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REVIEW

Metallic and lipid nanoparticles against multidrug resistant *Candida*: advances and translational hurdles

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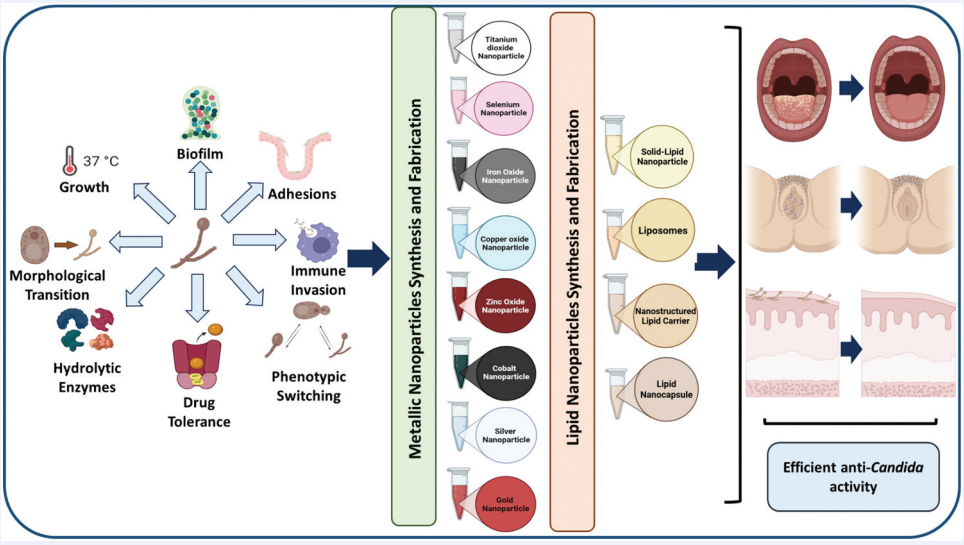
ABSTRACT

Introduction: Among the many ongoing difficulties, *Candida* infections present significant clinical hurdles due to the rapid development of resistance, recurrent episodes, and the limited effectiveness of conventional therapies. In recent decades, metallic nanoparticles (MNPs) and lipid nanoparticles (LNPs) have shown a specific impact (>84% *Candida* biofilm inhibition in preclinical models) by addressing the critical challenges of mitigating drug side effects and multidrug resistance (MDR).

Areas covered: This paper provides an in-depth overview of synthesis, fabrication, mechanistic insights, preclinical and clinical practices for MNPs and LNPs, discussing and highlighting their therapeutic efficacy against resistant *Candida* species over traditional methods. The literature was sourced from peer-reviewed journals and databases, including PubMed, Scopus, Web of Science, WIPO, and Clinical Trials up to May 2025.

Expert opinion: In this portion the potential of hybrid MNP–LNP systems with surface modification enables functionalization by targeting ligands and more specific binding toward fungal cells to enhance the therapeutic index. In addition, combining drug-loaded MNPs and LNPs with artificial intelligence (AI), photodynamic, gene, or immune therapies offers a comprehensive and innovative solution for MDR *Candida*. However, addressing regulatory complexity still needs to be considered toward optimizing the stability and scalability of MNPs and LNPs for clinically meaningful translation.



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Antifungal therapy; *Candida*; drug delivery; lipid nanoparticle; metallic nanoparticle; nanomedicine; nanotechnology

1. Introduction

Among the approximately 5 million fungal spp., only a few hundred are pathogenic to humans, colonizing sites such as the gastrointestinal tract, skin, respiratory system, bloodstream, and female genital tract [1,2]. *Candida*, especially *Candida albicans*, is a major cause of fungal infections, with high global mortality rates, particularly in immunocompromised individuals [3–5]. This opportunistic pathogen can cause conditions

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Article highlights

- Current *Candida* management unfortunately remains suboptimal due to MDR and recurrent episodes.
- Traditional therapies have failed to achieve desired outcomes while exhibiting side effects.
- Nanosystems, *viz*. MNPs and LNPs are reported to have favorable anti-*Candida* potential.
- Preclinical and clinical data highlight their superior efficacy, lower toxicity, and capacity to overcome MDR.
- However, some issues regarding regulation, stability, and scalability remain major hurdles for clinical translation.
- Expert insights propose upcoming research into integrated hybrid systems, with smart targeting modalities.

ranging from superficial mucosal infections to life-threatening systemic *Candida* infection, especially in patients with HIV, cancer, or undergoing organ transplantation [6–8]. *Candida* infections affect over 7 million people annually and contribute to more than 2.5 million deaths globally [9]. Despite the availability of antifungal therapies, mortality rates for invasive candidiasis remain as high as 40% [10]. *C. albicans* exhibit morphogenesis (see Figure 1, part A), transitioning from yeast to hyphal forms (*h*) during infection [11], which enhances tissue invasion, immune evasion, and virulence [12–15]. Its pathogenicity is supported by various factors, including thermal tolerance, enzyme secretion, tissue adhesion, filamentation, immune evasion, and biofilm formation [16,17]. Biofilms significantly contribute to antifungal resistance (see Figure 1, part B) due to their complex architecture, extracellular matrix (ECM), and metabolic heterogeneity [18,19], often accompanied by the activation of efflux pumps [20]. The increasing incidence of drug-resistant *Candida* strains, coupled with the limitations of current antifungal agents, underscores the urgent need for alternative therapies [21,22].

Nanotechnology offers innovative approaches to address these challenges such as liposomes (LIPs) [23], micelles [24], niosomes [25], solid lipid nanoparticles (SLNs) [26], metallic nanoparticles (MNPs), silica nanoparticles [27], nanocages [28], nanotubes [29], nanogels [30], dendrimers [31,32], and others [33,34], which have shown significant potential. Among these, SLNs, LIPs, nanostructured lipid carriers (NLCs), and MNPs have emerged as the most widely investigated platforms, owing to their favorable anti-*Candida* activities. MNPs combat *Candida* by disrupting fungal membranes, generating oxidative stress, and damaging DNA, thereby increasing membrane permeability and antifungal efficacy [35,36]. Metals such as gallium and cerium, known for antibacterial activity, have shown antifungal potential under specific conditions [37]. Functionalization of MNPs with targeting ligands or drugs can enhance specificity and reduce toxicity. Meanwhile, LNPs enhance drug solubility, stability, and controlled release as they cross biological barriers. They can encapsulate both hydrophilic and hydrophobic drugs and are composed of natural or synthetic lipids, offering excellent biocompatibility and low toxicity [38,39]. Additionally, they stand out for their unique physicochemical properties, high surface area, drug encapsulation ability, and biocompatibility, which address issues such as poor solubility, stability, and toxicity (See Table 1) [5,40]. Hybrid systems combining MNPs and LNPs show promise for tackling multidrug resistant (MDR) *Candida* spp., offering synergistic advantages such as enhanced stability, targeted delivery, and sustained drug release [41–47]. These advanced nanocarriers could revolutionize antifungal therapy by combining the antimicrobial activity of MNPs with the delivery efficiency of LNPs.

In this review, current research on MNPs and LNPs as promising tools to combat *Candida* is explored. The mechanisms of action are highlighted together with fabrication methods and functional physicochemical properties important for their therapeutic performance in treating *Candida* infections. It also discusses the challenges in clinical translation, including safety, efficacy, and regulatory aspects, and concludes with an expert opinion on future directions over the next 5–10 years. Data were sourced from ScienceDirect, The Lancet, Nature, Taylor & Francis, PubMed, and clinical trial repositories.

A literature search was conducted over a 10 year window from January 2015–May 2025. The search terms included combinations of MeSH terms and keywords, such as *'Candida albicans,' 'nanoparticles,' 'Candida resistance,' 'metallic nanoparticle,' 'lipid nanoparticle,' 'nanoparticle synthesis,'* and *'fabrication'*. Filters were applied to include original research articles, *in vitro* and *in vivo* evidence of MNPs and LNPs, clinical trials, and patent documents that explicitly demonstrated activity against *Candida*. Exclusion criteria comprised non-English publications, conference abstracts lacking full-text access, reviews, editorials, and studies on non-*Candida* infections or non-nanoscale systems, articles with low methodological quality, and patents without demonstrable utility data.

2. Mechanism of action of MNPs and LNPs with *Candida*

MNPs exert antifungal effects primarily by interacting with fungal cell membranes, causing structural disruption and increased permeability, which have been discussed in this section [48] (see Figure 2(a)). Nanoparticles obtained from metals such as silver (AgNPs), gold (AuNPs), and copper (CuNPs) bind to membrane components, including sulfur-containing proteins and phospholipids, generating reactive oxygen species (ROS) that induce oxidative stress and damage cellular components such as lipids, proteins, and DNA [49–52]. Some MNPs penetrate cells, disrupting DNA replication and transcription, and can trigger apoptosis *via* specific signaling pathways [53,54]. Additionally, MNPs enhance drug uptake by increasing membrane absorption. In addition to these, gallium- and cerium-based MNPs exhibit antifungal potential. Gallium disrupts iron metabolism, particularly under iron limiting conditions, affecting enzymatic activity and RNA synthesis [37–59]. Recent *in vivo* data further confirm the therapeutic promise of gallium-based nanosystems. He et al. [60] demonstrated that lyticase–gallium ion co-loaded nanosystems significantly suppressed *Candida* load and inflammation in a fungal keratitis mouse model and promoted corneal healing and cytokine reduction. Histological assay revealed a potential reduction of corneal thickness and inflammatory cytokine expression ($p < 0.0001$) with minimal toxicity, confirming its enhanced anti-*Candida* potential. Cerium oxide NPs have been

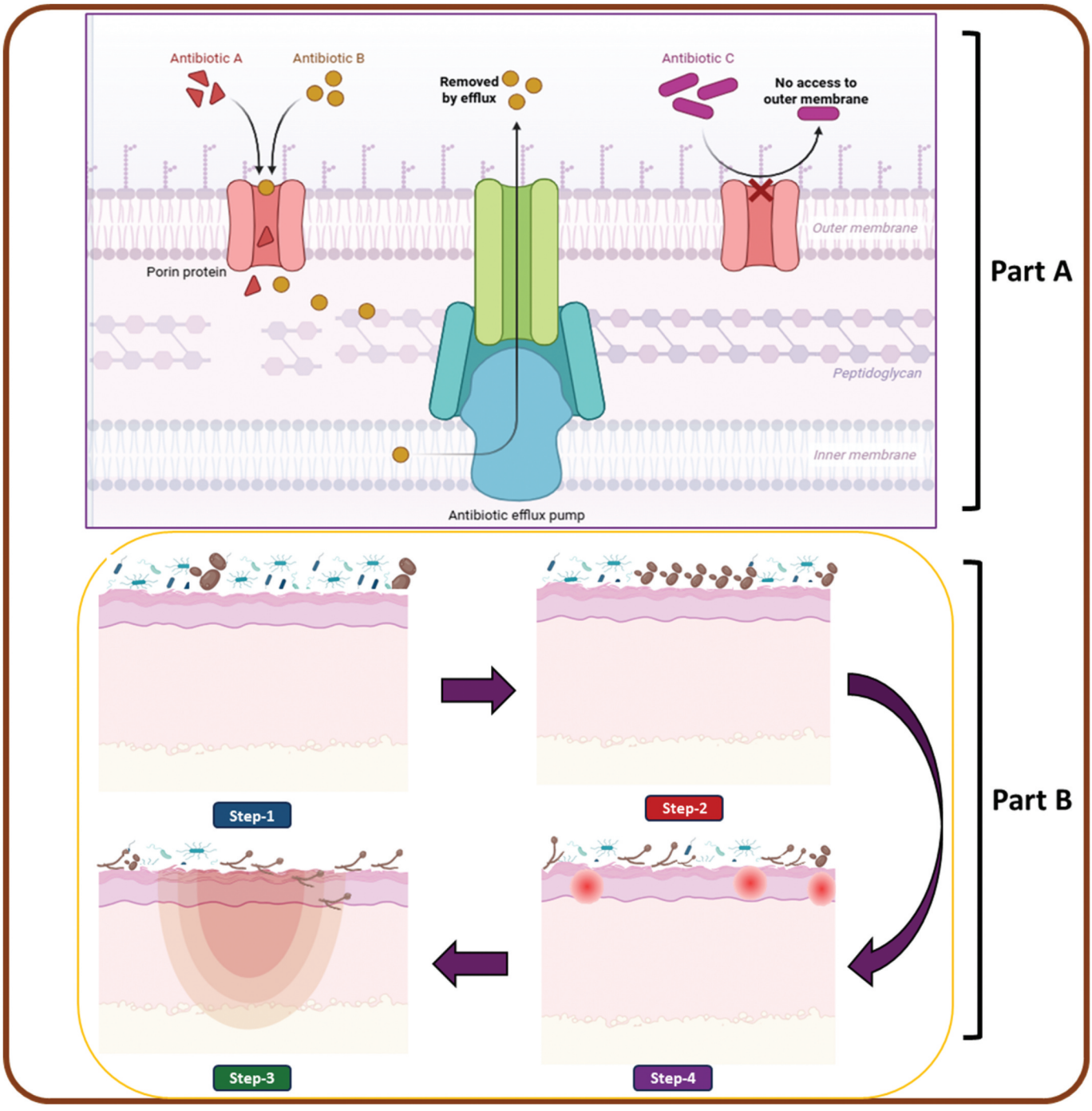

Figure 1. *Candida* multidrug resistance (part A) and its pathogenic transition (part B).

reported to promote fungal growth inhibition and spore germination [55,61].

LNPs, by contrast, offer effective antifungal targeting due to their biocompatible lipid matrix, which can encapsulate both hydrophilic and hydrophobic drugs. They fuse with fungal membranes, enhancing the intracellular delivery of antifungals (see Figure 2(b)). Lipids such as rhamnolipids disrupt membrane fluidity and interfere with ion transport and nutrient uptake [62,63]. Moreover, LNPs can modulate immune responses, potentially enhancing fungal clearance through the activation of immune cells and the release of cytokines [64].

3. Fabrication of nanoparticles (NPs)

The following sections outline the synthesis and fabrication strategies for antifungal nanocarriers: Section 3.1 compares top-down and bottom-up synthesis routes for MNPs, while Section 3.2 covers LNP methods, highlighting their roles in antifungal delivery.

3.1. Synthesis of MNPs

NPs can be synthesized *via* two primary strategies: the top-down and bottom-up approaches (see Figure 3(a)) [65]. The top-down method reduces bulk materials to nanoscale

Table 1. Preclinical investigation of MNPs concerning *Candida* Spp.

Sl. No.	Nanoparticles Used	Main excipient(s)	*Candida* Spp.	Outcomes	References
1.	AgNPs	Calcium hydroxide	*C. albicans*.	Combining AgNPs with calcium hydroxide significantly improved antifungal efficacy against *C. albicans* biofilms, showing the synergistic effect.	[115]
		Organic polymeric matrix	*C. albicans*	*Cyanobacteria*-derived AgNPs effectively inhibited and degraded *C. albicans* biofilms (MICs – 12.5 µg/mL).	[116]
		NA	*C. albicans*	AgNPs combined with FLU demonstrated a strong synergistic effect (fractional inhibitory concentration indices: 0.125–0.5) against *C. albicans*.	[117]
		Graphitic carbon nitride	*C. albicans*	The formulation demonstrated an effective and safe antifungal agent (MIC – 16–256 µg/mL) for the treatment of oral fungal infections.	[118]
		Chitosan	*C. albicans*	Developed formulation showed an efficient antifungal activity against *C. albicans* in both experimental models.	[119]
		Erodium glaucophyllum extract	*C. albicans*	EG-AgNPs demonstrated potent inhibitory action on the growth and biofilms (56.36%).	[120]
		Chitosan	*C. albicans*	The copper–silver–chitosan nanocomposite (MIC – 112 µg/ml) showed the strongest antifungal effect against *C. albicans*, surpassing individual nanoparticles and comparable to AmB.	[121]
		NA	*C. albicans*, *Candida dubliniensis*, and *Candida guilliermondii*	AgNPs suppressed the growth of *Candida* (*C. albicans,* MIC – 62.50 mg/ml) species and demonstrated potent antifungal activity.	[122]
		PVA, PEG, *Hyptis suaveolens* leaf extract	*C. albicans*	Biosynthesized AgNPs using *Hyptis suaveolens* leaf extract showed strong antifungal activity, outperforming AmB and causing *C. albicans* cell wall disruption.	[123]
		Royal jelly	*Candida guilliermondii* NP-4	Royal jelly-mediated AgNPs exhibited strong antifungal effects (90%) against *C. guilliermondii*, significantly inhibiting ATPase activity and inducing oxidative stress.	[124]
		Thymus vulgaris	*C. albicans, C. krusei, C. glabrata*	Thyme-coated AgNPs demonstrated strong antifungal activity against *Candida* species (MIC/minimum fungicidal concentration (MFC) values of 156.25–5000 µg/mL).	[125]
		Sodium dodecyl sulphate	*C. parapsilosis*	The vaginal cream demonstrated increased antifungal activity against *C. parapsilosis*, achieving greater inhibition zones (80%) with half the mcz concentration of commercial products.	[126]
		Seed extract of *Syzygium cumini*	*C. albicans, C. tropicalis, C. dubliniensis, C. parapsilosis, C. krusei*	Biosynthesized AgNPs effectively (MIC – 0.125–0.250 mg/ml) suppressed *Candida* spp. growth, biofilm formation, germ tube development, and hydrolytic enzyme release, causing severe cellular damage.	[127]
		Lotus lalambensis schweinf leaf extract	*C. albicans*	Nanoformulation showed potent anti-candidal activity, significantly inhibiting *C. albicans* biofilm formation (82.5%) and morphogenesis with minimal cytotoxicity, making it a promising treatment for oral candidiasis.	[128]
		Quercetin	*C. albicans, C. glabrata, C. parapsilosis*	Biogenic AgNPs synthesized *via* quercetin demonstrated excellent antifungal activity, increasing stress-induced damage in *Candida* species, with potent efficacy against *C. glabrata*.	[129]
		NA	*C. albicans, C. parapsilosis, C. krusei, C. guilliermondii, C. auris*	Nanoparticles showed antifungal activity against multiple *Candida* spp., synergized with FLU, inhibited biofilms, and modulated *C. albicans* (0.732 mg/mL for 50% inhibition) virulence genes.	[130]
		NA	*C. albicans*	*Borojoa patinoi*-based AgNPs effectively inhibited *C. albicans* filamentation and showed the highest inhibition.	
		Hyaluronic acid	*C. albicans*	The nanocomposite effectively promoted wound healing, inhibited *C. albicans* filamentation (97.2%), and modulated inflammatory and angiogenic markers, demonstrating strong therapeutic potential.	[131]
		Polyacrylamide	*C. albicans*	Nanocomposites demonstrated potent antifungal, anticancer, and antioxidant activities, effectively inhibiting *C. albicans* and modulating key gene expressions.	[132]
		NA	*C. albicans*	AgNPs demonstrated strong anti-candidal activity, inhibiting biofilm formation and dimorphic transition without cytotoxicity.	[133]
2.	AuNPs	N/A	*C. albicans*	The biosynthetic nanoparticles as novel adjuvants to extend the lifespan of existing antifungal drugs	[134]
		Polyethylene glycol	*C. tropicalis*	The combination aids the biofilm inhibition and reduces perister cells.	[135]
		Phospholipids and proteins	*C. albicans*	Exposure to AuNPs demonstrated significant phospholipid and protein spectral changes *via* synchrotron-FTIR analysis.	[136]
		Carbopol	*C. albicans*	The metallic nanoparticles enhanced drug diffusion and inhibited the growth in fungal strains.	[137]
		Olive leaf extract	*C. albicans*	The synthesized AuNPs showed effective action at MIC of 40.77 ng/mL toward *C. albicans*	[138]
		Cetyltrimethylammonium bromide	*C. tropicalis*	Functionalized nanoparticles disrupted *C. tropicalis* biofilms by inducing redox imbalance and oxidative stress.	[139]
		Ethnobotanical extracts	*C. albicans*	AuNP conjugates significantly inhibited *C. albicans* biofilm formation, downregulated *Bcr1* and *HSP90* genes.	[140]
		Chitosan	*C. albicans, C. glabrata*	The formulation demonstrated biofilm inhibition and biofilm eradication efficacy against both *Candida* spp.	[141]
		Resveratrol a natural polyphenol	*C. albicans*	Nanoformulation exhibited potent antifungal activity against *C. albicans* and reduced virulence factors.	[142]
		Brazilian red propolis extract	*C. albicans*	Biogenic nanoparticles demonstrated strong antimicrobial (MIC = 12.4 µg/mL) and dose-dependent cytotoxic activities.	[143]

(*Continued*)

Table 1. (Continued).

Sl. No.	Nanoparticles Used	Main excipient(s)	*Candida* Spp.	Outcomes	References
3.	SeNPs	SeNP@PVP_Nystatin	*C. albicans*	SeNPs functionalized with nystatin effectively inhibited *C. albicans* growth, morphogenesis, and biofilm *via* RAS/cAMP/PKA pathway modulation.	[144]
		Ginger@SeNPs nanoconjugates	*C. albicans*	The formulation effectively inhibited *Candida* growth and biofilm formation by targeting virulence genes, with moderate cytotoxicity observed in HEK293 cells.	[145]
		Chitosan, polyethylene glycol	*C. albicans*	Optimized SeNPs effectively inhibited over 70% of *C. albicans* growth.	[146]
		Acrylic denture resins	*C. albicans*	This formulation exhibited elevated potential at a concentration of 10%.	[147]
		Chitosan	*Streptococcus mutans*, *Lactobacillus acidophilus*, and *C. albicans*.	Nanoformulation exhibited strong antimicrobial activity, with the lowest MIC against *S. mutans*	[148]
		Chitosan, polyvinylalcohol	*C. albicans*, *C. glabrata*	SeNPs significantly reduced MIC values and downregulated antifungal resistance genes, demonstrating potent antifungal activity.	[149]
		Dextran	*C. albicans*	Biosynthesized nanoparticles showed potent antifungal activity in comparison to conventional formulations	[150]
		Nepeta and berberine	*C. albicans*	Nanoparticles demonstrated inhibition in fungal growth and potent antifungal activity (1 µg/mL).	[151]
4.	IONPs	Chitosan, polyethylene glycol	*C. albicans*	Magnetic nanoparticles exhibited potent antifungal effects against FLU-resistant *C. albicans*.	[152]
		Schiff – base/Cu {II}MNPs	*C. dubliniensis*, *C. krusei*, *C. tropicalis*, *C. parapsilosis*, *C. glabrata*, *C. albicans*	IONPs exhibited potent antifungal activity (MIC range: 8–64 µg/mL) against drug-resistant *Candida* species, with low cytotoxicity.	[153]
		Chitosan	*C. albicans*, *C. glabrata*	The nanocarrier exhibited superior antifungal and antibiofilm activity compared to free miconazole.	[154]
		Chitosan, polyvinylpyrrolidone	*C. albicans*	Iron-oxide nanoparticles exhibited antifungal activity against FLU resistant *C. albicans via* downregulating *ERG11* expression (concentrations of 250–500 µg/mL).	[155]
5.	CuONPs	N/A	*C. albicans*	Biosynthesized CuONPs exhibited strong antifungal activity against *C. albicans* (MIC of 35.5 µg/mL) with minimal cytotoxicity.	[156]
		Polycaprolactone	*C. glabrata*, *C. tropicalis*, *C. albicans*	Formulation exhibited uniform morphology and potent antifungal activity against *Candida* species.	[157]
		Cu20, Zn0 and Ag/Cu20	*C. albicans*	Biogenically and chemically synthesized metallic nanoparticles Cu_2O (0.73 mg/mL), ZnO (0.099 mg/mL), and Ag/Cu_2 O NPs (0.002–0.73 mg/mL) exhibited potent antimicrobial efficacy.	[158]
		Nanostarch and nanochitosan	*C. glabrata*, *C. tropicalis*	Mycosynthesized nanoparticles showed potent anticandidal activity (*C. albicans* – 15.3 mm) and cell wall disruption in multidrug-resistant *Candida* strains.	[159]
		Stabilizing agent	*C. albicans*	Both formulations CuO-NPs and Cu_2O-NPs (sub-MIC 50 µg/mL inhibited yeast-to-*hyphae* transition in *C. albicans*.	[10]
		N/A	*C. albicans*, *C. tropicalis*, *C. glabrata*, *C. parapsilosis*, *C. krusei*	Fungal-mediated CuNPs showed high stability, potent antibacterial, anticandidal, antioxidant, and selective anticancer activities.	[160]
		Polyalthia longifolia roots	*C. albicans*	NPs demonstrated effective antibacterial and antifungal activity against *S. aureus, E. coli, and C. albicans* (17.2 ± 0.2 mm).	[161]
6.	ZnONPs	Chitosan polyethylene glycol	*C. albicans*	ZnONPs exhibited dose-dependent (160 µg/mL – 95.86 ± 2.5%) antifungal activity against *C. albicans*.	[162]
		N/A	*C. albicans*	Prophylactic treatment with low-dose ZnONPs enhanced innate immunity in *Galleria mellonella* and protected against *C. albicans* infection.	[163]
		Lignin	*C. albicans*	NPs exhibited potent, nontoxic antifungal activity by inhibiting growth and virulence (more than 90%) of *C. albicans*.	[7]
		Laurus nobilis leaf extract	*C. parapsilosis*, *C. glabrata*, *C. auris*	Biosynthesized nanoparticles demonstrated strong antifungal and synergistic effects against drug-resistant *Candida* strains.	[164]
		Chitosan, polyethylene glycol	*C. glabrata*	ZnONPs exhibited strong antifungal and antibiofilm activity against Flu-resistant *C. glabrata*.	[165]
		Salvia officinalis leaf extract	*C. tropicalis*, *C. glabrata*, *C. albicans*	NPs demonstrated strong antifungal activity and synergistic effects with terbinafine, FLU, and nystatin against *Candida* strains (23.67 ± 0.29 mm).	[166]
		N/A	*C. albicans*	The metallic quantum dots demonstrated dose dependent (0–200 µg/mL and almost 90% growth) inhibition.	[167]
		Crinum latifolium	*C. albicans*	Nanoparticles exhibited strong inhibitory effects on *Candida* virulence factors.	[168]
		Chitosan, polyethylene glycol	*C. albicans*	ZnONPs significantly reduced initial adhesion and downregulated *ALS1* and *ALS3* gene expression in FLU-resistant *C. albicans* (MIC-0.05-296 µg/mL).	[169]
		Caspofungin	*C. auris*	ZnO nanoparticles effectively prevented caspofungin resistance-associated changes.	[170]

(*Continued*)

Table 1. (Continued).

Sl. No.	Nanoparticles Used	Main excipient(s)	*Candida* Spp.	Outcomes	References
7.	Tio_2NPs	N/A	*C. albicans, C. glabrata, C. tropicalis, C. parapsilosis, C. krusei*	Nanoparticles exhibited antifungal activity (64–128 µg/mL) against *Candida* spp. with higher safety margins than AmB.	[171]
		N/A	*C. albicans*	Green-synthesized nanoparticles showed 73% growth inhibition of *C. albicans*, highlighting their potential as effective antimicrobial coatings for dental applications.	[172]
		Polydimethylsiloxane	*C. glabrata*	Nanocomposite coating with 2.5 wt% TiO_2 effectively reduced *C. glabrata* biofilm formation.	[173]
		Withania somnifera	*C. albicans*	Biosynthesized nanoparticles exhibited broad-spectrum antibiofilm activity, antifungal effects against *C. albicans*, and anticancer potential against HepG2 cells.	[174]
8.	CoNPs	Cobalt sulfate heptahydrate	*C. albicans*	Nanoparticle suspension demonstrated effective in treating cutaneous candidiasis (9.4 µg/mL).	[175]
		N/A	*C. albicans*	CoNPs demonstrated durable antifungal efficacy, especially against *C. albicans*, even after 50 washing cycles.	[176]
		Calcium carbonate and cobalt oxide	*C. albicans*	The nanocomposite inhibited over 74% of *C. albicans* growth, demonstrating strong potential as an effective antifungal agent.	[177]

Abbreviations: AgNPs – Silver nanoparticles; MICs – Minimum inhibitory concentration; AmB – Amphotericin B; MFC – Minimum fungicidal concentration; AuNPs – Gold nanoparticles; SeNPs – Selenium nanoparticles; FLU – Fluconazole; IONPs – Iron oxide nanoparticles; CuONPs – Copper oxide nanoparticles; ZnONPs – Zinc oxide nanoparticles; TiO_2NPs – Titanium dioxide nanoparticles; CoNPs – Cobalt oxide nanoparticles.

particles and is considered 'destructive,' often requiring expensive equipment and high energy input. It also presents challenges in controlling the particle size and shape [66,67]. In contrast, the bottom-up method is 'constructive' and involves assembling NPs from atomic or molecular precursors. Due to its precision, cost-effectiveness, and scalability, the bottom-up approach is widely preferred and is the focus of this paper.

In antifungal drug delivery, bottom-up synthesis offers fine control over particle size, shape, and composition [68]. Techniques such as ultrasonic spray pyrolysis (USP) have demonstrated efficacy in producing MNPs, including AuNPs and silver AgNPs for multi-drug loading and targeted *Candida* therapies [69,70]. Additionally, biological synthesis, a subset of bottom-up methods, utilizes micro-organisms, plants, or their extracts, aligning with green chemistry principles due to fewer steps, lower waste, and eco-friendliness [71–75].

Several common bottom-up methods include (see Figure 3(c)):

(i) *Chemical Reduction*: One of the most common techniques is to reduce metal salts (*e.g.*, $AgNO_3$, $AuCl_3$) using agents such as sodium borohydride or ascorbic acid. Surfactants or polymers act as stabilizers to prevent NP aggregation and control morphology [76]. Sertbakan et al. utilized glucose as a reducing agent to synthesize AgNPs from silver nitrate [77], a method similar to that reported by Wang et al. [78].

(ii) *Sol–Gel Method*: Involves hydrolysis and condensation of metal alkoxides, forming a gel that is later dried and calcined. This method enables precise control over NP characteristics [79]. Tahir et al. and Hasnidawani et al. successfully employed this method to produce metal oxide nanostructures with a consistent size and biomedical applicability [80,81].

(iii) *Microemulsion Technique*: Utilizes nanodroplets formed in stable oil–water–surfactant systems as confined spaces for NP formation, ensuring uniformity and dispersion [82]. Malik et al. highlighted its benefits, including high interfacial area and solubilization capacity [83].

(iv) *Green Synthesis*: Employs biological agents (*e.g.*, plant extracts, bacteria, fungi) to reduce metal ions into NPs. This sustainable method is gaining traction due to its biocompatibility and environmental safety [84]. Usman et al. synthesized MNPs using citrus peels, characterized *via* UV–Vis spectroscopy and X-ray diffraction (XRD) [85].

(v) *Ultrasonic Spray Pyrolysis (USP)*: A highly efficient method where high frequency ultrasonic waves atomize a precursor solution into fine droplets. These droplets undergo rapid solvent evaporation and solute precipitation in a heated zone, resulting in the formation of solid NPs [86]. Shariq et al. synthesized monodispersed, spherical AuNPs using USP, demonstrating uniformity and precise size control [87].

3.2. Synthesis of LNPs

The production of LNPs requires careful control of their structural, dimensional, compositional, and physical properties (see Figure 3

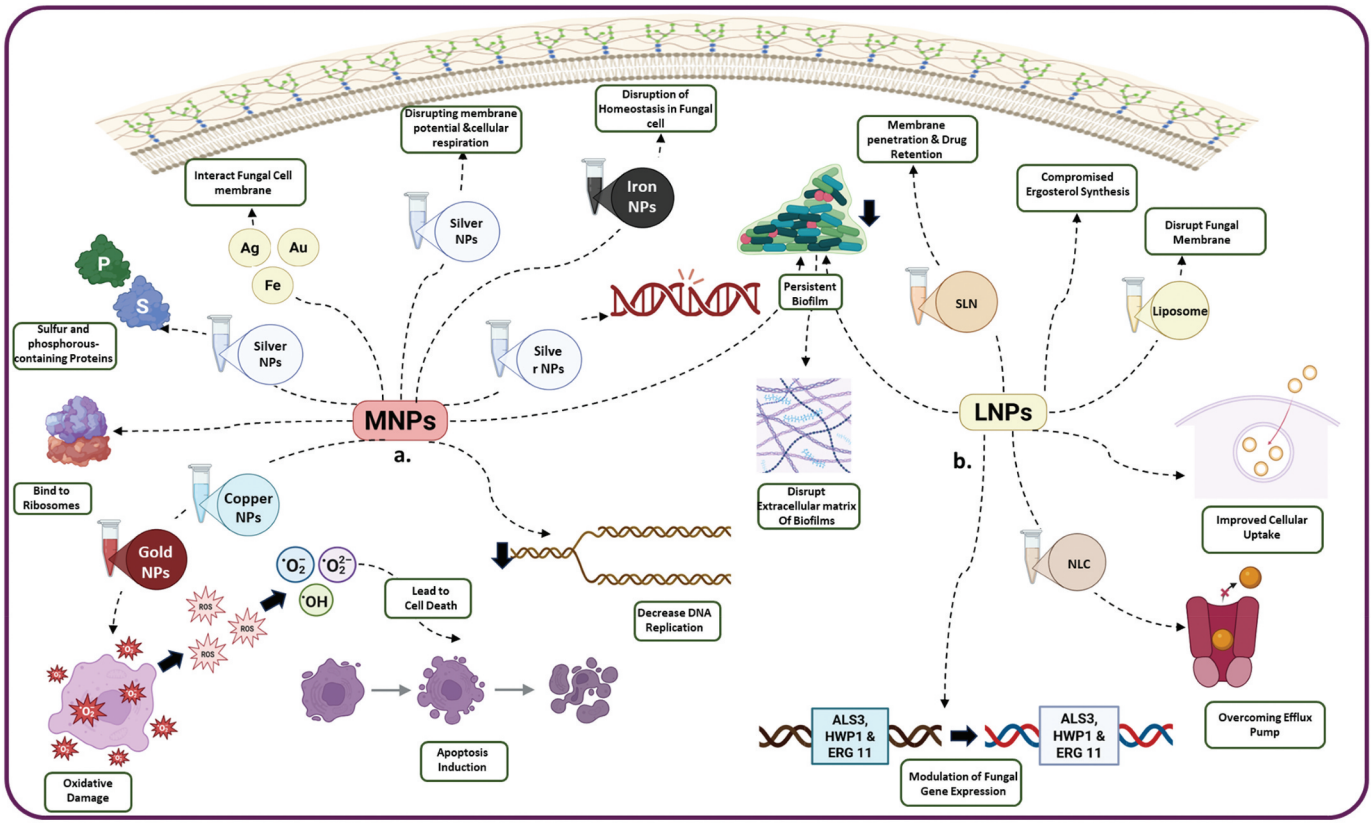

Figure 2. Schematic representation of the mechanistic insights of MNPs (a) and LNPs (b) concerning *Candida*.

(b)) [88]. These characteristics are primarily influenced by the choice of raw materials, including the type and source of lipids, as well as the synthesis conditions. Common lipids used include ionizable cationic lipids, phospholipids, PEGylated lipids, and cholesterol [89]. Additionally, monoglycerides, triglycerides, and certain waxes derived from animal, plant, or synthetic sources have also been utilized [90].

LNPs can be synthesized using the high-energy or low-energy methods [91]:

High-energy methods employ mechanical devices (*e.g.*, high-pressure homogenizers, microfluidizers, and sonicators) to forcibly disperse lipids in aqueous phases [92,93]. While effective, they are less favored due to high energy consumption, operational costs, risk of product degradation, and the need for specialized equipment [94,95].

Low-energy methods, which rely on spontaneous processes within surfactant–oil–water (SOW) systems, such as phase inversion temperature (PIT) or spontaneous emulsification, are increasingly preferred [96–99]. These techniques are cost-effective, energy-efficient, and more suitable for sensitive drug molecules, especially in antifungal delivery systems (see Figure 3d).

Low-Energy Methods for LNP Synthesis

(i) *Microemulsion Method*: Involves forming a thermodynamically stable oil–water–surfactant system at room temperature. This method enables uniform particle size, high drug encapsulation, and improved solubility of hydrophobic drugs [100]. For example, Fathy et al. used this method to prepare curcumin-loaded SLNs. They created an o/w microemulsion, diluted it with water and Poloxamer 188 (Pluronic F68) solution, and obtained stable SLNs with significant biological activity [101].

(ii) *Supercritical Fluid Method*: Utilizes supercritical CO_2 to dissolve lipids and drugs, followed by rapid expansion to precipitate NPs. This allows for precise control of particle characteristics and is ideal for creating stable formulations with controlled release profiles [102]. For example, Duong et al. used a water miscible solvent with CO_2 and an aqueous phase to generate SLNs *via* precipitation [103].

(iii) *Solvent Evaporation Method*: Lipids and drugs are dissolved in an organic solvent that is later evaporated under reduced pressure, forming NPs. This method is useful for heat-sensitive drugs, offering a high drug loading and controlled release [104]. For example, Grandhi et al. produced voriconazole loaded LNPs, where particle size and drug entrapment were influenced by surfactant concentration [105].

(iv) *Impingement Jet Mixing (T-Junction)*: Two high-speed liquid streams typically a lipid-containing organic phase and an aqueous anti-solvent collide to form NPs. This method is scalable and provides excellent size control [106]. As an example, Subraveti et al. demonstrated reproducible, controlled size LNPs using this approach with ionizable and stabilizing lipids [107].

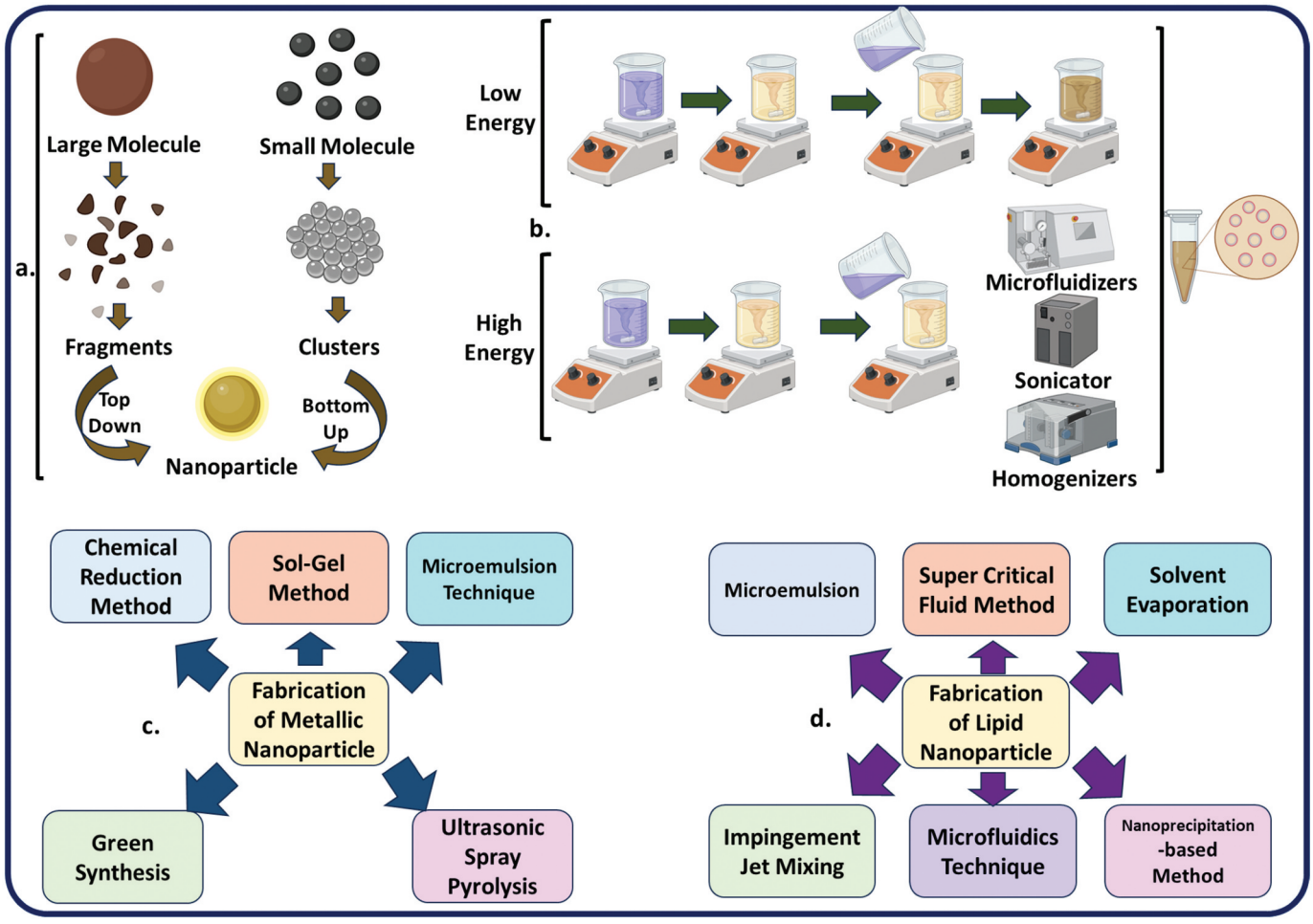

Figure 3. Schematic representation of MNPs (a and c) and LNPs (b and d) syntheses and fabrication techniques.

(v) *Microfluidics*: Employs microchannels for precise and rapid mixing of lipid and drug solutions, resulting in highly uniform and monodisperse LNPs. This technique supports multi-drug loading and targeted antifungal delivery [108,109]. Prakash et al. used microfluidics for scalable fabrication of gene delivery LNPs with high throughput, *i.e.*, 12 mL/min to 200 mL/min without altering process parameters, representing a nearly 17-fold increase in throughput [110].

(vi) *Nanoprecipitation*: A simple technique where a solvent containing lipids and drugs is rapidly mixed with a nonsolvent, causing precipitation of LNPs. It is room temperature compatible, cost-effective, and suitable for both hydrophilic and hydrophobic drugs [111,112]. For example, Xu et al. used a concentration controlled nanoprecipitation method to achieve a high drug loading (~70%) in antifungal LNPs [113].

4. Preclinical investigation of MNPs against *Candida*

MNPs have been successfully demonstrated to exhibit promising antifungal activity against *Candida* spp., as reported by various authors. Some of the essential MNPs, their properties, and their mechanisms of action have been covered in this section (see Table 1) [114].

4.1. Silver NPs (AgNPs)

AgNPs have demonstrated potent antifungal activity against *C. albicans*, particularly when used alone or in combination with other agents. Alghofaily et al. [115] reported that combining AgNPs (0.04%) with calcium hydroxide significantly reduced the viability of *C. albicans*, suggesting their potential for dental applications. Ahmad et al. [116] utilized *Cyanobacteria*-derived AgNPs with a minimum inhibitory concentration (MICs) of 12.5 µg/mL, demonstrating vigorous antibiofilm activity. AgNPs and fluconazole (Flu), tested individually and in combination, showed synergistic antifungal effects (fractional inhibitory concentration (FIC) indices: 0.125–0.5) against five molecularly confirmed *C. albicans* isolates. AgNPs reduced budding (78.2%) and germ tube formation (95%), while the combination further enhanced inhibition (92.6% and 99.2%) [117]. Arumugam et al. [118] synthesized Ag-embedded carbon nitrides (Ag@g-CN), which disrupted biofilms and cell membranes at MICs of 16–256 µg/mL, with demonstrated biocompatibility. Zhou et al. [119] developed iturin-loaded AgNPs (iturin-AgNPs) exhibiting MICs of 1.25–5 µg/mL, effective even after 15 fungal regenerations. These NPs enhanced membrane permeability and caused protein and nucleic acid leakage. Chitosan dressings incorporating iturin–AgNPs promoted the healing of infected wounds and were nontoxic to HaCaT cells. Abadallah and Ali [120] used *Erodium*

glaucophyllum leaf extract to synthesize AgNPs (EG-AgNPs), which inhibited biofilms (56.36%), dimorphic transition (52%), and enzymatic activity, while being noncytotoxic to HGF-1 cells in a mouse oral candidiasis model. Ashrafi et al. [121] formulated a copper–silver–chitosan nanocomposite with superior antifungal activity over individual or binary components, comparable to amphotericin B (AmB). Masoumizadeh et al. [122] observed significant growth inhibition of *C. albicans*, *C. dubliniensis*, and *C. guilliermondii* by AgNPs, with MICs of 62.5, 31.25, and 15.62 mg/mL, respectively. Scanning electronic microscope (SEM) imaging revealed cell membrane damage. Malathi et al. [123] biosynthesized AgNPs using *Hyptis suaveolens* leaf extract, demonstrating strong antifungal activity (MICs: 0.27–0.97 µg/mL), outperforming AmB. Similarly, Marutyan et al. [124] synthesized royal jelly mediated AgNPs (RJ-AgNPs) that acted as fungicides and fungistatics at 5.4 and 27 µg/mL, respectively, and modulated oxidative stress pathways. Thyme-coated AgNPs (T/AgNPs), synthesized by Khalil et al. [125] using *Thymus vulgaris*, showed antifungal efficacy against *Candida* strains from COVID-19 patients, with MIC/minimum fungicidal concentration (MFC) values of 156.25–5000 µg/mL and clear ultrastructural damage. Maciel et al. [126] developed a vaginal cream combining AgNPs with miconazole (Mcz), resulting in an 80% increase in inhibition zones and improved efficacy over commercial products. Jalal et al. [127] produced AgNPs from *Syzygium cumini* seed extract (ScAgNPs), which suppressed germ tube and biofilm formation and inhibited hydrolytic enzymes. Transmission electron microscope (TEM) confirmed NPs-induced cellular damage. Abdallah and Ali [128] synthesized AgNPs (L-AgNPs) from *Lotus lalambensis* leaves, with the L-AgNPs/LL combination showing synergistic effects (24 mm inhibition zone) and >78% suppression of morphogenesis and adhesion, along with low cytotoxicity (< 5%). Cervantes Chávez et al. [129] reported quercetin-functionalized AgNPs that disrupted *Candida* cell walls *via* osmotic and oxidative stress, with efficacy in the order of *C. glabrata* ≥ *C. parapsilosis* > *C. albicans*. AgNPs from *spruce bark* extract (SBE) showed synergistic effects with Flu and downregulated virulence genes like *SAP2*, while upregulating *ALS3* and *HSP70* [130]. Gómez Garzón et al. [131] demonstrated that synthesis temperature affects the antifilamentation activity of AgNPs produced using *Borojoa patinoi* extracts. AgNPs synthesized at 5°C inhibited filamentation of *C. albicans* strains by up to 97.2%. El Hamid et al. [132] developed a nanocomposite hydrogel with AgNPs, *pomegranate peel* extract, and hyaluronic acid, which significantly reduced fungal burden and modulated inflammation in infected wounds. Finally, Khalil et al. [133] formulated hydrogel nanocomposites using acrylamide, chitosan, and $AgNO_3$ *via* gamma irradiation. These hydrogels exhibited strong anti-*C. albicans* activity, cytotoxicity to HeLa cells, and apoptosis *via p53* upregulation, alongside suppression of *PDGFR-β*, *Bcl-2*, *cathepsin*, and *MMP-2* expression.

4.2. Gold NPs (AuNPs)

AuNPs have emerged as promising antifungal agents, particularly against MDR strains of *C. albicans*, due to their ability to enhance drug efficacy, disrupt biofilms, and modulate host immune responses. Yu et al. [134] biosynthesized AuNPs using *C. albicans* (Ca-AuNPs), which significantly potentiated the efficacy of azole antifungals (Flu, itraconazole (Itz), and voriconazole) against MDR *C. albicans*. Ca-AuNPs increased intracellular drug accumulation and induced cell membrane disruption, ROS generation, and ATP depletion, effectively overcoming fungal resistance. Moreover, this strategy promoted vaginal mucosa regeneration in infected murine models, indicating potential clinical applications. Da Silva et al. [135] examined cetyltrimethylammonium bromide (CTAB) stabilized AuNPs (CTAB-AuNPs) and cysteine conjugated variants in combination with AmB against *C. tropicalis* biofilms. The combination exhibited synergistic antifungal effects, significantly reducing biofilm biomass and disrupting matrix architecture, including persister cell populations, as confirmed by crystal violet staining and SEM. Penman et al. [136] explored the physicochemical interaction of citrate-capped AuNPs (100 nm) with *C. albicans via* advanced microscopy. AuNPs adhered predominantly to the fungal cell surface and induced increased cell stiffness, as well as alterations in membrane phospholipid and protein structures, suggesting notable impacts on membrane integrity. Balwierz et al. [137] developed a topical hydrogel containing ITZ and AuNPs, which enhanced drug diffusion and inhibited *C. albicans* growth. This suggests that AuNPs can improve topical antifungal formulations for clinical use. Kareem and colleagues [138] reported AuNPs using *olive leaf* and demonstrated their potential in cutaneous candidiasis. The synthesized AuNPs showed effective action at MIC of 40.77 ng/mL toward *C. albicans*. *In vivo* analysis revealed that AuNPs significantly healed infected skin in the mice model compared to Nystatin (Nyt). These findings highlight the effectiveness of green synthesis of AuNPs in combating *Candida*. Da Silva et al. [139] further evaluated CTAB-stabilized and cysteine conjugated AuNPs on *C. tropicalis* biofilms. Both types induced oxidative stress and redox imbalance, with CTAB-AuNPs demonstrating a stronger antifungal effect by altering ROS and reactive nitrogen intermediate (RNI) levels, alongside biofilm architecture disruption.

Jodan Cruz et al. [140] assessed ethnobotanically synthesized AuNPs and crude plant extracts for inhibiting *C. albicans* biofilms. Thirteen crude extracts and fourteen AuNP-enhanced formulations significantly inhibited biofilm formation, with downregulation of *Bcr1* and *HSP90* genes. These findings support the use of AuNPs to potentiate natural antifungal compounds and target biofilm-associated resistance. Yadav et al. [141] synthesized tyrosol functionalized chitosan AuNPs (ChiTY-AuNPs), which exhibited strong antifungal and antibiofilm activities against *C. albicans* and *C. glabrata*. These NPs disrupted mature biofilms, reduced ECM protein and DNA levels, induced ROS generation (notably in *C. glabrata*), and decreased ergosterol content. These effects were supported by FESEM, FTIR, UV–vis spectroscopy, and selected area electron diffraction (SAED) analyses. Fonseca do Carmo and coworkers [142] synthesized AuNPs and resveratrol-coated AuNPs (AuNpRSV) *via* green methods. Both formulations inhibited *C. albicans* growth, reduced filamentation and ergosterol levels, and altered biofilm viability and ROS production. TEM revealed cell wall and membrane damage. *In vivo* studies confirmed their low toxicity, highlighting their therapeutic

potential. Botteon et al. [143] utilized Brazilian red propolis (BRP) for green synthesis of AuNPs and various fractions (AuNP_hexane, AuNP_dichloromethane, AuNP_ethyl acetate). These NPs demonstrated significant antifungal, antibacterial, and anticancer activities. Notably, AuNP_dichloromethane and AuNP_hexane showed strong antimicrobial effects, reinforcing the potential of BRP-based green synthesis for multifunctional therapeutic agents.

4.3. Selenium NPs (SeNPs)

SeNPs have garnered increasing attention as promising antifungal agents due to their bioavailability, biocompatibility, and potent activity against *C. albicans* and other pathogenic fungi, particularly MDR strains. Nile et al. [144] developed biogenic SeNPs using *Paenibacillus terreus*, further functionalized with Nyt and polyvinylpyrrolidone (PVP) to form SeNP-PVP-Nyt nanoconjugates. These nanoconjugates significantly inhibited *C. albicans* growth by modulating the RAS/cAMP/PKA signaling pathway and exhibited minimal cytotoxicity toward human cells, indicating their potential as safe and effective antifungal drug carriers. Thombre et al. [145] synthesized SeNPs functionalized with *ginger extract* (Ginger-SeNPs), which exhibited enhanced antifungal and antibiofilm activity against *C. albicans*. These nanoconjugates inhibited both fungal growth and biofilm formation, targeting virulence associated genes and demonstrated moderate cytotoxicity in HEK293 cells. Spectroscopic and microscopic techniques confirmed successful synthesis and functionalization. Safaei et al. [146] employed a green synthesis approach using *Halomonas elongata* for SeNPs production. The optimization of sodium selenite and glucose concentrations and incubation time *via* the Taguchi method led to SeNPs with over 70% antifungal efficacy against *C. albicans*, underscoring their applicability in managing oral fungal infections. Rostamzadeh et al. [147] utilized SeNPs within acrylic denture resins at 0.2%, 2%, and 10% concentrations. The outcomes confirmed that SeNPs exhibited an MIC of 25%, and acrylic containing 10% of SeNPs significantly suppressed the *Candida* biofilm density. Statistical analysis revealed that antifungal impact was effective and the efficacy was dose-dependent. SEM further showed significant fungal cell wall damage. Darroudi et al. [148] prepared colloidal SeNPs in chitosan solution (Cts-SeNPs) through chemical reduction and evaluated their antimicrobial activity against *Streptococcus mutans*, *Lactobacillus acidophilus*, and *C. albicans*. The SeNPs exhibited strong antifungal activity, with an MIC of 0.274 mg/mL for *C. albicans*, suggesting their potential use in dental care formulations. Hosseini Bafghi et al. [149] biosynthesized SeNPs and demonstrated their antifungal activity against both *C. albicans* and *C. glabrata*. When combined with AmB or anidulafungin, SeNPs significantly reduced the MICs to 1 and 0.5 µg/mL, respectively. Furthermore, the NPs downregulated key resistance associated genes, including *ERG3*, *ERG11*, and *FKS1*, enhancing antifungal susceptibility. Bafghi et al. [150] reported on the biosynthesis of SeNPs *via Aspergillus flavus* and *C. albicans* cultures to address rising antifungal resistance. The SeNPs demonstrated high efficacy, inhibiting fungal growth at concentrations as low as 0.125 µg/mL substantially lower than the effective doses of conventional antifungals (2–64 µg/mL). In a related study, Bafghi et al. [151] synthesized SeNPs and AgNPs using Nepeta and berberine plant extracts, respectively. MIC evaluations revealed that both SeNPs and AgNPs prevented fungal growth at concentrations ≤1 µg/mL, outperforming standard antifungal agents. These results highlight the feasibility of ecofriendly, plant-based synthesis for generating potent antifungal nanotherapeutics.

4.4. Iron oxide NPs (MIONPs)

MIONPs have emerged as potent antifungal agents due to their unique physicochemical properties, including superparamagnetism, targeted delivery potential, and capacity to induce oxidative stress in fungal pathogens. Khodavandi et al. [152] evaluated the antifungal efficacy of MIONPs alone and in conjunction with visible light against *C. albicans*. The combined treatment significantly downregulated the expression of *HWP1* and *ALS1* genes associated with adhesion and biofilm formation and enhanced ROS generation. These findings suggest that MIONPs, particularly when photoactivated, represent a promising strategy to treat flu resistant *C. albicans* infections. Azadi et al. [153] developed a novel nanoantifungal agent Fe_3O_4@SiO_2/Schiff-base/Cu(II) to target MDR *Candida* spp. The embedded Fe_3O_4 core enhanced the nanocomposite's magnetic properties, aiding in site-specific delivery and therapeutic efficacy. This agent exhibited potent antifungal activity (MIC range: 8–64 µg/mL), with the lowest MIC (8 µg/mL) recorded against *C. parapsilosis*. Mechanistically, it induced ROS production and disrupted fungal cell walls. Importantly, the nanocomposite displayed low cytotoxicity and even promoted cell proliferation, indicating excellent biocompatibility. Arias et al. [154] engineered a chitosan functionalized iron oxide nanocarrier for Mcz delivery, evaluating its antifungal effects against biofilms of *C. albicans* and *C. glabrata*. The resulting nanocarrier (< 50 nm) significantly enhanced antifungal activity compared to Mcz alone, showing synergistic interaction against *C. albicans* (FICI < 0.12) but not *C. glabrata* (FICI < 0.53). TEM and SEM confirmed biofilm disruption and reduced CFUs. Interestingly, the application of an external magnetic field did not improve the antifungal efficacy, affirming that the nanoparticle formulation itself was primarily responsible for the observed effects. Zare Khafri et al. [155] analyzed *C. albicans* clinical isolates using WHONET software and confirmed high rates of Flu resistance (93%). Treatment with MIONPs at concentrations of 250–500 µg/mL downregulated the expression of *ERG11*, a gene critical for azole resistance, although no protein sequence variation was observed. A significant reduction in ergosterol content further supported the antifungal efficacy of MIONPs. These findings establish MIONPs as viable alternatives for managing drug-resistant *Candida* infections.

4.5. Copper oxide NPs (CuONPs)

Copper-based nanoparticles, particularly copper oxide (CuO) and cuprous oxide (Cu_2O), have gained attention for their strong antifungal activity against *Candida* and other pathogenic spp. due to their ability to generate ROS, penetrate biofilms, and modulate gene expression. Garcia Marin et al. [156] biosynthesized polydisperse CuONPs (~5.8 nm), which

demonstrated potent antifungal activity against *C. albicans* (ATCC SC5314), with an MIC of 35.5 µg/mL. The NPs induced substantial ROS production, leading to cellular damage. Ultrastructural analysis confirmed intracellular accumulation of CuONPs within the cytoplasm, cell wall, and extracellular space. Importantly, cytotoxicity assessments using fibroblasts, macrophages, and breast cell lines showed high viability at MIC concentrations, and hemocompatibility remained within safe limits (<5%), supporting the biocompatibility of CuONPs for potential topical antifungal therapy. To enhance the antifungal efficacy in biomedical materials, Muñoz Escobar et al. [157] developed CuONP-loaded polycaprolactone (PCL) nanofibers *via* an *in situ* electrospinning method. CuONPs synthesized using gallic acid were semi-spherical (35 ± 11 nm by TEM), with a uniform distribution (88 ± 11 nm by DLS). Raman spectroscopy confirmed CuO signatures, while SEM revealed fiber diameters of 925–1080 nm, influenced by the CuONP concentration. These PCL CuONP fibers displayed strong antifungal activity against *Candida* spp., suggesting their potential for use in cost-effective antimicrobial dressings. Cuprous oxide (Cu_2O) NPs have also shown robust antifungal activity. Rojas Jaimes et al. [158] synthesized Cu_2O, ZnO, and Ag/Cu_2O NPs and assessed their antimicrobial properties. Among them, Cu_2O exhibited 100% antifungal and antibacterial efficacy, underscoring its potential in preventing nosocomial infections, especially in immunocompromised patients. A novel nanocomposite incorporating biosynthesized CuONPs, nanostarch, and nanochitosan was developed by Saied et al. [159] to combat MDR *Candida* strains. Among 24 clinical isolates, three highly resistant strains, *C. glabrata* MTMA 19, MTMA 21, and *C. tropicalis* MTMA 24, showed significant susceptibility to the nanocomposite, with inhibition zones of 15.3, 27, and 28 mm, respectively. CuONPs played a central role in disrupting fungal cell walls and inducing cell death. Padmavathi et al. [10] compared the antifungal mechanisms of CuONPs and Cu_2O-NPs against *C. albicans*. CuONPs primarily exerted effects *via* ROS generation, whereas Cu_2O-NPs caused direct membrane disruption. Gene expression analysis revealed that CuONPs downregulated *cph1*, *hst7*, and *ras1*, while upregulating *tup1*; conversely Cu_2O-NPs downregulated *ras1* and upregulated *nrg1* and *tup1*. CuONPs demonstrated superior antifungal activity, attributed to their smaller particle size and stable Cu^{2+} oxidation state. Biogenic CuONPs synthesized from endophytic *Aspergillus terreus* BR.1 metabolites demonstrated broad-spectrum bioactivity, including antibacterial, antifungal, anticancer, and antioxidant properties [160], reinforcing their relevance in medical applications. Additionally, Maulana et al. [161] synthesized CuNPs using *Polyalthia longifolia* root extract. These NPs inhibited the growth of *S. aureus* (17.2 mm), *E. coli* (15.6 mm), and *C. albicans* (13.7 mm), with CuONPs identified as the key active component, highlighting their promise as multifunctional antimicrobial agents for pharmaceutical development.

4.6. Zinc oxide NPs (ZnONPs)

ZnONPs have emerged as potent antifungal agents due to their unique physicochemical properties, low toxicity, and diverse mechanisms of action against *C. albicans* and other non-albicans *Candida* spp., including MDR strains. These mechanisms include ROS generation, disruption of fungal membranes, interference with gene expression, and immunomodulation. Djearamane et al. [162] demonstrated that ZnONPs significantly inhibited the growth of *C. albicans* (ATCC 1023) at concentrations ranging from 10 to 160 µg/mL ($p < 0.05$), except at 5 µg/mL. FTIR spectroscopy indicated interactions between ZnONPs and fungal cell wall functional groups, while SEM with energy dispersive X-ray (SEM-EDX) confirmed nanoparticle accumulation on fungal cells. Morphological disruptions such as cell wall pitting, membrane invaginations, and rupture were evident, suggesting compromised membrane integrity as a key antifungal mechanism. In a *Galleria mellonella* model, Xu et al. [163] reported that low doses of ZnONPs (≤20 mg/kg) were nontoxic and significantly improved survival in *C. albicans* infected larvae by reducing fungal burden. ZnONPs enhanced host immunity by increasing hemocyte density, phagocytic activity, aggregation, and phenoloxidase levels, positioning them as immunomodulatory agents rather than solely fungicidal ones. Joshi et al. [7] synthesized ZnONPs using lignin based templates lignin (L), fragmented lignin (FL), and oxidized fragmented lignin (OFL), resulting in hierarchical 1D nanostructures (~40 nm) with a hexagonal wurtzite structure. Among them, FL-ZnONPs showed the most potent antifungal activity (> 90% inhibition) at concentrations of 31.2–125 µg/mL. RT-PCR analysis revealed gene modulation as a contributing factor. Importantly, FL-ZnONPs showed excellent biocompatibility in 3T3-L1 cell lines and *in vivo* (see Table 1). Maniah [164] synthesized ZnONPs *via* a green route using *Laurus nobilis* leaf extract. The crystalline, hexagonal shaped particles (~38 nm) exhibited significant antifungal activity, particularly against *C. parapsilosis*, with inhibition zones of 17.13 ± 0.74 mm and 25.78 ± 0.47 mm at 100 and 200 µg/disk, respectively. Furthermore, ZnONPs potentiated the antifungal activity of clotrimazole (CLZ) against *C. glabrata* and *C. auris* and showed low cytotoxicity (IC_{50} = 774.45 µg/mL). Anitha et al. [165] used Anacardium occidentale (cashew apple juice) for green synthesis of flower-shaped ZnONPs (106.7–169.2 nm). These particles exhibited potent anti-*Candida* activity against Flu-resistant *C. glabrata* (MIC: 48 µg/mL) and disrupted biofilms on prosthetic surfaces even at sub-MIC concentrations, underscoring their potential in antifungal device coatings. Yassin et al. [166] synthesized ZnONPs from *Salvia officinalis* leaf extract and observed strong antifungal effects against *C. tropicalis* (MIC: 40 µg/mL, MFC: 80 µg/mL). Synergism with terbinafine, Flu, and Nyt was evident across *C. glabrata*, *C. albicans*, and *C. tropicalis* strains. SEM analysis confirmed *Candida* cell wall disruption. These findings support ZnONPs as adjuvants in antifungal formulations such as mouthwashes and topical agents. Chand et al. [167] reported that ZnO quantum dots (ZnO QDs, 4–6 nm) inhibited nearly 90% of the *C. albicans* growth at 200 µg/mL. At 25 µg/mL, ZnO QDs exhibited synergistic effects (FIC index <0.5) with Flu, ketoconazole (Ktz), AmB, and Nyt. ZnO QDs showed no toxicity to HeLa cells, highlighting their promise for safe, combinatorial antifungal therapy. Jalal et al. [168] employed *Crinum latifolium* leaf extract to synthesize ZnONPs that significantly inhibited

germ tube formation (up to 86.4%) and secretory enzyme production phospholipase (58.8%) and proteinase (95.2%) at 0.25 mg/mL. CSLM revealed 85% biofilm reduction, and SEM/TEM confirmed nanoparticle penetration and cellular damage in *C. albicans*. Hossein et al. [169] investigated ZnONPs (20–40 nm) synthesized *via* XRD confirmed hexagonal wurtzite structures in *C. albicans* strains from urinary tract infections (UTIs). Sub-MIC doses (0.02–18.1 µg/mL) significantly downregulated *ALS1* and *ALS3*, critical for biofilm adhesion, especially in Flu-resistant isolates. These results highlight ZnONPs as promising anti-biofilm agents for catheter-associated UTIs. Fayed et al. [170] addressed emerging resistance in *C. auris* by studying caspofungin-exposed strains over 10 generations. ZnONPs incorporated with caspofungin mitigated resistance adaptation, biofilm formation, and cross resistance to Flu, demonstrating ZnONPs' potential to reverse resistance phenotypes and improve treatment durability.

4.7. Titanium dioxide NPs (TiO_2-NPs)

TiO_2-NPs have gained attention for their antifungal, anti-biofilm, and photocatalytic properties, making them attractive candidates for biomedical applications, such as coatings and drug delivery systems. Comparative studies also place TiO_2-NPs in context with other MNPs such as ZnONPs. Ahmadpour Kermani et al. [171] directly compared the antifungal efficacy and cytotoxicity of ZnONPs and TiO_2-NPs with AmB. ZnONPs exhibited MIC values of 64–128 µg/mL and MFCs of 256–512 µg/mL, whereas TiO_2-NPs showed slightly higher MICs (128–256 µg/mL) with comparable MFCs. Although both nanomaterials were less potent than AmB, they showed significantly reduced cytotoxicity. The half maximal cytotoxic concentration (CC_{50}) for TiO_2-NPs (862.1 µg/mL) and ZnONPs (706.2 µg/mL) was substantially higher than that of AmB (70.19 µg/mL), indicating a favorable safety profile and highlighting their potential as alternative antifungal agents. Moradpoor et al. [172] employed *Bacillus* sp. for the green synthesis of TiO_2-NPs to minimize toxic residues. Using the Taguchi method, they optimized synthesis parameters including incubation time, glucose, and meta titanic acid concentrations. The resulting TiO_2-NPs showed 73% growth inhibition of *C. albicans*, and SEM and TEM analysis confirmed well-formed nanoscale structures. These biogenic TiO_2-NPs were suggested for use in dental antimicrobial coatings. Nguyen et al. [173] investigated a polydimethylsiloxane/titanium dioxide (PDMS/TiO_2) nanocomposite designed to inhibit *C. glabrata*, a pathogen notable for its oxidative stress resistance. A 2.5 wt% TiO_2 load in the composite reduced biofilm formation by over 50%, even in the absence of UV activation. ROS quantification and surface analysis indicated synergistic interactions between TiO_2-NPs and the PDMS matrix, which disrupted surface hydrophobicity and microbial attachment. Al Shabib et al. [174] reported a green synthesis approach using *Withania somnifera* root extract to fabricate TiO_2-NPs with broad spectrum antimicrobial effects. These NPs significantly inhibited biofilm initiation (43–71%) and the development of mature biofilms (24–64%) at sub-MIC levels, underscoring their potential in treating biofilm-associated *Candida* infections.

4.8. Cobalt NPs (CoNPs)

CoNPs have recently emerged as promising antifungal agents due to their unique physicochemical properties, including redox potential, surface reactivity, and capacity for photocatalytic activity. Several studies have investigated the efficacy of CoNPs and related nanocomposites against *Candida* spp. Kareem et al. [175] synthesized CoNPs from cobalt sulfate heptahydrate using hydrazine monohydrate as a reducing agent. Structural and morphological analyses *via* XRD, atomic force microscopy (AFM), and SEM confirmed crystalline and nanoscale features. *In vitro* assays showed that CoNPs inhibited *C. albicans* growth at concentrations as low as 9.4 µg/mL, with increased efficacy at higher doses. In a rat model of cutaneous candidiasis, CoNP-treated lesions healed by day 6, whereas Nyt-treated wounds resolved by day 5. Although CoNPs demonstrated significant antifungal activity, they were marginally less effective than Nyt *in vivo*. Singh and coworkers [176] employed a green synthesis approach using *Azadirachta indica* (neem) extract to bioreduce CoNPs, which were subsequently integrated into cotton fabric for antifungal textile applications. Optimization *via* response surface methodology (RSM) and ANOVA considered variables such as neem concentration, temperature, and agitation speed. The CoNP-functionalized fabric exhibited robust antifungal activity against *C. albicans* and *A. niger*, with superior and durable effects against *C. albicans* even after 50 laundering cycles. These results highlight the potential of CoNPs for sustained antimicrobial textile applications. In another innovative approach, Fallahnia et al. [177] synthesized a calcium carbonate/cobalt oxide nanocomposite, optimizing conditions *via* the Taguchi method. The optimal formulation (20 mg/mL calcium carbonate, 3 mg/mL cobalt oxide, 90 min stirring) achieved over 74% inhibition of *C. albicans*. Structural characterization confirmed effective nanoparticle integration and morphology conducive to antifungal action. These findings support the potential of cobalt-based nanocomposites in disrupting fungal cell walls and interfering with biofilm formation. Collectively, these studies illustrate the antifungal efficacy of CoNPs and their composites. Their biocompatibility, photocatalytic properties, and ability to maintain activity in various matrices, such as fabrics or biological systems, make them promising candidates for future antifungal strategies, particularly in topical formulations and surface coatings.

Collectively, MNPs exhibited broad antifungal action through multi-faceted mechanisms. Among them, AgNPs demonstrated the broadest spectrum and potency, confirmed across multiple *in vitro* and *in vivo Candida* models. AuNPs and CuNPs offer functionalization versatility, while ZnONPs and TiO_2NPs enhance oxidative stress pathways. Meanwhile, MIONPs and CoNPs are not frequently explored but have shown promising anti-*Candida* activities compared to conventional ones. Overall, these systems summarizes the translational relevance, particularly for resistant *Candida*.

5. Preclinical investigation of LNPs against *Candida*

LNPs have also been successful in demonstrating promising antifungal activity against *Candida* spp., as reported by various authors. It is reported that LNPs act by enhancing the efficacy of antifungal drugs and by directly damaging fungal cells (see Table 2). Some of the important LNPs, their properties, and their mechanisms of action have been covered in this section (see Figure 4) [178,179].

5.1. Solid lipid nanoparticles (SLNs)

SLNs have gained significant attention as efficient drug delivery systems due to their biocompatibility, capacity for controlled drug release, and potential to overcome drug resistance in fungal pathogens such as *C. albicans*. Recent studies have explored various antifungal agents encapsulated in SLNs for enhanced therapeutic efficacy. Carbone et al. [178] investigated SLNs coloaded with CLZ and alphalipoic acid, including both uncoated and cationic formulations. These SLNs exhibited narrow particle size distributions (<150 nm) and varying zeta potentials, contributing to their physical stability. Differential scanning calorimetry (DSC) and release studies confirmed a stable and prolonged drug release profile without an initial burst effect. *In vitro* assays demonstrated retained antifungal efficacy, supporting the potential of SLNs for combination therapies targeting *C. albicans*. Kraisit et al. [180] developed Flu-loaded SLNs for buccal drug delivery using a Box–Behnken design (BBD). Prepared *via* hot homogenization and ultrasonication, the SLNs exhibited particle sizes ranging from 32.86 to 269.3 nm, polydispersity index (PDI) values of 0.254–0.495, and zeta potentials between −19.8 and −36.9 mV. Entrapment efficiencies (EE) ranged from 56.69% to 85.49%. TEM confirmed spherical morphology, and drug release followed diffusion controlled kinetics. This formulation effectively inhibited *C. albicans*, demonstrating its promise for localized buccal candidiasis therapy. Arshad et al. [181] incorporated miconazole nitrate-loaded SLNs into chitosan–gelatin–polyethylene glycol-based microneedle patches *via* vacuum micromolding. The patches showed uniform projections, mechanical stability, and swelling capacity. Both *in vitro* and *in vivo* studies confirmed enhanced drug release and significant inhibition of *C. albicans* biofilms, underlining the potential of SLNs in microneedle mediated antifungal therapy and biofilm management. In another study, Mockdeci et al. [182] developed a hydrogel containing tea tree oil (TTO)-loaded SLNs for oropharyngeal candidiasis. While free TTO was only active against *C. albicans*, TTO-loaded SLNs displayed broad spectrum antifungal activity against multiple *Candida* spp. The hydrogel matrix improved both the stability and antifungal efficacy of TTO, suggesting its utility as a topical therapeutic option for fungal infections. Samee et al. [183] optimized sulconazole (SCZ)-loaded SLNs using Monostearin (glyceryl monostearate), Phospholipon 90 H, and Polysorbate 20 (Tween 20). The resulting formulation exhibited a particle size of 89.81 nm, high-drug entrapment efficiency (86.52%), and sustained release for up to 12 h. Singh et al. [184] further incorporated these SLNs into a Carbomer 934 (Carbopol 934)-based gel (H-SLN2), achieving superior skin targeting and retention. *In vivo* studies revealed faster wound healing and improved skin architecture restoration compared to a marketed gel, with H-SLN2 exhibiting 1.63-fold greater stratum corneum retention and enhanced antifungal efficacy against *C. albicans*. Similarly, Rarokar et al. [185] developed terbinafine hydrochloride (TH)-loaded SLNs *via* high-pressure homogenization using glyceryl monostearate and Pluronic F68. These SLNs were integrated into a Carbopol 934P hydrogel. Rheological assessments confirmed desirable hydrogel properties, while antifungal assays showed superior activity and skin deposition compared to pure TH and commercial formulations.

Collectively, these studies demonstrate the versatility and effectiveness of SLNs in antifungal therapy, offering advantages such as controlled drug release, enhanced skin penetration, improved drug stability, and reduced toxicity. SLNs are particularly promising for topical and mucosal applications in managing *Candida* infections, including resistant strains and biofilm associated conditions in the future (see Figure 4).

5.2. Nanostructured lipid carriers (NLCs)

NLCs have emerged as promising drug delivery systems for antifungal therapy, particularly against *Candida* infections. They offer improved drug encapsulation efficiency (EE), controlled release, enhanced skin and mucosal permeability, and reduced toxicity. Moazeni et al. [186] evaluated *Zataria multiflora* essential oil-loaded NLCs (Zt-NLCs), incorporated into a Carbopol-based gel for treating *Candida*-associated onychomycosis. The formulation exhibited favorable physicochemical properties and no cytotoxicity. Both *in vitro* and clinical evaluations (see Table 3) demonstrated significant antifungal efficacy, with Zt-NLCs showing superior clinical and mycological outcomes compared to placebo after 2 weeks of treatment ($p < 0.005$), specifically targeting the *C. albicans* complex. Chilamakuri et al. [187] developed Ktz-loaded NLCs using 4-allyl-2-methoxyphenol (eugenol) as a liquid lipid excipient. The NLCs demonstrated high drug EE ($89.83 \pm 2.31\%$) and an effective dispersion of Ktz. Incorporation into a hydrogel provided desirable rheological properties, including excellent spreadability and shear thinning behavior. Compared to coarse Ktz, the NLC-hydrogel exhibited improved transdermal flux, increased skin retention, and potent antifungal activity by inhibiting both planktonic growth and biofilm formation of *C. albicans*. Baldim et al. [188] encapsulated *Lippia sidoides* essential oil (LSEO) in NLCs using hot emulsification and sonication techniques. The resulting NLCs, with particle sizes ranging from 213.1 to 445.5 nm, exhibited a PDI of 0.3 and a negative zeta potential. Both the free LSEO and NLC formulations exhibited strong antifungal activity against *C. auris*, with no observed *in vivo* toxicity, underscoring the suitability of NLCs for managing drug-resistant *Candida* infections. Hosny et al. [189] formulated Mcz and sesame oil (SO)-loaded NLCs for the treatment of oral candidiasis. *Ex vivo* permeation studies revealed significantly higher skin permeation and retention compared to a commercial Mcz formulation. *In vivo* studies further confirmed the enhanced antifungal efficacy of the optimized NLCs against *C. albicans*, demonstrating the

Table 2. Preclinical investigation of LNPs concerning *Candida* Spp.

Sl. No.	Nanoparticles used	Experimental model	Polymer and active component	*Candida* Spp.	Outcomes	References
01	SLNs	*In vitro*	Cationic lipid	*C. albicans*	The nanoparticles demonstrated stable, nontoxic, and prolonged dual-drug delivery with preserved antimicrobial activity (MIC_{50}-0.03 µg/mL).	[178]
		Porcine buccal mucosa	N/A	*C. albicans*	SLNs demonstrated effective nano-size, diffusion-controlled drug release, buccal permeation, and antifungal activity.	[180]
		In vitro	Chitosan and gelatin	*C. albicans*	Formulation demonstrated effective drug delivery, strong anti-biofilm activity, and successful *in vivo* healing of *C. albicans*- (~79%) infected wounds.	[181]
		In vitro	Hydrogels	*C. albicans*	SLNs-loaded hydrogel showed stable, efficient delivery with broad antifungal activity	[182]
		Rabbit	Carbopol	*C. albicans*	Developed formulation with demonstrated enhanced drug delivery, sustained release, and superior antifungal efficacy with improved skin healing in fungal infections	[183]
		Rat skin	Carbopol	*C. albicans*	NPs-based hydrogel showed superior skin retention (1.63-fold), sustained release, enhanced antifungal efficacy, and stability compared to a marketed gel.	[184]
		Rats and mice	Carbopol	*C. albicans*	The developed formulation demonstrated sustained drug release, increased skin deposition, and superior antifungal efficacy against *C. albicans* (34.5 ± 0.69 mm) compared to pure drug and marketed formulations.	[185]
02	NLC	*In vitro*	Carbopol	*C. albicans*	NLC-based gel significantly improved clinical and mycological outcomes in *Candida*-associated onychomycosis	[186]
		In vitro	Carbopol, chitosan	*C. albicans*	The developed nanocarrier demonstrated superior antifungal activity against *C. albicans (*2.58 and 6.35-fold).	[187]
		Galleria mellonella	Sodium dodecyl sulfate	*C. auris*	NLC demonstrated nontoxic and efficacious *in vivo*, highlighting their potential as a novel treatment for drug-resistant candidemia.	[188]
		Sheep	Sesame oil	*C. albicans*	The optimized NLC significantly promoted antifungal activity (29 mm), mucosal permeation, and *in vivo* efficacy.	[189]
		Female mice or rats	Poloxamer and chitosan	*C. albicans*	Developed nanosystem demonstrated strong antifungal and photodynamic efficacy against *C. albicans*.	[190]
		Rats	Solid and liquid lipids	*C. albicans*	NLC showed enhanced efficacy, skin accumulation, and safety.	[191]
03	LIPs	RAW 264.7	carvacrol, cinnamaldehyde, citral, thymol and dioctadecyldimethylammonium bromide	*C. albicans*, *C. auris*, *C. dubliniensis*, and *C. tropicalis*	Significant suppression (~41%) of *Candida* survival was revealed.	[193]
		Galleria mellonella larvae	N/A	*C. albicans*	This formulation surprisingly suppressed *Candida* burden (99%) and biofilm disruption.	[194]
		In vitro	Chitosan, epicatechin, and propyl gallate	*C. albicans*	Potential anti-Candida activity observed.	[195]
		Caenorhabditis elegans	Sphaeropsidin A	*C. auris*	Biofilm and vital biomass were inhibited at MIC 20 µg/mL	[196]
		Murine infection model	Penetratin	*C. albicans*	This formulation significantly elevated LIPs and fungal cell interaction from ~50% to >80%.	[197]
04	LNCs	*In vitro*	Miglyol®812	*C. albicans*	*In vitro* antimycotic activity showed 3.56 ± 0.12 cm of fungal inhibition.	[198]
		Rat model	N/A	*C. albicans*	ITC-LNCs exhibited a *C. albicans* inhibition zone of 29.4 mm.	[199]

Abbreviations: SLNs – Solid lipid nanoparticles; MIC – Minimum inhibitory concentration; NLC – Nanostructured lipid carrier; LIPs – Liposomes; ITC-LNCs – Itraconazole-Lipid nanocapsules.

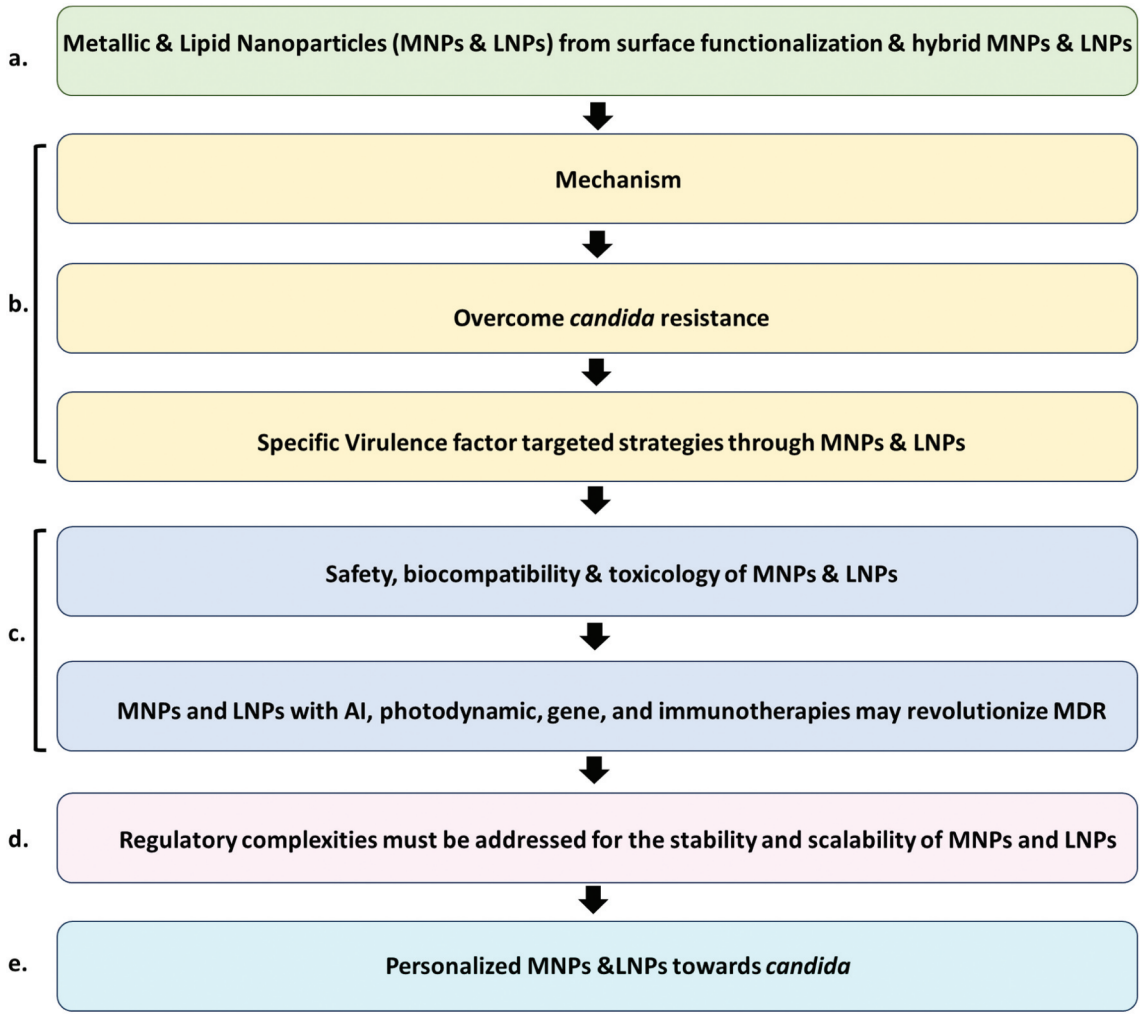

Figure 4. Represents future road map illustration regarding MNPs and LNPs toward *Candida.*

Table 3. Clinical practices of MNPs and LNPs concerning *Candida* spp.

Clinical trial id	Type of nanoformulations	Study type	Study design	Total enrolment	Date	Reference
NCT03666195	Tio_2NPs	Interventional	Randomized	20	2018–10–15–2019–01–15	[201]
NCT05901961	ZnONPs	Interventional	Randomized	84	2023–06–02–2023–09–09	[202]
NCT03635138	CuNPs and ZnNPs	Interventional	Randomized	35	2018–12–01–2020–01–01	[203]
NCT06089720	ZnONPs	Interventional	Randomized	18	2023–02–15–2023–10–04	[204]
NCT06172023	AgNPs	Interventional	Randomized	78	2020–01–01–2023–03–01	[205]
NCT04431804	AgNPs	Interventional	Randomized	210	2020–06–11–2020–09–30	[206]
NCT03752424	AgNPs	Interventional	Randomized	30	2019–11–13–2021–01–11	[207]
NCT03823040	SLNs loaded gel	Interventional	Randomized	28	2018–07–16–2018–12–30	[208]

Abbreviations: TiO_2NPs – Titanium dioxide nanoparticles; ZnONPs – Zinc oxide nanoparticles; CuNPs – Copper nanoparticles; AgNPs – Silver nanoparticles; SLNs – Solid lipid nanoparticles.

potential of lipid-based nanocarriers for mucosal delivery. In another study, Sato et al. [190] incorporated hypericin (Hy), a potent natural photosensitizer, into NLCs embedded in a hydrogel (NLC-HG) for photodynamic therapy (PDT) of vulvovaginal candidiasis (VVC). The formulation exhibited desirable mucoadhesive and injectability properties for vaginal applications, enabling controlled release. The NLC-HG system effectively reduced *C. albicans* viability both *in vitro* and *in vivo*, highlighting the synergistic potential of NLCs and PDT in treating recurrent fungal infections. Riaz et al. [191] developed AmB-loaded NLCs (AmB-NLCs) intended for the topical treatment of cutaneous leishmaniasis and VVC. The formulation showed enhanced *in vitro* drug release, significant *ex vivo* skin permeation, and effective skin deposition. *In vivo* evaluations confirmed the superior antifungal and antileishmanial efficacy of AmB-NLCs, with no observed toxicity, indicating their suitability for skin and mucosal applications.

Overall, these studies collectively emphasize the versatility and efficacy of NLCs as advanced antifungal delivery systems. Through enhanced bioavailability, sustained drug release, and superior targeting of *Candida* spp., NLCs represent a promising platform for the treatment of cutaneous and mucosal fungal infections, particularly in resistant or chronic cases.

5.3. Liposomes

Liposomes (LIPs) have garnered attention as effective lipid-based NPs for enhancing antifungal drug delivery, especially against biofilms and resistant strains, due to their ability for versatile drug release, targeted delivery, and improved solubility [192]. For instance, Kadena et al. [193] reported LIPs-based NPs loaded with carvacrol, cinnamaldehyde, citral, and thymol. LIPs were engineered using a 1:2 molar ratio of dioctadecyldimethylammonium bromide to monoolein utilizing lipid film hydration. When tested against clinical isolates of *C. albicans*, *C. auris*, *C. dubliniensis*, and *C. tropicalis*, the LIPs exhibited significant efficacy, particularly those containing cinnamaldehyde (64 µg/mL), citral (256 µg/mL), and thymol (128 µg/mL) with minimal cytotoxicity noticed on RAW 264.7. In another study, González et al. [194] engineered LIPs loaded with anidulafungin against *C. albicans*. The LIPs disrupted mature biofilms, achieving up to a 99% reduction in fungal load. *In vivo* (*Galleria mellonella*) demonstrated that the LIPs significantly improved survival rates ranging from 33% to 67% compared to just 25% survivors treated with free anidulafungin. Nonetheless, none of the formulations caused red blood cell lysis, indicating a favorable safety profile. In response to the urgent need for potential management options for VVC, Mork et al. [195] explored the development of chitosan and LIPs incorporating epicatechin (EC) and propyl gallate (PG). LIPs exhibited high EE (~64%), and potential mucoadhesive properties, confirmed by a significant elevation in viscosity upon mucin contact. Critically, EC demonstrated activity only when encapsulated in LIPs, with an MIC of 294 µg/mL, while PG was ineffective in all forms. These findings highlight the dual utility of chitosan and LIPs in enhancing drug delivery and suggest a promising, biocompatible strategy. Buonanno et al. [196] investigated the antifungal potential of Sphaeropsidin A (SphA)-loaded LIPs (SphA-L). Time kill kinetics revealed a consistent ability to suppress fungal growth and notably disrupt biofilm formation by *C. auris*. SphA-L altered ROS dynamics and interfered with the *Candida* cell cycle, thereby weakening the pathogen at a cellular level. Moreover, SphA-L significantly inhibited *C. auris* adhesion without cytotoxicity. *In vivo* (*Caenorhabditis elegans*) assay revealed suppression of fungal burden and improved nematode survival rates. LaMastro et al. [197] developed novel LIPs carrying posaconazole (POS), enhanced with penetratin (Pen). This peptide significantly boosted LIPs' interaction with *C. albicans* and *C. auris* from around 50% to over 80%. Pen-LIPs showed inhibition at concentrations up to eight times and suppressed biofilms at POS doses as much as 1300 times lower than free drug. In *in vivo* model of intradermal *C. albicans* infection, these targeted LIPs reduced the fungal load by approximately 60% compared to non-targeted POS-LIPs.

5.4. Lipid nanocapsules (LNCs)

LNCs emerged as one of the most significant LNPs in terms of managing *Candida*. Their tunable properties and minimal toxicity make them highly suitable for addressing challenges in antifungal therapy, especially in drug resistance and biofilm associated *Candida*. For example, Hussein et al. [198] developed O36 (40% orange oil) and E35 (35% eucalyptus oil) loaded LNCs and demonstrated that E35 exhibited an inhibition zone of 3.56 ± 0.12 cm against *Candida* growth, outperforming O36 (2.6 ± 0.1 cm). These results affirm not only the feasibility of using essential oils as active and structural components in LNCs but also their promise in delivering potent, nature-based antifungal treatments. El-Sheridy et al. [199] investigated itraconazole (ITC)-loaded LNCs-based gel and compared to conventional NLC. Both systems demonstrated over 98% EE, but the LNCs showed, more uniform particle sizes around 50 nm. *In vitro* assay revealed that, ITC-LNCs and ITC-NLC showed 29.4 and 26.4 mm inhibition zone against *C. albicans*. Gel formulation significantly enhanced dermal ITC retention and effectively eliminated fungal growth in the epidermis without causing any toxicity in *in vivo* model. Altogether, this study suggests that ITC-LNCs offer a potent and targeted approach toward *Candida*.

Overall, LNPs offer a biocompatible and scalable approach for targeted *Candida* delivery. SLNs and NLCs enhance mucosal retention and penetration, making them favorable for vaginal and mucocutaneous candidiasis. LIPs have demonstrated their ability in clinical translation, with the ability to encapsulate AmB and other agents. However, nanosystems such as LNCs and their applications across this field have remained underexplored; therefore, we propose future work on LNCs against *Candida*. Together, these systems provide a viable route for amplifying antifungal drug therapeutic index with minimal toxicity.

6. Conclusion and future perspectives

The application of MNPs and LNPs offers a promising and innovative strategy to combat resistant *Candida* infections. Both nanocarriers have demonstrated improved antifungal activity by targeting fungal cell membranes, enhancing drug solubility, and improving bioavailability. MNPs exert potent antimicrobial effects through mechanisms such as oxidative stress induction, membrane disruption, and apoptosis, while LNPs provide controlled drug release and lower toxicity. Hybrid MNP–LNP nanosystems provide synergism, improving the efficacy, stability, and targeted delivery of antifungal drugs. Despite their therapeutic potential, several challenges hinder the clinical translation of these nanocarriers. Comprehensive evaluation of their safety, toxicity, and long-term stability especially through clinical trials is essential to ensure a favorable risk-benefit profile. For instance, AgNPs have been shown to be cytotoxic to keratinocytes at concentrations below 10 µg/mL, highlighting the need for careful dosing. Similarly, certain LNPs can induce complement activation, which may lead to adverse reactions. Specifically, some studies have reported significant complement activation with cationic lipids and particle sizes above 200 nm. These findings underscore the importance of thorough safety assessments for nanoparticle-based therapies [200].

Additionally, large-scale manufacturing, cost-effectiveness, and regulatory standardization of fabrication processes remain critical for widespread clinical adoption. Looking ahead, the future of MNPs and LNPs in managing *Candida* infections is highly optimistic. Further research into combination therapies,

including integration with photodynamic therapy or immunotherapy, may potentiate antifungal efficacy. Advances in nanoparticle targeting such as ligand conjugation and surface functionalization, hold promise to enhance treatment precision, reduce off target effects, and improve patient outcomes. Continued innovation in nanomedicine is poised to revolutionize the management of resistant and persistent fungal infections by enabling more effective and personalized therapeutic interventions.

7. Expert opinion

MNPs and LNPs have emerged as promising tools in the treatment and management of fungal infections caused predominantly by *Candida* spp. *Candida* spp. are part of the normal human flora, with up to 75% of women experiencing at least one episode of VVC, also known as thrush or vaginal yeast infection, during their lifetime. Additionally, oral candidiasis affects up to 50% of individuals worldwide, highlighting the global prevalence of *Candida* infections. Currently available antifungal therapies offer limited efficacy due to the continuous emergence of drug resistance, associated side effects and adverse reactions. In this context, MNPs and LNPs provide a practical and innovative therapeutic modality, owing to their distinctive physicochemical characteristics that can revolutionize antifungal therapy. The primary advantages of MNPs and LNPs reside in their structural composition, which confers superior stability, safety, and biocompatibility alongside enhanced drug delivery capabilities. These nanocarriers can be engineered for tailored therapeutic regimens or targeted delivery of active pharmaceutical ingredients. Incorporation of specific ligands allows selective tissue targeting, improving site-specific drug accumulation. Moreover, the use of these NPs can reduce the required drug dosage, thereby minimizing toxicities and potentially lowering treatment costs. Their strong encapsulation abilities protect active compounds from premature degradation, ensuring efficient delivery to target tissues. These features collectively expand therapeutic options and enable personalized antifungal therapies. Recent technological advancements have also facilitated the development of hybrid nanoparticles, which combine the unique properties of both MNPs and LNPs. Such hybrid nanocarriers leverage the intrinsic antimicrobial properties of MNPs while benefiting from the biocompatibility and controlled-release profiles of LNPs. This synergy enhances stability, bioavailability, and targeted delivery of antifungal agents, potentially leading to more effective treatments against *Candida* infections. A critical aspect of nanoparticle-based therapies lies in the formulation strategies employed during their production. Advances in drug formulation science, supported by extensive databases, have provided researchers with clearer methodologies to optimize nanoparticle synthesis. Among these, green synthesis approaches have gained considerable attention due to their sustainable and environmentally friendly nature, which is particularly relevant for scaling up industrial manufacturing. Despite these promising advances, several challenges remain in translating MNPs and LNPs from bench to bedside. Comprehensive investigations into their safety profiles, toxicity, and long-term stability are necessary. The paucity of large-scale clinical trials, limited standardization protocols, and the absence of clear regulatory frameworks have impeded the clinical validation and approval of nanoparticle-based antifungal agents. Future research must rigorously demonstrate that the therapeutic benefits of these nanocarriers outweigh potential risks, paving the way for their successful integration into routine clinical practice.

Abbreviations

NPs	Nanoparticles
MNPs	Metallic Nanoparticles
LNPs	Lipid Nanoparticles
PM	Polymeric Micelles
MDR	Multidrug Resistance
ECM	Extracellular Matrix
ROS	Reactive Oxygen Species
USP	Ultrasonic Spray Pyrolysis
MIC	Minimum Inhibitory Concentration
MFC	Minimum Fungicidal Concentration
PVP	Polyvinyl Pyrrolidone
AgNPs	Silver Nanoparticles
AuNPs	Gold Nanoparticles
SeNPs	Selenium Nanoparticles
CuONPs	Copper Nanoparticles
ZnONPs	Zinc oxide Nanoparticles
TiO_2-NPs	Titanium di-oxide Nanoparticles
CoNPs	Cobalt Nanoparticles
SLNs	Solid Lipid Nanoparticles
NLCs	Nanostructured Lipid Carriers
LIPs	Liposomes
LNCs	Lipid Nanocapsules
AmB	Amphotericin B
NYT	Nystatin
FLU	Fluconazole
MCZ	Miconazole
CLZ	Clotrimazole
LUL	Luniconazole
SCZ	Sulconazole

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