NOVAL CYTOTOXIC COMPOUNDS FROM FUNGAL ENDOPHYTES

Abstract

Fungi and bacteria that live in the internal tissues of the plant are referred to as endophytes. They have no harmful effects on their host plant. Endophytic fungi synthesise metabolites that are structurally and functionally similar to those of their host plants. They are able to create a wide range of biomolecules from different classes with countless applications. Fungal endophytes such as *Penicillium, Fusarium, Aspergillus, Sclerotium, Myxormia, Alternaria, Colletotrichum, Cladosporium, Diaporthe,* and other endophytic species are well recognized to produce bioactive chemicals that have a crucial role in the management of disease. Bioactive compounds derived from endophytic fungi were classified as alkaloids, steroids, flavonoids, phenolic acids, benzopyranones, quinines, tannins, xanthones, terpenoids and they possess antimicrobial, antioxidant, cytotoxic, immunosuppressive, and anti-inflammatory activities.

The deadliest illness, cancer kills thousands of individuals annually. In this scenario, the scientific community is searching for new anticancer drugs to combat cancer. Studies on the discovery of anti-cancer drugs from endophytes began in the early 90s and gained prominence in the twenty-first century. More than 200 novel cytotoxic chemicals have been discovered in the last thirty years from endophytic fungi of both terrestrial and marine plants. The majority of these cytotoxic substances fall into the following categories: polyketides, terpenoids, sterols, macrolides, lactones, azaphilones, alkaloids, preussomerins, p-terphenyls, hybrid structures, and other substances. The most important anti-cancer

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drugs are from endophytes, including taxol, podophyllotaxin, camptothecin, vinca alkaloids, cytochalasin 1-3, malformin, graphislactone A, etc. Discovery of taxol and its analogue from endophytes marked a significant advance in cancer drugs research. Studies have reported the production of taxol by *Pestalotiopsis* v*ersicolor*, and an apoptotic experiment using the isolated fungal taxol demonstrated high cytotoxic action against tested human cancer cells in *in vitro* culture, demonstrating that an increase in taxol concentration causes more cell death.

In this review we have referred a total of sixty-one research papers during the year 2010 to 2022 and tried to highlight the significance of fungal endophytes and the bioactive substances produced by them in cancer treatment.

Keywords: fungal endophytes, secondary metabolites, anti-cancer compounds.

1. INTRODUCTION

1. Cancer

Uncontrolled and unchecked division of cells leads to cancer. Cancer can occur almost anywhere in the body, and these cells may form tumors. Based on the organ or tissue where the tumors form, more than 100 types of cancer have been reported (NIH). According to the American Cancer Society, there will be 1.9 million new cancer cases in the country in 2022. It is anticipated that by 2050, the annual death toll due to cancer will rise to 17.5 million [1]. The primary cause of the increase in cancer incidence can be attributed to the modern lifestyle, which includes drug use, smoking, exposure to toxins, environmental pollution, drunkenness, viral infections, etc. Although the use of genomic, proteomic, and bioinformatics approaches will assist to grasp the intricacy of cancer, the scientific community has not yet found a complete cure for the disease [2].

For the treatment of cancer, a number of medications have been suggested, and many of these contain plant-based ingredients. Plants are a rich source of natural compounds that have the potential to fight cancer and be used to make new medications. In the current market, there are four types of plant-based anticancer drugs are available such as: vinca alkaloids (vinblastine, vincristine, and vindesine), epipodophyllotoxins (etoposide and teniposide), taxanes (paclitaxel and docetaxel), and camptothecin derivatives (camptotecin and irinotecan) [3,4].

2. Endophytic Fungi and Cancer

The word "endophyte" includes bacteria and fungi that, at certain stage in their life cycles, colonies interior plant tissue without displaying any harmful symptoms. [5,6,7]. They can be found in root complexes and other parts of the host plant, and their host ranges differ from simple thallophytes to complex angiosperms [8]. Endophytic fungi are considered an important component of microbial diversity. These endosymbionts help alter the characteristics of the ecosystem. They change the host plant's growth and development, boost its productivity, and make it more resilient to biotic and abiotic stress [9]. In biotechnology, fungal endophytes are essential for studies like enzyme production, biocontrol potential, plant growth promotion, bioremediation, biodegradation, biotransformation, biosynthesis, and nutrient cycling. They also serve as sources for cutting-edge biological chemicals. [10].

The cytotoxic and anti- cancer activities of endophytic fungi were deemed the most important topics to the scientific community. There have been multiple reports of fungal endophytic strains that produce drugs like vincristine, irinotecan, topotecan, vinblastine, and others that are used in clinical trials to treat various types of cancer in humans. [11]. Studies revealed that taxol and taxol-like compounds might be produced by fungal endophytes from taxus and non-taxus plants. A number of endophytic genera, including *Alternaria, Aspergillus, Botryodiplodia, Botrytis, Cladosporium, Ectostroma, Fusarium, Metarhizium, Monochaetia, Mucor, Ozonium, Papulaspora, Periconia, Pestalotia, Pestalotiopsis, Phyllosticta, Pithomyces,* and *Taxomyces,* were reported for the production of taxol [11]. The Pacific yew tree (*Taxus brevifolia*), from which paclitaxel (commonly known as "taxol") is derived, exhibits broad-spectrum action against the treatment of a number of tumor types, including breast, ovarian, and Kaposi's sarcoma. The endophytic fungus *Taxomyces*

andreanae was found in the bark of *Taxus brevifolia* and is capable of producing taxol and other similar chemicals [12].

Similarly, podophyllotoxin is a plant based anticancer agent commonly used in lung cancer and testicular cancer treatment [13]. Fungal endophytes yielded podophyllotoxin. The common podophyllotoxin-producing endophytes include *Fusarium sp., Aspergillus sp., Mucor sp*., etc. Another fungal endophyte derived anti cancerous compound is camptothecin. The common camptothecin-producing endophytes includes *Fusarium sp,Phomopsis sp, Aspergillus sp, and Trichoderma sp.* Vinca alkaloids such vinblastine, vincristine, vinleunosine, and vinrosidine are used to treat acute lymphoblastic leukaemia and nephroblastoma by lowering the number of white blood cells [11]. Endophytic fungi such as *Alternaria sp., Fusarium sp* are found to produce vinca compounds [11].

3. Cytotoxic Activity of Endophytic Fungi

Research conducted by El-Kassem et al. in 2019 [14]. showed that *Emericella nidulans* (RSSSS-22, RSL24), *Fusarium oxysporum* SML-41, and *Penicillium sp*. RSL-43 endophytic fungal extracts had strong cytotoxic activity against human breast cancer cell lines (MCF-7), with IC50 values of 10.8, 11.0, 12.5, and 13.7 g/ml, respectively and with IC50 values of 14.8, 20.3, and 24.0 g/ml, respectively, *E. nidulans* (RSSSSSS-22, RSL-43), and Fusarium showed a strong cytotoxic effect on human liver cancer cell lines (HEP-G2). In addition, *Colletotrichum gloeosporioides* extract in ethyl acetate shown potential cytotoxicity against cancer cell lines HCT116, HeLa, and HepG2 with IC50 values of 76.59 g/mL, 176.20 g/mL, and 1750.70 g/mL, respectively [15]. Studies by Sunkar et al. (2017) [16] on Hep2 cells revealed that the cytotoxicity of cells was influenced by a fungal extract in a time- and dose-dependent manner. Similarly, marine plant-associated fungal endophytes were potentially cytotoxic to the cell lines M059J (brain), PC3 (prostate), DLD-1 (colon), MDAMD231 (breast), NCIH1299 (lung), B16F10 (melanoma), PC12 (pheochromocytoma), and Detroit 551 (fibroblast) [17]. Endophytes from the bacopa plant were toxic to the cell lines HCT-116, MCF-7, PC-3, and A-549, and extracts were more effective against HCT-116 cells than the other cell lines [18]. Endophytic fungi from the *Piper crocatum* strongly suppressed the growth of human ductal breast epithelial cancer cell lines (T47D) and human colon carcinoma cell lines (WiDr), and they also significantly inhibited the growth of MCF-7 and HCT116 cell lines [19,20]. AgNP nanoparticles produced from endophytic fungus reduced cell proliferation at an IC50 value of 100 g/mL in human MCF7 breast cancer cell lines and human A549 lung cancer cell lines [21].

4. Anti-Cancer Compounds Obtained From Endophytic Fungi

Therapeutically significant molecules have been manufactured from the secondary metabolites of endophytes. The discovery of potent anticancer medications at a reasonable price may be greatly aided by endophytic fungus. In light of this, investigating and employing endophyte metabolites is a great way to find new, potent medicines for severe human diseases. Research on anticancer properties and compound isolation from fungal endophytes has a significant impact (Table -1).

Table 1: Some Anti-Cancer Compounds From Fungal Endophytes

Name of Endophyte	Host Plant With Segment Where Endophyte Isolated	Name of Compound	Tested Cell Line And Activity	Reference
Penicillium melinii and *Penicillium janthinellum*	*Panax ginseng* – root segment	Ginsenocin, methyl 2,4-dihydroxy-3,5,6-trimethylbenzoate, 3,4,5-trimethyl-1,2-benzenediol, penicillic acid, mannitol, ergosterol, and ergosterol peroxide and brefeldin A	Action against MKN45, LOVO, A549, MDA-MB-435, HepG2, and HL-60 human cancer cell lines, with IC50 values ranging from 0.49 to 7.46 μg/ml.	[22]
Aspergillus tubingensis	*Pongamia pinnata* – Radix	Rubasperone D, Rubasperone E, Rubasperone F, Rubasperone G, Naphtho-G-Pyrones - TMC 256 A1, Rubrofusarin B, Fonsecin, and Flavasperone	MCF-7, MDA-MB435, Hep3B, Huh7, SNB19, and U87 MG tumour cell lines with IC50 values ranging from 19.92 to 47.98 mm	[23]
Talaromyces flavus	Mangroves	Talaperoxides A–D	Human cancer cell lines MCF-7, MDA-MB-435, HepG2, HeLa, and PC-3 with IC50 values between 0.70 and 2.78 μg/mL.	[24]
Trichoderma harzianum	*Cola nitida* - Leaves	4'-hydroxy-deacetyl-18-deoxycytochalasin H, deacetyl-18-deoxycytochalasin H, 18-deoxycytochalasin H	Cytotoxic action (IC50 0.19–6.97 μM) against the human ovarian cancer cell lines A2780 sens and A2780 CisR as well as the murine lymphoma (L5178Y) cell line.	[25]

Penicillium brefeldianum.	Rhizome of *Pinellia* ternate	Indoloditerpene, 6,7-dehydropaxilline, spirotryprostatin F, N-demethylmelearoride A	Cytotoxicities with IC50 values of 14.1 mmol/L and 35.5 mmol/L, respectively, against HepG2 and MDA-MB-231 cells.	[26]
Lasiodiplodia theobromae	Marine mangrove A. ilicifolius – Leaf	Chlorinated preussomerins, Chloropreussomerins A and B (1 and 2), Preussomerin analogues, 3−11	Cytotoxicity with IC50 values ranging from 5.9 to 8.9 μM against the human cancer cell lines A549 and MCF-7	[27]
Phomopsis sp.	Mangroves	Phomopchalasins D–O (1–3, 5–12, And 14)	Cytotoxicity against the MDA-MB-435 human cancer cell line, with an IC50 range of 0.2 to 8.2 μM.	[28]
Epicoccum nigrum	*Entada Abyssinica* – Leaves	Beauvericin, parahydroxybenzaldehyde, indole-3-carboxylic acid and quinizari	On Vero cells, THP-1, and RAW 264.7, the LC50 values varied from 40.42 to 86.56 μg/ml, 31.87 to 86.57 μg/ml, and 21.59 to 67.27 μg/ml, respectively.	[29]
Coniochaeta sp	*Ageratina Adenophora*	Phomoxanthone A and Penialidin A	Cytotoxicity in a cell line of mouse embryonic fibroblasts Balb/c3T3.	[30]
Penicillium chrysogenum	Marine Red Algal Species of the Genus *Laurencia*.	Penicisteroids A and B	Activity against HeLa, SW1990, and NCI-H460 tumour cell lines with IC50 values of 15, 31, and 40 lg/mL	[31]

Fusarium chlamydosporium	*Anvillea Garcinii*- Leaves	Fusarithioamide A 2(2-aminopropanamido)-N-(1-hydroxy-3-mercaptopropyl) benzamide, 4), 1-O-acetylglycerol, 8-acetylneosolaniol, and ergosta-7,22-diene-3b,5a,6b-triol	BT-549 and SKOV-3 cell lines are targets of strong and selective action, with IC50 values of 0.4 and 0.8 mM, respectively.	[32]
Cladosporium sp	*Rauwolfia serpentina* - Leaves	Anhydrofusarubin and methyl ether of fusarubin	Potential cytotoxicity was seen against human leukaemia cells (K-562) with IC50 values of 3.97 and 3.58 μg/mL	[33]
Eutypella scoparia	*Hevea Brasiliensis* – Leaves	Cytochalasin derivative, scoparasin C (**1**), four cytochalasins (**2**–**5**), four pimarane diterpenes (**6**–**9**) and two chromene derivatives (**10** and **11**)	The IC50 values for compounds 1, 3, 4, and 7 against Vero cell lines were 1.19, 0.04, 1.01, and 2.50 μM, respectively With an IC50 value of 2.46 μM, compound 3 showed strong cytotoxic action against KB-oral cavity cancer cell lines.	[34]
Pleosporales sp.	*Siraitia grosvenorii* - Tuberous roots	Pleospyrones A-E, congener	Hepatocellular carcinoma of the liver (HCT-116), gastric cancer (BGC-823), non-small-cell lung carcinoma (NCI-H1650), and medulloblastoma cells (Daoy) with 1.26 to 47.5 μM IC50 values.	[35]

Pleosporales sp	*Mahonia fortunei*. – Pedicel	Heptaketides, pleosporalins A–F and pleosporalin G	Against the cancer cell lines MDA-MB-231, SMMC-721, and A549. Compound 7's IC50 value of 22.4 1.1 μM against MDA-MB-231 indicated significant cytotoxicity.	[36]
Talaromyces flavus.	*Sonneratia apetala*	Talaperoxides A–D, teperoxide B	The MCF-7, MDA-MB-435, HepG2, HeLa, and PC-3 human cancer cell lines. The IC50 values for compounds 2 and 4 ranged from 0.70 to 2.78 μg/mL	[37]
Chaetomium globosum	*Ginkgo biloba*	Chaetoglobosins, C, E, F, Fex, 20-dihydrochaetoglobosin A	Cytotoxic effects on human colon cancer cell HCT116 with IC50 values between 3.15 and 8.44 μM	[38]
Talaromyces sp	*Kandelia candel* - Stem bark	7-epiaustdiol (**1**) and 8-O-methylepiaustdiol (**2**), stemphyperylenol (**3**), skyrin (**4**), secalonic acid A (**5**), emodin (**6**), and norlichexanthone (**7**)	Cytotoxicity against all tested cell lines.	[39]
estalotiopsis microspora	*Drepanocarpus lunatus*	Pestalotioprolides C (2), D−H(4−8), and 7-O-methylnigrosporolide,pestalotioprolide B (1), seiricuprolide (9), nigrosporolide (10), and 4,7dihydroxy-13-tetradeca-2,5,8-trienolide (11)	Cytotoxicity against the human ovarian cancer cell line A2780 with an IC50 value of 1.2 μM and against the murine lymphoma cell line L5178Y with IC50 values of 0.7, 5.6, 3.4, and 3.9 μM	[40]

Trichoderma harzianum	*Physalis angulate*	Trichodestruxins A, destruxin E2 chlorohydrin (5) and destruxin A2	Cytotoxicity with IC50 values ranging from 0.7 to 19.1 μM against the HT-29, A549, and/or P388 cell lines.	[41]
Penicillium brocae	*Avicennia marina.*	Brocazines A−F	IC50 values for the following cell lines: Du145, Hela, HepG2, MCF-7, NCI-H460, SGC-7901, SW1990, SW480, and U251 range from 0.89 to 9.0 μM	[42]
Phoma macrostoma	*Glycyrrhiza glabra*	Macrophin (1), rosellisin (2), 2-(2-hydroxy-5-6-methoxy-3-methylene-1,4-benzodioxin-2(3H)-one (3), and methoxyphenoxyacrylic acid	Cytotoxic activity against the cancer cell lines MDA-MB-231, T47D, MCF-7, and MIAPaCa-2, with IC50 values of 14.8, 8.12, 13.0, and 0.9 μM, respectively.	[43]
Phialophora mustea	*Crocus sativus*	Phialomustin A-D	Cytotoxic potential with an IC50 of 1 μM against the T47D human breast cancer cell line.	[44]
Mycoleptodiscus sp.	*Desmotes incomparabilis*	Mycoleptodiscin A (1) and mycoleptodiscin B	With IC50 values between 0.60 and 0.78 μM., limiting the proliferation of cancer cell lines	[45]
Curvularia verruculosa	*Cathranthus roseus* – Leaves	Vinblastine analogous	The HeLa cell line had a stronger activity with an IC50 of 8.5 μg/mL	[46]
Aspergillus niger	Taxus baccata.	Lovastatin	Human cancer cells (HeLa& HepG2)	[47]

Alternaria alternata and *Fusarium* species	Mappia foetida	Camptothecin	Cytotoxic activity against Hepatocellular carcinoma cell line (Hep G2), non-small cell lung carcinoma (H1975), breast cancer (MCF-7), and cervical carcinoma (HeLa)	[48]
Phoma sp.	-	α-pyrone derivatives	IC50 values in between0.52–9.85 μM.	[49]
A. niger and *A. fumigatus*	*Cinnamomum mollissimum*	Hydroxyramulosin	Cytotoxic against murine leukemia cells with IC50 value 2.10 μg/mL).	[50]
Allantophomopsis lycopodina	Beech branch	Allantopyrone A	Cytotoxic against HL60 cell lines	[51]
Aspergillus sp., *Nigrospora sphaerica*, *Talaromyces purpureogenus*, and *Talaromyces stipitatus*	*Argassum muticum*	Quinoline, indole, 2,4-bis(1,1-dimethylethyl) phenol, and hexadecenoic acid	Cytotoxicity against LN-229 (glioblastoma), HeLa (cervical adenocarcinoma), MCF-7 (breast adenocarcinoma), A-549 (lung carcinoma), A-431 (skin/epidermis carcinoma), and Hep G2 (hepatocellular carcinoma) with an IC50 value of 24 2 24 ± 2 μg/ml, HeLa cells were the most susceptible to ASE treatment.	[52]
Bipolaris sorokiniana	*Pogostemon cablin*	Isocochlioquinones D–E (1–2) and cochlioquinones G–H (3–4)	Cytotoxic effects on the tumour cell lines MCF-7, NCI-H460, SF-268, and HepG-2	[53]

Phoma bellidis,	*Tricyrtis maculate*-Leaves	Bellidisins A-D, pinolidoxin (5), 5,6-epoxypinolidoxin (6), and 2-epi-herbarumin II (7)	The IC50 value varied from 3.40 to 15.25 μM, which is stronger than cisplatin (4.86-27.70 M), for the human cancer cell lines HL-60, A549, SMMC-7721, MCF-7, and SW480.	[54]
Pseudolagarobasidium acaciicola	*Bruguiera gymnorrhiza*	Merulin A and merulin D	Selective activity against the HL-60 cell line and cytotoxic activity (IC50 0.28 μM).	[55]
Perenniporia tephropora	*Taxus chinensis* var. mairei,	Sesquiterpenoid, perenniporin A (1), ergosterol (2), rel-(+)-(2aR,5R,5aR,8S,8aS,8bR)-decahydro-2,2,5,8-tetramethyl-2H-naphtho[1,8-bc]genfuran-5-ol (3), and albicanol (4).	Cytotoxic action against PANC-1, SMMC-7721, and HeLa cells) and IC50 values for EPT with cytotoxicity range from 2 to 15 ug/mL. Compound 2 had IC50 values of 1.16, 11.63, and 11.80 ug/mL for each of the examined cell lines, making it the most cytotoxic component. While the IC50 values for compounds 1, 3, and 4 ranged from 6 to 58 ug/mL, they showed considerable cytotoxicity.	[56]
Pestalotiopsis clavispora KJ677242, *P. mangiferae*	*Dendrobium officinale*	(4S,6S)-6-[(1S,2R)-1, 2-dihydroxybutyl]-4-hydroxy-4-methoxytetrahydro-2H-pyran-2-one (1), (6S,2E)-6-hydroxy-3-	The cytotoxicities of compounds 1-4 against HL-60 cell lines exhibit IC50 values less than 100 M. The IC50 values for	[57]

		methoxy-5-oxodec-2-enoic acid (2), LL-P880γ (3), LL-P880α (4), & ergosta-5,7,22-trien-3b-ol (5)	compounds 1, 2, 4, and 5 are below 100 M, indicating cytotoxicity against the LOVO cell line.	
Periconia sp.	-	Periconiasins A–C	Cytotoxicity against human HCT-8 cancer cells.	[58]
Stachybotrys chartarum	*Pinellia ternate*	Stachybochartins A–G (**1–7**)	Cytotoxicity against breast cancer cells (MDA-MB-231) & osteosarcoma cells (U-2OS), with IC_{50} values in between 4.5 to 21.7 μM	[59]
Aspergillus oryzae	*P. polyphylla* var. yunnanensis,	Oryzaeins A–D(1-4),	IC50 values in between 2.8–8.8 μM.	[60]
Marine-derived Mangrove Endophyte	Marine-derived mangrove	Marinamide (**I**) and its methyl ester (**II**), pyrrolyl 1-isoquinolone	Cytotoxicity against HepG2, 95-D, MGC832 & HeLa tumour cell lines.	[61]

II. CONCLUSION

Although endophytic fungi aid in the production of new bioactive compounds, but these efforts are limited by low yields of active compounds, an incomplete understanding of the biochemical interactions between fungi and plants, and increasing contamination. The cytotoxic potential of endophytic fungi has, however, been extensively studied. Numerous endophyte-derived substances have been found to have potent anti-cancer effects.

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