International Journal of Pharmacy and Pharmaceutical Sciences

ISSN- 0975-1491 Vol 8, Issue 8, 2016

Review Article

ENDOPHYTIC FUNGI: TREASURE FOR ANTI-CANCEROUS COMPOUNDS

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Received: 22 Apr 2016 Revised and Accepted: 20 June 2016

ABSTRACT

Endophytic fungi that live asymptomatically inside the plant tissues have novel bioactive metabolites exhibiting a variety of biological activities, especially against cancer. This review highlights the research progress on the production of anticancer compounds by endophytic fungi from 1990-2015. Anticancer activity is generally associated with the cytotoxicity of the compounds present in the endophytic fungi. The ubiquitous nature of endophytic fungi synthesise diverse chemicals with promising anticancer activity from either their original host or related species. Modification in fermentation parameters and genetic insight of endophytes may produce novel anti-cancerous compounds.

Keywords: Cancer, Medicinal plants, Secondary metabolites

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INTRODUCTION

The interest in the biogenic medicines has revived throughout the world, as the increase in awareness of the health hazards and toxicity associated with the random use of synthetic drugs and antibiotics [1]. As chemotherapy and conventional treatment causes the adverse side effects for the cure of cancer (CA). Hence, there is an urgent necessitate effective and low toxic drugs. Natural products or their derivatives provide a continuous source of novel bioactive metabolites [2]. Microorganisms seem to cover almost all niches of earth and the probability increases of finding novel compounds by investigating the secondary metabolites of microorganisms from unusual or specialized niches.

Endophytes

Endophyte inhabited in internal tissues of plants without causing any immediate, overt adverse effect [3]. Approximately 1.5 million fungal species exist [4]; while 100,000 have been described. Fungal endophytes are diverse group of microorganisms that colonize plants in the Arctic [5] and Antarctic [6] and in geothermal soils [7], rainforest [8], desert [9], ocean [10], mangrove swamps [11] and coastal forests [12]. They had isolated from the root complexes and aerial parts of a range of hosts, including algae [10, 13], bryophytes [14], pteridophytes [15], gymnosperms [16] and angiosperms [17, 18].

Endophytic fungi: alternative source of secondary metabolites

The search for novel secondary metabolites seems to be characteristics of certain biotopes, centered on organisms that inhibit unique biotopes. A fungus producing secondary metabolite may vary with the biotope where it grows and to which it adapts. Genes involved in the production of secondary metabolites appear to cluster in fungi and bacteria [19] and have gained attention because genetic screening methods are rapid, economical and sensible. Fungal endophytes harbored a broad variety of bioactive secondary metabolites with a distinctive structure including, alkaloids, benzopyranones, flavonoides, phenolic acids, quinines, saponins, steroids, terpenoides, xanthones and others [20]. The respective ecological niche and persistent metabolic interaction between fungus and plant may augment the synthesis of secondary metabolites [21].

Data revealed in this review includes the diversity and taxonomy of endophytes of different species and genera and its anticancer compounds between the year 1990 and 2015 have been systematically represented in the table 1. The structure of these anticancer compounds isolated from the endophytes between 2010 and 2015 are represented in fig. 1. The selection criteria of the reference in the study were based on the bioactive components from endophytic fungi detectable by high-performance liquid chromatography, nuclear magnetic resonance, mass spectrophotometer and X-ray crystallography and its cytotoxicity of the bioactive compounds against cancer cell lines. The compounds with potential application were also considered in the selection of antitumor compounds that are produced by endophytes fungi.

Anti-cancerous natural products from fungal endophytes

Long term co-evolution between endophytic fungi and their host plant for making friendly relationship is believed to shape natural product patterns of endophytic fungi. Endophytic fungi residing in the plants biosynthesize important plant secondary metabolites. There are some natural lead compounds isolated from endophytic fungi acting as lead antiCA compounds viz., paclitaxel, podophyllotoxin, camptothecin, vincristine and vinblastine.

Endphytic fungi producing paclitaxel

Paclitaxel is the earliest antiCA compound secured from endophytes. It is a highly functionalized diterpenoid quarantined from the endophytes *Taxomyces andreanae* obtained from *Taxus brevifolia* plant species familiar as Pacific yew, which belongs to the *Taxus* family. The Taxol biosynthetic machinery differs specifically in combination of structural and regulatory genes for one *Pestalotiopsis microspora* isolate to another. Paclitaxel is produced from most commonly isolated endophytic species *P. microspora* from *Taxus wallichiana* [22] and *Tubercularia* sp. from the southern Chinese yew (*Taxus mairei*) in the Fujian province [23]. Paclitaxel production was manifold from *P. microspora* isolates quarantined from bald cypress in South Carolina [24], and in *Pestalotiopsis guepini* isolated from *Wollemi pine* (Wollemia nobilis) an extremely rare species from Australia [25]. The highest amount of Taxol produced from an endophytic fungus, *P. terminaliae* isolated from the *Terminalia arjuna* [26]. More than two dozen of Taxol producing fungi have been acknowledged [27], including mangrove endophytic fungi *Fusarium oxysporum* from *Rhizophora annamalayana* [28] and from an endophytic fungus, *Fusarium redolens* from Himalayan yew of *Taxus baccata* [29]. The *Alternaria* sp. isolated from the shells of *Corylus avellana* also exhibited an extracellular production of paclitaxel in the MID medium [30].

Endophytic fungi producing podophyllotoxin (PDT)

Podophyllotoxin (PDT) and aryl tetralin lignin with antiCA, antiviral, antioxidant, antibacterial, and immunostimulation capacity commonly occurred in genera of *Diphylleia*, *Dysosma*, *Sabina* [31-38]. The first report of an alternative strategy for efficient production of podophyllotoxin was encountered from *Sinopodo-*

phyllum hexandrum, *Diphylleia sinensis* and *Dysosma veitchii* [31]. It was found that PDT can produce from an endophytic fungus *Alternaria* sp. of *Sabina vulgaris* [34]. The two endophytes, *Phialocephala fortinii* strains PPE5 and PPE7 was also able to produce PDT from the rhizomes of *Sinopodophyllum peltatum* with the yield of 0.5-189 µg/l in liquid suspension culture [35]. It was also produced from an endophytic fungus *Trametes hirsute* of *Sinopodophyllum hexandrum* in Sabouraud broth culture [36], whereas *Alternaria* sp. isolated from *Sinopodophyllum hexandrum* [37] and also from endophytic fungus *Fusarium oxysporum* recovered from *Sabina recurva* [38]. A new endophytic PDT-producing fungus of *Fusarium solani* has been isolated from the roots of *Podophyllum hexandrum* [39]. Recently, an endophytic fungus, *Mucor fragilis* (TW5) was isolated from *Sinopodophyllum hexandrum* which produces podophyllotoxin [40].

Endophytic fungi producing camptothecin (CPT) and its analogues

Camptothecin (CPT), a pentacyclic quinoline alkaloid was first obtained from the wood of *Camptotheca acuminata* (Nyssaceae) [41]. CPT and its analogue10-hydroxycamptothecin are effective in inhibition of the intranuclear enzyme topoisomerase-1, required for DNA replication and transcription during the molecular events [42]. The first report of an endophytic fungus *Entrophospora infrequens* obtained from *Nothapodytes foetida* had the ability to produce camptothecin [43]. The *F. solani* obtained from *Camptotheca acuminata* may able to produce CPT, 9-methoxycamptothecin and 10-hydroxycamptothecin [44]. The endophytic fungi, *Alternaria alternata, Fomitopsis* sp., and *Phomposis* sp. isolated from *Miquelia dentate* (Icacinaceae) were produced CPT, 9-methoxy CPT (9-MeO-CPT) and 10-hydroxy CPT (10-OH-CPT), respectively. The fungal extracts are effective against colon and breast CA cell lines [45]. It was also found that an endophytic fungi *Trichoderma atroviride* LY357 isolated from *C. acuminata* produces highest yield 142.15 µg $l(^{-1})$ on subculturing [46].

Endophytic fungi producing Vinblastine/Vincristine

Vinblastine and vincristine, terpenoid indole alkaloids derived by the linking of vindoline and catharanthine monomers are acknowledged as antiCA agents [47, 48]. The primary mechanism of action of vincristine is to interfere with microtubule formation and mitotic spindle dynamics, further interruption of intracellular transport leads to anti-angiogenesis [47, 49]. The endophytic fungus *Alternaria* sp. and *F. oxysporum* isolated from the phloem of *Catharanthus roseus* has the ability to yield vinblastine [50] and Vincristine [51] respectively. Vincristine also isolated from an endophytic fungus of leaves of *C. roseus* [52]. Vinblastine and Vincristrine have been also isolated from an endophytic fungi *F. oxysporum* from *Catharanthus roseus* [53].

New secondary metabolites as an anticancer compound

It includes various chemical entities, including alkaloids and nitrogen-containing heterocycle, benzofluranthenes, chromones, cyclohexanthrone, depsidone, coumarins, ergochromes, esters, lactones, peptides, peroxide, polyketides, pyrans, quinines, steroids, stilbene, diterpenes, sesquiterpenes, triterpenes and xanthones.

Alkaloids and nitrogen-containing heterocycle

Plant-derived alkaloids reveal a wide range of biological activity. Many potential antiCA agents studied are plant alkaloids [54, 55]. A number of alkaloids have been isolated from endophytic fungi. Some alkaloid compounds explored for commercial purpose for clinical use for targeting tumors are Camptothecin (CPT), and Vincristine. In recent years, several new alkaloids isolated from endophytic fungi have shown antitumor activity.

Cytochalasin, is a highly substituted perhydroisoindol moiety usually attached to heterocyclic ring. There are>80 different cytochalasins reported from fungal isolate of different genera, with a wide range of biological activity. The mechanism of action of cytochalasins is to inhibit cell division, induce an apoptotic response and inhibit the polymerization of actin filaments [56]. Cytochalasin 1 showed cytotoxic activity against A2780S (ovarian), HCT-116 (colon) and SW-620 (colon) tumor cell line with IC_{100} values of 3.91, 15.6 and 3.91 µg/ml, respectively, while 14 showed values of 15.6, 62.5, 15.6 µg/ml respectively. Cytochalasin 3 exhibited an IC_{100} (inhibitory concentration, 100%) value of 3.91µg/ml against A2780S and 15.6µg/ml against SW-620 [57].

Chaetominine, alkaloidal metabolites, isolated from an endophytic fungus *Chaetomium* sp. IFB-E015 from healthy leaves of *Adenophora axilliflora*. Chaetominine 19 showed cytotoxicity against the K562 (human leukemia) and SW1116 (colon cancer) cell lines. Its potency was greater than that of 5-fluorouracil, with IC_{50} values of 33.0 and 76.0 nM, respectively [58].

The 9-Deacetoxyfumigaclavine C, an alkaloid was isolated from the endophyte *Aspergillus fumigatus* from a healthy stem of *Cynodon dactylon*. 9-Deacetoxyfumigaclavine C 2 exhibited selectively potent cytotoxicity against human leukemia cells (K562) with an IC_{50} value of 3.1 µM, which was similar to that of doxorubicin hydrochloride (1.2 µM) [59].

Novel fungal alkaloids Cytoglobosin C and D, cytochalasan derivatives isolated and identified from a culture of *Chaetomium globosum* QEN-14, an endophytic fungus of the marine green alga *Ulva pertusa*. Two cytoglobosins compounds C10 and D11 displayed very similar cytotoxicity profiles with IC_{50} values of 2.26 and 2.55 µM against the lung CA A549 tumor cell line [60].

Citriquinochroman, a structure consisting of quinolac-tacide and (3S)-6-hydroxy-8-methoxy-3,5-dimethylisochro-man linked by a C-C bond. It was isolated from *Penicillium citrinum,* an endophytic fungus from a fresh stem of the Moroccan plant *Ceratonia siliqua*. Citriquinochroman showed cytotoxicity (IC_{50}=6.1 µM) against the murine lymphoma L5178Y [61].

Aspochalasins D and J, two cytochalasans analogues were isolated from *Trichoderma gamsii*, obtain from the traditional Chinese medicinal plant *Panax notoginseng*. Compound aspochalasins D and J displayed inhibitory activity against the HeLa cells with an IC_{50} value of 5.72 and 27.4 µM, respectively [62].

Chaetoglobosin U, an alkaloid belonging to the cytochalasin family had an affinity for actin filaments. It was isolated from *Chaetomium globosum* IFB-E019 from healthy stem of *Imperata cylindrica*. It showed cytotoxic activity against the KB cell line with an IC_{50} value of 16.0 µM comparable to that of 5-fluorouracil as a positive reference (14.0 µM) [63]. Chaetoglobosin X isolated from an endophytic fungus *C. globosum* of medicinal plant *Curcuma wenyujin* exhibited potent cytotoxic activity against H22 and MFC CA cell lines [64].

Benzo[j] fluoranthenes

New benzo[j]fluoranthene structures, daldinone C and daldinone D isolated from an endophyte *Hypoxylon truncatum* IFB-18 reside inside the stem tissue of *Artemisia annua*. Both compounds exhibited potent cytotoxicity against human colorectal CA cell line SW1116 cells, with IC_{50} values of 49.5 and 41.0 µM, respectively, as compared to 5-fluorouracil with IC_{50} value 37.0 µM [65]. One contrasting thing to note is that the value of 5-fluorouracil as a standard was 76.0 nM [58] as compared to another study, eventhough the same researchers used the same cell line (SW1116) and the same MTT colorimetric method.

Chromones

Pestalotiopsone F, is a new chromone, 7-hydroxy-2-(2-hydroxypropyl)-5-methylchromone derivative isolated from an endophytic fungus *Pestalotiopsis* sp. of Chinese Mangrove plant *Rhizophora mucronata*. Among other chromone derivatives, compound 6 exhibited moderate cytotoxicity against the murine CA cell line L5178Y, with an EC_{50} value of 8.93µg/ml [66].

Pestaloficiols, novel isoprenylated chromone derivative was isolated from fungal endophyte *Pestalotiopsis fici* of *Camellia sinensis*. Four novel derivatives, pestaloficiol I, pestaloficiol J, pestaloficiol K and pestaloficiol L (heterodimer) had IC_{50} values ranging between 8.7 µM and>136.1 µM for HeLa cells and between 17.4 µM and>153.8 µM for MCF7 cells, compared to the positive control 5-fluorouracil with IC_{50} values of 10.0 and 15.0 µM, respectively. Pestaloficiol L showed potent cytotoxicity, with IC_{50} values of 8.7 and 17.4 µM respectively [67].

Coumarins

A new furanocoumarin, 5-methyl-8-(3-methylbut-2-enyl) furano-coumarin was isolated from the mangrove endophytic fungus, *Penicillium* sp. ZH16, which exhibited *in vitro* cytotoxicity against CA cell lines with IC_{50} values KB and KBV200 cells 5 and 10 mg. ml^{-1}, respectively [68].

Arundinone B, a polyoxygenated benzofuran-3 (2H)-one dimer was isolated from a plant endophytic fungus, *Microsphaeropsis arundinis*. Arundinone B showed cytotoxic activity against T24 and A549 CA cells [69].

Cyclohexanones

Epiepoxydon, a cyclohexanone derivative, was isolated from a marine endophytic fungus *Apiospora montagnei* of inner tissue of the North Sea alga *Polysiphonia violacea*. High cytotoxicity of the compound was observed in the brine shrimp assay. The breast adenocarcinoma cell line MCF7 exhibited an LC_{50} of 3.6µg/ml. The GI_{50} concentrations for human gastric carcinoma HM02, human liver carcinoma HepG2 an MCF7 were 0.7µg/ml, 0.75µg/ml and 0.8µg/ml respectively. The total growth inhibition (TGI) for HepG2, MCF-7 and HM02 was found to be 4.6µg/ml, 1.5µg/ml and 1.0 µg/ml respectively. The LC_{50} of compound 27 observed in HM02 and HepG2 cells were>10 µg/ml [70].

Depsidone

Depsidone 1 isolated from order *Pleosporales* (BCC 8616), an endophytic fungus was isolated from an unidentified leaf of the Hala-Bala evergreen forest. It showed weak cytotoxic activity against KB with IC_{50} values of 6.5 and 4.1 µg/ml activities for BC cell lines [71].

Ergochromes

Dicerandrol, a dimeric tetrahydroxanthone derivative was isolated from an endophytic fungus *Phomopsis longicola* of the endangered mint *Dicerandra frutescens*. The fungal endophyte produced three compounds designated dicerandrols A, B, and C. They have the same tricyclic C15 system with a similar arrangement of substituents, classified as ergochromes. The dicerandrols showed considerable cytotoxicity against lung adenocarcinoma epithelial cell line A549 and colorectal HCT-116. The IC_{100} value of compound A against both cell lines and the value of compound C against HCT-116 was 7.0µg/ml. The IC_{100} value of compound C against A549 and of compound B against both cell lines was 1.8µg/ml. The standard antiCA drug etoposide exhibited IC_{100} values of 30.0µg/ml against A549 and 125.0µg/ml against HCT-116, which were less significant than dicerandrol compound [72].

Ergoflavin, a dimeric xanthene, linked in position 2 classes of ergochrome compounds, were first isolated from the ergot fungus *Claviceps purpurea*, as well as *Aspergillus* sp., *Penicillium oxalicum*, *Phoma terrestris* and *Pyrenochaeta terrestris*. It has been isolated from ascomycetous endophyte of a leaf, *Mimosops elengi* ('bakul') designated PM0651480. Ergoflavin showed cytotoxicity against renal ACHN with IC_{50} value1.2±0.20, for lung H460 IC_{50} 4.0±0.08, for pancreatic Panc IC_{50} 12.4±0.02, for colorectal HCT116 IC_{50} 8.0±0.45 and 1.5±0.21 µM IC_{50} values for lung Calu1 cell lines. Flavopiridol has been used as standard for assessing the cytotoxicity of ergoflavin with the IC_{50} values in ACHN (0.84±0.03 µM); H460 (0.38±0.01µM); Panc-1 (0.23±0.07 µM); HCT116 (0.25±0.03 µM); and Calu1 (0.41±0.09 µM) CA cell lines [73].

Secalonic acid D, an ergochrome group of compounds isolated from the mangrove endophytic fungus no. ZSU44 [74], was first isolated from *Penicillium oxalicum* [75] with highly toxic and teratogenic properties. Secalonic acid D showed potent cytotoxicity to HL60 with IC_{50} values of 0.38 µM and 0.43 µM in K562 cells. It induced apoptosis in HL60 and K562 cells, confirmed by Annexin V-FITC/PI assay and Western blot. Secalonic acid D also downregulated c-Myc and cell cycle arrest of G(1) phase through activation of GSK-3beta followed by degradation of beta-catenin [74].

Esters

Globosumone, orsellinic acid ester, was isolated from endophytic fungus, *Chaetomium globosum* of Mormon tea, *Ephedra fasciculate*. Two isolated compounds Globosumone A and B exhibited moderate cytotoxic activity with IC_{50} for compound A 21.30 and 21.90 µM for compound B against MCF-7, IC_{50} values for compound A 10.60 and 30.20 µM for compound B against MIA Pa Ca-2 with IC_{50} values for compound A 6.50 and 24.80 µM for compound B against NCI-H460. The IC_{50} value for compound A 8.80 and 29.10 µM for compound B against SF-268, and against WI-38 with IC_{50} for compound A was 13 and 14.20 µM for compound B [9].

Lactones

Brefeldin A, a lactone antibiotic, was isolated from endophytic fungi *Aspergillus clavatus* and *Paecilomyces* sp. isolated from *Taxus mairei* and *Torreya grandis*. Brefeldin A has antifungal, antiCA and antiviral activities. It showed good cytotoxic activity against HeLa, HL-60, KB, MCF-7 and Spc-A-1 cell lines with IC_{50} values of 9.0, 10.0, 1.8, 2.0 and 1.0 ng/ml, whereas standard paclitaxel drug with IC_{50} values of 0.16, 1.2, 1.8, 5.0 and 0.8 ng/ml respectively. It has been also isolated from numerous fungal species, including *Alternaria, Ascochyta, Curvularia, Cercospora, Phyllosticta* and *Penicillium* [76]. Brefeldin A was also isolated from *Acremonium* species of a healthy twig of *Knema laurina* with potent activity against BC-1 (breast cancer), KB (epidermoid cancer of the mouth), and NCI-H187 (small-cell lung cancer), with IC_{50} values of 0.04, 0.18 and 0.11 µM, respectively [77].

Eutypellin A, a gamma-lactone isolated from *Eutypella* sp. BCC 13199, an endophytic fungus was isolated from *Etlingera littoralis* (Earth ginger). It showed cytotoxic activity against MCF-7, NCI-H187 (human small-cell lung cancer cells), KB and non-malignant Vero cells with IC50 values of 84, 12, 38 and 88 mM compared to the standard ellipticine, which exhibited IC50 values of 2.5, 3.6 and 5.5 µM respectively [78].

Cytospolide P, a nonanolide isolated from an endophytic fungus *Cytospora* sp. of *Ilex canariensis*. *In vitro* cytotoxicity assay showed the gamma lactone 17 with a potent growth inhibitory activity toward the cell line A-549, while nonanolide (Cytospolides P) with (2*S*) configuration showed potent activity against cell lines A-549, QGY and U973. It has significantly arbitrated G1 arrest in A549 tumor cells, as the role of C-2 methyl in the growth inhibition toward the tumor line [79].

Azalomycin F analogs including 25-malonyl demalony-lazalomycin F5a monoester, 23-valine demalonylazalo-mycin F5a ester, 23-(6-methyl)heptanoic acid demalonylazalomycins F3a ester, F4a ester and F5a ester, 23-(9-methyl) decanoic acid demalonylazalo-mycin F4a ester and 23-(10-methyl)undecanoic acid demalonylazalomycin F4a ester were isolated from endophytic fungus *Streptomyces* sp. 211726. All seven compounds exhibited good antimicrobial and anti HCT-116 activities (IC_{50} values of 1.81–5.00 µg/ml) [80].

Peptides

Leucinostatin A, a peptide was isolated from cultures of *Penicillium lilacum*, having potent biological activity against several different cell lines [81]. It inhibited prostate CA growth through reduced insulin-like growth factor-I expression in prostate stromal cells [82]. Leucinostatin A was also isolated from an endophytic fungus *Acremonium* sp. of European yew, *Taxus baccata*. The fungal endophyte also produced leucinostatin A beta di-O-glucoside from leucinostatin A which had an LD_{50} (50% lethal dose) of>25 nM against breast CA cell line BT-20, compared to leucinostatin A, which had an LD_{50} of 2 nM [83].

Verticillin D, depsipeptides pullularin A, C was isolated from endophytic fungus *Bionectria ochroleuca* of the inner leaf tissues of *Sonneratia caseolaris* (Sonneratiaceae). It showed good cytotoxic activity against the L5178Y cell line. Pullularin A, C and E showed EC_{50} values ranging between 0.1 and 6.7 µg/ml [84].

Beauvericin is depsipeptide, was isolated from *Aspergillus terreus* (No. GX7-3B), an endophytic fungus of *Bruguiera gymnoihiza* [85]. It was previously isolated from several other fungi [54]. The compound showed moderate cytotoxic activities with IC_{50} values 2.02 (MCF-7), 0.82 (A549), 1.14 (HeLa) and 1.10 µm (KB). It was also isolated from endophytic fungus *Fusarium oxysporum* EPH2RAA of the Sonoran desert plant *Ephedra fasciculata*. It inhibited

migration of PC-3M and MDA-MB-231 cells and antiangiogenic activity against HUVEC-2 cells in sublethal concentrations. It showed cytotoxic activity against four different cell lines, human CNS CA glioma (SF-268), human breast CA (MCF-7), human pancreatic CA (MIA Pa Ca-2) and human non-small-cell lung CA (NCI-H460) with IC_{50} values of 2.29, 1.81, 1.66 and 1.41 μM, respectively [86]. It was also isolated from mangrove endophytic fungi *Fusarium* sp. (DZ27), which inhibited growth of KB and KBv200 cells potently with IC50 values of 5.76 and 5.34 μM respectively [87].

Peroxides

Talaperoxides B and D, are norsesquiterpene peroxides isolated from an endophytic fungus, *Talaromyces flavus* collected from mangrove plant *Sonneratia apetala*. It showed *in vitro* cytotoxic activities against MCF-7, MDA-MB-435, HepG2, HeLa and PC-3 cell lines with IC_{50} values ranging between 0.70 and 2.78 μg/ml [88].

Polyketides

Sequoiatone A and B are novel polyketides isolated from fungus *Aspergillus parasiticus*, an endophyte of the bark of *Sequoia sempervirens*. The test results from the NCI human tumor 60 cell-line screen exhibited moderate activity and greatest efficacy against breast CA cell lines. The GI_{50} values of the compounds were between 4–10 μM and LC_{50} values>100 μM [89].

Sequoiamonascin A and B were isolated from *Aspergillus parasiticus* of a redwood tree bark, *Sequoia sempervirens*. The compound A and B exhibited cytotoxic activity against MCF-7, NCIH460, and SF-268 cell lines. In the 60-human cell line assay, compound A showed a median log GI_{50} of-5.00, below the potency threshold established by NCI [90].

Bikaverin, a polyketide was isolated from endophytic fungus *Fusarium oxysporum* strain CECIS of *Cylindropuntia echinocarpus*. It showed cytotoxicity against a panel of four sentinel CA cell lines, MCF-7 (breast), MIAPa Ca-2 (pancreatic), NCI-H460 (non-small-cell lung) and SF-268 (CNS glioma) with IC_{50} values of 0.42, 0.26, 0.43, and 0.38 μM, respectively. Doxorubicin was standard compound with IC_{50} values 0.07, 0.05, 0.01, and 0.04 μM respectively. The cytotoxic activity of bikaverin was due to its hydroxy group [86].

A new polyketide, 2-(7'-hydroxyoxooctyl)-3-hydroxy-5-methoxy-benzene acetic acid ethyl ester was isolated from mangrove endophyte *Phomopsis* sp. ZSU-H76 of the stem of *Excoecaria agallocha* from Dong Zai, Hainan, China. Compound A exhibited cytotoxicity against HEp-2 with IC_{50} values of 25 and 30 μg/ml for HepG2 cell lines [91].

Oblongolide, a polyketide was isolated from fungus *Phomopsis* sp. BCC 9789 associated with *Musa acuminata* (wild banana). Two compounds, oblongolide Y and Z showed cytotoxic activity against CA cell lines. Compound Y showed cytotoxic activity against BC cell line with an IC_{50} value of 48 μM. Compound Z exhibited cytotoxicity against BC, KB (human oral epidermoid CA), and NCI-H187 (small-cell lung CA), and non-malignant (Vero) cell lines with IC_{50} values of 26, 37, 32 and 60 μM, compared to doxorubicin as a positive control, which had IC_{50} values of 0.30 μM (BC), 0.24 μM (KB), and 0.08 μM (NCI-H187) [92].

Kasanosins A and B are novel azaphilones, isolated from cultures of *Talaromyces* sp. of seaweed. These compounds selectively inhibited specific DNA polymerases. Compound A was more potent than B, with IC_{50} values of 27.3 (DNA pol β) and 35.0 mM (DNA pol γ). The specificity of compounds toward DNA polymerase families might be useful in the development of anti-CA chemotherapy agents [93].

Hypericin, a naphthodianthrone derivative, is a plant derived isolate from the herb *Hypericum perforatum* (St. John's Wort). Hypericin had been reported effective in the treatment of depression, potent MAO inhibitor [94] and potent antiviral against a plethora of enveloped viruses [95]. In India, harvesting was done for the first time for isolation of hypericin and emodin from an endophyte *Thielavia subthermophila* from stem of *H. perforatum* [96].

Rubrofusarin B, naphtha-g-pyrone was isolated from an endophyte *Aspergillus niger* IFB-E003 of *Cynodon dactylon*. It showed cytotoxicity against colon cancer cell line SW1116, with an IC_{50} value of 4.5 μg/ml compared to the positive control 5-fluorouracil at 5 μg/ml [97].

The new S-containing benzophenone dimer guigna-sulfide was isolated from an endophytic fungus *Guignardia* sp. IFB-E028 of *Hopea hainanensis*. It exhibited cytotoxic activity (IC_{50}.5.2±0.4 μm) against the human liver cancer cell line HepG2 [98].

Penicitide A, polyketide derivative isolated from endophytic fungus *Penicillium chrysogenum* QEN-24S from *Laurencia,* an unidentified marine red alga. It showed cytotoxic effect against human hepatocellular liver carcinoma cell line with moderate cytotoxic activity [99].

Sclerotiorin is azaphilone polyketide obtained from an endophytic fungus *Cephalotheca faveolata* of *Eugenia jambolana*. It was found to be potent anti-proliferative against different CA cells, which caused apoptosis of colon CA (HCT-116) cells through the activation of BAX and down-regulation of BCL-2 [100].

Polyketide and benzopyran compounds isolated from *Phoma* sp., endophytic fungi of *Cinnamomum mollissimum*. 4-hydroxymellein (polyketide) showed high inhibitory activity (94.6%) whereas 4,8-dihydroxy-6-methoxy-3-methyl-3,4-dihydro-1H-isochromen-1-one (benzopyran) exhibited moderate inhibitory activity (48.8%) against P388 murine leukemic cell [101].

Pyrans and pyrones

(2*R**, 4*R**)-3, 4-dihydro-4-methoxy-2-methyl-2H-1-benzopyran-5-ol, a new benzopyran was isolated from an endophytic fungus *Nodulisporium* sp. A4, of *Aquilaria sinensis*. The compound showed less cytoxicity (57.9% inhibition rate) against the SF-268 cell line at 100 μg/ml concentration, compared with the positive control, cisplatin [102].

The genus *Aspergillus* is the main genus from which compounds pyrone or its derivatives have been produced. Three a pyrone derivatives nigerapyrones B, D, E and one known congener, asnipyrone A have been isolated from *Aspergillus niger* MA-132, an endophytic fungus isolated from *Avicennia marina*. The four compounds showed less cytotoxicity against some of the tested (Du145, HepG2, MCF-7, MDA-MB-231and NCI-H460) tumor cell lines [103].

A monomeric naphtho-g-pyrones, TMC 256 A1 isolated from the mangrove endophytic fungus *Aspergillus tubingensis* (GX1-5E) exhibited *in vitro* cytotoxicity activities against tumor cell lines of MCF-7, MDA-MB-435, Hep3B, Huh7, SNB19 and U87 MG (IC_{50} values 19.92-47.98 μM) [104].

Quinones

Torreyanic acid, dimeric quinine isolated from an endophyte *Pestalotiopsis microspora* of *Torreya taxifolia,* causes cell death by apoptosis. It showed cytotoxicity with IC_{50} values were between 3.5μg/ml for human colorectal neuroendocrine cell CA (NEC) to 45μg/ml for human adenocarcinoma alveolar basal epithelial cells (A549), with a mean value of 9.4μg/ml for 25 different cell lines. It also showed G1 arrest of G0 synchronized cells at the 1–5 μg/ml level depending on the cell line [105].

Anti CA compounds have been isolated from *Stemphylium globuliferum*, an endophyte of the Egyptian medicinal plant *Mentha pulegium*. Among compounds unresolved mixture of alterporriol G and its atropisomer alterporriol H exhibit cytotoxicity against L5178Y mouse lymphoma cells, with an EC_{50} value of 2.7μg/ml. The compound 6-O-methylalaternin also exhibited potent cytotoxicity, with an EC_{50} value of 4.2μg/ml. Kahalalide F tested as a positive control and exhibited an EC_{50} value of 6.3μg/ml. The atropisomers and 6-O-methylalaternin compounds were the most potent kinase inhibitors, displaying EC_{50} values between 0.64 and 1.4μg/ml towards each kinase [106].

Cochliodinol and isocochliodinol are compounds isolated from an endophytic fungus *Chaetomium* sp. which separated from the stem of *Salvia officinalis*. These exhibited cytotoxicity against L5178Y mouse lymphoma cells. Cochliodinol was in order of magnitude more potent than its isomer, with an EC_{50} of 7.0µg/ml, compared to 71.5µg/ml for compound [107].

2-chloro-5-methoxy-3-methylcyclohexa-2,5-diene-1,4-dione, a novel benzoquinone derivative isolated from *Xylaria* sp., an endophytic fungus of *Sandoricum koetjape* exhibited potent cytotoxicity against Vero cells with an IC_{50} value of 1.35 µM compared to the positive control ellipticine, with an IC_{50} value of 2.03 µM [108].

Alterporriol K and L, anthraquinone compounds were separated from extracts of the endophytic fungus *Alternaria* sp. ZJ9-6B of *Aegiceras corniculatum*. It showed moderate cytotoxic activity against breast CA cell line MDA-MB-435 and MCF-7 with IC_{50} values ranging from 13.1 to 29.1 µM [109].

Altersolanol A a natural product isolated from the endophytic fungus *Stemphylium globuliferum* of the medicinal plant, *Mentha pulegium* (Lamiaceae) showed cytotoxic activity against K562 leukemia and A549 CA cells. It induced cell death by apoptosis through the cleavage of caspase-3 and-9 and decrease of anti-apoptotic protein expression [110].

Steroids

Penicisteroids A and B are polyoxygenated steroids obtained from *Penicillium chrysogenum* QEN-24S, an endophytic fungus isolated from *Laurencia,* marine red alga. Penicisteroid A displayed potent cytotoxic activity [99].

Nigerasterols A and B are new 6,8 (14),22-hexadehydro-5a,9a-epidioxy-3,15-dihydroxy sterols isolated from an endophytic fungus *Aspergillus niger* MA-132 of the plant *Avicennia marina*. Nigerasterol B displayed potent activity against the tumor cell line and A541 with an IC_{50} value of 1.50 and 1.82 µm respectively, while nigerasterol A displayed stronger activity against HL60 with an IC_{50} value of 0.30 µM [111]. Another compound 3b, 5a-dihydroxy-(22E, 24R)-ergosta-7, 22-dien-6-one is a phytoecdysteroids isolated from mangrove endophytic fungus *Aspergillus terreus* of *Bruguiera gymnoihiza*. The compound exhibited potent cytotoxic activities against cancer cell lines with IC_{50} values 4.98 (MCF-7), 1.95 (A549), 0.68 (HeLa) and 1.50 µM (KB) [112].

Stilbene

Resveratrodehydes A–C was isolated from the mangrove endophytic fungus *Alternaria* sp. R6. It showed inhibitory activity against MDA-MB-435, HepG2, and HCT-116 (IC_{50}<50 µM) by MTT assay. Compounds A and B exhibited potent cytotoxic activities (IC_{50}<10 µM) against MDA-MB-435 and HCT-116 cell lines [113].

Diterpenes

Periconicin B, a fusicoccane diterpene from the endophytic fungus *Periconia atropurpurea* of *Xylopia aromatica* showed potent cytotoxic activity against HeLa and CHO (Chinese hamster ovary), with an IC_{50} of 8.0 µM. It exhibited potency similar to that of antineoplastic agent cisplatin (IC_{50} 5.0 µM) used as a cytotoxic positive control [114].

19-(2-acetamido-2-deoxy-a-Dglucopyranosyloxy)isopimara-7,15-dien-3b-ol and 19-(a-D-glucopyranosyloxy) isopimara-7, 15-dien-3-one, isopimarane diterpenes isolated from the endophytic fungus *Paraconiothyrium* sp. MY-42 showed moderate cytotoxicities against HL60 cell line [115].

Sphaeropsidins A and D, diterpenes isolated from *Smardaea* sp. AZ0432 of the moss *Ceratodon purpureus*. Together with one sphaeropsidins A derivative, 6-O-acetylsphaeropsidin A showed significant cytotoxic activity. Sphaeropsidin A showed cell-type selectivity in the cytotoxicity assay, while it inhibited migration of MDA-MB-231 cells at subcytotoxic concentrations [116, 117].

Sesquiterpenes

Merulin A, and merulin C are the two new sesquiterpenes produced by the endophytic fungus XG8D isolated from *Xylocarpus granatum* (Meliaceae). Compound A exhibited cytotoxicity against BT474 and SW620 cell lines with IC_{50} values of 4.98 and 4.84 µg/ml, while compound C exhibited IC_{50} values of 1.57 and 4.11 µg/ml, respectively. The standard compared to doxorubicin as a positive control with IC_{50} values of 0.53 and 0.09µg/ml against BT474 and SW620 cell lines, respectively [118].

Eremophilanolide is an eremophilane-type sesquiterpenes isolated from the endophyte *Xylaria* sp. BCC 21097 of *Licuala spinosa*. Its three novel compounds possess an alpha-methylene-gamma-lactone, eremophilanolide 1, 2 and 3 exhibited moderate cytotoxic activity with IC_{50} values of 3.8–21 µM against CA cell lines KB, MCF-7, and NCI-H187 [119].

Ceriponols F, G and K, are tremulane sesquiterpenes isolated from endophytic fungus *Ceriporia lacerate* of *Huperzia serrata*. Ceriponols F and K revealed moderate cytotoxicity against HeLa, HepG2 and SGC 7901 (IC_{50}=32.3±0.4 to 173.2±1.5 µM), while slightly better cytotoxicity was observed with ceriponol G against a HeLa cell line [120].

Triterpenes

Xylariacins A, B, C three new triterpenes were isolated from the fermentation extract from *Xylarialean* sp. A45, an endophytic fungus from *Annona squamosa* L. Their structures were determined by NMR and mass spectrometry. Xylariacin A-C showed modest cytotoxic activity against human tumor cell line HepG2 [121].

(+)-(3*S*, 6*S*, 7*R*, 8*S*)-periconone A and (-)-1*R*, 4*R*, 6*S*, 7*S*)-2-caren-4, 8-olide, new terpenoids isolated from an endophytic fungus *Periconia* sp. of plant *Annona muricata*. The *in vitro* assays of these two compounds showed low cytotoxic activities against six human tumor cell lines (A549, A2780, Bel-7402, BGC-823, HCT-8 and MCF-7) [122].

Xanthones

Phomoxanthones A and B were isolated from an endophytic fungus *Phomopsis* sp. BCC 1323 of *Tectona grandis*. Phomoxanthones A showed cytotoxic activity against KB cells, BC-1 cells and non-malignant Vero cells with IC_{50} values of 0.99, 0.51 and 1.4 mg/ml, respectively, while Phomoxanthones B had IC_{50} values of 4.1, 0.70 and 1.8 mg/ml, compared to the standard compound ellipticine, which had IC_{50} values of 0.46 mg/ml of KB cells and 0.60 mg/ml of BC-1 cells respectively [123].

CONCLUSION

This review highlights the role of natural products in drug discovery, endophytic fungi–their occurrence and importance as an alternative source of secondary metabolites with potential antiCA activity. Escalating cancer patient death rate, poor availability to chemotherapy and their side effects, high cost and multi-drug-resistance worsen the scenario of CA treatment. Fungal endophyte, which resides in specialized niche are constantly in a state of 'metabolic aggressiveness', thereby synthesizing an inimitable array of metabolites, exhibiting a plethora of antiCA efforts with different chemical classes.

In the near future, the search for isolation and identification of new endophytic fungi producing antiCA agents, their cultivation and improvement in fermentation conditions and study on molecular insight will endow us with a greater opportunity in combating the battle against CA. There are good prospects for understanding molecular mechanisms into drug discovery and clinical efficacy by the continued study of endophytes, which will pave the path for effective prevention and treatment of CA.

ACKNOWLEDGEMENT

The authors are thankful to Ms. Megha Vijayawargiaya, Director HR, and Dr. Vijay Thawani Director CSRD for providing laboratory facilities and Sarvajanik Jankalyan Parmarthik Nyas, People's Group for granting financial assistance to carry out the present research work.

CONFLICT OF INTERESTS

The authors declare no conflict of interest

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How to cite this article

Anand Dilip Firodiya, Rajesh Kumar Tenguria. Endophytic fungi: treasure for anti-cancerous compounds. Int J Pharm Pharm Sci 2016;8(8):35-42.