research on endophytic fungus and medicinal plants that produce one or more bioactive chemicals was conducted on various medicinal plants. Puri et al. [21] found that the anticancer medicine molecule Camptothecin was isolated from the endophytic fungus *Entrophospora infrequens*, derived from the internal bark of a medicinal plant called *Nothapodytes foetida*. The fungal endophytes were separated by sanitizing the leaves and branches of five Garcinia species [22]. *Penicillium*

thomi was isolated from the roots of *Bruguiera gymnorhiza*, according to Chen et al. [23]. The discovery of a new molecule, 4', 5 dihydroxy-2,3 dimethoxy 4(-hydroxy propyl)-biphenyl, was made possible due to the discovery of a fungus endophyte. They were tested on three human cell lines for their cytotoxic properties. *Colletotrichum, Phoma, Phomopsis,* and *Xylariales* were the most common isolates among the 1160 endophytic fungi found in 29 Chinese medicinal plants, and these fungi were mostly phenolic in nature [24]. Taxol, a critical anticancer compound, was discovered to be produced using the fungus *Bartalinia robillardoides*, which was isolated from the medicinal plant *Aegle marmelos* [25]. According to Liu et al. [26], the most common taxonomic genus was Acremonium, followed by Phomopsis and Pezicula. Fungal endophytes such as *Penicillium* sp. and *Aspergillus* sp. were shown to promote plant development by Ahmad et al. [27]. One of the most problematic weedy rice paddies, *Monochoria vaginalis*, yielded the two fungus endophytes studied in Korea. Fungi from both species considerably increased plant growth during screening and produced more gibberellins than other fungi. The detailed information on different endophyte fungi isolated from various host plants are presented in **Table 1**.

Katoch et al. [28] conducted study on *Monarda citriodora* Cerv. ex Lag. to isolate different endophytic fungi. There were 28 fungal endophytes reported in this plant, belonging to 11 distinct genera and Ascomycota phylum. Roots had the greatest tissue-specific fungal dominance, whereas leaves had a colossal diversity of fungi. Endophytic extracts from 28 fungal species were shown to be cytotoxic against one or more human cancer cell lines in 72% of the cases. Extracts from *Fusarium oxysporum* (MC-14 L, MC-14 F, and MC-26 F), *Aspergillus fumigatus* (MC-18 L), *Cladosporium tenuissimum* (MC-24 L), and *Fusarium* sp. (MC-25 L) showed the most notable anticancer action (IC_{50} values <10 μg/mL). In another investigation, a total of 154 fungal endophytes were identified from roots and stems from *Distylium chinense*. 27 (17.5%) of the 154 isolates examined demonstrated only anticancer activity against human papillary thyroid carcinoma cell line (IHH4) and human pancreatic adenocarcinoma cell line (CFPAC-1). For IHH4 cell line, DR46-1 (*Phomopsis* sp.) fungal extract demonstrated the strongest anticancer activity with IC_{50} values of 9.20±0.02 μg/mL [29].

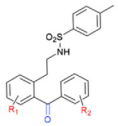
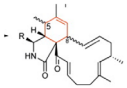
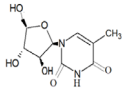
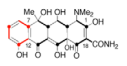
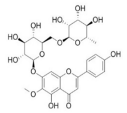
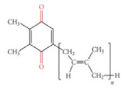
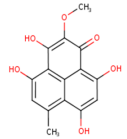
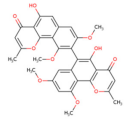
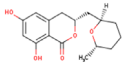
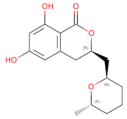
Anticancer activities of endophytic fungi

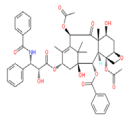
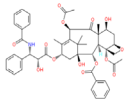
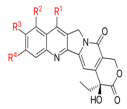
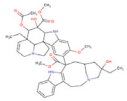
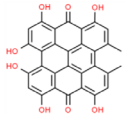
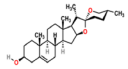
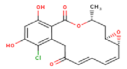
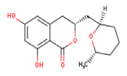
Chemotherapeutic agents have been used for the treatment of cancer for a few past decades, but most of them cause cellular toxicities. Due to toxicity concerns, chemotherapeutic agents have been replaced with natural anti-cancer compounds isolated and purified from an endophytic group of fungi and used against a variety of cancers such as Kaposi's sarcoma, prostate, lung, ovarian, and breast cancer. These compounds induced apoptosis and suppressed the progression of cancer development [30, 31]. The details of various anti-cancer compounds, sources, chemical structure, biochemical nature, and mechanism of action are shown in **Table 1**.

Anticancer activity and mechanism of action of paclitaxel

Several endophytic fungi such as *T. andreanae, Seimatoantlerium nepalense, Alternaria alternate* and *Chaetomella raphigera* have been reported in past studies that produced the paclitaxel as an anti-cancer drug [9]. Paclitaxel has been used for the treatment of skin cancer such as Kaposi's sarcoma, resulting in the masses arising from the accumulation of abnormal cells, prostate cancer, lung cancer, and ovarian cancer [32]. Due to its binding ability to the tubulin protein, it particularly inhibited the depolymerization during the cell division phase of the cell cycle [33]. Kumaran et al. [34] performed an experiment on the diseased fruits of Chilli plant to isolate the fungus bioactive compound such as taxol. They revealed that taxol significantly showed the cytotoxic effects against different human cell lines, including MCF-7, HLK-210, and HL-251, at different dose rates such as 0.005, 0.05, 0.5, and 5 μM. They also reported that fungal taxol showed the best anticancer activity of 79.37±7.57, 83.86±5.76, and 74.76±5.41% against MCF-7, HLK-210, and HL-251, respectively, at 0.5 μM as compared to other concentrations by inducing apoptosis and inhibiting cell proliferation by blocking mitosis. Another study revealed that administration of taxol and baccatin III (0.1, 5 μM) promoted apoptosis in ovarian cancer lines (OVCAR-3) and hepatic cancer lines (HepG2) and inhibited the meta-

Table 1. List of endophytic fungi produced from host plant for producing anticancer bioactive compounds

Endophytic fungi	Bioactive compound	Chemical structure	Biochemical nature	Biological activity	Reference
Myrothecium roridum	Myrotheciumone A		Lactones	Against the HepG-2 cells with IC_{50} value (5.36±0.26 μM)	[90]
Chaetomium globosum TY1	Chaetomugilides		Alkaloids	Against HepG-2 cells with IC_{50} value of 17-53.4 μM	[91]
Chaetomium globosum 7s-1	Xanthoquinodin B9		Xanthones	Exhibited cytotoxic potential against the human cancer cell lines KB, MCF-7 and NCI-H187 cancer cell lines (IC_{50} 0.04-18.40 μM)	[92]
Cerrena sp. *A593*	Triquinane		Sesquiterpenoids	Showed anti-cancer activity against SF-268, MCF-7, NCI-H460, and HepG-2 tumor cell lines with IC_{50} values of 41.01, 14.43, 29.67, 44.32 μM	[93]
Chaetosphaeronema hispidulum	Hispidulone B		Phenalenone	Cytotoxic potential against the human hepatoma cell line (Huh7) with IC_{50} value of 22.93±1.61 μM	[94]
Ascomycete sp. *F53*	Lijiquinone		Terpenoids	Against the human myeloma cell lines (RPMI-8226) with IC_{50} value of 129 μM	[96]
Aspergillus sp. *XNM-4*	Asperpyrone A		Polyketides	Anticancer activity against the human cancer cell line (SK-OV-3) with IC_{50} value of 8.00 μM	[95]
Asperpyrone B	Asperpyrone B		Polyketides	Against the human cancer cell line (PANC-1) with IC_{50} value of 7.5.00 μM	[95]
Cladosporium cladosporioides	Cladodosporol		Polyketides	Against the colon carcinoma HT-29 cells	[97]
Cladosporium cladosporioides EN-399	Cladodosporol C		Polyketides	Activity against the human cancer cell line (H446) with IC_{50} value of 4.00 μM	[97]

Seimatoantlerium tepuiense, Seimatoantlerium nepalense	Paclitaxel		Alkaloids	Used for the treatment of cancers such as Kaposi's sarcoma, prostate cancer, lung cancer	[9, 32, 33, 36, 116]
Aspergillus fumigatus, Phialocephala fortinii	Podophyllotoxin		Glycosides	Used for the treatment of cancers such as leukemia, testicular cancer, prostate cancer, lung cancer, ovarian cancer, and solid tumors	[11, 45, 117-119]
Entrophosporain, C. acuminate	Camptothecin		Pyranoindolizinoquinoline	Used for the cancer treatment against solid tumors found in the liver, bladder, lungs, and ovaries	[12, 41, 44, 120]
Catharanthus roseus, Fusarium oxysporum	Vinblastine		Vinca alkaloid	Used against lymphoblastic leukemia	[13, 46-49]
Thielavia subthermophila	Hypericin		Anthraquinone	Used as an anti-cancer drug and also showed potential against T-cell lymphoma	[56-58]
Rhizopus oryzae, Fusarium sp.	Diosgenin		Steroid saponin	Its anticancer potential has been investigated in different cell lines of breast cancer, lung cancer, hepatic carcinoma, chronic myeloid leukemia, prostate cancer, and colon cancer	[14, 15, 70, 75, 77, 78]
Ephedra fasciculate	Radicicol		Lactone	Radicicol showed its action against breast cancer	[88, 121]
Cladodosporol H	Cladodosporol H		Polyketides	Higher cytotoxicity against the cell line (Huh7) by the IC_{50} value of 1.00 μM	[97]

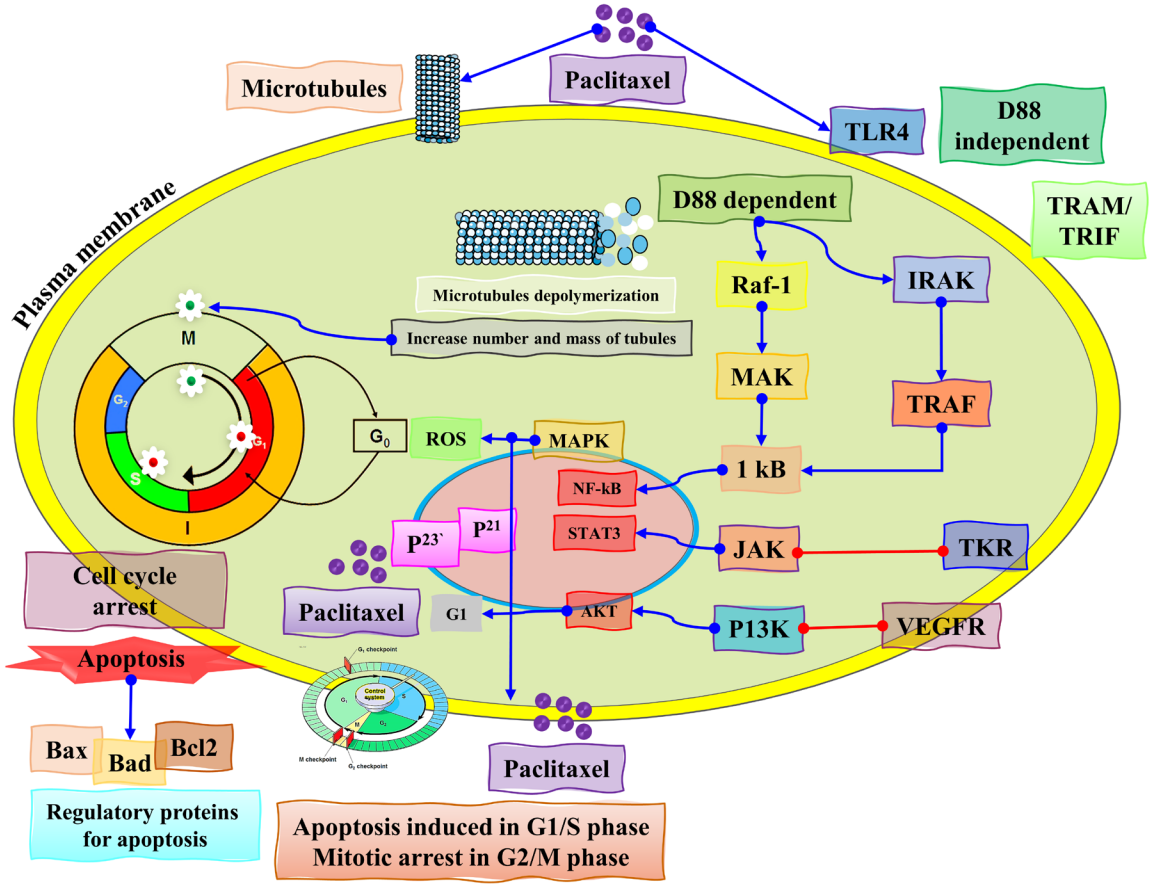


Figure 1. The representative mechanism of action of paclitaxel. Phosphorylation of Raf-1 kinase or p53/p21 induces G0 and G1/S-phase apoptosis at high concentrations of paclitaxel, whereas p53/p21 is activated at low concentrations. Paclitaxel may produce mitotic arrest even at modest doses, but only if it is inhaled for more than 24 hours. Paclitaxel also has a proapoptotic and immunomodulatory impact by activating various signaling pathways. These signaling pathways are similarly used by paclitaxel to produce resistance. MEK/MAPK: mitogen-activated protein kinase; TLR4: Toll-like receptor 4; Raf-1: Raf kinase family; NF-κB: nuclear factor kappa B; PI3K: phosphoinositide 3-kinase; TRAF: TNFR associated factor; VEGFR: vascular endothelial growth receptor; JAK: janus kinase; TRIF/TRAM: TIR-domain-containing adapter-inducing interferon-β. This figure is reproduced from Kampan et al. [38] (Attribution 3.0 Unported (CC BY 3.0)).

static invasions of 68 and 65%, respectively [35].

Paclitaxel has been used as an anti-cancer drug due to its high cytotoxicity during several molecular events occurring during the cell cycle. Paclitaxel has shown its effects on the formation and stabilization of microtubules during the spindle network by maintaining their structure through the polymerization of microtubules and resisting the depolymerization that disrupts the assembly of microtubules. Some previous studies showed that paclitaxel in combinations with calcium chloride (4 mM) also resists or slows down the process depolymerization that causes the instability of microtubules that interfere with the spindle network. Paclitaxel also plays a vital role in cell signaling pathways by revealing the disturbance of the microtubule network caused by increased levels of Bax and Bcl-2 that cause the arrest of the cell cycle during the G2-M phase. These events also induced apoptosis during the G1-phase of mitosis. It resulted in the cell cycle arrest at a mitotic phase that leads to cell death (see **Figure 1**) [36-38].

Anticancer activity and mechanism of action of podophyllotoxin

Several endophytic fungi have the ability to produce an adequate amount of podophyllotoxin. These fungi are *Sinopodophyllum hexandrum* and *Dysosma veitchii* [11]. Podophyllotoxin has

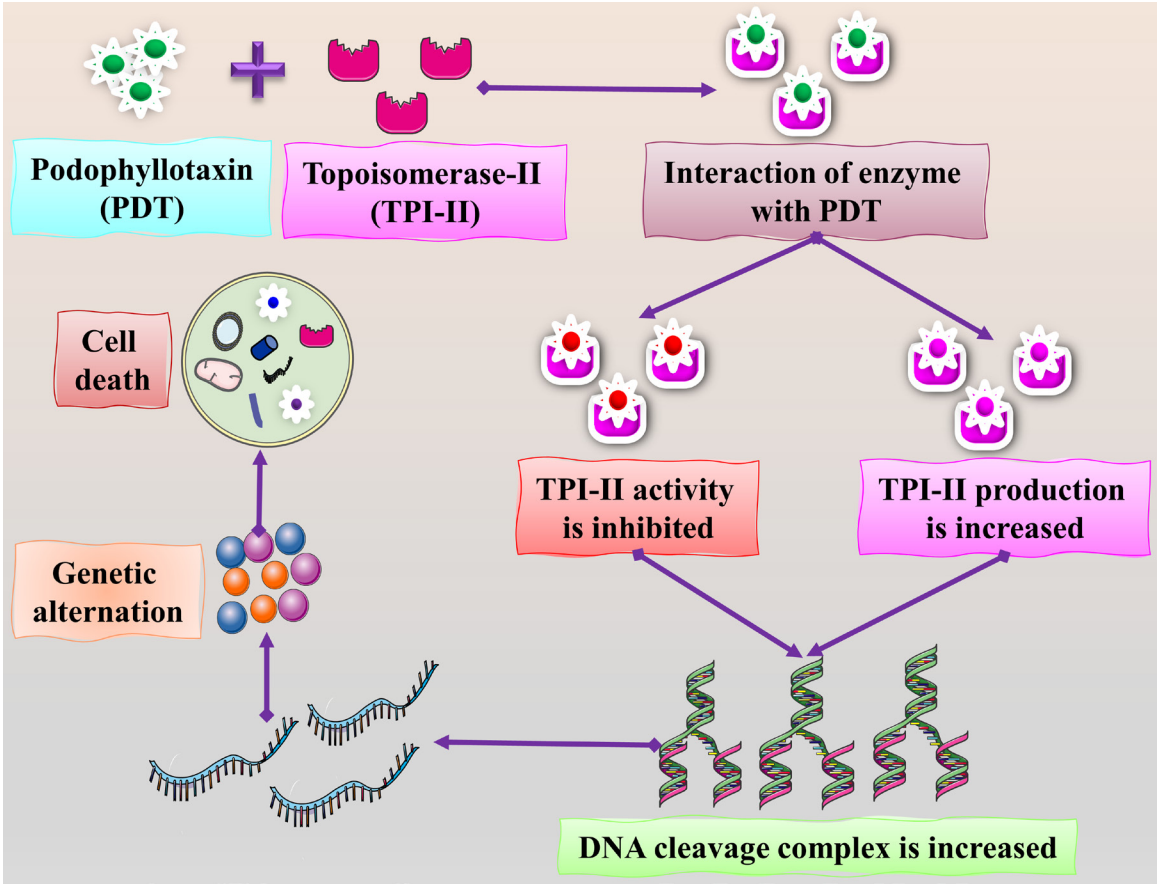


Figure 2. The mechanism of cell death by podophyllotaxin against cancer. Podophyllotoxin substitutes for etoposide and teniposide, which inhibit DNA replication by interacting with topoisomerase II. This bioactive chemical increases the expression of topoisomerase II, which increases DNA cleavage. Etoposide does not inhibit topoisomerase II's catalytic activity, but it is toxic to the enzyme, leading to enhanced DNA duplex cleavage and irreversible double-stranded DNA breakage. However, recombination, translocation, deletion, and insertion cause cell death. This figure is reproduced from Kumar et al. [40].

been used as an anti-cancer drug. Its precursors exhibit high potential for targeting the premature metastatic cells, thus wieldy used to treat different cancers such as leukemia, testicular, prostate, lung, and ovarian cancer [39].

Podophyllotoxin shows its cytotoxic effects by inhibiting the DNA replication by binding with topoisomerase II. Podophyllotoxin blocks the activities of topoisomerase II by increasing their levels. Etoposide, a precursor of podophyllotoxin is highly toxic to topoisomerase II, and their strong binding increases the damage to the DNA duplex by breaking the double-stranded DNA of the mammalian tissues and increasing the risk of DNA damage. The considerable accumulation of the DNA-damage induced cell death due to changes in the DNA alternations caused by the insertions, deletions, and genetic recombination (see **Figure 2**) [40].

Anticancer activity and mechanism of action of camptothecin

Camptothecin has been used as a cytotoxic drug and is widely used for cancer treatment against solid tumors in the liver, bladder, lungs, and ovaries. It showed promising inhibitory effects during clinical investigations in these organs by inhibiting cell growth, thus inducing apoptosis [41]. A study conducted by El-Sayed et al. [42] revealed that camptothecin significantly promoted apoptosis and cell death in different cancers. This compound showed promising anticancer effects against HEPG-2 (IC_{50} 0.9 mM), MCF7, and HCT29 (IC_{50} 1.2-1.35 mM) and increased the activity 3-fold at 150 µg/L. Another study reported that camptothecin isolated from *A. niger* promoted the apoptosis and cell death in colon cancer cell lines

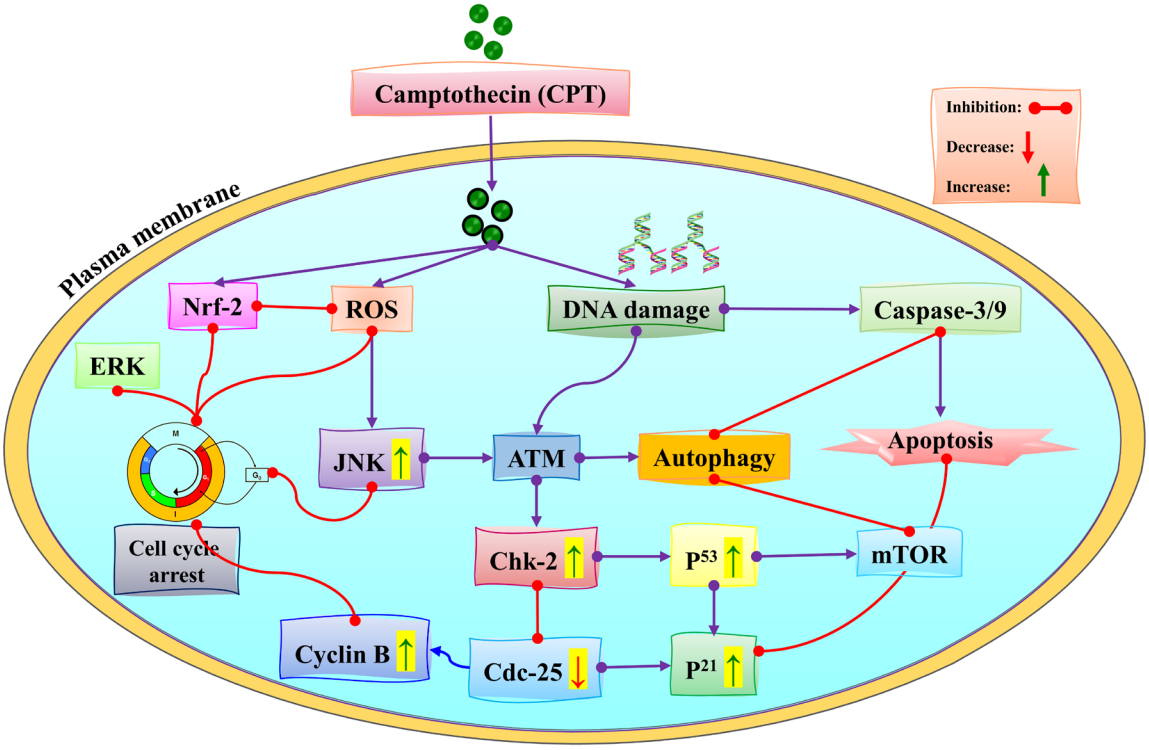


Figure 3. The anticancer mechanism of action of camptothecin. JNK: c-Jun N-terminal kinase; Chk2: checkpoint kinase 2; Nfr2: nuclear factor erythroid 2-related factor 2; ERK: extracellular signal-regulated kinase; Cdc25c: cell division cycle 25C; mTOR: mammalian target of rapamycin; CPT: Camptothecin; ATM: ataxia telangiectasia mutated gene. This figure is reproduced from Ghanbari-Movahed et al. [122] (Attribution 4.0 International (CC BY 4.0)).

when administrated at different doses as 7.8, 125, 250, 500 and 1000 mg/L and showed maximum and minimum cell viability of about 11.85 and 65.13%, at 1000 and 7.8 mg/L concentration, respectively on cancerous colon cells (HCT-15) [43]. Another study demonstrated that camptothecin isolated from *Nothapodytes foetida* significantly enhanced the apoptosis in ovarian (OVCAR-5) and hepatic (HepG2), and lung (A-549) cancer [21].

The anti-tumor activity of the camptothecin is greatly reflected due to its interaction with topoisomerase-I, which has the ability to bind with double-stranded DNA. These enzymes act during replication by creating a nick via cutting one of two strands of double-stranded DNA. They are also involved in relaxing the supercoiling in double-stranded DNA. Camptothecin binds non-covalently with topoisomerase-I and suppresses their catalytic activity, thus showing anti-cancer properties. It resultingly increased the expression of p21, p53, and mTOR. While on the other hand, camptothecin also elevates the activities of extracellular signal-regulated kinase and nuclear factor erythroid related factor 2. These molecular events induced apoptosis, leading to cell death (see **Figure 3**) [44, 45].

Anticancer activity and mechanism of action of vinblastine

Many endophytic fungi produce anti-cancer compounds that possess a high potential for tumor suppression. For example, *Catharanthus roseus, Catharanthus roseus,* and *Fusarium oxysporum* produce vinblastine from their hosts [13, 46]. Due to the large diversity of endophytic fungi, they can be used for tumor suppression. Vinblastine has been used against lymphoblastic leukemia and the cancer cell lines (HepG-2) with the ICM (7.48 μg/mL), thus promising candidates for cancer treatments [47, 48].

Vinblastine and its derivatives have been used as anti-cancer agents because they inhibit the activities of tubulin proteins involved in the formation of spindle fiber during mitosis. Actually, tubulins are involved in the polymerization of

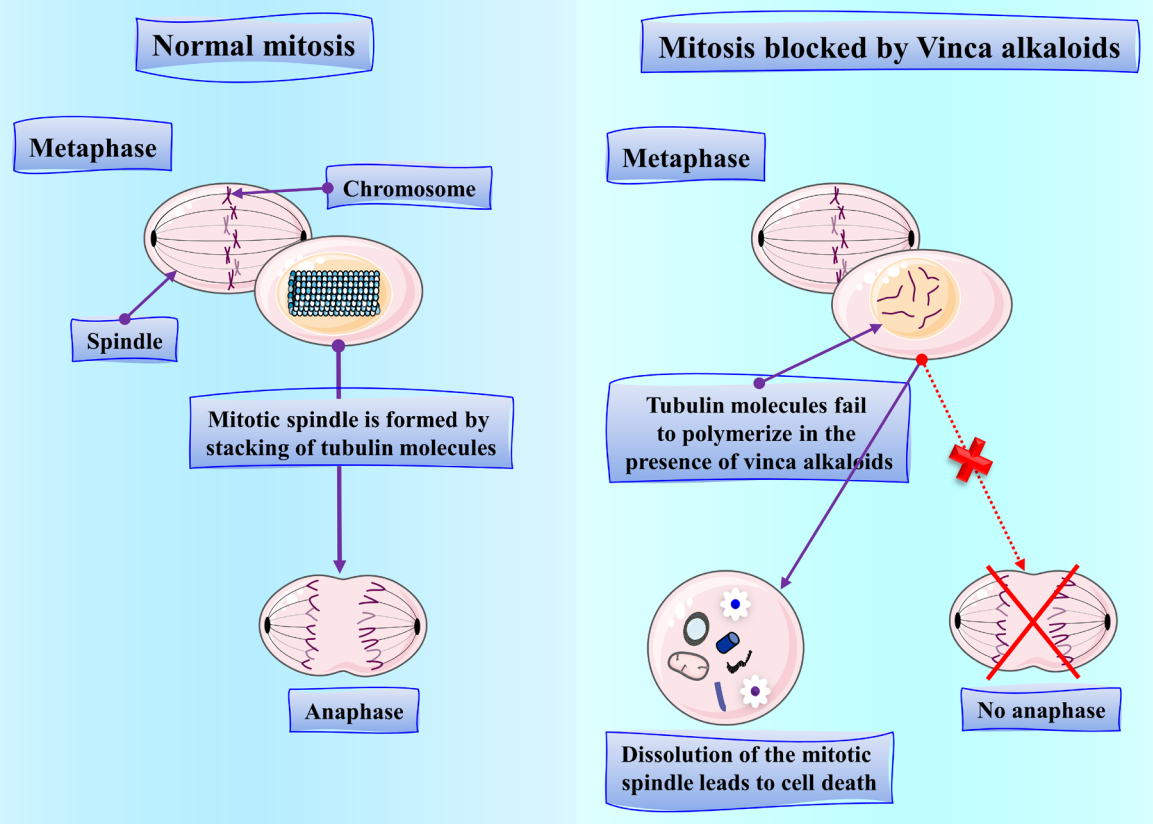


Figure 4. The representative mechanism of action of vinca alkaloids. The cytotoxicity of the vinca alkaloid is caused by its synergy with tubulin as well as its disruption of the function of microtubules. This mainly occurs in the microtubules that make up the mitotic spindles and causes a halt in the metaphase phase of the cell cycle. This figure is reproduced from Anitha [54] (Attribution 4.0 International (CC BY 4.0)).

spindle fibers during the mitotic phase. Vinblastine compounds bind with the receptor's sites on the tubulin protein by blocking the polymerization. It resulted in the impaired functions of tubulin and caused the microtubule assembly during mitosis. These events cause the cell to be arrested in the anaphase for a prolonged state that ultimately leads to cell death (see **Figure 4**) [49]. A study revealed that after treatment with fungal vinblastine, the proliferation of CHO-K1, MCF-7, and HepG-2 cell lines was suppressed, and the measured IC_{50} values of the corresponding cell lines were 12.15, 8.55, and 7.48 μg/mL, respectively [48]. Another study reported that cell proliferation in MCF-7 was reduced by 53% and 71%, respectively, when indibulin and vinblastine were taken in combination (50 and 150 nM), producing a combination index (CI) of 0.67 and 0.5, respectively. Indibulin and vinblastine had a synergistic impact on MCF-7 cell proliferation, as seen by the combination indices being ≤1, which indicates that the two drugs work together to inhibit cell proliferation [50].

Ashraf et al. [51] demonstrated that vinblastine and paclitaxel had an anticancer effect on HeLa cell growth with IC_{50} of 1.2 and 10 nmol/L and a median dosage of 1.10 and 9.21 nmol/L, respectively. Combining zerumbone with vinblastine and paclitaxel suppressed HeLa cell growth synergistically. Proliferation inhibition of about 84%, 98%, and 100% was observed when zerumbone was used in combination with vinblastine at concentrations of 5, 10, and 12 μmol/L, respectively. A PEGylated niosomal formulation of vinblastine (Pn-VB) was produced via a thin film hydration process by Amiri et al. [52]. A substantial increase in toxicity against TC-I cells was seen when Pn-VB was used instead of free VB. They revealed that Pn-VB had a more significant tumor-killing impact and a longer lifespan in an animal model compared to free VB. Pn-VB was shown to be

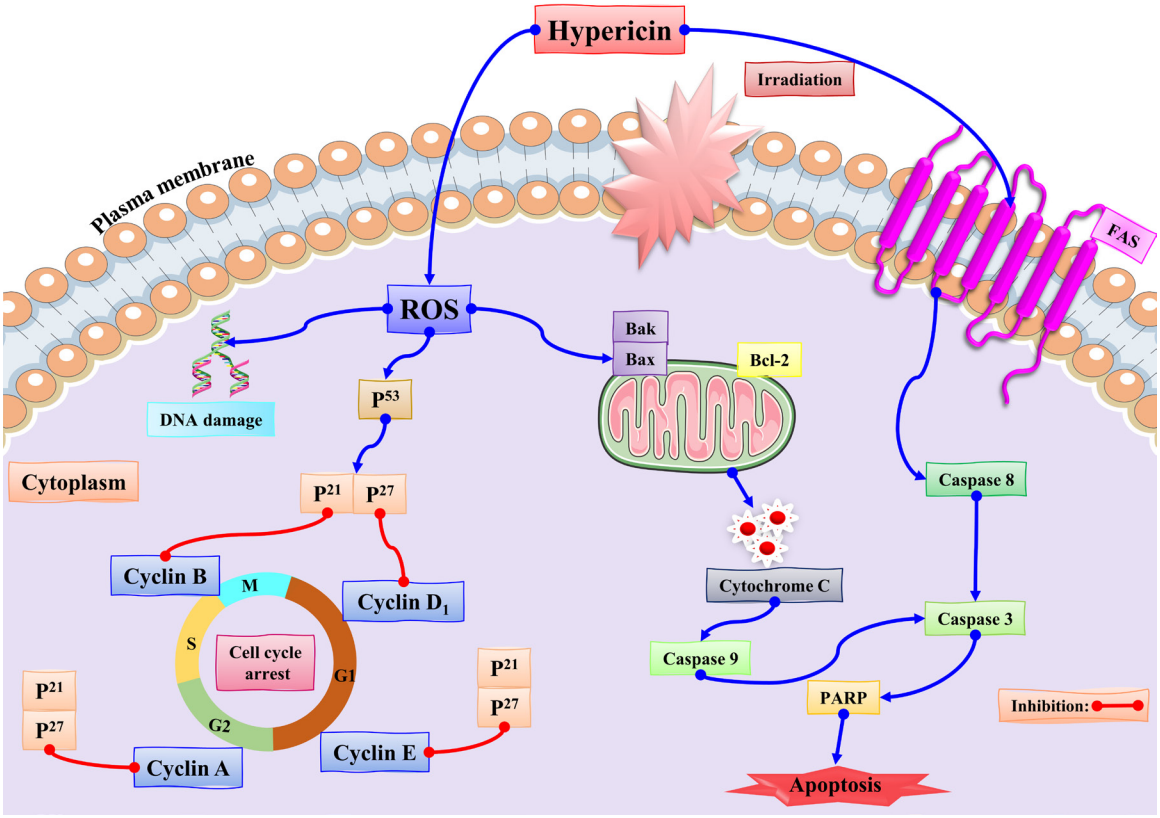


Figure 5. The schematic representation of cell death by hypericin against cancer. Hypericin's antitumor effects are due in part to its ability to inhibit a wide range of proteins and genes. The p38 MAPK, JNK, PI3K, CHOP/TRIB3/Akt/mTOR, TRAIL/TRAIL-receptor, mitochondria, and extrinsic signalling pathways may also be affected by hypericin. Hypericin-mediated photodynamic therapy has been shown to have the capacity to block a variety of cell proliferation, induce apoptosis, autophagy and angiogenesis-related activities and clearly shows its enormous promise in cancer treatment. This figure is reproduced from Dong et al. [59] after permission.

stable, effective in encapsulation, and more effective in killing lung cancer TC-1 cells compared to the free drug. To achieve high activity and toxicity against cancer cells, the vinblastine molecule interferes with the dynamic equilibrium between dissociation and aggregation of α-tubulin and β-tubulin. In addition, their results show that vinblastine had its structural basis for anticancer cytotoxicity due to its two compositions composed of a catharanthine moiety molecule and a vinblastine molecule, even though they have little toxicity against cancer cells when used alone [53, 54].

Anticancer activity and mechanism of action of hypericin

Some species of endophytic fungi produced hypericin, such as *Thielavia subthermophila,* within their host plant, *H. perforatum* [55, 56]. Hypericin has been used as an ant-cancer drug, and its potential has been investigated against T-cell lymphoma [57]. It acts by inhibiting several genes and activation of caspases assembly. Hypericin interacts with the ROS that causes damage to the DNA. It elevated the levels of p21, p27, and cyclins B/D1/E. Cytochrome c is released from the inner mitochondrial protein that activates the caspases-3,8. These molecular events increased the expression of PARP. It resulted in the arrested of the G-2 phase in the cell cycle, induced apoptosis and cell death (see **Figure 5**) [58, 59]. Studies revealed that different doses of hypericin (0.021, 0.2, and 0.02 μM) significantly promoted the apoptosis and cell death in breast cancer cell line (MCF-7), human lymphoma cancer cell line (U937), and human skin carcinoma cancer cell line (A431) and showed inhibition of metastatic invasion by 60-90%, and proved as a promising anticancer compound [60-62].

As Huygens et al. [63] showed the combination of hyperoxygenation with hypericin (HYP) signifi-

cantly inhibited the RT-112 bladder cancer cells by apoptosis. The photodynamic activity was increased in RT-112 cancer spheroids by using perfluorocarbons. Because HYP was shown to be concentrated in bladder cancer cells, it is possible that HYP and perfluorocarbons might be used for photodynamic therapy of the bladder wall. Han et al. [64] reported that hypericin, derived from *Hypericum perforatum* L., is a potent mitochondrial ligand. They revealed that hypericin graphene oxide (GO) loaded with doxorubicin (GO-PEG-SS-HY/DOX) improved the synergistic anti-tumor activity of phototherapy and chemotherapy with no evident side effects. GO-PEG-SS-HY/DOX enhanced the expression of critical mitochondria-mediated apoptosis pathway proteins and triggered apoptosis in breast cancer cells *in vitro* and *in vivo*. As well as being safe for normal cells, functionalized GO preparations are safe for use in anticancer treatment. Thus, HY-functionalized GO may be employed to target mitochondria in cancer cells and increase chemotherapeutic drug effectiveness. Mitochondrial membrane potential loss and activation of caspase-3 and PARP proteins were exacerbated in HT-29 cells after treatment with both hypericin and the inhibitor of survival expression, known as YM155 [65]. Manumycin A and photoactive hypericin synergistically had anticancer effects on HT-29-OxR cells, which had developed resistance to oxaliplatin. Cell viability, colony formation, and apoptosis may all be affected by this pathway [66].

Sardoiwala et al. [67] synthesized hypericin-loaded transferrin nano-formulations (HTfNPs) to overcome the placebo's hydrophobicity and bioavailability. Cell cycle arrest in G0/G1 phase and increased reactive oxygen species (ROS) formation confirm nanoformulation's anticancer impact. The nanotherapeutic intervention of PP2A, caspase3, and BMI1, EZH2, 3Pk, NF-κB was visible in the mechanism research. An epigenetic-driven nanotherapeutic strategy for colorectal cancer therapy was shown in their work, which confirmed the anticancer impact of HTfNPs-assisted PDT by triggering the degradation of BMI1 via PP2A. Kim et al. [68] reported that FRO cell death was accelerated by using hypericin dosage and laser power-dependent. ROS formation inside cells and damage to mitochondria were involved in the hypericin- and laser-induced cell death of FROs. For the treatment of human anaplastic thyroid cancer, hypericin has been shown to be an effective photosensitizer. Hypericin has a dose-dependent cytotoxic impact on the K562 cell line, according to Arani et al. [69]. Apoptosis in cells exposed to hypericin for 24 h was found to be 53%, as determined by flow cytometry and immunocytochemistry on p53. Hypericin at IC_{50} concentration enhanced the expression of p53 and Bax genes, but Bcl2, Myc, and Mdm2 gene expression reduced after 24 h of exposure. According to their findings, hypericin kills K562 cancer cells by inhibiting Mdm2 and Myc expression.

Anticancer activity and mechanism of action of diosgenin

Diosgenin is particularly used as an anticancer agent in different cell lines, and some recent studies showed potential exits properties of anti-tumor role in the preclinical studies. Its anticancer potential has been investigated in different cell lines of cancers such as breast, lung, hepatic carcinoma, chronic myeloid leukemia, prostate, and colon cancer. The anti-tumor potential of diosgenin in the different events of tumorigenesis included the control of the abnormal growth of metastatic cells, a proliferation of tumor cells, and induce apoptosis [70]. Chen et al. [71] reported that administration of diosgenin at different doses as 50 and 100 mg/kg to mice bearing prostate and hepatic (HepG2) cancer showed promising anticancer effects of 50% and 36.18%, respectively. Another study revealed that administering diosgenin at a dose rate of 0.1% into the rats (up to 48 weeks) bearing colon cancer cells showed promising anticancer effects. Administered diosgenin significantly inhibited the tumor invasion up to 60% in both invasive and non-invasive colon cancer incidence [72]. Another experiential study demonstrated that administration of diosgenin at 10 mg/kg to the mice showed promising anticancer effects against breast cancer cell lines (MDA-231) by 23-folds relative to the control groups [73].

Diosgenin induced apoptosis via AKT and JNK pathways driven by caspases in the Hep2 skin carcinomas. It also inhibited the expression of E-cadherin, integrin 5a and 6b, invasion, migration, and angiogenesis in hypoxia-sensitive BGC-823 gastric cancer cells. It was also reported that diosgenin binds with the E-cadherin,

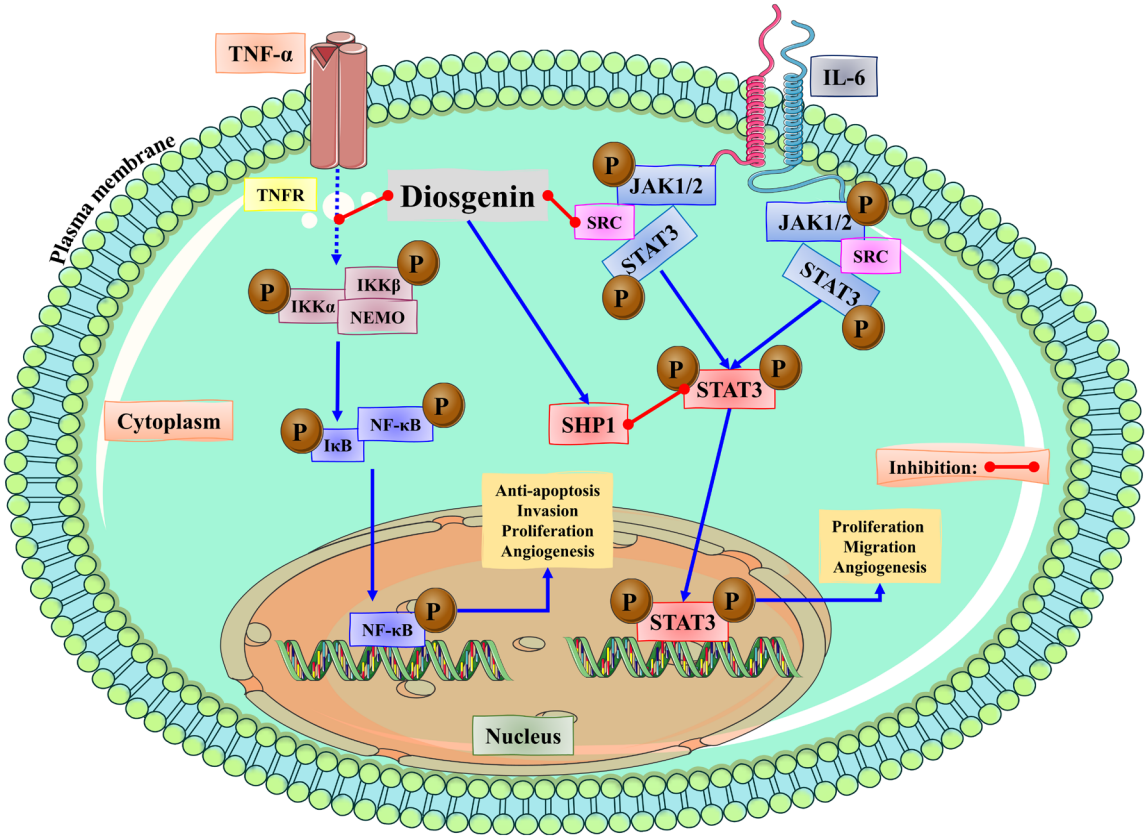


Figure 6. The schematic anticancer mechanism of action of diosgenin. TNF-α-induced activation of NF-κB and IL6-induced STAT3 signaling pathways in tumor cells are blocked by diosgenin. Because of this, diosgenin may inhibit cancer cell proliferation, invasion and angiogenesis; in addition to promoting apoptosis, a key feature in cancer treatment. SHP1: Src homology 2 domain-containing protein tyrosine phosphatase 1; *NEMO*: NF-κB essential modulator; TNFR: tumor necrosis factor receptor; JAKs: janus kinases; STATs: signal transducer and activator of transcription proteins. This figure is reproduced from Sethi et al. [78] (Attribution 4.0 International (CC BY 4.0)).

thus involved in the angiogenesis of BGC-823 gastric cancer cells [74]. Recent studies showed that diosgenin has the ability to bind with NF-κB induced surviving cyclin D1 and, Cdk-2 and thus decrease their expressions in the breast metastatic/cancer cells [75]. The steroidal sapogenin, diosgenin, has surfaced as a possible cancer therapy option. It triggers ROS-mediated autophagy, inhibits the PI3K/Akt/mTOR pathway, and generates cytotoxicity, specifically in cancer cells [76].

Although diosgenin acts at a cellular and molecular event are occurring during NF-κB and STAT3 signaling pathways. It suppresses the level of TNF-α via the NF-κB signaling pathway through the targeted abnormal cell proliferation and induces the process of apoptosis, while on the other hand, it also suppresses the level of IL6 via STAT3 signaling in metastatic cells. Diosgenin suppresses the abnormal cell proliferation induced by the process of apoptosis. On the other hand, it also suppresses the level of IL6 via the STAT3 signaling pathway through cell migration and angiogenesis, thus acting as a potential anti-cancer drug for the early management of cancers. Therefore, it is wieldy used for cancer therapy (see **Figure 6**) [77, 78].

Amina et al. [79] use an algal extract from *Dictyosphaerium* sp. strain DHM2 (LC159306) as a reducing agent to synthesize novel gold nano-formulations loaded with diosgenin (Dio-AuNPs). They found that Dio-AuNPs had GI_{50} values in HCT116 and HCC1954 cell lines of 1.03±0.27 and 1.69±0.18 g/mL, respectively. Dio-AuNPs, on the other hand, were about 18 times more powerful than AuNPs in both cell lines. Another study indicated that diosgenin

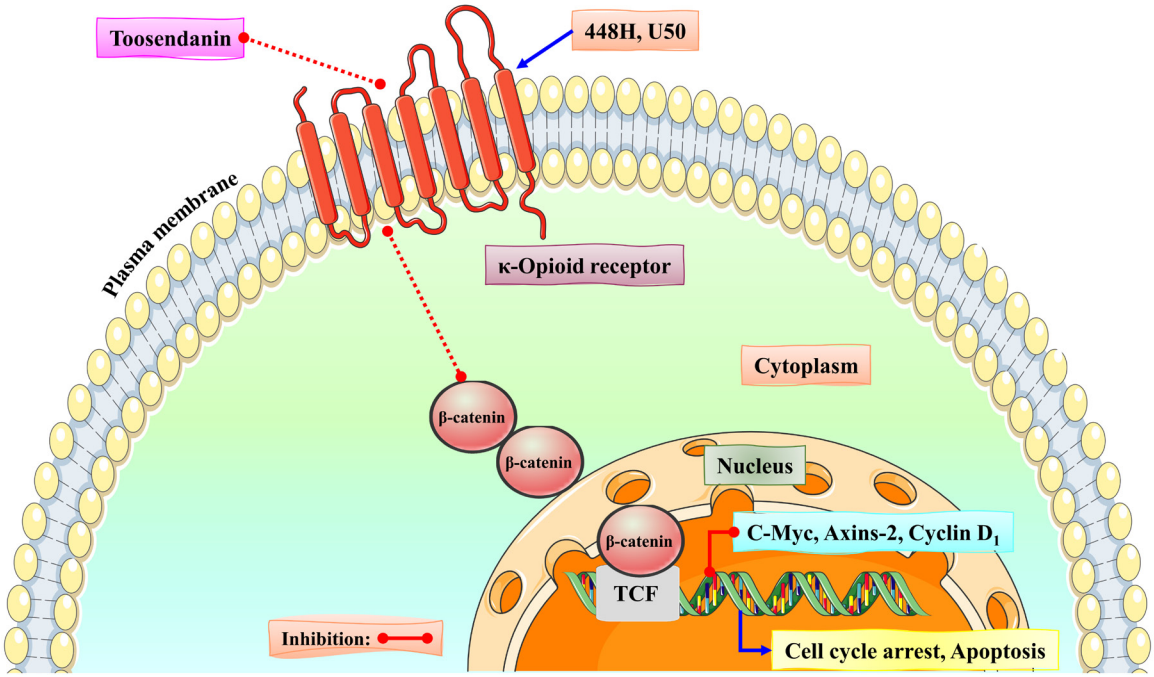


Figure 7. The schematic illustration depicted the process of cell death via apoptosis and cell cycle arrest by toosendanin. This figure is reproduced from Wang et al. [123] after permission.

decreased cell viability and triggered apoptosis. Furthermore, diosgenin was reported to inhibit breast cancer cell invasion. The expression of Skp2 was also reduced in breast cancer cells after treatment with diosgenin. Diosgenin suppressed Skp2 and decreased viability and motility in breast cancer cells, resulting in apoptosis [75]. Shishodia and Aggarwal, [80] found that diosgenin prevented TNF-α induced NF-κB activation and inhibited osteoclastogenesis in the RAW 264.7 macrophage cell line. Diosgenin caused apoptosis in Her-2 positive breast cancer cells by inhibiting the expression of AKT, mTOR, JNK, and their related pro-survival signaling pathways [77]. They found that diosgenin might suppress the STAT3 signaling pathway in HCC cells by reducing the activity of intracellular signaling molecules such as JAK1, JAK2, c-SRC, and JAK3 inside the cells [81].

The anticancer activity of toosendanin

Toosendanin (TSN) possessed special biological actions as well as extensive value in scientific research and clinical medicine [82]. Preclinical research has accumulated proof that highlights TSN as an anti-cancer effect on different cancer cells *in vivo* and *in vitro* [83]. The suppression of the PI3K/AKt, MEK/Erk, and MAPK/JNK pathways in leukemia, colorectal cancer, hepatocellular carcinoma, prostate cancer, lymphoma, and breast cancer have the molecular mechanism that involves initiation to seize the cell cycle and apoptosis. The current research on glioblastoma suggests that TSN inhibited cancer cell proliferation in U87 and U6 through apoptosis via estrogen receptor-dependent machinery (see **Figure 7**) [84].

TSN is a triterpenoid that is highly cytotoxic in several cancer cell lines. AGS and HGC-27 cells were treated with TSN, and the researchers found that it reduced cell viability, stopped cell growth by triggering G1/S arrest, and promoted caspase-dependent death. Involvement of the p38 MAPK pathway might be linked to TSN-induced cell death. TSN was shown to have therapeutic promise in the treatment of gastric cancer in these studies [85]. Zhang et al. [86] reported that TSN and isotoosendanin (ITSN) were shown to be cytotoxic to a wide range of tumor cells in a cell viability experiment, however, they were more effective against triple-negative breast cancer cells such MDA-MB-231, BT549, and 4T1. Cell apoptosis was seen in both MDA-MB-231 and 4T1 cells in the presence of TSN (20 nM) or ITSN (2.5 nM).

Pro-caspase-3 and Bcl-xL expression were also reduced in both MDA-MB-231 and 4T1 cells after treatment with TSN (20 nM) or ITSN (2.5 nM). According to the findings of a study, natural compounds TSN and ITSN decrease TNBC development by triggering necrosis, apoptosis, and autophagy. An investigation revealed that TSN reduced glioma cell growth *in vitro* using the CCK-8 and colony formation analysis. TSN induced apoptosis in glioma cells was assessed by Hoechst 33342 staining, flow cytometry, and western blotting tests. TSN also inhibited the PI3K/Akt/mTOR signaling pathways, assessed by western blotting research to exert its anti-glioma impact [87].

Recent isolated bioactive compounds from fungal endophytes and their mechanism of actions

Due to the large diversity of endophytic fungi, various novel cytotoxic compounds have been isolated and purified. These novel compounds act against different cell lines under IC_{50} values, thus becoming the most valuable for cancer therapy. The details of various novel cytotoxic compounds, sources, chemical structure, biochemical nature, and mechanism of action are shown in **Table 1**. Fusarubin and anhydrofusarubin are cytotoxic compounds and have been acted during the molecular events occurring during the cell cycle. These cytotoxic compounds have been isolated from the endophytic group of fungi Cladosporium sp. They showed anti-cancer activities against cancerous leukemia cells line OCI-AML3 by inhibiting their growth by arresting the cell cycle. Fusarubin showed its anti-proliferative effects for OCI-AML3 cells, particularly by binding with the p53 and p21. While on the other hand, fusarubin induced the apoptosis process in metastatic cells by binding with the Fas ligand, thus activating the caspase-8 [88].

Swainsonine is an alkaloids-based anti-cancer compound isolated from *Metarhizium anisopliae* and exhibited cytotoxicity potential against human hepatoma/leukemia with IC_{50} value (12.4 μM). It was reported that swainsonine showed its action on tumor cells by inducing apoptosis. It also affected the activities of the Golgi bodies by inhibiting the α-mannosidase II, thus blocking the synthesis of glycoproteins [89]. One of the novels lactones-based chemical compounds, myrotheciumone A has been isolated from the *Myrothecium roridum* and showed anti-tumor and cytotoxic activities and exhibited a high potential of cytotoxicity against the HepG-2 cells with IC_{50} value (5.1 μM). Myrotheciumone A showed its action in HepG-2 cells by releasing the cytochrome c, thus inducing apoptosis [90]. Several alkaloids have been isolated from the endophytic fungi and showed anti-tumor and cytotoxic activities. These alkaloids are chaetomugilides that were isolated from the *Chaetomium globosum TY1* and exhibited the high potential of cytotoxicity against the HepG-2 cells with IC_{50} value (53.4 μM) [91].

Xanthoquinodin B9, a novel anti-cancer compound that was isolated from the endophytic fungus, *Chaetomium globosum 7s-1* and exhibited cytotoxic potential against the human cancer cell lines (HL-60, MCF-7) with IC_{50} value (5.8, 20.15 μM) [92]. Incarxanthone B, a novel cytotoxic compound that was isolated from the endophytic fungus *Peniophora incarnata Z4* and showed anti-cancer activities against the tumor cell (HL-60) and human melanoma (A375) with IC_{50} value (4.9-7.5 μM) [93]. Hispidulone B, a new analog of phenalenone that was isolated from the endophytic fungus, *Chaetosphaeronema hispidulum* and exhibited cytotoxic potential against the human hepatoma cell line (Huh7) with IC_{50} value (22.93±1.61 μM) [94].

In several other novels, cytotoxic compounds have been recently discovered and possess anti-cancer. These compounds act on different cell lines thus exhibit potential cytotoxicity against cancerous cells. The details of the recently discovered anti-cancer compounds are shown in **Table 1**. Polyketides are novel anti-cancer compounds that have been isolated from the *Aspergillus sp. XNM-4* exhibited cytotoxic activities against different cancer lines. These compounds are asperpyrone A that showed anticancer activity against the human cancer cell line (SK-OV-3) with IC_{50} value (8.00 μM) while on the other hand, asperpyrone B that showed anticancer activity against the human cancer cell line (PANC-1) with IC_{50} value (7.5 μM) [95]. Lijiquinone, a novel polyketide that was isolated from the endophytic fungus, *Ascomycete sp. F53* exhibited anti-cancer activity against the human myeloma cell lines (RPMI-8226) with IC_{50} value (129 μM) [96].

Cladosporols are the most attractive group of endophytic fungi*, Cladosporium cladosporioides,* because of their high activity against different cancer lines. These cladosporols have different modes of action and act against the colon carcinoma HT-29 cells by stimulating the cell's arrested G-1 phase, thus demonstrating anti-tumor activities. Several other novel compounds have been screened and isolated from endophytic fungi*, Cladosporium cladosporioides EN-399*. These compounds are Cladodosporol C that showed activity against the human cancer cell line (H446) with IC_{50} value (4.00 μM) while on the other hand, Cladodosporol H showed higher cytotoxicity against the cell line (Huh7) by the IC_{50} value (5.00 μM) [97].

Mahmoud and coworkers [98] isolated anticancer compounds from *endophytic Alternaria* sp. *LV52*. These compounds are alternariol-9-methyl ether altertoxin I & II that showed anticancer activities against A549 and PC3 cell lines with IC_{50} values of 2.69 μM and 1.15 μM (see **Table 2**). Meshram et al. (2022) first reported resveratrol from the endophytic fungus, quambalaria cyanescens within their host, *Vitis vinifera*, which showed anticancer activities against them A549 cell lines with 82.7% with maximum reduction in cell count [99]. Ming and coworkers (2022) firstly reported griseophenexanthone A and digriseophene A from the endophytic fungus, *Penicillium* sp. *ct-28* within their host, *Corydlis tomentella* that showed anticancer activities against HepG2 cells with IC_{50} values of 18.12±2.42 μM [100]. Similarly, Kalimuthu et al. (2022) firstly reported 2-methyl-7-phenylindole from the endophytic fungus, *Curvularia geniculatawithin* their host, *Phyllanthus niruri,* that showed anticancer activities against HepG2 cells with IC_{50} by 50% reduction in cell death [101].

Verma et al. (2022) firstly reported novel ethyl acetate (EA) from the endophytic fungus *P. oxalicum* within their host*, A. rohitukathat* showed anticancer activities against breast cancer cells lines (MDA-MB-231) with IC_{50} values of 37.24±1.26 μM [102]. Moubasher and coworkers (2022) first reported asparaginase from the endophytic fungus, *Lasiodiplodia theobromae*, which showed anticancer activities against leukemic M-NFS-60 cell lines with IC_{50} values of 35±0.7 μM [103]. Cao et al. (2022) firstly reported taxol from the endophytic fungus*, Pseudodidymocyrtis lobariellae* within their host, *T. chinensisthat* showed anticancer activities of KL27-FB cells lines with IC_{50} values of 0.361±0.08 μM [104]. Another study reported pestalotiopin b and HQD6 anticancer compounds extracted from an endophytic fungus, *Laguncularia racemosa* within their host, *Rhizophora stylosa* showed anticancer activities against A549 cancer cell lines with IC_{50} values below 20 μM [105, 106]. Similarly. Georgousaki and coworkers isolated sorbicillin, a polykide from the endophytic fungal strain, *CF-090361* within their host, genus *Comoclathris* showed anticancer potential against cancer cell lines HepG2 also against inhibition activities of tyrosine with IC_{50} values of 25±0.16 μM [107].

Current challenges and future directions

Although entophytic fungi are a rich source of novel compounds, their isolation and purification are tedious due to high chances of contamination that ultimately decreaes their value for industrial purposes for the large-scale production of novel drugs. For example, some species of the endophytic fungi are not easy to grow on the culture media as sterile mycelia, which ultimately increases the chances of contamination and several problems in their isolation [108]. While on the other hand, some endophytic fungi that depend on their host and produce the bioactive compounds within their respective host are unable to produce the secondary metabolites outside their respective host. To overcome these challenges, Melanocyte Growth media (MGM) has been successfully designed for the growth of endophytic fungi. Their growth in such media might be helpful for the discovery of anti-cancer compounds with improved purification [109].

Entophytic fungi secreted low concentrations of natural compounds with cytotoxic nature that do not meet the industrial demands. For example, endophytic fungi produced a low concentration of paclitaxel in the range of 0.023% from their host plant, Taxus. The resolution of the natural compounds in their respective host becomes problematic and causes contamination. Supply issues also cause rapid destruction of some host plants of endophytic fungi that produce natural compounds with cytotoxic nature. The rapid extinction of these endangered host plants has become a serious concern [7, 110].

Table 2. Recent advancements of endophytic fungi isolated bioactive compounds against cancer

Endophytic fungi	Host plant	Extracted anticancer compound	Biochemical nature	Year	Study	Key findings	Conclusion	Reference
Endophytic alternaria sp. *LV52*	*Cystoseira tamariscifolia*	Alternariol-9-methyl ether, altertoxin I & II	Alkaloids	2022	*In vitro*	Showed anticancer activities against A549 and PC3 cell lines	IC_{50} values of 2.69 μM and 1.15 μM	[98]
Quambalaria cyanescens	*Vitis vinifera*	Resveratrol	Stilbenoid	2022	*In vitro*	Showed anticancer activities against A549 cell lines	82% reduction in cell death	[99]
Penicillium sp. *ct-28*	*Corydlis tomentella*	Griseophenexanthone A and digriseophene A	xanthone	2022	*In vitro*	Showed anticancer activities against HepG2 cells	IC_{50} values of 18.12±2.42 μM	[100]
Curvularia geniculatawithin	*Phyllanthus niruri*	2-methyl-7-phenyl-indole	---	2022	*In vitro*	Showed anticancer activities against HepG2 cells	50% reduction in cell death	[101]
P. oxalicum	*A. rohitukathat*	Novel ethyl acetate	Volatile organic	2022	*In vitro*	Showed anticancer activities against breast cancer cells lines (MDA-MB-231)	IC_{50} values of 37.24±1.26 μM	[102]
Lasiodiplodia theobromae	Not defined	Asparaginase	Biocatalyst	2022	*In vitro*	Showed anticancer activities against leukemic M-NFS-60 cell lines	IC_{50} values of 35±0.7 μM	[103]
Pseudodidymocyrtis lobariellae	*T. chinensisthat*	Taxol derivatives	Alkaloid	2022	*In vitro*	Showed anticancer activities of KL27-FB cells lines	IC_{50} values of 0.361±0.08 μM	[104]
Laguncularia racemosa	*Rhizophora stylosa*	HQD6 and pestalotiopin b	Terpenoids	2022	*In vitro*	Showed anticancer activities against A549 cancer cell lines	IC_{50} values below 20 μM	[105, 106]
CF-090361	*Genus Comoclathris*	Comoclathrin	Polykide	2022	*In vitro*	Showed anticancer potential against cancer cell lines HepG2 also against inhibition activities of tyrosine	IC_{50} values of 0.16 μM	[107]

Large numbers of derivatives compounds have been obtained from endophytes, but their mechanism of action and cytotoxic nature need to explore in order to use them for cancer therapies. Some natural compounds isolated from endophytic fungi are under clinical trials against different cell lines and will be used as cancer therapy after approval. A significant increase in the biodiversity of endophytic fungi indicates that anticancer activities of screened compounds from their respective host plant as cytotoxic nature can be used as cancer therapy [111, 112].

Recent developments in molecular biology have significantly improved the growth of the uncultivable endophytic fungi. Chemical structures of bioactive compounds produced by endophytic fungi might be utilized to design new drugs. This paved the screening of novel compounds to aim for action against infectious diseases. Some genes have been isolated from fungal endophytes, but their structural analysis lacks information about their roles in genetic engineering. Some recent molecular approaches such as multilocus sequence typing and next-generation sequencing have increased the efficient production of metabolites from fungal endophytes. In comparison, fermentation technology can be used for the large-scale production of secondary metabolites as therapeutic agents-metagenomics as an emerging field that provides the structural analysis of genes. Molecular biology studies of the endophytic fungi are also important for improving dug research due to the isolation of several genes involved in the biosynthetic pathways [113, 114].

Endophytic fungi can be utilized for the preparation of medicines to explore their roles in pharmaceutical industries. As entophytic fungi are a rich source of secondary metabolites, these can be used to develop biomarkers and thus aid in controlling the high rate of infectious diseases. This approach will help to discover the new fungal entophytes with enhanced bioactivities. Future studies look for the development of nanotechnology to improve the production of metabolites within the host. The transfer of genes is also helpful for the detection of new plant varieties producing cytotoxic compounds [113, 115]. In the future, genomic and metabolomics tools will be employed to better understand the mechanism of colonization of entophytic fungi with their host plants [113].

Conclusions

An investigation of endophytic growth and anticancer movement was presented in this paper. Researchers interested in bioactive mixtures produced by endophytic microbes will find a solid foundation in the present review. Endophytic fungi are significant producers of bioactive compounds and have gained special attention as therapeutic agents for the treatment of cancers. These compounds are paclitaxel, podophyllotoxin, camptothecin, vinblastine, hypericin, diosgenin, polyketides, cladosporols, lijiquinone, chaetomugilides, cladodosporol H, asperpyrone A, hispidulone B, myrotheciumone, fusarubin, anhydrofusarubin, swainsonine, cladodosporol C, incarxanthone B, and asperpyrone B. They play a significant role in developing novel chemical compounds, thus important targets for drug discovery. Due to a considerable increase in fungal biodiversity, a large number of bioactive compounds have been screened for clinical trials against different cell lines. Future research will focus on the endophytic fungal strain improvement for the discovery/development of novel anticancer compounds that can be utilized as ideal candidates for cancer therapy. Some of the potential bioactive compounds have been isolated from endophytic fungi, but their molecular studies and mechanism of action in cancer development are needed to explore for future studies.

Acknowledgements

The authors extend their appreciation to the Deanship of Scientific Research at King Khalid University for funding this work through Large Groups under grant number (RGP.2/64/43). The project was supported by grant from The Oman Research Council (TRC) through the funded project (BFP/RGP/HSS/19/198).

Disclosure of conflict of interest

None.

Address correspondence to: Abu Hazafa, Department of Biochemistry, Faculty of Sciences, University of Agriculture, Faisalabad 38040, Pakistan. Tel: 0923056517149; E-mail: abuhuzaifavirk@gmail.com; Abu.9093270@talmeez.pk; Drs. Ajmal Khan

and Ahmed Al-Harrasi, Natural and Medical Sciences Research Center, University of Nizwa, PO Box 33, 616 Birkat Al Mauz, Nizwa, Oman. E-mail: ajmalkhan@unizwa.edu.om (AK); aharrasi@unizwa.edu.om (AAH)

References

[1] Globocan. The global cancer observatory-all cancers. Int Agent Res Cancer WHO 2020; 419: 199-200.

[2] Subramaniam S, Selvaduray KR and Radhakrishnan AK. Bioactive compounds: natural defense against cancer? Biomolecules 2019; 9: 758.

[3] Bhadresha KP, Jain NK and Rawal RM. Assessing the protective effect of Moringa oleifera extract against bone metastasis: an in vitro simulated digestion approach. Nutr Cancer 2022; 74: 1023-1036.

[4] Garcia-Oliveira P, Otero P, Pereira AG, Chamorro F, Carpena M, Echave J, Fraga-Corral M, Simal-Gandara J and Prieto MA. Status and challenges of plant-anticancer compounds in cancer treatment. Pharmaceuticals (Basel) 2021; 14: 157.

[5] Abdel-Razek AS, El-Naggar ME, Allam A, Morsy OM and Othman SI. Microbial natural products in drug discovery. Processes 2020; 8: 470.

[6] Hridoy M, Gorapi MZH, Noor S, Chowdhury NS, Rahman MM, Muscari I, Masia F, Adorisio S, Delfino DV and Mazid MA. Putative anticancer compounds from plant-derived endophytic fungi: a review. Molecules 2022; 27: 296.

[7] Adeleke BS and Babalola OO. Pharmacological potential of fungal endophytes associated with medicinal plants: a review. J Fungi (Basel) 2021; 7: 147.

[8] Amirzakariya BZ and Shakeri A. Bioactive terpenoids derived from plant endophytic fungi: an updated review (2011-2020). Phytochemistry 2022; 197: 113130.

[9] Sonaimuthu V and Johnpaul M. Taxol (anticancer drug) producing endophytic fungi: an overview. Int J Pharm Bio Sci 2010; 1.

[10] Kasaei A, Mobini-Dehkordi M, Mahjoubi F and Saffar B. Isolation of taxol-producing endophytic fungi from Iranian yew through novel molecular approach and their effects on human breast cancer cell line. Curr Microbiol 2017; 74: 702-709.

[11] Xianzhi Y, Shiping G, Lingqi Z and Hua S. Select of producing podophyllotoxin endophytic fungi from podophyllin plant. Nat Prod Res Develop 2003; 15: 419-422.

[12] Bhanot A, Sharma R and Noolvi MN. Natural sources as potential anti-cancer agents: a review. Int J Phytomedicine 2011; 3: 9-26.

[13] Lee C and Shim SH. Endophytic fungi inhabiting medicinal plants and their bioactive secondary metabolites. Nat Prod Sci 2020; 26: 10-27.

[14] Cao XD, Li JR, Zhou LG, Xu LJ, Li J and Zhao JL. Determination of diosgenin content of the endophytic fungi from Paris polyphylla var. yunnanensis by using an optimum ELISA. Nat Prod Res Develop 2007; 19.

[15] Ding CH, Du XW, Xu Y, Xu XM, Mou JC, Yu D, Wu JK, Meng FJ, Liu Y, Wang WL and Wang LJ. Screening for differentially expressed genes in endophytic fungus strain 39 during co-culture with herbal extract of its host Dioscorea nipponica Makino. Curr Microbiol 2014; 69: 517-524.

[16] Gouda S, Das G, Sen SK, Shin HS and Patra JK. Endophytes: a treasure house of bioactive compounds of medicinal importance. Front Microbiol 2016; 7: 1538.

[17] Rana KL, Kour D, Sheikh I, Yadav N, Yadav AN, Kumar V, Singh BP, Dhaliwal HS and Saxena AK. Biodiversity of endophytic fungi from diverse niches and their biotechnological applications. Adv Endophytic Fun Res 2019; 105-144.

[18] Nisa H, Kamili AN, Nawchoo IA, Shafi S, Shameem N and Bandh SA. Fungal endophytes as prolific source of phytochemicals and other bioactive natural products: a review. Microb Pathog 2015; 82: 50-59.

[19] Rana KL, Kour D, Sheikh I, Dhiman A, Yadav N, Yadav AN, Rastegari AA, Singh K and Saxena AK. Endophytic fungi: biodiversity, ecological significance, and potential industrial applications. In: editors. Recent advancement in white biotechnology through fungi. Springer; 2019. pp. 1-62.

[20] Toofanee SB and Dulymamode R. Fungal endophytes associated with Cordemoya integrifolia. Fungal Divers 2002; 11: 169-175.

[21] Puri SC, Verma V, Amna T, Qazi GN and Spiteller M. An endophytic fungus from Nothapodytes foetida that produces Camptothecin. J Nat Prod 2005; 68: 1717-1719.

[22] Rana KL, Kour D, Kaur T, Devi R, Negi C, Yadav AN, Yadav N, Singh K and Saxena AK. Endophytic fungi from medicinal plants: biodiversity and biotechnological applications. Microbial Endophytes: Elsevier; 2020. pp. 273-305.

[23] Chen G, Zhu Y, Wang HZ, Wang SJ and Zhang RQ. The metabolites of a mangrove endophytic fungus, Penicillium thomi. J Asian Nat Prod Res 2007; 9: 159-164.

[24] Huang WY, Cai YZ, Xing J, Corke H and Sun M. A potential antioxidant resource: endophytic fungi from medicinal plants. Econ Bot 2007; 61: 14-30.

[25] Gangadevi V and Muthumary J. Taxol, an anticancer drug produced by an endophytic fungus Bartalinia robillardoides Tassi, isolated from a medicinal plant, Aegle marmelos Correa ex Roxb. World J Microbiol Biotechnol 2008; 24: 717-724.
[26] Liu KH, Ding XW, Deng BW and Chen WQ. Isolation and characterization of endophytic taxol-producing fungi from Taxus chinensis. J Ind Microbiol Biotechnol 2009; 36: 1171-1177.
[27] Ahmad N, Hamayun M, Khan SA, Khan AL, Lee IJ and Shin DH. Gibberellin-producing endophytic fungi isolated from Monochoria vaginalis. J Microbiol Biotechnol 2010; 20: 1744-1749.
[28] Katoch M, Phull S, Vaid S and Singh S. Diversity, phylogeny, anticancer and antimicrobial potential of fungal endophytes associated with Monarda citriodora L. BMC Microbiol 2017; 17: 44.
[29] Duan XX, Xu FF, Qin D, Gao TC, Shen WY, Zuo SH, Yu BH, Xu JR, Peng YJ and Dong JY. Diversity and bioactivities of fungal endophytes from Distylium chinense, a rare waterlogging tolerant plant endemic to the Three Gorges Reservoir. BMC Microbiol 2019; 19: 278.
[30] Tiwari P and Bae H. Endophytic fungi: key insights, emerging prospects, and challenges in natural product drug discovery. Microorganisms 2022; 10: 360.
[31] Dos Santos I, Mohamed T, Borges L, Nahas HA, Abdel-Azeem M, Carvalho C, Bezerra J, Gupta V, Xavier-Santos S and Mossa M. The global tendency in the research of biological activity in endophytic fungi: a scientometric analysis. Curr Res Environ Appl Mycol 2022; 12: 1-14.
[32] Pandi M, SenthilKumaran R, Rajapriya P, Yogeswari S and Muthumary J. Taxol, a potential drug for the treatment of cancer. Biores Bull 2013; 2: 1-9.
[33] Zhao J, Shan T, Mou Y and Zhou L. Plant-derived bioactive compounds produced by endophytic fungi. Mini Rev Med Chem 2011; 11: 159-168.
[34] Kumaran RS, Jung H and Kim HJ. In vitro screening of taxol, an anticancer drug produced by the fungus, Colletotrichum capsici. Eng Life Sci 2011; 11: 264-271.
[35] Chakravarthi BV, Sujay R, Kuriakose GC, Karande AA and Jayabaskaran C. Inhibition of cancer cell proliferation and apoptosis-inducing activity of fungal taxol and its precursor baccatin III purified from endophytic Fusarium solani. Cancer Cell Int 2013; 13: 105.
[36] Weaver BA. How Taxol/paclitaxel kills cancer cells. Mol Biol Cell 2014; 25: 2677-2681.
[37] Pasquier E, Carré M, Pourroy B, Camoin L, Rebaï O, Briand C and Braguer D. Antiangiogenic activity of paclitaxel is associated with its cytostatic effect, mediated by the initiation but not completion of a mitochondrial apoptotic signaling pathway. Mol Cancer Ther 2004; 3: 1301-1310.
[38] Kampan NC, Madondo MT, McNally OM, Quinn M and Plebanski M. Paclitaxel and its evolving role in the management of ovarian cancer. Biomed Res Int 2015; 2015: 413076.
[39] Uzma F, Mohan CD, Hashem A, Konappa NM, Rangappa S, Kamath PV, Singh BP, Mudili V, Gupta VK, Siddaiah CN, Chowdappa S, Alqarawi AA and Abd Allah EF. Endophytic fungi-alternative sources of cytotoxic compounds: a review. Front Pharmacol 2018; 9: 309.
[40] Kumar S, Aharwal RP, Jain R and Sandhu SS. Bioactive molecules of endophytic fungi and their potential in anticancer drug development. Curr Pharmacol Rep 2021; 7: 27-41.
[41] Li FZ, Jiang T, Li QY and Ling X. Camptothecin (CPT) and its derivatives are known to target topoisomerase I (Top1) as their mechanism of action: did we miss something in CPT analogue molecular targets for treating human disease such as cancer? Am J Cancer Res 2017; 7: 2350-2394.
[42] El-Sayed ASA, Zayed RA, El-Baz AF and Ismaeil WM. Bioprocesses optimization and anticancer activity of camptothecin from Aspergillus flavus, an endophyte of in vitro cultured Astragalus fruticosus. Mol Biol Rep 2022; [Epub ahead of print].
[43] Aswini A and Soundhari C. Production of camptothecin from endophytic fungi and characterization by high-performance liquid chromatography and anticancer activity against colon cancer cell line. Asian J Pharm Clin Res 2018; 11: 166-170.
[44] Beretta GL, Gatti L, Perego P and Zaffaroni N. Camptothecin resistance in cancer: insights into the molecular mechanisms of a DNA-damaging drug. Curr Med Chem 2013; 20: 1541-1565.
[45] Pommier Y. Topoisomerase I inhibitors: camptothecins and beyond. Nat Rev Cancer 2006; 6: 789-802.
[46] Lingqi Z, Bo G, Haiyan L, Songrong Z, Hua S, Su G and Rongcheng W. Preliminary study on the isolation of endophytic fungus of Catharanthus roseus and its fermentation to produce products of therapeutic value. Chin Tradit Herb Drugs 2000; 31: 805-807.
[47] Puri SK, Habbu PV, Kulkarni PV and Kulkarni VH. Nitrogen containing secondary metabolites from endophytes of medicinal plants and their biological/pharmacological activities-a review. Syst Rev Pharm 2018; 9: 22-30.
[48] El-Sayed ER. Discovery of the anticancer drug vinblastine from the endophytic Alternaria alternata and yield improvement by gamma irra-

diation mutagenesis. J Appl Microbiol 2021; 131: 2886-2898.
[49] Martino E, Casamassima G, Castiglione S, Cellupica E, Pantalone S, Papagni F, Rui M, Siciliano AM and Collina S. Vinca alkaloids and analogues as anti-cancer agents: looking back, peering ahead. Bioorg Med Chem Lett 2018; 28: 2816-2826.
[50] Kapoor S, Srivastava S and Panda D. Indibulin dampens microtubule dynamics and produces synergistic antiproliferative effect with vinblastine in MCF-7 cells: implications in cancer chemotherapy. Sci Rep 2018; 8: 12363.
[51] Ashraf SM, Sebastian J and Rathinasamy K. Zerumbone, a cyclic sesquiterpene, exerts antimitotic activity in HeLa cells through tubulin binding and exhibits synergistic activity with vinblastine and paclitaxel. Cell Prolif 2019; 52: e12558.
[52] Amiri B, Ahmadvand H, Farhadi A, Najmafshar A, Chiani M and Norouzian D. Delivery of vinblastine-containing niosomes results in potent in vitro/in vivo cytotoxicity on tumor cells. Drug Dev Ind Pharm 2018; 44: 1371-1376.
[53] Zhou XW, Xu ZR, Li AJ, Zhang ZQ and Xu SC. Double-sides sticking mechanism of vinblastine interacting with α, β-tubulin to get activity against cancer cells. J Biomol Struct Dyn 2019; 37: 4080-4091.
[54] Anitha SS. Pharmacological activity of vinca alkaloids. J Pharmacogn Phytochem 2016; 4: 27-34.
[55] Kusari S, Hertweck C and Spiteller M. Chemical ecology of endophytic fungi: origins of secondary metabolites. Chem Biol 2012; 19: 792-798.
[56] Kusari S, Lamshöft M, Zühlke S and Spiteller M. An endophytic fungus from Hypericum perforatum that produces hypericin. J Nat Prod 2008; 71: 159-162.
[57] Garnica S, Weiss M and Oberwinkler F. Morphological and molecular phylogenetic studies in South American Cortinarius species. Mycol Res 2003; 107: 1143-1156.
[58] Agostinis P, Vantieghem A, Merlevede W and de Witte PA. Hypericin in cancer treatment: more light on the way. Int J Biochem Cell Biol 2002; 34: 221-241.
[59] Dong XX, Zeng YW, Zhang ZQ, Fu J, You LT, He YY, Hao Y, Gu ZL, Yu ZF, Qu CH, Yin XB, Ni J and Cruz LJ. Hypericin-mediated photodynamic therapy for the treatment of cancer: a review. J Pharm Pharmacol 2021; 73: 425-436.
[60] Ferenc P, Solár P, Kleban J, Mikeš J and Fedoročko P. Down-regulation of Bcl-2 and Akt induced by combination of photoactivated hypericin and genistein in human breast cancer cells. J Photochem Photobiol B 2010; 98: 25-34.
[61] Vandenbogaerde AL, Cuveele JF, Proot P, Himpens BE, Merlevede WJ and de Witte PA. Differential cytotoxic effects induced after photosensitization by hypericin. J Photochem Photobiol B 1997; 38: 136-142.
[62] Paba V, Quarto M, Varriale L, Crescenzi E and Palumbo G. Photo-activation of hypericin with low doses of light promotes apparent photoresistance in human histiocytic lymphoma U937 cells. J Photochem Photobiol B 2001; 60: 87-96.
[63] Huygens A, Kamuhabwa AR, Van Laethem A, Roskams T, Van Cleynenbreugel B, Van Poppel H, Agostinis P and De Witte PA. Enhancing the photodynamic effect of hypericin in tumour spheroids by fractionated light delivery in combination with hyperoxygenation. Int J Oncol 2005; 26: 1691-1697.
[64] Han C, Zhang C, Ma T, Zhang C, Luo JG, Xu X, Zhao HJ, Chen Y and Kong LY. Hypericin-functionalized graphene oxide for enhanced mitochondria-targeting and synergistic anticancer effect. Acta Biomater 2018; 77: 268-281.
[65] Gyurászová K, Mikeš J, Halaburkova A, Jendželovský R and Fedoročko P. YM155, a small molecule inhibitor of survivin expression, sensitizes cancer cells to hypericin-mediated photodynamic therapy. Photochem Photobiol Sci 2016; 15: 812-821.
[66] Macejova M, Sačková V, Hradická P, Jendželovský R, Demečková V and Fedoročko P. Combination of photoactive hypericin and Manumycin A exerts multiple anticancer effects on oxaliplatin-resistant colorectal cells. Toxicol In Vitro 2020; 66: 104860.
[67] Sardoiwala MN, Kushwaha AC, Dev A, Shrimali N, Guchhait P, Karmakar S and Roy Choudhury S. Hypericin-loaded transferrin nanoparticles induce PP2A-regulated BMI1 degradation in colorectal cancer-specific chemo-photodynamic therapy. ACS Biomater Sci Eng 2020; 6: 3139-3153.
[68] Kim H, Kim SW, Seok KH, Hwang CW, Ahn JC, Jin JO and Kang HW. Hypericin-assisted photodynamic therapy against anaplastic thyroid cancer. Photodiagnosis Photodyn Ther 2018; 24: 15-21.
[69] Arani HZ, Olya M, Mirahmadi AS, Saleki H, Atashi HA, Marzouni HZ, Hoseinian M, Javidi MA and Zabolian A. Hypericin induces apoptosis in K562 cells via downregulation of Myc and Mdm2. J Cancer Res Ther 2021; 17: 242-247.
[70] Biswas D, Nazir R, Biswas P, Kumar V, Nandy S, Mukherjee A, Dey A and Pandey DK. Endophytic sources of diosgenin, a natural steroid with multiple therapeutic values. S Afr J Bot 2020; 134: 119-125.

[71] Chen J, Zhang HF, Xiong CM and Ruan JI. Inhibitory effect of diosgenin on experimentally induced benign prostatic hyperplasia in rats. J Huazhong Uni Sci Technolog Med Sci 2016; 36: 806-810.
[72] Lai Z, Wang H, Tang X, Zhang L, Wang T and Cheng J. Study on the mechanism of diosgenin targeting STAT3 to inhibit colon cancer proliferation and migration. Dis Marker 2022; 2022: 7494887.
[73] Srinivasan S, Koduru S, Kumar R, Venguswamy G, Kyprianou N and Damodaran C. Diosgenin targets Akt-mediated prosurvival signaling in human breast cancer cells. Int J Cancer 2009; 125: 961-967.
[74] Mao ZJ, Tang QJ, Zhang CA, Qin ZF, Pang B, Wei PK, Liu B and Chou YN. Anti-proliferation and anti-invasion effects of diosgenin on gastric cancer BGC-823 cells with HIF-1α shRNAs. Int J Mol Sci 2012; 13: 6521-6533.
[75] Liu YL, Zhou ZJ, Yan JZ, Wu XF and Xu GY. Diosgenin exerts antitumor activity via downregulation of Skp2 in breast cancer cells. Biomed Res Int 2020; 2020: 8072639.
[76] Bhardwaj N, Tripathi N, Goel B and Jain SK. Anticancer activity of diosgenin and its semi-synthetic derivatives: role in autophagy mediated cell death and induction of apoptosis. Mini Rev Med Chem 2021; 21: 1646-1665.
[77] Chiang CT, Way TD, Tsai SJ and Lin JK. Diosgenin, a naturally occurring steroid, suppresses fatty acid synthase expression in HER2-overexpressing breast cancer cells through modulating Akt, mTOR and JNK phosphorylation. FEBS Lett 2007; 581: 5735-5742.
[78] Sethi G, Shanmugam MK, Warrier S, Merarchi M, Arfuso F, Kumar AP and Bishayee A. Pro-apoptotic and anti-cancer properties of diosgenin: a comprehensive and critical review. Nutrients 2018; 10: 645.
[79] Amina SJ, Iqbal M, Faisal A, Shoaib Z, Niazi MBK, Ahmad NM, Khalid N and Janjua HA. Synthesis of diosgenin conjugated gold nanoparticles using algal extract of Dictyosphaerium sp. and in-vitro application of their antiproliferative activities. Mater Today Commun 2021; 27: 102360.
[80] Shishodia S and Aggarwal BB. Diosgenin inhibits osteoclastogenesis, invasion, and proliferation through the downregulation of Akt, IκB kinase activation and NF-κB-regulated gene expression. Oncogene 2006; 25: 1463-1473.
[81] Li F, Fernandez PP, Rajendran P, Hui KM and Sethi G. Diosgenin, a steroidal saponin, inhibits STAT3 signaling pathway leading to suppression of proliferation and chemosensitization of human hepatocellular carcinoma cells. Cancer Lett 2010; 292: 197-207.
[82] Wu JL, Leung EL, Zhou H, Liu L and Li N. Metabolite analysis of toosendanin by an ultra-high performance liquid chromatography-quadrupole-time of flight mass spectrometry technique. Molecules 2013; 18: 12144-12153.
[83] Zhang S, Cao L, Wang ZR, Li Z and Ma J. Anticancer effect of toosendanin and its underlying mechanisms. J Asian Nat Prod Res 2019; 21: 270-283.
[84] Cao L, Qu DD, Wang H, Zhang S, Jia CM, Shi ZX, Wang ZR, Zhang J and Ma J. Toosendanin exerts an anti-cancer effect in glioblastoma by inducing estrogen receptor β-and p53-mediated apoptosis. Int J Mol Sci 2016; 17: 1928.
[85] Zhou Q, Wu XB, Wen CY, Wang HH, Wang HS, Liu HL and Peng JS. Toosendanin induces caspase-dependent apoptosis through the p38 MAPK pathway in human gastric cancer cells. Biochem Biophys Res Commun 2018; 505: 261-266.
[86] Zhang JN, Yang F, Mei XY, Yang R, Lu B, Wang ZT and Ji LL. Toosendanin and isotoosendanin suppress triple-negative breast cancer growth via inducing necrosis, apoptosis and autophagy. Chem Biol Interact 2022; 351: 109739.
[87] Zhang CC, Gao HJ, Liu ZQ, Lai JC, Zhan ZX, Chen Y and Huang HY. Mechanisms involved in the anti-tumor effects of Toosendanin in glioma cells. Cancer Cell Int 2021; 21: 492.
[88] de Wit PJ. Cladosporium fulvum effectors: weapons in the arms race with tomato. Annu Rev Phytopathol 2016; 54: 1-23.
[89] Ren ZH, Song RJ, Wang S, Quan HY, Yang L, Sun L, Zhao BY and Lu H. The biosynthesis pathway of swainsonine, a new anticancer drug from three endophytic fungi. J Microbiol Biotechnol 2017; 27: 1897-1906.
[90] Lin T, Wang GH, Shan WJ, Zeng DQ, Ding R, Jiang X, Zhu D, Liu XX, Yang SY and Chen HF. Myrotheciumones: bicyclic cytotoxic lactones isolated from an endophytic fungus of Ajuga decumbens. Bioorg Med Chem Lett 2014; 24: 2504-2507.
[91] Li X, Tian Y, Yang SX, Zhang YM and Qin JC. Cytotoxic azaphilone alkaloids from Chaetomium globosum TY1. Bioorg Med Chem Lett 2013; 23: 2945-2947.
[92] Tantapakul C, Promgool T, Kanokmedhakul K, Soytong K, Song J, Hadsadee S, Jungsuttiwong S and Kanokmedhakul S. Bioactive xanthoquinodins and epipolythiodioxopiperazines from Chaetomium globosum 7s-1, an endophytic fungus isolated from Rhapis cochinchinensis (Lour.) Mart. Nat Prod Res 2020; 34: 494-502.
[93] Liu HX, Tan HB, Chen YC, Li SN, Li HH and Zhang WM. Cytotoxic triquinane-type sesquiterpenoids from the endophytic fungus Cerrena sp. A593. Nat Prod Res 2020; 34: 2430-2436.

[94] Zhang XY, Tan XM, Li YY, Wang YD, Yu M, Qing JC, Sun BD, Niu SB and Ding G. Hispidulones A and B, two new phenalenone analogs from desert plant endophytic fungus Chaetosphaeronema hispidulum. J Antibiot (Tokyo) 2020; 73: 56-59.
[95] Xu K, Guo CL, Shi DY, Meng J, Tian HY and Guo SJ. Discovery of natural dimeric naphthopyrones as potential cytotoxic agents through ROS-mediated apoptotic pathway. Mar Drugs 2019; 17: 207.
[96] Cain JW, Miller KI, Kalaitzis JA, Chau R and Neilan BA. Genome mining of a fungal endophyte of Taxus yunnanensis (Chinese yew) leads to the discovery of a novel azaphilone polyketide, lijiquinone. Microb Biotechnol 2020; 13: 1415-1427.
[97] Li HL, Li XM, Mandi A, Antus S, Li X, Zhang P, Liu Y, Kurtan T and Wang BG. Characterization of cladosporols from the marine algal-derived endophytic fungus Cladosporium cladosporioides EN-399 and configurational revision of the previously reported cladosporol derivatives. J Org Chem 2017; 82: 9946-9954.
[98] Mahmoud MM, Abdel-Razek AS, Soliman HSM, Ponomareva LV, Thorson JS, Shaaban KA and Shaaban M. Diverse polyketides from the marine endophytic alternaria sp. LV52: structure determination and cytotoxic activities. Biotechnol Rep (Amst) 2021; 33: e00628.
[99] Meshram V, Kapoor N, Dwibedi V, Srivastava A and Saxena S. Extracellular resveratrol producing endophytic fungus, quambalaria cyanescens. S Afr J Bot 2022; 146: 409-416.
[100] Ming QL, Li YN, Jiang XX, Huang XN, He YM, Qin LY, Liu YX, Tang Y and Gao N. Xanthones and benzophenones isolated from the endophytic fungus penicillium sp. ct-28 of corydlis tomentella and their cytotoxic activity. Fitoterapia 2022; 157: 105127.
[101] Kalimuthu AK, Parasuraman P, Sivakumar P, Murugesan S, Arunachalam S, Pandian SRK, Ravishankar V, Ammunje DN, Sampath M, Panneerselvam T and Kunjiappan S. In silico, in vitro screening of antioxidant and anticancer potentials of bioactive secondary metabolites from an endophytic fungus (Curvularia sp.) from Phyllanthus niruri L. Environ Sci Pollut Res Int 2022.
[102] Verma A, Gupta P, Rai N, Tiwari RK, Kumar A, Salvi P, Kamble SC, Singh SK and Gautam V. Assessment of biological activities of fungal endophytes derived bioactive compounds isolated from Amoora rohituka. J Fungi (Basel) 2022; 8: 285.
[103] Moubasher HA, Balbool BA, Helmy YA, Alsuhaibani AM, Atta AA, Sheir DH and Abdel-Azeem AM. Insights into asparaginase from endophytic fungus lasiodiplodia theobromae: purification, characterization and antileukemic activity. Int J Environ Res Public Health 2022; 19: 680.
[104] Cao XY, Xu LX, Wang JY, Dong MM, Xu CY, Kai GY, Wan W and Jiang JH. Endophytic fungus Pseudodidymocyrtis lobariellae KL27 promotes taxol biosynthesis and accumulation in taxus chinensis. BMC Plant Biol 2022; 22: 12.
[105] Zhou J, Feng Z, Zhang WF and Xu J. Evaluation of the antimicrobial and cytotoxic potential of endophytic fungi extracts from mangrove plants Rhizophora stylosa and R. mucronata. Sci Rep 2022; 12: 2733.
[106] Zhou J, Zheng DY and Xu J. Two new polyketides from endophytic fungus Pestalotiopsis sp. HQD-6 isolated from the Chinese mangrove plant Rhizophora mucronata. J Asian Nat Prod Res 2022; 24: 52-58.
[107] Georgousaki K, González-Menéndez V, Tormo JR, Tsafantakis N, Mackenzie TA, Martín J, Gumeni S, Trougakos IP, Reyes F, Fokialakis N and Genilloud O. Comoclathrin, a novel potent skin-whitening agent produced by endophytic Comoclathris strains associated with Andalusia desert plants. Sci Rep 2022; 12: 1649.
[108] Thirumalanadhuni V, Yerraguravagari LL and Palempalli UM. Endophytic microflora: the fountainhead of anticancer metabolites-a systematic review. Rec Develop Appl Microbiol Biochem 2021; 13-20.
[109] Thirumalanadhuni V, Yerraguravagari LL, Mathakala V and Palempalli UM. Anticancer and free radical scavenging potential of the marine algicolous endophytic fungus cladosporium uredinicola. Asian J Pharm Clin Res 2019; 12: 520-524.
[110] Kharwar RN, Mishra A, Gond SK, Stierle A and Stierle D. Anticancer compounds derived from fungal endophytes: their importance and future challenges. Nat Prod Rep 2011; 28: 1208-1228.
[111] Omeje EO, Ahomafor JE, Onyekaba TU, Monioro PO, Nneka I, Onyeloni S, Chime C and Eboka JC. Endophytic fungi as alternative and reliable sources for potent anticancer agents. Nat Prod Cancer Drug Discov. IntechOpen; 2017. pp. 52-60.
[112] Wen J, Okyere SK, Wang S, Wang J, Xie L, Ran Y and Hu Y. Endophytic Fungi: an effective alternative source of plant-derived bioactive compounds for pharmacological studies. J Fungi (Basel) 2022; 8: 205.
[113] Fadiji AE and Babalola OO. Elucidating mechanisms of endophytes used in plant protection and other bioactivities with multifunctional prospects. Front Bioeng Biotechnol 2020; 8: 467.
[114] Giddings LA and Newman DJ. Extremophilic fungi from marine environments: underex-

plored sources of antitumor, anti-infective and other biologically active agents. Mar Drugs 2022; 20: 62.
[115] Yadav AN, Kour D, Kaur T, Devi R and Yadav A. Endophytic fungal communities and their biotechnological implications for agro-environmental sustainability. Folia Microbiologica (Praha) 2022; 67: 203-232.
[116] Zhao J, Zhou L, Wang J, Shan T, Zhong L, Liu X and Gao X. Endophytic fungi for producing bioactive compounds originally from their host plants. Curr Res Technol Educ Trop Appl Microbiol Microbial Biotechnol 2010; 1: 567-576.
[117] Kusari S, Zühlke S and Spiteller M. An endophytic fungus from Camptotheca acuminata that produces camptothecin and analogues. J Nat Prod 2009; 72: 2-7.
[118] Puri SC, Nazir A, Chawla R, Arora R, Riyaz-ul-Hasan S, Amna T, Ahmed B, Verma V, Singh S, Sagar R, Sharma A, Kumar R, Sharma RK and Qazi GN. The endophytic fungus Trametes hirsuta as a novel alternative source of podophyllotoxin and related aryl tetralin lignans. J Biotechnol 2006; 122: 494-510.
[119] Kiran S, Hai ZJ, Ding ZL, Wang L, Liu YL, Zhang HF and Liang GL. Alkaline phosphatase-triggered assembly of etoposide enhances its anticancer effect. Chem Comm (Camb) 2018; 54: 1853-1856.
[120] Singh A, Singh DK, Kharwar RN, White JF and Gond SK. Fungal endophytes as efficient sources of plant-derived bioactive compounds and their prospective applications in natural product drug discovery: insights, avenues, and challenges. Microorganisms 2021; 9: 197.
[121] Verekar SA, Mishra PD, Sreekumar ES, Deshmukh SK, Fiebig HH, Kelter G and Maier A. Anticancer activity of new depsipeptide compound isolated from an endophytic fungus. J Antibiot (Tokyo) 2014; 67: 697-701.
[122] Ghanbari-Movahed M, Kaceli T, Mondal A, Farzaei MH and Bishayee A. Recent advances in improved anticancer efficacies of camptothecin nano-formulations: a systematic review. Biomedicines 2021; 9: 480.
[123] Wang HH, Wen CY, Chen SY, Wang F, He L, Li WQ, Zhou Q, Yu WK, Huang LL, Chen JX, Liu RX, Li WD, Yang XL and Liu HL. Toosendanin-induced apoptosis in colorectal cancer cells is associated with the κ-opioid receptor/β-catenin signaling axis. Biochem Pharmacol 2020; 177: 114014.