Review

Utilizing *Aspergillus* Fungi, a Significant Veterinary Pathogen, in Lung Cancer Treatment: A Novel Approach

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Abstract

Cancer stands as an enduring global health challenge, demanding innovative therapeutic approaches for effective intervention. Recent years have witnessed intensive investigations into the potential anti-cancer properties of various filamentous *Aspergillus* molds. This review endeavors to comprehensively examine the scientific evidence on the potential anti-tumor effects of distinct *Aspergillus* species and their secondary metabolites in the context of lung cancer. Numerous *Aspergillus* species, with *Aspergillus fumigatus* at the forefront, have demonstrated the capability to produce compounds holding substantial promise in anti-cancer therapeutics. Gliotoxin, one such compound, emerges as a notable agent inducing apoptosis in lung cancer cells while impeding tumor growth. Furthermore, Emericellamide A, derived from *Aspergillus nidulans*, exhibits significant cytotoxicity against lung cancer cells. Serotonin, sourced from *Aspergillus terreus*, has also been proven to exert cytotoxic effects on lung cancer cells. Cycloopiazonic acid, identified in *Aspergillus flavus*, has demonstrated cytotoxicity against lung cancer cells, adding to the diverse arsenal of potential anti-cancer agents. The inhibitory effects on cancer cells extend beyond mere cytotoxicity, involving processes such as apoptosis, regulation of angiogenesis, immune modulation, and suppression of proliferation. Despite the promising array of anti-cancer compounds presented by *Aspergillus* fungi, significant challenges persist in their identification, scalable production, and understanding of their interactions with existing therapeutic modalities. Addressing these challenges necessitates collaborative efforts, fostering synergy among researchers, clinicians, and industry stakeholders. Research into the pharmacological repertoire offered by Aspergillus fungi can only be successful with the concerted efforts of researchers in order to determine the best possible treatment options for lung cancer, leveraging the wide variety of therapeutic options available.

Keywords: *Aspergillus* fungi, Cancer, Lung Cancer, Secondary metabolites, Veterinary pathogens

1. Introduction

A significant global health challenge posed by cancer is the uncontrolled growth and proliferation of cells, which are crucial factors for its development and progression (1). Various organisms, including plants (e.g., Pacific yew, Madagascar periwinkle), fungi (e.g., maitake), and pathogens (e.g., hydatid cyst protoscolex, *Trichinella spiralis*, *Trypanosoma cruzi*) offer potential anti-cancer properties through bioactive compounds and immunomodulation (2-8). More research is needed to harness their full potential in cancer treatment. Despite significant advancements in cancer treatment, practical and innovative therapies remain needed. Due to their anti-cancer properties, fungi have gained more and more attention in the scientific community as potential sources of novel therapeutic agents. Globally, *Aspergillus* secondary metabolites have been shown to have promising pharmacological properties against cancer. The anti-cancer effects of gliotoxin, which comes from *Aspergillus fumigatus* (*A. fumigatus*), have been extensively studied (9, 10). In cancer cells, gliotoxin induces apoptosis and inhibits angiogenesis, tumor growth, and metastasis. Additionally, fumagillin, produced by *A. fumigatus* and *Aspergillus niveus* (*A. niveus*), inhibits matrix metalloproteinases (MMPs), essential in tumor invasion and metastasis. Fumagillin suppresses MMPs, preventing cancer cells from spreading to other body parts, which could improve cancer patients' prognosis (11, 12).

Aspergillus fungi also produce echinocandins and derivatives of helvolic acid, in addition to gliotoxin and fumagillin (13). Additionally, they produce other compounds. Most anti-cancer compounds reported from *A. fumigatus* were alkaloids, except for lignin and enzymes. Alkaloids are chemical compounds mainly containing basic nitrogen atoms (14). Animals, fungi, bacteria, and plants produce them. There are many biological activities associated with alkaloids, including antibacterial, analgesic (e.g., morphine), anti-cancer (e.g., vincristine), and antimalarial (15). *Aspergillus*-derived compounds employ complex mechanisms. Various therapies are available, some of which use cellular pathways, while others enhance the body's ability to recognize and eliminate cancer cells by modulating the immune system (16).

In addition, these compounds may synergize with conventional cancer therapies, increasing the chances of a better treatment outcome (17). Despite the potential therapeutic applications of mycotoxins, safety concerns regarding certain species of *Aspergillus* necessitate thorough evaluations to develop potential therapeutic uses (18). Another strain of *A. fumigatus* produced gliotoxin. This gliotoxin was found to have antiproliferative and inhibitory effects on farnesyltransferase (FTase) *in-vitro* (19, 20). Various cellular proteins, including the RAS family, are posttranslationally isoprenylated by FTase. Recent studies show that gliotoxin inhibited the proliferation of six breast cancer cell lines with IC50 values ranging from 38 to 985 nM (21, 22). Secondary metabolites from *Aspergillus* fungi have anti-cancer properties. Inhibitors of

cancer cell growth include gliotoxin, fumagillin, echinocandins, and helvolic acid derivatives. By inducing apoptosis, they prevent tumor development and metastasis (13). Some *Aspergillus* species produce mycotoxins that can harm humans, making thorough safety evaluations crucial in developing therapeutic applications.

The present review aims to develop new and targeted lung cancer therapies based on previous study results. Various mechanisms of action employed by *Aspergillus* fungi against lung cancer will be discussed in the following sections, along with promising preclinical and clinical results that illustrate their potential as drugs against cancer.

2. Current Challenges in Cancer Treatment

It is important to emphasize that cancer treatment is a complex and evolving field that faces many significant challenges (23). Even though tremendous progress has been made in understanding cancer biology and developing therapeutic approaches in recent years, several obstacles still impede the effectiveness of current cancer treatments (24). This section examines cancer patients' challenges, including drug resistance, toxicity, and limited efficacy. These problems emphasize the urgent need for alternative therapies to improve the outcomes of cancer patients.

2.1 Drug Resistance

As one of the most pressing challenges in cancer treatment, drug resistance represents one of the biggest challenges (25). It refers to cancer cells becoming resistant to the effects of chemotherapy, targeted therapies, and other anti-cancer drugs. There are many mechanisms by which resistance can develop (26, 27). Cancer cells can acquire mutations that render them less susceptible to anti-cancer medications. These mutations may influence drug targets, drug transporters, or signaling pathways involved in cell survival and proliferation as a result of these mutations. Cancer cells can modify their metabolic pathways to enhance the efflux of drugs, thus decreasing the accumulation of drugs within the cells and decreasing the effectiveness of these drugs. Cancer cells can activate survival pathways, such as PI3K/AKT/mTOR, to resist anti-cancer drugs. Different cancer cells can exhibit different characteristics within a tumor, leading to different drug sensitivity levels in other tumor regions based on their factors. Drug resistance poses a significant obstacle to treating cancer successfully since it can cause treatment failure, disease recurrence,

and metastasis due to drug resistance. As part of cancer research, one of the critical focuses is finding ways to overcome or prevent drug resistance.

2.2. Toxicity

Cancer treatments, such as chemotherapy and radiation therapy, can often have serious side effects because they are non-selective, affecting both cancer cells and healthy cells in equal measure (28). The lack of specificity of this drug leads to significant toxicity to normal tissues and organs, leading to adverse reactions such as nausea, hair loss, immunosuppression, and the damage of vital organs as a result (29, 30). It is imperative to reduce treatment-related toxicity to improve the quality of life for cancer patients during and after treatment. Researchers and innovators are developing targeted therapies that selectively target cancer cells while sparing healthy tissues to detect, treat, and eradicate cancer.

2.3. Limited Efficacy

Despite significant advancements in the field of cancer therapy, there are still some cancers that remain difficult to treat effectively. Certain cancer types are inherently resistant to treatment options, which makes it more difficult for patients with these cancers to achieve complete remission or to live a long and healthy life (31). Furthermore, late-stage diagnosis and advanced metastatic disease further limit treatment options and reduce the chances of successful treatment outcomes due to the limited available treatment options. More effective and innovative therapies must be developed to address these difficult-to-treat cancers and improve these patients' prognoses.

2.4. Immunotherapy Challenges

Certain cancer types have shown remarkable success with immunotherapy, a cutting-edge approach that targets cancer cells with the body's immune system (30). However, its effectiveness is not universal, and several challenges remain. Tumors can alter immune checkpoint molecules, which inhibit immune responses, to evade immune detection. Determining which patients will respond best to immunotherapy is challenging, resulting in variability in treatment results. Activated immune systems can lead to autoimmune side effects, in which the immune system attacks healthy tissues.

2.5. High Treatment Costs

In most cases, the cost of cancer treatment to patients and the healthcare system can be a significant burden (32). This applies particularly to novel therapies and targeted agents. Some cancer patients may be unable

to obtain potentially life-saving treatments due to the high cost of the drugs and medicines used to treat their disease.

3. *Aspergillus* species and their anti-cancer compounds

3.1. *Aspergillus fumigatus*

Aspergillus fumigatus is one of the most common and well-studied species within the genus *Aspergillus*. Various secondary metabolites are produced by gliotoxin and demethoxyfumitremorgin C, which inhibits cancer growth. A cytotoxic compound, demethoxyfumitremorgin C, was isolated from marine-derived *A. fumigatus* secondary metabolites and demonstrated cytotoxic activity against PC3 prostate cancer cells (33). Furthermore, its immunomodulatory properties stimulate the immune system's activity against cancer cells. In various studies, gliotoxin has been investigated as an anti-cancer agent, particularly for treating breast cancer, prostate cancer, and leukemia, and the alkaloid fumigaclavine C was isolated from *A. fumigatus* by (34).

3.2. *Aspergillus nidulans*

Aspergillus nidulans is another significant species that produces secondary metabolites that may contribute to developing anti-cancer drugs (35). The *in-vitro* studies conducted on emericellamide A, a compound isolated from *A. nidulans*, have shown that the compound exhibits cytotoxic effects on human lung cancer cells. This is in studies conducted on the substance. As more research is conducted on *A. nidulans* and its metabolites, it may be possible to discover other compounds with anti-cancer properties and expand our understanding of the mechanisms by which they work. Evidence shows that emericellamide A has an anti-cancer potential due to its cytotoxic effects on lung cancer cells (36). However, it is essential to note that these findings are based on *in-vitro* studies. Animal models and human clinical trials have yet to be conducted.

3.3. *Aspergillus terreus*

Aspergillus terreus is known for producing compounds with diverse biological activities, including some with potential anti-cancer effects (37). Terpenoids, a metabolite from *A. terreus*, have demonstrated cytotoxicity against cancer cells *in-vitro*. *Aspergillus terreus* produces a statin group of polyketides (e.g., lovastatin), which are of therapeutic significance. There are reports of lower cancer incidence rates in

patients administered with statins—lovastatin, mevastatin, pravastatin, and simvastatin. Simvastatin has entered clinical trials as an anti-cancer drug. Cancer cell lines were tested for their sensitivity to four statin drugs—lovastatin, mevastatin, pravastatin, and simvastatin (38). Several terpenoids with anti-cancer potential were also isolated from *A. terreus*. Terpenoids include a large and structurally diverse family of natural products derived from C5 isoprene units. Most of the known anti-cancer terpenoids belong to the sesqui- or diterpenoids. A recent study isolated an extracellular polysaccharide from Jinyun Mountain in Beibei district (Chongqing, China) (39). Exopolysaccharides from *A. terreus* have anti-tumor activity.

3.4. *Aspergillus flavus*

Aspergillus flavus is notorious for producing aflatoxins, which are highly toxic and carcinogenic mycotoxins (40). These mycotoxins are known to cause mutations in the DNA of cells, leading to cancer development. Upon ingestion, aflatoxin B1 is metabolized by liver enzymes into reactive intermediates that bind to DNA, forming DNA adducts. These DNA adducts interfere with cellular processes and may lead to the uncontrolled growth of cells, ultimately contributing to cancer development. Despite the well-known carcinogenicity of aflatoxins, recent research has revealed that certain compounds derived from *A. flavus* may have potential anti-cancer properties (41). For example, cyclopiazonic acid, a secondary metabolite from *A. flavus*, has shown cytotoxicity against human lung cancer cells *in-vitro* studies. The mechanism of cyclopiazonic acid's cytotoxicity against cancer cells is not yet fully understood (42). Further research is needed to elucidate the specific pathways and cellular targets through which cyclopiazonic acid exerts its anti-cancer effects.

3.5. *Aspergillus niger*

The solid-state fermentation of *A. niger* produced high levels of L-asparaginase (43). Several fungi produce L-asparaginase. Some of them exhibited cytotoxic effects on various human cancer cell lines. A recent study reported the production of L-asparaginase by another isolate of *A. niger* (44). While it is not typically associated with anti-cancer properties, some studies have suggested that certain compounds from *A. niger* may have cytotoxic effects on cancer cells. However, more research is needed to elucidate their potential anti-cancer mechanisms and therapeutic applications. While *A. niger* is primarily known for its industrial applications, recent studies have suggested that certain compounds derived from this fungus may have cytotoxic effects on cancer cells (Fig. 1).

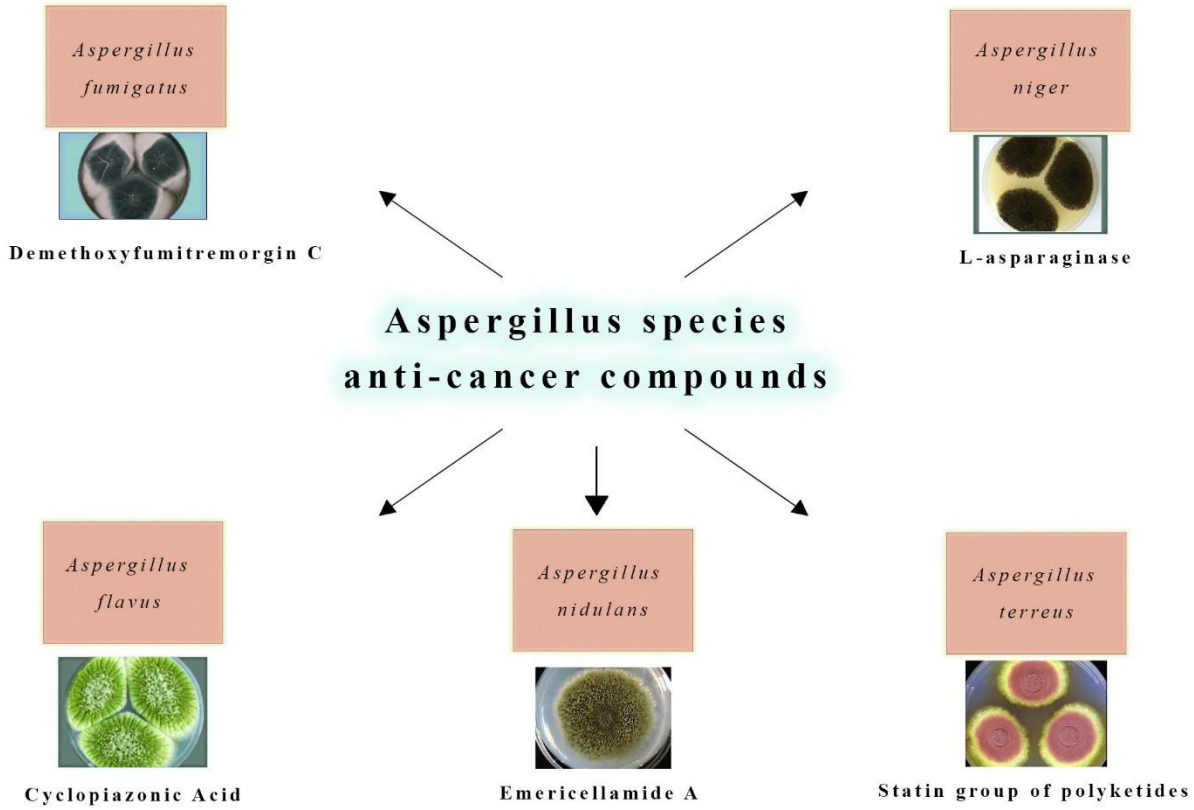

Figure 1: Some *Aspergillus* species produce compounds with potential anti-cancer properties: *Aspergillus fumigatus* (demethoxyfumitremorgin C), *Aspergillus nidulans* (emericellamide A), *Aspergillus terreus* (statins of polyketides), *Aspergillus flavus* (cyclopiazonic acid), and *Aspergillus niger* (L-asparaginase).

4. Mechanisms of action

According to recent research, various anti-tumor mechanisms are involved in the anti-tumor activity of compounds derived from *Aspergillus*, making them good candidates for treating cancer with the hope of preventing or slowing its progression (45, 46). The following sections aim to examine the specific mechanisms of action by which these compounds exert their anti-tumor effects. These include inducing apoptosis, inhibiting angiogenesis, modulating the immune system, and interfering with the proliferation of tumor cells, among other mechanisms that act in various ways.

4.1. Apoptosis induction

Apoptosis is also known as programmed cell death. Two pathways lead to apoptosis: the intrinsic mitochondrial and extrinsic death-receptor pathways (47). Several intracellular stress factors, including the Bcl-2 family, stimulate the inherent path, especially concerning cancer. The extrinsic pathway is initiated by a specific ligand binding to its cell surface receptors. These two pathways eventually converge in most cases, leading to apoptosis (48). Apoptosis has been observed to be induced by compounds derived from *Aspergillus*, which result in the death of cancer cells as a result of the death of cells. For example, gliotoxin triggers apoptosis in cancer cells by activating pro-apoptotic signaling pathways and inhibiting anti-apoptotic pathways (49). The mitochondrial pathway is one of them. When gliotoxin released from mitochondria triggers caspases, an enzyme that initiates the apoptotic process, apoptosis starts in the cell. As a result of DNA fragmentation and dismantling, cancerous cells are killed by DNA fragmentation and dismantling of cellular components.

4.2. Inhibition of angiogenesis

Angiogenesis occurs in response to inflammation and ischemia in tissue to form new blood vessels. Angiogenesis plays a crucial role in tumor growth and metastasis (50). A tumor must have a sufficient supply of blood so that nutrients and oxygen can be delivered to it for growth and survival. When endothelial cells interact with *A. fumigatus* hyphae, they release proinflammatory cytokines such as tumor necrosis factor-α (TNF-α) and interleukin-8 (IL-8) (51). These proangiogenic signaling pathways include vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF). By contrast, *A. fumigatus* synthesizes a variety of secondary metabolites whose potent antiangiogenic properties make them potential anti-cancer agents. Angiogenesis is inhibited by fumagillin by targeting methionine aminopeptidase 2 (MetAP2), a protein that promotes the proliferation of endothelial cells during angiogenesis (52). By inhibiting MetAP2, fumagillin limits tumor growth and prevents it from spreading.

4.3. Interference with tumor cell proliferation

One of the hallmarks of cancer is the rapid proliferation of cells, which is uncontrollably expanding (53). Several compounds derived from *Aspergillus* have been shown to inhibit the proliferation of tumor cells, preventing them from growing uncontrollably (54). For example, echinocandins are designed to block the formation of beta-glucans, an essential component for forming the fungal cell wall. They thus help block beta-glucans production (55). Furthermore, it has also been found that specific components of the membrane of proliferating cancer cells can also be affected by these compounds, which affects the growth and division of these cells similarly. As a result of the anti-tumor effect of echinocandins, the proliferation

of tumor cells is slowed down through the inhibition of a wide range of cellular processes, which results in the suppression of tumor growth (56)(Fig. 2).

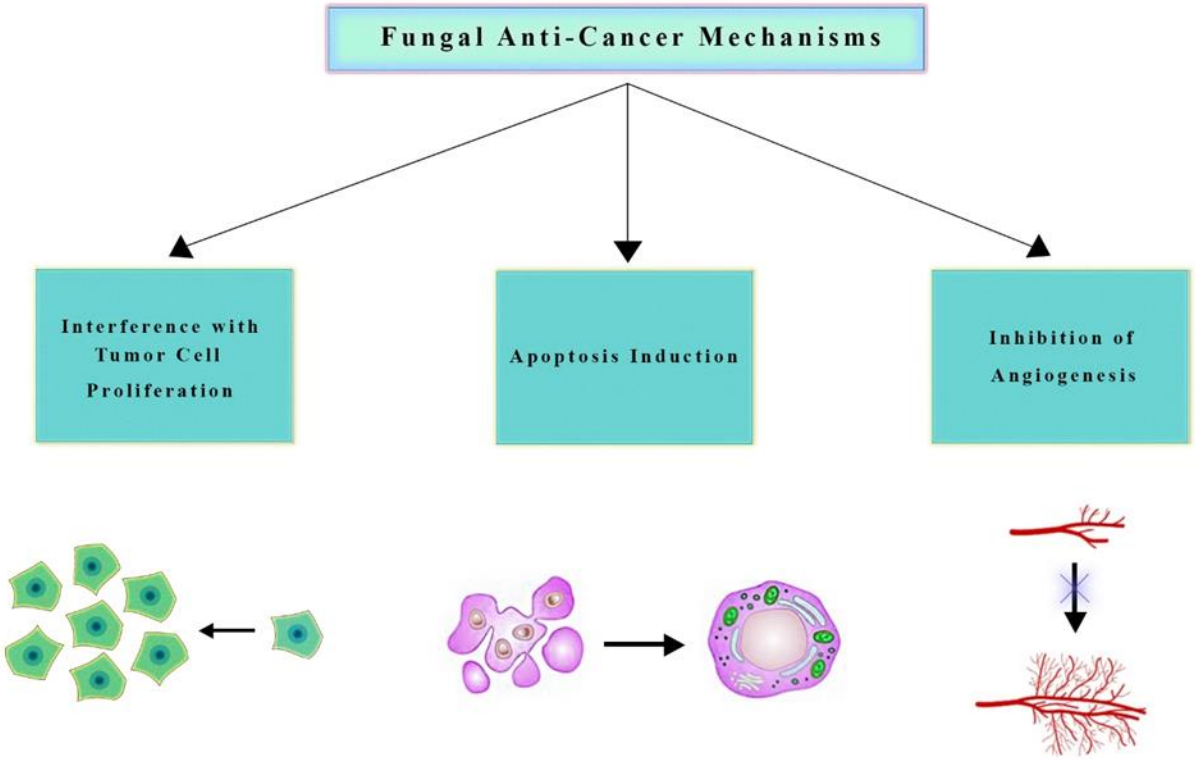

Figure 2: Compounds derived from Fungi exhibit various anti-tumor mechanisms, including apoptosis induction through intrinsic and extrinsic pathways, inhibition of angiogenesis by targeting proangiogenic signaling pathways, and interference with tumor cell proliferation by blocking essential cellular processes.

5. Animal models and *in-vivo* studies

Aspergillus fungi and their compounds have significant anti-tumor potential *in-vivo* studies using animal models (57). As a result of these studies, researchers can assess how the compounds affect whole organisms, tumor growth, metastasis, and potential toxicity. In this section, *Aspergillus*-derived compounds show anti-tumor activity *in-vivo*, and we discuss their implications for translational research and clinical trials (58).

5.1. Gliotoxin studies

Gliotoxin has been shown to have promising anti-tumor effects during *in-vivo* studies. The impact of gliotoxin on prostate cancer was evaluated using a xenograft mouse model. As part of the current therapeutic approach, pro-tumor macrophages (M2) are reprogrammed, while anti-tumor macrophages (M1) are preserved. This study explores a MYC inhibitor prodrug (MI3-PD) encapsulated in nanoparticles for targeting c-MYC in M2 macrophages. Using targeted MYC inhibitors in mouse models of lung cancer, pro-tumor M2-like TAMs were reduced while anti-tumor M1-like macrophages were preserved (59). It was also demonstrated that the exposure of lung epithelial cells A549 and L132 to gliotoxin for 24 h resulted in a significant increase in the proportion of cells in S-phase (30–39%), with a concomitant decrease in G2/M-phase; the early and late apoptotic cells were observed using Annex, PI stains, suggesting apoptosis in the two cells after gliotoxin treatment (60).

5.2. Fumagillin studies

The anti-tumor effects of fumagillin have also been demonstrated *in-vivo* (61). The impact of fumagillin on lung cancer was examined using a murine xenograft model. A mouse model of lung cancer (MDA-MB-231) was treated with fumagillin after being injected with human lung cancer cells (62). As predicted by the compound's antiangiogenic properties *in-vitro*, fumagillin treatment significantly reduced tumor growth and inhibited angiogenesis. Moreover, fumagillin treatment did not cause significant adverse effects on the mice, supporting its potential as a safe anti-cancer treatment.

5.3. Echinocandins studies

Echinocandins have also been recognized as potentially effective anti-tumor agents in research studies performed *in-vivo*. A mouse xenograft model was used to evaluate the efficacy of echinocandins on lung cancer (63, 64). It has been demonstrated that echinocandin can significantly slow down tumor growth in xenografts with lung cancer that have been treated. There were no significant toxic effects on the mice following the treatment with echinocandin, thus supporting its potential as a cancer-fighting agent (65).

5.4. Combination studies

There has also been an investigation into combining various techniques to investigate the possible effects of compounds derived from *Aspergillus* on animal models. A study by Ghanem et al. 2021, investigated the impact of gliotoxin combined with cisplatin, a chemotherapeutic drug, on treating lung cancer using gliotoxin as a component (66). To treat the cancer cells, in this study, a murine xenograft model was used, whereby human lung cancer cells (A549) were implanted into mice, and these mice were then treated with either gliotoxin, cisplatin, or a combination of both to kill the cancer cells. Compared with either of these

treatments alone, the combination treatment demonstrated a statistically significant reduction in tumor growth, suggesting that both treatments are probably effective when combined to treat lung cancer effectively (67) (Fig.3).

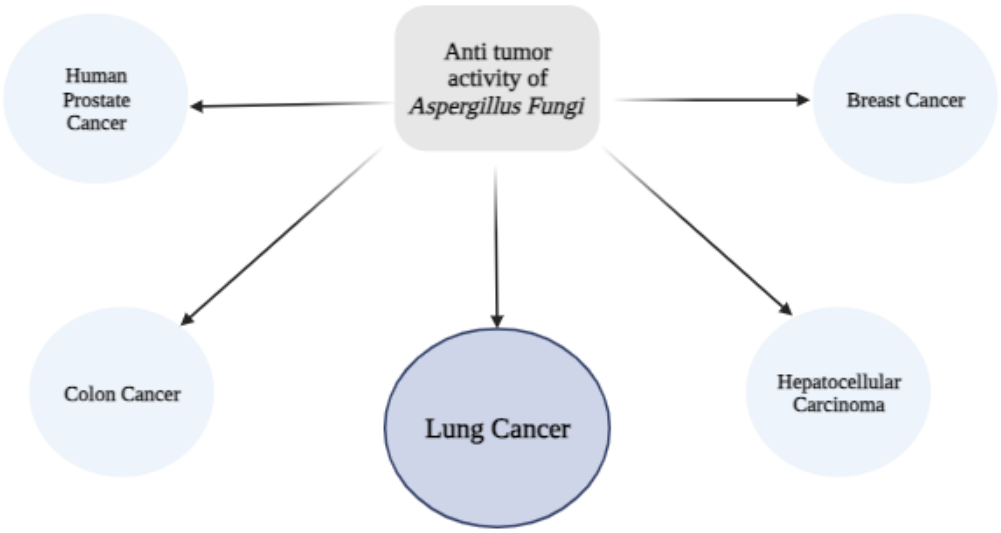

Figure 3: Various cancer types, including lung, breast, prostate, colorectal, and hepatocellular carcinoma, may respond to *Aspergillus*-derived compounds.

6. Challenges and future prospectives

6.1. Identification of specific anti-cancer compounds

The most challenging aspect of cancer therapeutics is developing an anti-cancer compound that can kill tumor cells without harming surrounding healthy cells (68). Therefore, many cancer biologists continue to pursue the discovery of novel anti-cancer compounds from natural sources. While some of these compounds may be capable of fighting cancer in the future, others may be harmful. Various methods of isolating and analyzing individual compounds from *Aspergillus* extracts are used in this study, such as chromatography,

mass spectrometry, and bioassays, to isolate and characterize these compounds (69). Various cancer cell lines are tested to identify compounds with the best anti-cancer activity. Furthermore, high-throughput screening can help identify potential anti-cancer compounds faster. Understanding these compounds' structure-activity relationship is essential to maximize their efficacy and minimize any potential adverse effects. Structure-based drug design and molecular docking can be used as computational approaches to predict and optimize the interactions between cancer compounds and their molecular targets.

6.2. Optimization of production processes

Approximately 100,000 of the 1.5 million known fungal species on Earth have been described so far, and this biodiversity can be explored to find anti-cancer therapeutic molecules (70). Researchers must optimize fermentation conditions, nutrient composition, and environmental parameters to enhance target compound production. Some techniques can be used to improve strains of *Aspergillus* through genetic engineering and strain improvement. To increase their yields, it is necessary to identify and manipulate the critical regulatory elements involved in their biosynthesis to improve them. Alternatively, heterologous expression in other microbes or plant-based production systems could offer more sustainable and scalable approaches to the large-scale production of *Aspergillus*-derived anti-cancer compounds.

6.3. Understanding interactions with conventional cancer therapies

Combined with conventional cancer therapies, such as chemotherapy, radiation, and targeted therapies, *Aspergillus*-derived compounds with anti-tumor properties may hold significant promise as adjuvants or synergistic agents. *Aspergillus* compounds should be understood in terms of their interaction with standard cancer treatments to ensure that they are both safe and effective when combined with them. Cancer cells may be sensitized to chemotherapy or radiation therapy by *Aspergillus*-derived compounds that target cell cycle regulation and DNA repair mechanisms. Furthermore, *Aspergillus* compounds may also interact negatively with certain anti-cancer drugs, causing the drug's toxicity and effectiveness to be reduced. It is necessary to conduct preclinical studies using both *in-vitro* and *in-vivo* models to investigate the interactions between *Aspergillus* compounds and conventional therapies. Clinical trials in the future can be safer and more effective with these studies. These studies can help determine optimal dosing schedules and potential drug-drug interactions.

6.4. Development of targeted drug delivery systems

Researchers are actively exploring targeting mechanisms to deliver anti-cancer compounds derived from *Aspergillus* to improve efficacy and reduce potential side effects (71). Targeted drug delivery delivers therapeutic agents directly to cancer cells or tumor tissues, sparing healthy cells and tissues from exposure. It is possible to deliver *Aspergillus*-derived compounds into tumor cells by encapsulating them within nanoparticles, such as liposomes, micelles, and nanoparticles, and then delivering them to specific tumor cells (72-74). Drug delivery can be accomplished by functionalizing these nanoparticles with antibodies or peptides that recognize markers on cancer cells. To increase the therapeutic efficacy of the anti-cancer compound, it is necessary to increase the accumulation of that compound at the tumor site to minimize the systemic toxicity of the compound. In addition, using targeted drug delivery systems can ensure that a combination is stable and bioavailable, improving its pharmacokinetics and therapeutic index. Despite this, developing a targeted drug delivery system combines many disciplines, and it can be both complex and time-consuming. Research into nanoparticle formulations, selection of appropriate targeting ligands, and rigorous evaluation of safety and efficacy in preclinical models are all critical to progressing to clinical trials. *Aspergillus* fungi and their secondary metabolites demonstrate promising anti-cancer properties, inducing apoptosis and inhibiting tumor growth. Prospects include mechanistic studies, drug development, combination therapies, and clinical trials to fully explore their potential in cancer treatment. Collaboration is vital to address challenges in compound identification, production, and interactions with conventional therapies, paving the way for effective and personalized cancer treatments (75).

Conclusion

In conclusion, the exploration of *Aspergillus* fungi-derived anti-cancer compounds represents a promising avenue in the quest for more effective lung cancer treatments. The diverse mechanisms by which these compounds target key aspects of cancer biology, including apoptosis, angiogenesis, immune response modulation, oncogenic signaling, and the tumor microenvironment, highlight their potential as valuable adjuncts to conventional therapies. However, realizing this potential requires concerted efforts to identify, isolate, and optimize these compounds, as well as to address challenges such as scalability, efficacy, and compatibility with existing treatments. Collaboration between researchers, pharmaceutical companies, and healthcare professionals is crucial in advancing the development of these therapies to a stage where they can significantly enhance the outcomes of lung cancer patients. By harnessing the unique properties of

Aspergillus-derived compounds and integrating them into comprehensive treatment strategies, researchers may ultimately improve survival rates and quality of life for individuals battling this devastating disease.

Declarations and statements

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No funding was received for conducting this study.

Conflict of interests

The authors declare no conflict of interest.

Data availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Ethical approval

All applicable international, national, and/or institutional guidelines for the care and use of animals were followed.

Author contribution

Conceptualization: [Daryoush Babazadeh], …; Methodology: [DB], …; Formal analysis and investigation: [AO], …; Writing - original draft preparation: [NA, BS, SGS]; Writing - review and editing: [MMB, DS], …; Funding acquisition: [Self-funding], …; Supervision: [DB]. All authors checked and approved the final version of the manuscript for publication in the present journal

Consent to participate

The participant has not granted consent to participate in the study.

Consent for publication

Publication consent is not applicable in this particular case.

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