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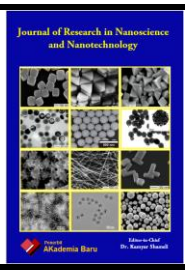

Mini Review: Biologically Synthesized Nanoparticles as Antifungal Agents

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ABSTRACT

Fungal infections are affecting millions of people in the world every year. Severity of infections range from superficial mycoses to more chronic systemic mycoses. As more fungi species evolve, emergence of drug resistant strains is becoming a serious concern to the public health. There is now less number of effective antifungal drugs available in the market for treatment of invasive fungal infections. In an effort to combat this escalating issue, the use of nanoparticles as antifungal agent has been proposed and explored. Versatility of nanoparticles and its unique physico-chemical properties are proven beneficial for developing new therapeutic methods in treatment of fungal infections. Nanoparticles produced from biological synthesis have attracted keen interests from researchers, as they are more environmentally friendly, sustainable, cost-effective, and biocompatible. This mini review will provide an insight on the current antifungal studies and discuss the theory behind mechanism of actions of nanoparticles.

Keywords:
Biological synthesis, nanoparticles,
antifungal, drug resistance.

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1. Introduction

Fungi are abundant group of organisms that can be found in a wide range of habitats around the world including forests, deserts, deep in the ocean as well as polar regions [1]. There are about 250,000 types of fungi species currently known worldwide. Most of the fungi play important roles in the ecosystems especially in the degradation process of organic matters [1, 2]. Besides that, fungi are considered essential towards human population as various drugs and enzymes are often derived from them. Nevertheless, about 300 types of fungi have been categorized as potentially pathogenic or true pathogens as they can cause infections in living things including humans, animals and plants [2].

Infection of fungi in humans can range from superficial, only affecting skin, to more severe systemic mycoses which can damage internal organs, leading to death in the worst case scenario [3]. These fungal infections can be classified into four types; superficial mycoses, cutaneous mycoses, subcutaneous mycoses and systemic mycoses [2]. Superficial mycoses are the most common fungal infections, affecting about 25% of human population. They can spread and grow to other skin regions, is contagious to other people, and can cause secondary bacterial infections, further decreasing host's quality of life [3]. While superficial, cutaneous and subcutaneous mycoses are rarely life threatening and still manageable with antifungal drugs, the same cannot be said for systemic mycoses. Every year, millions of people are diagnosed with the invasive fungal infections and require extensive therapy as well as long-term hospitalization. Systemic mycoses are usually associated with high morbidity and mortality rate, limited and expensive antifungal therapy options, long periods of treatment and drug toxicity [4]. Compared to healthy individuals, those who are immunocompromised are at a higher risk of opportunistic infections by pathogenic fungi due to their suppressed immune system. A few high-risk groups include HIV/AIDS patients, transplant patients, and cancer patients who are undertaking immunosuppressive therapy.

Examples of chronic, widespread systemic mycoses are candidiasis, cryptococcosis and aspergillosis typically caused by *Candida*, *Cryptococcus* and *Aspergillus* species, respectively. *Candida* spp. are ubiquitous and commonly found on human mucosal surfaces such as the gastrointestinal and urogenital tracts. They are a part of the human microbiota (commensal) but can readily become pathogenic under certain conditions such as immunosuppression, or when there are changes in the normal microbial flora [5]. The most prominent species usually found causing infections in humans is *C. albicans*. Other than that, infections by *C. auris* species have been garnering concern from healthcare professionals for its multidrug-resistance properties. In addition, *Candida* spp. are notorious for their ability to form biofilm, in order to provide the fungal cells extra protection from host immune system. This defense mechanism also often results in further increase of drug resistance, making it more complicated to treat, resulting in mortality rates as high as 41% [5]. Currently, three antifungal drugs; polyenes, azoles and echinocandins are mainly used in the treatment of invasive candidiasis but their effectiveness against biofilms vary [4]. Next, cryptococcosis is an infection by *C. neoformans*/*C. gatii* species complexes [4]. These opportunistic fungal pathogens will then cause patients to develop pneumonia and/or meningitis especially in immunocompromised hosts. Lastly, aspergillosis mostly involves the lungs and paranasal sinuses, inducing an allergic-like reaction in hosts. 90% of the invasive infections are caused by *A. fumigatus* species, which are also abundant in various environments. *A. fumigatus* is said to have azole drug resistance, making it an emerging threat to the healthcare system [4].

Throughout the years, increasing reports of multidrug resistant fungi species have been reported as they evolve with time. Decreasing number of effective antifungal drugs are now available for treatment, forcing us to limit the dosage and frequency of these drugs resulting in lower efficacy and even therapeutic failure [2]. At the same time, we still have to face challenges with negative side effects and toxicity of these drugs towards patients. To combat these alarming issues, there is a need to develop more efficient therapeutic methods with improved efficacy, allows for targeted delivery of drugs to reduce toxicity and side effects,

lower dosage requirement, as well as suitable production costs [4]. Since the new therapy methods are likely to demonstrate different mechanism of action, they might work synergistically with existing drugs to achieve better response [3].

Nanotechnology has risen as a preferred field in the pharmaceutical formulations for new antifungal therapeutics due to its ability to alter the physico-chemical properties of synthesized drugs. Specifically, various types of nanoparticles have been studied for their potential in becoming efficient antifungal agent. Nanoparticles are mainly employed due to their versatility as we can make use of their intrinsic antifungal activity or utilize them as drug delivery vehicles [4]. By using nanoparticles, a lot of major obstacles of current antifungal agents such as low drug stability, poor pharmacokinetic, limited penetration through the tissues, low solubility and high toxicity can be overcome [2]. Hence, development of nanoparticles as antifungal agents is a promising strategy to improve therapeutic efficacy and minimize adverse effects of current drugs towards systemic mycoses patients [1]. This mini review will be focusing on biologically synthesized nanoparticles, their antifungal activities and mechanism of actions.

2. Biological synthesis of nanoparticles

Typically, there are two means for nanoparticles synthesis; top-down approach and bottom-up approach. In top-down approach, nanoparticles are produced after breaking down process of larger materials using physical synthesis such as ultrasonication, and thermal decomposition. Procedure using physical synthesis usually requires high amount of energy, advanced laboratory equipment for electronic excitation and it can be quite expensive. On the other hand, bottom-up approach refer to the nanometric structure built up from atomic and molecular components [6]. This approach comprises of chemical and biological synthesis. A few examples of chemical synthesis methods are vapor flux condensation, electrochemistry and chemical reduction [6]. The main drawback of chemical synthesis is the use of highly toxic chemicals that are detrimental to the environment and human health when released as by-products [7].

Biological synthesis refers to the exploitation of plant materials or microbes during the fabrication process of nanoparticles. Plant materials contain abundant organic compounds such as phenolic compounds, alkaloids and terpenoids [6]. Similarly, microbes can also produce beneficial biomolecules like enzymes, proteins and secondary metabolites [6]. These compounds can function as a reducing agent and/or stabilizer to assist in the production of size-controlled and stable nanoparticles. **Table 1** shows a list of biologically synthesized nanoparticles for antifungal studies in recent years. Biological synthesis is a facile, cost-effective and sustainable method compared to other synthesis methods. Apart from that, it has lower toxicity and is more environmentally friendly as less hazardous by-products are released into the nature, since none or minimal toxic chemicals are used. Due to these reasons, biological synthesis can be easily scaled up for industrial use.

Antimicrobial activities of nanoparticles are directly related to their physico-chemical properties for instance size, shape, surface area, solubility, aggregation and type of coating [4]. Therefore, it is vital to control the method and conditions of formulation in order to

produce nanoparticles with specific characteristics. By altering reaction parameters such as temperature, type of reducing agent/stabilizers, concentration and nature of solvent, significant changes can be observed on the synthesized nanoparticles [7].

Table 1: Nanoparticles synthesized from various biological sources for use in antifungal studies.

No.	Sample	Biological source	Size (nm)	Target fungi	Ref.
1.	TiO_2 NPs	Biomass of *Trianthema portulacastrum* and *Chopodium quinoa*	6-8	*Ustilago tritici*	[8]
2.	Ag NPs	Microwave irradiation with *Ziziphus jujuba Mill* fruit extract	8	*Aspergillus niger* *Aspergillus fumigatus*	[9]
3.	Ag NPs	Green alga (*Scenedesmus obliquus*) and blue green alga (*Spirulina platensis*)	2.83-22.66	*Candida albicans* *Candida tropicalis* *Aspergillus niger* *Fusarium solani*	[10]
4.	ZnO NPs CuO NPs	*Penicillium chrysogenum* fungi	9-35 10.5-59.7	*Fusarium solani* *Fusarium oxysporum* *Sclerotium sclerotia* *Aspergillus terreus*	[11]
5.	Ag NPs	*Citrus limetta* (sweet lime)	18	*Candida albicans* *Candida glabrata* *Candida parapsilolis* *Candida tropicalis*	[12]
6.	Ag NPs	*Plantago major* seeds extract	10-39	*Penicillium digitatum*	[13]
7.	Ag-Au NPs	Triple helix glucan (Lentinan) polysaccharide	18	*Candida albicans*	[14]
8.	Hydroxyapatite (HAp) NPs	Curcumin extract	25.57	*Odium caricae* *Aspergillus niger* *Aspergillus favus*	[15]
9.	Ag NPs	Chitosan derivatives	10-25	*Aspergillus niger* *Cryptococcus neoformans* *Candida tropicalis*	[16]
10.	IO NPs	*Rhamnella gilgitica* leaves extract	21	*Aspergillus flavus* *Fusarium solani* *Aspergillus niger* *Candida albicans*	[17]

3. Antifungal activities and mechanisms of nanoparticles

The interdisciplinary studies of nanotechnology and biomedicine has opened the door to more exciting research possibilities and allowed valuable insights into molecular biology [18]. Over the last few years, a wide range of nanoparticles have been synthesized using various biological resources for antifungal studies. Examples include silver (Ag), zinc oxide (ZnO), titanium dioxide (TiO_2), copper oxide (CuO) and iron oxide (IO) nanoparticles. Antifungal studies using these nanoparticles have revealed great potential and excellent fungicidal activities against a broad range of fungi species. In particular, human infecting fungi species such as *C. albicans, C. tropicalis*, and *A. niger* have been extensively investigated. Supplementary to that, there are also a decent number of antifungal studies against phytopathogens such as *U. tritici* and *F. oxysporum*.

One of the most widely discussed antimicrobial mechanism of nanoparticles is the reactive oxygen species (ROS)-induced oxidative stress. Upon interaction with nanoparticles, levels of intracellular ROS such as hydroxyl radical (OH), superoxide radical (O^-), and hydrogen peroxide will increase excessively, inducing destructive effects towards fungi cellular components (lipids, DNA, and proteins), subsequently causing apoptosis [6].

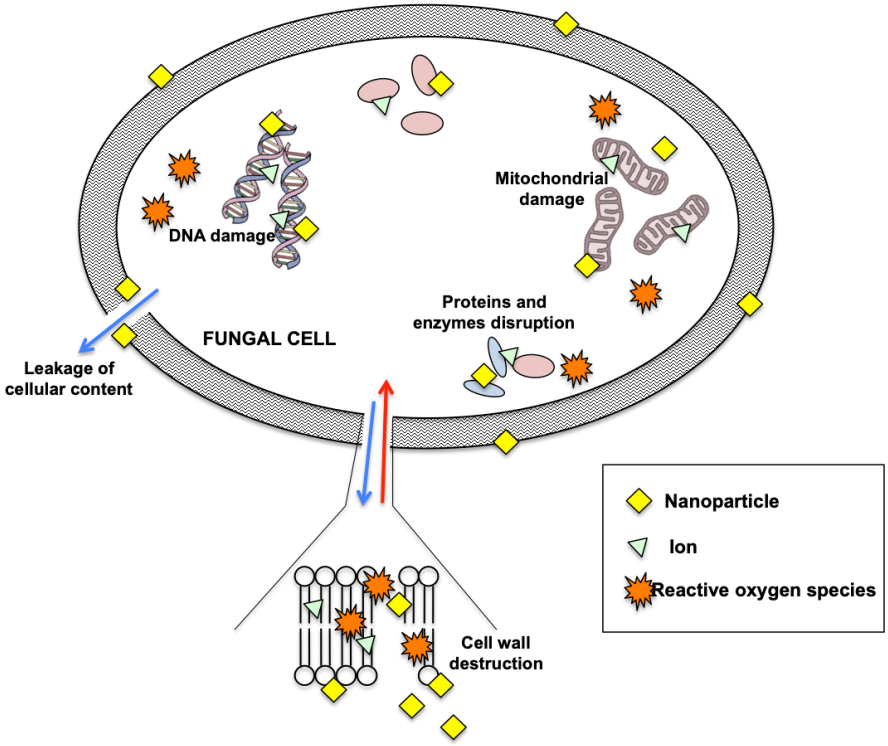

Fig. 1. Antifungal mechanism of actions of nanoparticles.

Another major mode of action is the release of metal ions from nanoparticles after crossing the cell interstitium. Due to charge difference, the metal ions will cause destruction to the fungal cell wall by inactivation of sulfhydryl group [10]. This in turn leads to leakage of cellular content such as disruption of membrane bound enzymes and lipids, which ends with pathogen death [4]. Besides that, since nanoparticles are small in size, it has larger

surface area which allows more molecules to be exposed, increasing damage. The antifungal mechanism of nanoparticles is illustrated as shown in Figure 1.

To increase the efficacy of their nanoparticles, some researchers opt to modification of the nanoparticles with certain compounds. For instance, a research by Noura et al. investigated the antimicrobial activities of Ag NPs modified with chitosan derivatives [16]. Results of the antifungal activities proved that combination of Ag NPs with chitosan were more potent compared to virgin chitosan. This highlights the importance of choosing the right material for nanoparticles alteration to enhance their antimicrobial properties. In the published report, chitosan was chosen as it is well known to inhibit spores germination, elongation of fungal tubes and growth of radials [16]. It is mentioned that nanoparticles modification might increase the susceptibility of fungal cell walls, leading to easier uptake of chitosan-Ag NPs which then disturb cell functions ultimately causing death [16].

Since fungi species are known to form biofilms, a moderate amount of antibiofilm studies have also been conducted in the last few years. A study by Xuewei et al. shows results indicated that nanomaterial could significantly inhibit the formation of biofilms in a dose-dependent manner [14]. Similar findings can also be observed in a paper by Tanmoy et al. showing Ag NPs fungicidal (MFC) values of around 10.7 ug/mL to 21.4 ug/mL for four different Candida species and their biofilm counterparts [12]. These studies are very important as treating biofilms is more challenging due to their tough structure and high drug resistance. From all these published results, it can be concluded that therapies using biologically synthesized nanoparticles could potentially be developed as antifungal agents in the near future.

4. Conclusions

Even though fungal infections are common, it is often overlooked as it rarely becomes life-threatening for healthy people. However, for immunocompromised patients, treating fungal infections can become complicated especially with the rise of multidrug resistant fungi strains and limited number of antifungal drugs available for use. There is an urgent need for new therapeutic methods to solve these problems before it becomes worse. Nanoparticles have been presented as a promising solution for these issues as it can enhance treatment effectiveness and reduce side effects during prolonged therapies. Nanoparticles can also be coupled with existing drugs for more synergistic results in an effort to overcome multidrug resistance problem. Since there is increasing awareness on environmental issues nowadays, biological synthesis of nanoparticles can be carried out to minimize harm and reduce toxic chemicals. By combining all these interdisciplinary knowledge together, more practical, effective, and safe therapeutic methods can be designed using biologically synthesized nanoparticles for antifungal applications.

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