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Review Article

Applications of Nanotechnology in Combating Fungal Diseases in Humans: An Updated Review

Anmar Saad Khalaf Hameed Al-Akidi[1*]

[1]Ministry of Higher Education and Scientific Research, Department of Medical Laboratory Technology, Imam Ja'afar Al-Sadiq University, Kirkuk, Iraq

***Corresponding Author:** Anmar Saad Khalaf Hameed Al-Akidi
Ministry of Higher Education and Scientific Research, Department of Medical Laboratory Technology, Imam Ja'afar Al-Sadiq University, Kirkuk, Iraq

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Abstract: In recent years, fungal infections caused by filamentous fungi have posed a serious threat to public health worldwide. Fungi such as Aspergillus, Coccidioides, and Mucorales (the most common filamentous fungi), as well as Candida auris (a non-filamentous fungus), can cause infections in humans. It can cause serious life-threatening diseases in individuals with weakened immune systems, patients infected with HIV/AIDS, uncontrolled diabetes, blood disorders, organ transplants, and chemotherapy. In this review, we describe the available nan formulations (metallic and polymeric nanoparticles) that have been developed to enhance efficacy and reduce the number of adverse effects following the administration of conventional antifungals. The burden posed by fungal infections on human health is increasing worldwide. Fungi such as Aspergillus, Candida, and Cryptococcus are among the most common pathogens responsible for human diseases, accounting for over 90% of infection-related deaths. Moreover, effective antifungal treatments are not available, primarily due to host toxicity, pathogen resistance, and immunodeficiency. In recent years, nanomaterials have proven to be not only more efficient antifungal therapeutic agents but also capable of overcoming fungal drug resistance".

Keywords: Fungal Diseases, Silver Nanoparticles, Antifungal Treatments, Aspergillosis, Coccidiosis, Mucormycosis, Candidiasis.

INTRODUCTION

Fungi are sophisticated, eukaryotic organisms that can live in a range of settings and have distinctive morphological characteristics. The most serious forms of fungal infections typically affect patients with compromised immune systems or those undergoing life-threatening medical conditions, such as patients with malignant cancer, those suffering from AIDS, those with significant surgical wounds, recipients of organ transplants, and dialysis patients (Xiao *et al*., 2019; Kazakou *et al*., 2020; Wong *et al*., 2020). More than two million individuals die each year from fungal infections, which are regarded as silent killers (Bongomin *et al*., 2017). This puts fungal illnesses above malaria and tuberculosis as one of the world's main causes of death. But when only underlying disorders (such leukaemia or chronic obstructive pulmonary disease) are listed, they are frequently hidden. In recent decades, there has been a notable increase in the total number of patients as well as the percentage of patients at risk for major systemic fungal illnesses. Worldwide, there are recorded incidences of invasive aspergillosis over 300,000 and invasive candidiasis exceeding 700,000 each year (Rodrigues *et al*., 2020). Aspergillus fumigatus, Cryptococcus neoformans, and Candida albicans are the main pathogens for invasive fungi (Limper *et al*., 2017). Of them, A. fumigatus is more prevalent in patients with high-risk haematologic malignancies and in patients receiving glucocorticoid therapy for chronic obstructive pulmonary disease, whereas C. albicans is more common in intensive care units. (Barcelo Roca *et al*., 2020). Cryptococcal meningitis is primarily caused by C. neoformans in HIV-positive patients (Limper *et al*., 2017). Invasive infections and secondary fungal infections of the skin and mucous membranes worsen the underlying condition, causing damage to organs and significantly lowering prognosis. Since the 1950s, a number of novel antifungal medications have demonstrated some therapeutic promise; yet, the prevalence of fungal infections remains elevated (Stott *et al*., 2021). The mechanism of fungus resistance to currently available antifungal medications may be one probable explanation. Furthermore, additional clinical uses are hampered by

the deficiencies in the adverse effects, therapeutic efficacy, and activity of currently available antifungal medications. Numerous infections, including invasive infections and infections of the skin and mucous membranes, are brought on by fungi that cause diseases in humans (Kim, 2016).

The ability of pathogenic fungi to tolerate high temperatures (37 degrees Celsius), develop quickly, invade tissue, use host nutrients for their own gain, and elude the host's immune system is what makes them successful in infecting humans with disease (Wall and Lopez-Ribot, 2020). Some of the fungal species responsible for the most common lethal infections are Aspergillus, Cryptococcus, Candida, Coccidioides, Mucor, and Rhizopus (Prakash and Chakrabarti, 2019). Even with the availability of both conventional and contemporary antifungal drugs, fungal infections are becoming more and more common. This situation might be related to the fungi's capacity to evolve various resistance mechanisms against currently available antifungal therapies. Furthermore, there are a few issues with the effectiveness, efficiency, selectivity, toxicity, resistance mechanisms, and range of activity of the antifungals that are now on the market (Perfect, 2017).

Even with the availability of both conventional and contemporary antifungal drugs, fungal infections are becoming more and more common. This situation might be related to the fungi's capacity to evolve various resistance mechanisms against currently available antifungal therapies. Furthermore, there are a few issues with the effectiveness, efficiency, selectivity, toxicity, resistance mechanisms, and range of activity of the antifungals that are now on the market. 2017's Perfect. The viability and safety of using nanoparticles (NPs) to deliver antifungal medications have been thoroughly investigated in recent years (Li *et al*., 2021). The effective development of novel pharmaceutical formulations to battle fungal infections and overcome the multi-drug resistance of current antifungal drugs may be aided by the creation of drug delivery systems based on nanomaterials or nanoparticles (NPs). Lipids, polymers, and metals can all be converted into nanoparticles (Escárcega-González *et al*., 2018; Vázquez-Rodríguez *et al*., 2020). Numerous studies have shown that nanoparticles have fewer adverse effects, are more specific to the infection site, do not cause medication resistance, increase the stability and solubility of antifungals, and boost their effectiveness. Due to these properties, different types of nanoparticles are considered promising biopharmaceutical systems because of their improved antifungal characteristics, in contrast to traditional drugs for treating various fungal pathogens "(Sousa *et al*., 2020).

1.1 The Purpose of the Review

As a result, this review will be divided into three main sections: Understanding the remarkable biology of fungi is crucial to harnessing their extraordinary potential and averting the devastation they can impose. The impact of fungi on global health, agriculture, and biodiversity has been highlighted by the intensification of human activity, modern medicine, and climate change.

- An overview of fungi and fungal infectious diseases.
- Current treatment plans and their limitations.
- The characteristics and functions of antifungal nanoparticles and their current clinical applications as a key tool for enhancing antifungal therapy.

2.1 Overview of Fungal Diseases

Invasive filamentous fungal infections have become much more common in recent years. Fungal infections are more common in those with compromised immune systems, HIV/AIDS patients, uncontrolled diabetes, blood problems, organ transplant recipients, and chemotherapy patients. Human infections can be caused by fungi like Aspergillus, Coccidioides, Mucorales (the most prevalent filamentous fungi), and Candida auris (the non-filamentous fungi). It has been extensively documented and is a major global health risk (Debourgogne *et al.*, 2016). Treatments for the most common invasive filamentous fungal infections have been presented as innovative approaches using nanomaterials (metallic and polymeric nanoparticles) and their applications. The geographic distribution and epidemiological information on the most prevalent filamentous and non-filamentous fungi that infect people are compiled in (Table 1).

Table 1: Geographical distribution and epidemiological data of the most common filamentous and non-filamentous fungi

Filamentous Fungi	Disease	Geographical Distribution (Incidence)	Epidemiological Data	References
Aspergillus fumigatus	Aspergillosis	Worldwide distribution	Immunocompromised individuals with altered or weakened immune responses are able to develop aspergillosis.	(van der Torre *et al*., 2021)
Coccidioides immitis and Coccidioides posadasii	Coccidioidomycosis	Central Valley of California, desert areas of Arizona, Texas, Utah; Mexico;	Elderly persons, pregnant women, and members of certain ethnic groups are at risk for severe or	(Ashraf *et al*., 2020)

Filamentous Fungi	Disease	Geographical Distribution (Incidence)	Epidemiological Data	References
		Central (Guatemala and Honduras), and South America (Colombia, Venezuela, Argentina, Paraguay, and Brazil).	disseminated coccidioidomycosis. Further, persons with immunodeficiency diseases, diabetes, transplant recipients, and prisoners are particularly vulnerable.	
Rhizopus, Mucor	Mucormycosis	Europe (34%), Asia (31%), North/South America (28%), Africa (3%), and Australia/New Zealand (3%)	Patients with uncontrolled diabetes mellitus, cancer, solid organ or bone marrow transplantation, hematological malignancy, corticosteroids treatment, and trauma and burns are especially vulnerable to *Mucorales* infection.	(Jeong *et al*., 2019)
Candida auris (non-filamentous fungus)	Candidiasis	Worldwide distribution	Elderly age, diabetes mellitus, recent surgery, the presence of an indwelling medical device, an immunosuppressed state, the use of hemodialysis, a neutropenic state, chronic renal disease, or the use of broad-spectrum antibiotic and/or antifungal drugs are related to *C. auris* infections".	(Chow *et al*., 2020; Du *et al*., 2020)

2.2 Fungal Infection

One significant group of microorganisms that affect human existence significantly is fungi. People frequently come into touch with fungi and contract infections through their skin, gastrointestinal tracts, or respiratory systems. Furthermore, individuals receiving chemotherapy, those with uncontrolled high blood sugar, and those with compromised immune systems as a result of HIV/AIDS are more likely to develop fungal infections. Charpak-Amikam *et al*., 2022).

1.2.2 Aspergillosis

Mycotoxins can be produced by certain kinds of mould. Mycotoxins can contaminate food and humans alike. Mycotoxins can cause allergies, liver damage, cancer, and other acute and long-term health problems in people. The genus Aspergillus, species niger, fumigatus, flavus, and ochraceus, class Eurotiomycetes, order Eurotiales, family Trichocomaceae, and phylum Ascomycota comprise the Aspergillus group in the kingdom of fungi. Moulds that can produce and release mycotoxins are Aspergillus flavus (A. flavus) and Aspergillus fumigatus (A. fumigatus), two common forms of mould. The formation of mold is ubiquitous in hospital surroundings, producing issues for patients and economic losses (Auyeung *et al*., 2017). A. fumigatus is an asexually reproducing mould that grows by means of a fungal vegetative life during the degradation of organic materials. Inhaling airborne spores from both indoor and outdoor locations might result in lung illnesses. Invasive pulmonary aspergillosis, chronic pulmonary aspergillosis, and fungal sensitivity are also linked to severe asthma. Aspergillus species are the primary cause of corneal disease. Likewise, filamentous fungi like Aspergillus spp. are linked to fungal keratitis, the third clinical sign of a fungal infection. Because of this, certain forms of aspergillosis pose a serious risk to life and are particularly dangerous in families where there is decreased immunity (Kosmidis and Denning, 2015).

2.2.2. Coccidiosis

Valley fever, or coccidioidomycosis, is a fungal infection of the system that is brought on by Coccidioides immitis or Coccidioides posadasii. The fungus belonging to the phylum Ascomycete, class Eurotiomycetes, order Onygenales, and family Onygenaceae are known as the genus Coccidioides, which includes the species immitis and posadasii. (Fierer and Kirkland, 2018). The main way that coccidiosis is spread is by respiratory inhalation of airborne joint spores; the disease can potentially be contracted from a single spore. Higher spore loads, however, have the potential to cause acute respiratory

distress syndrome (ARDS) and other serious illnesses (Twarog and Thompson, 2015). A person's risk of contracting coccidioidomycosis is significantly increased if they have weakened immune systems as a result of ageing, pregnancy, cancer (especially chronic lymphocytic leukaemia), corticosteroid treatment, diabetes, organ transplantation, or HIV infection, in addition to living in or visiting endemic areas (Benedict *et al*., 2017). The majority of infected persons do not exhibit any symptoms; however, those who do may develop serious, sometimes fatal problems, including as fever, exhaustion, coughing, shortness of breath, chest discomfort, and pneumonia. Furthermore, medical attention might be required if the infection extends beyond of the lungs. The brain, liver, spleen, bones, and many other body tissues can become infected as well (Kollath *et al*., 2019).

3.2.2 Candidiasis

Infections of the bloodstream related to healthcare are mostly caused by Candida fungus, which are the most frequent causes of invasive fungal infections in the US. The crude death rate from Candida fungus has reached 40% even with the use of antifungal medication (Pfaller *et al*., 2019). Mucocutaneous candidiasis and vulvovaginal candidiasis or thrush can both be brought on by Candida fungus. (Cooke and others, 2022). "According to the age and location of patients infection, a distinction can be made between several distinctive clinical types of leather mucous candidiasis, such as childish fungi, candidiasis between fingers, nail inflammation, nail inflammation caused by candidiasis, and oral candidiasis, this infection can occur frequently in Patients with severe weakness in immunity and who have undergone gaseous clinical procedures or catastrophic trauma among the types of white non -bleeding candidiasis, glabrata is highlighted as the main comet behind the invasive candidiasis, with a fixed increase in the number of cases reported in recent years and recently, The appearance of Candida Euris mushrooms caused tremendous concern all over the world, and this mushroom is seen as 'super bacteria' due to its high transition rates in clinical settings and its multiple drug -resistant properties (Lee *et al*., 2021)".

4.2.2 Cryptococcosis

The two main fungi that cause cryptococcosis are Candida neoformans and Candida gattii. 95% of human cryptococcal diseases are caused by C. neoformans, however C. gattii is becoming more well recognised as a global pathogen (Huang *et al*., 2022). Cryptococcal bacterial meningitis causes 250,000 cases and 180,000 fatalities globally each year; it is usually linked to advanced HIV infection (Iyer *et al*., 2021).

1.3 Current Traditional Therapeutic Drugs for Fungal Infections

There are very few possibilities for antifungal drugs compared to antibiotics. Fungi differ from host cells in numerous ways, including the structure of their cell walls, which makes it difficult to find novel medications (Arastehfar *et al*., 2021). Amphotericin B and its liposomal forms (lipid complexes and liposomes); azoles, especially triazoles, such as fluconazole, itraconazole, voriconazole, posaconazole, and isavuconazole; and echinocandins are currently available antifungal medicines for the treatment of systemic fungal infections. A few remedies for fungal diseases brought on by filamentous fungus are shown in Table 2.

Table 2: Recommendations for the treatment of fungal infections caused by filamentous fungi and *Candida auris*

Disease	Current Treatment	References
Aspergillosis	Amphotericin B, azoles (voriconazole, posaconazole, and itraconazole), and echinocandins.	(Aigner, and Lass-Flörl,2015)
Coccidioidomycosis	Azoles (fluconazole, itraconazole, posaconazole, voriconazole, isavuconazole) and amphotericin B.	(Dilshad *et al*., 2020)
Mucormycosis	Amphotericin B, posaconazole, and isavuconazole.	(Sipsas *et al*., 2018)
Candidiasis (*Candida auris*)	Echinocandins (caspofungin, micafungin, and anidulafungin) and isavuconazole"	(Larkin *et al*., 2017)

Because of its broad antifungal spectrum and low likelihood of drug resistance, amphotericin B (AmB), an antifungal agent belonging to the polyene group, is frequently employed in therapeutic settings. It exhibits laboratory action against a variety of fungal infections. Severe fungal illnesses that are invasive can be treated with it. Amphotericin B acts by attaching to ergosterol in the fungal cell membrane, which causes a pore to open and allow cytoplasmic contents (small metabolites, essential ions) to seep out. This disrupts metabolism and kills the cell. Because AmB has a higher affinity for fungal ergosterol than for cholesterol, it is more selective towards fungal cells even if it is poisonous to them. But AmB and cholesterol interact in key organs including the kidneys and heart, leading to major adverse effects like acute nephrotoxicity. AmB is still the accepted standard treatment for a variety of severe and invasive fungal infections, even with the advent of more recent antifungal medications for the management of systemic fungal diseases. AmB is useful in treating some fungal infections, such as meningitis caused by cryptococcal bacteria. Nephrotoxicity, hypokalaemia, hypomagnesaemia, and bone marrow suppression are the main side effects linked to AmB; the greatest worry with regard to treatment-related toxicity is renal impairment. (AmB). AmB comes in two forms: liposomal AmB (L-AmB) and AmB deoxycholate (D-AmB). Compared to conventional D-AmB, L-AmB is favoured since it produces fewer leakage-related

symptoms. As a result of the liposomal carrier's extended molecular and physical stability following venous delivery, AmB is persistently present in the central circulation. Moreover, data from multiple clinical studies show that L-AmB can be administered at much higher doses than D-AmB, which results in increased plasma exposure, improved antifungal efficacy, decreased kidney toxicity, and the absence of notable new side effects (Groll *et al*., 2019). This is due to the drug's increased distribution in the lungs and central nervous system. When treating persistent fungal infections, azole antifungals are appropriate for oral administration because they prevent the synthesis of ergosterol. Different azole antifungals have varying impacts on fungus-related illnesses. For example, fluconazole has proven to be particularly effective in treating cryptococcal meningitis and coccidioidal meningitis, while isavuconazole is known for its usefulness in treating mucormycosis. Furthermore, itraconazole has become the drug of choice for treating mild to severe instances of paracoccidioidomycosis, blastomycosis, and histoplasmosis as well as cutaneous lymphatic filariasis. For people with both impaired and adequate immunity, voriconazole is the recommended treatment for aspergillosis. The early 2000s saw the introduction of echinocandins, which include caspofungin, micafungin, and anidulafungin. Water-soluble lipopeptides called echinocandins have antifungal properties because they prevent the formation of β-1,3-D-glucan, which is an essential part of the fungal cell wall. It can only be administered intravenously because of the distinct mode of action it uses in contrast to other antifungal drugs. Targeting fungus without mammalian counterparts, echinocandins are appealing since they do not cross-resistance with other medications. They only target the fungal cell wall. It is therefore quite safe for use in therapeutic settings.

Echinocandins exhibit anti-Candida albicans and anti-non-Candida albicans action.Aspergillus is efficient against both biofilms and the planktonic form of Candida due to its inherent resistance to azoles. (Zuo and others, 2021). 5-Fluorocytosine (5-FC) is an antifungal agent that was first created in 1957. It does not exhibit any antifungal activity until it enters fungal cells via the cytosine deaminase enzyme. Once inside, it is phosphorylated by the enzyme and becomes 5-fluorouracil. This inhibits protein synthesis by integrating with fungal RNA and affects dematiaceous fungi, Candida, Cryptococcus, and Aspergillus. (Bhattacharya *et al*., 2020). Since 5-FC is highly likely to cause drug resistance when taken alone, it is virtually usually used in combination with another antifungal, most often AmB. Furthermore, 5-FC is dangerous and can cause bone marrow suppression and liver toxicity (Bouz and Doležal, 2021). The limited range of clinically accessible antifungal classes, the emergence of drug resistance to current antifungal agents, the prevalence of medication side effects, the rise of opportunistic pathogens (hepatic and renal toxicity), and the difficulties in treating biofilm infections are the main reasons why, despite the tremendous advancements in antifungal treatments, the results are still unsatisfactory. Apart from the innate and acquired resistance to antifungal treatments, nearly all of the current therapies exhibit drug resistance in some types of fungi.

2.3 The Spread of Drug Resistance

Effective antifungal therapy is necessary to treat the fungal infection and improve the patient's condition. Due to the small number of antifungal medication classes, treatment outcomes are greatly impacted by the emergence of drug class resistance as well as the rise in multidrug resistance. One of the largest barriers to clinical success in Aspergillus and Candida species is azole resistance, which is followed by multidrug resistance in some Candida species, especially C. glabrata, and echinocandin resistance. While non-albicans species, such as Candida krusei and Candida glabrata, have achieved international prominence due to their high levels of antifungal resistance, notably against fluconazole, Candida albicans is the most common type in cases of invasive infections across diverse institutions. (Van Leth and Schultsz, 2023). C. auris has garnered more attention lately in both the popular press and the medical literature. When it was isolated from a patient's external ear canal in Japan in 2009, this relatively new species was initially identified. In 2011, the first cases of recorded invasive infections happened in South Korea. As of right now, it has been determined that Candida auris is an endemic pathogen in both South Africa and India, accounting for 5% to 30% of documented cases of candidiasis in both countries, respectively. According to (Seagle *et al*., 2021), over 90% of C. auris isolates in the US are resistant to fluconazole, 30% to AmB, and 5% to echinocandins. Since this class of antifungals is commonly used to treat Aspergillus infections and Aspergillus has developed azole drug resistance in individuals who have been exposed to azoles for an extended period of time, the increasing spread of azole resistance in Aspergillus spp., particularly A. fumigatus, has raised significant concern. Patients treated with itraconazole have been reported to have the first incidences of azole resistance (Wiederhold and Verweij, 2020).

3.3 Nanotechnology in Antifungal Therapy

A vast range of particles at the nanoscale, typically ranging from 1 to 100 nanometres, are referred to as nanoparticles (NPs). These particles can be conical, helical, tubular, spherical, cylindrical, or have other forms. Currently, nanoparticles have received the attention of the scientific community due to their various potential therapeutic and diagnostic applications, such as medication administration and as a detection method for biological and chemical substances, among others (Barrak *et al*., 2019). These materials are also thought to be superior therapeutic substitutes since they are less toxic, can cross several biological barriers, and form covalent bonds with large molecules and hydrophobic or hydrophilic drugs to increase their solubility and stability (Mitchell *et al*., 2021). Nanoparticles can be categorised as organic or polymeric and inorganic (metallic) and carbon-based based on their shape, size, and chemical and physical

characteristics. Liposomes, micelles, and dendrimers are examples of organic nanoparticles that are heat-and light-sensitive, biodegradable, and non-toxic. This class of nanoparticles is typically the first choice in the biomedical industry, particularly for medication delivery because of its exceptional efficacy and capacity to be injected into precise locations. (Khan and others, 2019). All of the particles composed of metals and metal oxides are combined into inorganic nanoparticles. Cadmium (Cd), aluminium (Al), cobalt (Co), copper (Cu), gold (Au), iron (Fe), silver (Ag), and zinc (Zn) are major sources of metallic nanoparticles. Simultaneously, metal oxide nanoparticles are produced when oxygen is added to metal particles, increasing their efficiency and reactivity. Zinc oxide (ZnO), iron oxide (Fe2O3), titanium oxide (TiO2), and aluminium oxide (Al2O3) are some of the most common metal oxide nanoparticles. According to Ealia *et al*., (2017), carbon nanoparticles are fully synthesised carbon particles that fall into the following categories: fullerenes, graphene, carbon nanotubes, carbon nanofibers, carbon black, and activated carbon".

4.3 Properties of Nanoparticles against Fungal Infections

The application of conventional antifungal medications has proven difficult despite advancements in targeted antifungal therapy due to a number of treatment-related issues, such as the development of drug-resistant strains and inadequate drug absorption. Some of these restrictions can be addressed by using antifungal NP carriers, which offer controlled drug release, better pharmacokinetics, decreased dosage, improved localisation, and targeted administration. Additionally, nanoparticles can operate as a conduit for other substances that can interact with the targeted fungi, or they can interact directly with the fungus to provide antifungal effects, such as the cytotoxicity generated by silver nanoparticles (Kischkel *et al*., 2020).

5.3 Unmodified Nanoparticles against Fungal Infections

For the treatment of fungal infections, nanotechnology offers novel approaches that do not rely on blocking drug resistance pathways. The fundamental mechanism of these antifungal platforms is mediated by reactive oxygen species (ROS), membrane permeability, metal ion transport, pH gradients, and photothermal and magnetic effects, which prevent fungi from surviving. Unmodified nanoparticles alone have demonstrated antifungal activity against pathogenic fungi (Weldick *et al.*, 2022).

6.3 Recent Developments in the Field of Nanoparticles against Fungal Infections

In order to stop medication loss and premature degradation following chemical or enzymatic disruption, polymeric nanoparticles have been produced. The two primary ingredients utilised in the production of polymeric nanoparticles are chitosan and poly (lactic-co-glycolic) acid (PLGA) (Zielińska *et al*., 2020). PLGA nanoparticles modified with glucoseamine (PLGA-GlcN) were created to increase the nanoparticles' adherence to white blood cell walls. When compared to PLGA nanoparticles and pure nystatin, PLGA-GlcN loaded with nystatin shown more antifungal efficacy than nystatin against the C. albicans strain. Furthermore, ferulic acid (FA) and its byproducts prevent Candida fungus from forming biofilms. (Canturk, 2018).

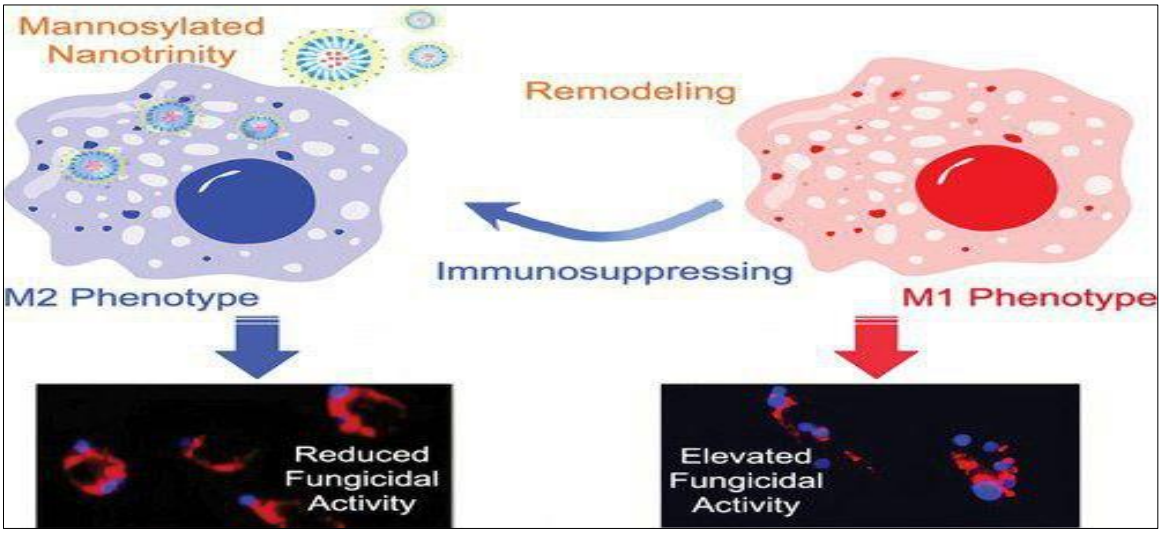

Figure 1: Synthesis of tri-nanoparticles added with mannose and remodeling of phagocytic cells

Mannose was covalently linked to chitosan oligosaccharide, and then the product was incubated with nanoparticles loaded with imatinib to obtain chitosan-coated nanoparticles. The nanoscale triad supplemented with mannose developed in this study can significantly stimulate the local remodeling of macrophages through the dual-process of "turning on" M1 phenotypic polarization while "turning off" M2 phenotypic polarization, thus allowing for the elimination of Candida albicans (Gao *et al*., 2020).

Table 3: Nanomaterials used in the treatment of *Aspergillus fumigatus* infections

Nanomaterial	Antifungal Effect
AgNPs	Growth inhibition at 10 µg/mL
	54% growth inhibition at 100 mg/L
	75.61% growth inhibition at 150 µg/mL
	Growth inhibition at 150 µg/mL
	Growth inhibition at 40 µg/mL
	60% growth inhibition at 50 µg/mL
Marketed AgNPs	90% growth inhibition at 0.5 µg/mL (clinical isolates)
AgO/Ag NPs	75.25% growth inhibition at 50 µg/mL
Ag-AuNPs	90.78% growth inhibition at 200 µg/mL
$Ag_2Cr_2O_4$	3.1 times higher inhibition than fluconazole
Maleic acid capped AgNPs	Growth inhibition
Milk protein synthesized AgNPs	Growth inhibition
Fibroin-AgNPs	Fungicidal activity at 2 µg/mL
Ag-Cu core-shell NPs	Growth inhibition at 0.1 M and fungicidal activity at 15

Table 4: Nanomaterials used in the treatment of *Coccidioidomycosis* infections

Nanomaterial	Antifungal Effect
Amphotericin B lipid complex (ABLC, Abelcet®)	Highly effective treatment.
Liposomal amphotericin B (L-AmB, AmBisome®)	Successfully used as an alternative and safe option of treatment.
Amphotericin B colloidal dispersion (ABCD, Amphotec®/Amphocil®)	Well tolerated and effective treatment

Table 5: Nanomaterials used in the treatment of *Mucorales* infections

Nanomaterial	Antifungal Effect
Nanoemulsions NB-201	Growth inhibition
Silver nanoparticles (AgNPs),	Growth inhibition
Zirconium oxide nanoparticles (ZrO2NPs)	Growth inhibition

Table 6: Nanomaterials used in the treatment of Candida auris infections.

Nanomaterial	Antifungal Effect
Silver nanoparticles (AgNPs)	Biofilm formation inhibition, planktonic growth inhibition
Trimetallic nanoparticles (Ag-Cu-Co NPs)	Growth reduction, lower viability, cellular arrest, mitochondria membrane damage
Bismuth nanoparticles (BiNPs)	Affect cellular morphology, biofilm formation inhibition
Nitric oxide (NO)	Biofilm formation reduction, planktonic growth inhibition"

CONCLUSIONS

The failure of present treatments has been shown by the rise in invasive fungal illnesses brought on by the scarcity of antifungals and the emergence of medication resistance. As a result, it is critical to develop novel therapeutic approaches. The continuous advancement of nanotechnology has intensified the hunt for novel and more potent medicinal substitutes to address invasive fungal diseases and their progression. An assessment and refinement of the several kinds of nanostructures that have been created are now in progress; these provide advantages over conventional antifungals in terms of efficacy and little or nonexistent adverse effects. Formulations based on nanoparticles can now be developed thanks to the application of nanotechnology, such as metal nanoparticles, the incorporation of coating materials, and substances made using green chemistry or in combination with polymers, which can improve patient quality of life and treatment efficacy by minimising side effects, particularly in the case of extended therapies. When compared to organic nanoparticles, the silver nanoparticles derived from plant extracts demonstrated a greater rupture of the membrane in Candida species. This disruption was done by acting in the cellular components of the fungi and generating cellular damage. Nanoparticles created using non-biological processes, such as physical and chemical approaches, can be harmful to people suffering from major illnesses or severe immune deficiencies. On the other hand, biologically produced nanoparticles are less harmful and can be applied to a range of medical conditions. The use of nanoparticles for diagnostic and therapeutic reasons is known as nanomedicine. These particles have been applied in various therapeutic fields, most notably cancer, where the application of nanomedicine has greatly increased the safety and effectiveness of widely used anticancer medications. As significant as nanoparticles are in the therapy of cancer, they are also crucial in the treatment of bacterial and fungal diseases.

Nanotechnology enables the development of formulations that can enhance the efficiency of treatment and the quality of life for patients by relieving negative effects, particularly in the course of extended therapy. While research on using nanoparticles to treat infectious fungal infections is still in its early phases, first findings indicate that this strategy has great potential.

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