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Nanotechnology-Based Strategies for Combating Emerging and Re-emerging Fungal Infections

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ABSTRACT

The emergence and re-emergence of pathogenic fungi pose a significant challenge, fueled by factors like increased immunosuppression and climate changes. Despite the development of new antifungal drugs and therapies, controlling these infections remains a pressing issue. *Candida auris*, a multidrug-resistant yeast, has caused invasive infections with high mortality rates in hospitals worldwide, with Iran experiencing a particularly high burden of invasive *C. auris* infections. The identification of new at-risk groups, rising prevalence of resistant infections, and the emergence of novel multidrug-resistant pathogenic fungi highlight the need for novel therapeutic approaches and effective prevention strategies. This review explores the potential of nanotechnology, an emerging field, in combating emerging fungal infections, such as *C. auris*, and re-emerging infections caused by *Fusarium* and *Rhizopus* species. We conducted a literature review of studies exploring nanotechnology-based approaches to control or inhibit these emerging and re-emerging fungal pathogens with a particular focus on Iran and globally, where antimicrobial resistance is a growing concern. Nanotechnology revolutionizes antifungal strategies with novel solutions. Nanoparticles (NPs) and nanomaterials possess unique properties, such as enhanced solubility, targeted delivery, and ROS generation, which can disrupt fungal cell membranes, inhibit biofilm formation, and prevent sporulation. Their tailored sizes, high surface-to-volume ratios, and customizable surface chemistries make them game-changing solutions to combat drug-resistant fungal infections and improve treatment outcomes. Numerous studies have demonstrated the ability of various NPs, including silver, metal oxide, and carbon-based nanomaterials, to inhibit the growth and virulence factors of *C. auris*, *Fusarium*, and *Rhizopus* species. These nanomaterials exhibit potent antifungal activities through mechanisms such as disrupting cell membrane integrity, inducing oxidative stress, and inhibiting fungal metabolic pathways.

INTRODUCTION

Climate change is a key driver of infectious disease dynamics, leading to the emergence and re-emergence of various pathogens, including fungi. Pathogenic fungi, such as *Candida*, *Aspergillus*, and *Fusarium* species, are particularly vulnerable to climate-related disruptions, leading to increased disease burden and novel infections. The absence of effective vaccines against most fungal pathogens highlights the urgent need for innovative strategies to combat the growing threat of fungal infections, exacerbated by climate change. Climate change has led to changes in temperature, precipitation, and humidity, altering the ecological niches of fungal pathogens and their vectors, resulting in the emergence of new diseases [1].

The multidrug-resistant yeast *Candida auris* has precipitated a significant global health crisis since its initial identification in Japan in 2009, with its rapid emergence underscoring the urgent need for effective therapeutic strategies and enhanced surveillance measures [2]. Phylogenetic studies have revealed that *C. auris* is closely related to environmental isolates, suggesting a possible origin from soil or water sources [3]. Zoonotic transmission from animal sources, potentially involving bird vectors, has been implicated in the spread of *C. auris*. It is a prime example of a fungal pathogen whose

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emergence and spread are directly attributed to climate change, and its rapid spread across continents highlights the challenges posed by emerging fungal diseases [4, 5]. Furthermore, the widespread use of fungicides in agriculture and the contamination of water sources with fungicide residues may have contributed to the selection and dissemination of *C. auris*, underscoring the need for a comprehensive approach to address the emergence of this pathogen.

Climate change has also impacted the emergence and spread of other fungal pathogens, including *Batrachochytrium dendrobatidis*, a chytrid fungus responsible for devastating amphibian populations, and *Cryptococcus deuterogattii*, a cryptococcal species causing meningitis in immunocompromised individuals. Furthermore, *Puccinia striiformis* and *Fusarium* exemplify the alarming adaptability of fungal pathogens to shifting environmental conditions, underscoring the need for innovative strategies to combat their emergence and spread. *P. striiformis*, previously confined to temperate regions, has expanded its range to tropical areas, with the emergence of heat-tolerant strains capable of thriving in warmer environments [6]. The expansion of *P. striiformis* into new regions has significant implications for global food security, as it poses a threat to wheat and barley crops, highlighting the need for climate-resilient agricultural practices. In temperate regions, a notable shift from *Fusarium culmorum* to *Fusarium graminearum* has occurred over the past two decades, mirroring changing environmental conditions [1]. This shift has significant implications for crop yields and food security, as *F. graminearum* is a more aggressive and toxigenic pathogen, capable of causing devastating head blight in wheat and barley. This shift has been documented, highlighting the adaptability and resilience of fungal pathogens in response to changing environmental conditions.

Several factors, including the increasing use of immune-modulating therapies, contribute to the emergence of pathogenic fungi beyond climate change. A 2019 review identified *Histoplasma capsulatum*, *Fusarium* species, and *C. auris* as emerging and re-emerging fungal pathogens, attributing their rise to the increasing use of immune-modulating therapies [7]. Solid organ transplant and HSCT recipients, as well as those receiving immunomodulatory therapies like TNF antagonists, are vulnerable to environmental fungal infections such as mucormycosis, aspergillosis, fusariosis, and candidiasis, which are a growing concern in the field due to increasing rates of resistance to current treatments [8].

A study conducted by Razzaghi-Abyaneh *et al*. (2014) at the Pasteur Institute of Iran investigated the prevalence of candidiasis and antifungal susceptibility patterns in outpatient samples between 2011 and 2012. The study found that 72.3% of the samples were identified as *C. albicans*, which is a significant finding given the high resistance rates to ketoconazole (34%) and the importance of effective treatment options for candidiasis [9]. A study conducted by Afshari *et al*. (2016) investigated the antifungal susceptibility of 69 dermatophyte strains belonging to the genera *Microsporum*, *Epidermophyton*, and *Trichophyton*. The study found that all 69 dermatophyte strains were resistant to fluconazole, which is a concerning finding given the high prevalence of fungal infections and the limited treatment options available [10]. The study's findings have important implications for the treatment of fungal infections, as fluconazole is a commonly used antifungal agent. The development of new antifungal agents and treatment strategies is urgently needed to combat the growing problem of antifungal resistance.

A two-year retrospective study in southern Iran involving 248 transplant patients investigated the prevalence of invasive fungal pathogens and identified *Candida* spp. as the most frequently isolated, with *C. albicans* accounting for the majority (51.8%) of cases [11]. The study's findings have important implications for the treatment of fungal infections, as *C. albicans* is a commonly isolated pathogen. Dabiri *et al*. (2016) investigated the expression of secreted aspartyl proteinase (*SAP*) genes, key virulence factors, in 73 *Candida* isolates from outpatients at the Pasteur Institute of Iran, to better understand the pathogenesis of candidiasis. The study found that *C. albicans*, representing 49.3% of the isolates, exhibited the highest aspartyl proteinase activity, which is a significant finding given the importance of *SAP* in fungal virulence and the high prevalence of *C. albicans* in candidiasis cases [12].

Sadeghi *et al*. (2018) conducted a study at the Pasteur Institute of Iran to investigate the prevalence of non-albicans *Candida* species in suspected cases of candidiasis, which is a growing concern due to increasing antifungal resistance. The study found that 79 cases (56.4%) were definitively diagnosed as non-albicans *Candida* species, with *Candida parapsilosis* and *Candida glabrata* being the most frequently identified species, which is a significant finding given the increasing prevalence of non-albicans *Candida* species in candidiasis cases [13]. Salehi *et al*. (2018) conducted a study at the Pasteur Institute of Iran to investigate the emerging problem of terbinafine resistance among dermatophyte isolates from patients, which is a growing concern due to the limited treatment options for fungal infections. The study found that *Trichophyton tonsurans* was the most prevalent species (19 isolates), and both *T. tonsurans* and *Trichophyton rubrum* exhibited terbinafine resistance [14]. Sadeghi *et al*. (2019) conducted a study at the Pasteur Institute of Iran to investigate the prevalence and risk factors of cutaneous candidiasis, a growing concern due to the increasing incidence of fungal infections in vulnerable populations. The study found that *C. albicans* was identified in approximately 40% of cases, which is a significant finding given the high prevalence of

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candidiasis in patients with compromised immune systems, such as those with diabetes and those receiving immunosuppressive therapy [15].

Further investigations using *C. albicans* isolates and BALB/c mice as a model system demonstrated the potential for cutaneous candidiasis to disseminate and cause systemic and oral infections, highlighting the importance of understanding the pathogenesis of candidiasis and developing effective treatment strategies [16, 17]. This finding underscores the risk of nosocomial candidiasis in vulnerable individuals, emphasizing the need for effective infection control and antifungal strategies to prevent and treat these life-threatening infections. Salehi *et al*. (2021) conducted a comprehensive study on the genetic diversity and molecular epidemiology of clinical dermatophyte isolates and reference strains from the Pathogenic Fungi Culture Collection of the Pasteur Institute of Iran, shedding light on the evolutionary relationships among dermatophytes and their impact on human, animal, and environmental health. The phylogenetic analysis revealed a branching pattern, with zoophilic and anthropophilic genera diverging from geophilic ancestors, demonstrating the interconnection of human, animal, and environmental health and highlighting the potential for zoonotic transmission and emergence of new fungal pathogens. The study identified *Trichophyton tonsurans* and *Trichophyton equinum* as a species complex, with *T. equinum* likely derived from *T. tonsurans*, which has important implications for understanding the evolution of antifungal resistance and developing effective treatment strategies [18]. This study emphasizes the critical need for surveillance for emerging antifungal resistance among all fungal pathogens, including dermatophytes, to prevent the spread of resistant infections and develop effective treatment strategies to combat these emerging threats.

Pashootan *et al*. (2022) conducted a comprehensive study on the antifungal susceptibility and point mutations of 123 dermatophyte isolates from the Pasteur Institute of Iran, shedding light on the emerging problem of antifungal resistance and its underlying mechanisms. The study identified 6 isolates with reduced terbinafine susceptibility, highlighting the growing concern of antifungal resistance and the need for effective treatment strategies to combat emerging and re-emerging fungal infections [19]. Notably, *Trichophyton indotineae* exhibited a mutation in the *SQLE* gene with a *Phe397Leu* substitution, potentially contributing to its reduced susceptibility and highlighting the importance of understanding the molecular mechanisms of antifungal resistance [19].

This review explores the potential of nanotechnology to combat emerging and re-emerging fungal infections in Iran, providing a comprehensive overview of its applications, advantages, and future directions in addressing this growing public health challenge. Given the alarming rise of emerging and re-emerging fungal infections in Iran, and the limited success of conventional treatment approaches, this review aims to explore the potential of nanotechnology as a novel strategy for controlling these infections and addressing the growing public health challenge. Based on recent studies and observations at the Pasteur Institute of Iran, three fungi-*C. auris*, *Fusarium* spp., and *Rhizopus* spp.-have emerged as significant pathogens in Iran, two of which (*C. auris* and *Fusarium* spp.) are also recognized as global emerging threats. Despite the growing concern about emerging and re-emerging fungal infections in Iran, there is a significant knowledge gap in understanding their landscape and exploring innovative solutions like nanotechnology for their control. Given the unique epidemiological and ecological context of Iran, this review will focus on the emerging fungal pathogens in this region, acknowledging the global interconnectedness of infectious disease dynamics and the potential for cross-border transmission.

Candida auris

C. auris is a multidrug-resistant (MDR) fungal pathogen associated with high mortality rates, reaching up to 60% in some reports [20]. Since its initial identification, *C. auris* has been reported in over 20 countries worldwide, posing a significant threat to public health worldwide [21]. Belonging to the *Clavispora* clade of the Metschnikowiaceae family, this opportunistic pathogen can cause infections in various body sites, including wounds, the digestive system, skin, and bloodstream [22]. *C. auris* is also known for its ability to form biofilms, which further complicates treatment. Over 500 cases of *C. auris* infection have been reported from the Arabian Peninsula, and its occurrence as a co-infection in COVID-19 patients has raised additional concerns during the pandemic [22].

Whole-genome sequencing analysis (WGS) of *C. auris* isolates has identified four distinct clades based on geographical origin: East Asian, South Asian, South African, and South American. A fifth clade has recently been reported in Iran [23]. Genomic comparisons reveal that *C. auris* shares approximately 78% to 85% sequence similarity with *C. albicans* and *C. glabrata* [22]. Following its initial identification in a case of otitis externa in Japan in 2009 1, *C. auris* has been reported globally, with a notable presence in Iran [1]. In 2018, a case of *C. auris* otomycosis was reported in a 14-year-old girl in Iran, with minimum inhibitory concentrations (MICs) of 16 µg/mL for fluconazole, 0.063 µg/mL for isavuconazole, 0.063 µg/mL for itraconazole, and 0.125 µg/mL for voriconazole [24].

Isolates belonging to the Latin American, South Asian, and South African clades have been observed to consistently display high MICs against fluconazole and other triazole antifungal agents [24]. In contrast, *C. auris* isolates from India have been found to exhibit relatively lower MICs against fluconazole [24]. Colombian isolates generally show low MICs to itraconazole, voriconazole,

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and isavuconazole [24]. In the aforementioned Iranian case of *C. auris* otomycosis, a combination of antibacterial and antifungal therapy was employed. The patient received a combination therapy comprising oral cefixime, topical gentamicin, topical nystatin, and oral terbinafine. Nevertheless, this treatment regimen failed to yield any notable clinical improvement [24]. As the patient had no history of international travel, the authors hypothesized that additional cases of *C. auris* infection may have gone undiagnosed or unreported within the country [25].

In 2017, a 33-year-old immunocompetent woman in Isfahan, Iran, was treated a fungal infection of the ear (otomycosis) initially thought to be caused by *Aspergillus flavus*. However, during a follow-up visit in 2021, *C. auris* was confirmed as the causative agent. Genotyping revealed that the isolate belonged to Clade V (a distinct genetic lineage of *C. auris*), similar to the previously mentioned case. Surgery and artificial eardrum replacement did not alleviate the patient's hearing loss in the right ear. Following the diagnosis of *C. auris*, repeated topical treatment with clotrimazole 1% solution, bactimide 10%, and hydrocortisone-acetic acid otic solution failed to improve symptoms of pain, redness, and itching in the left ear. Ultimately, the infection resolved after antifungal treatment and surgery [26].

In 2020, a case of *C. auris* otitis external was reported in a 40-year-old Iranian woman with a history of fluconazole-resistant otalgia. Antifungal susceptibility testing showed that the isolate required a high concentration of fluconazole to inhibit growth (≤32 µg/mL). Following diagnosis, the patient received topical clotrimazole 1% cream (MIC: 2 µg/mL) and micronazole 1% cream (MIC: >16 µg/mL) twice daily for eight weeks. Follow-up examination confirmed complete resolution of the infection with no evidence of recurrence [27].

A case of *C. auris* meningitis was reported in a 30-month-old infant of Iranian origin residing in Pakistan, who was admitted to Children's Medical Center Hospital in Tehran, Iran. Genotyping revealed that the isolate belonged to the South Asian clade. After ruling out bacterial meningitis, the child received treatment with antifungal medications: fluconazole (100 mg/kg/day), flucytosine (250 mg/kg/day), and liposomal amphotericin B (3 mg/kg/day). Although the child's condition improved, they were discharged at the parents' request, precluding further follow-up [28].

The widespread geographical distribution and increasing reports of *C. auris* infections highlight its potential as a significant public health concern. The cases identified in Iran, primarily from northern cities and Isfahan, belonged to a novel clade distinct from those previously reported globally. This raises the possibility of additional undetected or unreported cases within this region. Furthermore, international travel and migration facilitate the spread of diverse *C. auris* genotypes, potentially leading to outbreaks with varying severity in new host populations. The reduced susceptibility of *C. auris* to various antifungal agents, including multidrug resistance [29], coupled with the challenges and side effects associated with conventional antifungal treatments (*e.g.*, prolonged treatment duration, side effects) [27], underscores the pressing need for new and improved treatment approaches, such as those offered by nanotechnology.

Fusarium spp.

In addition to *C. auris*, species of *Fusarium*, commonly known as plant pathogens, have emerged as clinically significant opportunistic fungi in humans. *Fusarium* spp. infections in humans usually result from environmental exposure. Fusarium head blight (FHB), a major disease affecting wheat and other cereal crops, is primarily caused by members of the *F. graminearum* species complex (FGSC) [1]. A significant shift from *Fusarium culmorum* to the more virulent *F. graminearum* has been observed, resulting in enhanced crop damage. *F. graminearum* worsens FHB severity and produces elevated mycotoxin levels, posing a threat to both human and animal health [1].

Evidence suggests that mycotoxin production by *Fusarium* spp. increases under conditions of elevated temperature and water stress, raising concerns about potential effects on human and animal health [1]. *Fusarium* spp.'s ability to infect plants, animals, and humans emphasizes its significance in the One Health approach. One Health is a collaborative approach that involves multiple sectors that acknowledges the interconnectedness of human, animal, and environmental health. *Fusarium* spp.'s ability to infect multiple hosts across kingdoms demonstrates its broad host range and pathogenic potential and underscores the need for comprehensive disease management approaches [30].

Fusarium, filamentous ascomycete fungus that produces toxins, plays a crucial role in agriculture and natural ecosystems. Its widespread presence in soil acts as a reservoir for potential infections [31]. Notably, there has been an increase in reported *Fusarium* isolates from patient samples, raising concerns due to the high mortality rates associated with these infections. As ubiquitous environmental organisms, *Fusarium* species are frequently encountered in soil, decaying plant material, and organic substrates. They can enter into the human body through multiple routes, including the respiratory tract, compromised skin, and mucosal surfaces. As opportunistic pathogens, *Fusarium* species can cause a variety of infections in humans, with the clinical outcome largely dependent on the host's immune status and the specific site of infection [32].

Fusarium infections in humans have been reported worldwide, including in Iran and other countries. A notable example is a 2009 Italian study that described four cases of *Fusarium* infections presenting as: (1) acute paronychia with a pustule on the thumb; (2) progressive

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nail dystrophy; (3) separation of the nail plate with redness and swelling around the nail; and (4) progressive white discoloration of the nails on the hands [33]. Immunocompetent individuals typically develop *Fusarium* infections affecting the nails (onychomycosis) and the cornea (keratomycosis or mycotic keratitis). In addition, *Fusarium* infections have also been reported as secondary infections in individuals with underlying medical conditions. For instance, a rare case of disseminated meningospinal dylodiscitis caused by *Fusarium oxysporum* was reported in India, in a patient with Type II diabetes and hypertension, which involved a spinal nerve infection [34]. This report describes the first documented case of neurogenic *Fusarium* infection.

Notably, a case of *Fusarium* infection was reported in a multi-organ transplant patient in the US, which occurred several weeks after transplantation [35]. A study in a pediatric burn unit in Argentina, a study isolated *Fusarium* from the lesions of 15 patients, including one with a bone lesion [36]. The study found that 15 patients (100%) developed burn wound infections, with one patient (7%) having bone involvement and one patient (7%) developing fungemia. Furthermore, between October 2013 and February 2014, *F. oxysporum* was isolated from the blood of seven male children in Brazil, all of whom had suspected catheter-related infections [37]. Moreover, *Fusarium* was isolated from a femoral arteriovenous graft in a patient undergoing hemodialysis for end-stage renal disease, who also had a diagnosis of systemic lupus erythematosus [38].

Fusarium keratoplasticum was isolated from an HIV-positive patient in Spain, with no prior history of skin or mucosal lesions that could have predisposed them to localized infection. A comprehensive evaluation of risk factors for mold infections, including neutropenia, immunological deficiencies, and prior antifungal medication use, did not reveal any contributing factors. Notably, *Fusarium* often causes disseminated infections in individuals with compromised immune systems or critical health conditions, accounting for 70% of all *Fusarium* infections and associated with high morbidity and mortality rates [39]. Furthermore, a case of *Fusarium osteomyelitis* was reported in a multi-visceral transplant patient, with the fungus infecting bone and joints through the transplanted organ. The patient had a previous occupation involving the wholesale and distribution of palm trees [40].

A significant case of *Fusarium* infection was reported in Iran in 1998, involving a 15-year-old boy with chronic granulomatous disease and disseminated fusariosis [41]. The patient had a history of recurring ulcerative and infectious lesions on his ankle area since the age of two, and had received anti-TB therapy for 30 months. Despite subsequent treatment with cephalexin, cotrimoxazole, and gamma interferon, his condition did not improve. In 1995, he presented to Hazrat Rasool Akram Hospital with ulcers on his buttock and right ankle. Radiological imaging revealed parahilar lesions in both lungs, which were unresponsive to antibacterial therapy, suggesting a fungal infection. Further investigation at the Mycology Department of Pasteur Institute of Iran included direct examination and culture of blood, lesion biopsy samples, and broncho-alveolar lavage (BAL) fluid. Direct examination revealed branching hyaline septate hyphae, and *Fusarium* sp. was isolated from the lesion biopsy culture and BAL fluid, while blood culture was negative. The patient received intravenous amphotericin B (1 mg/kg/day) for 40 days and oral ketoconazole (150 mg/day) for 50 days, which led to his recovery. After treatment, the patient underwent a skin graft and was subsequently discharged from the hospital [41].

In 2012, a 32-year-old male patient with a 5-year history of *Pyoderma gangrenosum* (PG) was admitted to the Intensive Care Unit of Shafa Hospital (Sari, Iran) with extensive necrotic skin lesions on his upper limbs, back, and chest. Although the diagnosis of PG was confirmed, the underlying cause remained unknown. Microscopic examination of endobronchial washing and BAL samples revealed branching septate hyphae, and *Aspergillus flavus* was cultured. Furthermore, *Fusarium proliferatum* was isolated from a skin lesion biopsy sample using multiple culture media, confirming a diagnosis of cutaneous fusariosis. Molecular analysis supported these results. Despite treatment with voriconazole (6 mg/kg/IV BD) and antibiotics, including ciprofloxacin (400 mg BD), linezolid (600 mg BD), and meropenem (1g IV TDS), the patient's condition worsened, and he succumbed to sepsis 12 days later [42].

In 2007, a 50-year-old pistachio garden worker with no underlying immunodeficiency presented to the Mycology laboratory in Kerman, Iran, with a 5-year history of nail deformity on his second finger. Direct microscopic examination of nail scrapings revealed narrow, irregular, and septate hyphae. Culture analysis revealed colonies consistent with *Fusarium* spp. Histopathological examination showed microinvasive squamous cell carcinoma co-occurring with *Fusarium* spp-induced onychomycosis. Despite prior antibacterial treatments, the fungal infection persisted. Oral terbinafine (100 mg/day) was then prescribed for 2 months as antifungal treatment, but it did not lead to promote recovery. Due to the co-occurrence of squamous cell carcinoma, the affected finger was ultimately amputated [43]. This case illustrates the importance of the One Health concept, as a plant-origin fungal pathogen caused a severe human disease. This emphasizes the need to recognize the interconnectedness of human, animal, and environmental health. Furthermore, this case highlights the need for developing innovative and safer therapeutic agents to address emerging fungal infections.

In 2011, a 21-year-old female patient from Marivan, Iran, presented to Tehran University of Medical Sciences, with a 3-year history of chronic headache, anosmia, nasal obstruction, and mucopurulent nasal discharge. Despite

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prior treatments, including endoscopic nasal surgery and antibiotics (cotrimoxazole, cefixime, and cephalexin), as well as steroid nasal spray, her symptoms persisted. CT scans revealed diffuse and hyperdense materials occupying all sinus cavities. Microscopic examination and tissue culture revealed a *Fusarium* species infection. The patient underwent pan sinus surgery, which involved removal of all mucosal masses and mycelia from the sinuses. A one-year follow-up evaluation showed that the fungal infection had been successfully treated. Molecular testing identified the isolate as *F. proliferatum*, which showed *in vitro* resistance to most antifungals. The patient was successfully treated with functional endoscopic sinus surgery (FESS) [44].

In 2018, a 41-year-old woman with Stage III adrenal cortical carcinoma was admitted to Seyed-al-Shohada Hospital, Isfahan University of Medical Sciences, Iran. She had been receiving cancer treatment since 2014. After developing a high fever, she was treated with gentamicin and vancomycin. Despite treatment, her fever persisted, and two blood samples were collected on days 2 and 3. On day 3, liposomal amphotericin B was added to her treatment, but she showed no improvement. Her CRP level rose to 279, and she died six days after admission due to her worsening condition. Post-mortem analysis detected *Fusarium* growth in both blood cultures, and molecular testing identified *Fusarium solani* as the causative agent of fungemia [45].

Nosratabadi *et al*. (2022) evaluated the *in vitro* antifungal activity of 25 antifungal drugs against a panel of 282 *Fusarium* isolates, including both environmental and clinical isolates. Among the tested antifungals, including commonly used clinical agents, luliconazole and lanoconazole with MICs of 0.004 µg/mL and 0.012 µg/mL, respectively. Efinazole, a novel triazole, showed potent antifungal activity, inhibiting 83.87% of environmental isolates and 68.5% of clinical isolates at ≤ 1 µg/mL. In contrast, the *Fusarium* isolates showed widespread resistance to most of the remaining antifungal drugs, encompassing imidazoles such as sertaconazole, econazole, miconazole, tioconazole, clotrimazole, and ketoconazole [46].

Darazam *et al*. (2022) reported a case of *Fusarium meningoencephalitis* in a 32-year-old woman with a history of rheumatoid arthritis and a previous craniotomy for a colloidal cyst resection. The patient presented with headache and nausea, and brain imaging showed lesions consistent with fungal infection. A right parietal craniotomy was performed, and a biopsy specimen was collected. ITS region sequencing confirmed *F. proliferatum* infection with 99% sequence identity. The patient was treated with intravenous voriconazole, initially at a dose of 400 mg every 12 h on day one, followed by a maintenance dose of 300 mg every 12 h for a period of one month. Notably, this therapeutic regimen resulted in complete resolution of the cerebral lesion by week four, indicating a successful treatment outcome. The patient was discharged and completed an additional 12 weeks of oral voriconazole therapy. At the nine-month follow-up, the patient remained asymptomatic and healthy [47].

A case series from Shahid-Beheshti Hospital in Kashan, Iran, reported three patients with a diagnosis of invasive *Fusarium rhinosinusitis* post COVID-19 infection [32]. The patients, two women and one man aged 61-69 years, had underlying comorbidities and a history of COVID-19. Liposomal amphotericin B treatment was ineffective, leading to surgical intervention and subsequent voriconazole therapy. The identified *Fusarium* species responsible for the infection were *F. solani*, *Fusarium falciforme*, *F. oxysporum*, and *F. proliferatum* [32].

Fusarium species are ubiquitous filamentous fungi, primarily known as plant pathogens, causing substantial economic losses in global agriculture. They thrive in various environments, ranging from tropical and temperate regions. Notably, *Fusarium* species have also emerged as opportunistic human pathogens, especially in individuals with compromised immunity. A significant challenge in treating *Fusarium* infections is their intrinsic resistance to antifungal agents, which varies substantially between and within species complexes. Posaconazole and amphotericin B are commonly used as first-line therapeutic agents, although some isolates may show susceptibility to voriconazole. Surgical debridement of infected tissues is crucial for effective disease management. Despite available antifungal treatments, *Fusarium* infections have high mortality rates, primarily due to the underlying immunocompromised state of susceptible patients [7].

The challenges in treating *Fusarium* infections, combined with their impact on human, animal, and plant health, highlight the pressing need for innovative antifungal approaches. This is consistent with the One Health concept, which emphasizes the interconnectedness of human, animal, and environmental health. Nanotechnology offers a promising solution, with considerable evidence showing that nanoparticles (NPs) exhibit antifungal activity against a wide range of fungal pathogens, including *Fusarium* species.

The following sections will explore the potential of NPs as effective antifungal agents against *Fusarium*, regardless of its source, and discuss how nanotechnology supports the One Health approach.

Rhizopus

Mucormycosis is a rare and serious disease caused by opportunistic fungal infections of the Mucorales order that primarily affects people with weakened immune systems. Although historically rare, mucormycosis has become a significant concern in the context of the COVID-19 pandemic, with an increasing number of cases reported. Several types of mucormycosis have been reported in association with COVID-19 infections,

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including pulmonary, rhino-orbital-cerebral, cutaneous, and gastrointestinal forms. Several factors contribute to the increased susceptibility of COVID-19 patients to mucormycosis, including the immunosuppressive effects of the virus, corticosteroid therapy, and comorbidities like diabetes mellitus. Mucormycosis is a life-threatening complication in immunocompromised patients, especially those with COVID-19 pneumonia [48].

Diabetes mellitus is the most significant risk factor for mucormycosis globally. Ghosh *et al*. (2022) [48] conducted a study analyzing 59 cases of mucormycosis reported worldwide during the second wave of COVID-19, up to May 2021. The cases were geographically distributed, with 25 (42.3%) from India, 10 from the USA, 5 from Iraq, 4 from Bangladesh, 4 from Iran, 2 from Paraguay, and 1 each from Brazil, Mexico, Italy, the UK, China, France, Uruguay, Turkey, and Austria. *Rhizopus* species were predominantly identified as the cause of mucormycosis in both diabetic and non-diabetic COVID-19 patients. In India, the majority of mucormycosis cases following COVID-19 were caused by *Rhizopus oryzae*, *Rhizopus arrhizus*, *Rhizopus microsporus*, and *Rhizopus homothallicus*. These fungal pathogens can infect both immunocompromised and immunocompetent individuals. However, mucormycosis can be especially fatal in patients with compromised immune systems, such as those with cancer, AIDS, or other severe immunosuppressive diseases. Mucormycosis infections can affect multiple body parts, including the central nervous system (CNS), lungs, sinuses, nose, skin, gastrointestinal tract (GIT), joints, heart, and kidneys [49, 50]. The symptoms associated with mucormycosis include headache, cough, fever, shortness of breath, and bloody vomit. In severe cases, mucormycosis may manifest as blackish/bloody nasal discharge, cheekbone and facial pain during swallowing, and black discoloration of the upper nose or palate. Additional symptoms may include skin lesions, diplopia or vision loss, and loosening teeth [48].

The widespread use of systemic glucocorticoids, despite improving COVID-19 patient survival rates, has led to an increased incidence of secondary fungal infections, including mucormycosis. This underscores the urgent need for early detection and prompt treatment of mucormycosis, given its rapid progression [48]. According to the European Confederation of Medical Mycology (ECMM) and Mycoses Study Group Education and Research Consortium (MSGERC) guidelines, the cornerstone of mucormycosis treatment is surgical debridement combined with systemic antifungal therapy. Liposomal amphotericin B oral suspension, posaconazole, and amphotericin B lipid complex are recommended as first-line therapeutic agents, with isavuconazole reserved for salvage therapy. It is important to note that tocilizumab, an immunomodulatory drug used in some COVID-19 patients to prevent thrombus formation associated with elevated D-dimer levels and cross-linked fibrin, has also been linked to an increased risk of mucormycosis [48].

A 2020 case report from the United States described a 56-year-old male with end-stage renal disease undergoing hemodialysis, who was diagnosed with both COVID-19 and mucormycosis. Initially, the patient tested positive for SARS-CoV-2 without showing symptoms, but later developed symptoms that led to hospitalization and treatment with methylprednisone, tocilizumab, and convalescent plasma. When symptoms recurred, accompanied by increased airspace density in both lungs and pleural effusion on chest radiography, empirical intravenous vancomycin and piperacillin-tazobactam therapy was initiated. The patient's sputum sample showed filamentous fungal elements upon direct observation, leading to the initiation of empirical liposomal amphotericin B treatment and the discontinuation of antibacterial drugs. Fungal growth consistent with *Mucorales* group was observed on Sabouraud's dextrose agar medium, and similar findings were seen in the pleural fluid sample. Treatment progressed to include catheter placement and robotic decortication surgery. MALDI-TOF (Matrix-assisted laser desorption ionization time-of-flight) analysis identified the fungal species as *Rhizopus* spp., which was further confirmed as *Rhizopus azygosporus* through ITS and D1/D2 ribosomal DNA region sequencing. MIC testing showed susceptibility to isavuconazole (2 mg/ml), posaconazole (0.25 mg/ml), and liposomal amphotericin B (0.125 µg/ml). Despite antifungal therapy, the patient's condition worsened, requiring re-treatment with intravenous norepinephrine, piperacillin-tazobactam, and empirical intravenous vancomycin. Unfortunately, vancomycin-resistant bacteria were detected in blood cultures, leading to the patient's eventual cardiac arrest and death [51].

Özbek *et al*. (2023) published a systematic review of COVID-19-associated mucormycosis, which analyzed data from 958 cases reported across 45 countries. India had the largest proportion of cases (57%), followed by Iran (11%), Egypt (6%), and then France and Turkey, which both accounted for 3% of cases. The patients' average age was 53 years, with males making up 70% of the cases. The overall mortality rate was 38.9%, with higher rates observed among older individuals (over 65 years). The most common comorbidity was diabetes mellitus, which affected 77.9% of patients, with 5.7% of them developing diabetes after contracting COVID-19. Notably, 84.2% of diabetic patients had uncontrolled or poorly controlled diabetes. Corticosteroids were given to about 78.5% of patients, with dexamethasone being the most common choice (46.6% of the time). However, tocilizumab use was associated with a higher mortality rate compared to other medications. On average, it took 8.2 days for mucormycosis to be diagnosed after symptoms first appeared. The time between symptom onset and diagnosis was significantly longer for patients

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who died (10.6 days) than for those who survived (4.7 days), emphasizing the importance of prompt diagnosis for effective treatment. Posaconazole was the most frequently used antifungal agent among survivors, and the combination of antifungal therapy and surgery resulted in the highest survival rate. *Aspergillus* co-infection occurred in 8.5% of cases and was associated with a higher mortality rate. The primary risk factors linked to higher mortality rates were pulmonary mucormycosis, diabetic ketoacidosis (DKA), and mechanical ventilation related to COVID-19 [52].

Mucormycosis, a life-threatening fungal infection, is increasingly reported globally. Prompt diagnosis is essential due to the aggressive nature of the disease and high mortality risk. A recent systematic review by Salehi *et al*. (2022) analyzed 345 cerebral mucormycosis patients across 47 countries. The study found that 51% of patients had diabetes, while 26.9% had hematologic malignancies. Molecular identification of 133 cases revealed that 65% (87) were classified as *Mucorales*, with *Rhizopus* spp. being the most prevalent species. Specifically, *R. arrhizus* was detected in 31 cases, and *R. microsporus* in 4 [53]. *R. arrhizus* and *R. microsporus* are known to cause cerebral mucormycosis. However, the unique pathogenic characteristics and treatment options for each species are not well understood. Further research is needed to understand the role of these species in mucormycosis development, especially in diabetic patients. Rhinocerebral mucormycosis management is a complex challenge, often requiring a combination of antifungal therapy and surgical intervention [54]. Salehi *et al*. (2022) reported a mortality rate of 60.9% among patients, with 52.8% having diabetes mellitus and 26.8% having hematological malignancies as comorbidities. Surgical debridement was performed in 58% of patients. The following treatments were administered: anti-inflammatory therapy to 11% of patients, posaconazole to 25%, and liposomal amphotericin B and B-deoxycholate to 54%. Combination therapy with posaconazole and liposomal amphotericin B was used in 13% of patients [53]. A case report from Shahid Beheshti Hospital, Kashan, Iran, described a 70-year-old Afghan woman diagnosed with COVID-19, mucormycosis, and lomentospora co-infection who responded well to a combination treatment consisting of surgical debridement, voriconazole and liposomal amphotericin B [55].

Although there may be unreported cases of mucormycosis in Iran, particularly during the COVID-19 pandemic, our analysis relies on available data. The Mycology Department of Pasteur Institute of Iran diagnosed 9 cases of *Fusarium* spp. and 2 cases of *Rhizopus* spp. among patients referred for fungal infection diagnosis between 2017 and 2022 (unpublished data). The significant morbidity and mortality rates associated with mucormycosis, *Fusarium* spp. and *C. auris* infections highlight the importance of early diagnosis, particularly in individuals with compromised immune systems due to underlying diseases. Furthermore, there is a clear need for more effective, efficient, and accessible treatments. This raises the question of whether nanotechnology can offer a solution to address this need. In the following section, we will review the existing literature on this topic.

Nano- Antifungals

The rising prevalence of fungal infections as a significant public health issue has emphasized the need for novel and effective antifungal treatments. Conventional antifungal agents are limited by their suboptimal efficacy, toxicity, and development of resistance, emphasizing the need for alternative strategies. Nanotechnology provides a promising solution through the development of nano-antifungals, which harness the distinctive properties of nanomaterials to optimize drug delivery, bioavailability, and antifungal efficacy. This section examines the state-of-the-art applications of nano-antifungals in addressing emerging and reemerging fungal infections, and their potential to transform the treatment and management of these severe diseases.

Approximately 2 million people worldwide are affected by various fungal infections, resulting in substantial mortality rates [56, 57]. Despite efforts by major pharmaceutical companies such as Merck, Novartis, and Pfizer, the development of effective antifungal treatments has been slow. This is partly due to the eukaryotic nature of fungi, which share similarities with host cells, making it difficult to selectively target fungal cells [58]. Currently, the available systemic antifungal options include echinocandins, polyenes, azoles, and antimetabolites. Echinocandins, such as anidulafungin, caspofungin, and micafungin, are effective against *Candida* and *Aspergillus* infections, although they are only administered intravenously. Polyenes, including amphotericin B and nystatin, have a long history of use and a broad spectrum of activity, with a low incidence of reported resistance. Azoles, such as posaconazole, voriconazole, itraconazole, and fluconazole, are widely used, with voriconazole and posaconazole occasionally used as alternatives to amphotericin B. However, azoles interact with cytochrome P450 substrates and have been linked to resistance in certain *Candida* species [59].

Antimetabolites, nucleic acid analogs, inhibit pyrimidine metabolism and nucleic acid synthesis, demonstrating antifungal activity against *Aspergillus*, *Candida*, and *Cryptococcus* species. However, their use as monotherapy is restricted due to severe adverse effects, including hepatotoxicity and bone marrow suppression. Furthermore, the rapid emergence of resistance requires combination therapy with other drugs. Despite the development of new antifungal agents, significant challenges remain, including antifungal resistance, the emergence of new opportunistic fungi, limited efficacy against certain fungal strains, drug-related adverse effects, challenges in treating biofilms, and decreased fungal

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susceptibility to antifungal drugs due to their overuse in primary healthcare settings [60]. These challenges underscore the need for novel approaches, such as nanotechnology, to improve antifungal efficacy and combat the escalating concern of fungal infections.

Therefore, there is an urgent need for more effective and safer antifungal drugs to combat pathogenic fungi. Novel approaches are being investigated, including the development of analogs of existing compounds, combination therapy to improve antifungal efficacy, identification of new drug targets and mechanisms of action, targeting host-fungal interactions as a therapeutic strategy, and repurposing of existing drugs [61, 62]. Additionally, natural products like lactones, alkaloids, saponins, terpenoids, and proteins and peptides have demonstrated potential as antifungal agents [63, 64]. Nanotechnology has significant potential to transform the management of invasive fungal infections, providing innovative solutions for drug delivery, targeting, and efficacy. Its application in this field is highly anticipated. Notably, nanotechnology has recently made substantial advancements in this field, offering promising solutions for improved treatments of fungal infections. By leveraging nanotechnology, new treatments can be developed, and existing drugs can be reformulated into more efficacious and targeted formulations, leading to improved treatment outcomes [65].

Nanostructures are being investigated as complementary agents to conventional antifungal drugs to improve their effectiveness. For example, research has shown that nystatin-loaded PLGA-glucosamine nanoparticles (NPs) substantially improve the antifungal activity of nystatin against *C. albicans* strains [66]. Ketoconazole-loaded chitosan-gellan gum NPs display enhanced antifungal activity against *Aspergillus niger* compared to NPs or ketoconazole alone [67]. Polyvinylpyrrolidone-coated silver NPs combined with voriconazole and fluconazole successfully eliminate *C. albicans* cells resistant to the latter two drugs, possibly by disrupting cell wall impermeability, efflux pump function, and ergosterol signaling [68]. Additionally, palladium nanosheets coated with silver (Pd@Ag nanosheets) exhibit similar synergistic antifungal activity against *Rhizopus* species, *Aspergillus*, *Candida*, and *Cryptococcus* [69].

Ag nanosheets have been found to exhibit synergistic activity with amphotericin B, resulting in the degradation of intracellular proteins and disruption of energy metabolism, whereas no such synergy was observed with fluconazole [70]. Notably, amphotericin B indicated decreased hemolytic activity at the highest concentration tested. Moreover, the combination of chlorhexidine and nystatin with silver NPs was shown to be highly effective against *C. glabrata* and *C. albicans* biofilms [71]. Also, the co-administration of ZnO NPs with amphotericin or fluconazole enhanced antifungal activity against *Trichophyton mentagrophytes* and *C. neoformans* [72]. Interestingly, ZnO-based NPs were found to induce antioxidative stress in *C. albicans* cells, significantly enhancing the antibiofilm properties of polymethyl methacrylate, which may be beneficial for individuals prone to denture stomatitis.

However, it is crucial to recognize that nanomaterials can also exert toxic effects. Silver nanoparticles (Ag NPs), for example, were found to exhibit cytotoxicity and genotoxicity, possibly due to the disruption of the mitochondrial respiratory chain, resulting in an increase in reactive oxygen species (ROS), impairment of ATP synthesis, and DNA damage [73]. To counteract these toxic effects, researchers have devised a novel approach by coating silver nanoparticles with zinc oxide (Ag@ZnO), which preserves their antifungal efficacy while minimizing their toxicity. Notably, this combination has exhibited efficacy against *C. krusei*, a fungal pathogen renowned for its resistance to fluconazole and amphotericin B in clinical contexts [74, 75].

Nanotechnology can enhance drug delivery to its target site, leading to improved treatment outcomes. A prime example is voriconazole, an antifungal agent with excellent oral bioavailability and broad-spectrum antifungal activity. However, its limited aqueous solubility hinders its use in ocular administration for treating fungal keratitis. To overcome this challenge, researchers have utilized nanotechnology-based approaches to improve voriconazole's solubility and bioavailability. For instance, the addition of 2-hydroxypropyl-β-cyclodextrin (HP-β-CD) augmented voriconazole's solubility, while its incorporation into nanofibers composed of polyvinyl alcohol/hydroxypropyl-β-cyclodextrin (HPβCD) improved its efficacy for ocular administration [76-78]. Other effective formulations include liposomal [79] and oil-water microemulsion [80] delivery systems, as well as lipid-based nanocarriers [81, 82]. Furthermore, pullulan-based nanocapsule suspensions have been designed to improve the properties of tioconazole-based formulations for treating onychomycosis caused by *C. albicans* [83]. Additionally, iron oxide-based magnetic nanoparticles provide the potential for a multifunctional platform that can be utilized for both therapeutic and diagnostic applications [63].

The extensive use of broad-spectrum antibiotics has contributed to the development of multidrug-resistant pathogens (MDR), a major factor in the increasing incidence of nosocomial infections [17, 84, 85]. The growing prevalence of MDR pathogens presents a significant public health concern, leading to increased morbidity and mortality rates. To combat this issue, nanotechnology has emerged as a promising research area. Nanomaterials exhibit distinct properties, including a high surface area-to-volume ratio and small size, allowing them to penetrate biological barriers, such as microbial membranes, with ease. By interacting with the

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bacterial cell wall, nanomaterials can disrupt the cell membrane, either directly or through the production of reactive oxygen species (ROS), ultimately resulting in cell death. Research in nano-antibiotics has mainly concentrated on metal nanoparticles, with silver nanoparticles being the most widely investigated [86, 87].

In addition to nano-silver, several other nanometals have been investigated for their antifungal properties, including nanoparticles of copper, gold, magnesium oxide, titanium dioxide, platinum, silica-coated iron oxide, cesium oxide, aluminum oxide, and zinc oxide [88]. Recently, there has been a growing interest in the application of nanoparticles in microbiology, with an increasing number of studies exploring their potential in this field. Furthermore, several metalloid nanoparticles have been synthesized [89, 90], demonstrating strong antifungal activity [91-93]. To assess the antifungal efficacy of selenium sulfide nanoparticles against various pathogenic and non-pathogenic fungi, an antibiogram assay was performed. The results showed that selenium sulfide nanoparticles effectively inhibited the growth of *A. flavus*, *A. fumigatus*, *Alternaria alternata*, *T. rubrum*, *Microsporum canis*, and *Candida krusei*, with efficacy comparable to that of standard antibiotic disks [91]. The antifungal mechanism of these nanoparticles involves a complex process, comprising: 1) penetration into fungal cells, 2) disruption of the sulfur cycle, 3) modulation of sulfite reductase activity through altered expression of *MET5* and *MET10* genes, and 4) induction of oxidative stress via ROS production [92].

Kim *et al*. (2008) uncovered the mechanism of action of silver nanoparticles (Ag NPs) on *C. albicans*, revealing a complex mechanism of antifungal activity. Transmission electron microscopy (TEM) analysis demonstrated interactions between Ag NPs and the yeast membrane, resulting in significant morphological alterations. Firstly, pit formation occurred on the membrane surface, followed by the formation of pores, ultimately leading to cellular destruction. Flow cytometric analysis revealed that Ag NPs inhibited cell cycle progression of *C. albicans* in the G_2/M phase and also budding by compromising membrane integrity. Furthermore, Ag NPs caused the release of cellular contents from the pores, disrupting lipid bilayer organization of the *C. albicans* membrane. To investigate changes in membrane dynamics after exposure to Ag NPs, the researchers measured the membrane fluidity of the plasma membrane of *C. albicans* cells in the exponential phase using 1,6-diphenyl-1,3,5-hexatriene (DPH) labeling. The results showed a significant decrease in DPH fluorescence anisotropy with increasing Ag NP concentration, compared to amphotericin B. This decrease indicates that DPH, which reacts with the acyl group of the lipid membrane, could not penetrate the membrane, confirming the cell membrane as the site of antifungal effect. Additionally, the researchers examined the release of glucose and trehalose from *C. albicans* cells exposed to Ag NPs, observing the release of these sugars from the cell, further confirming membrane disruption. Notably, trehalose plays a crucial role in maintaining membrane homeostasis under stress conditions such as heat, cold, toxic compounds, water loss, desiccation, and oxidative stress. This study showed that Ag NP exposure led to the release of glucose, trehalose, and possibly other intracellular components from the cell [94].

A study published by Dananjaya *et al*. (2017) investigated the antifungal properties of chitosan nanoparticles (CNPs) and chitosan and silver nanocomposite (CAgNCs) against *F. oxysporum* species *in vitro* and *in vivo*. Both CNPs and CAgNCs induced membrane disruption, resulting in fungal cell death. Additionally, the study examined the gene expression of several target genes in *F. oxysporum*, including beta 1-3 glucanosyltransferase (*GEL2*), chitin synthesis gene (*CH14*), and cytochrome P450 lanosterol (*CYP-51-2*). The antifungal activity of CNPs and CAgNCs is attributed to the electrostatic interaction between positively charged chitosan and negatively charged fungal cell wall components. Chitosan may penetrate the fungal cell and interfere with DNA function, inhibiting mRNA and protein synthesis. Treatment with CNPs and CAgNCs led to significant downregulation of *GEL2*, *CH14*, and *CYP-51-2* genes, essential for cell wall biogenesis. This implies that CNPs and CAgNCs may exert their antifungal activity by disrupting ergosterol biosynthesis, similar to the mode of action of azole antifungals. Alternatively, chitosan may sequester essential metal ions, inhibiting fungal growth, due to its high metal-binding capacity and ability to chelate metal cations through its amine groups [95].

Sardella *et al*. (2017) evaluated the antifungal activity of zinc oxide nanoparticles (ZnO NPs) against four fungal species: *Rhizopus stolonifer*, *A. alternata*, *Penicillium expansum*, and *Botrytis cinerea*. The results indicated that ZnO NPs exhibited antifungal activity at concentrations above 60 mM. To investigate the antifungal mechanism of ZnO NPs, the researchers added EDTA, a metal chelator, to the fungal culture medium. The addition of EDTA diminished the antifungal activity of ZnO NPs, indicating that metal ions are essential for their antifungal properties. EDTA alone showed a moderate antifungal activity, possibly due to its capacity to form stable complexes with divalent metal ions. At a pH range of 6.6-7.7, zinc species are in equilibrium as Zn^{2+}(aq), $ZnO(OH)^{+}$(aq), and $Zn(OH)_2$(s), suggesting that ZnO NPs serve as a source of antimicrobial Zn^{2+} ions, which possess antimicrobial properties. This study emphasizes the crucial role of metal ions in the antifungal activity of metal nanoparticles. Furthermore, the presence of EDTA in the environment may influence the efficacy of these NPs [96].

Kumari *et al*. (2019) conducted a comparative study on the antifungal properties of silver nanoparticles (Ag NPs) synthesized through biological and chemical methods.

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Their results showed that biologically synthesized Ag NPs demonstrated superior antifungal activity, marked by enhanced fungal cell death and growth inhibition, compared to their chemically synthesized counterparts, highlighting the potential benefits of biological synthesis approaches in antifungal therapy. Further studies revealed that biological Ag NPs mediated their antifungal effects through ROS generation, disruption of osmotic balance and cell membrane integrity, suppression of the antioxidant system, and inhibition of oxidative enzymes [97].

Lengert *et al*. (2020) conducted a comprehensive review on the application of nanotechnology in enhancing the penetration and transdermal delivery of antifungal drugs. Their results demonstrated that nanoparticles with a size range of 300-600 nm showed optimal penetration into hair follicles and prolonged retention in the stratum corneum. Nanoparticles can act as effective carrier systems, facilitating controlled release and improved bioavailability of antifungal drugs. Notable examples of such carriers include lipid-based particles and nanoemulsions, as referenced in [98].

Nanotechnology against *C. auris*

The inadequate efficacy of traditional antifungal treatments against *C. auris* underscores the pressing need for novel approaches to combat this highly virulent fungus. Nanotechnology, with its potential to transform drug delivery, diagnostics, and antimicrobial approaches, presents promising solutions to address the challenges posed by *C. auris* and other emerging fungal pathogens.

Pierce *et al*. (2017) showed that AgNP-functionalized silicon elastomer (a medical surface) and bandage fiber (an environmental surface) effectively inhibited *C. auris* biofilm formation. The spherical AgNPs, produced using an irradiation-assisted heating method, measured between 1 and 3 nm in size on average. The researchers assessed the antibiofilm activity of the NPs against *C. auris* using an in-house developed 96-well microtiter plate model. They examined the effectiveness of AgNPs in preventing *C. auris* biofilm formation and disrupting established biofilms. The results revealed a dose-dependent inhibitory effect, with IC_{50} values of 60 ng/mL for biofilm formation and 480 ng/mL for disrupting pre-existing biofilms. Scanning electron microscopy (SEM) analysis following 24 h of incubation revealed substantial morphological changes in the cells, characterized by a shift from a smooth to a rough surface appearance, suggesting the NPs' robust antibiofilm activity. This finding indicated that AgNPs caused substantial ultrastructural changes in *C. auris* cells, leading to cell wall disruption, distortion, and damage [99].

Catheter-associated fungemia significantly contributes to mortality rates, primarily due to *Candida* biofilm formation on catheters. These infections frequently display resistance to traditional candidiasis therapies. In this context, the development of biofilm inhibitors offers a promising strategy for preventing biofilm formation and potentially improving patient outcomes. Moreover, the researchers investigated the potential of AgNPs-functionalized catheter surfaces to prevent *C. auris* biofilm formation. In this study, the researchers treated silicone elastomers with different concentrations of AgNPs and then exposed them to *C. auris* cells. The effectiveness of the functionalization was verified using SEM and energy-dispersive spectroscopy (EDS) analyses. The AgNPs-functionalized elastomer showed a significant, dose-dependent inhibition of biofilm formation, with an IC_{50} value between 2.3 and 0.28 ppm, compared to the control group. Electron microscopy analysis supported these results, providing further evidence. *C. auris*'s ability to persist on various surfaces contributes to its rapid spread and emergence as an opportunistic pathogen, posing a substantial threat to healthcare environments [100, 101].

In this study, the researchers explored the potential of AgNPs loaded onto bandage wrap dressings, a common hospital surface, to prevent C. *auris* biofilm formation. The researchers found that loading AgNPs onto bandage wrap dressings at concentrations between 2.3 and 0.017 ppm inhibited biofilm formation by over 80%, and at concentrations between 0.008 and 0.002 ppm, *C. auris* growth was inhibited by over 50% [86].

Research has shown that bismuth nanoparticles (BiNPs) have antifungal properties effective against *C. auris*. Vazquez-Munoz *et al*. (2020) researched the anticandidal properties of BiNPs on *C. auris* strains, focusing on its effects on biofilm and planktonic growth. The researchers also studied how BiNPs affected *C. auris* cell morphology and biofilm construction after treatment, gaining valuable knowledge about how BiNPs combat fungal infections. The researchers performed a susceptibility test to determine the effectiveness of BiNPs against *C. auris* under planktonic growth conditions. The MIC values ranged from 1-4 µg/mL across *C. auris* strains. *C. auris*. The researchers used an XTT assay to determine the effectiveness of BiNPs against *C. auris* biofilm formation. BiNPs inhibited *C. auris* biofilm formation, with IC_{50} values ranging from 5.1-113.1 µg/mL. The researchers used SEM analysis to study how BiNPs affected *C. auris* cell morphology and biofilm structure by comparing treated and untreated samples. The results showed that BiNPs treatment led to a reduction in biofilm formation in some *C. auris* strains, accompanied by alterations in cell size and shape, compared to untreated controls [102].

To improve the antimicrobial properties of surface coatings, researchers created AgNP cluster coatings on copper surfaces using a single-step electrochemical synthesis, followed by a salinization step to produce hydrophobic AgNP clusters and reduce surface corrosion. The resulting nanoparticles were less than 100 nm in diameter, and the clusters ranged from 70 nm to 1200 nm in size, with an average size of around 350 nm per cluster

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and a 1:14 aspect ratio (length to width). After 24 h, the growth of *Escherichia coli* and *C. auris* was significantly inhibited, with a 75% reduction for *E. coli* and a 98% reduction for *C. auris*. After 7 days, the viability of *E. coli* and *C. auris* cells decreased by over 90%, while copper surfaces without AgNPs showed minimal killing activity against both microorganisms [103].

Vazquez-Munoz *et al*. (2020) demonstrated that AgNPs exhibit robust antifungal activity against *C. auris* strains, effective across all stages of fungal growth, highlighting the potential of AgNPs as a therapeutic agent against this emerging pathogen. The researchers found that AgNPs effectively inhibit both planktonic (IC_{50} < 2 µg/mL) and biofilm-forming (IC_{50}: 1.2-0.2 µg/mL) *C. auris* cells. SEM analysis showed that AgNP treatment significantly reduced the surface area covered by *C. auris* yeast cells during biofilm formation, accompanied by a marked decrease in cell clustering (Fig. 1). Moreover, exposure to AgNPs at inhibitory concentrations damaged the cellular structure, resulting in changes to cell size and shape [104].

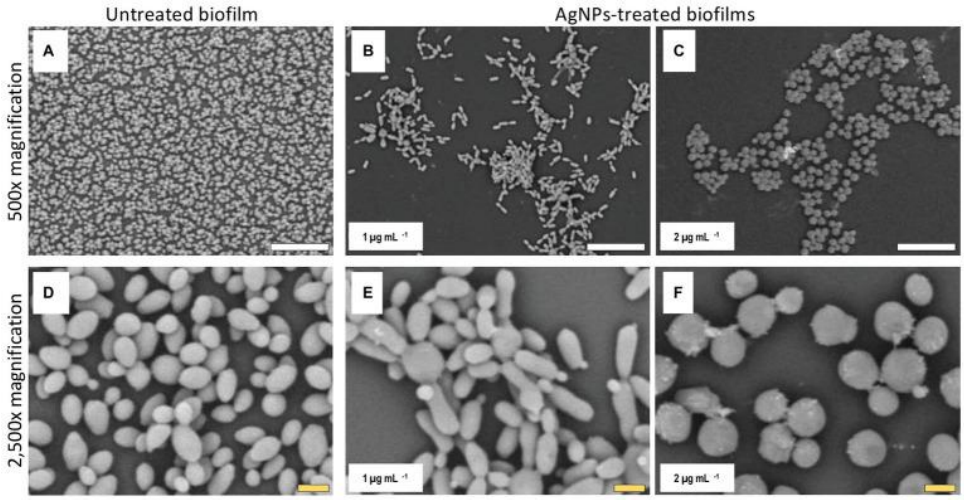

Fig. 1. Biofilms of *C. auris* strain #0386 were treated with AgNPs. SEM images show that biofilm structure and cell morphology were greatly affected by AgNPs. Compared to untreated biofilms (A), treated biofilms (B,C) show a significant reduction in covered area, whereas compared to cells in untreated biofilms (D), cell morphology is changed by treatment with AgNPs (E, F). Scale bar: White = 20 µm, yellow = 2 µm. Retrieved from [104], used under the Creative Commons CC-BY license version 4.0.

Kamli *et al*. (2021) evaluated the fungicidal activity of Ag-Cu-Co trimetallic nanoparticles (NPs) synthesized using *Salvia officinalis* extract as a reducing agent. This eco-friendly synthesis method produced Ag-Cu-Co NPs from Ag^{+}, Cu^{2+}, and Co^{2+} ions, which showed potent fungicidal activity against *C. auris*. The Ag-Cu-Co trimetallic NPs showed potent antifungal activity against clinical *C. auris* strains, with a MIC of 0.39-0.78 µg/mL and an MFC of 0.78-1.56 µg/mL. Further research into the anti-*Candida* mechanism revealed that trimetallic NP treatment significantly reduced mitochondrial membrane potential in treated cells compared to control cells, indicating disrupted cellular metabolism and contributing to antifungal activity. The Ag-Cu-Co trimetallic NPs demonstrated antifungal activity and induced apoptosis in *C. auris* cells, leading to programmed cell death. Moreover, Ag-Cu-Co NPs halted the cell cycle at the G_2/M phase, preventing additional cell division. Toxicity tests showed that Ag-Cu-Co trimetallic NPs had no hemolytic activity at sub-inhibitory and inhibitory concentrations. However, at higher concentrations, hemolysis occurred, with a maximum hemolysis of 11.73% [105].

Kamli *et al*. (2021) synthesized bimetallic silver-iron (Ag-Fe) NPs using an aqueous extract of *Beta vulgaris* L., which induced apoptosis and cell cycle arrest in *C. auris*, resulting in antifungal activity. This eco-friendly synthesis method utilized a plant-based reducing agent to produce Ag-Fe NPs, providing a promising strategy for controlling *C. auris* infections. The spherical Ag-Fe NPs (average size: 14.30 ± 2.20 nm) showed potent antifungal activity against *C. auris*, with a MIC of 0.19-0.39 µg/mL and an MFC of 0.39-0.78 µg/mL. The Ag-Fe NPs induced apoptosis in *C. auris* cells, leading to programmed cell death, and halted the cell cycle at the G_2/M phase, preventing further cell division and growth. Simultaneously, an increase in antioxidant enzyme activity was observed, including GPx, catalase, SOD, GLR, and GST. These enzymes are essential for primary and secondary oxidative defense mechanisms. Furthermore, toxicity tests showed that Ag-Fe NPs had no hemolytic activity against horse erythrocytes, even at concentrations twice the MIC, indicating minimal toxicity [106].

Hetta *et al*. (2023) published an article in which they examined the potential of nanotechnology as a strategy to combat *C. auris* infections and explored the underlying mechanisms contributing to MDR in *C. auris*. The article reports that around 29.44% of *C. auris* cases exhibit resistance to fluconazole, the most widely used azole

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antifungal. Furthermore, resistance was observed in 15.46% of cases to amphotericin B, 12.67% to voriconazole, 3.48% to caspofungin, and 1.95% to flucytosine. *C. auris* develops resistance to azole antifungals due to point mutations in the ERG11 gene, which codes for the lanosterol 14α-demethylase enzyme. These mutations prevent azoles from binding to their target, resulting in resistance. Additionally, *C. auris* develops resistance to amphotericin B through *ERG11* gene mutations and disruptions in ergosterol biosynthesis, resulting in altered membrane ergosterol content and decreased susceptibility to amphotericin B [107].

C. auris has developed mechanisms to evade antifungal therapy by overexpressing the *CDR1* and *MDR1* genes, which encode drug efflux pumps, specifically the ABC and MFS types. These efflux pumps decrease the intracellular concentration of antifungals, leading to resistance. Furthermore, the *FKS1* gene encodes the catalytic subunit of β-1,3-glucan synthase, a key enzyme responsible for synthesizing β-1,3-glucan, a main component of the fungal cell wall [107].

C. auris develops resistance to echinocandins through *FKS1* gene mutations, resulting in amino acid substitutions that decrease susceptibility to these antifungals. Furthermore, *C. auris* develops resistance to 5-flucytosine (5-FC) through *FUR1* gene mutations, leading to the substitution of isoleucine for phenylalanine at a critical site, disrupting 5-FC metabolism and impairing its cellular uptake and activation [107].

C. auris forms biofilms, which enhances fungal cell resistance and virulence, and increases the expression of multidrug efflux pumps (MFS and ABC transporters) by 2- to 4-fold. Considering *C. auris*'s alarming antifungal resistance profile and high mortality rates, it is crucial to develop innovative strategies to combat this fungal pathogen [107].

The precise mechanism of action of NPs on *C. auris* cells remains unknown. However, NPs' mechanisms of action vary depending on their physical and chemical properties, including shape, size, surface functional groups, and elemental composition. These properties influence NP-cell interactions, leading to various physiological responses [107]. Further research is needed to determine the specific mechanisms of NP-*C. auris* cell interactions.

NPs are thought to exert antifungal effects by creating pores in the fungal cell wall, disrupting membrane permeability. This allows additional NPs to enter, generating and accumulating ROS inside the cell. As a result, the cell undergoes apoptotic death. Additionally, NPs can disrupt intracellular signaling by inhibiting enzymes, disrupting the electron transport chain, inducing lipid peroxidation, and modifying proteins, ultimately leading to fungal cell death [107].

Nanotechnology against *Fusarium* spp.

The increasing incidence of *Fusarium* infections, particularly in immunocompromised individuals, coupled with the growing resistance to conventional antifungal therapies, underscores the need for novel and effective control strategies. Nanotechnology offers a promising solution to combat *Fusarium* infections and mitigate their impact on agricultural productivity and human health, by enhancing drug delivery, improving diagnostic accuracy, and developing innovative antimicrobial approaches**.**

Kasprowicz *et al*. (2010) synthesized silver NPs using the high-voltage arc discharge technique and investigated their effect on the growth and sporulation of *F. culmorum*. Silver NPs at concentrations of 0.12-10 ppm were mixed with $5x10^6$ fungal spores/mL in water. Controls consisted of spores without silver NPs. Samples were inoculated on PDA medium for 2 and 24 h. Three NP concentrations (0.12, 1.25, and 2.5 ppm) were selected and cultured on three media: nutrient-free agar, nutrient-poor PDA (2 g/L potato extract, 10 g/L D-glucose), and standard PDA (4 g/L potato extract, 20 g/L D-glucose). Mycelium growth was observed after 30 h, and it entered the logarithmic phase after 89 h. Spore formation was examined after 2 and 24 h of incubation with silver NPs (0.12-2.5 ppm) on PDA and nutrient-poor PDA media. The culture medium (50 mm diameter) was cut, added to flasks with distilled water, shaken, filtered, and the spore count was determined using a Bürker's chamber hemocytometer. Silver NPs at 5-10 ppm significantly inhibited mycelial growth from spores, compared to lower concentrations. Exposure to silver NPs led to increased spore production in mycelia, whereas 2.5 ppm NPs significantly inhibited spore germination. The observed slower germination, heavy sporulation, and shorter sprouts suggested that NPs induced stress responses in fungal spore formation and germination [108].

The antifungal activity of various carbon nanomaterials (CNMs), including multi-walled carbon nanotubes (MWCNTs), single-walled carbon nanotubes (SWCNTs), graphene oxide (GO), reduced graphene oxide (rGO), activated carbon (AC), and fullerene (C_{60}), was investigated against the plant pathogenic fungi *Fusarium poae* and *F. graminearum*. To evaluate the impact of CNMs on mycelial growth, various concentrations (62.5-500 µg/mL) of CNMs were incorporated into solid PDA medium, and the growth of *F. graminearum* and *F. poae* was assessed at 24 and 72 h. Additionally, the dry weight of the fungi was measured after washing and drying at 70°C. To evaluate the impact of CNMs on spore germination, spore suspensions (10^5 spores/mL) were mixed with CNMs at various concentrations (62.5-500 µg/mL), and the germination rate was assessed using a Leica microscope and digital camera after 5-10 h of incubation in darkness. The results revealed a dose-dependent reduction in biomass weight and spore germination with increasing CNM concentrations, possibly attributed to diminished hyphal branching and

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direct interaction between CNMs and spores. The antifungal efficacy of GO, rGO, SWCNTs, and MWCNTs was higher than that of AC and C_{60}, possibly due to differences in dispersity and van der Waals forces. Furthermore, CNM exposure reduced spore moisture and water absorption, resulting in plasmolysis, which could be an additional mechanism underlying the antifungal activity of CNMs [109].

Copper nanoparticles (Cu NPs) were synthesized via a chemical reduction method at room temperature, using copper nitrate and trimethylammonium bromide as precursors. The antifungal activity of the Cu NPs was assessed against *Fusarium equiseti* and *F. oxysporum* following the CLSI M38-A standard protocol. The results revealed that Cu NPs demonstrated excellent antifungal activity against both *Fusarium equiseti* and *F. oxysporum* [110].

Spherical Cu NPs with a diameter ranging from 20-50 nm were synthesized using a combination of cetyl trimethyl ammonium bromide (CTAB) and ascorbic acid as reducing agents at 80°C. The antifungal activity of these NPs was assessed against *Fusarium* spp. isolates from dragon fruit and tomato. In solid culture medium, a concentration-dependent reduction in colony diameter was observed with increasing NP concentrations. The maximum antifungal activity was achieved at 450 ppm after 9 days of incubation, highlighting the potential of Cu NPs as an effective antifungal agent against *Fusarium* spp. [111].

The antifungal activities of chitosan NPs (CNPs) with a size range of 15-30 nm and chitosan silver nanocomposites (CAgNCs) with a size range of 2-18 nm were investigated against *F. oxysporum*. The antifungal activities of chitosan NPs (CNPs) with a size range of 15-30 nm and chitosan silver nanocomposites (CAgNCs) with a size range of 2-18 nm were investigated against *F. oxysporum*. The minimum inhibitory concentrations (MICs) in PDB medium were 100 µg/mL for CAgNCs, 400 µg/mL for CNPs, and 600 µg/mL for chitosan, respectively. The antifungal activities of CNPs and CAgNCs were concentration-dependent, with CAgNCs showing greater growth inhibition of *F. oxysporum* than CNPs in PDB medium. Light microscopy revealed that CNPs and CAgNCs treatment caused morphological changes in the mycelium, characterized by large vesicle accumulation, membrane damage, and mycelial surface disruption, resulting in increased permeability and disintegration. The cell wall damage and altered membrane permeability led to growth inhibition and death of *F. oxysporum* mycelium. Moreover, CNPs and CAgNCs exposure significantly increased ROS production, likely the primary mechanism underlying growth inhibition and death. Additionally, treatment with a paste of CAgNCs and CNPs reduced cumulative mortality in *F. oxysporum*-infected zebrafish by 29-44% compared to the control group [95].

A recent study nanoencapsulated two strains of *Pseudomonas fluorescens* (VUPF5 and T17-4), a biocontrol bacteria, in alginate-gelatin nanocomposite beads. These nanocomposite beads were then evaluated *in vivo* against *F. solani*, a common causative agent of potato disease. The results showed that injection of these nanocomposite beads into potatoes resulted in a significant reduction in disease severity, with an efficacy of 87-91%, and also promoted plant growth [112].

Spherical AgNPs with a size range of 12-46 nm were synthesized using the aqueous extract of *Melia azedarach* leaves via a green method. The antifungal activity of these AgNPs against *F. oxysporum*, a common causative agent of tomato wilt, was evaluated. *In vitro* experiments showed that the AgNPs inhibited fungal mycelial growth by 79-98%. *In vivo* experiments indicated a significant increase in growth parameters and antioxidant enzyme activity in AgNP-treated plants compared to untreated plants infected with *F. oxysporum*. The AgNPs disrupted the cell membrane of the fungal mycelium, leading to changes in permeability and physiological conditions, resulting in the production of ROS in *F. oxysporum* [113].

The antifungal efficacy of a combination of rGO nanosheets and copper oxide (CuO) nanoparticles (rGO-CuO NPs) was investigated against *F. oxysporum in vitro* and *in vivo* on tomato and pepper plants to control *Fusarium* wilt and root rot diseases. CuO NPs of three sizes (5, 20, and 50 nm) were synthesized and then deposited onto rGO sheets using an ammonia reductant solution. High-resolution scanning electron microscopy (HR-SEM) revealed aggregates of rGO-CuO NPs on the outer surface of fungal cells in all tested isolates after exposure to 1 mg/mL of the 5-nm structures (Fig. 2). Transmission electron microscopy (TEM) analysis showed that the nanocomposites penetrated the cell wall and membrane, entering the intracellular space and interacting with cellular components, likely due to alterations in cell permeability. The nanocomposites significantly reduced the symptoms of *Fusarium* wilt and root rot diseases in tomato and pepper plants compared to control samples, with no significant difference observed between treatments using 1 or 100 mg/L of rGO-CuO NPs. did not exhibit any significant phytotoxic effects at any of the concentrations evaluated, suggesting a high degree of biocompatibility and potential for safe environmental application [114].

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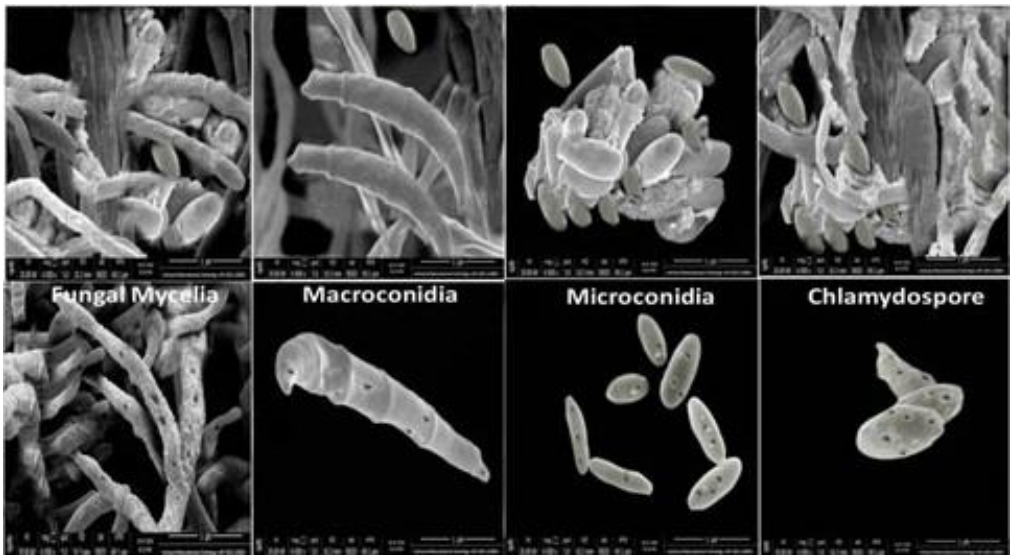

Fig. 2. Effect of rGO-CuO NPs at a concentration of 1 mg/L on *F. oxysporum* f. sp. *lycopersici* (FOL). SEM images of H_2O-treated (top) and NP-treated (bottom) fungi. Retrieved from [113], used under the Creative Commons CC-BY license version 4.0.

Mesoporous silica nanoparticles (MSNs) have been employed as delivery systems for pesticides, enhancing their solubility and absorption. In a recent study, MSNs were loaded with 10% fludioxonil fungicide and surface-functionalized with chitosan (CS) to control *Fusarium* crown and root rot in tomatoes. The negatively charged MSNs were coated with positively charged chitosan molecules, resulting in an impressive 84% efficacy, significantly higher than the 20% efficacy of uncoated particles. The drug loading did not increase the particle size, as most drug molecules were encapsulated within the mesoporous structure of the MSNs. Furthermore, chitosan-coated MSNs exhibited antifungal activity at half the dose required for the free drug, highlighting the potential of this delivery system for enhanced fungicide efficacy [115].

Nanotechnology against *Rhizopus* spp.

The rapid emergence of *Rhizopus* spp. as significant pathogens has been fueled by factors such as climate change, global trade, and the increasing vulnerability of immunocompromised populations. As conventional methods of control and treatment face limitations, nanotechnology presents a promising approach for innovation, offering potential solutions for targeted, efficient, and sustainable prevention and treatment of *Rhizopus* spp. infections, and mitigating the devastating impact of these fungi on human health and food security.

The antifungal efficacy of magnesium oxide (MgO) NPs with an average particle size of 50 ± 10 nm and ZnONPs with an average particle size of 30 ± 10 nm was investigated against *R. stolonifer*. The NPs exhibited a concentration-dependent inhibitory effect on fungal spore germination, with increasing concentrations resulting in greater inhibition. Notably, MgO NPs showed significantly higher inhibitory activity compared to ZnONPs [116].

A rapid and eco-friendly method was employed to synthesize AgNPs using *Aloe vera* plant extract, yielding nanoparticles with various shapes (spherical, rectangular, and triangular). AgNPs at a concentration of 1M showed the highest inhibitory effect on *Rhizopus* spp. growth. The antifungal efficacy of AgNPs is influenced by both the specific fungal species and nanoparticle size. Furthermore, this antifungal activity is closely linked to the formation of pits in the fungal cell wall. AgNPs exert their antifungal effect by targeting fungal cell membranes, disrupting membrane potential, and ultimately leading to deformations in cell membrane structure and impairment of membrane integrity. Microscopic examination revealed that the produced NPs affected both fungal hyphae and conidial germination, causing alterations in the normal budding process of *Rhizopus* spp. [117].

A nanoemulsion with a particle size of 115.3 ± 3.97 nm was formulated from cinnamon essential oil (*Cinnamon zeylanicum* L.) and its antifungal efficacy was evaluated against *R. stolonifer* in strawberry fruit, in comparison to the extract emulsion. *In vitro* assays on PDA medium showed that the nanoemulsion exhibited superior inhibitory effects compared to the extract emulsion at similar concentrations, with antifungal activity increasing in a concentration-dependent manner. Furthermore, the results of the strawberry gray mold assays after 10 days of storage in the dark at 25ºC revealed that the nanoemulsion was more effective than the extract emulsion, with efficacy increasing in a concentration-dependent manner. While both cinnamon essential oil emulsion and nanoemulsion showed minimal improvement in strawberry soft rot after 5 days of storage at 25°C at their lowest concentrations, the highest concentration of cinnamon essential oil nanoemulsion exhibited

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significantly enhanced efficacy compared to the cinnamon essential oil emulsion [118].

The antifungal efficacy of ZnO NPs with a size of 18.2 ± 6.3 nm was investigated *in vitro* and *in vivo* against *R. stolonifer*-induced soft rot of sweet potato. ZnO NPs exhibited inhibitory effects on fungal growth at concentrations above 50 ppm, whereas bulk ZnO showed no antifungal activity against *R. stolonifer*. In the *in vivo* study, potato tubers were treated with ZnO and ZnO NP solutions, and the resulting fungal cell populations were enumerated. The tubers treated with ZnO NPs had the lowest fungal population, with a layer of ZnO NPs forming on the tuber surface, exhibiting antifungal activity. Furthermore, ZnO NP treatment prevented decay and rotting of infected tubers. The antifungal mechanism of ZnO NPs involved the production of ROS, leading to cell death through interactions with cellular components, ultimately resulting in fungal growth inhibition. Additionally, ZnO NP-treated tubers showed reduced weight loss during 15 days of storage, compared to control samples. Furthermore, the activity levels of cellulose and α-amylase enzymes, the primary wall-degrading enzymes produced by *R. stolonifer*, were comparable to those in healthy plants in tubers pretreated with ZnO NPs. The substantial antifungal impact of green-synthesized ZnO NPs against *R. stolonifer* is attributed to protein leakage, leading to cell membrane damage [119].

Silver nanoparticles (AgNPs) synthesized from the aqueous extract of *Pongamia glabra* vent (Fabaceae) demonstrated antifungal efficacy against *Rhizopus nigricans* in *in vitro* studies [120].

The antifungal efficacy of three nanomaterials, CuO, titanium dioxide (TiO_2), and C_{60}, against *R. stolonifer*, the causative agent of soft rot disease in sweet potatoes, was evaluated. The results revealed that CuO nanomaterial exhibited the highest antifungal activity at a concentration of 50 mg/L, followed by TiO_2 nanomaterial. Furthermore, CuO and C60 nanomaterials exhibited antioxidant properties [121]. Further research is necessary to understand the underlying mechanism of the potent fungicidal properties of CuO nanomaterials. One possible explanation is the generation of Cu^{2+} ions, which may disrupt the growth and metabolism of *R. stolonifer*, resulting in the inhibition of fungal growth and reproduction [121].

AgNPs synthesized via a green method using coriander leaf extract exhibited potent antifungal activity against *R. stolonifer*, completely inhibiting growth at a concentration of 1 mg/mL. The antifungal activity of AgNPs is attributed to multiple mechanisms that disrupt fungal cell viability and ultimately lead to cell death. AgNPs aggregate around the cell membrane, generating ROS that inactivate cellular enzymes responsible for substance exchange across the membrane, resulting in cell dehydration and nutrient loss. Furthermore, the release of silver ions (Ag^+) from AgNPs is another key mechanism contributing to their antifungal properties. Notably, the cytotoxicity of AgNPs decreases in alkaline pH environments, which is consistent with the fact that most cells contain sulfur and phosphorus, weak bases found in ribonucleic acid (RNA). The action of Ag^+ ions released by AgNPs can alter these components, causing malfunctions and ultimately leading to cell death through apoptosis [122].

When considering the application of NPs in agriculture, particularly for crop protection, several limitations and challenges must be acknowledged. Although NPs offer potential benefits, practical constraints can limit the feasibility and widespread adoption of NP-based solutions. The production and application of NPs can be costly, posing significant economic challenges for farmers, particularly those in resource-constrained settings. The high costs associated with manufacturing, integrating NPs into agricultural practices, and scaling up production to ensure affordability are significant barriers to widespread adoption.

The successful implementation of NP-based solutions in large-scale agricultural practices is hindered by scalability issues. Developing scalable methods that maintain efficiency is crucial for widespread adoption. A significant challenge lies in ensuring that NP-based technologies are versatile and adaptable to various crops and farming systems. Although NPs offer potential benefits in crop protection, their environmental impact must be carefully considered and addressed. The long-term effects of NP accumulation in soil and water require thorough investigation, and potential unintended consequences on non-target organisms and ecosystems must be carefully considered to prevent ecological imbalances and ensure environmental sustainability.

The regulatory framework governing the use of NPs in agriculture is still in development. Establishing clear guidelines and regulations is crucial to ensure the safety of the environment, human health, and animal health, aligning with the One Health approach. Compliance with regulatory requirements poses an additional challenge to the adoption of NP-based solutions in agriculture. Significant knowledge gaps exist regarding the interactions between NPs and plants, soil, and other environmental components. Ongoing research is necessary to understand the long-term effects, optimal application methods, and potential risks associated with NP use in agriculture, as well as to address the existing knowledge gaps. Addressing these limitations and challenges requires collaborative efforts and interdisciplinary approaches involving scientists, policymakers, and agricultural practitioners. Overcoming these barriers is crucial for the sustainable and responsible integration of NPs into agriculture, enabling effective crop protection and harnessing their full potential.

The potential harm of NPs to organisms is closely linked to their accumulation, which occurs through aggregation of naturally occurring NPs over time and persistence of manufactured NPs due to surfactants and

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stabilizers. Microorganisms absorb NPs through their cell surface, while in more complex organisms like humans, absorption occurs through multiple routes, including respiratory, gastrointestinal, and skin exposure. The method of NP entry is influenced by organism characteristics; for example, the cylindrical shape of carbon nanotubes enables easy penetration into the human body through the pulmonary epithelium, leading to toxicity. Prokaryotes, lacking particle transfer mechanisms in their cell wall, are relatively resistant to NP uptake. In contrast, eukaryotes, with absorption pathways such as endocytosis and phagocytosis, are more susceptible to NP toxicity. The parameters influencing NP absorption include size, absorption-aiding components (such as glycoproteins and polysaccharides), membrane modifications, and environmental factors like pH variations, which affect NP uptake and toxicity. Plants play a crucial role in the study of environmental impacts, serving as a key interface between various environmental compartments containing NPs, including soil, water, and air. Their significance in the food chain highlights their role in transporting NPs to animals and humans. NP absorption in plants occurs through various parts, including leaves, flower surfaces, roots, and damaged areas. Toxicity studies, particularly on plants intended for human consumption like corn, wheat, or soy, often focus on critical parameters such as seed germination, root growth, or nitrogen fixation [123].

CONCLUSION

The rise of emerging and re-emerging fungal infections, exacerbated by factors like increased immunosuppression and climate change, necessitates innovative strategies to combat these threats. Nanotechnology offers promising solutions for combating fungal infections, including *C. auris*, *Fusarium*, and *Rhizopus*. Various NPs have shown inhibitory effects on biofilm formation, growth, and sporulation of these fungal pathogens. However, nanotechnology also poses several challenges that must be addressed, including biocompatibility and toxicity concerns, stability and agglomeration issues, size and shape dependencies, potential development of resistance, environmental impact, regulatory approval and standardization, cost and scalability, and ethical considerations. To fully harness the potential of nanotechnology in antifungal treatments, a multidisciplinary approach that integrates robust research, thorough risk assessments, and responsible deployment is crucial.

Future research priorities include elucidating mechanisms of NP antifungal action and synergies, studying NP-fungus interactions and impact of NP properties, comprehensive long-term toxicity assessments, investigating resistance mechanisms and strategies, optimizing NP characteristics for specific fungal targets, conducting *in vivo* studies and clinical trials, establishing standardized testing protocols, enhancing cost-effectiveness and scalability, and addressing ethical considerations and patient engagement. By addressing these priorities, the field can advance the understanding of NP mechanisms, safety, and clinical implementation of NP-based antifungal therapies, contributing to the global effort in managing evolving fungal health threats.

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CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest associated with this manuscript.

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