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Anticancer, Antimicrobial and Antiviral Therapeutic Potential of Fungi-Derived Substances

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Abstract

Microscopic fungi are prolific producers of bioactive secondary metabolites with potential applications in medicine, particularly in oncology, immunology, and antimicrobial therapies. The exploration of fungal-derived compounds as therapeutic agents has gained significant interest due to their structural diversity and wide range of biological activities, including anticancer, antimicrobial, immunomodulatory, and antiviral effects. This review focuses on the therapeutic potential of microscopic fungi-derived substances, with an emphasis on anticancer applications, and highlights notable compounds, their mechanisms of action, and emerging clinical evidence.

Keywords: Microscopic Fungi, cancer, microbes, viruses.

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Introduction

Microscopic fungi, including filamentous fungi and yeasts, represent a rich reservoir of biologically active secondary metabolites. These natural products have long been utilized for their antibiotic properties (e.g., penicillin. Fleming, 1929) and have recently emerged as promising candidates for treating a variety of diseases (Strobel, 2003). Fungi from genera such as *Penicillium*, *Aspergillus*,

Fusarium, and *Cladosporium* produce diverse metabolites that exhibit potent bioactivities (Li et al., 2020). Given the ongoing need for new therapeutic agents, fungi-derived compounds are increasingly investigated for their role in cancer therapy, immunomodulation, and antimicrobial resistance (Bills, G. F., Gloer, J. B. 2016). This review aims to summarize the current knowledge on microscopic fungi-derived substances, focusing on their therapeutic potential, particularly in cancer treatment, and highlighting the key challenges and future directions for this field.

Historical Data on the Therapeutic Potential of Microscopic Fungi-Derived Substances

The exploration of microscopic fungi for therapeutic purposes dates back several centuries, with significant milestones marking their contributions to medicine and pharmacology.

Early Uses in Traditional Medicine: Fungi have been utilized in traditional medicine systems for millennia. For example, *Ganoderma lucidum*, known as reishi or lingzhi, has been used in Traditional Chinese Medicine for over 2,000 years to enhance health and longevity. Similarly, *Cordyceps* species were historically used in Tibetan and Chinese medicine for their purported energizing and immune-boosting properties (Paterson & Lima, 2010).

Discovery of Antibiotics: The modern era of medicinal fungi began with the accidental discovery of penicillin by Alexander Fleming in 1928, derived from the mold *Penicillium notatum*. This groundbreaking finding marked the beginning of the antibiotic era, leading to the mass production of penicillin during World War II, which saved countless lives (Fleming, 1945).

Expansion of Antifungal Agents: Following the discovery of penicillin, research into other fungal metabolites expanded. The 1950s saw the introduction of griseofulvin, an antifungal derived from *Penicillium griseofulvum*, which became a standard treatment for dermatophyte infections (Hay et al., 1991). The 1990s brought the development of echinocandins, a class of antifungal agents derived from *Glarea lozoyensis* and other fungi, targeting the fungal cell wall, thereby providing new treatment options for invasive fungal infections (Denning, 2003).

Anticancer Research: The search for anticancer properties in fungal metabolites gained momentum in the latter half of the 20th century. The discovery of taxol (paclitaxel) in the bark of the Pacific yew tree and its subsequent identification in endophytic fungi such as *Taxomyces andreanae* emphasized the importance of fungi in cancer therapeutics (Wang et al., 2019). Research into fungal-derived compounds, such as gliotoxin and fumitremorgin C, further highlighted their potential in oncology, particularly in overcoming drug resistance (Dolan et al., 2015; Tsuruo et al., 2001). Also noteworthy is the effect of enzyme inhibitors associated with tumor growth, which were isolated from microscopic fungi (Khobelia et al., 2024)

Immunomodulatory Properties: As scientific techniques advanced, researchers began to uncover the immunomodulatory effects of fungal metabolites. The polysaccharide PSK (polysaccharide K) from *Coriolus versicolor* gained attention for its ability to enhance immune response in cancer patients, leading to its approval as an adjuvant therapy in Japan in the 1980s (Chan et al., 2009).

Current Research Trends: Today, the focus has shifted towards the biotechnological exploitation of microscopic fungi for drug discovery, including the use of omics technologies to identify novel metabolites and their therapeutic applications. Advances in genomics and synthetic biology are paving the way for the large-scale production of bioactive fungal compounds, making them more accessible for clinical use (Zhu et al., 2019).

The historical journey of fungi in medicine underscores their significant contributions to therapeutic agents and highlights the continued potential of microscopic fungi-derived substances in addressing current healthcare challenges.

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Anticancer Properties of Fungal Metabolites. **Fungal-Derived Compounds with Anticancer Activity.**

Numerous studies have shown that secondary metabolites from fungi exhibit significant anticancer properties. Some notable examples include:

1. **Taxol (Paclitaxel)**: Originally derived from the bark of the Pacific yew tree, *Taxus brevifolia*, Taxol was later discovered to be produced by endophytic fungi such as *Taxomyces andreanae* and *Pestalotiopsis* spp. Taxol is a well-known mitotic inhibitor that stabilizes microtubules, preventing cell division and inducing apoptosis in cancer cells. It is used clinically for the treatment of breast, ovarian, and non-small cell lung cancers (Dolan et al., 2015).
2. **Gliotoxin**: Produced by *Aspergillus fumigatus*, gliotoxin is a fungal metabolite that has demonstrated potent cytotoxic effects on cancer cells, particularly through the induction of oxidative stress and apoptosis. Gliotoxin inhibits tumor growth by interfering with NF-κB signaling pathways, which are crucial for cell survival and proliferation (Li et al., 2020, Dolan SK, et al 2015).
3. **Fumitremorgin C**: Another metabolite from *Aspergillus fumigatus*, fumitremorgin C has been identified as an inhibitor of breast cancer resistance protein (BCRP), a drug efflux pump that contributes to multidrug resistance in cancer cells (Tsuruo et al., 2001).
4. **Vincristine and Vinblastine**: Though originally discovered in *Catharanthus roseus*, these alkaloids are also produced by endophytic fungi associated with the plant. Both compounds disrupt microtubule dynamics and are used in chemotherapy regimens for Hodgkin's lymphoma, breast cancer, and leukemia (von der Heide et al., 2014).

Mechanisms of Action

Fungal metabolites act through various mechanisms to exert their anticancer effects:

- **Induction of Apoptosis**: Many fungal metabolites, such as gliotoxin and taxol, induce apoptosis in cancer cells by disrupting key signaling pathways and mitochondrial functions (Dolan et al., 2015).
- **Inhibition of Angiogenesis**: Some fungal compounds, like fumagillin from *Aspergillus fumigatus*, inhibit angiogenesis, thus restricting the blood supply to tumors and limiting their growth (Ingber et al., 1990).
- **Immune Modulation**: Fungal-derived compounds can modulate the immune response, enhancing the activity of immune cells such as macrophages and natural killer cells to target cancer cells (Wang et al., 2019).
- **Multidrug Resistance Modulation**: Fungal metabolites like fumitremorgin C inhibit efflux pumps, overcoming one of the major obstacles in cancer treatment—multidrug resistance (Robey et al., 2001).

Targeting Tumor-Associated Macrophages (TAMs)

The tumor microenvironment (TME) plays a critical role in cancer progression and immune evasion. TAMs, which are often immunosuppressive, promote tumor growth and metastasis. Some fungal metabolites, such as polysaccharide-K (PSK) from *Coriolus versicolor*, have shown the ability to modulate the immune environment by reprogramming TAMs from an immunosuppressive to an immunostimulatory phenotype (Cui et al., 2018).

Fungal Metabolites with Immunomodulatory Properties

Fungal metabolites also have immunomodulatory effects that make them potential candidates for treating immune-related disorders, including cancer and autoimmune diseases. For instance:

Beta-Glucans: These polysaccharides, found in the cell walls of fungi like *Saccharomyces cerevisiae* and *Aspergillus* spp., are potent immunomodulators. Beta-glucans activate immune cells, such as

macrophages, dendritic cells, and neutrophils, enhancing their ability to recognize and destroy cancer cells (Chan et al., 2009).

Cylindrospermopsin: A metabolite from *Penicillium simplicissimum*, cylindrospermopsin has shown potential in modulating immune responses and exerting anti-inflammatory effects (Shi et al., 2014).

Antimicrobial and Antiviral Potential

In addition to their anticancer properties, fungal metabolites exhibit antimicrobial and antiviral activities. For example:

Griseofulvin: Isolated from *Penicillium griseofulvum*, griseofulvin is an antifungal agent that disrupts fungal cell mitosis by interacting with microtubules. It is clinically used to treat dermatophytic infections (Hay et al., 1991).

Lovastatin: Produced by *Aspergillus terreus*, lovastatin is a cholesterol-lowering agent that also exhibits antiviral properties by inhibiting viral replication in hepatitis C virus (HCV)-infected cells (Ye et al., 2003).

Echinocandins: These are a class of antifungal drugs derived from *Aspergillus* and *Glarea* spp. that inhibit the synthesis of β-(1,3)-D-glucan, an essential component of the fungal cell wall (Denning, 2003).

Challenges and Future Directions

Despite the promising therapeutic potential of fungal metabolites, several challenges remain:

1. **Identification and Isolation**: Many fungal species produce metabolites in trace amounts, making isolation and large-scale production difficult. Advances in metabolomics and synthetic biology may help overcome this issue (Li et al., 2020).
2. **Toxicity and Selectivity**: While some fungal compounds exhibit potent bioactivity, their toxicity to non-cancerous cells or tissues remains a concern. Improving the selectivity of these compounds for cancer cells is a key area of research (Zhu et al., 2019).
3. **Resistance Development**: As with many antimicrobial agents, prolonged use of fungal metabolites may lead to resistance development. Combination therapies and novel drug delivery systems may mitigate this risk (Li et al., 2020).

Conclusion

Microscopic fungi-derived substances hold immense promise as therapeutic agents, particularly in cancer treatment and immunomodulation. With their wide-ranging bioactivities and structural diversity, fungal metabolites represent a valuable resource for drug discovery. However, further research is needed to fully harness their potential, particularly in terms of improving their selectivity, reducing toxicity, and scaling up production. Collaborative efforts in genomics, metabolomics, and synthetic biology will be essential for advancing this field and translating fungal metabolites into clinically viable therapies.

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