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Fungal Metabolites with Anticancer Activity

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Natural products from bacteria and plants have played a leading role in cancer drug discovery resulting in a large number of clinically useful agents. In contrast, the investigations of fungal metabolites and their derivatives have not led to a clinical cancer drug in spite of significant research efforts revealing a large number of fungi-derived natural products with promising anticancer activity. Many of these natural products have displayed notable in vitro growth-inhibitory properties in human cancer cell lines and select compounds have been demonstrated to provide therapeutic benefits in mouse models of human cancer. Many of these compounds are expected to enter human clinical trials in the near future. The present review discusses the reported sources, structures and biochemical studies aimed at the elucidation of the anticancer potential of these promising fungal metabolites.

Key Words

Fungal metabolites, anticancer, structure-activity relationships, mode of action

1. General introduction

Natural products and their derivatives have traditionally been a major source of new anticancer agents. According to the analysis of Newman and Cragg, in the timeframe from the 1940s to date, of the 175 small molecule cancer drugs, 131 (or 75%) belong to the category of "other than synthetic."[1] Of these, 85 (or 49%) are actually natural products or their direct derivatives.[1] Natural products derived from bacteria and plants play a leading role in cancer drug discovery, which is demonstrated by a large number of approved anticancer agents derived from these natural sources. These drugs include such effective chemotherapeutic agents as doxorubicin, daunomycin, mitomycin C, bleomycin, all obtained from *Streptomyces,* or etoposide, teniposide, topotecan, paclitaxel and the vinca alkaloids (vincristine, vinorelbine, …) derived from plant-based natural products.

Fungi-derived natural products have been an excellent source of pharmaceuticals as well. Antibacterial penicillins, cholesterol lowering lovastatin, antifungal echinocandin B, immunosuppressive cyclosporine A, serve to illustrate the importance of investigating fungal sources for new medicines. Fungi produce metabolites belonging to highly diverse structural

classes, including aromatic compounds, amino acids, anthacenones, butanolides, butenolides, cytochalasans, macrolides, naphthalenones, pyrones, terpenes, etc.[2-4] Surprisingly however, no fungi-derived agent has been approved as an anticancer drug so far, despite tremendous amount of research aimed at identification of fungal metabolites with promising anticancer activities.

The goal of the present review is to provide the reader with examples of research efforts aimed at exploration of fungal metabolites as potential anticancer agents. We will report the fungal source, the chemical structure and the *in vitro* growth inhibitory activity of selected fungi-derived agents. We will also discuss the results *in vivo* anticancer evaluation if those are available. The anticancer metabolites are grouped into three categories based on the fungal source from which they are isolated. These include metabolites produced by (i) phytopathogenic, (ii) toxigenic, and (iii) non-toxigenic fungi.

2. Phytotoxins produced by phytopathogenic fungi

2.1. Cytochalasins from *Pyrenophora* and *Phoma* species

Cytochalasins are part of a larger group of metabolites named cytochalasans and they incorporate diverse polyketide-amino acid hybrid structures with a wide range of distinctive biological functions.[5] Up to now, more than sixty different cytochalasans from several species of fungi have been purified, identified and sub-grouped as described in a comprehensive review by the Hertweck group.[5] The most thoroughly investigated biological effects of cytochalasans in cell culture involve the capping of actin filaments, which results in cytokinesis impairment during cell division[5] and also affects cancer cell migration properties.[6] While most cytochalasins are cytotoxic at their IC_{50} concentrations, some members of this group of fungal metabolites, including for example cytochalasin A (Fig. 1), are cytostatic,[7] a feature that could be explained,

at least partly, by the targeting of the Kv1.5 ion channel by cytochalasin A.[8] Because of their actin-binding properties cytochalasins have been broadly used to study actin microfilaments and their involvement in cell motility, ruffling, cell division, contraction and cell stiffness.[5] Furthermore, because tumor invasiveness and metastatic potential are tightly associated with deregulation of the actin cytoskeleton, there is an appreciation of actin-targeting agents as potential clinical anticancer drugs inhibiting tumor metastasis.[9-13] Yet, no actin-targeting agent has been advanced to clinical trials so far. Notwithstanding their diverse functional roles, different actin isoforms share significant structural homology. This is of greatest relevance to the cardiac muscle function, where the disruption of actin filaments by anti-actin compounds is incompatible with life. Direct actin-targeting agents are therefore associated with toxicity that impairs their oncologic development and, thus, the utilization of cytochalasins as anticancer agents is likely to be limited. More recently, research in this area has thus shifted to the exploration of actin-binding proteins and actin-regulating signaling pathways, which are aberrantly expressed in tumors and present new opportunities to selectively disable the actin cytoskeleton organization in cancer cells.[13]

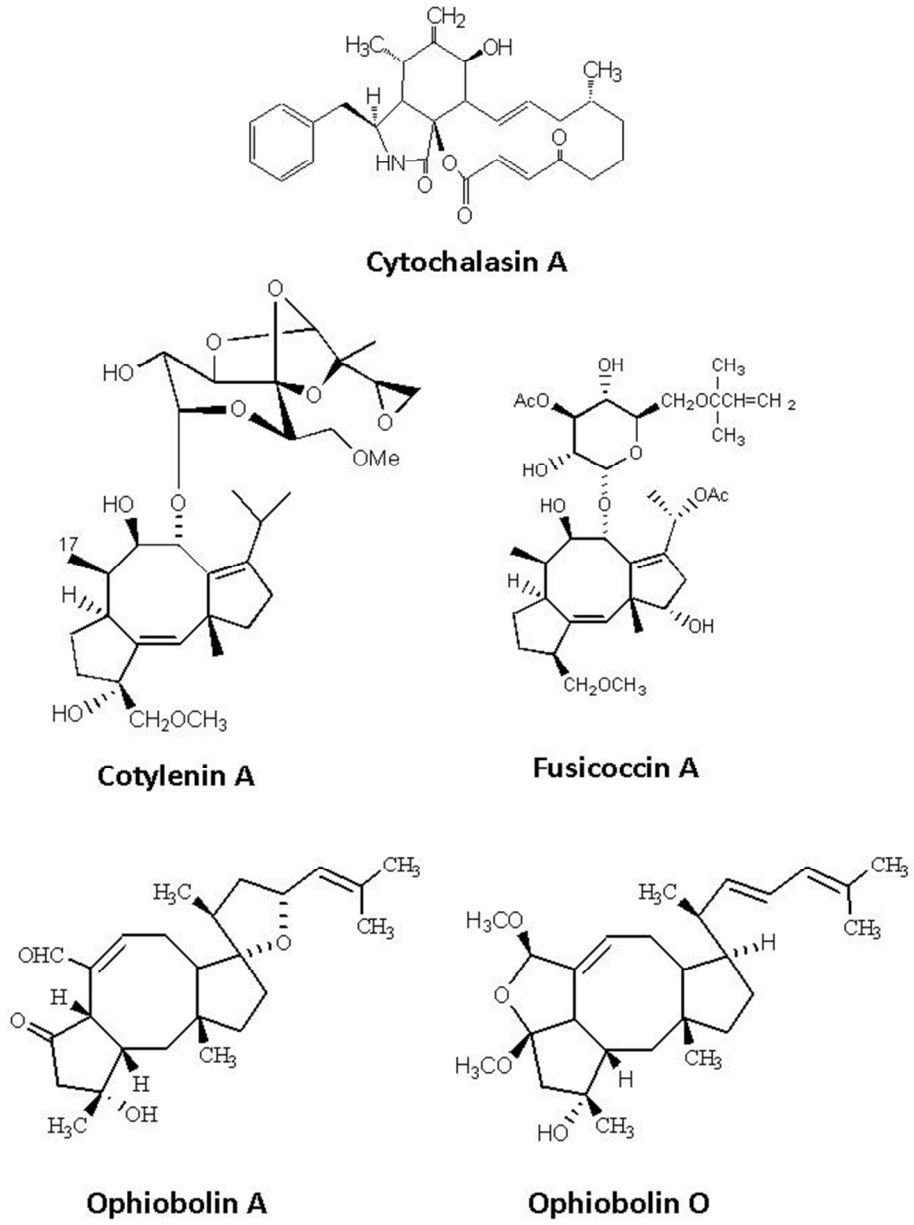

Figure 1

2.2. Fusicoccanes from *Fusicoccum amygdaly* and *Drechslera gigantea*

Cotylenin A (Fig. 1), a member of the fusicoccane family that includes small molecules incorporating a typical dicyclopenta[*a*,*d*]cyclooctane skeleton with the 5-8-5 core ring

structure,[14] inhibits the growth of various tumor types both *in vitro* and *in vivo* without apparent adverse effects in human xenograft models.[15]

In addition to cotylenin A, the fusicoccane family includes for example fusicoccin A and ophiobolins that differ in the side chains linked to the core structure (Fig. 1). Fusicoccin A (Fig. 1), an α-D-glucopyranoside of the diterpenoid 5-8-5 ring skeleton, is the main phytotoxin produced by *Fusicoccum amygdali*, the causative fungal agent of peach and almond canker.[14] Fusicoccin A activates the plasma membrane H^+-ATPase by stabilizing its binding to 14-3-3 proteins resulting in water loss and wilting of infected plants.[16] Similarly, fusicoccin A has been shown to target 14-3-3 proteins in cancer cells[17] and promote isoform-specific expression of 14-3-3 proteins in human gliomas.[18] Takahashi et al.[17] found that these 14-3-3 proteins play a critical role in serine/threonine kinase dependent signaling pathways through protein-protein interactions with multiple phosphorylated ligands. In fact, as emphasized by Milroy et al.[19], small-molecule modulation of protein-protein interactions is one of the most exciting but also difficult fields in chemical biology and drug development, and the 14-3-3 proteins are some of the most important intracellular "hubs" with at least 200-300 interactions partners. Milroy et al.[19] also emphasize that protein-protein interactions are involved in almost all biological processes, with any given protein typically engaged in complexes with other proteins for the majority of its lifetime. Finally, Milroy et al.[19] argue that a thorough appreciation and understanding of this concept and its regulation mechanisms could help to develop new therapeutic agents and concepts. de Vries-van Leuwen et al.[20] showed that fusicoccin A-induced anticancer activity can be enhanced by combining it with the cytokine interferon-gamma (IFNgamma); IFNgamma primes the tumor cells for apoptosis induction by fusicoccin A. Healthy cells (Human Umbilical Vein Endothelial Cells; HUVECs) are far less sensitive to IFNgamma/fusicoccin A treatment

and they need the continuous presence of both compounds in order to achieve a growth reduction.[20] Fusicoccin A mediates cytostatic effects in glioma cells through the inhibition of the activities of a dozen kinases, including Focal Adhesion Kinase (FAK), known to be implicated in cell proliferation and migration.[21]

Another subgroup of the fusicoccane family includes ophiobolins (Fig. 1), produced by phytopathogenic fungi mainly of the genus *Bipolaris*. The discovery of these sesterterpenes (C25) filled the gap between diterpenes (C20) having four isoprene units and triterpenes (C30) with six isoprene units.[22] Ophiobolin A (OP-A; Fig. 1) was the first member of the group to be isolated and characterized in the mid-1960s.[23,24] Currently, 25 biogenic analogues of ophiobolins have been identified.[25] They reduce seed germination, growth of roots and coleoptiles of wheat seeding, and at the cellular level, they affect membrane permeability, stimulate leakage of β-cyanine, electrolytes and glucose from roots, decrease photosynthetic CO_2-fixation, cause respiratory changes and enhance stomatal opening.[22]

Ophiobolins are usually cytotoxic compounds with respect to cancer cells.[26] For example, ophiobolin O (Fig. 1) induces growth inhibition of human breast cancer MCF-7 cells through G_0/G_1 cell cycle arrest and reduces the viability of these cells in a time- and dose-dependent manner through activation of apoptotic processes and modifications in JNK (c-Jun NH_2-terminal kinase), p38 MAPK (mitogen activated protein kinase) and ERK (extracellular signal-regulated kinase) kinase activity as well as the reduction of Bcl-2 phosphorylation (Ser70).[27] Ophiobolin A induces marked changes in the dynamic organization of the F-actin cytoskeleton and impairs the proliferation and migration of glioma cells, likely by inhibiting BKCa ion channel activity.[28] In a most promising discovery, Bury et. al.[28] found that ophiobolin A is a potent inducer of glioblastoma cell death occurring through the induction of paraptosis. Paraptosis is a form of cell

death distinct from the common apoptosis and characterized by a process of vacuolization that begins with the physical enlargement of mitochondria and the endoplasmic reticulum (ER).[29,30] The mechanisms underlying paraptosis, in particular, the signals responsible for triggering mitochondrial and ER dilatation, have not yet been elucidated and specific intracellular proteins involved in paraptotic signaling are yet to be identified.[31] Yet, these results lay the foundation for the development of novel anti-glioma agents on the basis of the pharmacophore derived from OP-A. Furthermore, an even more impactful approach would involve understanding of ophiobolin A mode of action in order to unravel the molecular sequence of events involved in paraptosis and identification of specific intracellular targets whose modulation will trigger this non-apoptotic cell death. Induction of paraptosis in cancer cells could become a new therapeutic strategy to combat glioblatoma, which is generally highly resistant to the traditional pro-apoptotic cytotoxic therapy.[32]

2.3.Alternethanoxins from *Alternaria sonchi*

A number of other fungal plant pathogens, for example *Stagonospora cirsii* and *Ascochyta sonchi*, have been found to produce phytotoxic metabolites.[33] Thus, two toxins isolated from *A. sonchi* and named alternethanoxin A and B (Fig. 2) were characterized as polycyclic ethanones containing a benzochromene moiety.[34] The structure of alternethanoxin A was also confirmed by preparing its triacetyl and monomethyl ether derivatives (Fig. 2).[34] These metabolites display *in vitro* growth inhibitory activity with respect to several cancer cell lines.[35] In addition, *in vitro* cytotoxic activity was found among closely related cynandiones A-D, cynanchone and analogues isolated from the root of different *Cynanchum* plant species.[36]

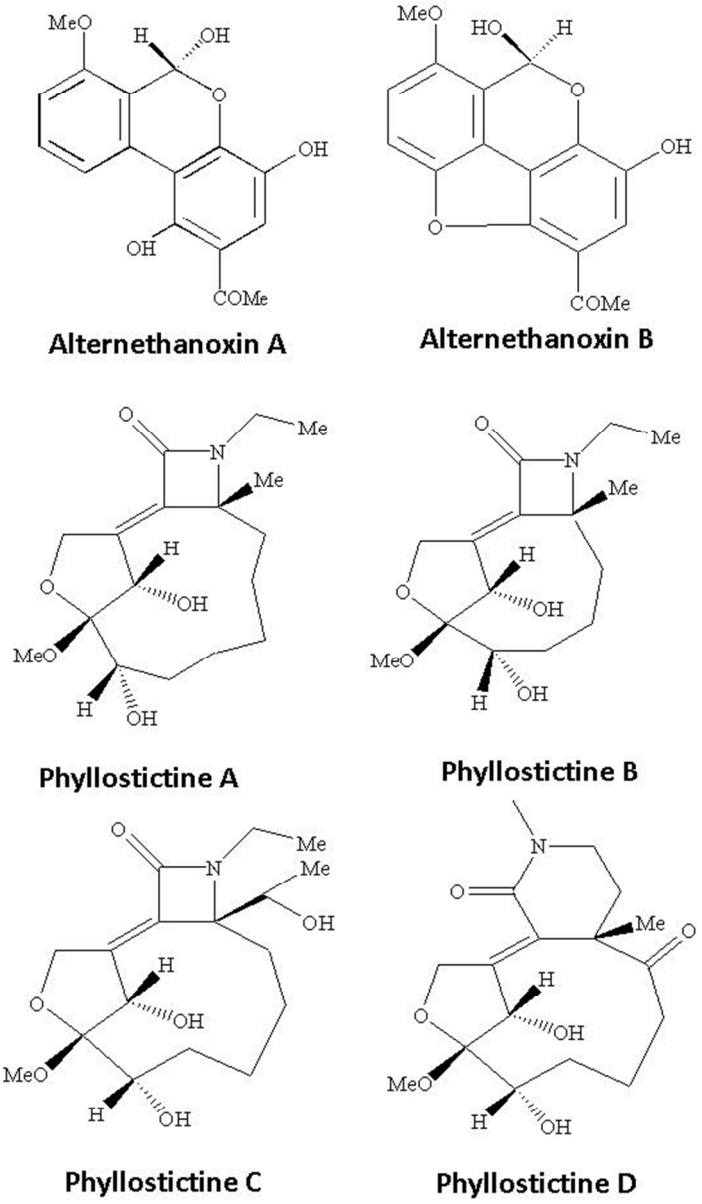

Figure 2

2.4.Phyllostictines from *Phyllosticta cirsii*

Four new oxazatricycloalkenones, named phyllostictines A-D (Fig. 2), were isolated from liquid cultures of *Phyllosticta cirsii,* a fungal pathogen isolated from *Cirsium arvense*.[37] The

structure assigned to phyllostictine A was further confirmed by converting the toxin into its mono- and diacetyl derivatives.[37] Phyllostictines A-D are the first fungal metabolites possessing the oxatricycloalkenone structure.[37] Although phyllostictine A was found to have *in vitro* growth inhibitory activity in cancer cell lines, it was equally toxic toward normal cells.[38] The main mechanism of action by which phyllostictine A displays cytotoxic effects in cancer cells does not seem to relate to direct activation of apoptosis and, in the same manner, phyllostictine A does not seem to bind DNA.[38] In contrast, the experimental data supports a mechanism involving a Michael attack of GSH at the C=C bond of the acrylamide-like system in phyllostictine A to form a covalent complex.[38] In addition, phyllostictine A could form covalent complexes with proteins rich in cysteine or with enzymes that display cysteine residues in their active center.[38] The SAR analyses of the *in vitro* growth inhibitory activity associated with phyllostictines A-D in various cancer cell lines suggest that the size and conformation of the macrocyclic ring are of crucial importance for the growth-inhibitory effects displayed by these fungal metabolites.[38] The development of these metabolites as anticancer agents may be limited due to the intrinsic reactivity of the Michael acceptor moiety leading to general toxicity and the fact that these compounds are equally toxic to normal cells[38] seems to confirm this unfavorable prognosis.

2.5. α-Pyrones and anthracenones from *Phomopsis foeniculi*

Using bioassay-guided purification, several metabolites from the culture of *Diaporthe angelicae* (anamorph of *Phomopsis foeniculi*), the causal agent of the fennel (*Foeniculum vulgare* Miller) disease, were isolated and identified as nectriapyrone, a pentaketide monoterpenoid (Fig. 3),[39] and three octaketide anthracenones, macrosporin and alternasolanol A and J (Fig. 3).[40]

Nectriapyrone is a monoterpenoid pentaketide first isolated from *Gyrostoma missouriense*.[40] Subsequently, nectriapyrone was isolated from different fungal genera, including *Phomopsis oblonga*, *Scytalidum* sp., *Phomopsis* sp., twelve different *Phomopsis* species, which are endophytes of *Erythrina crista-galli* L., and endophytic fungi isolated from *Viguiera arenaria* and *Tithonia diversifolia*.[40] Nectriapyrone displays cytotoxic activity in human T leukemia and melanoma cell lines.[41]

Macrosporin was isolated for the first time from *Macrosporium porri*.[40] This anthracenone was subsequently isolated from *Alternaria solani*, *Dactylaria lutea*, *Stemphylium eturmiunum*, *Alternaria tomatophilia*, *Ampelomyces* sp., an undetermined fungicolous hyphomycete resembling *Cladosporium* and *Stemphylium globuliferum*.[40] Macrosporin displays moderate cytotoxic activity in L5178Y mouse lymphoma cells.[42]

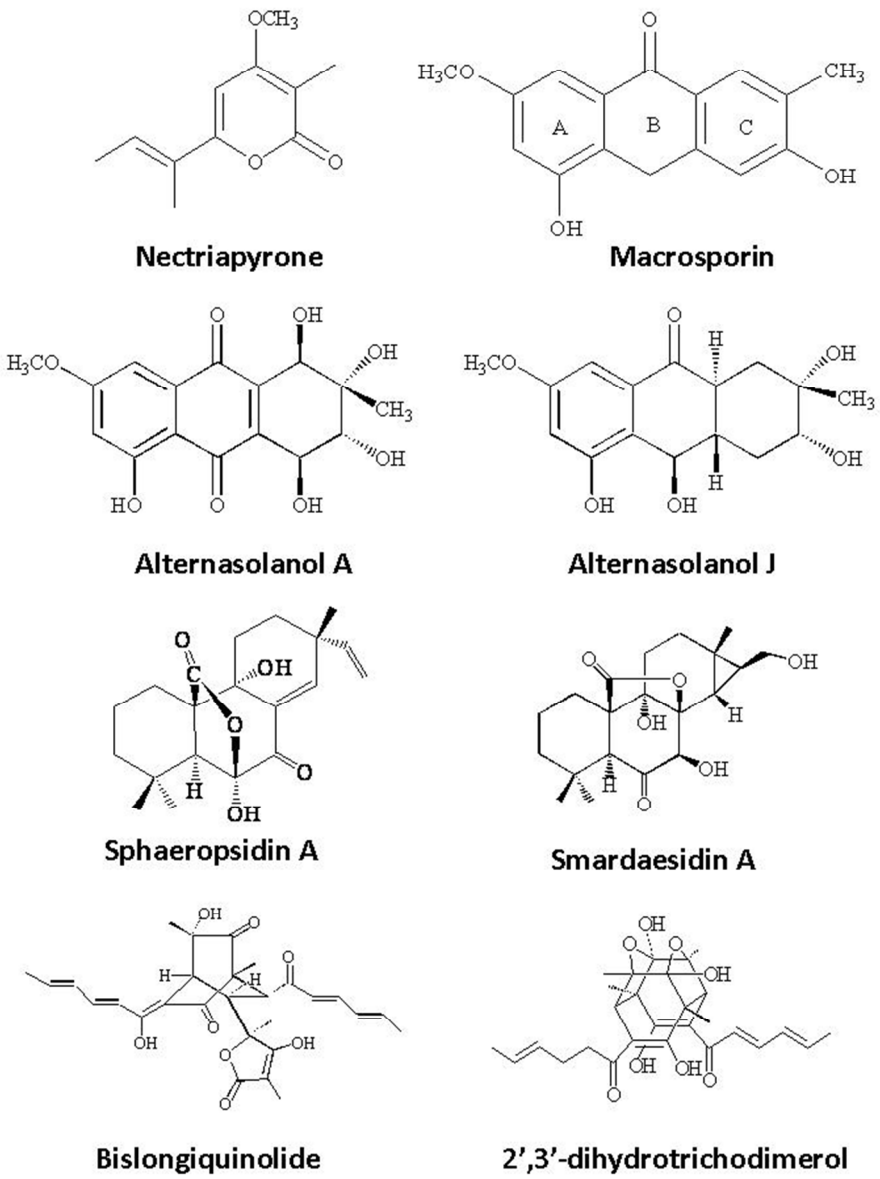

Figure 3

Alternasolanol A is a metabolite previously isolated from *Alternaria solani*, *D. lutea*, *Phomopsis juniperovora* and *A. porri*.[40] In addition, both altersolanols A and J were isolated from *Ampelomyces* sp., *S. globuliferum*[40] and from the above-mentioned undetermined *Cladosporium* sp.[43] Alternasolanol A displays inhibitory effects on lettuce and stone-leek seedlings, antibiotic activity against *Escherichia coli*, *B. subtilis* and *S. aureus*[44] and growth

inhibition of *Nicotiana rustica* L. cultured cells.[45] This metabolite is associated with marked cytotoxicity in various cancer cell lines, while the anthronol derivative alternasolanol J displays moderate to weak activity only.[42,46] This feature suggests that the *para*-quinone moiety could be of great importance for the cytotoxicity of these types of compounds with respect to cancer cells.

2.6. Sphaeropsidins and smardaesidins from *Diplodia cupressi* and *Smardae* sp.

The fungi that attack the Italian cypress (*Cupressus sempervirens* L.) and other species of *Cupressus* in the Mediterranean area belong to the genera *Diplodia*, *Pestalotiopsis*, *Seiridium* and *Sphaeropsis*. They produce a number of metabolites including tricyclic lactones sphaeropsidines (Fig. 3). The relationships between the structure and phytotoxic and antimycotic activities among sphaeropsidines are well documented.[47] In contrast, only few reports describe the cytotoxic activity of these metabolites in cancer cells.[48] Sphaeropsidine A is quite active with IC_{50} concentrations in low micromolar range.[49] Sphaeropsidin A also inhibits migration of metastatic breast adenocarcinoma MDA-MB-321 cells at subcytotoxic concentrations.[50] Related metabolites, such as isopimarane diterpenes, represented by smardaesidin A (Fig. 3), were isolated from the endophytic fungal strain, *Smardae* sp. A032, occurring in the living tissue of the moss *Ceratodon purpureus*; these compounds display weaker *in vitro* growth inhibition of cancer cells than sphaeropsidine A.[50]

3. Metabolites produced by toxigenic fungi

3.1.Bisorbicillinoids from *Trichoderma citronoviride*

The *in vitro* growth inhibitory activity of 14 metabolites (Figs. 3-5) isolated from terrestrial (including phytopathogenic and toxigenic) fungi were characterized in six cancer cell lines.[51] The natural products were classified as those metabolites associated with IC_{50} concentrations <

100 μM in all six cancer cell lines analysed as opposed to those metabolites associated with IC_{50} concentration > 100 μM in at least one out of the six cancer cell lines analyzed.[51] Two metabolites, namely bislongiquinolide (Fig. 3) and 2',3'-dihydrotricodimerol (bisorbibutenolide, Fig. 3) were found with IC_{50} concetrations < 100 μM in the six cancer cell lines analyzed.[51] These two natural products were isolated from the biomass of fungus *Trichoderma citrinoviride* on settling and feeding preference of the aphid *Schizaphis graminum*.[52] Bislongiquinolide is also named trichotetronine.[53,54]

The cytotoxic activity of 2',3'-dihydrotricodimerol had been reported previously;[55] 2',3'-dihydrotrichodimerol was also shown to activate the peroxisome proliferator-activated receptor-Y (PPAR-Y),[56] which exerts major roles in cancer cell biology.[57] This metabolite has also been reported to suppress the production of tumor necrosis factor-alpha (TNF-alpha) and nitric oxide in LPS (lipopolysaccharide)-stimulated RAW264.7 cells.[56]

The remaining 12 compounds displayed weak cytotoxic activity, if any, in the six cancer cell lines analysed.[51] These 12 metabolites include phyllostin, seiricardines B and C, cavoxin, cyclopaldic acid, flufuran, fusapyrone, scytolide, seiricuprolide, seiridin, verrucarin E and 16,17-dihydrobislongiquinolide (for structures, see Fig. 4). The origin of each of these compounds is detailed in Balde et al.[51]

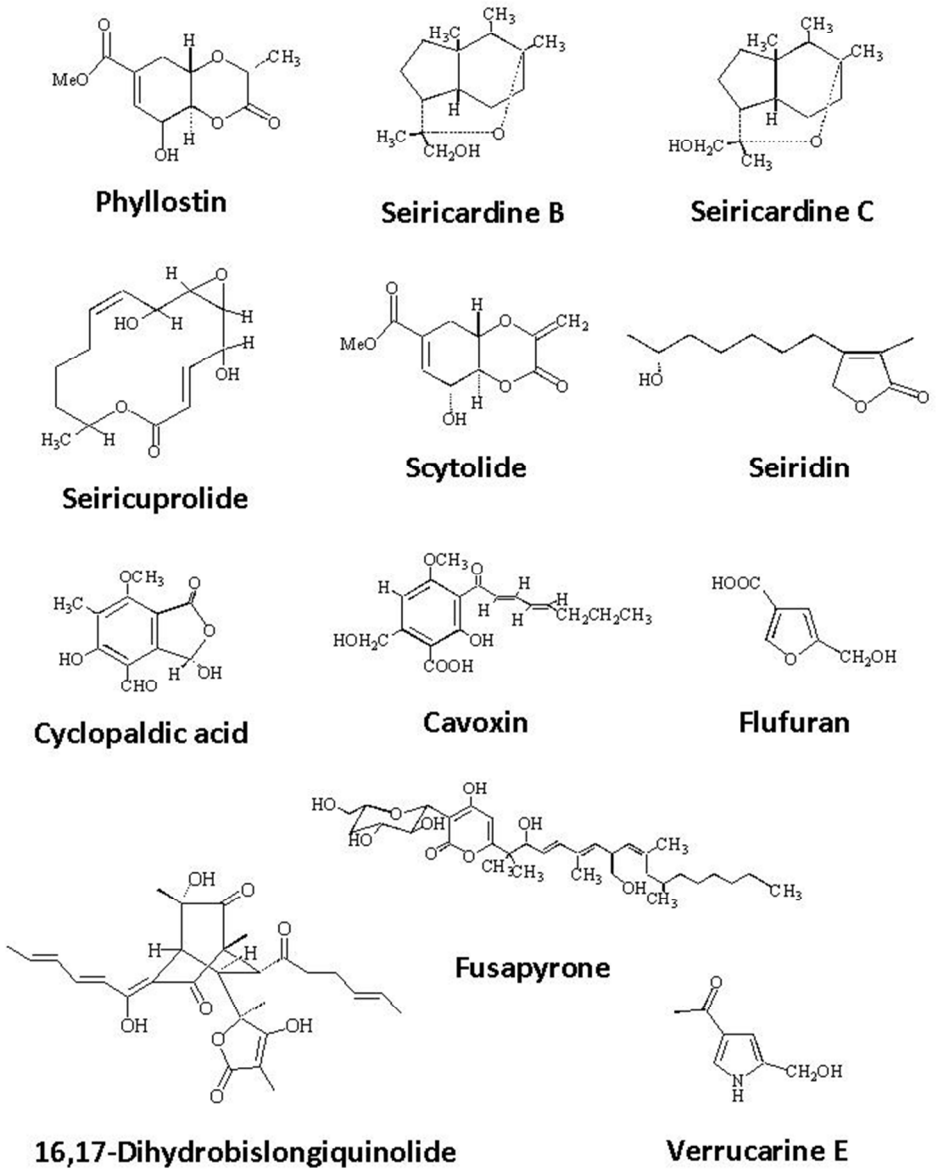

Figure 4

3.2.Sequiterpene and eurochevalierine from *Neosartorya pseudofischeri*

Neosartorya and *Eurotium* species are respectively sexual and imperfect stage forms of *Aspergillus* species and, like *Aspergillus*, they produce a variety of mycotoxins, such as gliotoxin

and pyripyropenes. Other metabolites of these species are 1,4-dihydroxy-2(1H)-pyridone derivatives, prenylated indole alkaloids, the angiogenesis inhibitor azaspirene, bioactive γ-lactones as well as polyketide derivatives, such as glabramycins A-C4.[58-61] The terpenoid sequiterpene and the trypthopan-derived terpene alkaloid eurochevalierine (Fig. 5) were isolated from the organic extract of rice culture of *N. pseudofischeri*.[61] Eurochevalierine additionally was obtained from *Eurotium chevalieri*.[60] Interestingly, sequiterpene and eurochevalierine can be considered as possible precursors in the biosynthesis of the potent benzoxazine natural product CJ-12662, a topoisomerase inhibitor, which was previously isolated from *Aspergillus fisheri* var. *thermomutatus*,[62] and then re-classified as *A. thermomutatus*. In its own right, eurochevalierine exhibits *in vitro* growth inhibitory activity in various cancer cell lines[60,61] with a potency higher than that displayed by sequiterpene and rivalling those of etoposide and carboplatin, two compounds used to treat cancer patients.[61] Computer-assisted phase-contrast microscopy revealed that eurochevalierine was not cytotoxic to human U373 glioblastoma (GBM) and A549 non-small cell lung cancer (NSCLC) cells with known tendencies to be resistant to apoptosis. Instead, cytostatic effects were observed involving marked inhibition of mitotic rates in these cells. Flow cytometry analysis further confirmed that eurochevalierine does not induce apoptotic features in U373 or A549 cancer cells. It thus appears that eurochevalierine represents a novel chemical scaffold for the development of anticancer agents effective against cancers unresponsive to traditional therapy with proapoptotic agents.[61] Because the ester bond linking the indole-containing portion of the molecule with the terpene residue is hydrolytically labile, the first question that needs to be addressed is whether both units are required in the cytostatic action of this promising anticancer agent and future studies will undoubtedly involve synthetic work aiming at resolving the minimum structural requirements in this scaffold.

4. Metabolites produced by non-toxigenic fungi

4.1. Tryprostatins from *Aspergillus fumigatus*

Tryprostatins A and B (Fig. 5) are indole alkaloidal fungal products isolated from *Aspergillus fumigatus*,[63] among other sources. They have also been obtained by total synthesis.[64] Tryprostatin A was first demonstrated to be an inhibitor of mitogen activated protein (MAP)-kinase-dependent microtubule assembly and, through the disruption of the microtubule spindle, to specifically inhibit cell cycle progression at the mitotic phase.[65] Neither tryprostatin A nor tryprostatin B directly targets tubulin or topoisomerases. The cytotoxic activity of a tryprostatin B stereoisomer equals the one displayed by etoposide in various human carcinoma cell lines.[66] Another promising activity of tryprostatin A involves its action against the multidrug resistance (MDR) phenotype, which is one of the major causes of chemotherapy failure in cancer patients.[67-69] One of the members of the superfamily of ABC transporters, BCRP, was demonstrated to confer an atypical MDR phenotype to tumor cells[70] and tryprostatin A acts as a BCRP inhibitor.[71,72]

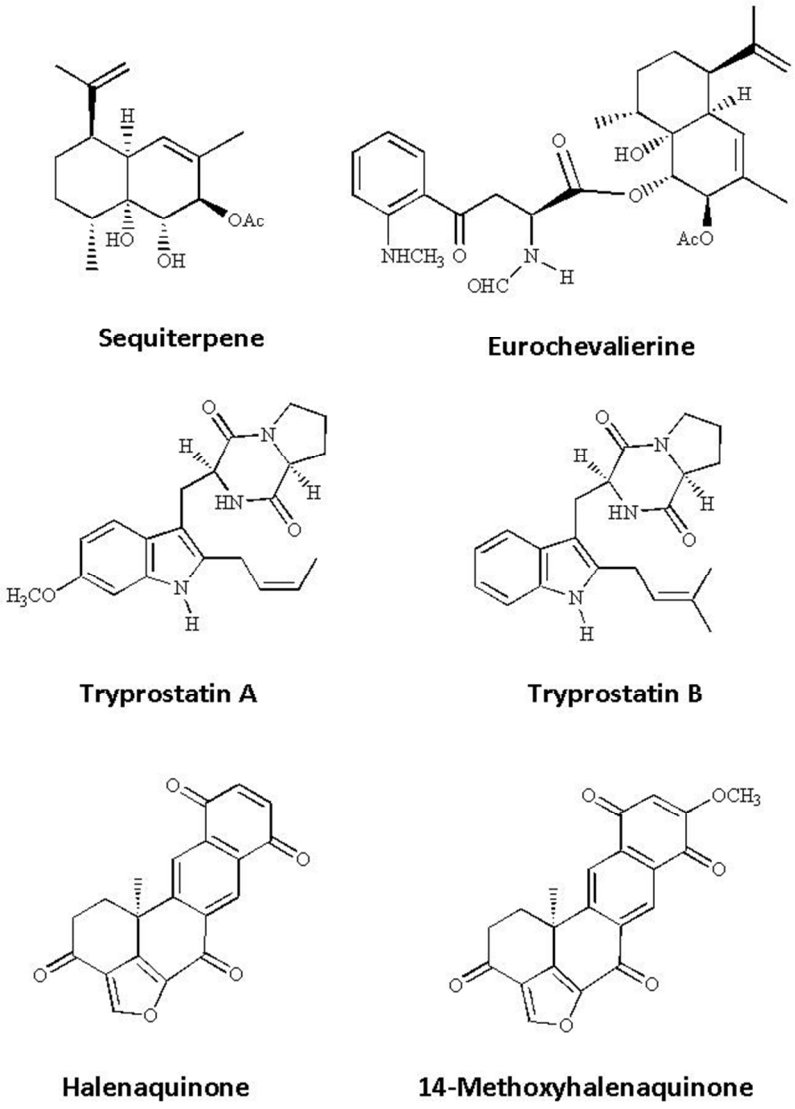

Figure 5

4.2. **Halenaquinones from *Xestospongia* cf. *carbonaria***

Halenaquinone (Fig. 5) was isolated from two Indo-Pacific collections of the sponge *Xestospongia* cf. *carbonaria*.[73] Additional metabolites isolated from this sponge include tetrahydrohalenaquinone B, 14-methoxyhalenaquinone (Fig. 5), xestoquinolide A, xestoquinolide B, halenaquinol, halenaquinol sulfate, xestoquinone**,** and

tetrahydrohalenaquinone A.[73] These natural products, along with halenaquinone derivatives, were tested for their ability to inhibit the activity of various protein tyrosine kinase (PTK); While halenaquinone inhibited EGF (Epidermal Growth Factor) receptor activity (IC_{50}= 19 μM), it was not active against protein kinase C, a result suggesting that halenaquinone is not a general kinase inhibitor.[74] Its congener 14-methoxyhalenaquinone showed a similar activity (IC_{50} = 5 μM), while synthetic derivatives were less active.[74] SAR analyses revealed the minimum structural requirements for strong PTK inhibitory activity of halenaquinone derivatives involving the presence of a pentacyclic skeleton with electrophilic sites at each end (e.g., the A/E- and D-rings of halenaquinone). The planar polyunsaturated framework with a quinone end ring was found to be a necessary but not a sufficient condition for PTK activity.[74]

4.3.Diketopiperazine TAN 1496 A-E from *Microsphaeropsis* sp. FL16144

Three epi-oligothiaketopiperazines, named TAN-1496 A, C and E (Fig. 6), were isolated together with the known TAN-1496 B and D from the culture filtrates of *Microsphaeropsis* sp. FL-16144, a strain isolated from a soil sample in Ibaragi prefecture, Japan.[75] These compounds display *in vitro* growth inhibitory activity in several mouse and human cell lines analyzed, while TAN-1496 A was found to inhibit topoisomerase I activity in a dose-dependent manner.[75]

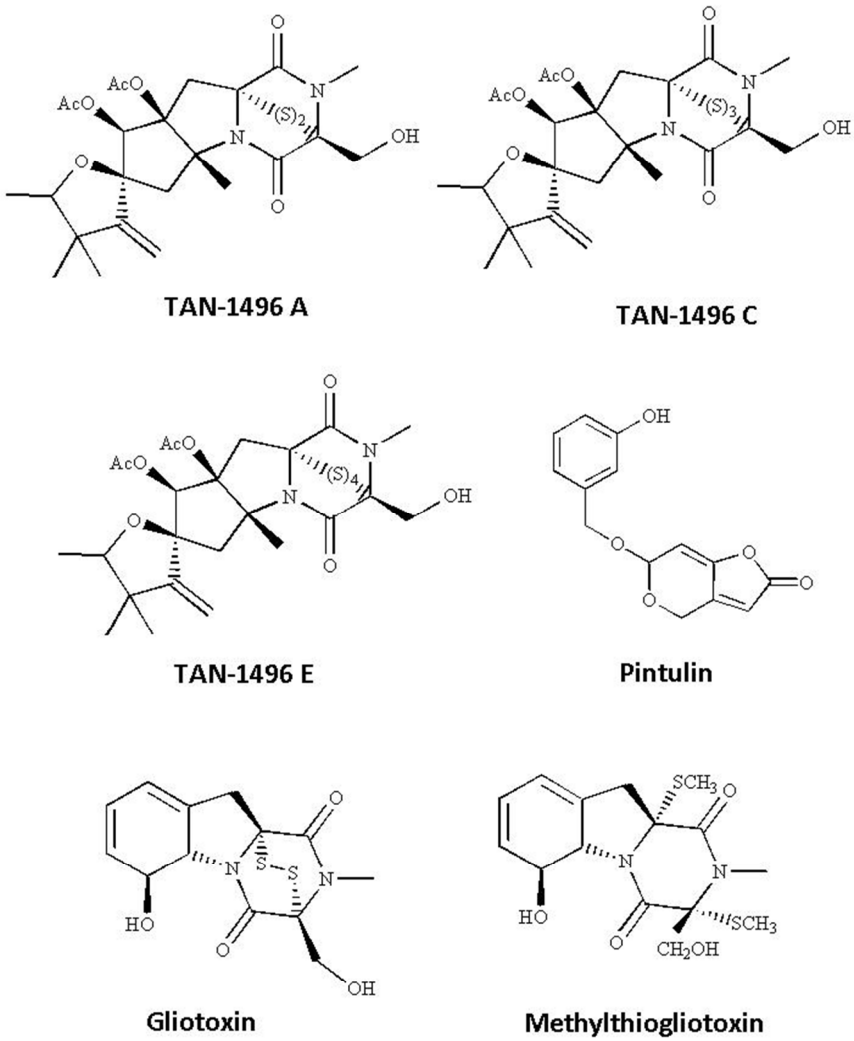

Figure 6

Due to their toxicity and insufficient water solubility, a SAR study was carried out to find more bioavailable and less toxic derivatives by means of chemical modifications. However, the introduction of a hydrophilic group was not favorable for specificity against topoisomerase I or growth inhibition of tumor cells.[75] Also, the reductive cleavage of the disulfide bond resulted in the loss of both topoisomerase I activity and tumor cell growth inhibition.[75] Further studies also

indicated that TAN-1496 A may inhibit topoisomerase I itself before it binds to DNA.[76] These findings suggest that these metabolites are antitumor agents with a mode of action different from that of camptothecin (CPT) and its derivatives, which are also topoisomerase I inhibitors.[62]

4.4.Pintulin from *Penicillium vulpinum*

Pintulin (Fig. 6) is produced in racemic form together with *m*-hydroxybenzylic alcohol and isopatulin in the liquid culture filtrates of *Peniciullium vulpinum*, a strain F-4148 isolated from a soil sample collected at Towada city, Aomori prefecture, Japan.[77] Pintulin displays forty times weaker cytotoxic activity against various cultured cancer cell lines than adriamycin.[77] Also, the administrations of 1.25 mg/kg of pintulin on days 1 and 3 provided weak therapeutic benefits in mice transplanted with p388 leukemia cells (i.p.-i.p.), while the continuous administration for 5 days at 3.13 mg/kg did not prolong the survival time of mice and resulted in toxicity.[77]

4.5.Gliotoxin and methylthiogliotoxin from strains Y90086 and Y80805

Gliotoxin and methylthiogliotoxin (Fig. 6) were isolated from the liquid culture filtrates of strains Y90086 and Y80805.[78] Gliotoxin and methylgliotoxin inhibit the proliferation of HUVEC cells in a dose dependent manner with IC_{50} values of 40 and 400 ng/mL, respectively.[78] Both compounds display weaker *in vitro* growth inhibitory activity in cancer than in HUVEC cells; in addition these compounds also reduce the migration of HUVEC cells and the formation of HUVEC-related tubes.[78] All these data highlight the potential antiangiogenic effects of gliotoxin and methylgliotoxin. The fact remains that gliotoxin also kills various types of cells, inducing for example caspase-dependent neurite degeneration and calpain-mediated general

cytotoxicity in differentiated human neuroblastoma cells.[79] Additional findings include gliotoxin-mediated enhancement of radiotherapy efficiency via inhibition of radiation-induced GADD45a, p38 and NFkappaB activation,[80] induction of apoptosis of cancer cells *in vitro* and *in vivo* anticancer activity in human cancer xenografts transplanted in SCID mice.[81] Finally, gliotoxin analogues possessing histone methyltransferase inhibitory activities have been isolated from marine-derived fungus (*Penicillium sp*.).[82]

4.6.Perybisin and macrosphelide from *Periconia byssoides*

Perybisin and macrosphelide (Fig. 7) are produced by a strain of *Periconia byssoides* originally isolated from the sea hare *Aplysia kurodai*.[83,84] These fungal metabolites are cell-adhesion inhibitors and could act as antimetastatic compounds: they potently inhibit the adhesion of human leukemia HL-60 cells to HUVEC cells.[83,84] Part of this mechanism of action has been deciphered. For example, macrosphelide B supresses metastasis through inhibition of adhesion of sLe(x)/E-selectin molecules.[85] A number of synthetic macrosphelides were prepared, including ring-enlarged analogues and epothilone-hybrid compounds, and found to exert potent apoptosis-inducing activity in human lymphoma cells.[86,87] Interestingly, the macrosphelide-induced apoptosis in human lymphoma cells can be enhanced by hypothermia.[86]

4.7.Fusarisetin A produced by *Fusarium* sp. FN080326

Fusarisetin A (Fig. 7) is produced by a strain of *Fusarium* sp. FN080326 isolated from a soil sample collected in Daejeon, Korea.[88] Fusarisetin A is an acinar morphogenesis inhibitor that possesses both an unprecedented carbon skeleton and a new pentacyclic ring system (Fig.

7).[88] Fusarisetin A is a potent cancer migration inhibitor and *ex vivo* studies show that this compound is able to inhibit different types of cell migration.[89]

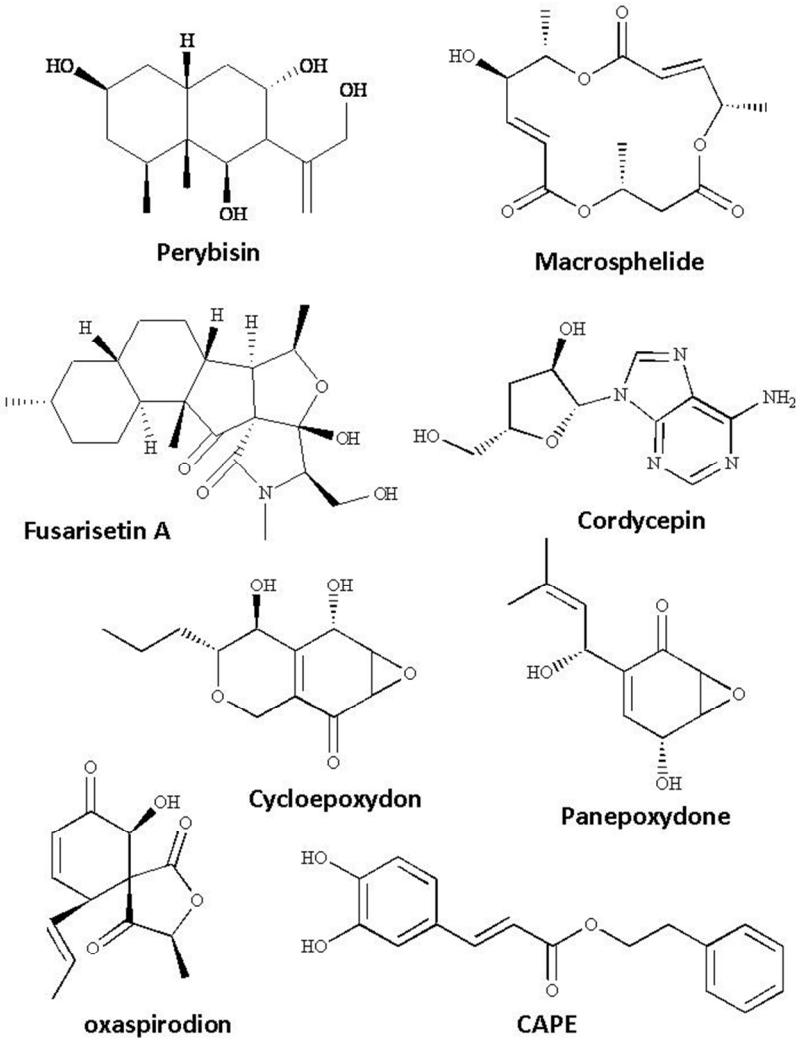

Figure 7

5. Metabolites from different mushroom species

Cordycepin (Fig. 7) is produced by *Cordyceps militaris* (one of the top three renowned traditional Chinese medicines[90]) and it displays a broad spectrum of pharmacological activity

including pleiotropic anticancer effects.[91] Cordycepin causes p21WAF1-mediated G2/M cell-cycle arrest in human bladder[92] and colon[93] cancer cells by regulating c-Jun N-terminal kinase activation. This metabolite also causes DNA double strand breaks in breast cancer cells,[94] induces apoptosis through the activation of various pathways including the generation of reactive oxygen species in human leukemia cells[90] and activates the calcium-calpain-caspase 7-PARP pathway in thyroid carcinoma cells.[95] Cordycepin also suppresses TNFalpha-induced NF-kappaB activation[96] and in the same manner it acts as a sensitizer to TNFalpha-induced apoptosis through eukaryotic translation initiation factor 2alpha (eIF2alpha)- and mammalian target of rapamycin complex 1 (mTORC1)-mediated inhibition of NF-kappaB.[97] Lastly, it must be mentioned that cordycepin inhibits migration and invasion of human prostate cancer cells through inactivation of Akt.[98]

Panepoxydone and cycloepoxydon (Fig. 7) are isolated from *Panus conhatus*.[99] Both compounds are potent inhibitors of NF-kappaB functions.[100-102] Panepoxydone may serve as a lead structure for the development of transcription-based inhibitors of pro-inflammatory gene expression.[101,103] Targeting NF-kappaB signaling is important because, as mentioned by Umezawa et al.,[102] NF-kappaB is a transcription factor that induces the immunoglobulin kappa chain, cytokines, such as interleukin (IL)-1, IL-2, IL-6, IL-8, TNF-alpha and interferon gamma, and cell adhesion proteins. It also induces anti-apoptotic proteins and inhibits TNF-alpha- and anticancer drug-induced apoptosis.[102] Thus, NF-kappaB is a major player in cancer progression and it represents a promising therapeutic target in various types of cancers.[99,104-106]

Oxaspirodion (Fig. 7) is isolated from *Chaetomium subspirale* and it also inhibits the activation of the transcription factor NF-kappaB.[107] Furthermore, oxaspirodion inhibits inducible TNF-alpha expression.[108]

Caffeic acid phenethyl ester (CAPE, Fig. 7), produced by several mushrooms used in folk medicine, such as *Agaricus bisporus*, *Lentinus edodes* and *Phellinus linteus*, specifically inhibits the NF-κappaB binding to DNA.[109,110]

6. Summary of the modes of action associated with the anticancer effects of the described fungal metabolites

The main mechanisms of action of 18 of the described fungal metabolites are summarized in Fig. 8. In particular, this figure highlights that these natural products exert a wide variety of anti-cancer properties *in vitro,* including pro-apoptotic, anti-proliferative, anti-angiogenic and anti-migratory effects through different pathways. The diversity and originality of the biochemical mechanisms associated with the anticancer properties of these natural products will undoubtedly encourage continued interest in fungal metabolites as potential anticancer agents.

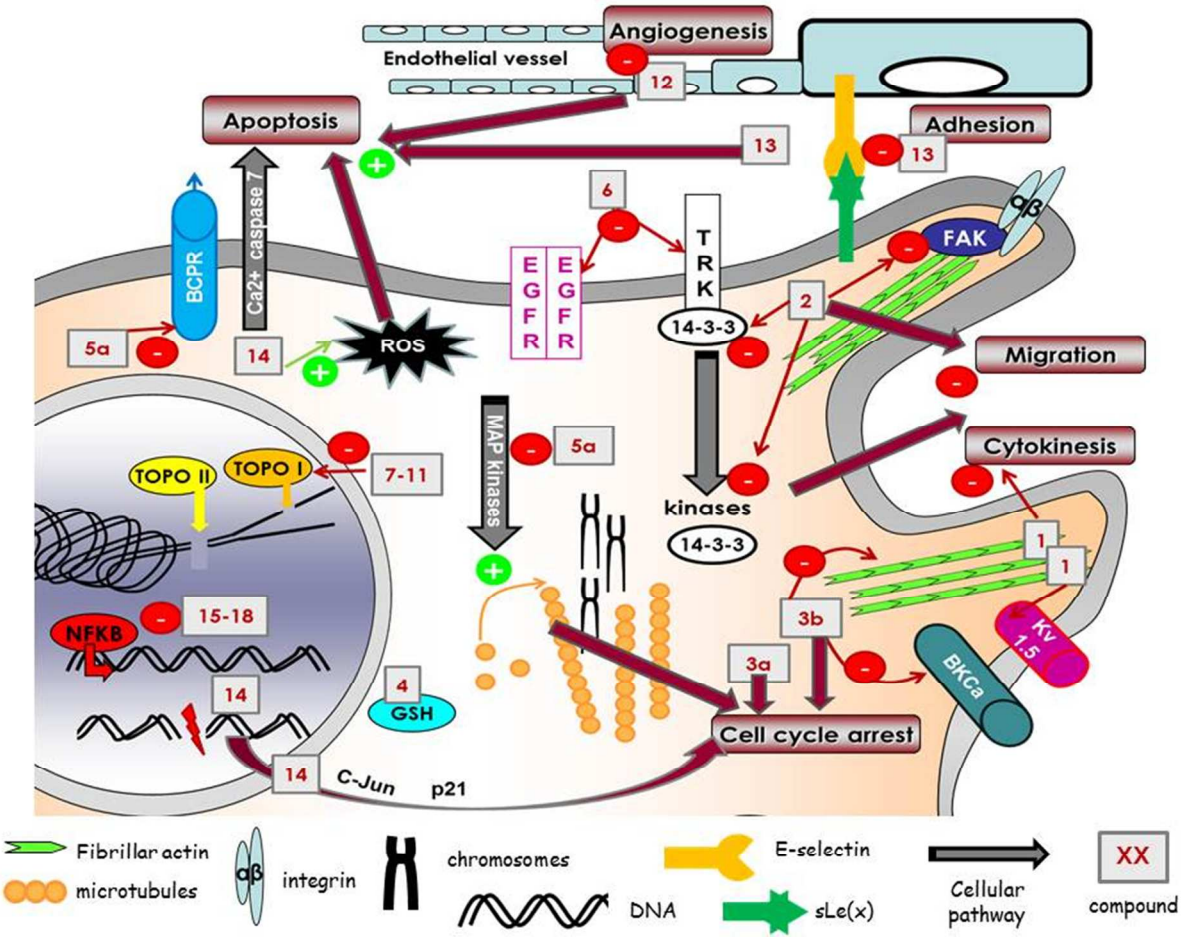

Figure 8: Illustration of the main molecular and cellular effects of fungal metabolites on cancer cell. The codes for the compounds in the gray squares are as follows: 1: cytochalasins; 2: fusicoccin A; 3: ophiobolins: 3a ophiobolin O, 3b ophiobolin A; 4: phyllostictin A; 5: tryprostatins, 5a: tryprostatin A; 6: halenaquinones; 7-11: TAN1496A-E; 12: gliotoxins; 13: macrosphelide; 14: cordycepin; 15: panepoxydone; 16: cycloepoxydone; 17: oxapyrodion; 18: caffeic acid phenethyl ester. TRK: tyrosine kinase receptor. GSH: glutathione. BCRP: breast cancer resistance protein. EGFR: epithelial growth factor receptor. ROS: reactive oxygen species. FAK: focal adhesion kinase. TOPO: topoisomerases. NFκB: nuclear factor kappaB. BKCa and Kv1.5 are ion channels. 14-3-3 are proteins involved in protein-protein interactions. c-

Jun and p21 are transcription factors. Red minus containing cycle means “inhibits” while green positive cycle means “stimulates”. Other graphical legend is presented within the figure. The biological roles of the various targets illustrated in this figure are explained in the body text.

7. Conclusions

Although the advent of high-throughput screens involving molecular targets created a demand for the generation of large combinatorial libraries of compounds, the shift away from purely synthetic to more natural product-like compounds, either derived from or inspired by natural products, has continued to work its way back to drug discovery programs. It has been now generally recognized that the hit rates obtained using the natural product-derived collections of compounds are significantly higher than those of resulting from combinatorial libraries.[1] Furthermore, the new understanding of the Lipinski’s rules emphasizes that they have to be applied with caution to natural products, which are recognized by active transport systems.[111] Thus, natural products, which have already proved their worth in many areas of human medicine, and particularly in cancer drug discovery, are expected to draw an increasing amount of attention yet again. Although a fungal metabolite is yet to lead to an approved anticancer drug, the examples in the current review demonstrate that the tremendous structural diversity and promising anticancer potential of many of these natural products will eventually lead to this desired breakthrough.

8. References

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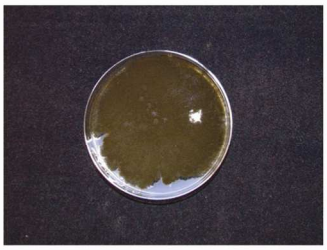
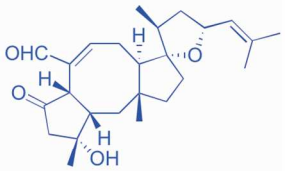
The review discusses the reported sources, structures and biochemical studies aimed at the exploitation of the anticancer potential associated with fungal secondary metabolites.



Drechslera gigantea



Ophiobolin A

inducer of a paraptosis-like cell death in glioma cells

promising antiglioma agent