Chapter 7

Nanoparticles as New Therapeutic Agents against *Candida albicans*

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Abstract

Candida albicans is an opportunistic dimorphic yeast. This organism is pathogen associated to superficial and systemic infections. Actually, *Candida albicans* represents an emergent pathogen especially in a patient with some immunity compromises. Added to this, the use of antifungal in an indiscriminate form has increased the resistance of the existing drugs. In this aspect, the nanotechnology generates the possibility of creating new therapeutic agents. Nanoparticles are structures of 1–100 nm with special physicochemical characteristics that allow it to function as therapeutic agents or as carriers of these. Palladium, silver, and gold metallic nanoparticles and iron, titanium, zinc, and copper oxides have been used as growth inhibitors. These nanoparticles have been proved alone or in form of nanocomposites. The objective of this chapter is to describe the state of the art of the use of nanoparticles as inhibitors of the growth of *Candida albicans*, as well as the most relevant results regarding the mechanisms involved in this inhibition.

Keywords: nanotechnology, resistance, metallic and oxide nanoparticles

1. Introduction

Candidiasis is one of the most common infections worldwide. These diseases are generated by *Candida albicans* and *Candida* non-*albicans* group. *Candida albicans* is an opportunistic dimorphic yeast. It is a commensal organism in gastrointestinal, respiratory, and genitourinary

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tracts. Normally, it is a harmless organism that can turn into an opportunistic organism in immunocompromised or immunologically deficient individuals [1–3].

Candida albicans represents the predominant yeast in oral, genital, and cutaneous infections (≥90%) [2, 4, 5]. However, the invasion of blood torrent by *Candida* species is the infection more frequently diagnosed. The frequency of *Candida albicans* isolated in candidemia is of 46.3%, followed by *C. glabrata* (24.4%) [3, 6]. The mortality frequency in patients with invasive candidemia ranges from 40 to >70%, generating a loss of about 1.7 billion dollars every year [1, 7].

For the treatment of invasive infection by *Candida*, few options are available. The polyenes (amphotericin B and nystatin) are the chosen treatment by excellence. However other antifungals are used as azoles [8]. The azoles (fluconazole and itraconazole) and new azoles (ravuconazole, posaconazole, and voriconazole) are selected for prophylaxis, empirical therapy, and diagnostic-driven therapy [9]. The use of echinocandins (caspofungin, anidulafungin, and micafungin) is driven to therapy on invasive candidiasis [1].

However, the adverse effects of antifungal therapy as nephrotoxicity, red blood cell (RBC) toxicity, and arrhythmias for amphotericin B, hepatotoxicity associated with fluconazole, cardiotoxicity and gastrointestinal (GIT) disturbances attributed to itraconazole, voriconazole exhibiting neurological and hepatic toxicities, and posaconazole shown to elevate serum aminotransferase levels and cause mild-to-moderate hepatic toxicity limit its use. These adverse effects are attributed to the action mechanism. Azoles and polyenes have ergosterol as a target from the cell membrane, and the ergosterol has a high similarity between ergosterol and human cholesterol [8]. Azoles inhibit the ergosterol biosynthesis, specifically the lanosterol 14α-demethylase. This generates sterol precursor accumulation, resulting in a cell membrane instability and the loss of viability [3].

The echinocandins are more specific for fungi. This therapeutic antifungal inhibits the enzyme 1,3-b-D-glucan synthase and generates the depletion of polymer synthesis and osmotic stability loss [1, 10].

Due to the discriminated antifungal agent use, *Candida albicans* has developed different resistance mechanisms. Three principal mechanisms have been reported: the efflux pump, which is a membrane transport protein that ejects the azoles out of the cell; the structural changes of the enzyme target, mutations on lanosterol 14 α-demethylase, changing the three-dimensional structure, and, as consequence, the decreased affinity for this enzyme; and the last mechanism is the increase in the production of the target enzyme; this generates the inhibition of only a portion of the enzyme, and the rest are still active [1–3, 8, 11].

On the other hand, the survival characteristics of *Candida albicans* in the host make this organism difficult to kill. The virulence factors include the biofilm formation capacity, the yeast-hyphae morphogenesis, the adhesion to surfaces, and the capacity to secrete enzymes as hydrolases.

Because of this, the research for more specific antifungal therapies has been the focus of attention. In this area, the nanotechnology offers an opportunity to design and create a new

pharmaceutical agent that can be specific. As pharmaceutical agent nanoparticles such as copper, silver, and palladium, among others, have been employed in order to inhibit the growth of any microorganism, in particular, *Candida albicans*.

The objective of this chapter is to describe the state of the art of the use of nanoparticles as inhibitors of the growth of *Candida albicans*, as well as the most relevant results regarding the mechanisms involved in this inhibition.

2. *Candida albicans* taxonomy

Fungi form one of the largest eukaryotic kingdoms; they have a very broad function of decomposing biopolymers and different compounds in dead or alive hosts, as well as synthesizing bioactive compounds. The yeast *Candida albicans* originally was described as Blastomycetes class belonging to Monilial order and Cryptococcaceae family. Actually, with gene sequencing, the new taxonomy classifies *Candida albicans* into *Ascomycota*, (dikaryon-producing fungi), *Hemiascomycetes* subclass, and *Saccharomycotina* order [12, 13].

Candida albicans is a common commensal on mucosal surfaces under normal conditions, mainly of the gastrointestinal and vaginal tracts. The commensal stage is frequently described as harmless to the host, and the fungus is controlled by the normal microbiota, epithelial barriers, and the innate immune system [14, 15]. This is the most important opportunistic medical pathogenic fungus, causing candidiasis, which is an acute, subacute, or chronic infection involving any part of the body [15]. The weakening of the defense mechanisms of the host and the adaptation capacity of the microorganism turn this fungus into an aggressive pathogen, starting with superficial infections into a systemic process, mainly in immunosuppressed or HIV patients [16].

3. *Candida albicans* cell wall

Candida albicans cell wall is composed mainly of carbohydrates; three basic main constituents are polysaccharides:

1. Branched polymers of glucose with β-1,3 and β-1,6 bonds, they are called β-glucans.
2. Unbranched polymers of N-acetyl-D-glucosamine (GlcNAc) with β-1,4 bonds; the chitin, which contributes to the fiber insolubility; and theβ-1,3 glucan-chitin complex, which is the major constituent of the inner wall. β-1,6 glucan links the components of the inner and outer walls; thus, chitin and β-1,3 are structural polysaccharides and convey strength and shape to the cell wall [15, 17, 18].
3. Finally mannose polymers, mannans, covalently associated with proteins (glucomannan proteins).

The mannan of the outer cell wall is less structured but allows this fungus breakage of epithelial barriers or dysfunction of the immune system converting *Candida albicans* from a commensal to a pathogen. The cell walls also contain proteins, 6–25%, and minor amounts of lipids, 1–7% [15, 17, 18].

This arrangement is responsible for its cell morphology and provides protection to the cell against physical, chemical, and biological (immune host system) aggression [16].

Likewise, the cell wall participates in both growth and morphological transitions between yeast and hyphae; this conversion from the unicellular yeast to multicellular filamentous fungus is essential for *Candida* virulence [19]. It has cell surface proteins linked to glycosylphosphatidylinositol (GPI) [20], including an N-terminal signal sequence and a C-terminal GPI-anchor addition signal; some of these proteins are secreted to the extracellular environment, but do not remain cell associated. Some of them are hydrolytic enzymes, which hydrolyze complex substrates into small units, to carry out into the cell as a source of nutrition. If these polymers are host targets, all of these facilitate colonization or invasion of *Candida albicans*, and then such enzymes also function as virulence factors [17]. For therapeutic strategies, to establish the functional relationships between *Candida albicans* cell wall's proteins and virulence is a challenge [20].

4. *Candida albicans* virulence factors

Candida spp. invade several anatomical hosts, mainly in patients who are immunocompromised or debilitated. This organism expresses several virulence factors that allow the host-pathogen interaction and that lead to the establishment of infection [21, 22].

Virulence factors include host recognition biomolecules (adhesins) due to cell surface hydrophobicity which enhanced adherence and resistance to phagocytosis; another important factor is its ability to grow either in yeast or in hyphal form (dimorphism, especially in the presence of N-acetyl-D-glucosamine) [23], secreting aspartyl proteases and phospholipases [21].

The phenomenon of the quorum sensing (QS) has been described as a contributor to morphogenesis, playing a role in regulating the yeast to filamentous fungus; one of the conditions is the dependence on cell density associated with the regulation by QS. The QS has an important role in the ability of *Candida albicans* to be virulent and survive within the host [23]. *Candida albicans* uses multiple redundant and/or synergistic signaling pathways to integrate host signals to promote hyphal development, tissue invasion, and virulence during infection, exacerbating the pathogenesis of invasive candidiasis [24].

5. *Candida albicans* biofilm formation

Candida virulence is a result of its capacity to form biofilms on the surface of biomaterials and on catheters and prosthetic devices [25–27]. *Candida albicans* biofilms are composed of hyphae,

pseudohyphae, yeast cells, and an extracellular matrix, where the hyphae play an integral role within this complex [26]. Biofilm formation presents an initial adherence of yeast cells (0–2 h), followed by germination and microcolony formation (2–4 h), filamentation (4–6 h), monolayer development (6–8 h), proliferation (8–24 h), and maturation (24–48 h). Serum and saliva preconditioning films and *Candida albicans* preconditioning films increased the initial attachment of the fungus but had minimal effect on subsequent biofilm formation [25, 28]. This kind of biofilm has clinical repercussions because it is the target of both chemical and immunological antifungals. Due of their intrinsic resistance to almost all antifungals in clinical use, increased resistance to this therapy, and the ability of cells within biofilms to withstand host immune defenses, the antifungal resistance of biofilms results most probably from the conjunction of several mechanisms that act in a time-dependent manner [26].

6. *Candida albicans* resistance mechanisms

In order for *Candida albicans* to survive, these microorganisms have developed diverse mechanisms. Biofilm formation, enzyme modification, and the pump efflux are the mechanisms reported to antibiotic resistance [29]. As described previously, biofilms are a complex of cells, DNA, and polymeric matrix, among others. The polymeric matrix has a crucial role in the antifungal resistance since it does not allow antibiotic penetration inside the biofilm. This phenomenon helps the internal cell to survive [25].

Resistance to azole antifungal has been described in three forms: [1] change in the affinity of cytochrome P450 sterol 14α-demethylase (gen Erg11p), [2] increase in the enzyme expression, and [3] changes in the sterol desaturase. Other alterations in an enzyme involved in the cell wall construction have been described [29, 30].

The pump efflux ejects the azoles outside the cell, without any effect inside of it. This efflux is mediated by an ATP-binding cassette (ABC) and the major facilitator superfamily. This is a complex family of genes that involve several CDR genes, including core membrane pore composed by ABC segments in the membrane; two segments are in the cytosolic side, which provide energy to pump the antibiotic outside of the cell [25, 29, 30].

It is an important highlight that this resistance could be a derivative in the resistance to other antifungals.

Candida albicans resistance could be due to one or a combination of all the resistance mechanisms described.

7. Nanotechnology as an antifungal

Nanotechnology is a new technology which manipulates the matter in a nanoscale order (1×10^{-9} m). In this order, the nanoparticles have been used as antimicrobial, as antifungal, or as carried molecules. Nanoparticles have a size from 1–100 nm on any of this dimension. In

this scale, nanoparticles have particularity physicochemical characteristics [31]. Within these characteristics, their electron configuration confers an extraordinary quantum effect. These quantum effects enhance their pharmacokinetic effect and generate nanoparticles that can be used as a protein, antibodies, or inclusive specific molecule carriers [32].

As an antifungal, nanoparticles show cell wall damage, an oxidative stress increase, and DNA interaction [33]. Nevertheless, the NPs toxicity mechanisms are dependent on the nanoparticle nature, size, and shape and capping nature, among other characteristics.

This chapter reviewed some NPs characteristics such as nanoparticle nature, synthesis, size, and shape and their influence on the toxic mechanisms in *Candida albicans* and their influence on the virulence factors.

7.1. Silver nanoparticles

Silver has been used for several decades as a disinfectant. Inclusively, silver nitrate was used in burns in order to control infections. However, with the discovery of penicillin, the use of silver was slow. Nowadays, the increase of resistance to antifungal puts attention again on the use of silver as an antibiotic, though the use of silver ions implies complications in their solubility and availability [34].

In this sense, the silver nanoparticles (AgNPs) offer a possibility. AgNPs offer the possibility of using minimal doses and act in microorganisms which present antibiotic resistance or decrease the virulence factors.

The use of different AgNPs synthesis methods caused different effects. The general method is the salt reduction by a reducing agent. However, the addition stabilizing agent has been proved. The stabilizing or capping agent limits the NPs' growth, avoids the agglomeration, and controls the shape, size, and superficial charge [35].

The NP synthesis by plant extract or secondary metabolites from microorganisms offers a new possibility. The phenolic compounds, proteins, anthocyanin, and carboxylic acid, among others, work as reducing agent and stabilizing or capping agent [35, 36].

The green AgNPs synthesis through the use of microorganisms as the use of Actinobacteria *Pilimelia columellifera* subsp. pallida [37], *Bacillus* species [38, 39], filamentous fungi *Monascus purpureus* [7], and Macromycetes as *Pleurotus sajor-caju* [40], as well as extract plant as *Tulsi* leaf extract [41] or extract from *Phoenix dactylifera* [34] has been proven. All these methods present inhibition of *Candida albicans*, with different efficiencies (**Table 1**).

The microorganisms *Bacillus amyloliquefaciens* 1853 and *Bacillus subtilis* 10,833 have been used for the AgNPs synthesis. Culture media were employed as a reducing agent. The scanning electronic microscopy has shown AgNPs produced with capping. *Bacillus* strains have been used in the AgNPS production. *Bacillus amyloliquefaciens* strain 1853 produced AgNPs with a size of 1.071 and other of 73.83 nm. The *Bacillus* subtilis strain 10,833 produced tree population sizes of AgNPs at 1.863, 10.866, and 135.78 nm. AgNPs produced by both microorganisms were employed to evaluate the *Candida albicans* inhibition. No differences were found between AgNPs; inclusive addition of antibiotic with the AgNPs does not improve the inhibition [38].

Inhibition test	**NPs size (nm)**	**Synthesis method**	**Capped**	**Reference**
18 mm (inhibition zone)	15–20	*Cassia roxburghii* + *Ketoconazole*	NR	Moteriya et al. 2017 [42]
64 μg/mL (MIC)	12.7	*Pilimelia columellifera* subsp. pallida SL19	Proteins	Wypij et al. 2017 [37]
16.7 ± 0.25 mm (inhibition zone)	2–8	*Monascus purpureus*	NR	El-Baz et al., 2016 [7]
10 μg/mL (BIC)	40–55	*Dodonaea viscosa* and *Hyptis suaveolens*	Detection of functional groups as phenol, alcohol, proteins, heterocyclic amines	Muthamil et al. 2018 [43]
40 μg/mL (MIC)	5–95	*Bacillus safensis*	Proteins	Lateef et al. 2015 [38]
12 mm (inhibition zone with 30 μL of solution)	18–46	*Gracilaria corticata*	Detection of functional groups as alcohol, carbonyl, amino groups	Kumar et al. 2013 [44]
250 μg/mL (MIC) and 500 μg/mL (MFC)	3.77–33.22	*Pleurotus sajor-caju*	NR	Musa et al. 2018 [40]
60 μg/mL (MIC_{90}) and 120 (MFC)	2–7	Tulsi leaf extract	NR	Khatoon et al., 2015 [45]
20 mm (inhibition zone with 80 μg/20 mL)	21.65–41.05	*Phoenix dactylifera*	Proteins	Oves et al. 2018 [34]
75 ppm reduce 83%/150 ppm (MFC)	70	Red cabbage	Anthocyanin compounds	Ocsoy et al. 2017 [46]
08 μg/mL (MIC)	9–130	*Enterococcus faecalis*	NR	Ashajyothi 2016 [47]
40–60 μg/mL(MIC)	4–39	Citrus lemon aqueous Juice + CTAB	Surrounded by a layer	Rahisuddin et al. 2015 [48]
10.8 ± 0.8 (inhibition zone)	12–85	Clove extract	Detection of functional groups such as methoxy, alcohol, carboxilic acid, aliphatic group	Parlinska-Wojtan et al. 2017 [49]
21–12 cm in combination with antifungal (inhibition zone)	10–90	Flower broth of *Tagetes erecta*	NR	Padalia et al. 2015 [50]
12.14 μg/mL (MIC)	47.0 ± 2.0	*J. curcas*	Protein layer	Kumar et al. 2017 [51]
10.78 μg/mL (MIC)	7.6 ± 0.5	*L. grandis*		

Inhibition test	NPs size (nm)	Synthesis method	Capped	Reference
70% fold increase (combination with antifungal, inhibition zone)	1.836–135.78	*B. subtilis* 10,833	NR	Ghiut et al. 2018 [39]
50% fold increase (combination with antifungal, inhibition zone)	1.012–73.83	*B. amyloliquefaciens*	NR	
14 mm(inhibition zone)	5–10	*Ocimum sanctum* + CTAB	Not visible	Aazam and Zaheer 2016 [35]
30 μg/mL (MIC)	4–36	Actinobacterial strain SF23	NR	Anasane et al. 2016 [52]
40 μg/mL (MIC)	8–60	Actinobacteria C9	NR	

MIC, minimal inhibition concentration.
MFC, minimal fungicide concentration.
NR, not reported.
BIC, biofilm inhibitory concentration.

Table 1. Biogenic synthesized AgNPs against ***Candida albicans.***

Clove extract was used in order to produce AgNPs. The high content of eugenol, β-caryophyllene, humulene, chavicol, methyl salicylate, α-ylangene, and eugenone; flavonoids such as eugenin, rhamnetin, kaempferol, and eugenitin; triterpenoids like oleanolic acid, stigmasterol, and campesterol; and several sesquiterpenes allowed the clove to act as a reducing and capping agent in AgNPs synthesis. The DLS analysis showed AgNPs size of 12 and 85 nm. The AgNPs produced to generate a complete inhibition of *Candida albicans* in 40-fold dilution were applied. The results obtained suggest that the functional groups' incorporation into the AgNPs generates a synergism between clove and NPs [49].

In order to evaluate the AgNPs effect on biofilms, some AgNPs have been evaluated. As described, biofilms are a *Candida albicans* virulence factor. The change from yeast to hyphae is crucial for the biofilm process. In this process, *Candida albicans* produces a polysaccharide matrix, carbohydrates, proteins, and signaling molecules [43]. Changes in the structural biofilm conformation of *Candida albicans* exposed to AgNPs were reported [28, 51, 53, 54].

The use of latex plants in the AgNPs green synthesis was proved. *J. curcas* and *L. grandis* extracts produced AgNPs with a size of 47 ± 2.0 nm and 7.6 ± 0.5 nm, respectively. The Fourier transform infrared (FTIR) spectra suggest the incorporation of phenolic OH, amides, amines, and aldehyde in the AgNPs as a stabilizing agent. The smallest AgNPs showed a better effect in plankton and biofilms of *Candida albicans* than the big ones. The AgNPs synthesized proved to be efficient in the inhibition of biofilm formation, changes in morphology and cell lysis when candida albicans was exposed [51].

Also, silver nitrate chemical reduction by sodium citrate was evaluated in intermediate and mature *Candida albicans* biofilms. The preformatted biofilms were exposed to 54 μg/mL of AgNPs. After 5 h of exposition, biofilms showed a decrease in the number of viable cells, and no differences were found in intermediate or mature biofilm [28].

The results obtained show the importance of the NPs size, being the smallest nanoparticles which show the highest inhibition [51]. Lara et al. (2015) showed that biofilm exposed to AgNPs exhibits a few *Candida albicans* filamentous formations. Electron microscopy analysis showed AgNPs accumulation and internalization [55].

Besides the AgNPs effect in biofilm, the AgNPs have been used alone showing the inhibition, cell wall damage, and incorporation of Ag into the cell. It was used in combination with different antifungals amphotericin b [51, 56] or nystatin and chlorhexidine digluconate, showing a synergic effect [54]. Other molecules as cationic carboxilane have been used, proving a high *Candida albicans* inhibition with small AgNPs concentration [1.8 mg/mL; [57]]. Also, the AgNPs have been capped with L-3,4-dihydroxyphenyl-alanine, showing a minimal fungicide concentration of 31.2–62.5 μg/mL [58].

The direction in the investigation with silver nanoparticles has been driven in the green synthesis due to the low toxicity generated in the human cell and the increase of the toxicity in bacteria and yeast [59]. Their chemical characteristics as a metallic oxidative state and superficial area, among others, allow the NPs to interact with the microorganism and inhibit their growth.

7.2. Zinc oxide nanoparticles

Due to ZnO low toxicity, ZnO has been used in a medical device such as drug carriers, antibacterial agents, and bioimaging probes, among others. For this reason, the ZnO nanoparticles (ZnONPs) have been used in *Candida albicans* control. The ZnONPs application is reflected by the annual production between 550 and 5500. This is more than 10–100 times higher than any other nanoparticle [60]. As the AgNPs, the ZnONPs characteristics depend on the size, synthesis method, and superficial charge, among others [61]. In order to control these characteristics, the green synthesis method has been used to fabricate ZnONPs with a size, shape, and superficial charge with the desirable characteristic [62, 63].

A promissory ZnONPs application area is their use as antimicrobial. Their effect has been evaluated in soil, plants, bacteria, and fungi [60, 64–66] ZnONPs different synthesis methods in ZnONPs have a big influence in the *Candida albicans* inhibition [68].

The use of *Atalantia monophylla* extracts produced ZnONPs 30 nm that have effect inhibition in *Candida albicans* growth. The author proposed the ZnONPs interaction with the cell wall, penetration to the cell, ion liberation, and the oxidative stress production, triggering the protein, lipid, and DNA oxidation [67].

The microwave aqueous extract from *Suaeda aegyptiaca* produced ZnONPs with a size of 80 nm with a capping produced by metabolites from the plant. The effect of the capping was studied. ZnONPs produced by precipitation method were studied and compared with the plant extract produced. ZnONPs *Suaeda aegyptiaca* produced a major inhibitory effect than the ZnONPs without capping agent, suggesting a synergic effect [68].

Extracts for different plants have been proved to synthesize ZnONPs in order to evaluate the toxicity of the resulting nanoparticles in *Candida albicans* inhibition (**Table 2**).

ZnONPs hybrid has been synthesized using chitosan, gelatin, and polystyrene, among others [75–77].

Dhillon et al. 2014 [75] used chitosan as a capping and bridge to carry on citric acid, glycerol, starch, and whey powder using the nanospray drying method. The ZnONPs produced have a size range of 93.2–402.5 nm. The smallest ZnONPs were the chitosan starch NPs. Aggregation effect was observed in the largest ZnONPs; this phenomenon could be explained by the superficial charge. However, these ZnONPs have a small effect in *Candida albicans* inhibition.

Collagen was used as a reducing and capping agent. The ZnONPs produced with this method showed a size between 20 and 50 nm negatively charged. ZnONPs coated by collagen

Inhibition test	**NPs size (nm)**	**Synthesis method**	**Capped**	**Reference**
24 mm (inhibition zone)	30	*Atalantia monophylla*	NR	Vijayakumar et al. 2018 [67]
80 μM (MIC)/>2590 μM (MFC)	8	*Chelidonium majus*	NR	Dobrucka et al. 2018 [69]
34 ± 1.28 mm (inhibition zone with 100 g/ml)	32–40	*Glycosmis pentaphylla*	Alkane, C=O stretching, other groups	Vijayakumar et al., 2018 [70]
25 μg/mL (MIC)/50 μg/mL (MFC)	18	*Azadirachta indica*	Proteins	Elumalai and Velmurugan 2015 [71]
Strong activity	36	*S. myriocystum*	Protein, carbohydrates, flavonoids, tannins, mannitol	Nagarajan and Kuppusamy 2013 [72]
12.5 mm (inhibition zone with 150 mg/ml)	68.64	*Cassia auriculata*	Alkene, alcohol, ether, and alkane	Padalia et al. 2018 [73]
20.3 ± 0.57 mm (inhibition zone with 200 μg/mL)/25 μg/mL (MIC) 50 μg/mL (MFC)	10–30	*Vitex trifolia*	Proteins, alkanes, aromatic group	Elumalai et al. 2015 [71]
18.01 mm (inhibition zone 100 μg/mL)	80	*Suaeda aegyptiaca*	Alcohol, aldehyde, amine	Rajabi et al. 2018 [68]
Inhibition test	**NPs size (nm)**	**Synthesis method**	**Capped**	**Reference**
24 mm (zone inhibition)	30 nm	*Atalantia monophylla*	NR	Vijayakumar et al. 2018 [67]
80 μM (MIC)/>2590 μM (MFC)	8 nm	*Chelidonium majus*	NR	Dobrucka et al. 2018 [74]

MIC, minimal inhibition concentration.
MFC, minimal fungicide concentration.
NR, not reported.

Table 2. Biogenic synthesized ZnONPs against *Candida albicans.*

showed a MIC of 99.7 ± 0.99 μg/mL, whereas the control with zinc acetate showed an MIC of 297.9 ± 2.0 μg/mL. Biofilms exposed to increase the concentration of ZnONPs showed inhibition as a result of the ZnONPs concentration [78].

Gelatin was used for the ZnONPs as well. ZnONPs produced with gelatin showed a diameter of 20 nm with a negative superficial charge. The ZnONPs produced were employed to biofilm exposition. ZnONPs in a concentration of 50 μg/mL showed a thickness diminution, resulting in a weak adherence biofilm compared with the biofilm treated with fluconazole [72].

Also, egg albumin was used as a ZnONPs template. The synthesis method produced spherical ZnONPs with a range between 10 and 20 nm. The FITR analysis showed the interaction of egg albumin and ZnONPs. In this work, ZnONPs characterization in the culture media showed importance. The use of 45 μg/ml in Sabouraud's dextrose (SD) nutrient media does not significantly affect ZnONPs stability, size, and integrity. The synthesized ZnONPs showed *Candida albicans* inhibition in a dose-dependent manner. Changes in the *Candida albicans* morphology show cavity formation in cells exposed to 15 μg/ml [79].

ZnONPs were evaluated both alone and as a part of nanocomposites with polystyrene. The use of ZnONPs alone showed *Candida albicans* inhibition. However, when ZnONPs are used in nanocomposites, a major concentration of ZnONPs to inhibit *Candida albicans* is necessary [77].

Nanocomposites with ZnONPs have been produced with different materials in order to increase the growth inhibition of microorganisms [45, 46]. However, the results of the antifungal activity were contradictory; ZnONPs capped by surfactant in cotton fiber have proved the inhibition of *Candida albicans* in 94% [68], while the incorporation of ZnONPs in polylactic acid films does not inhibit the *Candida albicans* growth [80].

The principal ZnONPs toxicity mechanisms reported are (1) ion liberation, (2) interaction of ZnONPs with the cell wall, and (3) stress oxidative generation [81]. The ion liberation and the interaction of NPs with the cell trigger the generation of oxidative stress; with that the cell lost their viability [79].

7.3. Copper oxide nanoparticles

Copper exhibits good characteristics such as its antimicrobial activity, chemical stability, and thermal resistance. Due to their toxicity characteristic, copper has been used by Egyptians for water disinfection. The Aztecs used copper to treat sore throats, and the Persian and Indians used it to treat eye infection and venereal ulcers [82].

Copper has an advantage in comparison with other materials, is cheaper than any other, and is easy to oxidize to copper oxide nanoparticles (CuONPs). The CuONPs can easily make nanocomposites with polymers, macromolecules inclusive of other metals [83, 84].

The CuONPs have recovered importance in the investigation due to their low cost and the variety of applications. CuONPs have been used in the pharmaceutical, medicine, and electronic industries, among others.

Diverse synthesis methods have been proved to create CuONPs including chemical [85], electrochemical [86], and green synthesis [87].

The synthesis method influences the characteristics as the size, shape, and agglomeration of the CuONPs [88].

CuONP electrochemical production with different solvents and reaction times produces different NPs sizes from 3 to 200 nm. The CuONPs were obtained in water-acetonitrile, with sodium hydroxide as the electrolyte. The CuONPs obtained in these conditions showed a size around 20 nm. The *Candida albicans* exposition to 25 and 50 μg/ml generates a delay in the growth curves. Added to that, 50 μg/ml inhibited completely *Candida albicans* growth [86].

CuONPs prepared by precipitation method coated with acetate were evaluated together with fluconazole. CuONPs coated with acetate were more toxic than CuONPs without coating. CuONPs in combination with fluconazole showed the complete *Candida albicans* inhibition. The fractional inhibitory concentration index (FICI) suggested the additive to moderate synergism between CuONPs and fluconazole [89].

The use of dispersant as ethylene glycol and Tween 80 proved to be efficient in the production of CuONPs capable to the *Candida albicans* growth inhibition. Inhibition with CuONPs was more efficient than the exposition to itraconazole [90]. Also, the effect of CuONPs was evaluated in *Candida albicans* from oral cavities [91], showing that strain isolated from the patients needs until 1000 ppm to generate an inhibitory effect in *Candida albicans*.

CuONPs capped with pyrimidine derivatives have shown a size of 10 nm. The CuONPs showed interaction with DNA and antioxidant activity. However, the CuONPs showed *Candida albicans* inhibition [92].

Nanocomposites with the incorporation of Fe [93] Cd and Ba CuONPs [94], as well as the incorporation of CuONPs into cotton fiber [95, 96], polyurethane [97], polyester [98], copolymer microgel [99], and open polyurethane foams with starch powder [100], have been proved be efficient in the *Candida albicans* growth inhibition.

As in the other nanoparticles, the green synthesis has captured the investigators' attention. Its methodology does not produce toxic subproduct in the nanoparticle production, and it covers the nanoparticles avoiding the agglomeration [31, 84, 87].

Extracts of garlic and ginger have been used for the oxidation of copper. Garlic produces the smallest CuONPs, with a size around 14.62–22.80 nm. However, ginger shows a big quantity of very small nanoparticles. *Candida albicans* has shown major inhibition when exposed to ginger ethanol extract NPs [101]. Few reports about the use of biological extract for the synthesis of CuONPs that inhibited *Candida albicans* were founded (**Table 3**).

Cu^{2+} ions realized from CuONPs are the principal toxicity mechanisms reported. However, it is not the only one. Some authors reported the CuONP accumulation in the cell wall as well as the oxidative stress increase. However, more studies are necessary in order to understand the NPs toxicity mechanisms.

Inhibition test	NPs size (nm)	Synthesis method	Capped	Reference
15.0 c ± 0.57735 (inhibition zone with 62 μg/mL)/1.93 ± 0.76376 (MIC)	31.7	Alginate	NR	El-Batal et al. 2018 [102]
10.5 (zone inhibition)	26 ± 4	*Acalypha indica*	NR	Sivaraj et al. 2014 [103]
22.5 mm (inhibition zone)	Nanostructures ~8000	*Viburnum opulus*	$Cu_3(PO4)_2$ $3H_2O$	Ildiz et al. 2017 [104]
20 mm (inhibition zone with 50 μg/mL)	NR	*Sargassum polycystum*	NR	Vishnu et al. 2016 [105]
0.15 Log_{10} growth reduction	22 ± 1 nm	Cellulose, chitosan, and keratin nanocomposites	Cellulose, chitosan, and keratin	Tram et al., 2017 [106]

Table 3. Biogenic synthesized CuONPs against *Candida albicans*.

7.4. Other nanoparticles

Other metal nanoparticles as gold [AuNPs, [36]], palladium [PdNPs, [91]], and selenium [SeNPs, [92]], among others, have been proven. The microorganisms' elimination by all these NPs has been proved to be effective.

Chemical reduction of palladium salt has produced PdNPs in an average size of 9 nm (±3.9 nm). The PdNPs showed a significative *Candida albicans* growth reduction at 150 ppm [107].

SeNPs were prepared by the reduction of selenium chloride inside *K. pneumoniae*. This synthesis produced SeNPs with a size range from 90 to 320 nm. The concentration necessary for growth inhibition of *Candida albicans* was 2000 μg/mL [109]. Another strategy for the *Candida albicans* inhibition induced the SeNPs formation inside of *Lactobacillus* and then used them as an antifungal. This strategy worked with *L. plantarum* and *L. johnsonii*. *Candida albicans* exposed to both microorganisms becomes more efficient than bacterium without NPs [108].

Schiff base ligand 2-((4,6-dihethoxypyr-imidine-2-yl)methyleneenamino)-6-methoxyphenol has been used in order to capped AuNPs and platinum nanoparticles (PtNPs). Nanoparticles synthetized presented a layer. The NPs showed a granular and spherical shape with size of 38.14 ± 4.5 and 58.64 ± 3.0 nm, respectively. Both nanoparticles showed greater inhibition than amphotericin [110].

Biogenic PdNP production with watery extract of *Moringa oleifera* flower was evaluated for the *Candida albicans* inhibition. However, these PdNPs had no effect in *Candida albicans* [111].

Candida albicans exposition to tellurium NPs produces complete inhibition with of ≥2000 μg/mL. Besides, the results showed a squalene accumulation and increase in the expression levels of the ERG1 gene of squalene monooxygenase enzyme [112].

7.5. Nanoparticle characteristics and toxicity and *Candida albicans* inhibition growth

The most important NPs characteristics are the size, shape, composition, superficial charge, and hydrodynamic. These characteristics directly influence their capacity to interact with the molecules or cells. Ocsoy et al. (2017) [46] indicate that the size is strictly related to charge density. The smallest of the NPs has the biggest charge density. This explains the big attraction between small NPs and their agglomeration. The NPs agglomeration is a phenomenon that changes their capacity to work as a caring or their toxicokinetic characteristic [33, 107]. In order to improve the distribution and decrease the agglomeration, a surfactant as Pluronic F® has been added to the synthesis process (**Figure 1**). Other surfactants as CTAB, SDS, cation surfactants [113], or PVP have been proved to be efficient [114].

Another synthesis methodology that improves these characteristics is the use of subproducts from plants, algae, bacteria, fungi, yeast, etc. [115]. The high content of proteins, reducing sugars or anthocyanins, works as reducing agent; additionally, some of these molecules are adhered in the NPs surface [31]. This addition gives different characteristics to the NPs produced by chemical reduction. The NPs obtained with biogenic methods offer homogeneous NPs with antioxidant characteristics that allow the addition of other molecules and control their toxicity characteristics.

The biogenic NPs production has proven to be efficient inhibiting the *Candida albicans* growth (**Tables 1–3**). The differences in the concentration necessary to inhibit their growth are directly related to NPs size, the capping nature, and the microorganisms evaluated [116]. These are evident in the work of Anasane et al. 2016 [52] et al. (2013), where two microorganisms were evaluated in the production of AgNPs, obtaining two NPs sizes. The AgNPs production by the strain SF23 was smaller than that produced by the strain C9. *Candida albicans* presented an MIC of 30 μg/mL with the small AgNPs (size 4–36 nm). Wypij et al. (2017) [37] reported the AgNPs synthesis with *Pilimelia columellifera* subsp. *pallida* SL19, with a capping

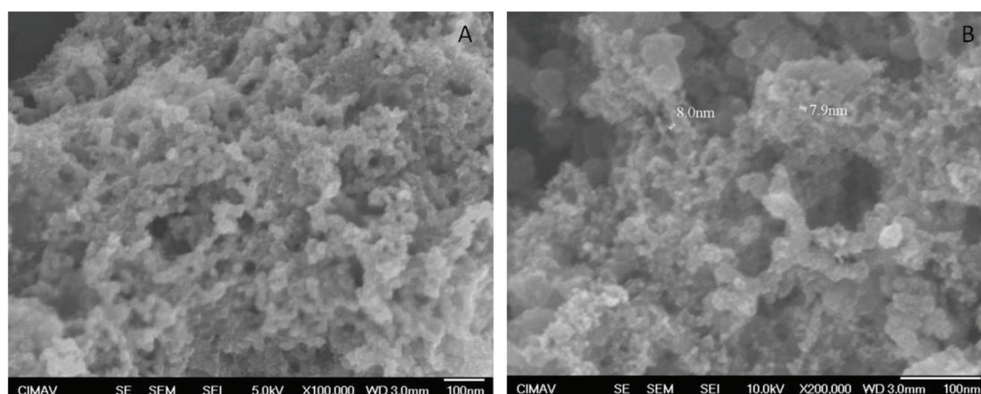

Figure 1. Scanning electronic microscopy of PdNPs produced by chemical reduction. (A) Without surfactant. (B) With Pluronic F® (5% W/V).

of proteins. The AgNPs size was on average 12.7 nm with a growth inhibition of 64 μg/mL. Tulsi leaf extract has been used to produce AgNPs with a size of 2–7 nm. The fungicide concentration in the AgNPs produced was of 120 μg/mL [25]. The production of ZnONPs by *Azadirachta indica* [61], *Vitex trifolia* [64], and *Suaeda aegyptiaca* [65], among others (**Table 2**), has been evaluated. The extract produced different ZnONPs sizes and capping (**Table 2**) that influence the growth inhibition.

Due to the NPs size (nanometer scale), diverse toxicity mechanisms have been proposed (**Figure 2**). One is the direct interaction of the nanoparticle with the cell membrane. The interaction of NPs microorganism is allowed by the NPs superficial charge but also the microorganism superficial charge. This interaction generates disruption of the cell wall and the leakage of ions and the intracellular material with the microorganism's death [117–119].

Consequent to NPs dilution, the ion interaction with the cell is another toxicity mechanism. The ions are incorporated into the cell, and they could interact with thiol groups of proteins and enzymes leading to the inhibition of crucial biological activities [82]. Also, the NPs internalization has been reported; this generates the interaction of NPs and ions with molecules of biological importance as DNA or enzymes [33, 120]. Inside the cell, the NPs or the ions provoke Fenton's type reaction. Due to this, the oxidative stress increases, and the proteins, lipids, and DNA release (**Figure 2**).

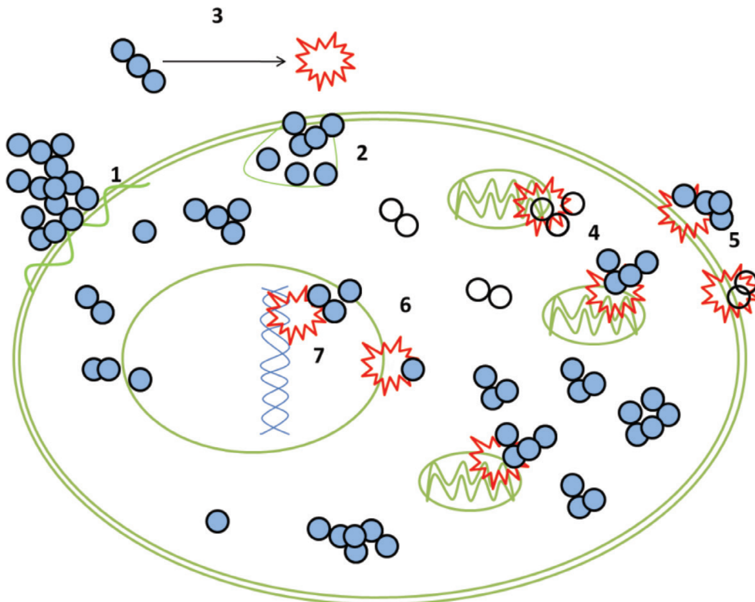

Figure 2. NPs toxicity mechanisms induced in *Candida albicans*. (1) NPs adhesion in the cell membrane causing disruption in the membrane and death. (2) NPs introduction to the cell with their posterior degradation and ion release. (3) NPs ROS generation outside the cell. (4) NPs and ions ROS generation in interaction with mitochondria. (6) Membrane lipid peroxidation with nucleus damage. (7) DNA damage by NPS and ions ROS generation.

Khan et al. (2014) [121] write "when $CoFe_2O_4P$ NCs gained a higher energy than Eg, the electrons (e^-) of $CoFe_2O_4P$ NCs were promoted across the band gap to the conduction band (Ec), which creates a hole (h+) in the valence band (Ec). These e^- in the E_C and holes in the Ev possibly have high reducing and oxidizing powers, respectively." These electron movements generate the NPs reactivity and the oxidative stress generation. The same phenomenon is reported by Setyawati et al. (2014) [122] for TiONPs. These NPs adsorbed UV light, and the adsorbed UV light generates electron excitation, creating a hole in the valence band. The electrons and holes migrate to NPs superficies where they can react with oxygen or water generating oxidative stress. The superficial e^- generates the liberation of hydroxyl increasing the mitochondria membrane depolarization and liberation of cytochrome c. Added to this, the results show DNA damage [120]. However, the oxidative stress is not the only mechanisms involved in the AgNPs toxicity; also the membrane fluidity, ergosterol content, and cellular and ultrastructure morphology are altered [123]. The squalene monooxygenase expression in *Candida albicans* exposed to TeNPs showed an increase [112]. The squalene monooxygenase catalyzes the conversion of squalene to 2,3-oxidosqualene; inhibition in this step generates the squalene increase and the disruption of the *Candida albicans* cell wall [107].

8. Conclusion

The antibiotic resistance increase in many microorganisms has encouraged researchers to focus their efforts on the synthesis and design of multiple effective compounds in order to combat the resistance mechanism of microorganisms. NPs offer a new and effective "antibiotic" that could work against the resistance mechanism in *Candida albicans*.

The biogenic NPs offer a new generation of NPs that work as a carrier. These NPs offer the possibility to drive the toxicity effect to a specific target, in such way the collateral damage could be diminished.

However, the NPs toxicity mechanisms are not completely understood. The oxidative stress is one of the described mechanisms; it is possible to investigate other mechanisms involving similarity to oxidative stress. More studies are necessary to understand the influence that nanoparticles have in the *Candida albicans* resistance mechanisms and if this exposition could not generate new ones.

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Conflict of interest

The authors declare no conflict of interest.

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