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Review

Host Immune Responses to Pathogenic Fungi and Contemporary Therapeutic Strategies

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ABSTRACT: Opportunistic infections such as *Candida*, *Aspergillus*, and *Cryptococcus* are significant contributors to illness and mortality, particularly in those with compromised immune systems. The innate and adaptive immune systems collaborate to ensure host protection. Pattern recognition receptors in innate immunity are the primary line of defense. They identify fungal fragments and emit signals that induce swelling. The immune system must generate cytokines and activate immune cells to eradicate fungi. This is particularly applicable to reactions from Th1 and Th17. Fungal diseases are emerging with numerous strategies to circumvent human defenses, such as altering their morphology, developing biofilms, and concealing characteristics that elicit an immune response. These modifications facilitate prolonged infection persistence. The rise of antifungal resistance, caused by genetic mutations, efflux pumps, and biofilm-associated protection, has diminished the efficacy of conventional antifungal medicines. This review delineates the host immune system's response to fungal infections and examines the primary mechanisms of antifungal resistance. It also discusses novel approaches to treatment, such as combination therapy and immunomodulatory techniques, aimed at enhancing the immune system and improving treatment efficacy. To enhance the efficacy and specificity of antifungal therapies, it is imperative to deepen our understanding of the interactions between infections and hosts.

Keywords: Antifungal Resistance, Drug Resistance, Immune Response, Immunotherapy, Pathogenic Fungi.
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1. INTRODUCTION

Pathogenic fungi are increasingly recognized as significant, though often overlooked, contributors to worldwide morbidity and mortality (Bastos et al., 2021; Rokas, 2022). Recent estimates indicate that fungal infections result in around 1.5 million fatalities annually and affect nearly one-third of the global population (Buscaino, 2019; Kollath et al., 2018). These fatality rates surpass those of other serious infectious and non-infectious diseases, such as malaria, TB, and breast cancer (Kollath et al., 2018). The escalating prevalence of fungal infections is attributed to the growing number of immunocompromised individuals, climate change, and the expansion of medicinal interventions that predispose patients to opportunistic infections (Denning, 2024).

There are an estimated 3.5 to 5.0 million distinct species of fungi, although only a minimal fraction have the potential to cause illness in humans. Nonetheless, about one million fungal species are considered potentially dangerous under suitable settings (Kim, 2016). Four principal genera, *Aspergillus*, *Candida*, *Cryptococcus*, and *Pneumocystis*, account for the majority of worldwide fungal-related mortality (Buscaino, 2019). These fungi cause both invasive and chronic

diseases, substantially affecting global morbidity and mortality rates. Fungal infections are frequently associated with chronic and recurrent conditions, including allergic fungal illnesses, recurrent candidiasis, and chronic pulmonary aspergillosis. These disorders significantly diminish quality of life and necessitate prolonged medical attention (Bongomin et al., 2017).

The risk is especially pronounced in immunocompromised individuals, including those with acquired immunodeficiency syndrome (AIDS), cancer, organ transplants, and those receiving immunosuppressive therapies, as opportunistic fungi such as *Aspergillus*, *Candida*, and *Cryptococcus* can cause severe, frequently fatal invasive diseases (Brown et al., 2012). *Aspergillus*, *Candida*, and *Cryptococcus*, can cause invasive infections in these populations, leading to elevated mortality rates. Furthermore, detecting fungal infections remains challenging due to the ambiguity of symptoms and the limited availability of rapid testing methods. This frequently results in postponed treatment and adverse outcomes (Fisher et al., 2020). A significant issue in the management of fungal infections is antifungal resistance. The proliferation of drug-resistant fungal species has accelerated due to the extensive application of antifungal agents in both clinical and agricultural environments (Fisher et al., 2020). Fungi employ many tactics to counteract antifungal agents, including altering the target sites of therapy, overactivating efflux pumps, forming biofilms, and activating stress-response pathways (Cowen et al., 2015).

Significant clinical cases include azole-resistant *Aspergillus fumigatus*, multidrug-resistant *Candida auris*, and *Candida glabrata*, which is increasingly resistant to echinocandins. These resistant infections are associated with increased treatment failure rates and elevated mortality rates. The limited variety of antifungal drugs complicates treatment selection and underscores the necessity for novel therapeutic approaches to address these infections (Cowen et al., 2015; Fisher et al., 2020).

While host immune responses are essential for managing fungal infections, many gaps remain in our comprehension of antifungal immunity. The innate and adaptive immune systems must collaborate to battle fungal infections. Innate immunity encompasses complement activation, neutrophils, macrophages, epithelial barriers, and pattern-recognition receptors that detect fungal components (Romani, 2011). Adaptive immunity, particularly Th1 and Th17 responses, contributes to pathogen clearance and long-term immune protection (Brown et al., 2012). Immunological responses vary with fungal species, infection site, and host immunological status, complicating the development of treatment protocols and vaccines (Lionakis & Levitz, 2018). Fungi also use techniques to avoid the immune system, such as hiding their cell walls, changing their antigens, and making biofilms, which make it harder for the host to recognize them and clear them out (Lionakis & Levitz, 2018). Immunological issues such as neutropenia, T-cell dysfunction, and corticosteroid use increase susceptibility to fungal infections and impair therapy efficacy. The absence of validated immunological biomarkers and inadequate understanding of protective immune responses hinder the progress of effective immunotherapies and vaccines (Romani, 2011; Lionakis et al., 2023).

Current investigations underscore the necessity for enhanced surveillance systems, expedited diagnostic technologies, and tailored treatment techniques to combat the increasing incidence of fungal infections (WHO, 2022). Advancements in antifungal immunology and host-targeted therapeutics demonstrate the potential for enhancing patient outcomes. However, further mechanistic and translational research is essential to improve the comprehension of host-fungus interactions and to develop innovative antifungal treatments.

This review aims to delineate the immune system's response to fungal infections and elucidate the mechanisms of contemporary therapies. It highlights significant research deficiencies and future opportunities in antifungal immunity and therapy, focusing on domains where existing data indicate unmet therapeutic needs and insufficient understanding.

2. INNATE IMMUNE RESPONSES TO FUNGAL PATHOGENS

2.1. Natural (Innate) Immunity Overview

Through coordinated barrier, cellular, and soluble mechanisms, innate immunity, the immediate, non-specific defense system, plays a crucial role in early recognition and control of fungal pathogens. Fungi have the potential to confer immune-enhancing benefits to humans. The modulation of immune responses may be influenced by Taneem factors, which encompass both external and internal elements (Shallal, 2025c, 2026a, 2026b, 2026c). Recent reviews highlight how its regulation significantly affects the outcome of infection and subsequent adaptive responses (Erwig and Gow, 2016). Fungal colonization is restricted by physical and chemical barriers, such as intact skin, mucosal epithelium, antimicrobial peptides, and the local microbiota.

Meanwhile, tissue-resident macrophages and dendritic cells function as first responders, identifying components of the fungal cell wall through a variety of pattern-recognition receptors, including C-type lectin receptors (Dectin-1, Dectin-2, Mincle), scavenger receptors, and intracellular sensing pathways that initiate antifungal signaling cascades (Lionakis et al., 2023). The high susceptibility of neutropenic patients is explained by neutrophils' use of phagocytosis, oxidative burst, nutritional immunity (metal sequestration), and neutrophil extracellular traps (NETs) to limit fungal growth. Neutrophils are now known to be particularly important in invasive mold and yeast infections (Urban and Nett, 2019). Further influencing antifungal defense and serving as new therapeutic targets are complement activation, cytokine networks (including IL-1, IL-6, and GM-CSF), and trained innate immunity, a recently described phenomenon in which previous fungal exposure epigenetically boosts innate responses (Netea et al., 2020).

2.2. Fungal Recognition (PRRs)

The ability of pattern recognition receptors (PRRs) to identify fungal pathogens and distinguish them from host cells by identifying conserved microbial structures known as pathogen-associated molecular patterns (PAMPs) makes them a crucial component of innate defense (Drummond and Lionakis, 2016). For pattern recognition receptors (PRRs), toll-like receptors (TLRs) are essential because they can identify fungal components, including zymosan, phospholipomannan (from Candida), and fungal nucleic acids. This identification triggers the NF-κB and IRF signaling pathways, which generate pro-inflammatory cytokines and type I interferons (Gantner et al., 2005). Certain carbohydrates found in fungal cell walls, like β-glucans, α-mannans, and chitin, are recognized only by C-type lectin receptors (CLRs) such as Dectin-1, Dectin-2, Mincle, and the mannose receptor. This triggers Syk-CARD9, which, in turn, activates NF-κB, generates reactive oxygen species, promotes bacterial phagocytosis, and initiates inflammasome activation (Willment and Brown, 2008). Because TLRs and CLRs work together, the immune system can differentiate between fungal infections and the body's own cells and control the strength and quality of the inflammatory response. Immunotherapy may target pattern recognition receptors (PRRs), which are essential to the body's defense processes. Invasive and mucocutaneous fungal infections are more likely to occur in people with compromised PRR function or genetic abnormalities in Dectin-1 or CARD9 (Drummond and Lionakis, 2016; Netea et al., 2020).

2.3. Cellular Responses

In the innate immune response to early-stage fungal infections, neutrophils are essential first responders. They assist in diminishing the prevalence of filamentous fungi and yeasts (Brown et al., 2012). They swiftly move into areas where fungi are invading, thanks to chemokines and cytokines like GM-CSF and IL-8. To detect fungal infections, they employ complement receptors, TLR2/4, and Dectin-1 as pattern recognition receptors (PRRs). The fungal cell wall's mannans and β-glucans can be distinguished by these receptors (Erwig and Gow, 2016). Numerous processes, including phagocytosis, the production of reactive oxygen species (ROS), the release of proteolytic enzymes, and the creation of neutrophil extracellular traps (NETs), allow neutrophils to eradicate fungi. Fungal hyphae and spores may be killed and rendered immobile by these techniques (Lionakis et al., 2023). By producing chemokines and cytokines that attract and activate more immune cells, they also contribute to adaptive immunity. There is a strong correlation between neutropenia or functional impairments in neutrophils and serious, frequently fatal fungal infections like invasive aspergillosis and candidemia. It is crucial to find medications that improve neutrophil function in individuals with compromised immune systems (Brown et al., 2012; Netea et al., 2020).

Macrophages are essential immune cells that perform two functions: they coordinate broader immune responses with other immune cells and directly eliminate fungal infections (Erwig and Gow, 2016). They either originate from monocytes during an infection or reside as resident macrophages in tissues. To locate fungi, they employ pattern recognition receptors (PRRs), such as complement receptors, Toll-like receptors, and C-type lectin receptors (Dectin-1 and Dectin-2). Fungal cell walls contain mannans and β-glucans (Drummond & Lionakis, 2016). Macrophages use phagocytosis to ingest fungi and subsequently employ fungicidal mechanisms, including nitric oxide, reactive oxygen species (ROS), hydrolytic enzymes, and phagolysosome acidification, to eradicate internalized fungi (Lionakis et al., 2023). By directly eliminating fungal infections and modulating the inflammatory response through cytokine production, natural killer (NK) cells and innate lymphocytes contribute to antifungal immunity (Vivier et al., 2018).

In contrast to phagocytes, NK cells do not mainly rely on phagocytosis; instead, they can identify fungal components and stressed or infected host cells indirectly through activating and inhibitory receptors such as NKG2D, NKp30, and NKp46, which identify alterations in microbial ligands or infected cells (Schmidt et al., 2017). When NK cells are activated, they release granzymes and perforin-containing cytotoxic granules that might harm fungal hyphae or in-

fected host cells. They also release pro-inflammatory cytokines, including TNF-α and IFN-γ, that boost the antifungal activity of neutrophils and macrophages (Vivier et al., 2018). The bone marrow produces NK cells, which are then released into the bloodstream by target cells that express NK cell receptor ligands or cytokines. In contrast to B-cell and T-cell antigen receptors, which undergo somatic recombination, NK cell receptors are germline encoded. On the contrary, a combination of signals from both activating and inhibitory receptors affects the result of NK cell activation (Shallal et al., 2025b).

2.4. Soluble Mediators

Through direct pathogen detection, opsonization, and the stimulation of inflammatory responses, the complement system, a crucial part of innate immunity (Speth et al., 2008), improves host protection against fungal pathogens. Fungal cell wall components such as mannans, glucans, and chitin are recognized by complement proteins either directly or through lectin, classical, and alternative routes. This recognition triggers a proteolytic cascade that deposits C3b on the fungal surface (Zipfel and Skerka, 2025). Through the action of lysosomal enzymes and reactive oxygen species, this opsonization promotes cell death and facilitates phagocytosis by neutrophils and macrophages. Furthermore, complement activation produces small cleavage fragments, such as C3a and C5a, which function as potent anaphylatoxins, attracting and stimulating neutrophils, monocytes, and other immune cells at the infection site and intensifying the inflammatory response (Speth et al., 2008). By improving dendritic cell maturation and antigen presentation, complement also indirectly supports adaptive immunity by fostering Th1 and Th17 responses, which are crucial for managing fungal infections (Zipfel & Skerka, 2025).

3. ADAPTIVE IMMUNE RESPONSES To FUNGAL PATHOGENS

The vertebrate immune system's highly specialized adaptive immunity is characterized by clonal expansion, antigen specificity, and long-term immunological memory, enabling the host to mount more accurate and potent responses when repeatedly exposed to the pathogen (Murphy & Weaver, 2016). Through somatic gene rearrangement, B and T cells generate a diverse array of antigen receptors, enabling recognition of a wide range of foreign antigens (Abbas et al., 2023).

The foundation of humoral immunity is formed by B cells' recognition of native antigens and differentiation into plasma cells that produce antibodies that neutralize, opsonize, block toxins, and activate complement. In contrast, T cells' recognition of processed peptide antigens displayed on major histocompatibility complex (MHC) molecules by antigen-presenting cells connects innate and adaptive immune mechanisms (Bonilla and Oettgen, 2010). According to Abbas, Lichtman, and Pillai (2023), $CD8^+$ cytotoxic T cells destroy diseased and cancerous cells by inducing apoptosis, whereas $CD4^+$ helper T cells control immune responses by secreting cytokines and by supporting functional subsets such as Th1, Th2, Th17, and regulatory T cells. Tight tolerance and regulatory controls are necessary to prevent autoimmunity and immunopathology while maintaining protective defense (Bonilla and Oettgen, 2010). There are two components to the adaptive response: memory cells and high-affinity class-switched antibodies drive the faster, stronger secondary phase, whereas the slower primary phase primarily drives IgM synthesis (Murphy & Weaver, 2016).

In Th1 and Th17 cells work together to coordinate cell-mediated immunity and mucosal inflammation in the adaptive immune response to fungal infections, such as those brought on by *Aspergillus* and *Candida*. Th1 responses are especially important in the treatment of invasive aspergillosis and systemic candidiasis. Interferon-γ (IFN-γ) and tumor necrosis factor (TNF), which stimulate macrophages, increase their fungicidal activity, encourage phagolysosome maturation, and aid in the intracellular destruction of fungal components, are the main ways that Th1 cells provide protection (Abbas et al., 2023; Murphy and Weaver, 2016).

Th17 cells are essential for antifungal immunity at mucosal and epithelial barriers because they produce interleukin-17 (IL-17) and interleukin-22 (IL-22), which direct stromal and epithelial cells to secrete chemokines and antimicrobial peptides, attract and activate neutrophils, and improve barrier integrity. These actions are essential for preventing mucocutaneous Candida infections and operate as the main line of defense against inhaled *Aspergillus* conidia (Hernández-Santos and Gaffen, 2012). Th1 activity needs to be balanced to prevent excessive tissue injury and fungal growth. Th17 responses are crucial because IL-17/Th17 axis abnormalities are intimately linked to chronic mucocutaneous candidiasis. The outcome of T-cell responses during infection depends on a critical balance between effective immune defense and immunopathology since the same effector pathways that eliminate pathogens can also harm host tissues if they become overactive or poorly regulated. Effector T cells, particularly Th1, Th17, and cytotoxic $CD8^+$ T

cells, can increase antimicrobial activity, activate phagocytes, and eliminate infected cells, provided they produce enough cytokines and cytolytic chemicals. For instance, IL-17-mediated neutrophil recruitment in mucosal defense and IFN-γ-driven activation of macrophages in intracellular infections. However, producing excessive amounts of pro-inflammatory cytokines (such as IFN-γ, TNF, and IL-17) and maintaining T-cell activation can harm other tissues, lead to fibrosis and chronic inflammation, and impair organ function (Murphy & Weaver, 2016). Autoimmune and inflammatory diseases are linked to issues with these systems, while overregulation can prolong infections. Immunological checkpoint pathways (CTLA-4 and PD-1), inhibitory cytokines (IL-10 and TGF-β), regulatory T cells (Treg), and the reduction of effector T-cell populations following antigen clearance are all crucial regulatory mechanisms that minimize damage and restore the body to normal (Paul and Zhu, 2010).

As the primary soluble mediators of humoral immunity, antibodies are antigen-specific glycoproteins made by plasma cells that bind foreign antigens and guide their neutralization or removal via a variety of effector pathways. According to Schroeder and Cavacini (2010), each antibody molecule consists of paired heavy and light chains, with variable regions that produce highly specific antigen-binding sites and constant regions that determine isotype and biological activity. These interactions allow antibodies to interact with complement components and Fc receptors on immune cells to promote opsonization, neutralization of toxins and viruses, formation of immune complexes, and antibody-dependent cellular cytotoxicity (Schroeder Jr & Cavacini, 2010).

Following antigen exposure, antibody responses go through affinity maturation and class-switch recombination, resulting in different isotypes with specific functions: IgM makes up the majority of early primary responses and is effective at complement activation; IgG offers placental transfer and systemic protection; IgA aids in mucosal defense in secretions; IgE mediates allergic and anti-parasite responses; and IgD primarily functions as a receptor on naïve B cells (Vidarsson et al., 2014). Durable protection following infection or vaccination is based on the production of memory B cells, long-lived plasma cells, and high-affinity antibodies, which are key products of germinal center responses (Schroeder Jr and Cavacini, 2010).

Antibodies assist the immune system in fighting off fungal pathogens by making them easier to locate, helping to get rid of them, and influencing how the body reacts to inflammation. It's evident how important they are when you get sick again or for a long time, when cellular immunity isn't enough on its own. Fungal adhesins and enzymes necessary for tissue invasion can be neutralized, complement activation can increase fungal killing and inflammation, and opsonization can increase phagocytosis by neutrophils and macrophages when antifungal antibodies bind to the surface polysaccharides and proteins of fungi like *Candida* and *Aspergillus*. IgG antibodies improve systemic clearance and antibody-dependent cellular cytotoxicity, while secretory IgA protects mucosal surfaces by reducing fungal adherence and colonization, which is particularly important in recurrent mucocutaneous candidiasis (Casadevall & Pirofski, 2012; Shallal, 2025a).

Following binding, the Fc region of immunoglobulin triggers immune pathways that support opsonization, which improves neutrophil and macrophage uptake and death via Fc receptors, as well as classical complement activation, which places C3 fragments on the fungal surface to further boost phagocytosis and encourage inflammation. Antibodies can also mediate antibody-dependent cellular cytotoxicity (ADCC) and modulate fungal physiology and host inflammation, with mucosal IgA preventing colonization and systemic IgG supporting clearance in invasive disease; these mechanisms are particularly important as cooperative defenses alongside phagocytes and T-cell responses in controlling fungal infections (Erwig and Gow, 2016).

By identifying and eliminating host cells that contain intracellular fungal pathogens and by generating cytokines that strengthen antifungal effector mechanisms, cytotoxic T lymphocytes (CTLs, $CD8^+$ T cells) aid in the management of invasive or persistent infections. By detecting fungal antigens on MHC class I molecules of infected cells, CTLs kill intracellular niches that shield fungi from extracellular immune factors, inducing apoptosis via perforin- and granzyme-mediated cytotoxicity and Fas–FasL interactions. They also release TNF and interferon-γ, which activate macrophages and boost their fungicidal activity, resulting in an enhanced cellular antifungal response. CTL responses have been demonstrated to be significant in infections involving intracellular or facultatively intracellular fungi as well as in immunocompromised hosts, where $CD8^+$ T-cell activity correlates with improved fungal control and reduced disease severity, even though neutrophils and Th1/Th17 $CD4^+$ T cells are the main defenses against many fungi (Brown et al., 2012; Romani, 2011).

4. IMMUNE EVASION MECHANISMS OF PATHOGENIC FUNGI

Fungal pathogens have developed a number of ways to avoid being detected by the host immune system, frequently by secreting enzymes and effector proteins that directly disrupt immune cell function, enabling ongoing colonization and infection. For instance, *Aspergillus fumigatus* produces gliotoxin, a secondary metabolite that causes neutrophils and macrophages to undergo apoptosis and inhibits the production of reactive oxygen species (ROS), which hinders fungal killing. *Candida albicans* secretes aspartyl proteases that break down host complement proteins, immunoglobulins, and antimicrobial peptides, thereby decreasing opsonization and phagocytosis. Enzymes that alter their cell wall components to conceal pathogen-associated molecular patterns (PAMPs) from pattern recognition receptors, reducing identification by dendritic cells, macrophages, and neutrophils, or catalase and superoxide dismutase that neutralize ROS, are secreted by other fungi. Furthermore, fungi can evade both innate and adaptive immune responses and contribute to chronic or recurrent infections by secreting proteins like Candidalysin, which break down epithelial barriers and alter cytokine signaling to inhibit effective immune recruitment (Lionakis and Netea, 2013).

The release of virulence factors, like Candidalysin, which weakens epithelial barriers and alters local immunological communication to reduce effective immune recruitment, is also linked to hyphal development. Furthermore, morphological alterations might reduce the activation of both innate and adaptive responses by hiding cell wall components, including β-glucans, from immune cell pattern recognition receptors. By decreasing the effectiveness of phagocyte-mediated clearance and antibody-mediated opsonization, morphological plasticity not only promotes tissue invasion but also makes it easier to persist during long-term infections and leads to recurrent fungal diseases (Netea et al., 2020).

Fungal biofilm production forms thick, multicellular communities encased in an extracellular matrix (ECM) that chemically and physically protects the organisms, greatly increasing resistance to immune attack and antifungal treatment. Biofilms hinder neutrophil and macrophage phagocytosis, decrease antibody and complement protein penetration, and restrict exposure to reactive oxygen species in pathogens like *Candida albicans*, *Aspergillus fumigatus*, and *Cryptococcus neoformans*, thereby reducing the effectiveness of both the innate and adaptive immune systems (Fanning & Mitchell, 2012). Composed of proteins, lipids, extracellular DNA, and polysaccharides (mannans, β-glucans), the extracellular matrix (ECM) not only maintains structural integrity but also binds and sequesters antifungal medications, lowering their effective concentration and enabling the survival of highly drug-tolerant persisted cells (Netea et al., 2020).

Additionally, biofilm-dwelling fungi alter gene expression by activating stress-response pathways and efflux pumps, for example (Seneviratne et al., 2008). This increases their resistance to the body's defenses and antifungal medications. Together, these pathways enable fungi that form biofilms to flourish inside host tissues, on mucosal surfaces, and on medical equipment. This makes treatment more difficult and raises the risk of long-term or recurrent infections (Pierce et al., 2013).

5. MAJOR HUMAN FUNGAL PATHOGENS

5.1. *Candida* spp.

Human mucosal surfaces, including the mouth, genitourinary system, and gastrointestinal tract, are home to an opportunistic yeast-like fungus called *Candida* spp (Gow et al., 2017). However, both superficial and deep infections can result from insufficient defenses. Their morphological versatility is demonstrated by their capacity to transition between yeast, pseudohyphal, and hyphal forms. They can more easily penetrate tissues, evade the immune system, and proliferate as a result. Among the virulence factors that aid in bacterial invasion, phagocyte avoidance, and antibody elimination are adhesins, hydrolytic enzymes (such as secreted phospholipases and aspartyl proteases), and biofilm development (Netea et al., 2020). The host immune system utilizes both innate and adaptive strategies to counteract *Candida*. Th1 and Th17 cells secrete cytokines (IFN-γ, IL-17) to enhance fungus elimination, while pattern recognition receptors, including dectin-1 and Toll-like receptors, stimulate phagocytes. Furthermore, antibodies promote opsonization and complement-mediated destruction, particularly in mucosal or recurring infections (Pfaller and Diekema, 2010).

Both innate and adaptive mechanisms are used by the host's immune system. However, in those with weakened immune systems, including those with diabetes, this resistance is not very robust. Pattern recognition receptors (PRRs) such as dectin-1 and Toll-like receptors are used by neutrophils, macrophages, and dendritic cells to recognize fungal pathogen-associated molecular patterns (PAMPs) such as mannans and β-glucans. Innate immunity emerges as the

main defense mechanism as a result of this recognition. It releases pro-inflammatory cytokines, produces reactive oxygen species (ROS), and initiates phagocytosis (Netea et al., 2020).

Stronger antifungal effect results from the regulation of adaptive immunity by Th1 and Th17 $CD4^+$ T cells. To attract neutrophils and fortify mucosal barriers, Th17 cells release IL-17 and IL-22. In contrast, Th1 cells produce IFN-γ to prepare macrophages to eliminate intracellular cells (Gow et al., 2017). Hyperglycemia increases the risk of mucosal and systemic candidiasis in people with diabetes or other immune-compromising conditions by altering neutrophil movement and eating, reducing Th17 responses, and altering cytokine production (Casqueiro et al., 2012).

Candida species have developed a variety of strategies that allow extended colonization and infection to avoid host immune defenses, including neutrophil and T-cell responses. One significant mechanism is morphological switching: when yeast changes into hyphal or pseudohyphal forms, phagocytosis decreases because hyphae are often too large for neutrophils and macrophages to engulf (Gow et al., 2017). Additionally, *Candida* produces hydrolytic enzymes that degrade complement proteins, antibodies, and chemokines. Phospholipases and secreted aspartyl proteases (SAPs) are two examples of enzymes that hinder neutrophil function and access to the infection site (Naglik et al., 2003). Dectin-1 and other pattern recognition receptors may have a tougher time detecting β-glucans and other PAMPs because the fungal cell wall can conceal them. This lowers the activation of both innate and adaptive immunity (Netea et al., 2020).

5.2. *Aspergillus* spp.

Among the most significant opportunistic fungal diseases in humans, *Aspergillus* species are filamentous, saprophytic fungi widely found in soil, air, decomposing vegetation, and preserved foods. *Aspergillus fumigatus*, *A. flavus*, *A. niger*, and *A. terreus* are clinically significant species. Because of its small airborne conidia and thermotolerance, A. fumigatus is the most frequent cause of invasive illness (Latgé & Chamilos, 2019). Spores are typically inhaled to cause infection, which can result in a variety of illnesses, from life-threatening invasive aspergillosis to allergic bronchopulmonary aspergillosis and chronic pulmonary aspergillosis, particularly in immunocompromised people like neutropenic patients, transplant recipients, and those on corticosteroids. Numerous virulence mechanisms, such as the synthesis of gliotoxins, the creation of biofilms, thermotolerance, and effective iron acquisition systems, assist pathogenicity by enabling the fungus to elude host immune responses and endure in tissues (Van De Veerdonk et al., 2017). Aflatoxin production by some species, such as A. flavus, can contaminate food and crops and pose a serious threat to human health and food safety (Bennett & Klich, 2003).

The strongest defense against *Aspergillus* infections is innate immunity. To identify and eliminate inhaled conidia, alveolar neutrophils and macrophages are crucial. However, innate immunity is significantly lower in cancer patients receiving chemotherapy and transplant recipients. Conidia are often recognized by pattern recognition receptors, such as Toll-like receptors and C-type lectin receptors (e.g., Dectin-1). These receptors initiate phagocytosis and the synthesis of pro-inflammatory cytokines. Macrophages eliminate bloated conidia, whereas neutrophils assault developing hyphae via neutrophil extracellular traps and oxidative bursts (Van De Veerdonk et al., 2017). T-cell responses are compromised, neutrophil numbers and function are decreased, and corticosteroids further suppress macrophage activity, allowing for the hyphal invasion and angioinvasion typical of invasive aspergillosis in patients with prolonged neutropenia following chemotherapy or those undergoing immunosuppressive therapy following hematopoietic stem cell or solid organ transplantation (Latgé and Chamilos, 2019). Adaptive immunity is also involved, even though immunosuppressive regimens frequently used in transplant therapy might impair these protective mechanisms. Th1 and Th17 responses improve fungal clearance through IFN-γ and IL-17 signaling, while a skewed Th2 response is linked to allergic forms of aspergillosis (Van De Veerdonk et al., 2017).

Several immune-evasion techniques are used by *Aspergillus* species, especially *A. fumigatus*, to enable tissue penetration and survival in spite of host defenses. The outer layer is coated with a hydrophobic rodlet layer and melanin pigments that conceal pathogen-associated molecular patterns (PAMPs) such as β-glucans, making it more difficult for host pattern-recognition receptors to locate resting conidia and preventing neutrophils and macrophages from becoming activated too soon (Latgé and Chamilos, 2019). The fungus produces gliotoxin and other immunomodulatory substances during germination. These chemicals inhibit NADPH oxidase activity, impair T-cell responses, prevent neutrophils and macrophages from functioning, and kill immune cells (Sugui et al., 2007).

Aspergillus synthesizes antioxidant enzymes, such as catalase and superoxide dismutase, to combat reactive oxygen species produced by phagocytes, thereby enhancing cellular resistance to oxidative stress-induced apoptosis. The fungus facilitates the formation of inflammatory or nutrient-deficient tissues by adapting to the host environment via efficient iron-acquisition mechanisms (siderophores), hypoxia tolerance, and stress-response pathways (Latgé and

Chamilos, 2019). Biofilm formation enhances immune evasion, especially in pulmonary cavities and on medical devices, by creating a protective extracellular matrix that obstructs antifungal penetration and safeguards hyphae from immune cell attacks (Van De Veerdonk et al., 2017).

5.3. *Cryptococcus* spp.

Yeasts that thrive in their surroundings and seize opportunities are called *Cryptococcus* species. They are especially prevalent in soil contaminated by rotting wood and bird droppings. These factors have a significant impact on potentially lethal fungal illnesses. The two most hazardous species combinations are *Cryptococcus neoformans* and *Cryptococcus gattii*. They are mostly transmitted by humans ingesting yeast spores or cells. Individuals with compromised immune systems are more susceptible to illness. HIV/AIDS patients, recipients of transplants, and those on immunosuppressive therapy fall under this category. By initially entering the lungs and then moving on to the brain and spinal cord, they can cause cryptococcal meningitis (Zaragoza, 2019).

The thick polysaccharide capsule is an essential virulence factor because it suppresses phagocytosis, lowers inflammation, and stops antigen presentation. Other virulence characteristics that help the bacteria survive in host tissues include urease activity, the ability to make melanin, and the capacity to thrive at 37 °C (Zaragoza, 2019). Individuals with compromised immune systems are generally the only victims of C. neoformans, but even people with robust immune systems may become ill from *C. gattii*. Moreover, it is associated with outbreaks in particular areas (May et al., 2016).

For the treatment of persistent *Cryptococcus* infections, cell-mediated immune responses that trigger granuloma formation and macrophage fungicidal activities are very important. Th1-type $CD4^+$ T-cell responses, which generate interferon-γ (IFN-γ), interleukin-12 (IL-12), and tumor necrosis factor-α (TNF-α), are the main drivers of protective immunity. These cytokines make macrophages more cytotoxic, increase nitric oxide and reactive oxygen species generation, and allow *Cryptococcus* to persist in organized granulomatous lesions in the lungs and other organs. (May et al., 2016; Zaragoza, 2019). Th17 responses help attract neutrophils and strengthen antifungal defenses in the lungs and mucosal membranes, despite their minor importance. Conversely, a Th2-dominated response (IL-4, IL-5, and IL-13) is linked to persistent infection, increased capsule formation, and insufficient fungal elimination.

Cryptococcus species use both active immunological control and structural shielding to evade antibody and T-cell-mediated immunity. The crucial element is the thick polysaccharide capsule, which is primarily made of glucuronoxylomannan. It prevents complement deposition and opsonization, hides underlying cell wall antigens, and reduces the effectiveness of antibody binding, all of which limit the effectiveness of phagocytosis. Additionally, shed capsular polysaccharide can circulate and directly prevent the synthesis of cytokines and T-cell proliferation (May et al., 2016; Zaragoza, 2019). Melanin is produced by the fungal cell wall, which helps it survive in macrophages, reduces the likelihood that the immune system will detect it, and shields it from oxidative damage. By shifting host responses away from protective Th1/Th17 pathways and toward non-protective Th2 responses, decreasing IFN-γ-mediated macrophage activation, and undermining T-cell-driven clearance of Cryptococcus, the fung*us* further disrupts adaptive immunity (Zaragoza, 2019). In order to evade external antibodies and immunological attacks, it can live and multiply inside macrophages and use them as "Trojan horse" vehicles for dissemination, especially to the central nervous system (May et al., 2016). Further hindering antigen presentation and T-cell activation, cryptococcal enzymes such as urease and phospholipases, as well as capsule expansion during infection, promote persistence and chronic illness.

5.4. Mucorales

A serious and frequently fatal opportunistic infection, mucormycosis is caused by a group of quickly developing filamentous fungi called Mucorales spp., which are members of the order Mucorales (class Mucoromycetes). *Rhizopus*, *Mucor*, *Rhizomucor*, *Lichtheimia* (formerly *Absidia*), and *Cunninghamella* are common pathogenic taxa. These fungi are commonly found in soil, compost, decomposing organic materials, and the air. Infection mainly occurs through inhalation of spores, direct wound contamination, or ingestion. Mucormycosis primarily affects those with uncontrolled diabetes (particularly those with ketoacidosis), blood malignancies, recipients of transplants, and those undergoing chemotherapy or corticosteroids. This is due to the fact that when phagocyte function is compromised, spores may develop into invasive hyphae (Cornely et al., 2019).

Clinically, this may show up as widespread illness, pulmonary, cutaneous, gastrointestinal, or rhino-orbital-cerebral. A feature of Mucorales infection is angioinvasion, in which broad, ribbon-like, sparsely septate hyphae enter blood vessels, causing necrosis, tissue infarction, and thrombosis. Crucial virulence traits include re-

sistance to specific innate immune elimination processes, fast hyphal proliferation, and strong iron acquisition systems that perform well in acidic and high-glucose environments (Cornely et al., 2019; Ibrahim et al., 2008).

The body's primary defense against Mucorales is the innate immune system, particularly the function of neutrophils and macrophages. Those with weakened immune systems, such as those with uncontrolled diabetes or those using immunosuppressive medications, have very weak defenses. Pattern-recognition receptors on dendritic cells and macrophages in healthy hosts allow them to distinguish between injected and inhaled spores. These cells draw neutrophils by consuming the spores and releasing cytokines that promote inflammation. Through extracellular traps, oxidative bursts, and degranulation, neutrophils harm growing hyphae (Cornely et al., 2019). Individuals with diabetes, particularly those experiencing ketoacidosis, have diminished phagocyte chemotaxis and oxidative cell death. Elevated levels of free iron facilitate fungal proliferation and impede the immune system's ability to combat them, hence increasing the likelihood of invasive infections (Ibrahim et al., 2008).

The Mucorales species. Escape NK cells' and macrophages' defenses by rapidly changing their form, concealing their cell walls, and aggressively inhibiting the activities of antifungal effectors. Spores can resist being killed inside cells because, once inside, they rapidly develop into broad hyphae that are too large for macrophages to consume. Immunostimulatory ligands become less visible and pattern-recognition receptor signaling is slowed down as a result of the cell wall's altered composition (Spellberg et al., 2005). They are more resilient to oxidative stress due to melanin and other polymers in their cell walls, which help scavene reactive oxygen species produced by macrophages. Mucorales also secrete enzymes (e.g., catalase, superoxide dismutase) and metabolic factors that blunt oxidative damage and impair phagocyte killing (Ibrahim et al., 2008).

Generally, In diabetics and other acidotic, high-glucose diseases, fungal iron acquisition methods perform better. While host phagocyte chemotaxis and oxidative burst are intrinsically impaired, this unintentionally encourages growth and escape. Mucorales decrease susceptibility by rapid hyphal extension, stress-response pathways, and surface properties that limit stable NK–fungus interactions and cytotoxic efficacy, thereby reducing NK-mediated damage, even though NK cells can damage fungal hyphae via perforin/granzyme and cytokines (Cornely et al., 2019; Schmidt et al., 2017).

6. CURRENT ANTIFUNGAL THERAPIES AND IMMUNOMODULATORY STRATEGIES

6.1. Conventional Antifungal Agents

Antifungal agents are compounds with antifungal properties that can prevent fungal infections (Seyedmousavi et al., 2016). Conventional antifungal drugs can be applied topically or systemically and fall into roughly five groups: azoles, polyenes, echinocandins, allylamines, and pyrimidine analogs (Hokken et al., 2019). Since the 1950s, more than 200 polyenes with antifungal properties have been discovered; yet, amphotericin B (AmB) remains the sole polyene drug of choice for the management of invasive fungal infections (Zotchev, 2003). Unfortunately, frequent and occasionally major side effects, including nephrotoxicity and infusion responses, limit its usefulness (Bates et al., 2001). The first systemic azole, ketoconazole, was on sale in the early 1980s. Fluconazole and itraconazole, the first-generation triazoles, became accessible ten years later. AmB was eventually replaced as the recommended drug for the treatment of invasive aspergillosis and most other filamentous fungal infections by the second-generation triazole, voriconazole, because of its greater effectiveness and lower toxicity (Herbrecht et al., 2002). As first-line treatments for invasive candidiasis, echinocandins were launched in the 2000s (Alexander et al., 2013). Originally created and used to treat cancer, the antimetabolite 5-flucytosine (5-FC) is also administered in conjunction with AmB, mostly to treat cryptococcal meningitis (Rogers et al., 2022).

Although there have been significant advancements in antifungal therapy in recent decades, fungal infection-related morbidity and mortality are still rising despite greater awareness and the creation of novel antifungal medications (Denning, 2024). Currently, antifungal drugs fall into five main types according to how they work: azoles, polyenes, echinocandins, antimetabolites (like flucytosine), and allylamines (like terbinafine), Figure 1 (Robbins et al., 2016). Polyenes, such as natamycin, nystatin, and amphotericin B (AmB), were identified in the 1950s. By attaching itself to ergosterol, a crucial part of the fungal cell membrane, AmB destabilizes and creates pores. It is available in both traditional (deoxycholate, AmB-d) and lipid formulations (ABLC lipid complex, liposomal L-AmB). To reduce the toxicity of AmB, especially the nephrotoxicity associated with the deoxycholate formulation, lipid formulations of the drug have been developed. Lipid formulations dramatically reduced nephrotoxicity compared with traditional formulations, according to a meta-analysis (Steimbach et al., 2017).

Azoles, which have been around since the 1960s, are separated into two categories: imidazoles, which are mostly applied topically or with little systemic usage, and triazoles, which are extensively used systemically and include fluconazole, itraconazole, voriconazole, posaconazole, and isavuconazole. By inhibiting the cytochrome P450-dependent enzyme lanosterol 14α-demethylase, they prevent the formation of ergosterol, which changes membrane function by causing harmful methylated sterols to accumulate and ergosterol to be depleted. Azoles are often fungicidal against *Aspergillus* species and fungistatic against yeasts. but are susceptible to hepatotoxicity and medication interactions (Balcerek et al., 2022).

Echinocandins, such as caspofungin, target the enzyme 1,3-glucan synthase, which is essential for the production of a healthy cell wall. This causes cell lysis and death since the cell's structural integrity is compromised (Hoenigl et al., 2023). Allylamines impede the ergosterol production route by inhibiting squalene epoxidase, an enzyme located at the pathway's initiation. This results in the buildup of squalene and a deficiency of ergosterol in the fungal cell membrane (Vanreppelen et al., 2023). Pyrimidine analogs, such as flucytosine, impede DNA and RNA synthesis by mimicking natural nucleotides, thereby obstructing the fungal cell's capacity to replicate and produce vital proteins, ultimately leading to cell death (Osset-Trénor et al., 2023).

The development of antifungal treatments is significantly hampered by the biological similarities between humans and fungi as eukaryotes. Because of this, it is challenging to find antifungal targets that may be specifically blocked without endangering patients. Furthermore, even with combination medicines that target several biological pathways, therapeutic efforts are made more difficult by the emergence of fungal species' resistance to antifungal medications (Sun et al., 2020). Promising new antifungal agents are under development, targeting novel mechanisms and minimizing unwanted effects. Recently authorized medications for clinical use include ibrexafungerp, rezafungin, oteseconazole, and miltefosine, while other novel drugs such as fosmanogepix, olorofim, and opelconazole are presently undergoing phase 3 clinical studies (Wolfgruber et al., 2024). Table 1 presents the targets and mechanisms of action of antifungal drugs.

Table 1. Conventional and Emerging Antifungal Agents: Targets and Mechanisms

Class of Antifungal	Examples	Target Site	Mechanism of Action	Reference
Polyenes	Amphotericin B, Liposomal amphotericin B, Nystatin, & Natamycin	Cell membrane	Attach to the ergosterol in the membrane of fungi to create holes that eventually lead to cell death by allowing intracellular substances to leak through.	(Robbins et al., 2016)
Azoles	Ketoconazole, Miconazole, Clotrimazole, Fluconazole, Itraconazole, Voriconazole, Posaconzole, & Isavuconazole	Cell membrane	Inhibit lanosterol 14-alpha-demethylase, blocking ergosterol synthesis and disrupting membrane structure and function.	(Gupta et al.,1994)
Allylamines	Terbinafine	Cell membrane	Stop the production of ergosterol by inhibiting squalene epoxidase, which leads to a hazardous build-up of squalene.	(Vanreppelen et al., 2023)
Echinocandins	Caspofungin, Micafungin, & Anidulafungin	Cell wall	Inhibit β-1, 3-glucan synthase, impairing fungal cell wall synthesis and integrity.	(Hoenigl et al., 2023)
Pyrimidine analogues	Flucytosine	Nucleic acid synthesis	Inhibit DNA and RNA synthesis, interfering with fungal replication and function.	(Osset-Trénor et al., 2023)

Schematic depiction of antifungal pharmacological (Figure 1) targets within a fungal cell. Azoles and polyenes compromise the cell membrane, whilst echinocandins obstruct β-glucan production in the cell wall. Griseofulvin disrupts microtubules and impedes mitosis. Flucytosine obstructs nucleic acid synthesis. Triphenylethylenes obstruct calcineurin signaling, while sordarins impede protein synthesis during the elongation phase (Hetta et al., 2025).

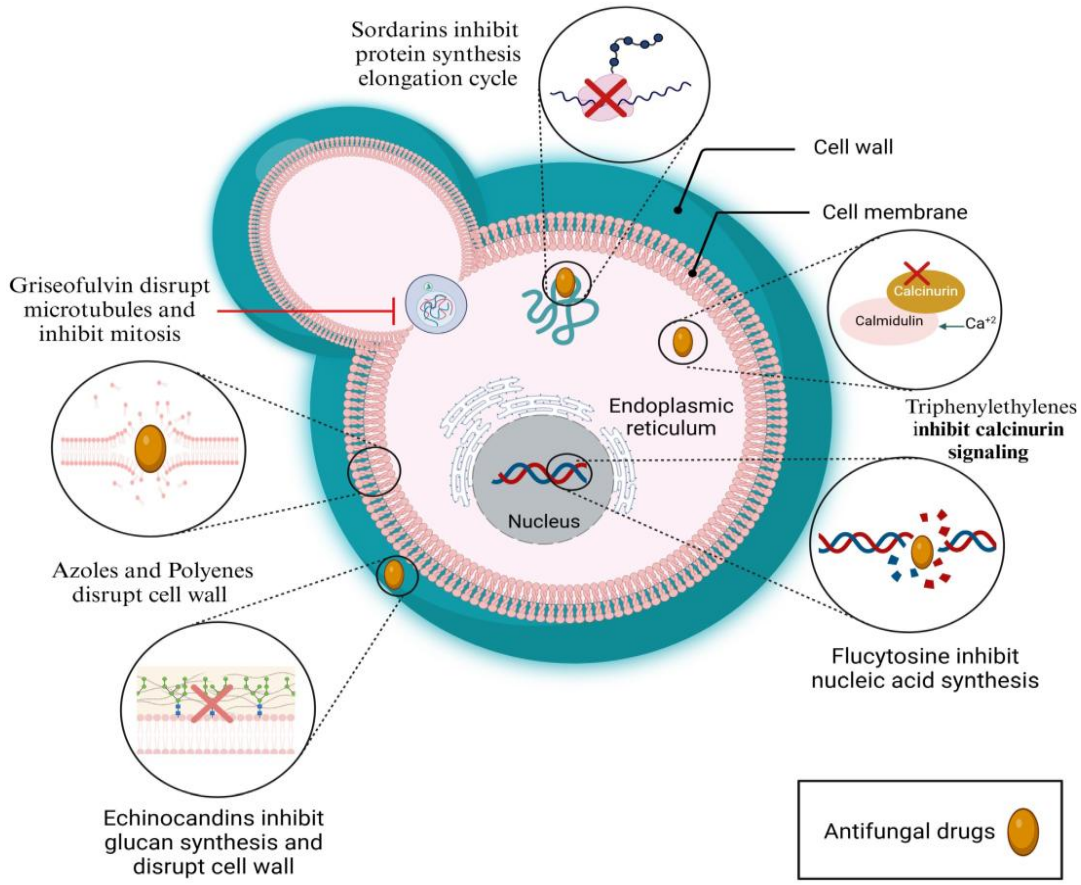

Figure 1. Mechanisms of action of antifungal agents targeting fungal cellular structures (Hetta et al., 2025).

6.2. Combination and Emerging Antifungal Therapies

Compared with monotherapy, combination therapy improves treatment efficacy and reduces drug resistance more effectively (Fioriti et al., 2022). The advantages of combined antifungal medication have been assessed in several experimental investigations, randomized trials, and clinical series (Lee et al., 2019; Qiu et al., 2019). When compared to monotherapy, the majority of clinical studies demonstrate comparable results for combination antifungal medication; however, secondary endpoints and sub-analyses frequently highlight benefits for the combinations in endpoints like culture sterilization (Ostrosky-Zeichner, 2008). It improves efficacy and bioavailability by focusing on several biological processes. This strategy involves taking two antifungal medications or combining an antifungal with a non-antifungal to increase its efficacy, such as with Hsp90 inhibitors, calcineurin (as cycloserine), lysine deacetylase, or lysine acetyltransferase (Spitzer et al., 2017). Combination therapy is a promising approach to treating drug-resistant fungal infections. When compared to individual pharmacological treatments, drug combination therapy offers advantages, including increased efficacy and specificity and can prevent the emergence of resistance (Hill and Cowen, 2015).

Additionally, through a process known as selection inversion, microbial drug resistance may not only be mitigated but potentially reversed by carefully selecting particular medication combinations (Baym et al., 2016). Combination therapy has several advantages, including the potential for synergistic effects. The most widely recognized advantage is that it can enhance antifungal activity beyond what each medication alone can do; this is known as a synergistic interaction (Kontoyiannis and Lewis, 2004).

The combination of amphotericin B and flucytosine is the gold standard for treating cryptococcosis, notwithstanding the therapeutic potential. This combination has been thoroughly verified in clinical trials for fungal infections (Day et al., 2013). Interestingly, in a model of *Galleria mellonella* infection, the combination of clofazimine and capsafungin demonstrated notable in vivo activity against *Candida albicans* (Robbins et al., 2015). The fact that fungal life is governed by a highly interconnected and functionally redundant network of biological interactions means that combination therapy may also reveal an abundance of new antifungal targets (Costanzo et al., 2010). Combination antifungal medication can have certain drawbacks, though. These include the potential for antagonistic effects between

specific antifungal drugs, elevated risk of medication toxicity, drug–drug interactions, and increased treatment expenses (Groll et al., 1998; Kontoyiannis and Lewis, 2004).

6.3. Immunotherapy for Fungal Infections

6.3.1 Antifungal Immunotherapy

The different immune components' respective roles in combating fungal infections vary depending on the type of fungal infection, whether it is hyphae, yeast, or pseudohyphae, as well as the infection's anatomic location (Shoham and Levitz, 2005). Most invasive fungal infections happen to immunocompromised hosts, including patients with chronic respiratory conditions, severe HIV illness, neutropenia, and solid and haematological organ transplants (Armstrong-James et al., 2020). The ability of antifungal therapy to restore the host immune response, either by treating the underlying illness, altering immunosuppressive treatments, or using immunotherapeutic techniques, is a crucial factor in determining the outcome of infection (Cortegiani et al., 2016). One important idea is to tailor immunotherapy to the specific immunological abnormality believed to underlie the patient's vulnerability to fungal infection (Williams et al., 2020). The use of recombinant cytokines as immunotherapies for fungal infections is well-established (D Armstrong-James et al., 2012). In the context of hematological malignancies specifically, colony-stimulating factors such as GM-CSF and G-CSF have been used to target both neutrophil activation and recovery of the myeloid cell population (Boots et al., 1999). This approach has been demonstrated to be beneficial for both mucosal and invasive candidiasis, and other case reports support its efficacy for invasive aspergillosis and cryptococcal meningoencephalitis (Buddingh et al., 2015). G-CSF is frequently employed to increase neutrophil counts in individuals with neutropenia, a significant risk factor for invasive fungal infections (Wang et al., 2021). The primary antifungal cytokine, interferon-γ, has been approved for preventive use in chronic granulomatous disease and enhances the function of neutrophils and macrophages (Bemiller et al., 1995).

Immunomodulating agents are becoming vital for the treatment of allergic fungal conditions, including allergic bronchopulmonary aspergillosis, which is characterized by TH2/17 responses and eosinophilic inflammation (Guerra et al., 2017). Several monoclonal antibody treatments that target IgE (such as omalizumab) or eosinophilic inflammation (such as mepolizumab, an anti-IL5 monoclonal antibody) have been developed for severe asthma, and they can also be useful in ABPA **(**Edris, A. Lahousse, 2021). Since eosinophil-targeting medicines are influenced by infection susceptibility, concurrent antifungals are frequently used when fungal airway colonization or infection is evident. The effectiveness of dupilumab, an IL-4 monoclonal, in ABPA is still being investigated (Ramonell et al., 2019). The possibility of fungus vaccines and antibodies is gaining attention. The fact that many at-risk individuals have impaired immune systems and are therefore unlikely to develop a protective immunological response is a significant factor when it comes to vaccines. Nonetheless, there is a window of opportunity to obtain protective immunization for patients receiving immunosuppressive treatments or undergoing transplant evaluation. Fungal desensitization for allergic fungal illnesses is another area that needs improvement; proof of principle for allergic fungal sinusitis has been produced (Melzer et al., 2015). Chimeric antigen receptor T cell therapy is rapidly becoming an integral part of the treatment of hematological malignancies (Arcangeli et al., 2022). This method facilitates the reprogramming of T lymphocytes to exhibit activity against specific antigens, thereby allowing targeted destruction of affected cell types. This method was employed using Dectin-1 to modify cytotoxic T cells to effectively eliminate fungal pathogens in vitro and in animal models of aspergillosis (Kumaresan et al., 2014). A promising treatment option for invasive fungal infections is innate cellular therapy, which is commonly used in the setting of aplastic anemia and follows the well-established paradigm of granulocyte infusions in neutropenia hosts (Grigull et al., 2006).

6.3.2 Adjuvant Immunotherapy

Both conventional antifungal medications and immune-stimulating medications are used in adjuvant antifungal immunotherapy to improve treatment outcomes and strengthen the body's defences. Granulocyte colony-stimulating factor, granulocyte-macrophage colony-stimulating factor, and interferon-γ are three molecules that boost neutrophil and macrophage activity, help the body eliminate fungus, and enhance survival, particularly in those with compromised immune systems (Posch et al., 2020; Safdar et al., 2007). Table 2 provides a quick summary of the primary categories, their functions, and their medicinal uses.

Table 2. Adjuvant Immunotherapeutic Strategies Enhancing Host Immune Responses in Antifungal Therapy

Immunotherapeutic Agent / Strategy	Category	Mechanism of Action	Target Immune Component	Clinical Applications / Indications	References
Interferon-γ (IFN-γ)	Cytokine therapy	Enhances macrophage and neutrophil activation; increases production of reactive oxygen and nitrogen species; promotes intracellular fungal killing.	Macrophages, Neutrophils, Th1 cells	Adjunct therapy in cryptococcal meningitis, invasive candidiasis, and chronic granulomatous disease	(Bemiller et al., 1995; Safdar et al., 2007)
Granulocyte Colony-Stimulating Factor (G-CSF)	Growth factor	Stimulates proliferation, differentiation, and activation of neutrophils; reduces the duration of neutropenia	Neutrophils	Neutropenic patients (chemotherapy, transplantation); invasive fungal infections	(Safdar et al., 2007; Wang et al., 2021)
Granulocyte-Macrophage Colony-Stimulating Factor (GM-CSF)	Growth factor	Enhances neutrophil and macrophage function; promotes myeloid cell recovery	Neutrophils, Macrophages, Dendritic cells	Hematologic malignancies; invasive aspergillosis; cryptococcal infections	(Posch et al., 2020)
Monoclonal Antibodies	Targeted immunotherapy	Neutralize specific immune mediators (IgE, IL-5) to reduce eosinophilic inflammation and Th2 responses.	Eosinophils, Th2 cells	Allergic bronchopulmonary aspergillosis (ABPA), severe asthma with fungal sensitization	(Hamad, 2008)
Adoptive T-cell Therapy	Cellular immunotherapy	Transfer of pathogen-specific or genetically engineered T cells to enhance antifungal immune response	T lymphocytes	Post–allogeneic stem cell transplantation; refractory invasive fungal infections	(Papadopoulou, Kaloyannidis, Yannaki, & Cruz, 2016)
Granulocyte Transfusion	Replacement immunotherapy	Provides functional neutrophils to restore innate immune defense	Neutrophils	Severe neutropenia with invasive fungal infections	(Grigull et al., 2006)
Immune Checkpoint Modulation (PD-1/PD-L1 pathway)	Immunomodulatory therapy	Reverses T-cell exhaustion and restores antifungal immune response	T cells, Dendritic cells	Investigational approach in invasive aspergillosis and immunocompromised hosts	(Okazaki & Wang, 2005; Winn et al., 2003)

6.3.3. Immunomodulatory pathways in Antifungal Treatment

The goal of host immunological modulation is to improve or restore a person's immune system's ability to fight fungal infections, particularly in those with compromised immune systems (Loh and Lam, 2023). Cytokine therapy is a crucial method for enhancing immune cell activity by external stimulation. Administering cytokines to enhance the immune system is one approach to address fungal infections. Cytokines are signalling chemicals that regulate the host's immune response by selectively facilitating the formation, differentiation, and activation or suppression of certain target cells (Gulati et al., 2016). Cytokines like TNF-α, interleukins, interferon-gamma (IFN-γ), and colony-stimulating factors (CSFs) change the immune system and are used as medications to treat fungal infections (Ademe et al., 2020). Studies have shown that IFN-γ treatment increases the number of macrophages and neutrophils, which makes antifungal action much stronger (Lehrnbecher et al., 2011). Randomised studies demonstrate that IFN-γ therapy increases the production of reactive oxygen and nitrogen species in macrophages. This aids in the removal of *Cryptococcus* within cells and expedites the removal of fungal particles from the cerebrospinal fluid (Jarvis et al., 2012). Interleukins have also been shown to boost Th1-mediated immunity, which is important for stopping fungal infections (Akdis et al., 2011). The development of Th1 immunity is closely linked to IL-12 production, which inhibits Th2 responses and fortifies host defence. Fluconazole was more effective in treating *Candida* infections in neutropenic mice

when IL-12 was present. Additionally, it was demonstrated that IL-12 functioned independently in animal models of aspergillosis, histoplasmosis, coccidioidomycosis, and cryptococcosis (Winn et al., 2003). It has been demonstrated that colony-stimulating factors, such as monocyte-CSF (M-CSF) and GM-CSF, or IFN-γ enhance the capacity of neutrophils, monocytes, and macrophages to consume and eliminate.

Additionally, the duration of neutropenia (G-CSF and GM-CSF) is shorter (Hamad, 2008). By promoting neutrophil production, survival, and activity, G-CSF can benefit individuals with neutropenia, such as those undergoing organ transplantation or undergoing chemotherapy for cancer. This is due to the fact that it increases the quantity and intensity of neutrophils. Since the duration and intensity of neutropenia are strongly correlated with the risk of fungal infection, G-CSF may be used in conjunction with standard antifungal therapies to enhance clinical outcomes in these individuals (Grigull et al., 2006).

Modifying immunological checkpoints is another innovative strategy. An immune system checkpoint that suppresses the immune response and fosters tolerance is the PD-1/PD-L1 complex (Okazaki and Wang, 2005). It has been shown that PD-L1 increases tolerance in dendritic cells during the early phases of A. fumigatus infection, leading to increased auto-inflammatory cytokine release and increased CTLA-4 activity (Stephen-Victor et al., 2017). Additionally, therapy can alter the host's immune system. They are increasingly being considered as a way to strengthen antifungal defences. Chimeric antigen receptor (CAR) T cells are genetically modified T cells engineered to recognize fungal antigens (Loh and Lam, 2023; Posch et al., 2020). In adoptive T-cell therapy, T lymphocytes are extracted from a patient's or donor's blood, cultured and expanded in a laboratory, and subsequently reintroduced into the patient. During this procedure, the patient receives multiple injections of targeted T cells. These T cells recognize their targets and help the immune system eliminate them (Papadopoulou et al., 2016). Adoptive T-cell therapy is often used after allogeneic stem cell transplantation (allo-SCT) because the adaptive immune system recovers more slowly than the innate immune system, and because some T cells can be artificially activated to eradicate fungal infections (Bacher et al., 2015). The first innate cellular defense mechanisms during fungal infections include neutrophils, macrophages, dendritic cells (DCs), NK cells, and monocytes. These cells quickly identify PAMPs on fungi by their highly expressed surface PRRs (Lass-Flörl et al., 2013). Numerous oxidative and non-oxidative effector processes that aid in fungal clearance are triggered by innate immune cells upon identification of fungal pathogen-associated molecular patterns (PAMPs) by their corresponding pattern recognition receptors (PRRs) (Loh and Lam, 2023).

7. ADVANCEMENT & NOVEL STRATEGIES IN THE MANAGEMENT OF INVASIVE FUNGAL INFECTIONS

Numerous clinical trials have demonstrated the established effectiveness of traditional antifungal medicines against a variety of fungal illnesses. Randomized controlled trials show that echinocandins, such as micafungin and caspofungin, are first-line treatments for invasive candidiasis and candidemia because they are less toxic and have better treatment outcomes than amphotericin B and azoles (Pg, 2009). While isavuconazole is not inferior to voriconazole and is better tolerated in large RCTs, voriconazole has been shown to improve 12-week survival in invasive aspergillosis compared with amphotericin B deoxycholate, with fewer side effects (Maertens et al., 2016).

Amphotericin B plus flucytosine induction therapy for cryptococcal meningitis improves survival and accelerates fungal clearance compared with monotherapy. Posaconazole or isavuconazole are utilized as step-down or salvage therapy in less prevalent molds like Mucorales, although lipid formulations of amphotericin B continue to be the standard, mostly backed by observational evidence (Cornely et al., 2019). The evidence base for selecting antifungals based on patient risk factors, infection location, and pathogen is provided by these trials taken together. The way antifungal drugs function varies based on the type of fungus. *Candida albicans* responds well to fluconazole, although resistant non-albicans strains, including *Candida krusei,* respond less well. Echinocandins, on the other hand, such as capsafungin, are quite efficient against the majority of species, including *Candida glabrata* (Pg, 2009). Azoles have broad-spectrum substitutes in amphotericin B and its lipid formulations. Voriconazole is the best treatment for invasive *Aspergillus* infections because it is highly effective (Herbrecht et al., 2002). Fluconazole is frequently employed for consolidation therapy, but amphotericin B and flucytosine are effective treatments for *Cryptococcus neoformans* infections (Perfect et al., 2010).

Alongside traditional antifungal drugs, immunotherapy has demonstrated promise in boosting host immune responses against invasive fungal infections. It has been demonstrated that immunotherapeutic methods such as adoptive T-cell therapy, monoclonal antibodies, and cytokine administration (e.g., IFN-γ, GM-CSF) improve clinical outcomes by reducing fungal load, accelerating recovery, and, in certain cases, increasing survival rates in patients with compromised immune systems (Lionakis and Netea, 2013). Adoptive transfer of fungus-specific T cells has been shown

to reduce fungal load in recipients of haematopoietic stem cell transplants, while adjunctive IFN-γ therapy has been associated with increased neutrophil activity and accelerated pathogen clearance in patients with invasive aspergillosis or refractory candidemia (Perfect et al., 2010).

Antifungal resistance significantly diminishes the efficacy of traditional therapies, increasing morbidity, mortality, and the likelihood of recurrent infections, particularly in individuals with compromised immune systems. By altering drug targets, overexpressing efflux pumps, and forming biofilms, bacteria may become resistant to azoles, echinocandins, and polyenes (Cowen et al., 2015). Combination therapy, which combines medications with complementary effects, has been used to address resistance by increasing fungal killing and preventing the emergence of resistant strains. Fungal infections that are resistant to several drugs may also be treated with novel antifungal drugs, such as orotomides and glucan synthase inhibitors. To optimise results in resistant fungal infections, susceptibility profiles must still be monitored, and therapy must be adjusted in response to resistance trends (Pristov and Ghannoum, 2019).

8. FUTURE DIRECTIONS IN FUNGAL INFECTION THERAPY

8.1. Research in New Antifungal Drugs

Studies are still investigating novel antifungal medications that target immune evasion strategies and particular fungal virulence factors. The medications will become less dangerous and more effective as a result. Compounds that target critical enzymes that aid in the formation of cell walls, such as chitin synthase, glucan synthase, and heat shock proteins that are unique to fungi, are examples of novel techniques. Additionally, they prevent fungal biofilms and adhesion molecules from growing (Perlin et al., 2017). As potential remedies for pathogens like *Candida* and *Aspergillus* that attempt to evade the immune system, researchers are investigating monoclonal antibodies, immune checkpoint modulators, and tiny chemicals that facilitate the immune system's recognition of fungi (Perfect et al., 2010). These methods have the potential to treat fungal infections that are difficult to treat or resistant, since they not only immediately stop fungal development but also strengthen or rebuild the host's defenses.

8.2. Immunotherapy and Host-Directed Therapies

Next-generation immunotherapies aim to enhance the treatment of invasive fungal infections by targeting specific immune receptors or fungi to bolster the body's defences. Strategies include monoclonal antibodies that target antigens on fungal cell walls, immunological checkpoint modulators that enhance T-cell activity, and customised cytokines such as interferon-gamma or GM-CSF that increase phagocyte activity (Lionakis and Netea, 2013). The adoptive transfer of fungus-specific T cells and chimeric antigen receptor (CAR)-T cells is under investigation to provide pathogen-specific, targeted immunisation, particularly for persons with compromised immune systems. These therapies, serving as alternatives to conventional antifungal agents, aim to disrupt specific molecular interactions between the pathogen and the host to reduce fungal burden, expedite recovery, and enhance survival rates.

8.3. Future Challenges in Fungal Infection Treatment

Since resistant strains of *Aspergillus*, *Candida*, and other opportunistic fungi reduce the effectiveness of conventional antifungal drugs and are linked to increased morbidity and mortality, drug resistance poses a serious challenge in the treatment of fungal infections. Biofilm generation, overexpression of efflux pumps, and mutations at target sites are examples of resistance mechanisms that call for alternative or combination therapy (Perlin et al., 2017). To optimise antifungal efficacy and improve clinical outcomes, recent research underscores the importance of personalised treatment strategies that consider the patient's immunological status, including neutrophil function, T-cell function, and cytokine responses, alongside the infecting pathogen's susceptibility profile. One of the most crucial tactics for mitigating resistance and reducing the likelihood of treatment failure is customising medication to the specific characteristics of both the infection and the host (Lionakis and Netea, 2013). Individuals with compromised immune systems, such as those undergoing immunosuppressive therapy, those infected with HIV/AIDS, or those who have received haematopoietic stem cell transplants, encounter significant challenges in managing fungal infections. This is due to their compromised immune systems, rendering them more susceptible to illness. Toxicology, drug interactions, and increasing resistance may diminish the efficacy of traditional antifungal medications. These individuals frequently experience increased morbidity, prolonged recovery periods, and higher mortality rates (Perlin et al., 2017). As a result, we sorely need innovative, viable answers to this challenge. These include next-generation antifungal medications that

target virulence factors, immunotherapies that boost pathogen-specific immune responses, and therapy regimens customised to each patient's immunological profile and the pathogen's susceptibility. By combining these approaches, high-risk patients with compromised immune systems should have better treatment outcomes, a lower fungal load, and a higher chance of survival (Lionakis and Netea, 2013).

8. CONCLUSION

The rising incidence of severe fungal infections, especially among immunocompromised individuals, underscores the critical need for improved treatment strategies. Our understanding of the immune system's response to fungal infections has improved; however, treating many diseases remains challenging, largely due to the increasing prevalence of antifungal resistance. Fungi employ various mechanisms to evade the human immune system, including morphological alterations and biofilm formation. This complicates the eradication and treatment of infections. The lack of antifungal drugs and the growing problem of resistance make it even clearer that new ways of treating these diseases are needed. Cytokine-based therapeutics, immune checkpoint inhibitors, and adoptive T-cell therapy represent innovative immunotherapies that may surpass or complement conventional antifungal medications. These medications may enhance immune system functionality and fortify the host's defences against infections. Research indicates that combination therapy, which addresses multiple fungal pathways, has reduced resistance and enhanced efficacy. Developing effective vaccines and targeted therapies will require substantial effort. The primary objectives of forthcoming research should be to enhance diagnostic methodologies, discover novel antifungal therapies, and deepen the understanding of the impact of fungal infections on the immune system. These measures will be crucial for enhancing global health and mitigating the impact of fungal infections.

Ethical Statement

Not Applicable.

Conflicts of Interest

The authors declare no competing interests.

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