Review Article

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

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ABSTRACT

Cancer is a persistent global health problem that necessitates innovative therapeutic approaches for effective intervention. In recent years, there has been a significant increase in research focusing on the potential anti-cancer properties of various filamentous Aspergillus molds. This review aims to systematically assess the scientific evidence regarding the potential anti-tumor effects of distinct Aspergillus species and their secondary metabolites in the context of lung cancer. A multitude of Aspergillus species, with Aspergillus fumigatus being a prominent example, have exhibited the capacity to generate compounds that hold considerable promise in the realm of anti-cancer therapeutics. Gliotoxin, a notable example, has been identified as a crucial agent inducing apoptosis in lung cancer cells while impeding tumor growth. Furthermore, Emericellamide A, a secondary metabolite derived from Aspergillus nidulans, exhibits significant toxicity against lung cancer cells. Serotonin, a natural product of Aspergillus terreus, has also been shown to have significant cytotoxic effects on lung cancer cells. Cycloopiazonic acid, a natural product of Aspergillus flavus, has exhibited significant anti-lung cancer properties, thus augmenting the existing repertoire of potential anti-cancer agents. The inhibitory effects on cancer cells extend beyond mere toxicity, involving processes such as apoptosis, regulation of angiogenesis, immune modulation, and suppression of proliferation. Despite the encouraging 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 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.

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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). A diverse array of organisms, encompassing plants (e.g., Pacific yew, Madagascar periwinkle), fungi (e.g., maitake), and pathogens (e.g., hydatid cyst protoscolex, Trichinella spiralis, Trypanosoma cruzi), have been identified as possessing the potential to offer anti-cancer properties through bioactive compounds and immunomodulation (2-8). However, further research is necessary to fully harness the potential of these organisms in cancer treatment. Despite significant advancements in cancer treatment, there is a continued need for both practical and innovative therapies. Given their established anti-cancer properties, fungi have garnered increased attention from the scientific community as a potential source of novel therapeutic agents. A substantial body of research has demonstrated the pharmacological properties of Aspergillus secondary metabolites, indicating their potential to combat cancer. The anti-cancer effects of gliotoxin, a secondary metabolite of A. fumigatus, have been extensively studied (9, 10). Gliotoxin, a secondary metabolite of A. fumigatus, has been shown to induce apoptosis in cancer cells and to inhibit angiogenesis, tumor growth, and metastasis. Fumagillin, a secondary metabolite produced by A. fumigatus and Aspergillus niveus (A. niveus), has also demonstrated the ability to inhibit matrix metalloproteinases (MMPs), which play a critical role in tumor invasion and metastasis. Fumagillin exerts its anti-tumorigenic effects by suppressing MMPs, thereby impeding the dissemination of cancer cells to other bodily regions and potentially enhancing the prognosis of cancer patients (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). Aspergillus fungi have been found to produce echinocandins and derivatives of helvolic acid, in addition to gliotoxin and fumagillin (13). Furthermore, these organisms are capable of producing additional compounds. A substantial proportion of the anti-cancer compounds reported from A. fumigatus are alkaloids, with the exception of lignin and enzymes. Alkaloids are defined as chemical compounds primarily comprising basic nitrogen atoms (14). These compounds are produced by a diverse array of organisms, including animals, fungi, bacteria, and plants. These compounds exhibit a wide range of biological activities, including antibacterial, analgesic (e.g., morphine), anti-cancer (e.g., vincristine), and antimalarial properties (15). The mechanisms employed by Aspergillus-derived compounds are notably intricate. A variety of therapeutic interventions are available, some of which target cellular pathways, while others enhance the body's capacity to recognize and eliminate cancer cells by modulating the immune system (16). Furthermore, these compounds may enhance the efficacy of conventional cancer therapies, thereby improving treatment outcomes (17). Notwithstanding the therapeutic potential of mycotoxins, safety concerns regarding certain species of Aspergillus necessitate thorough evaluations to ascertain their potential therapeutic uses (18). Another strain of A. fumigatus produces gliotoxin. This gliotoxin has been shown to possess antiproliferative and inhibitory effects on farnesyltransferase (FTase) in vitro (19, 20). It is imperative to note that various cellular proteins, including the RAS family, undergo posttranslational isoprenylation by FTase. Recent studies have demonstrated that gliotoxin inhibited the proliferation of six breast cancer cell lines with IC50 values ranging from 38 to 985nM (21, 22). Secondary metabolites derived from Aspergillus fungi have been shown to possess antineoplastic properties. Notable examples of such inhibitors include gliotoxin, fumagillin, echinocandins, and helvolic acid derivatives, which have been shown to impede the growth of cancer cells. These secondary metabolites induce apoptosis, thereby preventing tumor development and metastasis (13). However, it is crucial to note that certain Aspergillus species are known to produce mycotoxins that pose a threat to human health. This underscores the necessity for rigorous safety evaluations in the development of therapeutic applications. The present review aims to develop new and targeted lung cancer therapies based on the results of previous studies. The subsequent sections will address the various mechanisms of action employed by Aspergillus fungi against lung cancer, along with the promising preclinical and clinical results that illustrate their potential as drugs against cancer.

2. Current Challenges in Cancer Treatment

It is imperative to underscore the intricacy and perpetual progression of the field of cancer treatment, which is confronted with numerous substantial challenges (23). Despite significant advancements in understanding cancer biology and developing therapeutic approaches in recent years, several obstacles impede the effectiveness of current cancer treatments (24). This section will examine the challenges faced by cancer patients, including drug resistance, toxicity, and limited efficacy. The prevalence of these challenges underscores the pressing need for the development of alternative therapeutic modalities that can enhance the outcomes of cancer patients.

2.1 Drug Resistance

Among the most pressing challenges in the field of cancer treatment is the phenomenon of drug resistance, which represents a significant obstacle to effective therapeutic management (25). This phenomenon occurs when cancer cells exhibit a reduction in sensitivity to the therapeutic effects of chemotherapy, targeted therapies, and other anti-cancer medications. The development of resistance is a multifaceted process involving various mechanisms (26, 27). For instance, cancer cells can acquire mutations that render them less susceptible to anti-cancer medications. These mutations can impact various aspects of the cell, including its drug targets, drug transporters, or signaling pathways that regulate survival and proliferation. Furthermore, cancer cells can modify their metabolic pathways to enhance the efflux of drugs, thereby decreasing the accumulation of drugs within the cells and decreasing the effectiveness of these drugs. Furthermore, cancer cells can activate survival pathways, such as PI3K/AKT/mTOR, to resist anti-cancer drugs. The heterogeneity of cancer cells within a tumor can result in variations in drug sensitivity across different regions of the tumor, influenced by various factors. The development of drug resistance poses a significant obstacle to the successful treatment of cancer, as it can lead to treatment failure, disease recurrence, and metastasis due to drug resistance. Consequently, a critical focus in cancer research is the identification of methods to overcome or prevent drug resistance.

2.2. Toxicity

Cancer treatments, including chemotherapy and radiation therapy, frequently result in deleterious side effects due to their non-selective nature, which impacts both cancerous and healthy cells alike (28). The lack of specificity of these treatments leads to significant toxicity to normal tissues and organs, resulting in adverse reactions such as nausea, hair loss, immunosuppression, and damage to vital organs (29, 30). Consequently, there is an urgent need to mitigate treatment-related toxicity to enhance the quality of life for cancer patients during and after treatment. Consequently, researchers and innovators are developing targeted therapies that selectively target cancer cells while sparing healthy tissues. The objective of these therapies is to detect, treat, and eradicate cancer.

2.3. Limited Efficacy

Despite considerable progress in the field of cancer therapy, some cancers continue to pose significant challenges in terms of effective treatment. Certain cancer types exhibit intrinsic resistance to treatment modalities, impeding patients' ability to achieve complete remission or to lead 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. The development of more effective and innovative therapies is imperative to address these cancers and improve patient prognoses.

2.4. Immunotherapy Challenges

A subset of cancerous neoplasms has demonstrated a notable response to immunotherapy, a pioneering modality that harnesses the body's immune system to target cancerous cells (30). However, its effectiveness is not universally applicable, and several challenges persist. Tumors have been observed to modify immune checkpoint molecules, which impede immune responses, thereby facilitating immune evasion. The ability to predict which patients will respond best to immunotherapy remains a significant challenge, contributing to variability in treatment outcomes. Furthermore, the activation of immune systems can lead to autoimmune side effects, wherein the immune system attacks healthy tissues.

2.5. High Treatment Costs

In the majority of cases, the financial burden of cancer treatment on patients and healthcare systems can be substantial (32). This phenomenon is particularly evident in the context of novel therapeutic interventions and targeted pharmacological agents. The financial constraints imposed by the high cost of pharmaceuticals and therapeutic agents can impede access to potentially life-saving treatments for cancer patients, underscoring the need for comprehensive cost-effectiveness analyses and policy interventions to address these challenges.

3. *Aspergillus* species and their Anti-Cancer Compounds

3.1. *Aspergillus Fumigatus*

Aspergillus fumigatus is one of the most prevalent and extensively studied species within the genus Aspergillus. A variety of secondary metabolites are produced by gliotoxin and demethoxyfumitremorgin C, which has been shown to inhibit cancer growth. A study revealed that a cytotoxic compound, demethoxyfumitremorgin C, isolated from marine-derived A. fumigatus secondary metabolites, exhibited significant 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 noteworthy species that produces secondary metabolites that may contribute to the development of anti-cancer drugs (35). In vitro studies conducted on emericellamide A, a compound isolated from A. nidulans, have demonstrated that the compound exhibits cytotoxic effects on human lung cancer cells. This finding aligns with the results of in-vitro studies conducted on the substance. As research continues to expand on A. nidulans and its metabolites, the potential exists for the identification of additional compounds with antineoplastic properties, thereby enhancing our comprehension of the mechanisms through which they operate. Emericellamide A's potential anti-cancer properties have been demonstrated by its

cytotoxic effects on lung cancer cells (36). However, it is imperative to acknowledge that these findings are primarily derived from in-vitro studies. Conducting animal models and human clinical trials is imperative to validate these findings.

3.3. *Aspergillus Terreus*

Aspergillus terreus is recognized for its ability to produce compounds that exhibit a variety of biological activities, including some that possess potential anti-cancer properties (37). Terpenoids, a metabolite from A. terreus, have demonstrated in vitro toxicity against cancer cells. Aspergillus terreus also produces a statin group of polyketides (e.g., lovastatin), which are of therapeutic significance. There is a corpus of reports indicating a lower incidence of cancer in patients administered with statins, including lovastatin, mevastatin, pravastatin, and simvastatin. Notably, simvastatin has advanced to clinical trials as an anti-cancer agent. Cancer cell lines were tested for their sensitivity to four statin drugs: lovastatin, mevastatin, pravastatin, and simvastatin (38). In addition, a number of terpenoids with potential anticancer properties have been isolated from A. terreus. Terpenoids represent a substantial and structurally diverse group of natural products derived from C5 isoprene units. A significant proportion of the documented anti-cancer terpenoids are classified as sesqui- or diterpenoids. A recent study isolated an extracellular polysaccharide from Jinyun Mountain in Beibei district (Chongqing, China) (39). Exopolysaccharides from A. terreus have been shown to possess anti-tumor activity.

3.4. *Aspergillus Flavus*

Aspergillus flavus is notorious for producing aflatoxins, which are mycotoxins that are both highly toxic and carcinogenic (40). These mycotoxins have been shown to induce mutations in the DNA of cells, thereby contributing to carcinogenesis. Upon ingestion, aflatoxin B1 is metabolized by liver enzymes into reactive intermediates that bind to DNA, forming DNA adducts. These DNA adducts have been shown to interfere with cellular processes, contributing to uncontrolled cell growth and, ultimately, cancer development. Despite the well-established carcinogenic potential of aflatoxins, recent research has identified a potential for certain compounds derived from A. flavus to possess anticancer properties (41). For instance, cyclopiazonic acid, a secondary metabolite derived from A. flavus, has demonstrated in vitro studies to be cytotoxic to human lung cancer cells. The precise mechanism through which cyclopiazonic acid exerts its anticancer effects remains to be fully elucidated (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). It is noteworthy that several species of fungi have been observed to produce L-asparaginase. A subset of these fungi has been observed to exhibit cytotoxic effects on various human cancer cell lines. A recent study documented the production of L-asparaginase by an additional isolate of A. niger (44). While A. niger 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, further research is necessary to elucidate their potential anti-cancer mechanisms and therapeutic applications. While A. niger is predominantly recognized for its industrial applications, recent studies have indicated that certain compounds derived from this fungus may possess cytotoxic effects on cancer cells (Figure 1).

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 promising candidates for treating cancer with the hope of

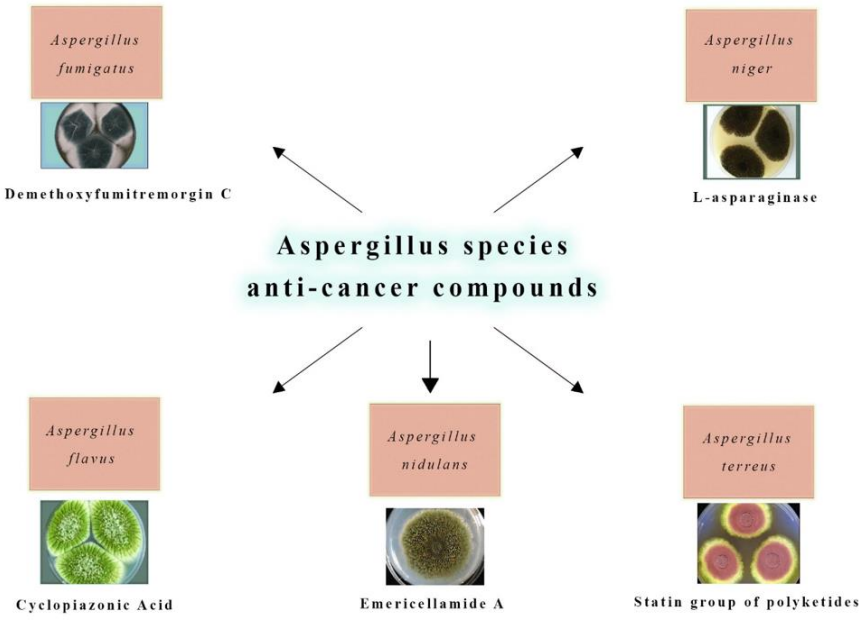

Figure 1. Some *Aspergillus* species produce compounds with potential anti-cancer properties: *Aspergillus fumigatus* (demethoxyfumitremorgin C), *Aspergillus nidulans* (emericellamide A), *Aspergillus terreus* (statins of polyketides), *Aspergillus flavus* (cyclopiazonic acid), and *Aspergillus niger*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

preventing or slowing its progression (45, 46). The subsequent sections aim to examine the specific mechanisms of action by which these compounds exert their anti-tumor effects. These mechanisms encompass the induction of apoptosis, the inhibition of angiogenesis, the modulation of the immune system, and the interference with the proliferation of tumor cells, among other processes that act in diverse ways.

4.1. Apoptosis Induction

Apoptosis, a term denoting a type of cell death that is genetically programmed, has been the subject of extensive research. Two distinct pathways have been identified as the mechanisms that lead to apoptosis: the intrinsic mitochondrial pathway and the extrinsic death-receptor pathway (47). Intracellular stress factors, including the Bcl-2 family, have been identified as stimulators of the intrinsic pathway, particularly in the context of cancer. The extrinsic pathway is initiated by a specific ligand binding to its cell surface receptors. In most cases, these two pathways ultimately converge, resulting in apoptosis (48). Compounds derived from Aspergillus have been observed to induce apoptosis, resulting in the death of cancer cells. For instance, gliotoxin instigates apoptosis in cancer cells by activating pro-apoptotic signaling pathways and impeding anti-apoptotic pathways (49). The mitochondrial pathway is one such example. The initiation of this process is triggered by the release of gliotoxin from the mitochondria, which in turn activates the enzyme known as caspases. This enzyme, in turn, initiates the apoptotic process within the cell. The process of DNA fragmentation and dismantling leads to the death of cancerous cells by disrupting their DNA and other cellular components.

4.2. Inhibition of Angiogenesis

Angiogenesis, the process of new blood vessel formation, occurs in response to inflammation and ischemia in tissue. Angiogenesis plays a crucial role in tumor growth and metastasis (50). A tumor necessitates a sufficient supply of blood to ensure the delivery of nutrients and oxygen, thereby facilitating its growth and survival. The interaction of endothelial cells with A. fumigatus hyphae has been shown to result in the release of 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). Conversely, A. fumigatus synthesizes a variety of secondary metabolites, which possess potent antiangiogenic properties, rendering them potential anti-cancer agents. Fumagillin, a secondary metabolite produced by A. fumigatus, exerts its antiangiogenic effects by targeting methionine aminopeptidase 2 (MetAP2), a protein that plays a crucial role in the proliferation of endothelial cells during the process of angiogenesis (52). The anti-tumor property of fumagillin is attributed to its capacity to inhibit MetAP2, thereby curtailing the proliferation of endothelial cells and the subsequent spread of tumors.

4.3. Interference With Tumor Cell Proliferation

A hallmark of cancer is the uncontrolled proliferation of cells, which rapidly increases in number. A number of compounds derived from Aspergillus have demonstrated the capacity to impede the proliferation of tumor cells, thereby preventing their uncontrolled growth (54). Echinocandins, for instance, are compounds designed to impede the formation of beta-glucans, which are vital components of the fungal cell wall. This process effectively impedes the production of beta-glucans, thereby disrupting the fungal cell wall's integrity and structure (55). Furthermore, it has been observed 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. The anti-tumor effect of echinocandins is characterized by the inhibition of a broad spectrum of cellular processes, leading to the suppression of tumor growth (56) (Figure 2).

5. Animal Models and *In-Vivo* Studies

Aspergillus fungi and their compounds have been shown to possess significant anti-tumor potential in in vivo studies utilizing animal models (57). Consequently, researchers can evaluate the impact of these compounds on whole organisms, tumor growth, metastasis, and potential toxicity. This section will focus on the anti-tumor activity of Aspergillus-derived compounds in vivo and its implications for translational research and clinical trials (58).

5.1. Gliotoxin Studies

Gliotoxin has demonstrated significant potential in the fight against tumors, as evidenced by 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. In mouse models of lung cancer, the targeted MYC inhibitors reduced pro-tumor M2-like TAMs while preserving anti-tumor M1-like macrophages (59). Furthermore, the study revealed that the exposure of lung epithelial cells (A549 and L132) to gliotoxin for 24 hours led to a substantial augmentation in the proportion of cells in S-phase (30–39%), accompanied by a concurrent diminution in G2/M-phase. The early and late apoptotic cells were discerned through the utilization of Annexin V and PI stains, thereby substantiating the occurrence of apoptosis in the aforementioned cells following 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. Specifically, a mouse model of lung cancer (MDA-MB-231) was treated with fumagillin after being injected with human lung cancer cells. In accordance with the compound's in-vitro antiangiogenic properties, fumagillin

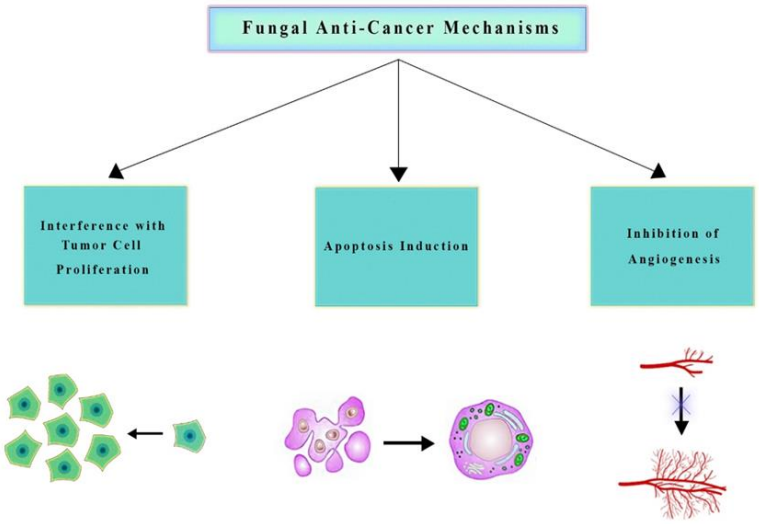

Figure 2. Compounds derived from Fungi exhibit various anti-tumor mechanisms, including the induction of apoptosis through intrinsic and extrinsic pathways, the inhibition of angiogenesis by targeting proangiogenic signaling pathways, and the interference with tumor cell proliferation by blocking essential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

treatment led to a substantial reduction in tumor growth and the inhibition of angiogenesis. Notably, the treatment did not result in substantial adverse effects on the mice, thereby supporting its potential as a safe anti-cancer treatment.

5.3. Echinocandins Studies

Echinocandins have also been identified as potentially effective anti-tumor agents in research studies performed in vivo. A mouse xenograft model was utilized to assess the efficacy of echinocandins in the treatment of lung cancer (63, 64). The results of this study demonstrated that echinocandin treatment led to a substantial reduction in tumor growth in xenografts with lung cancer. Notably, these treatments did not result in significant toxic effects on the mice, further supporting the potential of echinocandins as a safe and effective cancer therapeutic agent.

5.4. Combination Studies

A recent investigation has explored the potential of combining various techniques to assess the 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). The murine xenograft model was utilized in this study to treat the cancer cells. In this model, human lung cancer cells (A549) were implanted into mice. The mice were then treated with gliotoxin, cisplatin, or a combination of both to kill the cancer cells. A comparison of the combination treatment with either of the individual treatments revealed a statistically significant reduction in tumor growth. This finding suggests that the combination of both treatments is likely to be effective in the treatment of lung cancer (67) (Figure 3).

6. Challenges and Future Prospective

6.1. Identification of Specific Anti-Cancer Compounds

The most challenging aspect of cancer therapeutics is the development of an anti-cancer compound capable of eliminating tumor cells without causing harm to surrounding healthy cells (68). Consequently, numerous cancer biologists persist in their pursuit of the identification of novel anti-cancer compounds derived from natural sources. While the potential for these compounds to combat cancer exists, their safety is yet to be ascertained. This study employs a range of sophisticated methods, including chromatography, mass spectrometry, and bioassays, to isolate and characterize these compounds from Aspergillus extracts (69). The efficacy of these compounds is determined by testing them on various cancer cell lines. Furthermore, high-throughput screening methodologies can expedite the identification of potential anti-cancer compounds. A comprehensive understanding of the structure-activity relationship of these compounds is imperative to optimize their efficacy while minimizing 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

It is estimated that approximately 100,000 of the 1.5 million fungal species currently documented have been adequately characterized. This extensive biodiversity offers a potential source of anti-cancer therapeutic molecules (70). Researchers must optimize fermentation conditions, nutrient composition, and environmental parameters to enhance target compound production. Genetic engineering and strain improvement techniques have been employed to enhance Aspergillus strains. To enhance their productivity, it is imperative to identify and manipulate the critical regulatory elements involved in their biosynthesis to

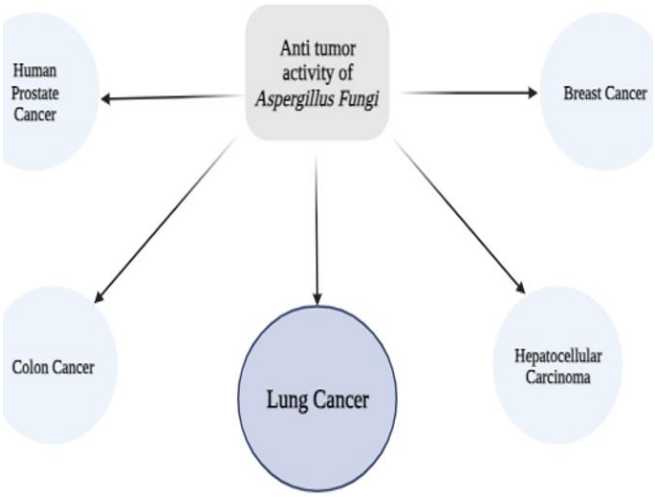

Figure 3. Various cancer types, including lung, breast, prostate, colorectal, and hepatocellular carcinoma, may respond to *Aspergillus*-derived compounds.

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

Incorporated with established cancer therapies, including chemotherapy, radiation, and targeted therapies, Aspergillus-derived compounds that exhibit anti-tumor properties may offer substantial potential as adjuvants or synergistic agents. It is imperative to comprehensively assess the interaction between Aspergillus compounds and standard cancer treatments to ensure their safety and efficacy when utilized in combination. The sensitization of cancer cells to chemotherapy or radiation therapy by Aspergillus-derived compounds, which target cell cycle regulation and DNA repair mechanisms, is a promising area of research. However, it is crucial to note that Aspergillus compounds may also exhibit adverse interactions with certain anti-cancer drugs, potentially diminishing the drug's toxicity and effectiveness. Conducting preclinical studies employing both in-vitro and in-vivo models is imperative to investigate the interactions between Aspergillus compounds and conventional therapies. These studies are crucial for enhancing the safety and efficacy of future clinical trials. These studies can facilitate the determination of optimal dosing schedules and identify potential drug-drug interactions.

6.4. Development of Targeted Drug Delivery Systems

Researchers are currently investigating the targeting mechanisms that would enable the delivery of anti-cancer compounds derived from Aspergillus. The objective of this research is twofold: first, to enhance the efficacy of these compounds, and second, to mitigate any potential adverse effects. The targeted delivery of therapeutic agents directly to cancer cells or tumor tissues, while sparing healthy cells and tissues from exposure, is a key area of research. The encapsulation of Aspergillus-derived compounds within nanoparticles, such as liposomes, micelles, and nanoparticles, allows for targeted delivery to specific tumor cells (72-74). The functionalization of these nanoparticles with antibodies or peptides that recognize markers on cancer cells is a critical aspect of drug delivery. To enhance the therapeutic efficacy of the anti-cancer compound, it is essential to augment its accumulation at the tumor site to mitigate the systemic toxicity of the compound. The employment of targeted drug delivery systems is instrumental in ensuring the stability and bioavailability of the combination, thereby enhancing its pharmacokinetics and therapeutic index. However, the development of targeted drug delivery systems is a multifaceted process that can be both complex and time-consuming. Research into nanoparticle formulations, the 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 have demonstrated promising anti-cancer properties, including the induction of apoptosis and the inhibition of tumor growth. A comprehensive exploration of their potential in cancer treatment necessitates further investigation, including mechanistic studies, drug development, combination therapies, and clinical trials. Addressing challenges in compound identification, production, and interactions with conventional therapies necessitates collaboration, paving the way for effective and personalized cancer treatments (75).

Conclusion

In summary, the investigation of Aspergillus fungi-derived anti-cancer compounds offers a promising approach in the pursuit of more effective lung cancer treatments. The diverse mechanisms by which these compounds target critical aspects of cancer biology, including apoptosis,

angiogenesis, immune response modulation, oncogenic signaling, and the tumor microenvironment, underscore 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. The integration of the distinctive properties inherent in Aspergillus-derived compounds into comprehensive treatment strategies has the potential to enhance survival rates and the quality of life for individuals afflicted with this pernicious malady.

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Authors' Contribution
Conceptualization: D.B.
Methodology: D.B.
Formal analysis and investigation: A.O.
Writing - original draft preparation: N.A, B.S, S.GS.
Writing - review and editing: MM.B, DS.
Supervision: D.B.

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

Conflict of Interest
The authors have declared no conflicts of interest.

Consent to Participate
The participant has not yet provided consent to participate in the study.

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

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