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Antifungal Potency of Green-Fabricated Nanoparticles-An Overview of Recent Advances

AUTHORS DETAIL

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INTRODUCTION

Fungi are eukaryotic unicellular or multi-cellular organisms found in all types of environments across the world. They have various shapes and sizes, ranging from the size that can be seen with the naked eye, like mushrooms, to tiny yeasts and molds. Several hundred fungi cause fungal infections or diseases, even though the majority of fungi do not significantly contribute to human diseases (McKeny et al. 2021).

Invasive fungal diseases (IFDs), which collectively affect more than a billion people worldwide, are common diseases caused by fungi that range from allergic syndromes to superficial, and debilitating diseases that may be fatal (Bongomin et al. 2017). Invasive fungal infections severely threaten public health and are an underappreciated aspect of the global antimicrobial resistance crisis. Pathogenic fungi that infect people are developing resistance to all approved systemic antifungal medications during a time of significant environmental change worldwide and growing at-risk populations (Fisher et al. 2022).

Opportunistic fungal pathogens are frequently found in our close environments, and many have a high spore production capacity. As a result, various environmental fungal pathogens are regularly inhaled by humans as bioaerosols. Those with weakened health or immunity are more susceptible to several illnesses, including superficial, allergic, chronic, and life-threatening IFDs. At the same time, most environmental fungi do not manifest any observable pathophysiological events in healthy people. The number of patients at risk for IFDs is rising, and older people are among those (Fisher et al. 2022). Indoor and outdoor environments are both favourable to fungi, according to the statement "Risk increases synchronously with a time of exposure," however, indoor airborne fungi are more effective on human health than outdoor airborne fungi (Omolola et al. 2018; Al-Bader et al. 2021).

Aspergillus species., *Candida* spp., involving *C. auris*, and *Mucoromycota* spp., which display strong innate and acquired resistance to antifungal therapies, have increased their prevalence in patients with severe viral infections for instance the influenza virus and COVID-19 patients (Singh et al. 2016; Arastehfar et al. 2020; Janssen et al. 2021). The vulvovaginal candidiasis is also more prevalent among women (Shnawa et al., 2018). Invasive infections brought on by filamentous fungi have posed a significant threat to public health over the past few years on a global scale. Human infections can be acquired by *Aspergillus*, *Coccidioides*, *Mucorales* (the most prevalent filamentous fungi), and *C. auris* (a non-filamentous fungus). They can cause life-threatening illnesses in immunosuppressed people, HIV/AIDS patients, people with uncontrolled diabetes, people with haematological diseases, people undergoing chemotherapy, and transplant recipients (León-Buitimea et al. 2021).

Just four classes of systemically acting antifungal medications have historically dominated. The treatment includes polyenes, azoles, echinocandins, and the pyrimidine analogue 5-flucytosine (Robbins et al. 2017). They all have disadvantages regarding pharmacokinetics, pharmacodynamics, resistance mechanisms, and the compounds' toxicity, in addition to their range of activity limitations. Additionally, there are some restrictions on clinical efficacy and efficiency, primarily due to their physical and chemical characteristics, such as their hydrophobic nature, which results in low solubility in water, and selectivity issues resulting from the similarities between fungi and human cells (Chang et al. 2017; Souza et al. 2017). Moreover, Traditional systemic mycosis antifungal therapy is expensive, frequently limited, and has significant toxic side effects. Nanotechnology has emerged as a novel strategy to increase the effectiveness of conventional antifungal medications and enhance the activity of antifungal drugs. It enables lower toxicity, better biodistribution, drug targeting and promising in vitro and in vivo outcomes (Souza et al. 2017). Nanoparticles are considered significant alternatives to help in drug delivery (Renzi et al. 2021). Using these NPs in conjunction with antifungals has been shown to raise solubility, improve permeability, and bioavailability, increase storage stability, prolong half-life, reduce therapeutic cost, and ensure proper drug dosage (Faustino et al. 2020). Although, finding new antifungal drugs faces a

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particular challenge due to the rising incidence of fungal diseases resistant to treatment. Recently, nanotechnology applications have been included among the most promising areas of study to address these issues. The ability of nanoparticles to target specific locations where fungi are found, their capacity to improve the pharmacological effects of medications, and their potential to optimize their physiochemical properties have all been mentioned as reasons why they represent possible solutions (Sousa et al. 2020).

Nanobiotechnology

Nano-biotechnology is a division of nanotechnology that offers NPs production for specific applications with little risk of bio-systems resource influences. " Nanobiotechnology" refers to a broad field that includes the production and subsequent use of particles smaller than 100 nm (Ahmad et al. 2003; Shnawa et al. 2021 a).

Recent studies have concentrated on developing practical, eco-friendly green methods for generating metal NPs.The Green production of metal NPsis easy, clean, effective, safe and non-expensive as they use bio-resources (plants, fungi, algae, and microorganisms) that can serve as reducing and stabilizing agents. Currently, NPs of some metals or metal oxides are used as a medication to treat different diseases and enhance human health due to their antimicrobial action (Lee et al. 2011; Shnawa 2018). Plants, algae, filamentous fungi, yeast, bacteria, and viruses are a few examples of the various organisms that could be considered sources for NPs. Some scientists looked into using microorganisms to make NPS out of eco-friendly materials like cadmium, gold sulphide, and silver (Ahmad et al. 2016; Mukherjee et al. 2001). Bacteria, Actinomycetes, and fungi were applied to make NPs (Singh et al. 2016). The biosynthesis of nanoparticles has certain advantages over other techniques; 1- phytochemicals found in plant extracts will reduce, cap, and stabilize the nanoparticles. 2- these phytochemicals can be produced in a single pot and are non-toxic, inexpensive, and environmentally friendly. 3- some OH and other functional groups continue to bind with the nanoparticles even after the separation and purification stages of NP preparation, making the nanomaterials more reactive than those made using other techniques (Raj et al. 2018; Shnawa et al. 2021 b) as shown in Fig. 1.

Nowadays, under experimental and greenhouse circumstances, the fungicidal activity of MgO nanoparticles (nMgO) is assessed against soilborne *Phytophthora nicotianae* and *Thielaviopsis basicola*. According to in vitro research, nMgO is more effective than macroscale equivalents at suppressing sporangium development, spore germination, and fungal growth. It was discovered that there were direct contact interactions between nanoparticles and fungal cells or that they adhered to them, which led to changes in cell morphology (Chen et al. 2020). Depending to Jamdagni et al. (2018) study, green-synthesized ZnO nanoparticles (NPs) demonstrated effective antifungal activity. They found that *Aspergillus niger* was the most sensitive among the tested fungi. Furthermore, extensive studies have used nanoparticles to treat mycoses, especially corneal and invasive infections (Balabathula et al. 2020; Faustino et al. 2020). Previously, Xia et al. (2016) demonstrated the effectiveness of silver nanoparticles by showing antifungal properties against the pathogenic and medication-resistant fungus *Trichosporon asahii*.

Regarding the biocompatibility of the green synthesized nanoparticles, Jalil et al. (2021) showed no noticeable toxic effect of Ag NPs at low concentrations on RBCs. They emphasized that the green fabricated AgNPs are biocompatible and can be used as safe agents at low concentrations. Another recent finding concluded that the bio-synthesis ZnO-NPs from *Z. spina-christi* leaf were biocompatible at the tested experimental levels (Shnawa et al. 2022). Some significant recent articles summarizing the biosynthesis of different nanoparticles with their antifungal potency are shown in Table 1.

Mechanisms of Action of Nanoparticles against Fungi

Regarding antifungal compounds, it's crucial to consider the nanoparticles' site of action (on the cell membrane, cell wall, DNA, or RNA), as well as their surface properties. The portion of the cell that communicates with the outside world is the fungal wall, which regulates cell permeability. ZnO nanoparticles caused the cytoplasmic contents to liquefy, which reduced the cytoplasm's electron density and resulted in a noticeable separation of the fungal cell wall (Arciniegas-Grijalba et al. 2017). Moreover, Gunalan et al. (2012) concluded that compared to chemical ZnO nanoparticles and other common antimicrobials, biologically synthesized ZnO had a higher growth inhibition of fungi and bacteria. Smaller particles' increased bioactivity is attributed to their high surface area-to-volume ratio. According to Jamdagni et al. (2018), Ag-NPs significantly disrupt the target microorganisms' cell walls and plasma membranes, causing pores to form and electrolyte imbalances. The broken membrane allows fungicides to enter cells more effectively (Khatami et al. 2018).

Additionally, these ZnO-NPs demonstrated antifungal activity against the pathogenic fungus *Erythricium salmonicolor*, which causes the coffee crop disease, which is also known as the pink disease (Arciniegas-Grijalba et al. 2017).

Erazo et al. (2019) further concluded that reactive oxygen species are produced due to the electronic properties of the semiconductor material and the ZnO-NPs' capacity to obstruct electron transfer in biological systems. The ZnO-NPs' surface reaction with water produces hydroxyl radical (OH) and hydrogen peroxide H_2O_2.

The fungal cell wall significantly contains chitin and chitosan. They have more than 7% nitrogen (N) content. Additionally, they have a regular distribution of free amino groups, which particular acids can positively charge them by protonation and giving them a polycation performance.

Table 1: Antifungal potency of nanoparticles fabricated from bio sources.

Nanoparticles	Green sources	Antifungal potency	References
Selenium (SeNPs)	*Halomonas elongate* bacterium	Antifungal properties against *C. albicans*.	(Safaei et al. 2022)
Selenium (SeNPs)	Green synthesis	Antifungal properties of nanoparticles (SeNPs) against *C. albicans* and *C. glabrata*	(Hosseini Bafghi et al. 2022)
Selenium (Se NPs)	Fabricated by Bacillus species Msh-1	Against *A. fumigatus* and *C. albicans*. They demonstrated that mould cells were less sensitive than yeast cells.	(Shakibaie et al. 2015)
Silver (AGNPs)	Green production of AgNPs using ribose as a reducing agent	They demonstrated high action against *C. albicans* and *C. tropicalis*	(Mallmann et al. 2015)
Silver (AgNPs)	Silver nanoparticles (AgNPs) were synthesized by *Ligustrum lucidum* leaf extract.	The antifungal properties particularly notable against the phytopathogen *Setosphaeria turcica*	(Huang et al. 2020)
Silver (AgNPs)	Green biosynthesized	*A. fumigates*, *A. niger*, *A. flavus*, *Trichophyton rubrum*, *C. albicans*, and Penicillium species have all displayed growth inhibition by AgNPs.	(Mansoor et al. 2021)
Zinc oxide (ZnO NPs)	Aloe leaf broth extract	Revealed activity against fungal strains *A. flavus*, *A. nidulans*, *Trichoderma harzianum*, and *Rhizopus stolonifer*	(Gunalan et al. 2012)
Zinz oxide (ZnO NPs)	Flower extract of *Nyctanthes arbor-tristis*	*Active against Alternaria alternata* , *Aspergillus niger* , *Botrytis cinerea* (ITCC 6192), *Fusarium oxysporum* and *Penicillium expansum*	(Jamdagni et al. 2018)
Silver (AgNPs)	Waste-grass-mediated green synthesis	*Fusarium solani and Rhizoctonia solani*. The highest effect of AgNPs against *F. solani* was 90% at a concentration of 20 µg/ml of AgNPs.	(Khatami et al. 2018)
Gold (Au NPs)	AuNPs produced from *Garcinia kola* leaf	Activity against *Fusarium oxysperium* was greater than *C. albican*, and *Penicillium camemeri* was greater than *A. flaws*	(Adekunle et al. 2020)
Gold (AuNPs)	AuNPs biosynthesized by mycelial biomass of endophytic fungus *Phoma* sp.	Antifungal activity against *R. solani* (the rice fungal pathogen).	(Soltani Nejad et al. 2022)
Silver (AgNPs)	Biofabricated AgNPs using cell-free filtrate of *Trichoderma viride*	Compared to chemically fabricated Ag, biosynthesized Ag NPs improved the reduction in dry weight of *Fusarium oxysporum* and *Alternaria brassicicola* by 20% and 48.8%, respectively.	(Kumari et al. 2019)
Ag-Cu NPs	Ag-Cu NPs from bark extracts of *Garcina kola*	Showed antifungal activity and ordered as *A. flavus* > *Candida albicans* > *Fusarium oxysperium*> *Candida tropicalis*	(Akintelu and Folorunso 2019)

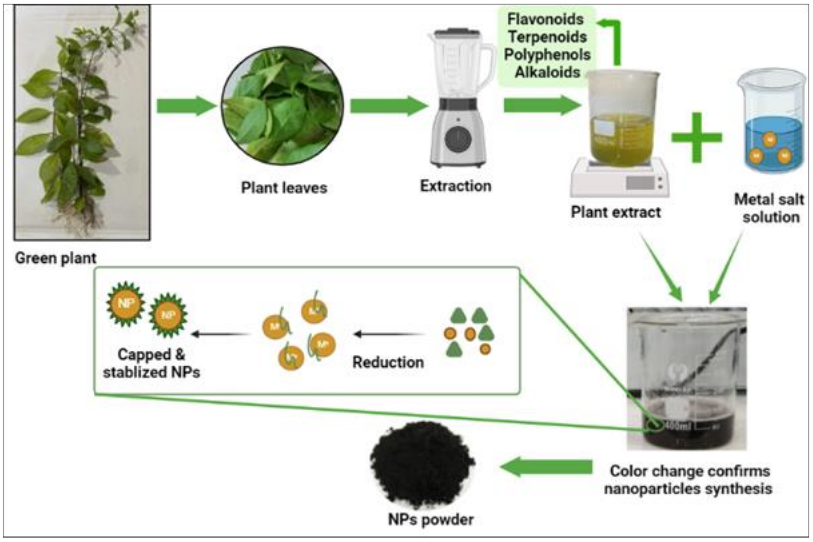

Fig. 1: General mechanism for green synthesis of nanoparticles. Phenols, flavonoids and others are secondary metabolites of plants that have been reported to act as bio-reductants of metallic ions in an aqueous environment. The functional groups in these plant components serve as reducing, capping and stabilizing agents for nanoparticle synthesis

This led to, lipids, proteins, dyes, and other negatively charged substances can all be bound to chitin. As a result, these characteristics would also make the chitosan vulnerable to attack by reactive oxygen species (ROS) (Erazo et al. 2019).

It is shown that various metal nanoparticles, for instance, Ag-NPs, ZnO-NPs, and CuO-NPs, as well as their ions (Ag+, Zn2+, and Cu2+), are toxic to fungi. The toxicity mechanism against fungi varies depending on the metal nanoparticles' physicochemical properties, the concentration used, and the soil environment (Ameen et al. 2021).

A study examined the antifungal activity of AgNPs and their mechanisms against the fungicide-resistant and fungicide-sensitive strains of *F. graminearum*. They also clarified their effects on the production of mycotoxin deoxynivalenol (DON) and evaluated the potential of AgNPs for the management of *Fusarium* head blight (FHB) disease in cereal crops.

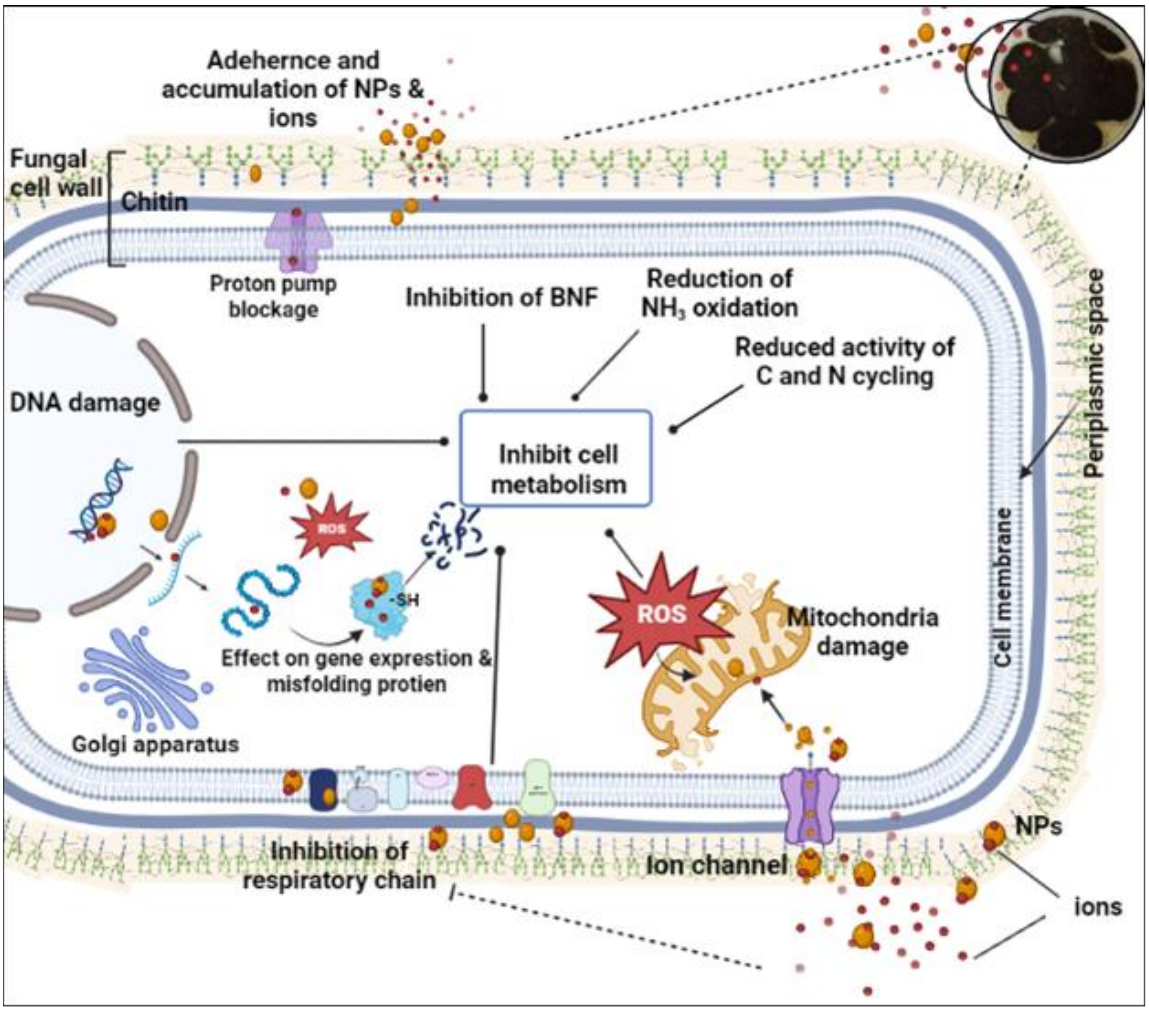

Fig.2: Proposed mechanisms for antifungal activity of NPs. The NPs are introduced into the cell through proton pumps and enhance reactive oxygen species, causing harm to the cytoplasmic organelles, inhibiting proton pumps, damaging the cell wall, and targeting the metabolic process. ROS: Reactive oxygen species, NPs: Nanoparticles, and BNF: Biological nitrogen fixation.

Silver nanoparticles (AgNPs) exhibit excellent antifungal activity against both fungicide-sensitive and -fungicide-resistant *F. graminearum* strains through several mechanisms, including disruption of fungal development and cell membranes as well as disruption of cellular energy utilisation and metabolism pathways. Even though AgNPs may upregulate azole resistance-related ATP-binding cassette (ABC) transporter genes, the control efficacy of the fungicides was unaffected. But each coin has double sides: AgNPs have potent antifungal action against *F. graminearum.* However, these can also be able to lead to increased production of the infamous mycotoxin deoxynivalenol (DON). AgNPs must be utilized as efficient and alternative medicinal candidates for pathogens that produce mycotoxin by balancing their antifungal action and DON fabrication. Combining AgNPs and DON-reducing fungicides may be an option for managing FHB disease. Future research is required to assess AgNPs' antimicrobial potential in practical agricultural settings (Jian et al. 2022).

To overcome fungi resistance, AgNPs are used. AgNPs disrupt cell walls, damage surface proteins, harm nucleic acids by generating and accumulating ROS and free radicals, and obstruct proton pumps. According to Du et al. (2012), AgNPs cause the accumulation of silver ions, which interferes with intracellular ion efflux and inhibits respiration, causing harm to the electron transport system. The antifungal activity of nanoparticles is attributed to their smaller size to large surface ratio. AgNPs that are smaller in size can easily cross cell boundaries. AgNPs' toxicity is partially explained by the generation of ROS, which triggers apoptosis. According to various theories (Beer et al. 2012; Kim and Ryu 2013), the in vitro toxicity of AgNPs is caused by either the interaction of Ag ions and AgNPs or their effects. Further research is required to determine the precise mechanisms and modes of action of AgNPs (Mansoor et al. 2021). The proposed mechanisms of NPs action against fungi are illustrated in Fig. 2.

Antifungal Drugs and Nanoparticles for Antifungal Drug Delivery

The main variety of antifungal drugs used in mycoses therapy contains polyenes (amphotericin B, hamycin, natamycin, and nystatin), azoles (imidazoles such as ketoconazole, miconazole, etc.), triazoles (fluconazole, itraconazole, ravuconazole, posaconazole, etc.), thiazole (abafungin), pyrimidine analogue (flucytosine), squalene monooxygenase (allylamines (naftifine, and terbinafine), benzylamine (butenafine), and mitotic inhibitor (griseofulvin) (Campoy et al. 2017; Nami et al. 2019). Nanoparticles are particularly used to treat fungal infections. Because of their unique properties, these particles—unlike pure antibiotics—can exert a more substantial inhibitory power even when used in lower concentrations than pharmaceuticals. Antifungal drugs have been used in delivery systems despite their poor pharmacokinetics, decreased efficacy, limited tissue penetration, poor aqueous solubility, decreased bioavailability, side effects, and drug stability. These factors are significant and well-known (Soliman 2017; Hassanpour et al. 2020).

New therapeutic options for treating aspergillosis and infections caused by *Candida* have been developed using various strategies, including incorporating coating materials, complexes made through green chemistry, or combining polymers. However, there are few treatment options for coccidioidomycosis and mucormycosis, and the majority of them are still in the research and development stage (León-Buitimea et al. 2021). Hence, more studies are needed to explore novel therapeutic opportunities that solve this problem. Nanoparticles can overcome several unfavourable drug characteristics of flexibility, multifunctionality, and broad properties (Nami et al. 2021).

Various NPs subtypes are used as antifungal delivery systems, which include:

1-Solid lipid Nanoparticle

The characteristics of the drugs loaded in such a formula depend on the components used and the characteristics of the drugs. Real problems are observed in the cases of cutaneous infections treated by traditional systemic medicines. The first is poor medication accessibility at the infection site and the second is the drug toxicity and side effect of drugs. The new drugs are characterized by continued release, biocompatibility, and decreasing side effects (Pople et al. 2006; Trombino et al. 2016).

2- Nanostructured Lipid Carrier

In this application, solid and liquid lipids are composed of an essential matrix (Aghebati-Maleki et al. 2020). The solubility of the compound increase when mixed with antifungals. The shape of molecules is also betters encapsulated, and they have a high affinity to bind with cell receptors; thus, they are absorbed faster. Finally, using NLCs as drug carriers expands the drug's effective period in the body by protecting the composition from biodegradation (Haider et al. 2020). Amphotericin-B was loaded in such a composition and gave a better result in treating keratitis (Fu et al. 2017).

3- Cubic Liquid Crystalline Nanoparticle

This structure, also known as cubosomes, is a discrete nanostructured particle characterized by its bio-adhesive and biocompatibility properties (Spicer 2005). Several properties were observed for cubosomes when they were used as drug carriers, and they possess a small size with minimal viscosity and larger interfacial areas. The core of the molecule is hydrophobic. The structural properties result in efficient drug loading (Yang et al. 2012; Zhang et al. 2020).

4- Silver Nanoparticles

Silver nanoparticles (AgNPs) have been widely used in medicine. The particles have distinctive chemical and physical characteristics. They possess thermal, high electrical conductivity and biological properties (Nozari et al. 2012; Zhang et al. 2016). Studies showed that the combination (amphotericin-B /silver nanoparticles) has high antifungal activity against *Candida, Aspergillus,* and *Fusarium* than the pure drug (Ahmad et al. 2016; Tutaj et al. 2016).

5- Polylactic-co-glycolic Acid Nanoparticle

For the past 20 years, polylactic-co-glycolic acid (PLGA) is one of the greatest alluring polymeric candidates used to create devices for tissue engineering and drug delivery. In addition to having a wide range of erosion times, tunable mechanical properties, and of utmost importance, being an FDA-approved polymer, PLGA is also biocompatible and biodegradable. In particular, PLGA has received extensive research attention for creating devices for the controlled delivery of small-molecule medications, proteins, and other macromolecules in both commercial and academic settings (Makadia et al. 2011).

6- Gelatin as a Natural, Adaptable Biopolymer

Collagen is hydrolyzed to produce the protein known as gelatin. For use in nanobiotechnology and nanopharmaceuticals, gelatin is a desirable biodegradable material. Due to their biocompatibility and biodegradability, gelatin nanoparticles (NPs) have been widely used as a drug and gene carrier to target sick tissues, including cancer, tuberculosis, HIV infection, and the treatment of vasospasm and restenosis (Yasmin et al. 2017). In a 2017 study on managing infection and inflammation in keratitis, Ahsan and

Rao created a double-desolvation ketoconazole-encapsulated gelatin nanoparticle. They discovered that these NPs could lengthen drug residence time, reduce inflammatory cytokines, and release antifungal drugs in their study on *Aspergillus flavus*- infected corneas of rats (Ahsan and Rao 2017).

Conclusion

Due to their rising annual incidences and mortality rates, fungal infections are becoming more and more critical in today's world. The majority of commercially available antifungals are successful in treating these fungi, but due to problems with tissue penetration, aqueous solubility, reduced bioavailability, drug efficacy and resistance, side effects, and drug pharmacokinetics, researchers have been looking for ways to enhance the effectiveness of the currently available medications. In order to maximize the effectiveness of antifungals over the past 20 years, the use of NPs drug-delivery systems to broaden the scope of antifungal functions has become increasingly important. Consequently, more study is needed to develop promising therapeutic opportunities that lead to advancement in this field.

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