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Fungal metabolites: Nature's key to antiangiogenic cancer therapies

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Abstract

Fungi have been thriving on planet Earth for millions of years, playing multiple roles in diverse ecosystems. Both free-living and endophytic fungi contain a plethora of secondary metabolites with rich bioactivity, which can be harnessed for therapeutic purposes. Many tumors grow rapidly due to the neovasculature formed by the activity of angiogenic genes. One of the strategies to curb such cancers is the use of anti-angiogenic drugs. Many fungi are treasure houses of chemicals such as fumagillin, barbatolic acid, usnic acid, trichodimerol and cordycepin. These can be utilized as anticancer drugs to reduce the neovascularization of tumors, thereby leading to the cessation of growth and the shrinkage of the tumor. This strategy could be significantly enhanced by using fungal nanoparticles synthesized through green methods, providing a more targeted treatment. By exploiting the unique properties of the tumor, these nanoparticles can offer more efficient means of delivering anticancer drugs directly to tumor sites, facilitating precise targeted therapy. This review emphasizes the significant potential of green-synthesised nanoparticles and fungal metabolites as novel molecules for targeted cancer therapy. Further research into their synergistic effects may lead to improved treatment outcomes and the development of more potent anti-angiogenic medications than those currently available.

Keywords

anti-angiogenic; cordycepin; fumagillin; green synthesis; triple-negative cancer

Introduction

Fungi are important members of any ecosystem due to their roles in decomposition and nutrient recycling, contributing significantly to forest ecosystems. The study of fungi and their secondary metabolites has garnered significant scientific interest because of the broad range of bioactive compounds, they produce. Certain fungi have formed symbiotic associations with many plant species for thousands of years. Their antimicrobial properties and anti-inflammatory properties further enhance their medicinal potential. Endophytic fungi colonize the interior of healthy host plant tissues for part or all their life cycle, usually without causing disease. Both free-living and endophytic fungi contain an unexploited pool of valuable metabolites and are more metabolically active than their free-living counterparts. This makes them a promising source of new metabolites for agriculture, medicine and the food industry (1). Endophytic organisms can synthesise chemicals with immunosuppressive, insulin-mimetic, antiviral, antibacterial and antioxidant activities (2).

Recent research has identified several fungi that produce anticancer compounds., such as cordycepin, usnic acid and toluquinol (3-5). These bioactive molecules offer exciting possibilities for overcoming challenges in cancer treatment, particularly in aggressive and difficult-to -treat cancers. One of such examples is triple- negative breast cancer (TNBC), which accounts for 15% of all breast cancer cases. TNBC is defined by the absence of estrogen (ER), progesterone (PR) and HER2 receptors, making it unresponsive to hormone- suppressant therapies. This challenge underscores the importance of exploring alternative treatments, such as fungal-derived anticancer compounds (6). One approach to combating TNBC is the use of antiangiogenic drugs, which inhibit new blood vessel formation in the tumor and thus inhibit growth. However, many synthetic anticancer drugs cause side effects such as hair thinning, muscle and joint pain, dizziness and vaginal bleeding. As a result, scientists are seeking natural anti-angiogenic compounds.

Anti-angiogenic therapy treats conditions such as cancer, psoriasis, atherosclerosis and diabetic retinopathy by inhibiting excessive formation of new blood vessel formation and preventing pathological angiogenesis (7). Fungal metabolites have significant therapeutic potential because they target angiogenesis-related genes, influencing the intricate genetic mechanisms that regulate blood vessel formation. Additionally, fungi are notable for their ability to produce a diverse array of secondary metabolites with exceptional bioactivity and structural variety. Marine fungi have emerged as a rich and abundant source of molecular diversity, surpassing many other natural resources (5). However, the synergistic effects of green-synthesised nanoparticles and fungal metabolites for targeted cancer drug delivery remain underexplored and current understanding of their interactions with angiogenic genes is still insufficient. While anti-angiogenic therapy has been found to be effective for treating cervical and ovarian cancers, some cancers like skin cancer and prostate cancer, do not respond to anti-angiogenic therapy. Furthermore, more accurate biomarkers are needed to predict which patients are likely to benefit from such therapy.

Mechanism of angiogenesis

Blood vessel formation involves vasculogenesis, the process by which endothelial progenitor cells create the primary vascular network and angiogenesis, the process by which new blood vessels form through the expansion of pre-existing ones (8). The main vascular plexus forms at the end of the vasculogenesis stage and all subsequent vascular net modifications take place during angiogenesis through the expansion of the plexus (9). Angiogenesis occurs during wound healing, solid tumor formation, rheumatoid arthritis, diabetic retinopathy, psoriasis and atherosclerosis. Interactions among cells and the immune, nervous and endocrine systems contribute to the formation of a self-sustaining tumor ecosystem (10). Tumors are therefore managed as "organ systems" (11), with neovasculature resulting from angiogenesis providing the necessary oxygen and nutrients. The cells within the tumor produce pro-angiogenic factors such as PDGF (platelet-derived growth factor), HGF (hepatocyte growth factor), FGF (fibroblast growth factor), as well as VEGF (vascular endothelial growth factor) and its relative receptors, VEGFRs. These factors are responsible for the expression of angiogenic genes in the tumor and endothelial cells. Cancer-associated fibroblasts (CAFs) also play a pivotal role in inducing angiogenesis in the tumor microenvironment (8).

Sprouting angiogenesis is the process by which endothelial cells proliferate from pre-existing blood vessels to create new ones. Tumors depend on this process to secure the blood flow necessary for their growth and dissemination. In response to injury or growth spurt, VEGF and other pro-angiogenic factors are “switched on” to initiate the process. VEGF promotes the attachment of VEGFR to surrounding endothelial cells, which, in turn, triggers the release of metalloproteases in the cell environment. This degrades the basement membrane and detaches pericytes from the vessel walls. The combined effect of the angiogenic factors stimulate the formation of endothelial cells into tip cells and stalk cells. In the former, fusion of intracellular vacuoles and adjacent cells forms a continuous lumen, while in the latter, the plasticity of the endothelial cells allows them to form a central tubular structure that is the lumen. Vasculogenic mimicry is an alternative process in which cancer cells form blood vessel-like structures, by passing conventional angiogenesis process that relies on endothelial cells. This mechanism allows tumor cells to assemble into a de novo network of blood vessels, supporting the tumor growth and metastasis (12). The stages of angiogenesis are depicted in Fig. 1. The first stage is the hypoxia-inducible factor 1 (HIF-1) activation, where cells activate a protein called HIF-1 in response to low oxygen levels (hypoxia). HIF-1 induces the production of various growth factors. In the second stage, endothelial cell activation, growth factors bind to specific receptors on endothelial cells. Then the matrix metalloproteinases (MMPs) produced by activated endothelial cells facilitate cell migration by breaking down the basement membrane. The next stage is migration and proliferation, during which the activated endothelial cells move toward the angiogenic signal source. Tip cells guide this migration and leading the development of new blood vessel sprouts. Finally in the stage of maturation and stabilization, the newly formed blood vessels undergo a process of strengthening and integration into the existing vascular network (11).

Growth factors involved in angiogenesis

The process of angiogenesis begins with the disintegration of the basement membrane, followed by endothelial cell migration and division. In the final phase, the newly formed conduit connects with an already- existing blood vessel (13). The primary trigger for activating the transcription factor HIF-1, which regulates the expression of matrix elements, growth factors, cell-adhesion molecules and metabolic proteins, is hypoxia (a low oxygen condition). Pro-angiogenic and anti-angiogenic

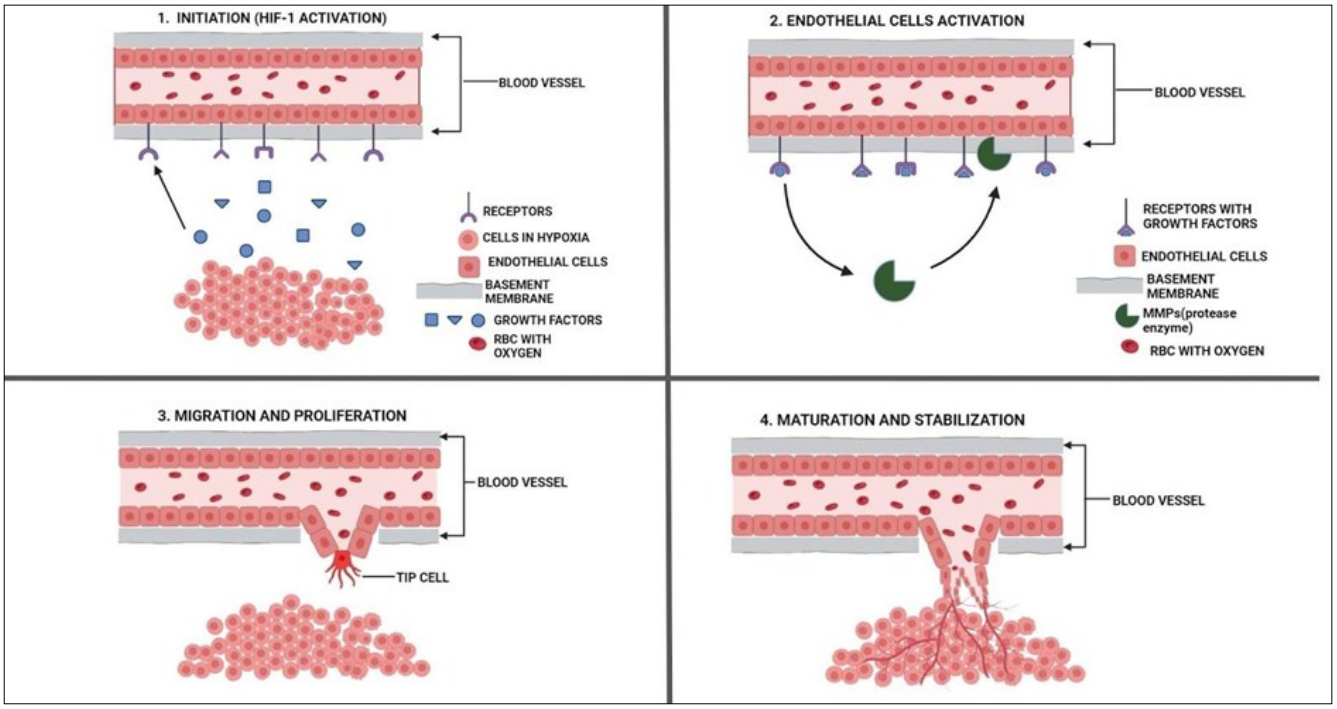

Fig. 1. Progress of angiogenesis depicting the initiation through HIF-1 activation, endothelial cell activation, migration of endothelial cells and maturation of new blood vessels to integrate into existing networks.

factors must be in equilibrium for blood vessel formation to be triggered. An imbalance between these factors can disrupt this process: with excessive pro-angiogenic activity causes abnormal blood vessel growth, contributing to tumor development while, excessive anti-angiogenic activity inhibits necessary blood vessel formation, leading to impaired healing. Growth factors that promote angiogenesis, such as transforming growth factor- β (TGF-β), angiopoietin-1, PDGF, FGFs, VEGF and epidermal growth factor (EGF), are released when a cell is oxygen-depleted (14). The endothelial cell membrane receptors bind to these factors, activating vascular endothelial cells to initiate angiogenesis. Tip cells guide the sprouting of new blood vessels by releasing matrix metalloproteinases, which degrade the basement membrane. Behind them, stalk cells multiply and elongate, contributing to the formation and structural integrity of the new blood vessels. They achieve this by proliferating to extend the sprout, forming the lumen to enable blood flow and facilitating vessel stabilization through pericyte recruitment and basement membrane deposition (15).

VEGF is a thoroughly studied pro-angiogenic protein. The development of new blood vessels is induced by VEGF signalling through EC-expressed VEGFRs (15). VEGF includes mammalian factors such as VEGF-A, VEGF-B, VEGF-C, VEGF-D. These factors interact with three structurally related tyrosine kinase receptors: VEGFR-1/Flt-1, VEGFR-2/Flk1/KDR and VEGFR-3/Flt-2. These receptors, expressed on the surface of endothelial cells, function as homo- or heterodimers (16). The notch signalling pathway has a significant impact on the expression of these receptors, regulating the differentiation of stalk and tip endothelial cells to ensure proper branching, sprouting and vessel stability. Prototypic VEGF-A forms the best-characterized signalling pathway involved in angiogenesis, along with its receptors, VEGFR-2 and VEGFR-1 (17).

Transforming growth factor-β (TGF-β) functions as a strong tumor suppressor. TGF-β causes cell cycle arrest in the G1 phase through several mechanisms in distinct cell types. By activating the promoter of the protein 4E-BP1, which inhibits translation (a regulator of eukaryotic translation initiation factor 4F) through SMAD4, TGF-β block translation, cell growth and proliferation. However, the exact mechanisms by which TGF-β exerts these effects in different cell types remain unknown. Interestingly, as cancer progresses to later stages, cells often develop resistance to TGF-β's cytostatic effects. In fact, TGF-β can induce epithelial to mesenchymal transition (EMT) in cancer cells, thus promoting carcinogenesis (18).

FGFs interact with the tyrosine kinase receptors FGFR1, FGFR2, FGFR3 and FGFR4 (19). The FGF-FGFR signalling pathway is essential for physiological functions, influencing cells behaviour to promote healthy organismal development, angiogenesis and adult wound healing. Many cancers exhibit increased levels of growth factors (FGFs), such as FGF2 in lung, breast and leukemia; FGF8 in prostate cancer and breast cancer and FGF19 in TNBC and hepatocellular carcinoma. Notably, several FGFs may be co-expressed in the same tumor type. For example, TNBC may simultaneously elevate FGF3, FGF4 and FGF19. Understanding these correlations offers discernment into the complex functions of FGF-FGFR signalling in the development of tumors, directing possible remedial approaches (20).

Angiopoietins are another important family of growth factors, with angiopoietin-1 and angiopoietin-2 being the most studied. Their actions are mediated by tyrosine kinase receptors Tie1 and Tie2. Angiopoietins-1 (Ang1) is a potent angiogenic growth factor signalling through Tie2. Initially, Ang2 was thought to have an antagonistic effect through the same receptor; however, recent findings indicate that Ang2 can exhibit context-dependent agonist actions (21). Angiopoietin-1 produced

by perivascular cells, binds to the Tie2 receptor, stimulating vessels quiescence and stability. Angiopoietin-2 binds to Tie2 and induces vessel permeability, instability and vascular remodelling. These work together to preserve vascular homeostasis in the absence of disease (22).

Platelet-derived growth factors (PDGF-AB, CC, DD, AA and BB) and their associated receptors (PDGFR-αα, ββ and αβ) also play a key role in angiogenesis. They were found to be low or undetectable in normal cells, they have been observed to accumulate in a certain human cancer (23). HGF is a cytokine with pleiotropic effects, regulating inflammation, angiogenesis, morphogenesis, tissue repair and tumor growth. Many biological effects arise from the phosphorylation of the HGF receptor, c-Met. HGF can induce angiogenesis without vascular inflammation or enhanced permeability, implying that it may act independently of any prior trigger (8).

Fungal metabolites targeting angiogenesis

Many fungal metabolites have been discovered to affect angiogenic genes and hence have therapeutic potential for conditions related to angiogenesis, including cancer and vascular diseases. A few of these fungal compounds and their properties are discussed below.

***Trichodimerol*:** It was identified from the deuteromycete strain *Trichoderma longibrachiatum* IBWF049-2000. In recent years, various significant investigations have found that the TGF-β pathway is a potentially effective approach to reducing tumor development and angiogenesis. Trichodimerol inhibits TGF-β signalling by preventing the phosphorylation of Smad2/3 transcription factors, which, in turn, inhibits these transcription factors from binding to DNA and interfering with TGF-β signalling, according to research done on fungal extracts using a cell-based reporter assay. However, trichodimerol did not inhibit hypoxia-inducible factor HIF-1α-dependent transcriptional reporter activity, suggesting that the signalling cascade leading to the oxygen-dependent induction of pro-angiogenic genes remained unaffected. HIF-1α regulates the hypoxic response by activating pro-angiogenic genes like VEGF, which stimulate the development of blood vessels in tumors. Since trichodimerol does not reduce HIF-1α activity, it is unlikely to impact this angiogenic mechanism in hypoxic environments. (24, 25).

***Usnic acid*:** Usnic acid, a secondary metabolite extracted from *Usnea antartica*, possess anti-angiogenic properties. It is one of the few commercially available lichen metabolites. Lichens are symbiotic organisms composed of algae, cyanobacteria and fungi. The unusual biological activities of lichen secondary metabolites have led to their classification as unique natural compounds. Usnic acid is an anti-angiogenic substance that prevents angiogenesis induced *in-vitro* and *ex-vivo* by VEGF and BFGF. It inhibits the growth of OVCAR-3 ovarian cancer cells with an IC_{50} of 20 µM, while showing no toxicity to non-cancerous cells. In addition to stopping the growth of new blood vessels, usnic acid's anti-angiogenic activity is achieved by blocking endothelial cell migration, proliferation and tube formation (4, 26, 27).

***Cordycepin*:** Cordycepin (3′-deoxyadenosine, $C_{10}H_{13}N_5O_3$, Cor) is isolated from *Cordyceps militaris.* It is a bioactive molecule that functions as an adenosine analogue. Several pharmacological activities, including anti-aging, anti-oxidation, anti-cancer, anti-atherosclerosis and immunomodulation, have been linked to cordycepin. In Ang II-induced HASMCs, cordycepin decreased the relative protein expressions of endothelial nitric oxide synthase (eNOS), cluster of differentiation 31 (CD31), VEGF and VEGF receptor 2 (VEGFR2) (3). By downregulating focal adhesion kinase (FAK) and activating p53 and p21, cordycepin reduces the proliferation, migration, angiogenesis and tumor formation of endothelial cells. When used with anti-tumor medications, its anti-angiogenic properties may improve the effectiveness of cancer therapies by preventing blood vessel formation (28, 29).

***Toluquinol*:** It is also referred to as 2,5-toluenediol or 2-methylhydroquinone, isolated from the fermentation broth of the marine fungus *Penicillium* sp. HL-85-AL55-R004. Toluquinol targets the angiogenesis process, which is essential for tumor growth and shows significant potential as an anti-cancer drug. Because it does not directly inhibit VEGF and FGF2 receptors, it has a unique effect on endothelial cell differentiation, proliferation, migration and invasion. This suggests that its action is downstream and could affect the PI3K/Akt pathway. Through this approach, toluquinol demonstrates its dual anti-angiogenic and anti-tumor characteristics by inhibiting the development of endothelial and tumor cells and inducing apoptosis. Its potential mechanism is supported by its capacity to decrease Akt activity in response to VEGF and FGF2 (5, 30).

***Monacolin X*:** The fungus *Monascus* sp. NMK7, linked with sponge *Clathria frondifera* secretes monacolin X, an anticancer/antiproliferative chemical (31). *In vitro,* monacolin X effectively suppresses PKCα activity *via* VEGFR2, drastically limiting HUVEC proliferation, migration, invasion, tube formation and inducing apoptosis. Endothelial cell proliferation was inhibited by monacolin X in a concentration-dependent manner, with its greatest effect occurring at 300 µM. The results obtained clearly imply that TPA-induced PKC activation is inhibited by monacolin X. Furthermore, it was also found that after treatment with monacolin X, VEGFR2 mRNA expression was downregulated in HUVECs. PKC-mediated suppression of angiogenesis is demonstrated by the inhibition of PKCα *via* VEGFR2 in HUVEC cells when monacolin X is present. According to the findings, monacolin X controls the signal transduction pathway that activates TPA-responsive PKC isozymes, particularly PKCα and reduces the expression of VEGFR2 in HUVECs (32).

***Ophiobolin A*:** Ophiobolin A, isolated from the endophytic fungus *Bipolaris setariae,* has been shown to be cytotoxic to a variety of cancer cell types at nanomolar quantities. Tumor cells with damaged membrane asymmetry exhibit an enhanced surface representation of phosphatidylethanolamine (PE), a lipid bilayer component generally confined to the inner layer of the cell membrane. By employing a retroviral gene trap technique to mutate the near-haploid cell line KBM7 through insertional mutagenesis, OPA was shown to generate PE-OPA adducts, which are linked to membrane rupture and ultimately, cell

death. This finding demonstrated the potential significance of PE as a small-molecule target, encouraging researchers to investigate PE as a novel chemotherapeutic strategy, especially for cancer types to respond poorly to existing chemotherapy (33, 34).

***Barbatolic acid*:** Barbatolic acid was isolated from the lichens *Bryoria capillaris.* Lichens produce several types of secondary metabolites. This research describes for the first time the anticancer and antiangiogenic activities of barbatolic acid. Barbatolic acid is toxic at high concentrations (200 and 400 µM), as indicated by cytotoxicity tests. In addition to impeding endothelial cell migration, barbatolic acid is believed to have antiangiogenic properties due to its capacity to suppress other angiogenesis-related factors (35, 36). Barbatolic acid's cytotoxic action was identified using the cell viability test with Alamar Blue, the cellular membrane degradation activity (LDH assay) and the dsDNA degradation activity (7).

***Fumagillin*:** It is a mycotoxin produced by the saprophytic fungus *Aspergillus fumigatus*. Fumagillin is a strong inhibitor of the enzyme MetAP type 2 (methionine aminopeptidase). This mycotoxin irreversibly binds to the MetAP2 gene, preventing the hydrolysis of the starting amino acid methionine in newly produced proteins. The stability essential for cellular safety could be disrupted by the suppression of the MetAP2 gene. Fumagillin and its derivative fr-11887 have been shown to inhibit colorectal development and the metastatic process in murine models of colorectal carcinoma. Fumagillin derivatives effectively suppress colon cancer cell lines when combined with antitumor drugs like 5-fluorouracil (37). Both *in vitro* and *in vivo*, fumagillin and its synthetic analogs, such as TNP-470, have antiangiogenic effects by inhibiting endothelial cell migration and proliferation, as well as stopping the cell cycle in the G1 phase (29, 38). Some of the important fungal metabolites inhibiting angiogenesis are depicted in Fig. 2 and 3. Many fungi produce multiple metabolites that disrupt angiogenesis as depicted in Table 1.

Table 1. Fungal species and their associated anti-angiogenic extracts

Fungal species	Fungal metabolites	Effects	Reference
Clitocybe nuda	Ergothioneine, eritadenine and adenosine	Delays formation of sub intestinal vessel formation in zebrafish embryo; suppress expression of angiogenic genes, human umbilical vein endothelial cell formation.	(39)
Agaricus blazei Murrill	Ergosterol, β-1,3- D-glucan, β-1,4-D-glucan and β-1,6-D-glucan	Anti-neovascularization and antitumor properties (the β-D-glucans limit the expression of cytochrome P450).	(40)
Epicoccum sorghinum	4,5-dihydroxy-6-(6′-methyl salicyl oxy)-2-hydroxymethyl-2-cyclohexenl-one	Prominent inhibitory effects on factors contributing to platelet aggregation, collagen and U46619.	(41)
Antrodia cinnamomea	ß-glucan antrodan	Blocks cell growth and metastatic spread by decreasing the action of the VEGFR2-STAT3 signalling mechanism in tumor cells.	(42)
Schizophyllum commune	Schizophyllan	Blocks endothelial cell migration and neovascular network formation within a tumor (similar to β-Caryophyllen).	(43)
Lentinus edodes	Lentinan, 1 → 3 linked β-D-glucan	Expression of IFN_y, an angiostatic factor, is increased; tumor infiltration of IFN_y-expressing T-cells and myeloid cells.	(44)
Ganoderma tsugae	Glucan-protein complex	Regulates endothelial cells, decreasing vascular permeability and influences the survival of the extracellular matrix.	(43)
Streptomyces sp. *15JA150*	Ahpatinin C, Ahpatinin E and Ahpatinin G	Suppress the hypoxia-inducible factor- 1α and downregulate VEGFR2 and its signaling mediators AKT, ERK ½, JNK, P38 and NF-κB in HUVECS; inhibit matrix metalloproteinases, MMP-2 and MMP-9; in chick embryos, suppressed neovascularization in the chorioallantoic membrane.	(45)
Pleurotus tuber- regium	Phenolic-rich ethyl acetate fraction of mushroom sclerotium	Inhibits neovascularization, VEGF-induced proliferation and tube formation.	(46)
Monascus sp. NMK7 (associated with marine sponge *Clathria frondifera*)	Monacolin X	Induces dose dependent cytotoxicity and apoptosis in tumor cells.	(31)
Microporus xanthopus	Hot water extract of fungus	Apoptosis in cancer cells, inhibiting proliferation and being cytotoxic to various cancer lines.	(47)
Echinodontium tinctorium	Polysaccharide EtGIPL1a	Induces apoptosis in tumor cells; arrests the cell cycle at subG0 stage.	(48)
Aspergillus oryzae	Terpestacin	Inhibits UQCRB (Ubiquinol-cytochro-me c reductase) of Mitochondrial Complex III, thereby disrupting the stabilization of hypoxia-inducible factor 1α.	(49, 50)
Chromolaenicola sp. (HL-114 -33-R04)	Danthron (1,8-dihydroxyanthraquinonen)	Induces dose-dependent antiangiogenic changes including the suppression of the proliferation, reduction of the proteolytic and invasive properties and inhibition of tube formation in endothelial cells.	(51)
Penicillium sp. HL-85- ALS5-R004	Toluquinol	Inhibits the proteolytics, invasive and motility-related in endothelial cells.	(5)
Mortierella polycephala	Monascinol (azaphilone compound)	Inhibits the production and activity of VEGFR2 (vascular endothelial growth factor receptor 2).	(52)
Arthrinium sp. EL000127	3-O-p-hydroxyphenylethylcyclopolic acid	Suppresses the expression of genes responsible for regulating the motility and growth of epithelial cells.	(53)
Penicillium sumatraense SC29	Penisterine D	Inhibited growth and migration of human endothelial progenitor cells, which are key components in the development of the neovasculature.	(54)
Ophiocordyceps sinensis (Chinese cordyceps)	Cordycepin	Increased antitumor immunity responses, decreased CT 26 cell migration, increased CT 26 cell apoptosis.	(55)

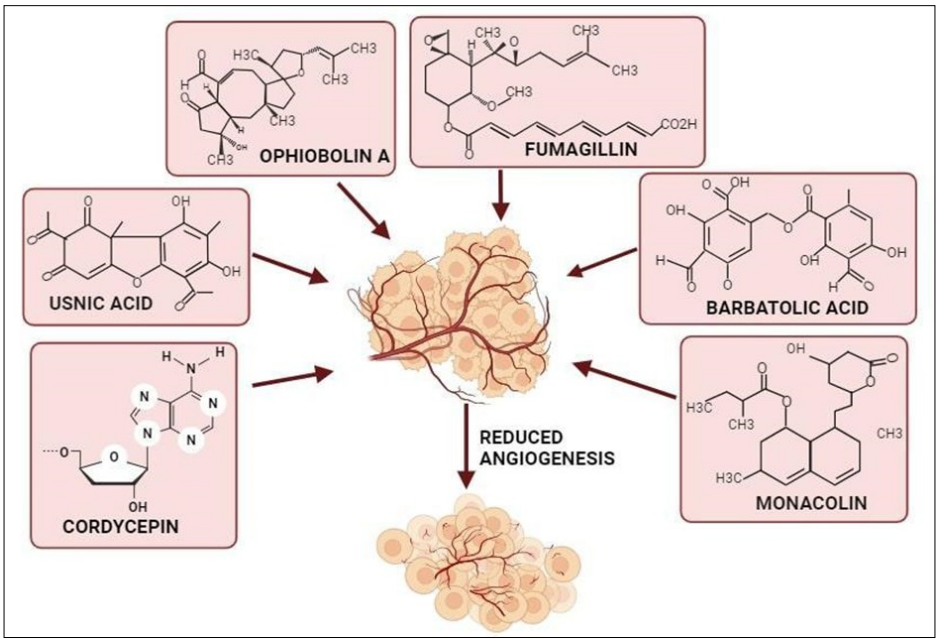

Fig. 2. Fungal metabolites capable of disrupting angiogenesis.

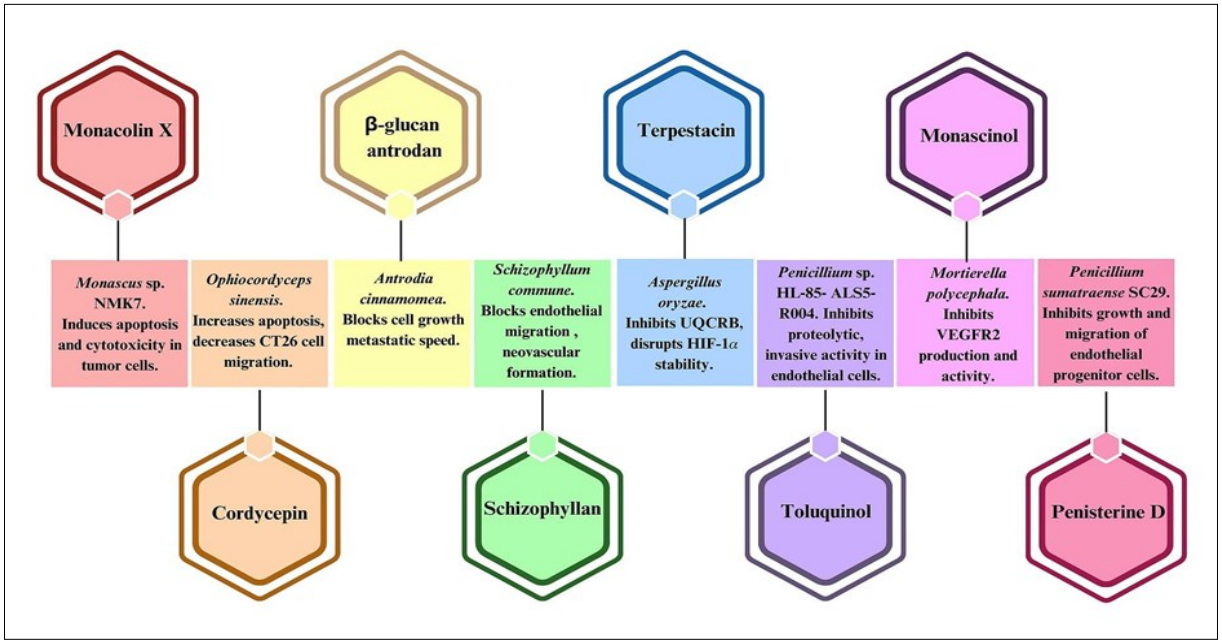

Fig. 3. Fungal metabolites involved in reducing tumor angiogenesis.

Green synthesized fungal nanoparticles with anticancer effects

Myconanotechnology uses mold, yeast and mushrooms to create nanoparticles (NPs). Nanomaterials, typically 1-100 nm in size and possessing unique properties, are predicted to revolutionize cancer detection and treatment by enabling targeted drug delivery, imaging and precise therapy (2). Because of their varied material production and controlled development, fungi are highly adept at making nanoparticles. Fungal species can be used to manufacture nanoparticles with a various property by adjusting their growth conditions and types, making them a useful tool in nanotechnology (56). The synthesis of nanoparticles by microbes has distinct benefits plant-based synthesis, as microorganisms are more readily reproducible. However, a challenge in green synthesis lies in identifying non-toxic, natural products and developing environmentally friendly solvent systems that are both effective and sustainable. Fungi may be the most effective biotechnological mediators for the sustainable synthesis of nanoparticles. They are a flexible, durable, straightforward and cost-effective living system that has already been extensively utilized in industry due to their capacity to reduce metal ions, generate stable nanoparticles and support large-scale production processes.

Using green chemistry and an environmentally friendly approach, the biological technique of synthesising nanoparticles utilizes active compounds from plants, bacteria, fungi, actinomycetes, yeast and algae. Endophytic organisms reside within healthy plants and form various relationships with their host plants. Numerous opportunities exist for these endophytic microbes to produce antimicrobial, antioxidant, antiviral, immunosuppressive and insulin-mimetic compounds (57). Moreover, green synthesis is less toxic, cost effective and environmentally sustainable compared to traditional chemical and physical methods, which often require hazardous reagents (58). The most widely synthesized metal nanoparticles from fungi are silver and

gold nanoparticles. Silver nanoparticles, or biosynthesized silver nanoparticles, are a class of biocompatible, economical and environmentally friendly substances that have garnered interest due to their potential uses in bioengineering and biomedicine. Silver nanoparticles, like many other inorganic and organic nanoparticles, including gold nanoparticles (AuNPs), iron oxide and quantum dots, have been extensively researched as components of advanced anticancer medicines aimed at improving cancer treatment in clinical settings (59). Gold nanoparticles are frequently used in many different health applications because they are non-toxic and possess strong absorption properties. Gold nanoparticles are an excellent material for biosensors and an ideal agent for destroying cancer cells (57). Another important class is copper nanoparticles. Compared to their bulk counterparts with the same chemical composition, biosynthesized copper nanoparticles (CuNPs) offer several exceptional qualities, including ductility, high yield strength, flexibility, stiffness, a high surface-to-volume ratio, eco-friendliness, low toxicity and quantum size and excellent stability. The human body has an effective system for handling copper metabolism because it is a micronutrient, the use of CuNPs as antitumor therapeutic agents is particularly advantageous due to their high surface-to-volume ratio, which enables them to pass through cell membranes *via* passive diffusion. Additionally, the body can efficiently manage leftover drug-containing copper nanoparticles due to the formation of a protein corona (coat) on their surface upon contact with cellular components. This protein corona enhances their physicochemical properties and reduces aggregation (60).

The biosynthesis of zinc oxide (ZnO) nanoparticles using microorganisms has gained attention due to their safety, biocompatibility and environmental friendliness compared to chemical methods. Over the past 20 years, ZnO nanoparticles have been increasingly used in a wide range of commercial products, including paint, coatings, cosmetics and biomedicine, particularly in the antibacterial and anticancer fields, due to their low cost, low toxicity and biodegradability (61). Selenium is an essential element for plants, animals and humans. Compared to both organic and inorganic Se compositions, nanoparticles have lower toxicity, greater biocompatibility, antimicrobial, oxidation-inhibitor and photosensitive capabilities. In addition to eliminating infections from host cells, selenium nanoparticles can control reactive oxygen species (ROS) and stimulate autophagy or programmed cell death. These properties have been utilized in anti-tumor therapy and as delivery vehicles to help kill cancer cells (62). The anticancer effects of various metal nanoparticles synthesized using fungi are listed in Table 2.

Strategies for enhanced delivery of fungal antiangiogenic agents

Despite fungal products like penicillin and other fungal strains saving countless lives, few fungal-based treatments are explicitly used against tumors in healthcare. In recent decades, research into fungal-derived materials has advanced significantly, particularly in developing targeted drug delivery systems, isolating anticancer compounds such as cordycepin and enhancing cancer immunotherapy through immune-modulating fungal metabolites (77). Primary sprouts are formed when vascular endothelial cells multiply and move into the perivascular region. Following the subsequent lumen formation of these initial sprouts, capillary loops are formed. A new basement membrane is then synthesised and blood vessels mature into fully formed tube-like structures that facilitate blood flow (78).

Table 2. Anticancer effects of metal nanoparticles synthesised using fungal extracts

Fungus	Type of metal nanoparticles	Anticancer activity	Reference
Aspergillus terreus	Copper oxide nanoparticles	On colon cancer cell lines.	(63)
Aspergillus niger	Silver nanoparticles	Anti-angiogenesis potential against cervical cancer.	(64)
Cladosporium sp.	Gold nanoparticles	On breast cancer cell line MCF-7 through the induction of apoptosis.	(65)
Penicillium crustosum EP-1.	Selenium nanoparticles (Se-NPs)	More effect on human liver cancer cell lines (HepG2) compared to human breast cancer cell lines (T47D).	(62)
Schizophyllum commune	Silver nanoparticles	On breast (MCF-7), lung (A549), colon (HT-29) and liver (HUH-7) cancer cell lines.	(66)
Penicillium citrinum CGJ-C2	Silver nanoparticles	Antioxidant activity on MCF-7 (breast adenocarcinoma), A431 (skin carcinoma), HepG2 (hepatoma) and HEK-293 (human embryonic kidney) cell lines.	(67)
Alternaria tenuissima	Zinc oxide nanoparticles	Reduction of growth of normal human melanocytes, human breast cells lines and liver cancer cell lines.	(1)
Cladosporium perangustum	Silver nanoparticles	On human breast adenocarcinoma cells.	(68)
Aspergillus austroafricanus CGJ-B3	Silver nanoparticles	More cytotoxicity towards MCF-7 (breast adenocarcinoma), HepG2 (hepatoma), A431 (skin carcinoma) and HEK293 (human embryonic kidney) cell lines.	(69)
Fomes fomentarius	Titanium oxide and silver nanoparticles (TiO_2 and silver nanoparticles, respectively)	On human colorectal carcinoma cells (HCT-116).	(70)
Monascus purpureus	Cobalt ferrite nanoparticles	On human breast carcinoma (MCF-7), hepatocellular carcinoma (HepG-2).	(71)
Cladosporium halotolerans	Silver nanoparticles	On human breast cancer cell line.	(72)
Trichoderma asperellum	copper oxide nanoparticles	On human lung carcinoma A549 cells.	(73)
Pleurotus djamor	Zinc oxide nanoparticles	On human lung carcinoma A549 cells.	(74)
Ganoderma lucidum	Gold nanoparticles	On HT-29 colon cancer cell line.	(2)
Fusarium solani	Gold nanoparticles	Apoptosis on cervical cancer cells (He La) and against human breast cancer cells (MCF-7).	(57)
Talaromyces purpureogenus	Silver nanoparticles	On human lung carcinoma.	(75)
Pseudomonas silesiensis	Copper nanoparticles	On human lung carcinoma.	(60)
Penicillium oxalicum	Silver nanoparticles	On human breast cancer.	(76)

Developing an angiogenesis inhibitor is a desirable anticancer strategy with potentially minimal side effects because angiogenesis is a fundamental mechanism in tissue formation and a limited process in healthy individuals. Moreover, resistance to antiangiogenic medications is improbable, or at least considerably less likely than with conventional cytotoxic chemotherapeutics, especially if the genetically stable endothelial cells (ECs) are targeted. Targeting the distinct characteristics of tumor ECs and vasculature could enable selective targeting. In contrast to the well-coordinated process of physiological angiogenesis, which is tightly regulated by a balance of pro-angiogenic and anti-angiogenic factors, tumor angiogenesis is characterized by random distribution, irregularity and poorly formed, leaky vessels (79). In the process of crystal nucleation and biosynthesis, macromolecules derived from fungi act as effective surface decorations for inorganic nanoparticles such as gold, selenium and iron oxides. The macromolecules, especially polysaccharides and proteins, have several benefits, including acting as capping agents that control particle size, shield nanoparticles from plasma protein adsorption and clearance, improve stability and prolong systemic circulation and cellular uptake (80).

The production of metal nanoparticles (MNPs) is a topic of great interest due to their critical role in advancing fields such as nanotechnology, material science and biomedical applications. The distinct surface area-to-volume ratio endows MNPs or their composite nanomaterials with particular physical-chemical, electrical, magnetic, biological and catalytic properties that are being investigated for a variety of uses in health, agriculture and other industries. Metal nanoparticles are synthesised using a variety of chemical and physical techniques. However, recent research has introduced an alternative approach: biosynthesis using biological organisms to bio fabricate MNPs. Green synthesis refers to the use of biological resources, such as plants and microbes, to produce nanoparticles. This method offers several advantages over traditional chemical methods, including low toxicity, eco-friendliness, cost-effective and alignment with SDG 12 (responsible consumption and production). This biosynthetic approach has garnered attention for its safe and environmentally beneficial process, resulting in MNPs with unique physiological and biological properties (81). The potential benefits of using fungi as a “nanofactory” for the production of MNPs, including their enormous biomass, quick growth, ease of scaling up and ability to reduce metallic ions for both internal and extracellular biosynthesis, have led to their use. While the extracellular process involves treating the fungal filtrate or extract with the appropriate precursor salts, the intracellular technique produces nanoparticles inside the fungal cell by treating its biomass with a precursor salt solution after a day of incubation in a dark environment. The extracellular method is efficient for large-scale production and easy extraction, while the intracellular method offers better control over nanoparticle size and shape for specific applications (82).

Among metal nanoparticles, nano-Au has been extensively employed for anticancer therapies such as optical bioimaging, medication administration and photo thermolysis of cancer cells and tumors. Because of its adjustable nature and biocompatibility, AuNPs have also been shown to prevent HUVEC cell growth that is stimulated by VEGF165. Additionally, AuNPs were shown to suppress VEGF-induced angiogenesis as well as basic fibroblast growth factor (bFGF) and fibroblast proliferation. The ability of nanogold to prevent VEGF-165-induced angiogenesis has been demonstrated in a mouse ear model. Numerous research teams have shown that nanosilver possesses anti-angiogenic characteristics and it is well-known for its many uses in nanomedicine (83).

There have been various documented mechanisms attributed to the anti-angiogenic properties of NPs. Binding to VEGF and stopping it from adhering to VEGFR is the primary mechanism of anti-angiogenesis. This results in downregulation of VEGRF, which inhibits angiogenesis. VEGF A-E starts downstream pathways that cause angiogenesis, such as AKT, JNK/c-Jun and MAPK signalling pathways. The down-regulation of downstream pathways that results in anti -angiogenesis can be caused by either of the two down-regulated proteins, VEGF or VEGFR. Additionally, heparin-binding EGF-like growth factor (HB-EGF), HGF, FGF, vascular endothelial growth factor 165 (VEGF-165), stromal cell-derived factor 1 (SDF1), insulin-like growth factor (IGF) and PDGF are a few of the growth factors which can result in anti-angiogenesis (84).

Challenges and future prospects

There is significant potential to develop antiangiogenic drugs by exploring exotic and under-researched fungal species, particularly endophytes in extreme environments such as hot springs, polar ice caps, deep-sea hydrothermal vents, acidic or alkaline soils and desert. Many fungal extracts possess antiangiogenic and antiapoptotic properties and further investigation is needed to elucidate the precise functions and mechanisms of these fungi in the defending against pathogenic microorganisms and cancer (85-88). In addition, fungal nanoparticles hold great promise, but they must be standardized to address challenges such as limited efficiency, contamination risks and scalability to achieve reliable, high-quality production at an industrial scale (89, 90). By accurately targeting malignant cells and tumors, these microscopic particles enhance treatment efficiency and improve patient survival rates while minimizing adverse effects. A study showed that spermine-modified AcDEX nanoparticles, containing the chemotherapy drug Nutlin-3a combined with the cytokine GM-CSF, enhanced the growth of immune cells, particularly CD8+ T cells. This combination stimulated an immune response, induced tumor cell death, protected immune cells and reducing toxicity (91). Advances in nanotechnology have developed techniques to enhance chemotherapy effectiveness and reduce side effects by enabling direct delivery of medicine to tumors through specific transporters. By integrating natural fungal compounds with advanced nanotechnology, researchers are creating more effective treatments that directly target cancer cells while minimizing harm to healthy tissues (92).

Conclusion

Fungi with antiangiogenic and anticancer qualities are emerging as a prominent focus in cancer research. Fungal metabolites and green-synthesized fungal nanoparticles have the potential to serve as safer and more effective cancer treatments. The promising anticancer properties of fungal extracts include triggering apoptosis, preventing cell division, obstructing angiogenesis and causing damage to the DNA of cancer cells. The delivery and effectiveness of these fungal-derived therapies are further improved by advances in nanotechnology, providing focused therapy with fewer adverse effects. Further studying fungal compounds and nanoparticles for their mechanisms, effectiveness and optimization could lead to the discovery of novel, natural cancer treatments with significant therapeutic potential.

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Authors' contributions

SS conceived the idea. DS, TC, KD, RK and SS were involved in data collection, analysis, interpretation and writing the article. All authors have read the final draft of the article and approved.

Compliance with ethical standards

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