Antifungal Activity of Silver Nanoparticles against *Candida* Species

Subjects: Mycology

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Silver nanoparticles have long been known for their antibacterial properties. Increasing numbers of studies confirm that they have antifungal properties as well.

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1. Introduction

Nanoparticles are generally considered to be particles whose size is in the range of 1–100 nm. They are an interesting and desirable object of modern research because they very often show various unique properties compared to their macro-scale counterparts [1]. They arouse constantly growing interest due to the discovery of new applications in many fields of science and industry. The main direction in recent times is medicine, where nanoparticles are used for diagnostic and therapeutic purposes. This is mainly related to the large active surface-to-mass ratio of nanoparticles. In addition, the active surface is able to bind and transfer other compounds; hence, nanoparticles are considered good carriers of proteins or drugs, as they can deliver these compounds directly to the target site [2]. In addition, nanoparticles, mainly of such metals as gold (Au), silver (Ag), and platinum (Pt), are used as catalysts for chemical reactions or in optical biosensors and chemosensors. Considering their biological activities, silver nanoparticles are a matter of special interest in biology and medicine. Depending on their physicochemical properties, e.g., dimensions, formulation, and high reactivity, metal nanoparticles show different biological activities [3][4][5][6]. They can act as antibacterial, anticancer, antioxidant, and anti-inflammatory agents [7][8][9][10]. Taking into account the medical applications of silver nanoparticles (AgNPs), the most popular is their antibacterial activity. Colloidal silver has long been a popular antibacterial agent. In the history of the use of silver in medicine, 1884 was a breakthrough year, when Carl Crede used a solution of silver nitrate to treat gonococcal conjunctivitis in newborns. Silver nitrate was also used in dentistry to treat caries. Currently, silver can be found in many antibacterial cosmetics, such as soaps, deodorants, shampoos, and mouthwashes [1][11]. Data indicate that, in 2023, over 1000 consumer products containing nanosilver were identified (approved and not by the FDA in the USA), which are mainly used in the medical, textile, and cosmetics sectors [12]. Silver nanoparticles exhibit a broad spectrum of anticancer activity, making them highly promising for application as novel therapeutic agents or drug carriers. However, in order to develop a safe and effective anticancer agent based on AgNPs in the future, it is essential to investigate more mechanisms of the anticancer action of these nanoparticles. AgNPs also demonstrate potential as a new therapeutic strategy for wound healing. Studies have shown that the action of AgNPs in this context involves the regulation of the production of various cytokines and proteins participating in the wound-healing process. They also promote early adhesion, contraction, and closure of the wound. Silver nanoparticles also exhibit favorable properties in bone healing. They can be used as osteoconductive material or as a doping material for synthetic bone scaffolds, providing protection against potential bacterial infections, which are common and risky in bone grafts. Another biomedical application involves incorporating AgNPs into dental biomaterials due to their antibacterial and anti-biofilm effectiveness. Additionally, research indicates that AgNPs also have the potential for use as adjuvants in vaccines, antidiabetic agents, or as biosensors [13].

Silver nanoparticles are also widely used in food processing and packaging designed to protect food against microorganisms [14].

As a feed additive, it has been shown that they reduce the occurrence of pathogenic microorganisms, so they could reduce the use of antibiotics in livestock. Additionally, their potential use in water treatment has been demonstrated by incorporating them into foam filters or by the impregnation of ultrafiltration membranes. Moreover, AgNPs are good candidates for use in food packaging due to their good stability and slow release of silver ions in stored food. In the context of food safety, another approach is emerging to use AgNPs as biosensors. This approach involves creating smart packaging to detect pathogens and transforming this information into a detectable signal that would allow for the early detection of food contamination. Due to the fact that there is insufficient research on the safety of AgNPs in food, the EU does not allow their use in dietary supplements or food packaging [15]. However, in 2021, the EFSA published information in which it was concluded that the use of AgNPs as an additive in an amount of up to 0.025% *w*/*w* in polymers such as polyolefins, polyesters, and styrenes that do not swell in contact with hydrated food does not raise concerns regarding their use. A summary of the most important applications of AgNPs is shown in **Figure 1**.

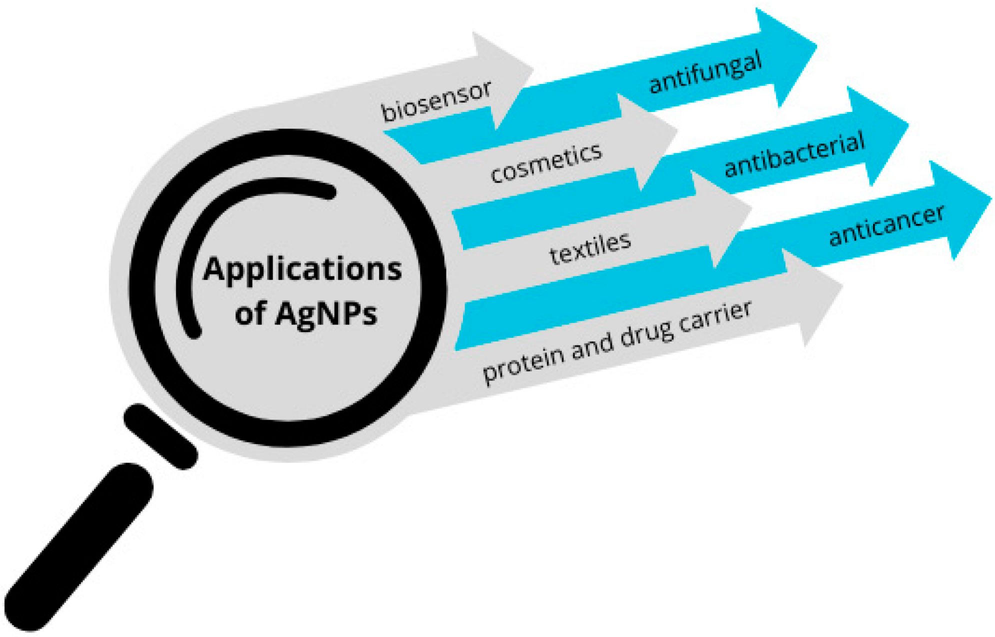

Figure 1. Applications of AgNPs.

The antibacterial properties of silver nanoparticles are well known and have been confirmed by numerous studies [7][16]. AgNPs have been shown to inhibit the growth and multiplication of such bacteria as *Escherichia coli*, *Bacillus cereus*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Citrobacter koseri*, *Salmonella typhi*, *Klebsiella pneumoniae*, and *Vibrio parahaemolyticus* [14]. However, especially recently, a lot of research has been published on the antifungal activity of silver nanoparticles against many species of fungi. Nanoparticles synthesized by chemical, physical, and green synthesis methods are active (**Figure 2**). Testing the activity of AgNPs against fungi is particularly important due to the enormous resistance of pathogenic strains to systemic drugs.

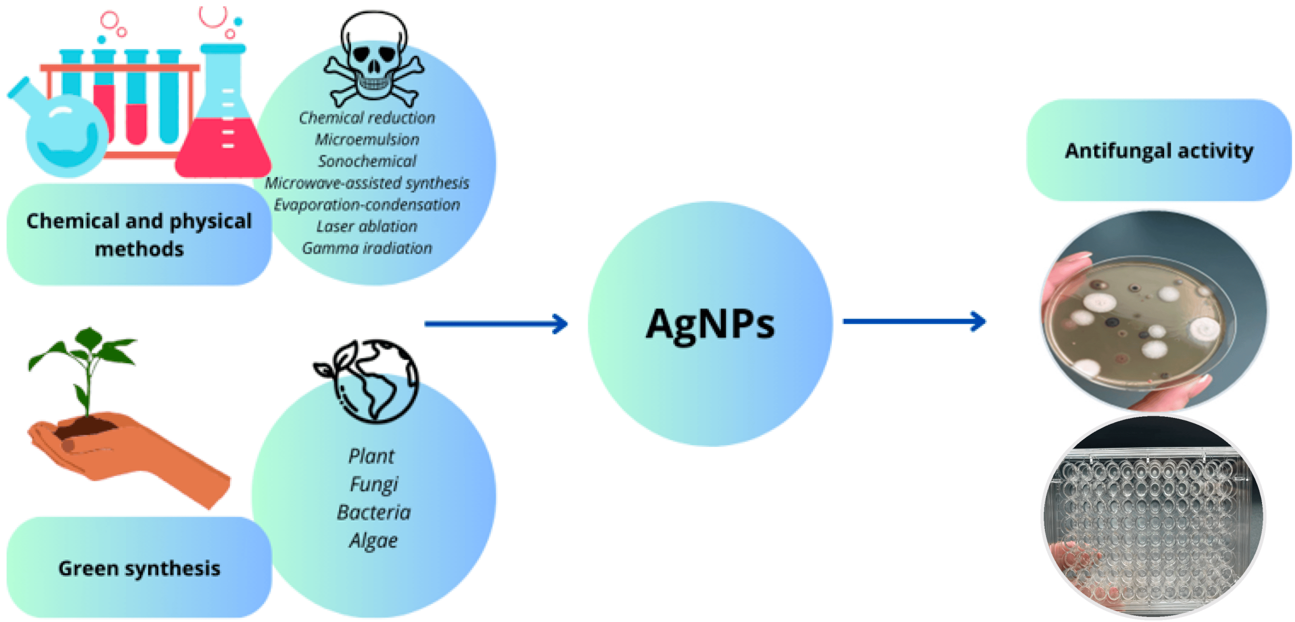

Figure 2. AgNPs' synthesis methods and testing their antifungal activity.

We can observe that silver nanoparticles accompany us in everyday life in household and biomedical products and possess significant positive properties, including the ability to eliminate pathogenic microorganisms. However, it should be noted that their use also raises concerns about their potential threat to human health and the environment. The major routes of entry of AgNPs are ingestion, inhalation, and dermal contact. Their toxicity is due to the fact that AgNPs are able to induce inflammation and oxidative stress at the site of exposure. Despite numerous toxicological studies, long-term toxicity data are still lacking. However, an occupational respiratory exposure limit value of 0.19 μg/m^3 for AgNPs has recently been proposed based on a subchronic inhalation toxicity study in rats [17]. Research using in vitro cell cultures indicates that AgNPs are toxic to several human cell lines (human bronchial epithelial cells, human umbilical vein endothelial cells, red blood cells, human peripheral blood mononuclear cells, immortal human keratinocytes, liver cells). Furthermore, tests conducted in vivo using mice, rats, and zebrafish have demonstrated that AgNPs can penetrate the blood–brain barrier and accumulate in organs such as the liver, kidneys, and spleen. The induced cytotoxicity, however, largely depends on the size of the nanoparticles, dosage, and duration of exposure [17][18].

2. Antifungal Activity of Silver Nanoparticles against *Candida* Species

Silver nanoparticles are regarded to have antifungal properties, but the number of studies confirming this feature is currently insufficient. Although fungal infections are not as widespread as bacterial infections, the incidence of fungal infections has been increasing in recent years. An especially alarming phenomenon is the increasing drug resistance, which is an even more serious problem due to the small arsenal of antifungal agents available on the market. Currently, the most commonly used systemic drugs are amphotericin B, nystatin, fluconazole, and itraconazole, but their solubility and bioavailability are not satisfactory [19][20][21]. In addition, their use is associated with the risk of side effects, such as allergic and severe skin reactions. Fungal infections often affect and pose a serious threat to immunocompromised patients [22][23][24]. Yeasts of the genus *Candida* are considered to be the most common cause of invasive fungal disease in such individuals. They can lead to bloodstream infections, which are associated with high mortality despite treatment [25]. The most common representative of this species is *Candida* albicans. It is part of the healthy human microflora, where it exists as a harmless commensal. However, if the natural balance in the microbiome is disturbed, e.g., in subjects with reduced immunity, it can become the cause of life-threatening infections. In addition, *C. albicans* has the ability to form a biofilm. It is a tightly packed community of cells that can grow on biotic and abiotic surfaces. This form is very difficult to combat with the use of traditional drugs [26].

Studies have shown that AgNPs have good activity against *Candida* spp. They can both inhibit the growth of yeast cells and influence various virulence factors, e.g., biofilm formation. The antifungal activity of AgNPs against *C. albicans* was investigated by Alshaikh et al. [27]. AgNPs were coated with polyvinylpyrrolidone (PVP) for water dispersion. Five isolates of *C. albicans* were used in the study and the minimum inhibitory concentration (MIC) was determined. The MIC values of AgNPs against *C. albicans* isolates ranged between 24 and 12 µg/mL. They were compared to fluconazole, which had an MIC value of 20 µg/mL. In this study, AgNPs were even more potent than fluconazole against some strains of *C. albicans*. In another study, AgNPs were synthesized using ribose sugars as reducing agents and sodium dodecyl sulfate (SDS) as a blocking agent. The antifungal activity of these nanoparticles was evaluated against 30 strains of *Candida* spp. (14 *C. albicans* and 16 *C. tropicalis*) isolated from blood samples from hospitalized patients. The tested strains showed a strong sensitivity to the nanoparticles used [28]. It was shown that silver nanoparticles are also effective against *C. albicans* biofilm with the half maximal inhibitory concentration (IC_{50}) of 0.089 ppm [29]. Recent studies conducted using an iturin–AgNPs complex also showed excellent antifungal activity of the synthesized molecules (MIC = 1.25–5 µg/mL) against *C. albicans*. Moreover, the mechanism of the antifungal activity of the tested complex was revealed. Iturin–AgNPs caused damage to the integrity of the cell membrane, which in turn increased its permeability and the leakage of intracellular proteins and nucleic acids outside the cell [30]. In a study conducted by Dorgham et al. [31], silver nanoparticles were synthesized using the sugarcane process by-product (molasses) and named Mo-capped AgNPs. The synthesized molecules showed promising activity against *C. albicans* DAY185 with an MIC of 16 µg/mL. With the use of a scanning electron microscope and through the determination of the minimal biofilm eradication concentration (MBEC), it was also confirmed that the nanoparticles penetrated the preformed biofilm and eliminated the microbial cells. Moreover, the activity of AgNPs against *Candida* species was tested in vivo in a mouse model of oral candidiasis. In this study, nanoparticles synthesized with the use of the green synthesis method using Erodium glaucophyllum extract were used. The effect of the treatment was a significant reduction in candidal tissue invasion, fewer inflammatory changes, and no tissue modification [32]. Another in vivo study concerned AgNPs individually and combined with fluconazole. Activity was tested in a murine model of systemic candidiasis against *C. albicans*. The best results were obtained for combined treatment with AgNPs and fluconazole. This treatment reduced the fungal burden and increased the survival rate of infected mice [33]. Although the body of evidence for the anti-*Candida* activity of AgNPs is limited, the nanoparticles show promising potential to be developed as antimycotic agents.

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