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Anticarcinogenic Properties of Metabolites Extracted from Endophytic Fungi: A Review of the Literature

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ABSTRACT: In the field of research into new cancer treatment alternatives, compounds from natural sources are being explored, such as endophytic fungi which have significant potential because of their fast growth and low-cost scalable production. Mechanisms of action of metabolites produced are not completely clear. A search strategy on PubMed was based on a research PICOT question searching research papers between 2015 and 2024 in english or spanish. 197 papers were obtained and 67 articles remained eligible after the selection process. Different endophytic producing fungi were recorded, active compounds were classified on tables according to their cytotoxicity shown by each cell line. The most commonly used cell lines were the cervical cancer cell line HeLa, as well as the hepatocellular carcinoma cell line HepG2. Studies evaluated in the present review were mostly exclusively in vitro and up to seven mechanisms of action were explained. Our review coincides with the presence of these mechanisms of action and it is hoped that the routes proposed by previous research may favor the search for anticancer treatments in the near future. Although it is true that we were able to extract exhaustively the articles related to the subject, studies with more databases that can complete the vision of endophytic fungi in anticancer management are required. Several of the compounds evaluated have outperformed the results of chemotherapy-related drugs, so it is expected that several of them can continue with the next phases to obtain better therapies against cancer.

1. INTRODUCTION

Cancer, a pathology characterized by the uncontrolled proliferation of cells and their dissemination to adjacent tissues (Krieghoff-Henning et al., 2017), currently represents one of the main causes of mortality worldwide (*Estadísticas del cáncer—NCI*, n.d.). The current therapeutic approach to neoplasms includes both pharmacological interventions (such as chemotherapy, immunotherapy and radiotherapy) and non-pharmacological interventions (resection surgery). However, the identification of novel, accessible and effective treatments remains essential to improve patient survival. In addition, cancer prevention through the reduction of risk factors and the implementation of appropriate screening strategies is equally relevant.

In the field of research into new cancer treatments, compounds from natural sources are being explored, including those derived from endophytic fungi, which have significant potential. Endophytic fungi are symbiotic microorganisms that inhabit plant tissues such as leaves, roots and bark, establishing a mutualistic relationship with their hosts by conferring resistance to phytopathogens and, in exchange, obtaining nutrients.

In addition, these fungi can be used in the treatment of diseases because they require little space for their cultivation, have a rapid growth and their production can be scaled up to an industrial level at low cost. From them, several metabolites have been identified, such as paclitaxel, terpenoids and polysaccharides, increasing the knowledge about their properties and mechanisms of action through in vitro studies with representative cell lines such as HeLa or MCF-7.

It should be noted that the mechanisms of action of these metabolites are not fully elucidated; some hypotheses postulate the activation of proapoptotic caspases, generation of reactive oxygen species and depolymerization of microtubules.

It is essential to review the current findings in order to raise new hypotheses that favor the advancement of research towards new therapeutic possibilities. Therefore, the aim of the following review is to report the metabolites derived from endophytic fungi with anticarcinogenic properties identified so far and to describe the mechanisms of action involved.

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2. METHODOLOGY

2.1. Search Strategy in PubMed and PICOT question

In order to elaborate the search strategy in PubMed, it was followed a research PICOT question, in which was determined the population as cancer cell lines (not specified in the search strategy); the intervention was conformed by the families, species or active substances of possible endophytic fungi with anticancer activity.

The comparator was not defined in the search strategy either, but it was expected to be rather conventional therapy or a placebo.

The outcome was defined on the basis of cancer cell mortality, and the variation of indicators of anticarcinogenic activity (inhibition of tumor growth, decrease in cell proliferation, half of the maximum inhibitory concentration, etc.); finally, the type of study considered was preclinical, those in vitro, in vivo or in silico.

The strategy in PubMed executed on April 23, 2024, (”Endophyte”[Mesh] OR endophyt*[tiab]) AND (”Neoplasms”[Mesh] OR Neoplasm*[tiab] OR ”Carcinogenesis”[Mesh] OR Carcinogenesis[tiab] OR ”Cell Proliferation”[Mesh] OR ”Antineoplastic Agents”[Mesh] OR Antineoplastic Agents[tiab] OR cell cycle arrest[tiab] OR metastasis inhibition[tiab] OR anticancer*[tiab]) AND (preclinic*[tiab] OR ”in vitro”[tiab] OR ”in vivo”[tiab] OR ”ex vivo”[tiab]) NOT (Case Reports[Publication Type]), yielded 197 results.

2.2. Inclusion and Exclusion Criteria

From the 197 results obtained, we excluded studies that were not conducted between 2015 to 2024, clinical studies, studies of anticarcinogenic secondary metabolites isolated from endophytic bacteria, those in a language other than English or Spanish, those that did not test the cytotoxicity of metabolites on cancer cells, and those that used the endophytic fungus as a chassis to confer anticarcinogenic properties to compounds.

2.3. Selection Process

In the present review, a total of 197 articles identified in Pubmed were obtained, of which those that were duplicated or not written in English or Spanish were removed, leaving 191 articles for the screening phase. The screening consisted of evaluating whether the study was potentially eligible based on the title and abstract, where they were distributed in such a way that each article had to be evaluated by a minimum of two researchers, and in case of controversy or doubt, the entire team of researchers was called to evaluate the inclusion or exclusion of the article.

After applying the aforementioned inclusion and exclusion criteria and evaluating articles for retrieval, a total of 67 eligible articles were obtained and included in the review.

3. RESULTS AND DISCUSSION

3.1. Cytotoxicity

Different endophytic producing fungi were recorded, among which the genera Alternaria, Aspergillus, Fusarium, Penicillium and Phomopsis stand out. The active compounds were classified according to their cytotoxicity shown by each cell line (Tables 1 and 6). The most commonly used cell lines were the cervical cancer cell line HeLa, as well as the hepatocellular carcinoma cell line HepG2. Gastric cancer cells, hepatocellular carcinomas, colon carcinoma, melanomas, leukemia line, breast cancer line, ovarian cancer, among others, were also used.

The studies evaluated in the present review were mostly exclusively in vitro, with the exception of Hoque et al. (Hoque et al., 2022) and Da Tang et al (Tang et al., 2022), which were performed in silico, the first one with the aim of evaluating the different active compounds of the fungus Fusarium oxysporum in the colon carcinoma line HCC 2998m, Oligodendroglioma (Hs 683) among others, where it was concluded that 3β, 5α-dihydroxy -ergosta-7, 22-dien-6-one [1], 3β, 5α, 9α-trihydroxy-ergosta-7,22-dien-6-one [2] and beauvericin [5] as cytotoxic agents, however, the compounds p-hydroxybenzaldehyde [3] and 3-(R)-7-butyl-6,8-dihydroxy-3-pent-11-enylisochroman-1-one [4] were found to be mutagenic. The second one evaluated Porric acid E in HT29 cells.

Although several active compounds have shown cytotoxicity to cancer cell lines, polonicin A, polonicin B and 3,5 -hydroxydihydrofusarubins D, derived from Penicillium polonicum, did not achieve this objective according to Wen et al (Wen et al., 2020), however, they have antidiabetic activity by increasing glucose uptake.

Another fungus that did not obtain cytotoxicity from its derivatives was Aspergillus fumigatus (Astuti et al., 2020), whose compounds did not show cytotoxicity against T47D breast cancer in synergy with doxorubicin (Dox).

4. MECHANISMS STUDIED

4.1. Celular Cycle arrest

Trichothecin (TCN) promotes the expression of Dehydrogenase Reductase member 2 (DHRS2) in in vitro studies with the nasopharyngeal carcinoma cell line NPC. An alteration of the cellular lipid profile associated with DHRS2 overexpression was demonstrated by gas chromatography coupled to mass spectrometry. DHRS2 evidences a close association with inhibition of cell proliferation, migration, and quiescence in the cell lines examined (Luo et al., 2019). In addition, RNA sequencing was performed to identify genes involved with the anticarcinogenic effects of TCN.

Ascomylactam A (AsA) showed growth inhibition in 6 lung cancer cell lines (L. Wang et al., 2020). These effects were seen by phase contrast microscopy after 48 h exposure at different concentration levels (IC50: 4-8 uM).

Table 1
Digestive Cancer Line

Cell line	Scientific name of the fungus	Active Compound	Cytotoxicity (IC50 - IC75) / Growth Inhibition Rate (%)	Reference
251L gastric cancer line	*Phomopsis sp.*	Altersolanol A	IC50 = 0.052 ug/ml	(Mishra et al., 2015)
gastric cancer line SGC-7901	*Alternaria sp*	tricycloalternarene 3a (3)	IC50 = 53.2 ± 2.9	(Shen et al., 2018)
		ACTG-Toxin D (6)	IC50 = 35.1 ± 0.8 μg/mL	
Stomach Adenocarcinoma AGS Cell line	*Aspergillus spp.*	aspertaichamide A (1)	ID50 = 1.7 μM	(Y. Chen et al., 2024)
colon cancer line Caco-2	*Pichia kudriavzevii, Fusarium oxysporum, Mucor circinelloide, Trametes versicolor, Polyporales sp., Bjerkandera adusta, Fusarium tricinctum*	IIIM2	100.00 ± 0.00%	(Dar et al., 2016)
		IIIM3	76.00 ± 1.00%	
		IIIM7	72.00 ± 2.00%	
		IIIM8	100.00 ± 0.00%	
	Aspergillus terreus	Fungal mycelia fermented in Modified Potato Dextrose Broth (MPDB)	IC50 = 7.3 ± 0.004 μg mL-1	(El-Hawary et al., 2023)
Colon cancer line SW620	*Clonostachys sp*	Clonostachys sp Compound 5	IC50 = 66.55 ± 0.82 μM	(M. Wang et al., 2023)
colon carcinoma CXF HT29 colon carcinoma line	*Phomopsis sp.*	Altersolanol A	IC50 = 0.001 ug/ml	(Mishra et al., 2015)
colon carcinoma line DLD1	*Penicillium ochrochloronthe*	Trichodermic Acid	IC50 = 3.866 μg/mL	(Qu et al., 2021)
HCT colon carcinoma line	*Aspergillus TRL1*	pulchranin A	IC50 = 63, 80 and 91 mg/Ml	(Moussa et al., 2020)
colon carcinoma line HCT116	*Aspergillus terreus*	Cowabenzophenone A	IC50 = 10.1 μM	(Ukwatta, Lawrence, & Wijayarathna, 2019)
	Fusarium chlamydosporium	Fusarithioamide B (6)	IC50 = 0.59 μM, respectively compared to doxorubicin 0.24 μM	(Ibrahim et al., 2018)
	Hypomontagnella monticulosa	griffthiiene	IC50 = 0.05 ppm	(Lutfia et al., 2021)
		scalaradial	IC50 = 0.67 ppm	
	Lasiodiplodia sp. 318.	Lasiodiplodins	IC50 = 11.92 mM	(Li et al., 2016)

	Nigrospora sphaerica	nigronapthaphenyl	IC50 = 9.62 ± 0.5 uM	(Ukwatta, Lawrence, & Wijayarathne, 2019)
	Penicillium ochrochloronthe	Trichodermic Acid	IC50 = 3,410 µg/Ml	(Qu et al., 2021)
	Phoma multirostrata	Ergocytochalasin A	IC50 = 22.28 ± 2.65	(Peng et al., 2020)
HT29 colon carcinoma line	*Alternaria sp. sb23*	1,2,3: Alterchothecenes A,B,C; (4), trichothecinol A (5), 8-dihydrotrichothecinol A (6)	(4) IC50 = 9.38, (5) IC50 = 5.29, (6) IC50 = 9.02 uM	(Gao et al., 2020)
	Ovatospora senegalensis NR-03 (1), Thielavia subthermophila NR-06 (3)	Extracts in general	(1) IC50 = 0.1 ± .004 ug/ml) (3) IC50 = (3.85 ± 0.15 ug/ml)	(Niu et al., 2022)
	Phoma multirostrata	Ergocytochalasin A	IC50 = 15.23 ± 0.67 µM	(Peng et al., 2020)
murine colon carcinoma line CT26	*Phoma multirostrata*	Ergocytochalasin A	IC50 = 6.92 ± 0.71 µM	(Peng et al., 2020)
hepatocellular carcinoma line HCC	*Alternaria alternata MGTMMP031*	alternariol methyl ether (AME)	IC50 = 50 umol-1	(Palanichamy et al., 2019)
hepatocellular carcinoma line HepG2	*Aspergillus TRL1*	pulchranin A	IC50 = 63, 80 and 91 mg/mL	(Moussa et al., 2020)
	Aspergillus terreus	Fungal mycelia fermented in Modified Potato Dextrose Broth (MPDB)	IC50 = 4.2 ± 0.13 µg mL-1	(El-Hawary et al., 2023)
	Bipolaris sorokiniana	Isocochlioquinones D, E (1, 2), cochlioquinones G, H (3, 4) and analogs (5-9)	IC50 = 1.2 uM	(M. Wang et al., 2016)
	Cerrena sp. A593	Cerrenins D (1)	IC50 = 44.32 uM	(H.-X. Liu et al., 2020)
	Colletrichum gloesporioides A12	Compounds not known 1 may be nigrosporanenas A and B	IC50 = 46.8 uM	(H.-X. Liu et al., 2018)
	Cytospora rhizophorae	Cytorhizins A-D (1-4)	IC50 = 29.4 ± 4.4 uM	(H. Liu, Tan, et al., 2019)
		new compounds (1-3), named as cytosporaphenones A-C	(1) IC50 = 60 uM	(H.-X. Liu et al., 2017)
	Cytospora rhizophorae A761	Cytorhizins A, B, C,D	The cytotoxic activity is weak, compound 1 and 4 have no cytotoxicity. 2 and 3 have cytotoxicity against all lines between 29.4 to 68.6 uM.	(H. Liu, Tan, et al., 2019)

	Diaporthe lithocarpus A740.	One new benzophenone derivative, named tenllone I (1), two new eremophilane derivatives lithocarins B (2) and C (3), and a new monoterpentoid lithocarin D (4)	Compounds 2, 3, and 5 showed weak inhibitory activities against tumor cell lines. IC50 30-100uM	(H. Liu, Chen, et al., 2019)
	Lasiodiplodia sp. 318.	Lasiodiplodins	IC50 = 12.5 mM	(Li et al., 2016)
	Lasiodiplodia theobromae ZJ-HQ1	Chloropreussomerins A and B (1 and 2), and analogues 3-11	4-7 inhibit cell growth of HepG2 (3.8 ± 0.9 uM, 4.4 ± 0.5 uM, 8.5 ± 0.8 uM, 3.6 ± 0.6 uM)	(S. Chen et al., 2016)
	Pestalotiopsis microspora	7-epi-10-deacetyltaxol	IC50 = 32.1 μM	(Subban et al., 2017)
	pestalotiopsis sp HQD-6	demethylincisterol a3 (Sdy-1)	IC50 = 14.16 ± 0.56 nM/m	(Sun et al., 2022)
	Pestalotiopsis sp.	demethylincisterol A3 (1), ergosta-5,7,22-trien-3-ol (4), stigmastan-3-one (6), stigmast-4-en-3-one (7), stigmast-4-en-6 -ol-3-one (8), flufuran (9)	1, 4 and 6-9 inhibit growth of HeLa, A549 and HepG2.	(C. Chen et al., 2017)
	Phoma multirostrata	Ergocytochalasin A	IC50 = 21.32 ± 0.3	(Peng et al., 2020)
	Trichoderma viride	Trichoderma viride L-asparaginase	IC50 = 21.2 g/mL	(El-Ghonemy et al., 2023)
hepatocellular carcinoma line SMMC-7721	*Alternaria sp*	2H-(2E)-tricycloalternarene 12a (1), tricycloalternarene 3a (3), tricycloalternarene F (4),	1, 3, and 4 inhibit SMMC-772 cell growth (IC50 values of 49.7 ± 1.1, 45.8 ± 4.6, and 80.3 ± 3.8 μg/mL), respectively.	(Shen et al., 2018)
	Aspergillus terreus.	Fumigaclavine I	Growth inhibition rate being 20.3% at 10 μg-mL-1	(Shen et al., 2015)
pancreatic cancer PAXF 1657L	*Phomopsis sp.*	Altersolanol A	IC50 = 0.049 ug/ml	(Mishra et al., 2015)
pancreatic cancer PAXF PANC1	*Hypomontagnella monticulosa*	griffthiiene	IC50 = 0.05 ppm	(Lutfia et al., 2021)

Table 2
Neurological Cancer Line

Cell line	*Scientific name of the fungus*	Active Compound	Cytotoxicity (IC50 - IC75)	Ref
IMR-32 neuroblastoma line	*Pichia kudriavzevii, Fusarium oxysporum, Mucor circinelloide, Trametes versicolor, Polyporales sp., Bjerkandera adusta, Fusarium tricinctum*	IIIM2	67.00 ± 1.00%	(Dar et al., 2016)
		IIIM3	22.00 ± 2.00%	
		IIIM7	37.00 ± 1.00%	
		IIIM8	10.00 ± 1.00%	
SGC 7901 cells	*endophytic fungus xkc-s03*	petroleum ether (S03-PE)	25.89 μg/ml	(Tan et al., 2015)
glioblastoma line 498NL	*Phomopsis sp.*	Altersolanol A	IC50 = 0.001 ug/ml	(Mishra et al., 2015)
Glioblastoma line SF-268	*Bipolaris sorokiniana*	Isocochlioquinones D, E (1, 2), cochlioquinones G, H (3, 4) and analogs (5-9)	2, 4 and 7 IC50 = 1.5 uM	(M. Wang et al., 2016)
	Cerrena sp. A593	Cerrenins D (1)	IC50 = 41.01 uM	(H.-X. Liu et al., 2020)
	Colletrichum gloesporioides A12	Compounds not known 1 may be nigrosporanenas A	IC50 = 40.5 uM	(H.-X. Liu et al., 2018)
	Cytospora rhizophorae	Cytorhizins A-D (1-4)	2 and 4 (>100 uM vs all) inhibit SF-268 growth (34.8 ± 1.4 uM).	(H. Liu, Tan, et al., 2019)
	Cytospora rhizophorae A761	Cytorhizins A, B, C, D	The cytotoxic activity is weak, compound 1 and 4 have no cytotoxicity. 2 and 3 have cytotoxicity against all lines between 29.4 to 68.6 uM.	(H. Liu, Tan, et al., 2019)
	Diaporthe lithocarpus A740.	One new benzophenone derivative, named tenllone I (1), two new eremophilane derivatives lithocarins B (2) and C (3), and a new monoterpentoid lithocarin D (4)	IC50 = 30-100uM	(H. Liu, Chen, et al., 2019)
	Phomopsis sp.	Altersolanol A	IC50 = 0.001 ug/ml	(Mishra et al., 2015)

Table 3
Respiratory Cancer Line

Cell line	*Scientific name of the fungus*	Active Compound	Cytotoxicity (IC50 - IC75)	Ref
526L lung cancer line	*Phomopsis sp.*	Altersolanol A	IC50 = 0.001 ug/ml	(Mishra et al., 2015)
629L lung cancer line	*Phomopsis sp.*	Altersolanol A	IC50 = 0.001 ug/ml	
Lung cancer line 95D	*Didymella sp.*	Ascomylactam A	IC50 = 4.39 ± 0.1 – 8.04 ± 0.13 uM	(L. Wang et al., 2020)
LU-1 (Human lung adenocarcinoma)	*Morinda citrifolia Linn. (Noni)*	MRL1-3A	IC50 = 4 µg/mL	(Wu et al., 2015)
		XILP7-2	IC50 = 4 µg/mL	(Wu et al., 2015)
		XILP5	IC50 = 5 µg/mL	(Wu et al., 2015)
Lung cancer line A549	*Alternaria alternata MGTMMP031*	alternariol methyl ether (AME)	IC50 = 75 umol-1	(Palanichamy et al., 2019)
	Alternaria alternata	ethylacetate extract of A.alternata	IC50 = 393.52µg/ml	(Ashoka & Shivanna, 2023)
	Aspergillus terreus (JAS-2)	Terrein	IC50 = 170.99 ± 4.24 and 121.91 ± 4.82 µgml-1	(Goutam et al., 2017)
	Cladosporium cladosporiodes	Cladosporol A	IC50 = 11.7 ± 0.505 µM	(Koul et al., 2017)
	Diaporthe lithocarpus A740.	One new benzophenone derivative, named tenllone I (1), two new eremophilane derivatives lithocarins B (2) and C (3), and a new monoterpentoid lithocarin D (4)	IC50 = 30-100 uM	(H. Liu, Chen, et al., 2019)
	Didymella sp.	Ascomylactam A	Cytotoxicity vs 6 cell lines (IC50 = 4.39 ± 0.1 – 8.04 ± 0.13 uM)	(L. Wang et al., 2020)
	Lasiodiplodia sp. 318.	Lasiodiplodins	IC50 = 13.31 mM	(Li et al., 2016)
	Lasiodiplodia theobromae ZJ-HQ1	Chloropreussomerins A and B (1 and 2), and analogs 3-14	(1) IC50 = 8.5 ± 0.9 uM (2) IC50 = 8.9 ± 0.6 uM). (4-7) IC50 = 5.4 ± 0.3 uM, 9.4 ± 0.8 uM, 6.2 ± 0.1 uM, 7.7 ± 0.5 uM	(S. Chen et al., 2016)
	Meconopsis grandis Prain	Alkaloid D1399	IC50 = 1.18 ± 0.36 µM	(Huang et al., 2023)
	Pestalotiopsis sp	HLP46 (demethylincisterol A(3))	IC50 = 41.46 ± 8.34 µM	(C. Chen et al., 2017)

	Pestalotiopsis sp.	demethylincisterol A3 (1), ergosta-5,7,22-trien-3-ol (4), stigmastan-3-one (6), stigmast-4-en-3-one (7), stigmast-4-en-6 -ol-3-one (8), flufuran (9)	1, 4 and 6-9 inhibit growth of HeLa, A549 and HepG2.	(J. Zhou et al., 2018)
	Phoma multirostrata	Ergocytochalasin A	IC50 = 19.11 ± 0.99 μM	(Peng et al., 2020)
	Phomosis sp., Pestalotiopsis sp., Neofusicoccum sp., Penicillium sp., Hypocrea lixii sp.	Extracts in general 1	64.4%	(H.-X. Liu et al., 2017)
		Extracts in general 10	49.7%	
		Extracts in general 2	59.5%	
		Extracts in general 3	81.9%	
		Extracts in general 4	43.9%	
		Extracts in general 5	58.3%	
		Extracts in general 6	56.2%	
		Extracts in general 7	48.3%	
		Extracts in general 8	42.4%	
		Extracts in general 9	93.0%	
	Phyllosticta elongata MH458897	Camptothecin (CPT)	IC50 = 58.28 μg	(Dhakshinamoorthy et al., 2021)
	Pichia kudriavzevii, Fusarium oxysporum, Mucor circinelloide, Trametes versicolor, Polyporales sp., Bjerkandera adusta, Fusarium tricinctum	IIIM2	75.00 ± 2.00%	(Dar et al., 2016)
		IIIM3	58.00 ± 2.00%	
		IIIM7	70.00 ± 2.00%	
		IIIM8	71.00 ± 3.00%	
non-small cell lung cancer line NCI-H460	*Colletrichum gloesporioides A12*	Compounds not known 1 may be nigrosporanenas A	IC50 = 36.4 uM	(H.-X. Liu et al., 2018)
	Cytospora rhizophorae	Cytorhizins A-D (1-4)	2 and 4 IC50 = 32.8 ± 4.1 uM	(H. Liu, Tan, et al., 2019)
	Cytospora rhizophorae A761	Cytorhizins A, B, C,D	The cytotoxic activity is weak, compound 1 and 4 have no cytotoxicity. 2 and 3 have cytotoxicity against all lines between 29.4 to 68.6 uM.	(H. Liu, Tan, et al., 2019)
non-small cell lung cancer line NCI-H460	*Cerrena sp. A593*	Cerrenins D (1) and E (2), plerocybellone A (3), chloriolin B (4)	(1) IC50 = 29.67 uM	(H.-X. Liu et al., 2020)

	Phomosis sp., Pestalotiopsis sp., Neofusicoccum sp., Penicillium sp., Hypocrea lixii sp.	Extracts in general 1	41.2%	(H.-X. Liu et al., 2017)
		Extracts in general 10	45.6%	
		Extracts in general 2	49.3%	
		Extracts in general 3	82.7%	
		Extracts in general 4	40.7%	
		Extracts in general 5	53.9%	
		Extracts in general 6	52.6%	
		Extracts in general 7	56.8%	
		Extracts in general 8	64.3%	
		Extracts in general 9	91.0 %	
Lung cancer line H1299	*Didymella sp.*	Ascomylactam A	IC50 = 4.39 ± 0.1 − 8.04 ± 0.13 uM	(L. Wang et al., 2020)
Lung cancer line H1975	*Didymella sp.*	Ascomylactam A	IC50 = 4.39 ± 0.1 − 8.04 ± 0.13 uM	
Lung cancer line H226	*Didymella sp.*	Ascomylactam A	IC50 = 4.39 ± 0.1 − 8.04 ± 0.13 uM	
Lung cancer line H460	*Didymella sp.*	Ascomylactam A	IC50 = 4.39 ± 0.1 − 8.04 ± 0.13 uM	

Table 4
Gynecological Cancer

Cell line	*Scientific name of the fungus*	Active Compound	Cytotoxicity (IC50 - IC75)	Ref
MCF-7 breast cancer line	*Alternaria sp. sb23*	1,2,3: Alterchothecenes A,B,C; (4), trichothecinol A (5), 8-dihydrotrichothecinol A (6)	(4) IC50 = 4.59, (5) IC50 = 0.89, (6) IC50 = 0.92 uM	(Gao et al., 2020)
	Aspergillus fumigatus strain KARSV04	pyrophene in synergy with doxorubicin (Dox)	IC50 = 70.57 μg/mL	(Astuti et al., 2020)
	Aspergillus TRL1	Pulchranin A	IC50 = 63, 80 and 91 mg/mL	(Moussa et al., 2020)
	Aspergillus terreus	Fungal mycelia fermented in Modified Potato Dextrose Broth (MPDB)	IC50 = 5.9 ± 0.013 μg mL-1	(El-Hawary et al., 2023)
	A. flavus	Ethyl acetate extract from A. flavus	IC50 = 16.25 μg/mL	(Kalimuthu et al., 2022)
	Bipolaris sorokiniana	Isocochlioquinones D, E (1, 2), cochlioquinones G, H (3, 4) and analogs (5-9)	IC50 = 2.4 uM	(M. Wang et al., 2016)
	Cerrena sp. A593	Cerrenins D (1) and E (2), plerocybellone A (3), chloriolin B (4)	IC50 = 14.43 uM	(H.-X. Liu et al., 2020)
	Cladosporium cladosporiodes	Cladosporol A	IC50 = 8.7 uM	(Koul et al., 2017)
	Colletrichum gloesporioides A12	Compounds not known 1 may be nigrosporanenas A	IC50 = 15.7 uM	(H.-X. Liu et al., 2018)
	Colletotrichum gloeosporioides	Ethyl acetate (EA) extract of C. gloeosporioides	IC50 = 270.70 ± 2.917 μg/mL	(Rai et al., 2023)
	Cytospora rhizophorae	Cytorhizins A-D (1-4)	2 and 4 (>100 uM vs all) inhibit MCF-7 growth (30.1 ± 3.3 uM).	(H. Liu, Tan, et al., 2019)
		new compounds (1-3), named as cytosporaphenones A-C	(1) IC50 = 70 uM	(X. Liu et al., 2017)
	Cytospora rhizophorae A761	Cytorhizins A, B, C,D	The cytotoxic activity is weak, compound 1 and 4 have no cytotoxicity. 2 and 3 have cytotoxicity against all lines between 29.4 to 68.6 uM.	(H. Liu, Tan, et al., 2019)
	Diaporthe lithocarpus A740.	One new benzophenone derivative, named tenllone I (1), two new eremophilane derivatives lithocarins B (2) and C (3), and a new monoterpentoid lithocarin D (4)	Compounds 2, 3, and 5 showed weak inhibitory activities against tumor cell lines. IC50 = 30 − 100 uM	(H. Liu, Chen, et al., 2019)

Fusarium chlamydosporium	Fusarithioamide B (6), a new aminobenzamide derivative with unprecedented carbon skeleton	6 It had a selective and potent effect towards MCF-7 cell lines with IC50s 0.21 compared to doxorubicin (IC50s 0.05 μM).	(Ibrahim et al., 2018)
Lasiodiplodia theobromae ZJ-HQ1	Chloropreussomerins A and B (1 and 2), and analogs 3-13	1 and 2 inhibit MCF-7 cell growth (5.9 ± 0.4 uM and 6.2 ± 0.4 uM), 4-7 inhibit cell growth of MCF-7 (2.5 ± 0.2 uM, 2.6 ± 0.2 uM, 4.2 ± 0.6 uM, 3.1 ± 0.2 uM)	(S. Chen et al., 2016)
Morinda citrifolia Linn. (Noni)	MRL1-3A	IC50 = 2 μg/mL	(Wu et al., 2015)
	XILP7-2	IC50 = 0.6 μg/mL	(Wu et al., 2015)
	XILP5	IC50 = 10 μg/mL	(Wu et al., 2015)
Ovatospora senegalensis NR-03 (1), Chaetomium globosum NR-04 (2), Thielavia subthermophila NR-06 (3), Aspergillus calidoustus NR-10 (4), Aspergillus keveii XJF-23 (5), Aspergillus terreus XJF-3 (6)	Extracts in general	(3) IC50 = 9.99 ± 0.69 ug/ml	(Niu et al., 2022)
Paraconiothyrium brasiliense	Brasilamide analog E 12b	IC50 = 0.24 ± 0.050	(Zhang et al., 2016)
	Brasilamide E	IC50 = 8.47 ± 0.36	
Penicillium oxalicum	Penicillium oxalicum (POAgNPs)	IC50 = 40.038 ± 1.022 μg/mL	(P. Gupta et al., 2022)
Penicillium ramusculum	Crude extract derived from P. ramusculum	IC50 = 17.23 ± 1.43 μg/mL	(Varghese et al., 2024)
Pestalotiopsis sp	HLP46 (demethylincisterol A(3))	IC50 = 37.88 ± 1.72	(C. Chen et al., 2017)
Phoma multirostrata	Ergocytochalasin A	IC50 = 26.63 ± 0.13	(Peng et al., 2020)
Phomopsis sp.	Sir-G5	IC50 = 19.20 μg/mL	(null Minarni et al., 2017)

	Pichia kudriavzevii, Fusarium oxysporum, Mucor circinelloide, Trametes versicolor, Polyporales sp., Bjerkandera adusta, Fusarium tricinctum	IIIM2	53.00 ± 2.00%	(Dar et al., 2016)
		IIIM3	50.00 ± 3.00%	
		IIIM7	48.00 ± 2.00%	
		IIIM8	73.00 ± 2.00%	
	Trichoderma harzianum	L-methioninase	IC50 = 5.0 µg/m	(Ashkan et al., 2023)
Invasive ductal tumor BT-549	*Fusarium chlamydosporium*	fusarithioamide A (2-(2-(2-aminopropanamido)-N-(1-hydroxy-3-mercaptopropyl) benzamide, (4)	Compounds 4 possessed potent and selective activity towards BT-549 0.4 µM, compared to doxorubicin (IC50 0.313 µM)	(Ibrahim et al., 2016)
		Fusarithioamide B (6)	6 It had a selective and potent effect towards BT-549, IC50s 0.09 µM compared to doxorubicin (IC50s 0.046 µM).	(Ibrahim et al., 2018)
	Nemania sp. UM10M	Cytochalasins: 19,20-Epoxycytocytochalasin D (2), 18-Deoxy-19,20-epoxycytochalasin C (3)	(2) IC50 = 7.84 Um; (3) IC50 = 6.89 uM	(Kumarihamy et al., 2019)
MDA-MB-468 Adenocarcinoma of the breast	*Penicillium ramusculum*	Crude extract derived from P. ramusculum	IC50 = 62.83 ± 0.93 µg/mL	(Varghese et al., 2024)
MDA-MB-231 Breast cancer Line	*Penicillium oxalicum*	Penicillium oxalicum (POAgNPs)	IC50 = 20.080 ± 0.761 µg/mL	(P. Gupta et al., 2022)
	Colletotrichum gloeosporioides	Ethyl acetate (EA) extract of C. gloeosporioides	IC50 = 62.09 ± 1.780 µg/mL	(Rai et al., 2023)
HeLa cervical cancer line	*Grammothele lineata*	Paclitaxel	IC35 = 0.005 uM	(Das et al., 2017)
	Ovatospora senegalensis NR-03 (1), Chaetomium globosum NR-04 (2), Thielavia subthermophila NR-06 (3), Aspergillus calidoustus NR-10 (4), Aspergillus keveii XJF-23 (5), Aspergillus terreus XJF-3 (6)	Extracts in general	(1) IC50 = 0.09 ± 0.005 ug/ml, (3) IC50 = 5.89 ± 0.35 ug/ml, (6) IC50 = 0.1 ± 0.005 ug/ml	(Zhang et al., 2016)

	Paraconiothyrium brasiliense	Brasilamide analog E 12b	IC50 = 0.25 ± 0.02	(Zhang et al., 2016)
	Penicillium crustosum extract SM2	Sir-SM2	IC50 = 29.14 ± 5.72	(Hasan et al., 2022)
	pestalotiopsis sp HQD-6	demethylincisterol a3 (Sdy-1)	IC50 = 0.17 ± 0.00 nM/mL	(Sun et al., 2022)
	Pestalotiopsis sp.	demethylincisterol A3 (1),	IC50 = 0.17 ± 0.00	(J. Zhou et al., 2018)
		ergosta-5,7,22-trien-3-ol (4),	IC50 = 21.06 ± 0.68	
		stigmastan-3-one (6),	IC50 = 19.66 ± 0.00	
		stigmast-4-en-6 -ol-3-one (8),	IC50 = 36.73 ± 1.07	
	trichothecium roseum	rosoloactone	IC50 = 8ug/ml	(L. Zhou et al., 2017)
	Xylaria sp.	nalgiovensin	94.1% inhibition at 10 ug/mL	(Lin et al., 2016)
ovarian cancer line 1619L	*Phomopsis sp.*	Altersolanol A	IC50 = 0.001 ug/ml	(Mishra et al., 2015)
ovarian cancer line HO8910	*Paraconiothyrium brasiliense*	Brasilamide analog E 12b	IC50 = 0.13 ± 0.02	(Zhang et al., 2016)
ovarian cancer line OVCAR3	*Cladosporium cladosporiodes*	Cladosporol A	IC50 = 10.3 ± 0.556	(Koul et al., 2017)
SKOV-3 cell lines	*Fusarium chlamydosporium*	fusarithioamide A (2-(2-(2-aminopropanamido)-N-(1-hydroxy-3-mercaptopropyl) benzamide (4)	Compounds 4 possessed potent and selective activity towards SKOV-3 cell lines with IC50 values of 0.8 µM, compared to doxorubicin (IC50 0.313 µM).	(Ibrahim et al., 2016)
		Fusarithioamide B (6), a new aminobenzamide derivative with unprecedented carbon skeleton	SKOV-3 cell lines with IC50s 1.23, compared to doxorubicin IC50s 0.321	(Ibrahim et al., 2018)

Table 5
Urological and Prostate Cancer Line

Cell line	*Scientific name of the fungus*	Active Compound	Cytotoxicity (IC50 - IC75)	Ref
prostate cancer line DU145	*Phomopsis sp.*	Altersolanol A	IC50 = 0.001 ug/ml	(Mishra et al., 2015)
PC-3, human prostate adenocarcinoma	*Morinda citrifolia Linn. (Noni)*	MRL1-3A	IC50 = 5 μg/mL	(Wu et al., 2015)
		XILP7-2	IC50 = 0.4 μg/mL	(Wu et al., 2015)
		XILP5	IC50 = 10 μg/mL	(Wu et al., 2015)
prostate cancer line PRXF PC3M	*Cladosporium cladosporiodes*	Cladosporol A	IC50 = 15.6 ± 0.360 (μM)	(Koul et al., 2017)
	Phomopsis sp.	Altersolanol A	IC50 = 0.001 ug/ml	(Mishra et al., 2015)
	Pichia kudriavzevii, Fusarium oxysporum, Mucor circinelloide, Trametes versicolor, Polyporales sp., Bjerkandera adusta, Fusarium tricinctum	IIIM2	80.00 ± 1.00%	(Dar et al., 2016)
		IIIM3	67.00 ± 1.00%	
		IIIM7	55.00 ± 2.00%	
		IIIM8	88.00 ± 1.00%	
Bladder cancer 1218L	*Phomopsis sp.*	Altersolanol A	IC50 = 0.001 ug/ml	(Mishra et al., 2015)
Bladder cancer NBT-T2	*Hypomontagnella monticulosa*	griffthiiene	IC50 = 0.75 ppm	(Lutfia et al., 2021)
		scalaradial	IC50 = 0.30 ppm	
Bladder cancer T24	*Phomopsis sp.*	Altersolanol A	IC50 = 0.001 ug/ml	(Mishra et al., 2015)
epithelial renal cancer RXF LLC-PK11	*Nemania sp. UM10M*	Cytochalasin , 19,20-Epoxycytochalasin D (2),	IC50 = 8.4 uM	(Kumarihamy et al., 2019)
Bladder SW780 cell line	*T. convolutispora*	TalaA	IC50 = 5.7 μM	(Xia et al., 2023)
Bladder UM-UC-3	*T. convolutispora*	TalaA	IC50 = 8.2 μM	(Xia et al., 2023)

Table 6
Lymphoid and melanoma cancer

Cell line	*Scientific name of the fungus*	Active Compound	Cytotoxicity (IC50 - IC75)	Ref
THP-1 leukemia line	*Pichia kudriavzevii, Fusarium oxysporum, Mucor circinelloide, Trametes versicolor, Polyporales sp., Bjerkandera adusta, Fusarium tricinctum*	IIIM2	79.00 ± 1.00%	(Dar et al., 2016)
		IIIM3	60.00 ± 1.00%	
		IIIM7	56.00 ± 2.00%	
		IIIM8	88.00 ± 2.00%	
HL60 Leukemia Cell Line	*Penicillium sp.*	Averufin (1)	IC50 = 1.00 µm	(Kaliaperumal et al., 2023)
MDA-MB-435 cells	*Lasiodiplodia sp. 318.*	Lasiodiplodins	IC50 = 10.13 mM	(Li et al., 2016)
melanoma 394NL	*Phomopsis sp.*	Altersolanol A	IC50 = 0.001 ug/ml	(Mishra et al., 2015)
melanoma 462NL	*Phomopsis sp.*	Altersolanol A	IC50 = 0.034 ug/ml	
melanoma 514L	*Phomopsis sp.*	Altersolanol A	IC50 = 0.001 ug/ml	
melanoma 520L	*Phomopsis sp.*	Altersolanol A	IC50 = 0.001 ug/ml	
melanoma A-375	*Pyrenochaetopsis sp. FVE-001*	pyrenosetins A-C (1-3)	IC50 = 2.8 and 6.3 µM, 140.3 uM, 37.3 uM	(Fan et al., 2020)
SK-MEL cell lines	*Nemania sp. UM10M*	Cytochalasins: 9,20-Epoxycytochalasin C (1)	IC50 = 8.02 uM	(Kumarihamy et al., 2019)

This investigation revealed two mechanisms: First, the interference of AsA in the generation of CDK4 and CDK6 kinases and cyclin D1, indispensable for the passage from G1 to S phase. Subsequently, an increase in the amounts of reactive oxygen species was observed in cells stationed in G0/G1 phase and the continuation of the cell cycle upon addition of antioxidants. This represents a particular advantage since cancer cells show greater vulnerability to cytotoxicity in in-vitro assays.

Demethylincisterol A3 (Sdy-1), on the other hand, demonstrated an anticarcinogenic effect by inducing cell apoptosis and G1-phase cell cycle arrest in human HepG2 liver carcinoma and HeLa cervical cancer lines. Both mechanisms, inhibition of Wnt/beta-catenin signaling pathways were demonstrated as beta-catenin levels and other pathway components (cyclin-dependent kinase CDK4, cyclin D1 and c-myc genes) decreased in both lines upon addition of Sdy-1. For the following mechanism, it was evidenced that Sdy-1 increases the cleavage of caspases 3 and 9, in addition, chromatin condensation, nuclear fragmentation and apoptotic debris were evidenced in the post-treatment samples (Sun et al., 2022).

Pulchranin-A demonstrated cytotoxic activity in HCT colorectal cancer, Hep-G2 liver carcinoma and MCF-7 breast cancer cell lines by sulfurodamine assay. In addition, inhibition of 3 cyclin-dependent kinases (CDK1, CDK2 and CDK4) was recorded in the MCF-7 line. This inhibition allows the interruption of the cell cycle in the G2/M and G1/S phases, and CDK4 activity is promising since, together with cyclin D1, they are the proteins most frequently affected by mutations in various types of cancer (Moussa et al., 2020).

Cell toxicity generated by Tricycloalternarene (Shen et al., 2018) was demonstrated in hepatocarcinoma cell lines SMMC-7721 and gastric cancer SGC-7901 by MTT assay, also cell cycle retention in G1 phase caused by overexpression of p27 protein was proved by Western Blot. The p27 protein interferes with the cell cycle as it prevents the formation of Cliklin-CPK complexes, and is already considered a potential tumor suppressor protein, and abnormal expression of the p27 gene is closely related to the occurrence and development of multiple malignant tumors.

Finally, a study by Zhu S et al showed that the metabolite produced after Phomosis sp, Deacetyl-mycoepoxydiene (DM), was capable of induce the reorganization and polymerization of tubulin and the G2/M cell cycle arrest of MCF-7 cell lines (Zhu et al., 2015).

4.2. Protein Inhibition

Sclerothiorin (Kabbaj et al., 2015) demonstrated activity on certain chaperones (Hsp90 inhibition, Hsp70 overexpression and Hsp40 degradation) in a progesterone receptor assay. However, this compound did not show cytotoxicity in breast cancer cell lines Hs578T, MCF7, MDA-MB-231 and MDA-MB-453, prostate cancer LNCaP and cervical cancer HeLa.

These results changed upon deacetylation of sclerostin: inhibition of Hsp90 chaperone function was reduced and cytotoxicity was evident against some cell lines (Hs578T, MDA-MB-231 and LNCaP) within 48 hours.

Penicisulfuranol A (PEN-A) is a promising anti-carcinogenic agent by inducing apoptosis in tumor cells in in vitro studies. The triple action of this compound was demonstrated: it inhibits the C-terminal polymer dimerization of Hsp90, inhibits the polymerization of Hsp90 target proteins and obstructs the co-activity of other chaperones with Hsp90 (Dai et al., 2019).

Myrothecine A (Fu et al., 2019) can restrain cell proliferation induced by miR-221, a type of microRNA with oncogenic activity, in a hepatocarcinoma cell line SMMC-7721. According to the studies performed, miR-221 negatively affects the levels of p27 protein, a cyclin-dependent kinase inhibitor and a direct target molecule of miR-221 that negatively regulates cell proliferation and differentiation. Myrothecin A increased p27 levels in cultured cells by inhibiting miR-221 expression.

It is also able to induce maturation of dendritic cells in simultaneous culture with the hepatocarcinoma cell line, including an increase in CD40 and CD86 during miR-221 inhibition, which favors a better specific response against cancer cells.

Camptothecin (CPT) is a quinoline alkaloid of plant origin capable of inhibiting topoisomerase 1 in tumor cells by binding to the active site of tyrosine during the DNA replication process. Another effect observed is the activation of hypoxia-induced factor 1a (HIF1a), which causes a ribosomal blockade responsible for stopping the translational response (Dhakshinamoorthy et al., 2021).

The effects of CPT were studied in a lung carcinoma cell line A-549 in an MTT assay, in this research the cytotoxic effect generated by CPT in cancer cells was evidenced.

4.3. Apoptosis Induction

The process of cell apoptosis is favored by certain active compounds of endophytic fungi, such as rosolactone evaluated by Zhou et al (L. Zhou et al., 2017), which increases proteins involved in oxidative stress of the endoplasmic reticulum, which induces apoptosis and autophagy. This inductive capacity was evaluated in HeLa cells and it was seen how rosolactone generated an increase in ROS, which generates activation of mitochondrial apoptotic pathways, as well as increasing proteins such as BAx, caspase 3 and cytoplasmic cytochrome c.

Another of the endophytic fungi with apoptotic capacity was Aspergillus terreus (JAS-2), which according to Goutam et al (Goutam et al., 2017), cytotoxicity against HCT 116 of the active compound Terrain produced changes in the sub G1 stage of the cell cycle, in addition to producing apoptosis in the A-459 cell line. To reach this conclusion, the research required analysis of DNA bases through FACS (Fluorescence Activated Cell Sorting).

On the other hand, it has been found that the active compound of the fungus has different apoptotic metabolic pathways, such as increasing ROS expression and increasing apoptosis through the protein expression of Bax, as well as increasing the expression of cyclin-dependent p21 inhibitor kinase, evaluated through the MCF7 cell line.

Apoptotic pathways evaluated in Subban et al, a Taxol derivative, EDT, was able to induce apoptosis in HepG2 cells in the G2/M phase of the cell cycle evaluated by flow cytometry. In addition, DNA fragmentation was observed in agarose with cells with the active compound and not in controls (Subban et al., 2017).

The active compound HLP46 derived from Pestalotiopsis sp, according to Chen C et al, is able to disrupt the Gab1-Shp2 association, which was corroborated by immunoprecipitation methods. Furthermore, after evaluation by Ras Activation Assay, the derived compound was found to block EGF-induced activation of the Shp2-dependent Ras/ERK signaling pathway (C. Chen et al., 2017).

The active compound demethylincisterol A3 was able to induce G0/G1 cell stage in tumor cells, in addition to inducing necrosis of these cells, was evaluated by Zhou et al through flow cytometry (J. Zhou et al., 2018).

Li Shen et al. evaluated the endophytic fungus Alternaria sp associated with Laminaria japonica, and found that active compounds promote apoptosis in five ways. Triccycloalternarene 3a induces apoptosis in SMMC 7721 dose-dependently by overexpressing the pro-apoptotic protein Bax and decreasing the anti-apoptotic protein Bcl2, i.e. the Bcl2/bax ratio decreases with increasing dose, as evidenced in samples 48h after sample treatment (7). Caspases are affected by the active compound, since this tricycloalternarene 3a was found to be related to the receptor death pathway and the mitochondrial pathway, the samples were evaluated in Western blot to conclude this statement.

Another experiment by Wang X et al (X. Wang et al., 2015) showed the capacity of the metabolite SZ-685C to enhance the expression levels of the AKT pathway in the in vitro study of NFPA cells.

4.4. Angiogenesis Inhibition

In Liu et al., to evaluate the angiogenesis of HPV-16, E7-transfected A549 or NCI-H460 cell lines, the in vitro evaluation kit ECM 625 was used, where it was found that in addition to cytotoxic activity, angiogenesis was caused by the active compounds zj-14 , zj-17 and zj-36 inhibited microtubule formation in HPV-16 (H.-X. Liu et al., 2017).

4.5. Cellular Migration Inhibition

The research by Vasarri et al evaluated the anti-migratory capacity of dihydroauroglaucine (DAG) and detetrahydroauroglaucine (TAG) in the SH-SY5Y cell line through wound healing assay obstructs cell migration, where it was demonstrated that DAG presents anti-migratory, plus or cytotoxic capacity; however, this research provides grounds for further in vitro and in vivo investigations (Vasarri et al., 2022).

4.6. Antioxidant Activity

According to Pan F. et al (Pan et al., 2019), the active compound of Fusarium sp. A14, Exopolysaccharides, has antioxidant capacity, compounds A14EPS-1 and A14EPS-2 were evaluated at low concentrations (0.1e4.0 mg mL1), which showed cell carving activities of 47.22 2.30% and 23.74 4.15% respectively.

4.7. Autophagy Induction:

Co-cilioquinone B (CoB1) derivatives demonstrated cytostatic autophagy-inducing activity in the lung carcinoma cell line A-549, the experiments were performed in an MTT assay and the results were verified by western blot (Xu et al., 2021).

The postulated mechanism is related to the blockade of the PI3K/Akt1/mTOR signaling pathway and at the same time to the activation of the TAK1/MKK4/JNK/Smad pathway and the consequent expression of miR125b which reduces Foxp3 levels.

Trichodermal acid (TDA) demonstrated induction of autophagy in colorectal cancer cell lines as studies showed that TDA inhibited the proliferation of these cells. TDA generates cellular stress at the endoplasmic reticulum level which generates apoptosis in the IRE1α/XBP1 and PERK/ATF4/CHOP pathways. During the investigation it was also evidenced that cell autophagy in the tumor line was a defense mechanism, proof of this was the joint treatment with TDA and an autophagy inhibitor where the inhibited proliferation was even higher. The cell cycle could be retained in the G0/G1 phase with TDA treatment (Qu et al., 2021).

Endophytic fungi have been developed over the years in order to find better drugs for anticancer management; however, it requires both pharmacokinetic knowledge and an understanding of the mechanisms of action of each of the extracted metabolites. Our review details the IC50 and possible proposed mechanisms of action of different endophytic fungal metabolites.

According to the IC50 values of current antimitotics, Paclixatel has an IC50 of 2.5 and 7.5 nM in human tumor cells (Liebmann et al., 1993); Vincristine on the other hand, managed to inhibit SH-SY5Y cells at O.1 µM (Donoso et al., 1977) and Vinblastine to MCF-7 cells at 0.68µM (Sobottka & Berger, 1992); according to the in vitro investigations included in our literature search, metabolites such as Alternaria, Aspergillus, Fusarium or Penicillium may become a future equivalent in that sense, so the cell type they inhibit should be taken into account, in addition to the concentration used, this requires further investigations to complement these initial results.

Alternaria was one of the most frequently used in the studies described. Gao et al (Gao et al., 2020) evaluated 3 novel (1-3) and 3 known (4-6) alterchothecenes along with 9 additional compounds (7-15), which were evaluated for cytotoxicity in human colon carcinoma cell lines HT-29 and breast cancer cell line MCF-7. A higher cytotoxicity was demonstrated in groups 4-6 for both cell lines. Also, a larger group of compounds evaluated (1-6) showed synergistic activity with TNF-a related apoptosis inducing ligands (TRAILs), such finding is relevant since it favors the apoptotic activity of the ligands in a context where a large number of neoplasms showed to develop resistance to cytotoxicity induced only by TRAILs. On the other hand, Palanichamy et al. performed the purification, crystallization and evaluation of the anticancer activity of alternariol-methyl-ether present in Alternaria alternata. Cell lines of hepatocellular carcinoma HUH-7 and lung cancer A549 were used. The compound evaluated showed induction of apoptotic activity when apoptotic bodies were found in the cells cultured for more than 24h in the compound-generated extract.

Fusarium was employed as well in several studies, Dar et al (Dar et al., 2016) evaluated anticancer properties of the extract generated from Fusarium in several cell lines (colon cancer Caco-2, prostate cancer PC-3, lung cancer A549, leukemia THP-1, neuroblastoma IMR-32 and breast cancer MCF-7) and in murine models, however, despite demonstrating tumor growth inhibition, it was outperformed by extracts from other endophytic fungal species which demonstrated dose-dependent cell growth inhibition in all cell lines. On the study of Ibrahim et al (Ibrahim et al., 2018) determined the cytotoxic activity of fusarithionamide in ovarian, epidermoid, malignant melanoma, mammary adenocarcinoma, colorectal and ductal adenocarcinoma cancer lines, demonstrating cytotoxicity with IC50 comparable to doxorubicin.

Aspergillus is described as well, Goutam et al (Goutam et al., 2017) evaluated the anticarcinogenic activity of "Terrein" compound extracted from Aspergillus terreus in lung cancer cell line A-549. The extract showed antiproliferative activity in the cell model evaluated, nevertheless, further analysis is required in order to determine the possible mechanism of action. The study by Moussa et al (Moussa et al., 2020) reported the activity of pulchranin A from Aspergillus evaluated in MCF-7 breast cancer, Hep-G2 hepatocarcinoma and HCT colorectal cancer cell lines. Cell growth restriction occurs through inhibition of cyclin-dependent kinases CDK1, CDK2 and CDK4. These results were further supported by an in-silico model. Finally, Ukwatta (Ukwatta, Lawrence, & Wijayarathne, 2019) et al demonstrated cytotoxicity of cowabenzophenone A extracted from Aspergillus terreus in HCT116 colon cancer cells, with the IC50 being higher than the control (doxorubicin).

Penicillium was the subject of different studies, Hasan et al (Hasan et al., 2022), for instance, evaluated the anticarcinogenic capacity of Penicillium ethyl extract "Sir-SM2" on HeLa cervical cancer cells. Cytotoxicity and growth inhibition were demonstrated by observing a compromised cell morphology under microscopy. Furthermore, "Sir-SM2" showed very low toxicity levels against Chang's normal human cells, therefore, can be a potential natural anticancer. Wen et al (Wen et al., 2020) , on the other hand, studied the anticarcinogenic properties of ethanol extract belonging to Penicillium polonicum in hepatocellular carcinoma HepG2 cells. Nine compounds were determined and four of them showed cytotoxic activity against the cell line used, even one compound showed a lower IC50 than cisplatin which was used as a control, this is a big step for developing more anticarcinogenic treatment options derived from metabolites.

In spite of showing promising anticancer potential in the last studies, an exact mechanism of action was not determined. Subsequent research could be helpful to fully understand cytotoxic activity and enhance our current knowledge about this endophytic fungus species.

In comparison with previous research, the review by Gupta et al. (S. Gupta et al., 2020) mentions that recently discovered active compounds from endophytic fungi can be as effective as conventional antimitotics, which is a similar result compared to our literature review and the IC50s described. The review performed by Kharwar et al. (2011) between 1990 and 2010, recorded more than 100 metabolites, of which compounds with alkaloid structures such as chaetomugilide A, B were considered effective, as well as Xanthones, Peroxides and Quinones. On the other hand; the review by L. Chen et al. (2016) focused on active compounds reported from 2010 to 2013, made a count of about 100 potentially antitumor metabolites and 8 discovered in that time frame. Both investigations demonstrate how relevant endophytic fungi will be for the development of antitumor drugs in the coming years that can match taxol and other antimitotics.

On the other hand, our review details different proposed mechanisms of action that may support the use of endophytic fungi in anticancer management in the near future, the methods necessary for metabolite extraction require constant updating. A review by Kumar et al (Kumar et al., 2021) details the mechanisms of conventionally employed antitumor drugs, as is the case of taxol, where its intervention in stabilizing microtubules and preventing depolymerization is highlighted. In addition, its antiangiogenic activity continues to be studied.

A previous literature review by Hridoy et al. (Hridoy et al., 2022) details in depth the mechanisms of action of endophytic compounds, where it is emphasized that alkaloid compounds such as Camptothecin (CPT) and terpenes such as paclitaxel (Taxol) were the most used in the last thirty years. CPT was shown to be related to DNA replication arrest by inhibiting topoisomerase I; however, another alkaloid such as vincristine was associated with cell cycle arrest in metaphase. Taxol, on the other hand, is related to the induction of apoptosis.

Our review coincides with the presence of these mechanisms of action and it is hoped that the routes proposed by previous research may favor the search for anticancer treatments in the near future. Although it is true that we were able to extract exhaustively the articles related to the subject, studies with more databases that can complete the vision of endophytic fungi in anticancer management are required.

5. CONCLUSION

The results evaluated in this narrative review included the evaluation of the cytotoxicity of the active compounds of different endophytic fungi in cancer-related cell lines. Several of these compounds have outperformed the results of chemotherapy-related drugs, so it is expected that several can continue with the next phases to obtain better therapies against cancer.

CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to declare.

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