Nanoparticles Arsenal, Emerging Innovations as Antifungal Agents Against Candidiasis

Muhammad Najamul Hassan[1], Munir Hussain[2], Ayesha Sana[1], Faiza Muzammal[1], Zainab Saeed[1], Hooria Akram[1], Maira Waheed[1], Muhammad Sajid*[3].

1. Department of Biochemistry, University of Agriculture Faisalabad,38000, Pakistan
2. Faculty of Animal Husbandry and Veterinary Science, Sindh Agriculture University Tandojam.
3. Faculty of Veterinary Science, University of Agriculture, Faisalabad, 38000, Pakistan.

Abstract

This comprehensive review explores the potential of nanoparticles as a novel therapeutic approach for treating candidiasis. Candidiasis, caused by various species of the Candida genus, poses significant challenges due to its increasing incidence and resistance to conventional antifungal medications. Nano-biotechnology offers promising solutions by leveraging nanoparticles' unique properties to enhance drug delivery, overcome drug resistance, and improve therapeutic outcomes. The review discusses the mechanisms of candidiasis pathogenesis, including biofilm formation, cell membrane disruption, and immune evasion, highlighting the importance of understanding these processes for developing effective treatments. Nanoparticles, such as silver, zinc oxide, chitosan, and copper nanoparticles, exhibit potent antifungal activity through multiple mechanisms, including disrupting biofilms, enhancing drug delivery, and inducing oxidative stress. Furthermore, the review explores the synergistic effects of combining nanoparticles with traditional antifungal drugs, leading to enhanced efficacy against drug-resistant Candida strains. This synergism is attributed to various factors, including increased cellular uptake, complementary mechanisms of action, and disruption of fungal biofilms. Safety considerations, including biocompatibility, cytotoxicity, long-term effects, and environmental impact, are also addressed. Preclinical studies are essential for evaluating the safety and efficacy of nanoparticle-based antifungal therapies, paving the way for clinical trials and regulatory approval. In conclusion, while nanoparticle-based antifungal therapies hold great promise for combating candidiasis, further research is needed to optimize their formulation, dosage, and targeting strategies. Regulatory approval and clinical validation are essential steps toward harnessing the full potential of nanoparticles in clinical practice for the treatment of fungal infections.

Keywords: Nanoparticles, Antifungal Agents, Candidiasis, Personalized Medicine, Smart Nanomaterials.

Introduction

Candidiasis is a fungal diseases caused by the yeast which is known as Candida, which acts as an immune system depressant (Sudbery et al., 2004). The Candida genus consists of more than 200 species that cause candidiasis (Sudbery, 2011). Most commonly, it affects the gastrointestinal tract and genital area, such as the vagina. It causes both systemic and local diseases, leading to mucosal, deep-seated, invasive, and cutaneous infections in various body organs, such as osteomyelitis and

intra-abdominal abscesses (Calderone and Fonzi, 2001). The most common type of candidiasis is candidemia, an infection of the bloodstream, which is caused by disruptions in the gastrointestinal and cutaneous barriers. Candida species are organisms that reside in the gut microbiota and on the skin through the mechanism of commensalism (Whiteway and Bachewich, 2007). Over the past few years, various research works have been conducted to analyze the mechanisms of candidiasis on a large scale. These research studies have been beneficial in understanding the host defense mechanisms, host susceptibility, and the genetic virulence factors of candidiasis (Berman, 2012). Advanced medical technologies are closely linked to this disease because of its intrusive nature and high prevalence of infection in the organisms (Chen et al., 2020). Candidiasis has been declared the leading cause of morbidity and mortality in accordance with maintaining a healthy environment (Wingard, 1995). The most significant focus of clinical research is on non-albican species of Candida (NAC), with samples being collected from hospitals worldwide, while *Candida albicans* is still considered the primary causative agent of candidiasis (Lo et al., 1997). *Candida krusei, Candida glabrata, Candida albicans, and Candida parapsilosis* are the major pathogens responsible for causing disease more aggressively compared to the other 15 Candida species that are responsible for causing diseases in human (**See figure 1**). In various parts of the world, *Candida auris* has emerged as a significant pathogen (Moran et al., 2012). In the advanced era, fungal diseases are becoming increasingly severe, with high morbidity rates and up to 60% mortality among patients diagnosed with invasive fungal disease (Mayer et al., 2013). This disease is often diagnosed in patients with weak immune systems. During the most recent COVID-19 outbreak, individuals with severe COVID-19-associated pneumonia showed a significant frequency of systemic candidiasis (Hoenigl et al., 2022). Systemic candidiasis was found to be prevalent in up to 14.4% of cases, with the two predominant isolated species being *Candida parapsilosis* and *Candida albicans* (Leleu et al., 2002). Genes involved in Candida ergosterol production are crucial for Candida pathogenesis in both invasive and superficial ulceration, exerting a significant impact on cellular stress (Scherer and Magee, 1990). Hydrolases associated with the cell wall play a role in host-pathogen interactions. Adhesins are essential for colonization and biofilm development, which is a significant virulence factor for candidiasis. Calcineurin plays a role in virulence, cell wall stress, and membrane stress (Staib et al., 1999). Candidalysin, a toxin that specifically affects hyphae, penetrates mucosal cells and facilitates fungal invasion deep into tissues (Sudbery, 2011). The expression of this protein increases resistance to neutrophil death in candidiasis patients (Aoki et al., 2011). The immune-stimulatory factors provided by virulence factors stimulate dendritic cell activation, T cell infiltration, and activation. Infections with Candida may be less likely to develop resistance if virulence factors are targeted (Cutler, 1991). In the past, Candida species, notably *C. glabrata*, were associated with infections in elderly individuals (>64 years) (Haynes, 2011). *C. parapsilosis* infections typically affect more newborns under the age of one (Coleman et al., 1998). Recent research suggests that all Candida species are becoming less common in newborns, at least in the United States, which may be related to the standardization of central line care (Abi-Said et al., 1997).

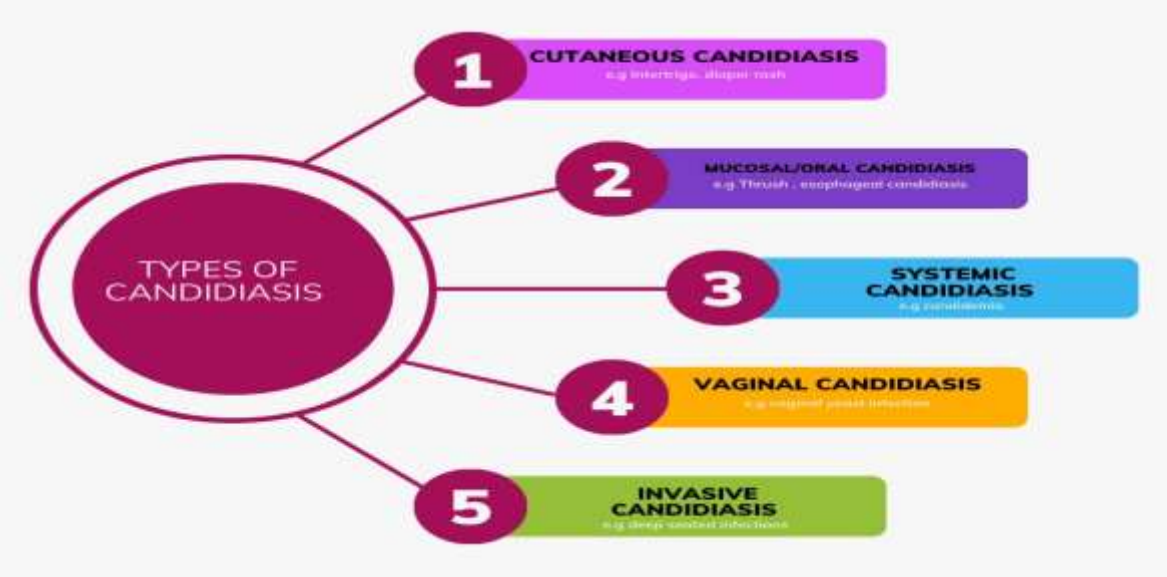

Fig. 1: Types of candidiasis responsible for causing diseases in human

Nano-biotechnology

Nano-biotechnology is a fast-developing field of study that enables us to control objects at the molecular or microscopic level. This method, which combines nanotechnology and biotechnology to tailor the features of medicinal substances, is commonly used today. It is applicable to both therapeutic and diagnostic purposes (Ghormade et al., 2011). It aids in enhancing the therapeutic action of a medicine to the intended location in the medical profession (Jain, 2007). It is boosting medical research and enhancing medical procedures all across the world. The application of nanotechnology in the medical arena calls for a higher level of technical proficiency and precision so that the created mechanisms and devices can interact with molecules with excellent specificity (Zhaou et al., 2020). It enables us to engage with a substance's molecularly-level physical and chemical features (Giraldo et al., 2019). The growth of nano-biotechnology will have a significant impact on the medical industry. These nanomaterials have been employed in a variety of biomedical applications, including photo-thermal cancer therapy, MRI, optical imaging, and targeted drug administration (Kayser et al., 2005). Design and synthesis of nanomaterials, which fall under a number of categories are as follows:

- **Nanocomposites:** Materials called nanocomposites are made of nanoparticles incorporated in a matrix, like ceramics or polymers. The electrical, thermal and mechanical properties of the composites are improved by the introduction of nanoparticles (Komarneni, 1992).
- **Quantum Dots:** Depending on their size, quantum dots, semiconductor nanocrystals with unique optical properties, can emit light of various colors, which makes them useful for displays, biological labeling and imaging (Jamieson et al., 2007).
- **Nanowires and Nanotubes:** These nanostructures are elongated and have nanometer-sized dimensions. Nanosensors, energy storage and nanoelectronics all use nanotubes and nanowires (Hu et al., 1999).
- **Nanoparticles**: These are tiny particles with dimensions in the nanometer range. Nanoparticles can be made from various materials, including metals (e.g., gold, silver), metal oxides (e.g., iron oxide, titanium dioxide), semiconductors (e.g., quantum dots),

carbon-based materials (e.g., carbon nanotubes, graphene), and polymers. Nanoparticles exhibit unique properties due to their size and have applications in various fields, such as electronics, medicine and environmental remediation (Biswas and Wu 2005).

Despite the fact that nanoparticles have numerous applications, there are multiple challenges and ethical dilemmas associated with their use.

1. **Regulation:** Since current regulatory frameworks might not cover some nanoparticles, regulating nanotechnology is a never-ending difficulty. For development to be safe and responsible, proper oversight is necessary (Arruda et al., 2015).
2. **Safety:** The security of nanomaterials is a serious issue. Thorough toxicity analyses and risk assessments are required since some nanoparticles may have adverse effects on both human health and the environment (Rocco, 1999).
3. **Standardization and Characterization:** Results in research and applications must be reproducible and authentic (Pestovsky and Martinez 2017).
4. **Ethical Implications:** Concerns regarding privacy, equal access to advantages, and potential misuse of nanotechnology are only a few of the ethical issues that are brought up by this technology (Liu, 2006).

Future Prospects of Nano-biotechnology

Nanotechnology has a tremendous promise for solving difficult problems and enhancing many facets of human life (Pandey, 2018). Future nanotechnology developments include:

- **Nano-Bio Interfaces:** For biomedical and bioengineering applications, it is important to comprehend and engineer interactions between biological systems and nanoparticles. Wide-ranging applications and great promise for scientific and technological progress make nanotechnology a revolutionary field. It is a potent instrument for tackling problems in medicine because of its special qualities and interdisciplinary character (Cai et al., 2018).
- **Personalized Medicine:** Nano-medicine advancements that result in therapies that are tailored to a patient's unique traits and medical circumstances (Kim et al., 2010).
- **Smart Nanomaterials:** the creation of responsive and adaptable nanomaterials whose characteristics can alter in response to outside stimuli (Choi et al., 2014).

Collaboration between scientists, engineers, decision-makers and stakeholders will be essential as nanotechnology develops to ensure its successful and ethical integration into the community (Levchenko et al., 2018).

Nanoparticles and candidiasis

Scientist are searching for advanced therapeutic alternatives against several resistant strains of candidiasis since they have caught their notice. The use of nanoparticles in the fight against *Candida albicans* has the potential to be very successful and practical (Panacek et al., 2009). The Successful synthesis of ag-embedded mesoporous silica nanoparticles (mSiO2@AgNPs) has allowed for the investigation of these particles' anti-candida properties against *C. albicans* (Adam and Khan 2022). Azadirachta indica leaf extract and silver nitrate have been used to create silver (Ag) nanoparticles in a straightforward, affordable and environmentally benign manner (Lara et al., 2015). Antifungal medications are currently only sometimes used to treat Candidiasis.

However, nanoparticles offer a higher level of fungicidal action than traditional antifungal medications due to their superior host cell and tissue penetration (Lai et al., 2008).

Effective antibacterial agents against Candida species and other oral microbial species, carbon-based nanomaterials such as silica, silver oxide, titanium oxide, copper oxide, ZnO, and hydroxyapatite have been recognized by utilizing silver nitrate and Azadirachta indica leaf extract (Monteiro et al., 2015). Nanoparticles have been studied for antifungal therapy, and results show evident improvements in drug aspects such as solubility and tissue penetration, stability in water and increased bioavailability, which result in increased efficacy and reduced toxicity (Jarvis, 1995). Drug-loaded nanoparticles can improve the profile of fungal inhibition even in lower concentrations compared to plain antifungals (Gullo, 2009).

Mechanism of action

Nanoparticles have been researched as potential treatments for candidiasis, a fungal infection

brought on by a species of the fungus known as Candida (Donaldson et al., 2010). Nanoparticles' ability to combat Candida is based on a number of elements, including:

- **Disruption of Biofilm Formation**: The capacity of Candida species to create biofilms, which are extremely resistant to traditional antifungal medications, is well documented. By disrupting the adherence of Candida cells to surfaces and preventing the release of extracellular matrix components, specific nanoparticles can prevent the formation of biofilms. The biofilm structure is weakened by this disturbance, which also makes Candida cells more vulnerable to additional antimicrobial treatments (Vera and Shukla 2020).
- **Physical Interaction:** Nanoparticles and the cell membrane of some species of candida can physically interact. Because of their small size and large surface area, nanoparticles can cling to the fungal cell wall and damage its integrity and structure. This connection could eventually result in cell death by allowing proteins and ions to seep out of the cell (Florence, 2012).
- **Drug Delivery:** Antifungal medications can also be transported via nanoparticles. Antifungal drugs can have improved distribution and bioavailability by being enclosed within nanoparticles. This strategy enables focused drug delivery to Candida-infected areas, increasing treatment efficacy and lowering the risk of systemic toxicity (De Jhong and Borm 2008).
- **Immunomodulation:** Nanoparticles can alter the immune system's response to candida infections. They can activate the immune system and boost the production of pro-inflammatory cytokines, both of which are essential for battling fungus infections. This immune modification can aid in limiting infection spread and accelerating the removal of fungal cells (Lawrence and McCabe 2002).
- **Oxidative Stress:** Many nanoparticles have innate characteristics that cause them to release reactive oxygen species (ROS) when they come into contact with biological systems. In Candida cells, ROS can cause oxidative stress, which can damage several cellular components like DNA, proteins, and lipids. Cell death eventually takes place (Manke et al., 2013).

The precise method of action can differ based on the type of nanoparticles utilized, their surface characteristics and the particular Candida species targeted; it is crucial to highlight (**See figure 2**).

Additionally, additional study is still being conducted to enhance the layout and potency of nanoparticles against candida infections (Frohlich et al., 2009).

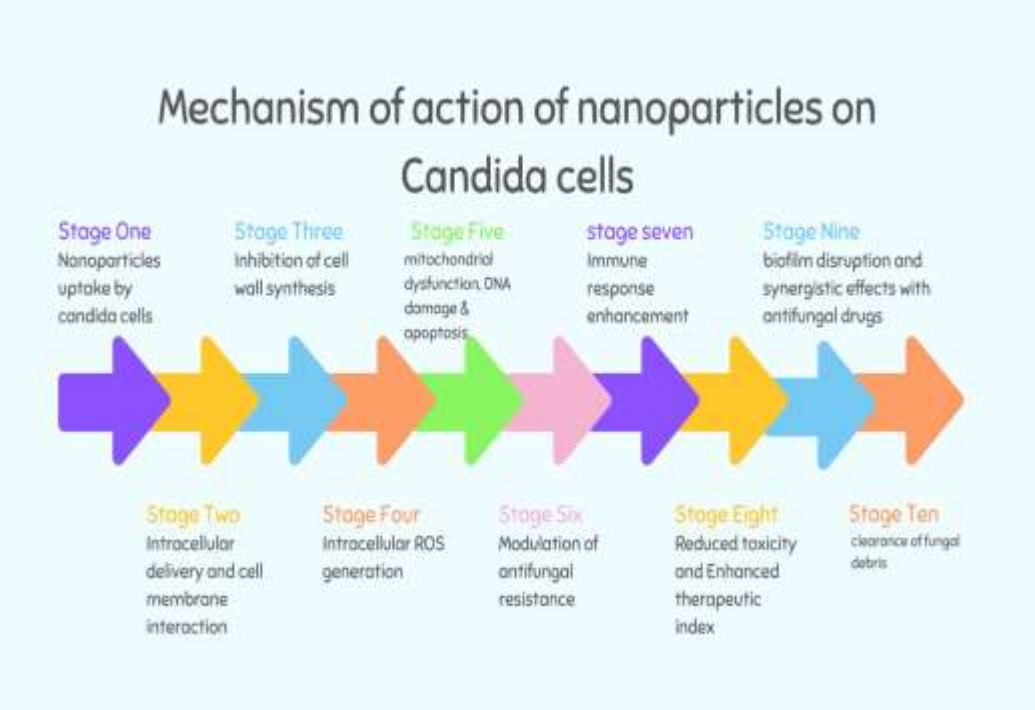

Figure 2: Mechanism of action of nanoparticles on candida cell

Types of nanoparticles used against candidiasis

As we previously noted, a variety of nanoparticle kinds have been investigated for their ability to treat candidiasis, including:

- **Lipid-based nanoparticles:** Candida-specific antifungal activity of lipid-based nanoparticles such as liposomes and solid lipid nanoparticles (SLNs) has been investigated. Antifungal medications can be encapsulated in these nanoparticles, which improves their delivery to Candida-infected areas. Lipid-based nanoparticles can boost the effectiveness of treatment by directing the medicine to the site of infection (Carmo et al., 2023).
- **Zinc oxide nanoparticles (ZnO NPs):** ZnO nanoparticles demonstrate antimicrobial activity against candida species. They have the ability to provoke oxidative stress and harm fungal cell membranes, which results in cell death. Effectiveness against Candida infections and biofilms has been shown for ZnO NPs (Sabir et al., 2014).
- **Silver nanoparticles (AgNPs):** Copper nanoparticles display strong antibacterial activity against Candida species. They can kill Candida cells by rupturing the cell membrane and impeding crucial cellular functions. AgNPs have demonstrated potential in preventing the development of biofilms and Candida growth (Silva et al., 2013).
- **Chitosan nanoparticles:** Chitosan, a biopolymer made from chitin, has antibacterial properties when it is processed into nanoparticles. Chitosan nanoparticles can interact with the cell wall of candida, harming the membrane and ultimately leading to cell death. Their antifungal effectiveness against Candida species has been studied (Grenha, 2012).

- **Copper nanoparticles (CuNPs):** Strong antibacterial action is displayed by copper nanoparticles against a variety of microbes, including Candida species. CuNPs have the ability to damage cell membranes and obstruct a variety of biological processes, killing Candida cells. They have shown potential in preventing the development of biofilm and Candida growth (Umer et al., 2012).

NANOPARTICLE TYPE	MECHANISM OF ACTION	ADVANTAGES	DISADVANTAGES
Ag NPs	• Disrupt CW membrane • Inhibit enzyme activity	Broad spectrum activity	Potential cytotoxicity
Au NPs	• Inhibit fungal growth	Biocompatible	Limited antifungal spectrum
ZnO NPs	• Disrupt cell wall mechanism	Low toxicity	Poor stability in biological media
Chitosan nanoparticles	• Bind to CW, induce apoptosis	Biodegradable mucoadhesive properties	Valuable efficacy across candida spp.
Lipid nanoparticles	• Deliver antifungal drugs efficiently	Enhanced drug delivery	Costly production
Polymeric nanoparticles	• Sustain drug release • Improve bioavailability	Tailored drug release profile	Potential biocompatible issues

Table 1: Types of nanoparticles

It should be noted that the efficacy of nanoparticles against different species of Candida may differ based on elements including nanoparticle size, concentration, surface characteristics, and the particular strain of Candida being targeted. Further study is required to assess the safety and long-term consequences of nanoparticles used to treat candidiasis and to optimize their utilization (Wang and Wang 2014).

Enhanced antifungal activity of nanoparticles against candidiasis

Antifungal activity of nanoparticles can be activated in different manners such as:

- **Synergistic Effects:** When coupled with traditional antifungal medicines, nanoparticles can have synergistic effects. For instance, the activity of antifungal medications like azoles or polyenes can be increased by combining them with silver nanoparticles or other metal-based nanoparticles. When antifungal medications are used in conjunction with

nanoparticles, there may be synergistic interactions where the nanoparticles increase the drugs' potency, improving their antifungal activity against candida (Lara et al., 2018).

- **Improved Drug Delivery:** Antifungal medications can be transported via nanoparticles, enhancing their delivery to the infection site. The stability of the medicines can be improved and they can be shielded against deterioration by encapsulating them inside nanoparticles. Drug solubility and bioavailability can be enhanced by nanoparticles, enabling more precise targeting and prolonged release. This tailored administration increases the antifungal agent's concentration at the infection site, increasing its effectiveness against Candida (Kraisit et al., 2021).
- **Increased Surface Area:** Compared to bigger particles, nanoparticles have a higher surface area-to-volume ratio. The interaction between the nanoparticles and different kinds of candida is improved by the expanded surface area, which enables more contact with fungus cells. As a result, nanoparticles may have more antifungal activity than bulk compounds (Sharma and Ghose 2015).
- **Alternative Mechanisms of Action:** Compared to traditional antifungal drugs, nanoparticles can exert antimicrobial effects through alternative pathways. For instance, nanoparticles may damage the integrity of the cell membrane, cause oxidative stress, obstruct biological functions, or alter gene expression in Candida cells. These other methods of action can get beyond fungi's defenses and boost the antifungal effect as a whole (Ahmed et al., 2019).
- **Disruption of Biofilms:** Conventional antifungal medications are not effective against Candida biofilms. However, some nanoparticles can prevent the growth of new biofilms and destroy existing ones. Nanoparticles can impair the biofilm structure and make the biofilm more susceptible to antifungal drugs by interfering with the adherence of Candida cells and preventing the development of the biofilm matrix. By working together, these antifungal agents can be more effective against candida biofilms (Lara et al., 2015).

It is crucial to remember that the ideal concentration, composition, and combination of antifungal drugs and nanoparticles may differ based on the particular species and strain of candida, among other things. More study is being done to determine how best to employ nanoparticles to increase antifungal action against candida (Gupta et al., 2021).

Synergistic effects of nanoparticles against candidiasis

The improved antifungal activity obtained when nanoparticles are used in conjunction with traditional antifungal medications is referred to as the synergistic impact of nanoparticles against candidiasis (Otta et al., 2001). In circumstances when the fungi have become resistant to conventional antifungal medications, this combination strategy can result in increased efficacy in treating Candida infections (Inigo et al., 2012). A number of mechanisms causes the synergistic effect:

- **Disruption of Fungal Biofilms**: Candida biofilms are groups of fungi that are embedded in an extracellular matrix and, are therefore, very hard to treat with traditional antifungal medications. It has been demonstrated that specific nanoparticles prevent the growth of new biofilms or weaken those that already exist. With better access to the fungal cells thanks to this disruption, antifungal medications may be more effective at curing the infection (Lohse et al., 2020).

- **Increased Cellular Uptake:** Nanoparticles can improve the cellular absorption of antifungal drugs by candida cells. Higher intracellular concentrations of the antifungal agent result from their small size and unique features, which make it easier for them to penetrate the fungal cell wall (Campbell et al., 2022).
- **Synergistic Drug Interactions:** In some circumstances, combining antifungal medications with nanoparticles might result in a synergistic interaction, where the combined effect is much greater than the sum of the individual products. For instance, the antifungal medicine's development may be enhanced by the nanoparticles' inherent antimicrobial characteristics once they help the drug enter the fungal cell (Cui et al., 2015).
- **Complementary Mechanisms of Action:** Because of their size and surface qualities, nanoparticles frequently have built-in antibacterial properties. They may operate differently from conventional agents when coupled with antifungal medications. It is more difficult for the candida species to acquire resistance because of this complementing action's capacity to simultaneously target various facets of fungus cells (Vikrant et al., 2015).
- **Overcoming Drug Resistance:** Over time, antifungal medications can cause some Candida species to become resistant. It is feasible to circumvent some of the mechanisms of resistance by mixing nanoparticles with antifungal medicines, increasing the treatment's efficacy against drug-resistant bacteria (Sanguinetti et al., 2015).
- **Reduced Drug Dosages:** The bioavailability and targeted delivery of antifungal medications can both be enhanced by the use of nanoparticles. With a targeted approach, lesser medication dosages can still have a significant antifungal effect while lowering the risk of toxicity and adverse effects (Ben-Ami, 2018).

The most effective nanoparticle-drug combinations may differ based on the particular Candida strain and other circumstances, according to continuing research into the synergistic effect of nanoparticles against candidiasis (Mba and Nweze 2020). To enhance the management of Candida infections, particularly those that are challenging to treat with traditional antifungal drugs alone, this technique shows promise (Weitz et al., 2015).

Antifungal drugs used in combination with nanoparticles

The use of antifungal medications in combination with nanoparticles to treat candidiasis was still a topic of ongoing research as of the most recent update in September 2021. It has been demonstrated that the use of nanoparticles in drug delivery can improve the therapeutic effectiveness of antifungal medications while lowering their adverse effects (Singh et al., 2013). For this, a variety of nanoparticle types, including metal nanoparticles, polymeric nanoparticles, and liposomes, have been researched (Lipovsky et al., 2011).

Here are some instances of antifungal medications that have been investigated in conjunction with nanoparticles (see figure 3) for the treatment of candidiasis:

Amphotericin B: Amphotericin B is a strong antifungal medication; however when used systemically, it can be hazardous to the kidneys. Amphotericin B has been investigated as encapsulated within nanoparticles to lessen its toxicity and enhance its targeted delivery to the infection site (Lemke et al., 2005).

Fluconazole: Another widely used antifungal medicine is fluconazole. Its nanoparticle encapsulation seeks to increase bioavailability and delay release, which will result in better antifungal action against Candida species (Reboli et al., 2007).

Voriconazole: An antifungal drug with broad-spectrum action against different Candida species is Voriconazole. Its encapsulation in nanoparticles might increase its solubility and stability and provide prolonged release at the infection site (Saravolatz et al., 2003).

Itraconazole: Itraconazole is used to treat candidiasis and other fungal infections. Itraconazole nano-formulations have been created to enhance its pharmacokinetic profile and increase its accumulation at the infection site (Heykants et al., 1989).

Ketoconazole: Azole antifungal ketoconazole has a broad spectrum of effectiveness against different fungi. Formulations based on nanotechnology may improve pharmacokinetics and lessen side effects (Nguyen et al., 2010).

Caspofungin: The antifungal caspofungin, which belongs to the echinocandin class, is used to treat invasive candidiasis. Its antifungal efficacy and selectivity may be improved by combining it with nanoparticles (McCormak and Perry 2005).

Miconazole: An imidazole antifungal drug called miconazole is frequently applied topically. Its skin penetration and antifungal actions can be improved with nanoparticle compositions (Kobayashi et al., 2002).

Figure 3: Antifungal drugs used in combination with nanoparticles

In order to facilitate targeted distribution and uptake by the fungus cells, the surface of the nanoparticles utilized for drug delivery can be modified with ligands that have an affinity for Candida cell surfaces (Kraisit et al., 2021). With this focused strategy, less medication is exposed to healthy tissues while more medication is concentrated at the injection site, enhancing therapeutic results and reducing adverse effects (Mathur and Devi 2017). Such nanoparticle-based antifungal

medication combinations would need to undergo clinical studies and regulatory authorization in order to be shown safe and effective for human usage (Spadari et al., 2019).

Safety consideration of nanoparticles against candidiasis

Because nanoparticles might interact differently with biological systems, it is important to carefully assess their safety before using them to treat candidiasis. Important safety factors include:

- **Biocompatibility:** Nanoparticles should be biocompatible, which means they shouldn't cause the body to overreact or have negative effects when they're ingested. To make sure the nanoparticles are well-tolerated and don't cause systemic toxicity, biocompatibility testing is essential (Rana et al., 2021).
- **Cytotoxicity:** Some nanoparticles have the potential to be harmful to mammalian cells, including human cells. Their cytotoxicity must be evaluated for nanoparticles to effectively target Candida cells without harming healthy tissues (Chaudhari et al., 2016).
- **Long-term Effects:** When frequent or protracted therapy is required, the long-term safety of nanoparticles is a crucial factor. To evaluate any long-term impacts, research on the persistence and potential buildup of nanoparticles in the body is required (Zhang et al., 2016).
- **Accurate Targeting:** Nanoparticles should specifically target Candida cells while preserving healthy tissues to reduce the possibility of off-target effects. The specificity of nanoparticle delivery can be improved by appropriate surface functionalization and modification (Soliman, 2017).
- **Risk of Fungal Resistance:** Candida species may acquire resistance as a result of the usage of nanoparticles as antifungal medicines. To detect any new resistant strains, ongoing resistance pattern monitoring is crucial (Balkis et al., 2002).
- **Clearance and Metabolism:** It is essential to comprehend the bodily clearance mechanisms for nanoparticles. To stop nanoparticles from building up in organs or tissues, they should be removed effectively (Yang et al., 2019).
- **Environmental Impact:** The potential environmental impact of nanoparticles should be taken into account during the safety evaluation, particularly if they are released into the environment during waste disposal (Dwivedi et al., 2011).
- **Drug Interactions:** Potential drug interactions should be taken into account if antifungal treatments are transported via nanoparticles to prevent negative side effects or changed pharmacokinetics (Dobrovolskaia et al., 2016).

Preclinical studies utilizing suitable *in vivo* and *in vitro* models are required to confirm the safety of nanoparticles for the treatment of candidiasis (Desai et al., 2010). These investigations can be used to evaluate nanoparticle formulations, find potential toxicities, and evaluate how well they work against different Candida species (Rencber et al., 2016). When transferring nanoparticle-based medicines from research to clinical practice, regulatory standards and ethical issues should be followed (Qais et al., 2019).

Conclusion

It is important to remember that the effectiveness of antifungal nanoparticles might vary based on a number of variables, including the kind, size, surface charge, and the particular fungus species targeted. To ensure their therapeutic applicability, nanoparticles' safety and long-term effects need

to be thoroughly assessed. While antifungal medicines based on nanoparticles show significant potential, further study is required to improve the formulation, dosage, and targeting methods. Before they can be widely utilized in clinical settings for the treatment of fungal infections, regulatory authorization and clinical trials are required to confirm their safety and effectiveness. Despite these difficulties and ongoing discussions, research into using nanoparticles as an antifungal to treat candidiasis is still moving forward. Nanoparticle research is fascinating because of the potential advantages of tailored medication delivery, decreased drug resistance, and increased efficacy. However, further extensive studies, including clinical trials and preclinical, are required to make a firm determination regarding the safety and effectiveness of nanoparticles for treating candidiasis in people.

Acknowledgments

First Author: Muhammad Najamul Hassan

Corresponding Author: Muhammad Sajid

Conflict

No conflict of interest.

References

Abi-Said D et al., 1997. The epidemiology of hematogenous candidiasis caused by different Candida species. Clinical Infectious Diseases 24:1122-1128.

Adam RZ and Khan SB, 2022. Antimicrobial Efficacy of Silver Nanoparticles against Candida Albicans. Materials 15:5666.

Ahmad NS et al., 2019. Antifungal activity of titanium dioxide nanoparticles against Candida albicans. BioResources 14:8866-8878.

Aoki W et al., 2011. Comprehensive characterization of secreted aspartic proteases encoded by a virulence gene family in Candida albicans. The journal of biochemistry 150:431-438.

Arruda SCC et al., 2015. Nanoparticles applied to plant science: a review. Talanta, 131:693-705.

Balkis MM et al., 2002. Mechanisms of fungal resistance: an overview. Drugs 62:1025-1040.

Ben-Ami R, 2018. Treatment of invasive candidiasis: A narrative review. Journal of Fungi 4:97.

Berman J, 2012. Candida albicans. Current biology 22:620-622.

Biswas P and Wu CY, 2005. Nanoparticles and the environment. Journal of the air and waste management association 55:708-746.

Cai P et al., 2018. Combinatorial nano–bio interfaces. ACS Nano 12:5078-5084.

Calderone RA and Fonzi WA, 2001. Virulence factors of Candida albicans. Trends in microbiology 9:327-335.

Campbell JX et al., 2022. Zinc binding inhibits cellular uptake and antifungal activity of Histatin-5 in Candida albicans. ACS Infectious Diseases 8:1920-1934.

Carmo PHFD et al., 2023. Metal Nanoparticles to Combat Candida albicans Infections: An Update. Microorganisms 11:138.

Chaudhari MB et al., 2016. Solid lipid nanoparticles of amphotericin B (AmbiOnp): in vitro and in vivo assessment towards safe and effective oral treatment module. Drug Delivery and Translational Research 6:354-364.

Chen H et al., 2020. The regulation of hyphae growth in Candida albicans. Virulence 11:337-348.

Choi S et al., 2014. Smart nanomaterials for biomedics. Journal of Biomedical Nanotechnology 10:3162-3188.

Coleman DC et al., 1998. Importance of Candida species other than Candida albicans as opportunistic pathogens. Medical Mycology 36:156-165.

Cui J et al., 2015. Synergistic combinations of antifungals and anti-virulence agents to fight against Candida albicans. Virulence 6:362-371.

Cutler JE, 1991. Putative virulence factors of Candida albicans. Annual review of microbiology 45:187-218.

Desai P et al., 2010. Interaction of nanoparticles and cell-penetrating peptides with skin for transdermal drug delivery. Molecular Membrane Biology 27:247-259.

Dobrovolskaia M A et al., 2016. Current understanding of interactions between nanoparticles and the immune system. Toxicology and Applied Pharmacology 299:78-89.

Donaldson K et al., 2010. Possible genotoxic mechanisms of nanoparticles: criteria for improved test strategies. Nanotoxicology 4:414-420.

Dwivedi PD et al., 2011. Impact of nanoparticles on the immune system. Journal of Biomedical Nanotechnology 7:193-194.

Florence AT, 2012. "Targeting" nanoparticles: the constraints of physical laws and physical barriers. Journal of Controlled Release 164:115-124.

Frohlich E et al., 2009. Cytotoxicity of nanoparticles independent from oxidative stress. The Journal of Toxicological Sciences 34:363-375.

Ghormade, V et al., 2011. Perspectives for nano-biotechnology enabled protection and nutrition of plants. Biotechnology advances 29:792-803.

Giraldo JP et al., 2019. Nanobiotechnology approaches for engineering smart plant sensors. Nature nanotechnology 14:541-553.

Grenha A, 2012. Chitosan nanoparticles: a survey of preparation methods. Journal of Drug Targeting 291-300.

Gullo A, 2009. Invasive fungal infections: the challenge continues. Drugs 69:65-73.

Gupta P et al., 2021. Dissecting the anti-biofilm potency of kappa-carrageenan capped silver nanoparticles against Candida species. International Journal of Biological Macromolecules 172:30-40.

Haynes K, 2001. Virulence in Candida species. Trends in microbiology 9:591-596.

Heykants J et al., 1989. The clinical pharmacokinetics of itraconazole: an overview. Mycoses 32:67-87.

Hoenigl M et al., 2022. COVID-19-associated fungal infections. Nature microbiology 7:1127-1140.

Hu J et al., 1999. Chemistry and physics in one dimension: synthesis and properties of nanowires and nanotubes. Accounts of chemical research 32:435-445.

Inigo M et al., 2012. Antifungal activity against Candida biofilms. The International journal of artificial organs 35:780-791.

Jain KK, 2007. Applications of nanobiotechnology in clinical diagnostics. Clinical chemistry 53: 2002-2009.

Jamieson T et al., 2007. Biological applications of quantum dots. Biomaterials 28:4717-4732.

Jarvis WR, 1995. Epidemiology of nosocomial fungal infections, with emphasis on Candida species. Clinical Infectious Diseases 20:1526-1530.

Kayser O et al., 2005. The impact of nanobiotechnology on the development of new drug delivery systems. Current pharmaceutical biotechnology 6:3-5.

Kim BY et al., 2010. Nanomedicine. New England Journal of Medicine, 363:2434-2443.

Komarneni S, 1992. Nanocomposites. Journal of Materials Chemistry 2:1219-1230.

Kraisit P et al., 2021. Fluconazole-loaded solid lipid nanoparticles (SLNs) as a potential carrier for buccal drug delivery of oral candidiasis treatment using the Box-Behnken design. Journal of Drug Delivery Science and Technology 63:102437.

Lai CC et al., 2008. Current challenges in the management of invasive fungal infections. Journal of Infection and Chemotherapy 14:77-85.

Lara HH et al., 2015. Effect of silver nanoparticles on Candida albicans biofilms: an ultrastructural study. Journal of Nanobiotechnology 13:1-12.

Lara HH et al., 2018. Synergistic antifungal effect of chitosan-stabilized selenium nanoparticles synthesized by pulsed laser ablation in liquids against Candida albicans biofilms. International Journal of Nanomedicine 2697-2708.

Lawrence DA and McCabe JrMJ, 2002. Immunomodulation by metals. International Immunopharmacology 2:293-302.

Leleu G et al., 2002. Systemic candidiasis in intensive care units: a multicenter, matched-cohort study. Journal of critical care 17:168-175.

Lemke A et al., 2005. Amphotericin b. Applied Microbiology and Biotechnology 68:151-162.

Levchenko I et al., 2018. Recent progress and perspectives of space electric propulsion systems based on smart nanomaterials. Nature Communications 9:879.

Lipovsky A et al., 2011. Antifungal activity of ZnO nanoparticles—the role of ROS mediated cell injury. Nanotechnology 22:105101.

Liu WT, 2006. Nanoparticles and their biological and environmental applications. Journal of Bioscience and Bioengineering 102:1-7.

Lo HJ et al., 1997. Nonfilamentous C. albicans mutants are avirulent. Cell 90:939-949.

Lohse MB et al., 2020. Combination of antifungal drugs and protease inhibitors prevent Candida albicans biofilm formation and disrupt mature biofilms. Frontiers in Microbiology 11:1027.

Manke A et al., 2013. Mechanisms of nanoparticle-induced oxidative stress and toxicity. BioMed research international.

Mathur M and Devi VK, 2017. Potential of novel drug delivery systems in the management of topical candidiasis. Journal of Drug Targeting 25:685-703.

Mayer FL et al., 2013. Candida albicans pathogenicity mechanisms. Virulence 4:119-128.

Mba IE and Nweze EI, 2020. The use of nanoparticles as alternative therapeutic agents against Candida infections: an up-to-date overview and future perspectives. World Journal of Microbiology and Biotechnology 36:1-20.

McCormack PL and Perry CM, 2005. Caspofungin: a review of its use in the treatment of fungal infections. Drugs 65:2049-2068.

Monteiro DR et al., 2015. Susceptibility of Candida albicans and Candida glabrata biofilms to silver nanoparticles in intermediate and mature development phases. Journal of Prosthodontic Research 59:42-48.

Moran GP et al., 2012. Candida albicans versus Candida dubliniensis: why is C. albicans more pathogenic?. International journal of microbiology.

Nguyen M et al., 2010. Infantile hypercalcemia and hypercalciuria: new insights into a vitamin D-dependent mechanism and response to ketoconazole treatment. The Journal of Pediatrics 157:296-302.

Ota C et al., 2001. Antifungal activity of propolis on different species of Candida. Mycoses 44:375-378.

Panacek A et al., 2009. Antifungal activity of silver nanoparticles against Candida spp. Biomaterials 30:6333-6340.

Pandey G, 2018. Challenges and future prospects of agri-nanotechnology for sustainable agriculture in India. Environmental Technology and Innovation 11:299-307.

Pestovsky YS and Martínez-Antonio A, 2017. The use of nanoparticles and nanoformulations in agriculture. Journal of Nanoscience and Nanotechnology 17:8699-8730.

Qais FA et al., 2019. Potential of nanoparticles in combating Candida infections. Letters in Drug Design and Discovery 16:478-491.

Rana S et al., 2021. Evaluation of in vivo toxicity of novel biosurfactant from Candida parapsilosis loaded in PLA-PEG polymeric nanoparticles. Journal of Pharmaceutical Sciences 110:1727-1738.

Reboli AC et al., 2007. Anidulafungin versus fluconazole for invasive candidiasis. New England Journal of Medicine 356:2472-2482.

Rençber S et al., 2016. Development, characterization, and in vivo assessment of mucoadhesive nanoparticles containing fluconazole for the local treatment of oral candidiasis. International Journal of Nanomedicine.

Roco MC, 1999. Nanoparticles and nanotechnology research. Journal of nanoparticle research 1:1.

Sabir S et al., 2014. Zinc oxide nanoparticles for revolutionizing agriculture: synthesis and applications. The Scientific World Journal.

Sanguinetti M et al., 2015. Antifungal drug resistance among Candida species: mechanisms and clinical impact. Mycoses 58:2-13.

Saravolatz LD et al., 2003. Voriconazole: a new triazole antifungal agent. Clinical Infectious Diseases 36:630-637.

Scherer S and Magee PT, 1990. Genetics of Candida albicans. Microbiological reviews 54:226-241.

Sharma RK and Ghose R, 2015. Synthesis of zinc oxide nanoparticles by homogeneous precipitation method and its application in antifungal activity against Candida albicans. Ceramics International 41:967-975.

Silva S et al., 2013. The effect of silver nanoparticles and nystatin on mixed biofilms of Candida glabrata and Candida albicans on acrylic. Medical Mycology 51:178-184.

Singh M et al., 2013. Metallic silver nanoparticle: a therapeutic agent in combination with antifungal drug against human fungal pathogen. Bioprocess and Biosystems Engineering 36:407-415.

Spadari CDC et al., 2019. Alginate nanoparticles as non-toxic delivery system for miltefosine in the treatment of candidiasis and cryptococcosis. International Journal of Nanomedicine.

Soliman GM, 2017. Nanoparticles as safe and effective delivery systems of antifungal agents: Achievements and challenges. International Journal of Pharmaceutics 523:15-32.

Staib P et al., 1999. Host-induced, stage-specific virulence gene activation in Candida albicans during infection. Molecular microbiology 32:533-546.

Sudbery P et al., 2004. The distinct morphogenic states of Candida albicans. Trends in Microbiology 12:317-324.

Sudbery PE, 2011. Growth of Candida albicans hyphae. Nature Reviews Microbiology 9:737-748.

Umer A et al., 2012. Selection of a suitable method for the synthesis of copper nanoparticles. Nano Research 7:1230005.

Vera-Gonzalez N and Shukla A, 2020. Advances in biomaterials for the prevention and disruption of Candida biofilms. Frontiers in Microbiology 11:538602.

Vikrant P et al., 2015. Plants with anti-Candida activity and their mechanism of action: a review. Journal of Environmental Research and Development 9:1189.

Wang EC and Wang AZ, 2014. Nanoparticles and their applications in cell and molecular biology. Integrative Biology 6:9-26.

Weitz IS et al., 2015. Combination of CuO nanoparticles and fluconazole: preparation, characterization, and antifungal activity against Candida albicans. Journal of Nanoparticle Research 17:1-9.

Whiteway M and Bachewich C, 2007. Morphogenesis in Candida albicans. Annual review of microbiology 61:529-553.

Wingard JR, 1995. Importance of Candida species other than C. albicans as pathogens in oncology patients. Clinical infectious diseases 20:115-125.

Yang G et al., 2019. Degradability and clearance of inorganic nanoparticles for biomedical applications. Advanced Materials 31:1805730.

Zhang W et al., 2016. The neglected nano-specific toxicity of ZnO nanoparticles in the yeast Saccharomyces cerevisiae. Scientific Reports 6:24839.

Zhao L et al., 2020. Nano-biotechnology in agriculture: use of nanomaterials to promote plant growth and stress tolerance. Journal of agricultural and food chemistry 68:1935-1947.