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Host Immune Modulation: A Strategy to Enhance the Efficacy of Antifungal Therapy

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Abstract

Fungal infections present a major global health challenge, particularly among immunocompromised individuals due to the development of antifungal drug resistance, demanding innovative therapeutic strategies for treatment. One promising approach is host immune modulation, which strengthens the body's innate and adaptive immune responses to enhance fungal clearance and improve treatment outcomes. This strategy encompasses various techniques, including cytokine therapy, immune checkpoint modulation, vaccination, adoptive cell therapy, and personalized treatments, all aimed at effectively reinforcing the immune system's ability to combat fungal pathogens. Additionally, cutting-edge approaches such as metabolic reprogramming, epigenetic modulation, microbiome-targeted therapies, and nanotechnology-driven immune modulation are emerging as powerful tools to fine-tune host defences. Targeting host pathways through autophagy and cellular stress responses further enhances the body's ability to resist fungal infections. These host-directed therapies not only reduce reliance on conventional antifungal drugs but also help curb drug resistance by promoting long-lasting and pathogen-specific immunity. Understanding the intricate interplay between the immune system and fungal pathogens is crucial for developing precise, durable, and patient-centric treatments. By leveraging these advanced therapeutic strategies, researchers can revolutionize antifungal therapy, offering more effective, sustainable, and personalized interventions, ultimately reducing the burden of fungal diseases and improving patient survival worldwide.

Keywords: Host, Fungal Infections, Immune modulation, Pathogens, Target.

1. Introduction

Fungal infections are increasingly recognized as a significant global health challenge, particularly for individuals with compromised immune systems caused due to chemotherapy, organ transplants, or living with HIV/AIDS [1]. Invasive fungal infections can be life-threatening while mild infections affecting the skin or nails are common Globally, fungal infections account for approximately 11.5 million serious cases and over 1.5 million deaths annually, with their rising prevalence linked to factors such as the ageing

population's increased use of immunosuppressive therapies, growing prevalence of diabetes and irrational use of antibiotics [2].

Fungi can be broadly categorized into two groups based on their ability to cause disease:

- **Primary fungal pathogens**: These fungi have the ability to infect even individuals with a fully functioning immune system[3].
- **Opportunistic fungal pathogens**: These fungi primarily infect individuals with compromised immune systems or other underlying risk factors[4].

The development of fungal infections is influenced by several factors including:

a. Granulocytopenia (Low levels of a type of white blood cell known as granulocytes.)
b. Depressed cellular immunity, which may be caused by viral infections such as cytomegalovirus; the use of corticosteroids, cytotoxic drugs like cyclophosphamide and purine antagonists; total body irradiation
c. Mucosal barrier injury.
d. Poor hygiene.
e. Genetic predisposition.
f. Use of anti-bacterial, which can lead to manipulation of the patient's microbiological flora.
g. Co-morbidity with Increasing age of patients.
h. Use of H2 receptor antagonists.
i. Central venous lines with or without hyperalimentation [5].

Approaches to managing fungal infections are evolving due to the emergence of drug-resistant fungal pathogens, which pose a major challenge to effective treatment [6]. moreover, Certain patients fail to respond to antifungal treatment even when the pathogen is susceptible to the medication being administered, a phenomenon known as tolerance [7]. As a result, treatment failure in clinical settings is a multifaceted problem influenced by the patient's weakened immune system, the effectiveness of the antifungal drug, and the characteristics of the fungal pathogen.[8]. Resistance development of fungal pathogens to current antifungal drugs propagated deep clinical concern towards understanding various Host-related factors, causative fungi, and the environment contributing to the resistance offered. The development of antifungal resistance is driven by mechanisms such as adaptive phenotypic plasticity, mutations in target genes followed by selection, chromosomal aneuploidy, sexual reproduction, and horizontal gene transfer [9].

The mechanisms and strategies that foster the development of drug resistance by fungi involve

- Reduction of effective drug concentration
- Modification of the drug target
- Employment of metabolic bypass strategies [9]

Antifungal treatment is often less effective in individuals with weakened immune systems. This makes immunotherapy a promising approach, as it focuses on strengthening immune function. Immunotherapy can be categorized into two types: replacement or reconstitution therapy, which aims to correct immune deficiencies that increase susceptibility to fungal infections, and augmentative therapy, which enhances the immune response to better combat the pathogen[10-12].

Fungal pathogens exhibit a diverse range of pathogen-associated molecular patterns (PAMPs), necessitating a specialized set of pattern recognition receptors (PRRs) in host cells to detect them and initiate specific immune responses. Innate immune cells, including dendritic cells, monocytes, macrophages, and neutrophils, express various PRRs that enable them to recognize fungal infections, mount protective responses, and activate adaptive immunity. Several PRRs, such as C-type lectin receptors (CLRs), Toll-like receptors (TLRs), and NOD-like receptors (NLRs), play crucial roles in detecting fungal pathogens and initiating appropriate antifungal defences. However, the ability of fungal pathogens to undergo morphological transitions, such as shifting between conidial and hyphal forms, presents challenges in identifying precise therapeutic targets, particularly as these adaptations vary depending on tissue compartments and environmental conditions. Recent advances in genetic, genomic, and experimental research have enhanced our understanding of the context-dependent immune mechanisms against fungal infections, the evasion strategies employed by fungal pathogens, and potential host and pathogen targets for novel therapeutic development. [13-14].

Immune System in Fungal Defence

Innate Immunity

The innate immune system acts as the body's initial defence against fungal infections. It relies on physical barriers, soluble molecules, and cellular mechanisms to protect against pathogens. Immune cells use pattern recognition receptors (PRRs) to identify fungal pathogens by detecting specific components on their cell walls, such as β-glucans, mannans, and chitin, which are classified as pathogen-associated molecular patterns (PAMPs). Table 1 summarises the receptors and their roles in fungal recognition, while Figure 1 illustrates the mechanism of innate immunity[15].

Table 1 : Immune Components and their role in Fungal Defence

Component	Role	Fungi Targeted	References.
Toll-Like Receptors	Detect β-glucans, fungal RNA/DNA	Candida albicans, Aspergillus fumigatus	[16]
C- Type Lectin Receptors	Recognize.β-glucans and mannans; stimulate cytokines	Candida albicans, Cryptococcus neoformans	[17]
Neutrophils	Phagocytosis, ROS production, NETs	Aspergillus fumigatus, Candida albicans	[18]

Toll-Like Receptors (TLRs): Toll-like receptors (TLRs) act like security sensors, recognizing unique fungal markers and alerting the immune system to respond. As a type of pattern recognition receptor (PRR), TLRs play a crucial role in detecting fungal pathogens by identifying pathogen-associated molecular patterns (PAMPs), such as β-glucans and fungal nucleic acids, and triggering an immune defense.TLR7, for example, critical in recognising fungal single-stranded RNA (ssRNA), and its

deficiency has been linked to an increased susceptibility to infections such as Candida albicans. Similarly, TLR9 contributes to antifungal immunity by modulating the innate response to swollen Aspergillus conidia, highlighting its importance in host defence mechanisms [16].

C-Type Lectin Receptors (CLRs): Theses are a key type of pattern recognition receptor (PRR) that play a crucial role in the body's defence against fungal infections. CLRs, which are mostly expressed by myeloid cells, include Dectin-1, Dectin-2, Dectin-3, Mincle, and DC-SIGN receptors. Dectin-1 identifies β-1,3-glucans, while Dectin-2 and Dectin-3 detect α-mannans. This allows the immune system to identify various fungal infections. The activation of CLRs activates intracellular signalling pathways that stimulate the generation of pro-inflammatory cytokines required for successful antifungal immune responses [17].

Neutrophils: Neutrophils act as frontline soldiers, deploying reactive oxygen species and traps (NETs) as weapons to neutralize invaders. Neutrophils play a vital role in the innate immune system, particularly in the initial defence against fungal infections. They are rapidly mobilized to infection sites, where they phagocytose and generate reactive oxygen species (ROS) to kill fungal pathogens. Their function is closely related to the IL-17 axis, a critical pathway for host defence against certain fungal infections emphasizing their significance in effective antifungal immunity. (Neutrophil Extracellular Traps) [18].

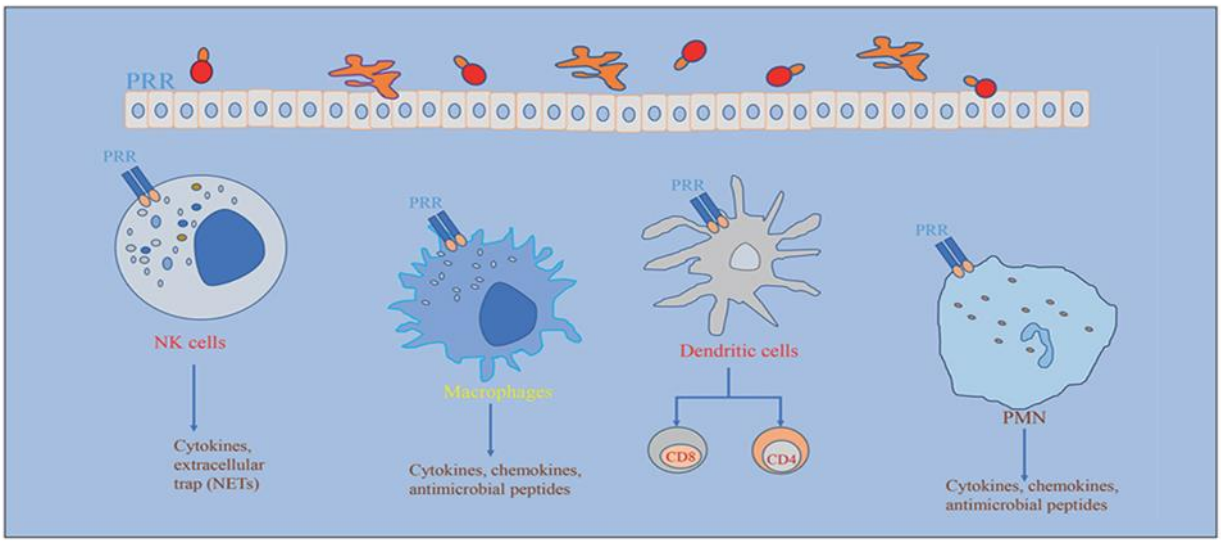

Fig 1: Innate Immune Response to Fungal Infections

Macrophages and Dendritic Cells:

Macrophages and dendritic cells are key players in the innate immune system, identifying and responding to fungal infections through specialized receptors like Toll-like receptors (TLRs) and C-type lectin receptors (CLRs).These cells facilitate antigen presentation and activate adaptive immune responses, producing cytokines that shape and amplify the immune response. When fungal pathogen-associated molecular patterns (PAMPs) are recognized, signalling pathways are activated that drive the transcription of genes required for inflammation and immune defence [19].

The innate immune response to fungal infections showcases how key immune cells like NK cells, macrophages, dendritic cells, and polymorphonuclear neutrophils (PMNs) collaborate to combat fungal

pathogens. These cells use pattern recognition receptors (PRRs) to identify harmful structures on fungal cell walls, triggering immune responses. NK cells release protective proteins (cytokines) and form extracellular traps (NETs) to neutralize fungi, while macrophages and PMNs produce cytokines, chemokines, and antimicrobial peptides to eliminate pathogens. Dendritic cells serve as a link between the innate and adaptive immune systems by presenting fungal antigens to CD4+ and CD8+ T cells, thereby triggering a more specific immune response. This coordinated response ensures early fungal detection and effective immune activation, highlighting the central role of PRRs in antifungal immunity[20-21].

2. Adaptive Immunity

Adaptive immunity is a highly specialized defence mechanism that evolves over time, offering long-term protection against specific pathogens. A key feature of this immunity is its ability to retain memory of previous pathogen encounters, allowing for a faster and more efficient response upon subsequent exposure. It primarily relies on two types of lymphocytes: B cells and T cells. [22].

T-helper Cells: T-helper cells play a crucial role in the immune system by coordinating the adaptive immune response and activating other immune cells to fight infections. Based on their role the Th cells are categorised as - Th1 cells that fight intracellular pathogens such as viruses and certain bacteria by producing IFN-γ, which activates macrophages; Th2 cells focus on defending against extracellular pathogens viz helminths and allergens helping B cells produce antibodies; Th17 cells on the other hand release IL-17 and IL-22 to recruit neutrophils and enhance the body's epithelial defences. Both Th1 and Th17 cells are particularly important in antifungal immunity [23-24].

B Cells: B cells are specialized lymphocytes essential for the adaptive immune system, contributing significantly to immune defence, mainly by producing antibodies that help defend the body through humoral immunity. They can be activated either by T-helper cells or by directly recognizing foreign antigensOnce activated, B cells grow and transform into plasma cells, which produce antibodies (immunoglobulins) specifically designed to target antigens found on pathogens. These antibodies help defend the body by neutralizing pathogens, alerting other immune cells to eliminate them, and preventing them from invading healthy cells. Additionally, some activated B cells develop into memory B cells, which remain in the body for the long term. This memory allows the immune system to respond more quickly and effectively if the same pathogen attacks again.[25-26].

To initiate an effective immune response, it is essential to establish a connection between innate and adaptive immunity. The innate immune system plays a significant role in influencing and activating the adaptive immune response, thereby forming a crucial link between the two. Dendritic cells, which are part of the innate immune system, are key players in this process. Fungal pathogens are recognized by pattern recognition receptors (PRRs), including Toll-like receptors (TLRs) and C-type lectin receptors (CLRs).). Dendritic cells phagocytose the fungi and process their antigens.. These antigens are then presented on major histocompatibility complex (MHC) molecules to naive T cells in lymphoid tissues, effectively initiating the adaptive immune response. This antigen presentation not only activates T cells but also influences their differentiation into specific subsets, such as Th1 and Th17 cells, which are critical for antifungal immunity. Dendritic cells play a key role in the immune response by releasing cytokines like IL-12 and IL-23 when they detect fungal antigens. These cytokines help shape the immune reaction by promoting the development of Th1 cells, which produce IFN-γ, and Th17 cells, which release IL-17 and

IL-22. These signals strengthen the body's defences by boosting neutrophil activity and reinforcing the protective barrier of epithelial tissues. This interaction ensures that the adaptive immune system mounts a targeted and effective response, amplifying the innate immune mechanisms for fungal clearance [27-30].

Strategies Adopted by Fungal Pathogens for Immune Evasion

Masking PAMPs (Pathogen-Associated Molecular Patterns): Fungi can alter or hide molecular patterns that the immune system normally recognizes, preventing detection by immune cells. To narrate, Candida albicans, for instance is known to modify the presentation of β-glucans on its surface by coating them with a layer of mannans which prevents recognition by immune receptors Dectin-1 and Toll-like receptors (TLRs) [1]. This ability to mask β-glucans is particularly effective in avoiding early immune detection, allowing the pathogen to evade both innate and adaptive immune responses [31-32].

Biofilm Formation: Fungal pathogens can form biofilms, which are protective layers of cells that shield them from immune cells and antifungal treatments, making it harder for the immune system to clear the infection. Aspergillus fumigatus, a major opportunistic pathogen, is capable of forming complex biofilms on both abiotic surfaces and host tissues in the lungs of immunocompromised patients [33-35].

Production of Immunosuppressive Molecules: Some fungi produce substances that dampen or suppress the immune response, such as melanin which protects them from oxidative damage, or enzymes like superoxide dismutase that neutralize reactive oxygen species (ROS) generated by immune cells [36-37].

3. Strategies to Enhance the Immune Modulation

1. Cytokine Therapy

Cytokine therapy is an innovative approach to enhance the immune system's response against fungal infections. Cytokines, signalling proteins that mediate and regulate immunity, play a pivotal role in bolstering the host's antifungal defences. To illustrate, Interferon-gamma (IFN-γ), GM-CSF, and G-CSF play crucial roles in antifungal immunity by enhancing macrophage and neutrophil functions. IFN-γ activates macrophages, promoting reactive oxygen species (ROS) and nitric oxide production, which aid in fungal clearance, while also driving Th1 differentiation and pro-inflammatory cytokine release. Studies highlight its efficacy in clearing Candida albicans and Aspergillus fumigatus, with clinical trials supporting its use as an adjunct to antifungal therapy, especially in immunocompromised patients. GM-CSF and G-CSF further boost immune responses by stimulating macrophages and neutrophils, enhancing phagocytosis, oxidative burst, and fungal clearance. Their combined use with antifungal drugs improves survival rates and helps combat drug resistance in invasive fungal infections [41-43].

2. Immune Checkpoint Modulation

Immune checkpoint inhibitors (ICIs), such as anti-PD-1 and anti-CTLA-4 traditionally used in cancer therapy, are being explored for their potential to enhance antifungal immunity, particularly in immunocompromised individuals at high risk of severe infections caused by Candida and Aspergillus. These inhibitors work by blocking immune checkpoints PD-1 and CTLA-4, which normally act as regulatory brakes to prevent excessive T-cell activation. During fungal infections, these checkpoints can suppress the immune response, allowing fungal pathogens to evade detection. Immune checkpoint inhibitors (ICIs) work by blocking the interaction between PD-1 and CTLA-4 with their ligands (PD-L1

and CD80/86). This helps restore T-cell function, allowing the immune system to better recognize and eliminate fungal pathogens. As a result, ICIs show great potential as an additional strategy to improve antifungal therapy[44-45].

3. Vaccination Strategies

Vaccination strategies refer to systematic approaches in designing and administering vaccines to induce a protective immune response against infectious diseases. These strategies involve the selection of suitable antigens and innovative delivery methods to enhance immune efficacy and longevity. The development of vaccines against fungal pathogens Candida albicans, Aspergillus fumigatus, and Cryptococcus neoformans represents a promising preventive strategy to combat invasive fungal infections. Subunit vaccines, which target key fungal cell wall antigens β-glucans and mannoproteins, are a major focus due to their ability to generate strong and specific immune responses. These vaccines are considered safer than live-attenuated vaccines, making them suitable for immunocompromised individuals. Conjugate vaccines, which link fungal antigens to carrier proteins, have shown enhanced immunogenicity and durability. Candida albicans cell wall-targeting conjugate vaccines have demonstrated improved immunity in animal models. Similarly, Aspergillus fumigatus vaccines incorporating galactomannan antigens have progressed to preclinical and clinical trials, while Cryptococcus neoformans vaccines targeting polysaccharide capsular components have shown protective efficacy in experimental studies [46-48].

Advancements in antigen selection, adjuvant formulations, and delivery systems are shaping the future of fungal vaccine development. Combination strategies targeting multiple fungal antigens simultaneously and vaccine platforms such as mRNA-based approaches offer the potential for enhanced immune responses and broader protection. Clinical trials are crucial for verifying the safety and effectiveness of fungal vaccines across various patient groups. Ongoing research and advancements offer hope that, in the future, these vaccines could greatly reduce the impact of invasive fungal infections, particularly in those who are most at risk.[49].

4. Adoptive cell therapy

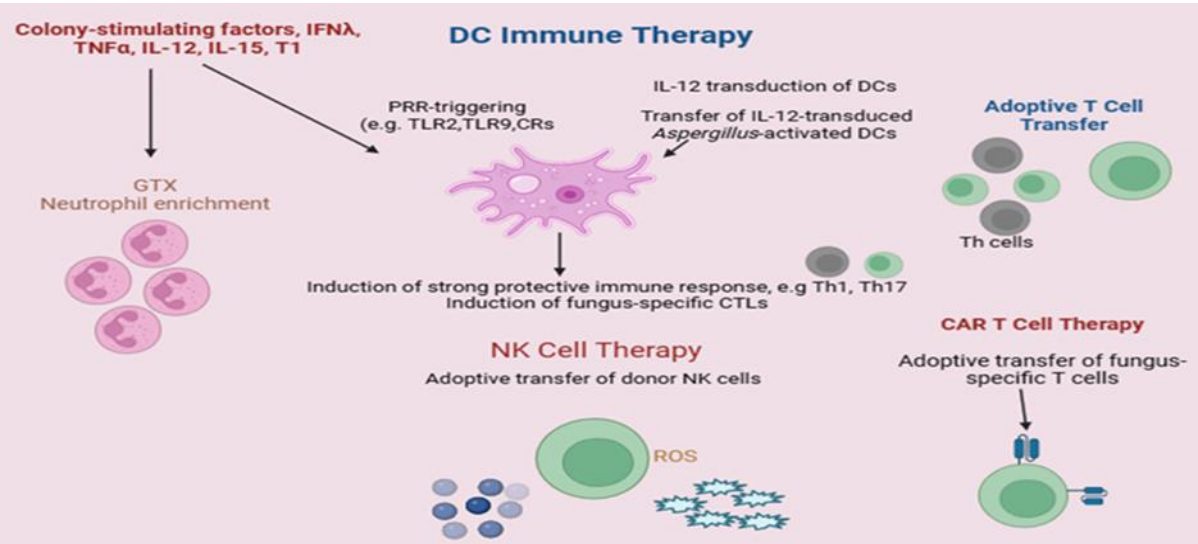

Fig 2: Strategies of Immunotherapies with their mechanism to fight fungal infections

Adoptive cell therapy (ACT), initially designed for cancer treatment, is now being explored for fungal infections due to increasing drug resistance and the limitations of conventional antifungal therapies. Figure 2 depicts the mechanism involved in the ACT. By engineering immune cells to recognize fungal-specific antigens, ACT offers a targeted approach to eliminating fungal pathogens. The fungal cell wall, composed of β-glucans, mannoproteins, and chitin, serves as a crucial immune target, where β-glucans interact with dectin-1 to activate antifungal defences, while mannoproteins aid in adhesion and immune evasion[50]. Researchers have engineered T cells to express dectin-1 or chimeric antigen receptors (CARs), allowing precise fungal cell destruction with minimal toxicity. Several ACT approaches have demonstrated potential, including Dendritic Cell (DC) therapy, which activates pattern recognition receptors (PRRs) like TLR2 and TLR9**,** triggering Th1 and Th17 responses that enhance antifungal immunity. Natural Killer (NK) cell therapy involves donor-derived NK cells that eliminate fungal pathogens through cytotoxic activity and reactive oxygen species (ROS) production [51]**.** Adoptive T cell transfer enhances antifungal immunity by introducing fungus-specific T-helper (Th1 and Th17) cells, which activate macrophages and recruit neutrophils for fungal clearance. CAR T cell therapy, an advanced method, involves engineering T cells with chimeric antigen receptors (CARs) to selectively target fungal pathogens like Candida and Aspergillus, providing a highly specific treatment option[52]. These ACT-based therapies hold significant potential for managing invasive fungal infections, particularly in immunocompromised patients with recurrent or drug-resistant infections.

5. Personalized Strategies

The variability in immune responses among patients, influenced by factors such as genetic background, health conditions and immune status underscores the importance of personalization in immune-modulatory therapies. Different fungal species provoke unique immune responses, further emphasizing the need for tailored treatments. By combining host immune profiling with pathogen-specific data, clinicians can design therapies that are more effective and less likely to induce resistance. Such strategies can also reduce the risks associated with broad-spectrum immune interventions, ensuring safer and more targeted outcomes [53-54].

Bioinformatics has emerged as a vital component in tailoring immune modulation strategies. Genomic sequencing and computational modelling allow researchers to map host-pathogen interactions, offering insights into designing personalized treatment protocols. These technologies help clinicians identify an individual's immune profile and determine the specific fungal species involved, ensuring precise therapeutic interventions. High-throughput data analyses have enabled the development of predictive models that guide the use of immune modulators and antifungal drugs in tandem, optimizing patient outcomes while minimizing resistance risks [55].

6. Novel Therapies

Recent advancements in immune modulation present promising avenues for overcoming the limitations of traditional antifungal therapies. Table 2 outlines the differences between conventional and novel antifungal therapies. By enhancing precision and efficacy, these innovative approaches aim to improve outcomes in managing fungal infections while addressing the growing issue of antifungal resistance [56].

Nanotechnology has revolutionized drug delivery by enabling targeted and efficient therapeutic applications. In immune modulation, nanoparticles are designed to deliver cytokines or immune-stimulatory agents directly to sites of fungal infection. This targeted delivery minimizes systemic toxicity, reduces required doses and enhances treatment outcomes. Additionally, nanoparticles have been employed to improve the bioavailability of antifungal drugs, offering a synergistic effect when combined with immune modulatory strategies. Preclinical studies have shown that nanoformulations can boost immune responses against fungal pathogens while minimizing adverse effects, making nanotechnology a crucial tool in modern antifungal therapies [57-58].

Combination strategies in immune modulation have emerged as a promising approach to enhance the efficacy of antifungal therapies, particularly in addressing drug resistance and improving host immune responses. These strategies integrate multiple therapeutic modalities, such as immune checkpoint inhibitors, cytokine therapy, adoptive cell therapy, and nanotechnology-based drug delivery systems, to achieve a synergistic antifungal effect. Combining traditional antifungal drugs with immune-enhancing agents not only eliminates fungal pathogens more effectively but also strengthens the host's immune system to prevent recurrent infections [59-60].

Table 2: Comparison between Conventional Antifungal Therapy and Immune Modulation Strategies

Parameter	**Conventional Antifungal Therapy**	**Immune Modulation Strategies**
Target	Fungal cell wall/membrane	Host immune system
Resistance Potential	High	Low
Adverse Effects	Significant	Minimal (if specific)
Personalization Feasibility	Low	High
Cost	Moderate high	Varies by Strategy

4. Challenges in Immune Modulation

Despite its promise, immune modulation for antifungal therapy faces several challenges. Safety remains a primary concern, as immune-stimulatory agents may trigger unintended immune responses, such as cytokine storms or autoimmune reactions. Another challenge is ensuring the specificity of immune therapies to avoid off-target effects that can damage healthy tissues. The high cost of immune-modulating agents and the technologies supporting them, such as nanoparticle manufacturing and genomic sequencing, limits their accessibility in resource-constrained settings. Addressing these challenges requires the development of cost-effective and scalable approaches while maintaining safety and specificity.

5. Future Perspective

The future of antifungal therapies is increasingly focused on enhancing the body's immune response rather than solely targeting fungal pathogens. Promising approaches include metabolic reprogramming of

immune cells like T-cells, dendritic cells, and macrophages to better combat infections, the use of iron chelators to restore balance of Iron and zinc levels to improve immune defence, repurposing of existing drugs for their immune-boosting properties and Epigenetic modifications using histone deacetylase (HDAC) inhibitors or altering DNA methylation patterns could further boost immune responses. The microbiome's role in antifungal immunity is gaining attention with inclusion of probiotics, postbiotics, and fecal microbiota transplantation (FMT) showing promise in supporting immune function. Nanotechnology offers new ways to deliver immune-modulating agents precisely with engineered exosomes carrying antifungal peptides or cytokines as a potential innovation. Enhancing natural defence mechanisms through autophagy with compounds like spermidine and resveratrol; targeting endoplasmic reticulum (ER) stress responses and heat shock proteins (HSPs) to weaken fungal defences are other areas of focus. Research into host-targeted strategies by adoption of novel approaches holds the key to developing more effective antifungal treatments that not only eliminate infections but also strengthen the body's immune responses.

6. Conclusion

Opportunistic fungal infections pose a serious global health challenge, particularly for vulnerable individuals. Recent research has shed light on how the immune system responds to fungal infections at both the cellular and organ levels, identifying key receptors and pathways involved in defence. It has also revealed how disruptions in these pathways can increase the risk of infection. The field of fungal immunology has progressed rapidly, deepening our understanding of the molecular and cellular mechanisms behind antifungal immunity. Immunomodulation strategies offer a promising avenue to enhance antifungal treatments, ultimately helping to reduce illness and death caused by these infections. Novel therapies emphasis on metabolic reprogramming, epigenetic modulation, microbiome-targeted treatments, nanotechnology-based immune modulation, and interventions targeting host autophagy and stress pathways. These emerging strategies hold the potential to improve treatment outcomes, reduce antifungal resistance, and provide more effective management of fungal infections. Understanding of host-pathogen interactions and the development of advanced immunotherapeutic interventions enhance the ability to combat fungal diseases, offering hope for better patient outcomes and more targeted, durable therapies.

7. Declarations

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Authors' contribution

We affirm that "all authors have read and approved the manuscript." Each contributor played an equal role and actively engaged in this research project. **Mrs. Rajashree Massareddy** conscientiously reviewed the manuscript titled **"Host Immune Modulation: A Strategy to Enhance the Efficacy of Antifungal Therapy".** Her efforts were conducted under the supervision of **Mrs. Rajashree Masareddy**, who offered guidance and assistance in navigating the review complexities.

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