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Advancing cryptococcal treatment: The role of nanoparticles in mitigating antifungal resistance

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ABSTRACT

Cryptococcus, a ubiquitous and formidable fungal pathogen, contributes to a substantial global disease burden, with nearly 250,000 cases and 181,000 fatalities attributed to cryptococcal meningitis annually worldwide. The invasive nature of *Cryptococcus* presents significant challenges in treatment and management, as it mostly affects vulnerable populations, including HIV patients, organ transplant recipients, pregnant women, and elderly individuals. Moreover, these difficulties are exacerbated by the development of antifungal resistance, which emphasizes the need for efficient control measures. In this context, research efforts focusing on infection control and novel therapeutic strategies become paramount. Nanoparticle-based therapies emerge as a solution, offering advanced antifungal properties and improved efficacy. Developing effective treatment options requires understanding the complex landscape of cryptococcal infections and the innovative potential of nanoparticle-based therapies. This review highlights the urgent need for novel strategies to combat the growing threat posed by antifungal resistance while offering insights into the intricate realm of cryptococcal infections, particularly focusing on the promising role of nanoparticle-based therapies.

1. Introduction

Cryptococcus is an opportunistic fungus responsible for cryptococcosis, a widespread infection that predominantly affects immunosuppressed individuals. Found in tree hollows, soil, and bird droppings, *Cryptococcus* encompasses more than thirty species, of which *Cryptococcus neoformans* (*C. neoformans*) and *Cryptococcus gattii* (*C. gattii*) are the most common human pathogens. Cryptococcosis primarily affects the central nervous system (CNS)—including the brain and spinal cord—as well as the lungs, though other organ systems can also be involved (Serna-Espinosa et al., 2023, Sim et al., 2022).

One of the most significant factors in the pathogenicity of *C. neoformans* is its polysaccharide capsule. The formation of this capsule is triggered by host-related environmental factors such as neutral or alkaline pH, elevated CO_2 concentrations, and iron deficiency (Oscar et al., 2003). This process involves intricate metabolic adjustments, allowing the fungus to quickly assemble glucose precursors necessary for the capsule's formation. Along with its capsule, *C. neoformans* produces melanin, as well as enzymes like urease and phospholipase, all of which contribute to its ability to survive in hostile environments and invade tissues. Melanin production helps the fungus endure temperature variations within the human body, while urease and phospholipase promote tissue invasion and the spread of spores throughout the body (P et al., 2024) (Lionakis et al., 2023).

Despite the availability of antifungal treatments, managing cryptococcal infections remains a challenge, especially due to the growing problem of drug resistance, the emergence of new pathogens, and the need for extended treatment regimens. Currently, three main classes of antifungals—polyenes, flucytosine, and azoles—are used to treat *Cryptococcus* infections. (Carneiro et al., 2020). These agents are often administered in combination through a three-phase therapy approach: induction, consolidation, and maintenance. In patients with cryptococcal meningitis, particularly those with HIV, Amphotericin B (AmB) and flucytosine (5FC) are typically used for the induction phase, followed by fluconazole (FLC) for consolidation and long-term maintenance (Jarvis et al., 2019a, Zhang et al., 2022, Billmyre et al., 2020a).

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However, echinocandins, a newer class of antifungals, are ineffective against *Cryptococcus* spp.

The rise of antifungal resistance has severely limited available treatment options (Lathakumari et al., 2024). Resistance mechanisms often involve genetic mutations affecting drug targets and altering essential biological pathways (Yin et al., 2022). For instance, while the mechanisms behind AmB resistance remain unclear, 5FC resistance is linked to mutations in the FCY1 and FCY2 genes, and azole resistance is frequently associated with changes in the ERG11 gene (Billmyre et al., 2020b). As a result, addressing these resistance mechanisms has become critical in the development of effective treatments. Recent studies show a concerning upward trend in antifungal resistance (Fig. 1), emphasizing the urgent need for novel therapeutic strategies (Mane et al., 2022).

In response to the growing antifungal resistance crisis, research into nanoparticle-based therapies has gained momentum. Nanoparticles (NPs) offer promising solutions by enabling the encapsulation of antifungal agents, enhancing their efficacy while reducing side effects. Furthermore, the small size of NPs allows them to penetrate fungal cells and biofilms more effectively, which could help overcome existing drug resistance mechanisms (Rajesh et al., 2022). These advances in nanotechnology offer hope for improving treatment outcomes and tackling the persistent challenge of cryptococcal infections. This review specifically focuses on the potential of NP-based strategies to combat antifungal resistance in *Cryptococcus* infections, with an emphasis on their therapeutic applications and mechanisms of action.

2. Pathogenicity

The intriguing pathogenic fungus, *C. neoformans* uses a variety of complex strategies to cause disease in humans. When inhaled, it initially encounters the lung defense mechanisms, particularly alveolar macrophages, immune cells responsible for engulfing and eliminating infections (Rodrigues et al., 1999). These macrophages are capable of entirely eradicating *Cryptococcus*, although it has developed defenses against them (Zhao et al., 2023a). Despite having a defense capsule that prevents phagocytosis, the yeast can still be ingested by macrophages, particularly in the presence of opsonin such as complement proteins and antibodies (Tugume et al., 2023). *C. neoformans* is categorized as a facultative intracellular fungal pathogen since it may avoid the usual defense mechanisms inside the macrophage. This implies that the yeast can not only endure but also grow and reproduce inside these immune cells, producing a safe environment (Casadevall et al., 2018).

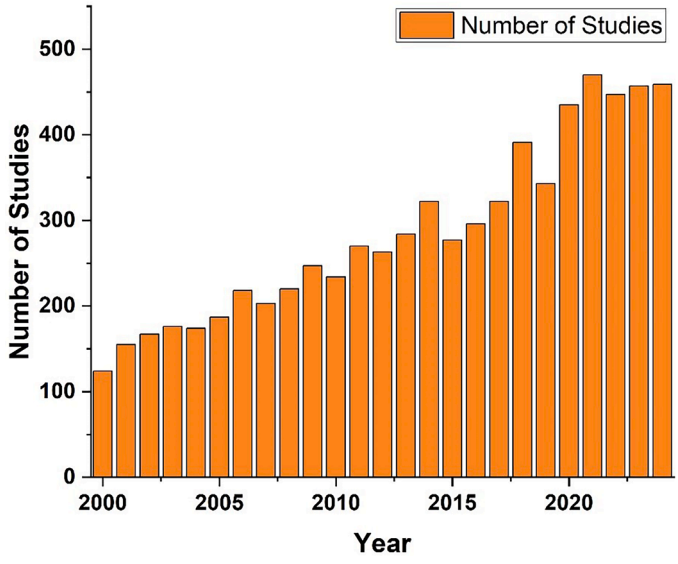

Fig. 1. Trends in antifungal resistance studies (2000–October 2024). The graph depicts a consistent rise in the number of studies on antifungal resistance over the past two decades, with a marked increase in recent years. This trend underscores the escalating global concern and the urgent need for innovative antifungal therapies to address the challenge of emerging resistance. Data was retrieved from PubMed using the search terms "antifungal resistance" and "antifungal drug resistance".

The persistence of the yeast in macrophages is facilitated by a number of strategies. The cytoplasmic body formed by the fusion of phagosome and lysosome, known as the phagolysosome, which is in charge of destroying infections that are taken in, can become less acidic as a result of *Cryptococcus*. Because of the decreased acidity, the antibacterial action of phagolysosome is also decreased (Bosch et al., 2024). *Cryptococcus* achieves this by producing urease, an enzyme that converts urea into ammonia and carbon dioxide to counterbalance the pH alteration (McClelland et al., 2007). Furthermore, the yeast can induce the rupture of phagolysosomes, which would further reduce their efficiency. Due to its antioxidant characteristics, the capsule also aids in immune evasion by shielding the yeast from the free radicals produced by the phagolysosome (Yong-Sun and Kwang-Woo, 2013).

The complicated interplay between *C. neoformans* and macrophages produces a range of effects. In rare situations, the yeast reproduces vigorously inside the macrophage, leading to the cell rupture and the release of newly formed yeast cells. However, other processes may occur simultaneously (Ke et al., 2024). Vomocytosis, also known as non-lytic exocytosis, is a mechanism capable of expelling cryptococcal cells from macrophages (Pacifici et al., 2023). The yeast cells can also be passed from one macrophage to another. The outcome is influenced by factors such as the individual circumstances of the host and the level of activation of the macrophage.

C. neoformans has created other methods of immune evasion in addition to its interactions with immune cells. The dynamic capsule of this fungus, which can alter in size, epitope framework, and density during spread of infection, is one of its distinguishing characteristics (Hilbert et al., 2023). The initial responses after infecting different hosts, including humans, is capsule expansion. Larger capsules impair phagocytosis and increase the stress resistance of yeast cells to free radicals and antimicrobial peptides. Increased capsule density further enhances tolerance to environmental influences, while alterations in epitope structure may help evade immune detection (Voelz and May 2010).

Furthermore, during infection, *C. neoformans* experiences distinct morphological alterations. It is capable of changing into a larger cell type called ‘titan cells. These titan cells have increased resilience to stress stimuli and are too large to be phagocytosed. Despite the fact that they are large to directly enter host tissues, they can reproduce and create daughter cells that are normal size can spread to other organs (Irene et al., 2023). The host immune system may also be affected by titan cells, leading to a change towards non-protective immunological responses, or Th2 polarization (Dyląg et al., 2020, Dambuza et al., 2018).

The propensity of *C. neoformans* to spread to the brain, where it can cause meningoencephalitis, is one of the most crucial elements of its pathophysiology. Uncertainty surrounds the causes of its remarkable affinity for the brain. However, it is understood that *Cryptococcus* has a variety of ways to enter the brain. These include adhering to the blood-brain barrier and being taken up by endothelial cells, disrupting the tight junction of blood-brain barrier to pass between endothelial cells, and, most importantly, using a ‘Trojan horse’ dissemination method. In this final approach, yeast is transported across the blood-brain barrier by phagocytic cells like macrophages (Liu et al., 2024). *Cryptococcus* can create persistent infections once it has entered the brain (Santiago-Tirado et al., 2017) (Fig. 2).

It is capable of infecting numerous organs and evading different facets of the host immune response through a variety of highly developed methods. The difficulty of successfully treating cryptococcal infections is made more difficult by these intricate interactions between the yeast and the host (Tumino et al., 2021).

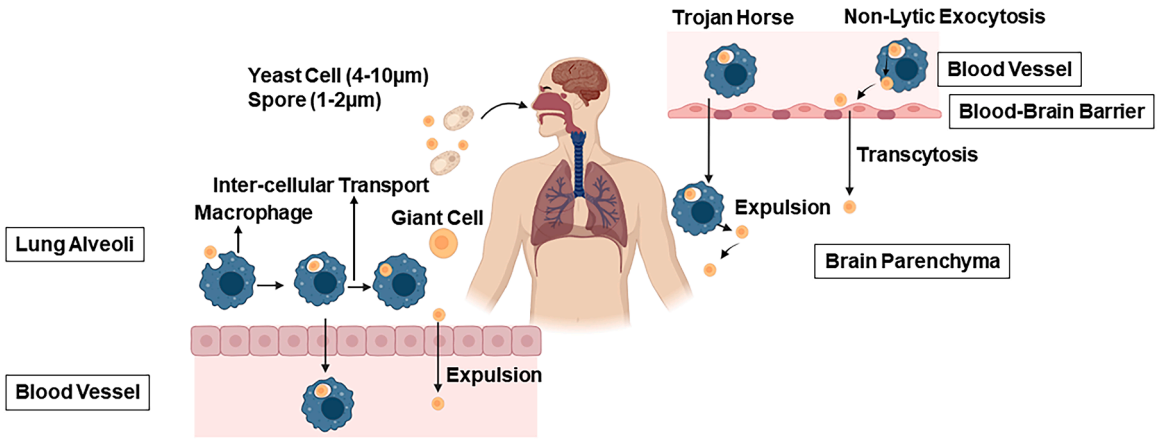

Fig. 2. The interaction between *C. neoformans* and the lung defence mechanism is illustrated on one side of the diagram. This includes the contact of yeast with alveolar macrophages, evasion techniques, and intracellular survival. Conversely, the diagram depicts the pathways by which *C. neoformans* enters the brain, including adhesion to the blood-brain barrier, absorption by endothelial cells, rupturing of tight junctions, and trojan horse dissemination by phagocytic cells. When combined, these illustrations provide insight into the intricate pathophysiology of cryptococcal infection ranging from the lungs to the brain.

3. Antifungal agents and their resistance mechanisms

Due to the fact that *Cryptococcus* spp. is innately resistant to echinocandins and deploys a variety of defenses that permit resistance to azoles, treatment options for invasive cryptococcal infection are constrained (Table 1) (Iyer et al., 2021). As a result, despite its significant toxicity and restricted availability due to logistical and financial issues, polyene AmB has remained the main treatment for cryptococcal infection for over half a century. Its ability to kill fungi is correlated with the affinity of AmB for ergosterol in the membranes of those organisms. AmB causes membranes to function improperly, which leads to cellular leakage and eventual cell death (Spadari et al., 2020). The first commercially available product was Fungizone®, a traditional micellar formulation made up of AmB and deoxycholate (Cavassin et al., 2021). Currently, available parenteral drugs based on lipid carriers include liposomal formulations (LAmB), lipid complex formulations (ABLC), and colloidal dispersions (ABCD). The reduction of undesirable effects of AmB is its main advantage (Rodriguez et al., 2020).

The toxicities associated with conventional AmB have been reduced by the development of liposome bilayer-coated amphotericin B (LAmB), which still retains antifungal action. Because of the immense potential of these lipid formulations, phase II of certain clinical trial revealed that a heavy dose of LAmB is equivalent as that of a seven-day AmB treatment. Resistance towards AmB has not been reported so far, but the binding efficiency, mutation and concentration of ergosterol are the factors that affect the activity of AmB (Iyer et al., 2021, Zhao et al., 2023b).

Another antifungal agent, 5FC, was not advised for monotherapy due to side effects (bone marrow suppression and liver disfunction) and drug

Table 1
Current antifungal agents and combinations for cryptococcal infection: mechanisms of action, typical use, and FDA approval status.

Drug/combination	Class	Mechanism of action	Typical use in cryptococcal infection	FDA approval status
Amphotericin B(Liesbeth et al., 2020)	Polyene	Binds to ergosterol, disrupting cell membrane	Initial treatment for severe cryptococcal infections	Approved for fungal infections (including cryptococcosis)
Liposomal Amphotericin B (Jarvis et al., 2019b)	Polyene	Binds to ergosterol, disrupting cell membrane	Reduced toxicity version of Amphotericin B	Approved for fungal infections (used for cryptococcosis based on guidelines)
Flucytosine (5-FC) (Loyse et al., 2012)	Pyrimidine analog	Inhibits DNA and RNA synthesis	Used in combination with Amphotericin B or Fluconazole for initial treatment	Approved for fungal infections (used in combination therapy for cryptococcosis based on guidelines)
Fluconazole(Feng et al., 2021)	Azole	Inhibits ergosterol synthesis	Maintenance therapy after initial treatment, also used for less severe cases	Approved for fungal infections (including cryptococcosis)
Voriconazole(Song and Guan, 2022)	Azole	Inhibits ergosterol synthesis	Alternative to Fluconazole in cases of resistance or intolerance	FDA Approved (for other fungal infections, used off-label for cryptococcosis)
Itraconazole(Perfect et al., 1986)	Azole	Inhibits ergosterol synthesis	Alternative or adjunctive therapy	FDA Approved (for other fungal infections, used off-label for cryptococcosis)
Posaconazole(Li et al., 2022)	Azole	Inhibits ergosterol synthesis	Alternative or adjunctive therapy	FDA Approved (for other fungal infections, used off-label for cryptococcosis)
Isavuconazole(P et al., 2016)	Azole	Inhibits ergosterol synthesis	Alternative or adjunctive therapy	FDA Approved (for other fungal infections, used off-label for cryptococcosis)
Amphotericin *B* + Flucytosine(Ngan et al., 2019)	Combination	Binds to ergosterol and inhibits DNA/RNA synthesis	Standard initial treatment for cryptococcal meningitis	Combination used based on clinical guidelines, individual drugs FDA Approved
Fluconazole + Flucytosine(Zhao et al., 2023)	Combination	Inhibits ergosterol synthesis and inhibits DNA/RNA synthesis	Alternative initial treatment when Amphotericin B is contraindicated	Combination used based on clinical guidelines, individual drugs FDA Approved
Amphotericin *B* + Fluconazole(Zhao et al., 2022)	Combination	Binds to ergosterol and inhibits ergosterol synthesis	Used when Flucytosine is not available or cannot be tolerated	Combination used based on clinical guidelines, individual drugs FDA Approved
Liposomal Amphotericin *B* + Flucytosine(O'Connor et al., 2013)	Combination	Binds to ergosterol and inhibits DNA/RNA synthesis	Reduced toxicity version of standard combination for initial treatment	Combination used based on clinical guidelines, individual drugs FDA Approved
Liposomal Amphotericin *B* + Fluconazole (A et al., 2004)	Combination	Binds to ergosterol and inhibits ergosterol synthesis	Reduced toxicity combination for initial treatment	Combination used based on clinical guidelines, individual drugs FDA Approved

resistance but is used in combination with AmB for the treatment of HIV co-infection (Bellmann and Smuszkiewicz, 2017). The Cytosine permease on the cell wall serves as a receptor for the drug, which then enters the cell and binds to RNA to prevent the synthesis of DNA by inhibiting thymidylate synthase (Fig. 3). Despite the genetic difference between asco- and basidiomycetous yeasts, the molecular basis of 5-FC resistance of *C. neoformans* has been suggested to be due to mutations in pyrimidine salvage enzymes, similar to *C. albicans* (Chandra et al., 2009). According to several research, 5-fluorouracil (5-FU) resistance was almost always present together with 5-FC resistance, was stable, and was not drug-induced (Delma et al., 2021).

FLC is a triazole drug that prevents the ergosterol production of fungi by inhibiting the cytochrome P450-dependent lanosterol C14-alpha-demethylase (Erg11 or Cyp51). Clinical isolates of *C. neoformans* have gradually developed more resistance to FLC over time, and these days, resistance is a fairly regular occurrence in recurrent cases of cryptococcal meningitis (Lee and Lee, 2018). The FLC resistance phenotype of *Cryptococcus* spp. has been linked to ERG11 gene alterations. Nevertheless, hetero-resistance in them can increase FLC tolerance by favouring hetero-resistant clones after induction as a result of prior FLC exposure. Both in vitro and in vivo, hetero-resistance is generally caused by the development of aneuploid cells, most frequently involving the disomy of chromosome 1, which contains the efflux pump gene AFR1 and ERG11 (Du et al., 2021). The second most frequent aneuploidy causing azole hetero-resistance is chromosome 4 disomy, which is mostly a result of three genes: SEY1, which codes for a GTPase, and GLO3 and GCS2, each of which code for ADP-ribosylation factor molecules (Moreira et al., 2022). Other chromosomes, such as chromosomes 6, 10, 11, and 14, have also been discovered to be aneuploid, but the precise genetic components causing the selection advantage are still unknown (Torres et al., 2022).

Contrary to the extensive genome changes underlying hetero-resistance, a subset of *Cryptococcus* isolates known as hypermutator strains have been identified. These strains feature mutations in key DNA mismatch repair pathway genes, most notably MSH2. However, mutations in other genes, like MSL1 and PMS1, can also cause hypermutator phenotypes (Fisher et al., 2022). They cause mutations at a rate that of 200 times higher than that of common laboratory strains (Iyer et al., 2021). Noteworthy is how quickly medicines like FLC, 5FC, and even AmB become resistant when hypermutator isolates from both the clinic and the research setting are used.

In order to improve the antifungal spectrum of FLC, Voriconazole was developed and had adverse effects such as transient visual disturbances and hepatotoxic effects in human body (Zheng et al., 2021). Resistance to FLC is not so common but has been reported in a very few studies (van Duin et al., 2004).

4. Nanoparticle based therapeutic approach

Present-day antifungal agents often face limitations such as poor biological distribution, low therapeutic efficacy, lack of selectivity, and significant side effects, which hinder the effective treatment of systemic fungal infections. Nanotechnology offers a promising solution to these challenges, as NPs can function as targeted, controlled drug delivery systems. This approach has the potential to enhance the treatment of cryptococcosis, improving therapeutic outcomes while minimizing adverse effects on patients (Haleem et al., 2023). There are many methods that can be used to produce NPs, however, when compared to biological techniques, which do not require severe circumstances or poisonous chemicals, physical and chemical procedures are constrained by electronic stimulation utilizing large equipment and hazardous chemicals (Sreelakshmi et al., 2021, Abdelhameed et al., 2023). Nano formulations are vital in preventing toxicity and boosting the biological activity of NPs (Nam and Luong, 2019, Lathakumari et al., 2022).

In particular, metal NPs have received extensive research; as a result, they have been examined and have produced noteworthy outcomes because of their exceptional antifungal capabilities. Numerous metal NPs have been created and put to use so far to manage systemic fungal infections (Fahim et al., 2023). Numerous strategies are used by NPs to demonstrate antifungal activity. First of all, nanometric particles have the ability to infiltrate cells and discharge metal ions from their surfaces (Madkhali, 2023). These metal ions then react with proteins, damage

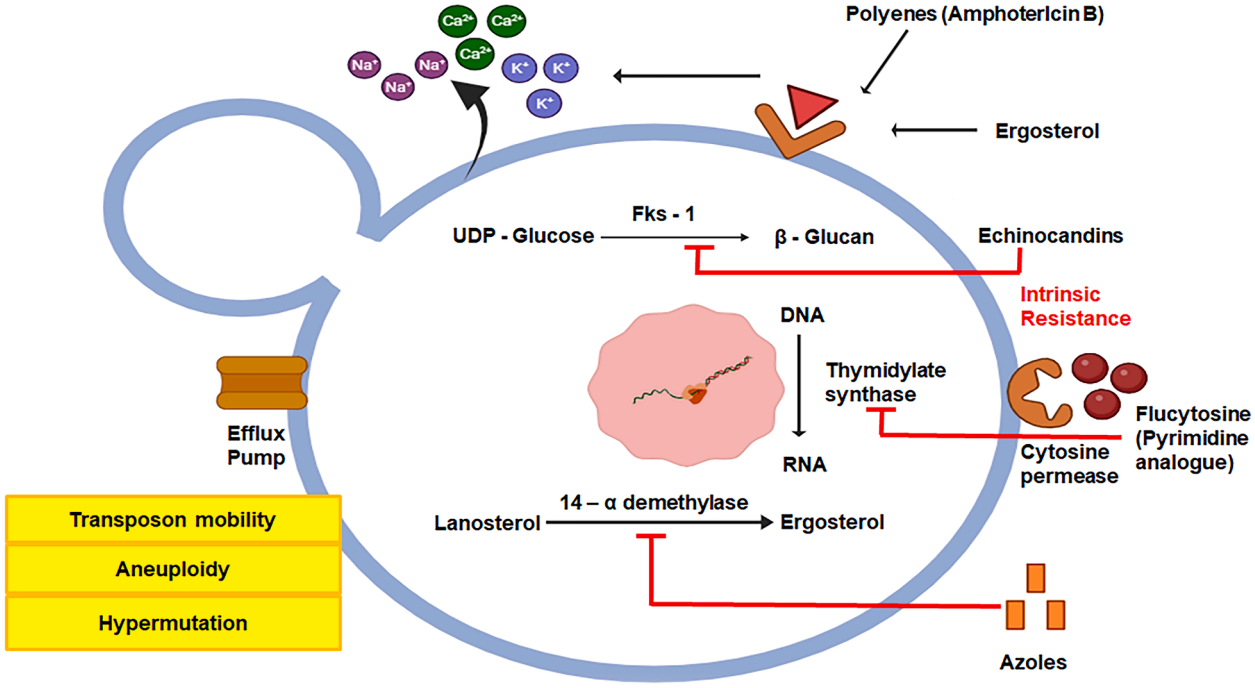

Fig. 3. Mechanism of action of antifungal agents. *Cryptococcus* develops antifungal resistance through efflux pump, transposon mobility, aneuploidy, hypermutation and by mutation of genes that codes for 14 alpha-demethylase, cytosine permease, and glucan synthases. This diagram illustrates different molecular mechanisms through which different class of antifungal agents target cryptococcal cell.

cell walls, and finally result in pathogen death (León-Buitimea et al., 2021). Oxidative stress is a different process, wherein NPs with particular chemical characteristics form reactive surface groups that produce reactive oxygen species (ROS). ROS can harm cell membranes by oxidizing the double bonds in fatty acids, changing permeability, and causing osmotic stress and cell death (Slavin and Bach, 2022). The DNA, RNA, and proteins of pathogens can also be damaged by ROS (Fig. 4). Notably, the toxicity of NPs rises with decreasing size because smaller NPs have more surface area available for interactions and harm (Hua et al., 2017).

The efficacy of amphotericin B-polybutylcyanoacrylate nanoparticles (AmB-PBCA-NPs) in treating cryptococcal meningitis was examined in a study conducted by Nan Xu in 2011. These polysorbate 80-coated NPs displayed encouraging findings in their ability to pass the blood-brain barrier and greatly raise the survival rate of infected mice. AmB-PBCA-NPs were less toxic than free AmB, which made them an option for administering antifungal drugs while limiting side effects (Xu et al., 2011). This study underlines how successful nanoparticle-based drug delivery systems could be in treating severe illnesses like cryptococcal meningitis. Broader uses in the treatment of infections may be possible with further advancements in medication release and potency balance (Kischkel et al., 2020).

Later in 2014, silver NPs, green synthesized from a filamentous fungi named *Fusarium oxysporum* were utilized as it showed a high antifungal activity against *Cryptococcus*, with minimum inhibitory concentration (MIC) value $\leq$ 1.68 μg/mL (Ishida et al., 2014, Khojasteh-Taheri et al., 2023). Palladium-conjugated silver nanosheets (Pd@Ag NSs), a new family of core-shell nanostructures, were found to have significant antifungal action against a variety of molecular types of cryptococcal strains, including isolates that were resistant to FLC. However, the synergistic impact with AmB revealed promising results. Their antifungal activity was comparable to that of AmB and significantly superior when compared with FLC (Zhang et al., 2016). Further investigations detailing the mechanism of action in clinical settings would have improved its potential application.

Since the effectiveness of Ag NPs were already explored against a variety of fungal infections, numerous modifications and combinational approaches have been developed. One such study used gold nanoparticles (Au NPs) synthesized from *Phaffia rhodozyma* (carotenoid producing fermentative yeast). The research discovered that although exhibiting no harm to human keratinocytes, these NPs efficiently suppressed the growth of numerous pathogenic fungi, including *Candida, Cryptococcus, Microsporum, and Trichophyton* (Rónavári et al., 2018a). To improve nanoparticle formulations and investigate their modes of action, more study is required. Positively charged Ag NPs were later coupled with surface-enhanced Raman scattering (SERS) for differentiating *C. neoformans* and *C. gatti* with 100% accuracy. These NPs improved selectivity and enhanced SERS signals relative to negatively charged Ag NPs (Hu et al., 2020).

In addition to Ag and Au, other NPs like selenium, zinc, iron and chitosan were also made utilized(Hashem, Al-Askar, Saeb, et al., 2023). The Se NPs showed promising antifungal action against *C. neoformans* with a MIC of 7.81 g/mL while green synthesized zinc oxide NPs showed activity with a MIC of 32.00 μg/mL (Hashem et al., 2022, Hashem, Al-Askar, Haponiuk, et al., 2023). ROS can be produced as a result when fungus cells are exposed to Zn and Se NPs (Moghadam et al., 2023). Superoxide radicals and hydrogen peroxide, two types of ROS, harm cellular components like lipids, proteins, and DNA by causing oxidative stress. For the fungus cell, this kind of oxidative stress could be fatal. Particularly Se NPs have the ability to interact with fungal DNA. It can cause DNA damage, such as breakage of strands and genetic changes, which hinder the ability of fungi to reproduce and survive (Shields et al., 2021, Redza-Dutordoir and Averill-Bates, 2016).

A study conducted in the year 2022 had found the antifungal properties of honeybee venom, specifically *Apis mellifera* bee venom loaded into chitosan nanoparticles (BV-CNPs), against unicellular fungal (UCF) pathogens such *C. neoformans*. They conclude that a minimum concentration of 3.12 mg/mL of BV-CNPs can inhibit the fungal growth. Additionally, the ability of UCF to build biofilms and switch from yeast to hyphae was effectively inhibited by BV-CNPs (El-Didamony et al., 2022). Studies on 2-amino-thiophene (6CN10) NPs demonstrate their potential to be a viable therapeutic for cryptococcosis, with MIC values of 0.32–83.3 g/mL (Neves et al., 2020).

Pathogens both within and outside of cells can be successfully eliminated using nanotechnology. The effective treatment of systemic infections with extracellular pathogens depends on their biocompatibility and the duration of their stay in the bloodstream at sufficient concentrations. A more sophisticated strategy is needed for intracellular pathogen therapy, one that involves precisely directing **nanocarriers** to diseased cells using various proteins (Hong et al., 2020). Some nanocarriers use endocytic processes to enter the cell, where they remain secure until they can reach the cytoplasm and deliver the drug. Otherwise, the release of the drug into the Endo lysosome could render it ineffective. (Manzanares and Ceña, 2020).

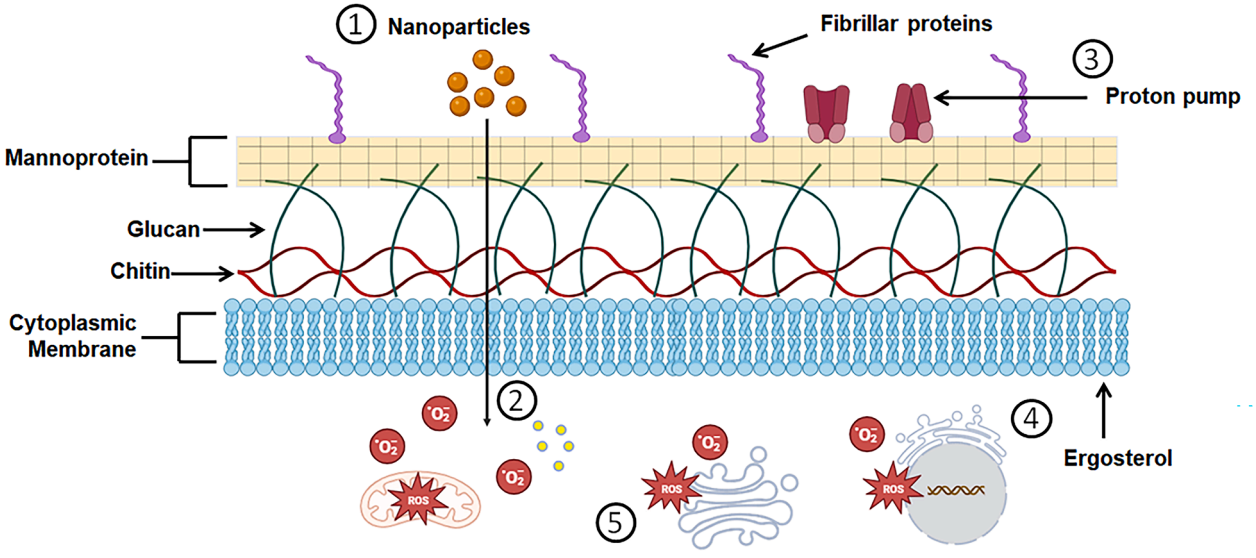

Fig. 4. Mechanism of action of nanoparticles. 1) Uptake and attachment of NPs into the fungal cell, 2) NP release metal ions or ROS when comes in contact with cell membrane, 3) Proton pump blockage, 4) DNA damage, 5) Oxidative stress on mitochondria and golgi apparatus.

In order to create nanoparticles for prospective antifungal treatments against mycoses brought on by fungus like *Candida* and *Cryptococcus*, this study (Martinez et al., 2010) investigates the use of several polymers, including alginate, chitosan, and Poly Lactic-co-Glycolic Acid (PLGA). Because of its positive charge and hydrophobic characteristics chitosan is suitable for driving a variety of compounds, including drugs and vaccines, through mucosal barriers (Hasanin et al., 2019, Turky et al., 2021). Alginate-based nanoparticles, on the other hand, have non-cytotoxic qualities and are biocompatible. Because PLGA is a synthetic co-polymer with minimal cytotoxicity and biodegradability, it can be used to combine drugs or immunogenic chemicals, which has been approved by the FDA. These polymers offer flexible frameworks for the creation of nano therapies that may enhance the management of systemic fungal infections (Essa et al., 2020, Gómez-Sequeda et al., 2017).

The flexible lipid particles known as liposomes, which resemble cellular membranes, have a special shape with hydrophilic and hydrophobic sections that makes them effective transporters for many compounds. They can control the release of molecules and transport significant loads, making it possible to administer drugs effectively. Sterols have the ability to alter their stiffness, making it easier to anchor molecules for direct distribution (Nakhaei et al., 2021). Liposomes have the ability to mimic pathogens and elicit an immune-like response. Drugs like AmB are combined into liposomes to create formulations like Abelcet and AmBisome, which are used all over the world to treat fungal infections (Stone et al., 2016).

A wide range of nanoscale delivery methods, including dendrimers, polymersomes, polymeric micelles, and mesoporous NPs, show promise for treating fungal infections. Highly branched polymers called dendrimers have precise molecular structures and can be modified to provide specialised surfaces for improved bioavailability and targeted administration of medicine (Mitchell et al., 2021, Abbasi et al., 2023). Polymersomes are self-assembling vesicles made of amphiphilic block copolymers. Their variable membrane permeability makes them perfect for releasing antifungal drugs under regulated conditions. Polymeric micelles, formed by the self-assembly of amphiphilic block copolymers in aqueous solutions, provide a stable and biocompatible platform for solubilizing hydrophobic antifungal drugs and improving their pharmacokinetic profiles (Hwang et al., 2020). Mesoporous NPs are a viable option for the localised delivery of antifungal drugs because of their structured pore designs, high surface areas, and effective drug loading capacities and prolonged release kinetics(Kolimi et al., 2023, Vallet-Regí et al., 2022).

To improve the efficiency and safety of antifungal drug delivery, several cutting-edge nanoparticle-based strategies have been investigated. For instance, it has been discovered that PLA-b-PEG coated with polysorbate 80 (Tween-80) enhances the AmB entrapment efficiency, potentially resulting in a more successful treatment (Gupta, 2019). AmB-loaded polybutylcyanoacrylate (PBCA) nanoparticles have demonstrated potential for lowering the toxicity of this medication to important organs such the liver, kidney, and circulation (Fatemeh et al., 2014). A critical development for treating fungus infections in the brain, Angio pep-PEG-PE polymeric micelles have been created to increase the permeability of AmB to the central nervous system (CNS) (Shao et al., 2010). Furthermore, the use of a chloroaluminum phthalocyanine nano emulsion (CIAIP/NE) has been proven successful because fungi do not establish particular defense mechanisms against this cutting-edge therapeutic strategy (Rodrigues et al., 2012) (Table 2).

Solid and liquid lipids are combined in nanostructured lipid carriers (NLCs), a second-generation carrier technology that addresses problems with solid lipid nanoparticles (SLNs). Due to their compatibility with lipophilic medicines, NLCs provide enhanced drug administration, longer-lasting stability, and increased drug retention capacity (Viegas et al., 2023). Liquid lipid fractions can be added to increase encapsulation effectiveness and enable stable storage. Because their biological distribution in the body is influenced by characteristics including particle size and charge, NLCs are emerging as useful alternatives for drug

Table 2
The table below provides a comprehensive overview of nanoparticle formulations and their advantages in combating cryptococcal infections. Every formulation has different advantages, such as the strong antifungal activity of Ag NPs and the reduced toxicity of AmB-PBCA-NPs when they cross the blood-brain barrier. Additionally, synergistic strategies such as combining NPs with existing antifungal drugs like AmB or FLZ, show improved efficacy and less toxicity. These results highlight the possibility of medicines based on NPs as effective approaches to treating infections caused by *cryptococcus*.

Nanoparticle	Advantages	Synergistic approach	References
Silver (Ag) NPs	High antifungal activity against Cryptococcus MIC $\leq$ 1.68 μg/mL	–	(Ishida et al., 2014, Khojasteh-Taheri et al., 2023)
Amphotericin B polybutylcyanoacrylate nanoparticles (AmB-PBCA-NPs)	Ability to pass the blood-brain barrier (Animal study) & less toxic	AmB	(Xu et al., 2011)
Pd@Ag nanosheets (Pd@Ag NSs)	Active against fluconazole resistant isolates	AmB	(Zhang et al., 2016)
Positive charged Ag NPs coupled with surface-enhanced Raman scattering (SERS)	Differentiate *C. neoformans* and *C. gatti* with 100 % accuracy & improved selectivity of $+^{ve}$ charged Ag NPs	–	(Rónavári et al., 2018a, Hu et al., 2020)
Selenium (Se NPs)	Promising antifungal action MIC 7.81 g/mL	–	(Hashem et al., 2022)
Zinc oxide NPs	Less toxicity MIC 32.00 μg/mL	–	(Moghadam et al., 2023)
Bee venom loaded chitosan nanoparticles (BV-CNPs)	BV-CNPs suppressed the biofilm formation as well as yeast to hyphal transition MIC 3.12 mg/mL	–	(El-Didamony et al., 2022)
2-amino-thiophene (6CN10) nanoparticles	MIC 0.32–83.3 g/mL	–	(Neves et al., 2020)
Solid lipid	Enhanced efficiency with minimal toxicity	AmB/FLZ	(Almawash, 2023)
Nanostructured lipid carrier	More effective than both AmB itself and Fungizone®	AmB/FLZ	(Cavassin et al., 2021
Ag NPs and Au NPs	Exhibits no harm to human keratinocytes	–	(Chintalacharuvu et al., 2021, Rónavári et al., 2018b)
PLA-b-PEG coated with polysorbate 80 (Tween-80)	Tween-80 enhanced the entrapment efficiency	AmB	(Gupta, 2019)
Polybutylcyanoacrylate (PBCA)	AmB-PBCA-NPs are able to reduce the toxicity of AmB to the liver, kidney, and blood system	AmB	(Fatemeh et al., 2014)
Angio pep-PEG-PE polymeric micelles	Improve the CNS permeability of AmB	AmB	(Shao et al., 2010)

(*continued on next page*)

Table 2 (*continued*)

Nanoparticle	Advantages	Synergistic approach	References
Chloro-aluminium phthalocyanine nano emulsion (CIAIP/NE)	Fungi do not form any specific defence mechanism against PACT	–	(Rodrigues et al., 2012)
PAMAM-sulphonamide dendrimers	Inhibitors of carbonic anhydrases, active against bacteria, parasites and fungi	–	(Winnicka et al., 2011)
Nanoparticle crystal encapsulated	Provided efficacy equal to a parental preparation of amphotericin B plus flucytosine	AmB/5FC	(Kalagatur et al., 2018)
BSA nanoparticles coated with polysorbate- 80	Comparing with AmB, demonstrated an absence of cytotoxicity toward erythrocytes	AmB	(Pedroso et al., 2018)

(PAMAM- Polyamidoamine dendrimers, Polylactic acid (PLA) and polyethylene glycol (PEG), Bovine Serum Albumin (BSA)).

delivery investigations (Salvi and Pawar, 2019).

With droplet sizes typically ranging from 10 to 500 nm, **Nano emulsions** (NEs) are stable mixes of pharmaceuticals, lipids, hydrophilic surfactants, and co-solvents (Shaker et al., 2019). Because they can solubilize lipophilic medicines and make it easier for substances to pass through biological membranes, like intranasal mucosa, they represent a promising drug delivery mechanism for antifungal medications (Marena et al., 2023). NEs have been studied for a variety of medication delivery applications, including brain-targeted medicines, making them a viable treatment option for meningitis brought on by *Cryptococcus* spp. (Wang et al., 2010). In-depth research into topical therapy for fungus infections has been stimulated by their versatility in creating gels, creams, and foams. Due to their stability and effective absorption qualities, NEs constitute a useful method for improving medication delivery in antifungal therapies (Garcia et al., 2019).

5. Conclusion and future directions

In conclusion, this review underscores the urgent need for novel strategies to combat the growing threat of antifungal resistance in *Cryptococcus* infections. Nanoparticle-based therapies offer promising avenues for improving drug delivery, overcoming resistance strategies, and minimizing side effects. The demonstrated efficacy of various NPs, including Ag, Se and bee venom-loaded chitosan NPs, highlights their potential as effective antifungal agents against *Cryptococcus*. Additionally, there is a great deal of promise in enhancing therapeutic efficacy and safety profiles with nanoparticle formulations such liposomes, dendrimers, and nanostructured lipid carriers. Addressing the limitations of the antifungal treatments that are currently available and the enhancement of patient outcomes, these developments are essential. There is a significant opportunity to influence the treatment of cryptococcal infections by utilising the potential of nanoparticle-based therapeutics, which will ultimately lower the morbidity and mortality linked to this powerful fungal pathogen.

Future research should focus on optimizing nanoparticle designs, exploring synergistic combinations with existing antifungal drugs, and elucidating their precise mechanisms of action. Integration of cutting-edge technologies like CRISPR-Cas9 for genetic manipulation, high-throughput screening for new drug discovery, artificial intelligence for predictive modelling, next-generation sequencing to understand resistance mechanisms, phage therapy, RNA interference, and bioprinting for tissue modelling presents promising avenues for addressing antifungal resistance comprehensively. By leveraging these innovations, we can advance the management of cryptococcal infections, reduce global disease burden, and enhance patient outcomes in clinical settings.

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CRediT authorship contribution statement

Rahul Harikumar Lathakumari: Writing – review & editing, Writing – original draft, Visualization, Validation, Resources, Methodology, Data curation, Conceptualization. **Leela Kakithakara Vajravelu:** Formal analysis, Conceptualization. **Abhishek Satheesan:** Resources, Project administration, Investigation. **Jayaprakash Thulukanam:** Visualization, Validation, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability

Data will be made available on request.

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