Journal of Drug Delivery Science and Technology 113 (2025) 107329

Contents lists available at ScienceDirect

Journal of Drug Delivery Science and Technology

journal homepage: www.elsevier.com/locate/jddst

Review Article

Innovative nanomedicine for fungal infections: Advancing treatments through nanotechnology and mycological approaches

Alka Lohani [a,*], Ritika Saxena [b], Shahbaz Khan [b], Ana Figueiras [c,d], Filipa Mascarenhas-Melo [e,f,**]

[a] Amity Institute of Pharmacy, Amity University Uttar Pradesh, Noida, 201313, India
[b] Pharmacy Academy, IFTM University, Moradabad, Uttar Pradesh, 244102, India
[c] Laboratory of Drug Development and Technologies, Faculty of Pharmacy, University of Coimbra, 3000-548, Coimbra, Portugal
[d] REQUIMTE/LAQV, Department of Pharmaceutical Technology, Faculty of Pharmacy, University of Coimbra, Azinhaga de Santa Comba, 3000-548, Coimbra, Portugal
[e] Higher School of Health, Polytechnic University of Guarda, Rua da Cadeia, Guarda, 6300-307, Portugal
[f] BRIDGES - Biotechnology Research, Innovation and Design for Health Products, Polytechnic University of Guarda, Avenida Dr. Francisco Sá Carneiro, nº 50, Guarda, 6300-559, Portugal

ARTICLE INFO

Keywords:
Nanomedicine
Drug delivery systems
Mycological approaches
Fungal infections

ABSTRACT

Infections caused by fungi such as aspergillosis, mucormycosis and candidiasis have created a huge threat globally. These invasive infections have become a public health problem and a serious concern, especially for immune-compromised patients. Currently, there are several antifungal therapies, however, associated with numerous issues such as toxicity, low bioabsorption, and fungal resistance. Nanotechnology offers several benefits, such as high surface area, high drug payload, targetability, and lower toxicity. Therefore, the development of nanomedicine-based therapy, which is known as nanotherapeutics, has improved the treatment of fungal infections. In this manuscript, we comprehensively describe the drug delivery systems (polymeric, lipidic, inorganic, and metallic nanoparticles) available based on nanotechnology for treating fungal infections. The use of mycology for the production of nanoparticles to treat fungal infections is a burgeoning field that combines the benefits of nanotechnology and fungal metabolites to create effective antifungal treatments. By utilizing the special qualities of nanoparticles and the natural biosynthetic capabilities of fungi, researchers can develop new, more effective antifungal therapies that address the limitations of conventional treatments. Therefore, much research is needed for the development of new therapeutic alternatives that can enhance antifungal therapy.

1. Introduction

Advancements in nanotechnology have made it possible to develop cutting-edge drug delivery systems and formulate new materials. Recent advancements in nanotechnology have revolutionized healthcare strategies and are anticipated to have a big influence on the delivery of improved healthcare services. Medical nanotechnology in this context refers to the design, production, control, and use of therapeutic medications and devices with a nano-range size (1–100 nm) [1]. Given its potential, researchers have focused in the last years on developing controlled-release drug delivery systems that can target and treat diseased areas using nanotechnology.

A branch of nanotechnology with a significant positive influence on therapeutic strategies is called “Nanotherapeutics”. Nanotherapeutics, as a field of medicine, has a vast scope for research and development. It offers fresh opportunities to enhance the safety and effectiveness of well-known conventional drugs. In this approach, the medicine is formulated using nanosystems in which the drug is attached, allowing it to act more precisely and efficiently, with fewer adverse effects. Since the advent of nanotherapeutics, it is now possible to deliver the drug in a site-specific manner [2]. The main domains that potentially benefit from nanotherapeutics include diabetes, infectious diseases, haematological disorders, and cancer. Furthermore, the emergence of multifunctional nanotherapeutics has the potential to fill some current therapeutic gaps

* Corresponding author. Department of Pharmaceutics, Amity Institute of Pharmacy, Amity University Uttar Pradesh, Noida Campus, India.
** Corresponding author. Higher School of Health, Polytechnic University of Guarda, Rua da Cadeia, 6300-307 Guarda, Portugal.
E-mail addresses: alohani@amity.edu (A. Lohani), ritikasaxena63@gmail.com (R. Saxena), shahbazkhanmaju123@gmail.com (S. Khan), rfigueiras@ff.uc.pt (A. Figueiras), filipamelo@ff.uc.pt (F. Mascarenhas-Melo).

https://doi.org/10.1016/j.jddst.2025.107329
Received 9 April 2025; Received in revised form 19 July 2025; Accepted 25 July 2025
Available online 25 July 2025

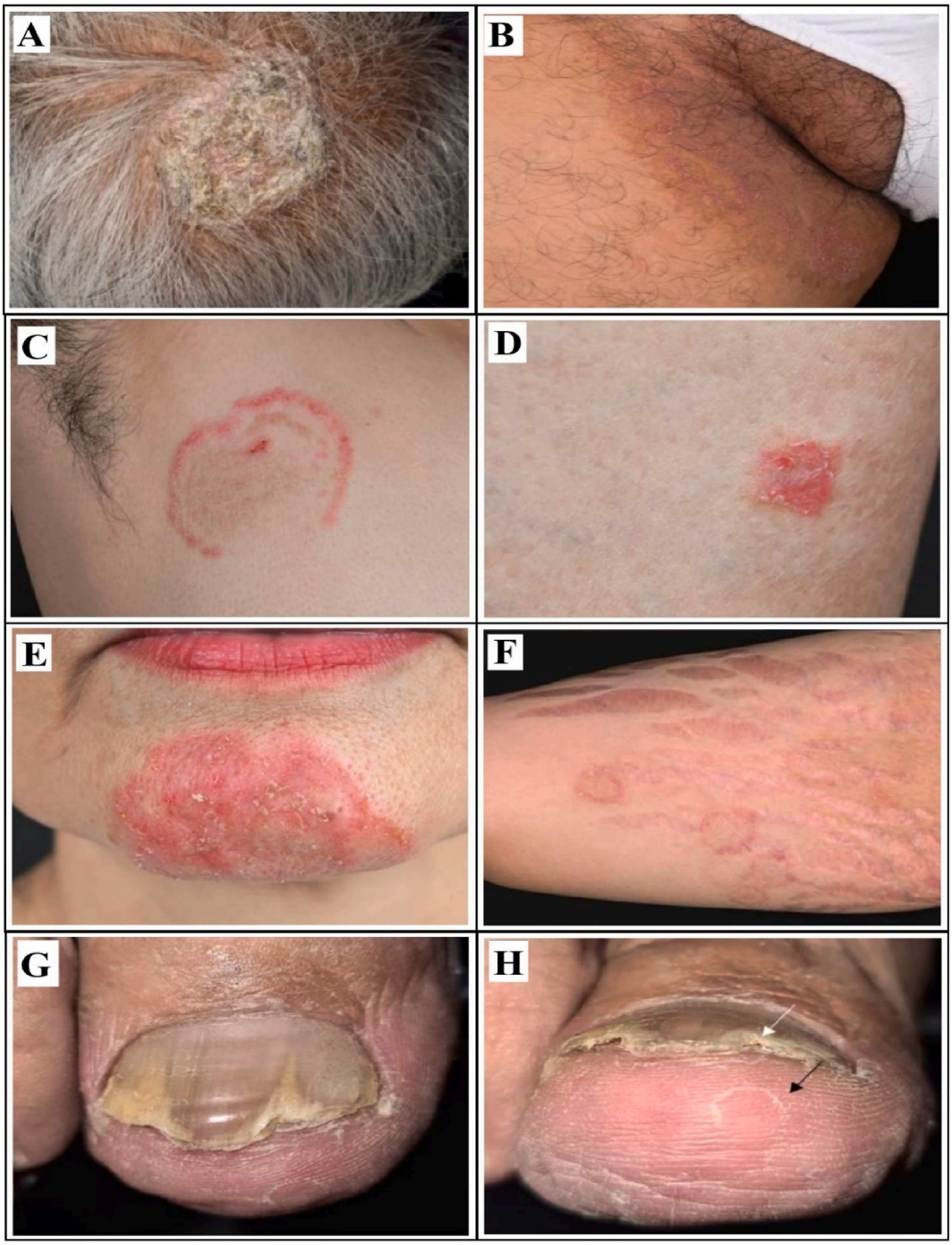

Fig. 1. Clinical presentations of various cutaneous fungal infections. **A)** Tinea capitis: Grayish patch observed on the scalp's crown. **B)** Tinea cruris: Multiple annular, scaly, and red lesions located in the groin region. **C)** Tinea incognito: Characteristic ring-within-a-ring appearance. **D)** Tinea corporis: Circular, inflamed, scaly red lesion on the right leg, associated with *Microsporum canis.* **E)** Tinea faciei: Several scaly, red concentric rings on the chin, also linked to *Microsporum canis*. **F)** Tinea corporis: Numerous red annular lesions resembling rubber rings on the right arm, caused by *Trichophyton mentagrophytes*. **G)** Dorsal aspect of the right hallux: Onychomycosis due to *Trichophyton mentagrophytes*, showing a dermatophytoma with longitudinal striations alongside it. **H)** Hyponychial view of the same toenail: Subungual debris with a sulfur-like appearance (white arrow) accompanied by tinea pedis, seen as an annular, scaly lesion (black arrow). Adapted from Ref. [12]. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

[3]. In treating serious illnesses, including cancer, diabetes, cardiovascular disease, HIV/AIDS, among others, the healthcare sector is currently confronted with several difficulties in providing high-quality, affordable care. One of the biggest concerns has also been using antimicrobials to treat infectious diseases and the rise of drug resistance.

Fungal infections are a major and expanding public health issue these days. In individuals with impaired immune systems, invasive fungal infections can raise death and morbidity rates [4]. In spite of the presence of multiple antifungal treatments, the approach to managing fungal infections is still considered insufficient because of the development of fungal resistance, low drug absorption, considerable drug toxicity, and poor therapeutic efficacy. There is hope for a revolution in addressing fungal infections with the use of cutting-edge drug delivery technologies based on nanotechnology. The solubility and stability of

the active ingredient are improved [5], the biological action and absorption are enhanced, and the degree of hydrophilicity/lipophilicity is adjusted by nanoencapsulation of antifungal drugs, which is suggested as a potentially effective treatment method against fungal infections [6].

2. Overview of fungal infections and antifungal therapy

Every year, fungi infect billions of individuals, but their impact on the global burden of disease is usually underappreciated. There have been reports of over 600 distinct fungi infecting people, causing illnesses such as allergies, as well as common to deadly infections of the skin, mucosa, hair, and nails. As fungal infections become more prevalent, healthcare professionals encounter a range of complex and pressing challenges that demand urgent attention [7]. David Denning reviewed the prevalence and mortality of serious fungal diseases worldwide [8]. According to statistics, around 2.1 million people get invasive aspergillosis every year, especially those who have lung cancer, haematological malignancy, chronic obstructive pulmonary disease, or are in intensive care. This causes over 1.8 million fatalities (85.2 %). Chronic pulmonary aspergillosis affects around 1.8 million people each year, causing 340,000 deaths (18.5 %). About 1.6 million individuals suffer from *Candida* bloodstream infections or invasive candidiasis annually, with 995,000 fatalities (63.6 %). 505,000 individuals are affected by pneumocystis pneumonia annually, which causes 214,000 fatalities (42.4 %). Annually, 194,000 people are afflicted with cryptococcal meningitis, and 147,000 of them die (75.8 %). About 300,000 persons are afflicted by other serious, life-threatening fungal diseases, which result in 161,000 fatalities (53.7 %). Approximately 11.5 million individuals suffer from fungal asthma, which may be a contributing factor in 46,000 asthma-related fatalities annually. These data suggest that invasive fungal infections cause 6.5 million cases each year, leading to approximately 3.8 million deaths. Among these fatalities, roughly 2.5 million, representing 68 % (with a range of 35 %–90 %), can be directly linked to fungal diseases [9].

The two primary types of fungi are yeasts and molds. Mold colonies are made up of filamentous strands called hyphae, whereas yeast is often isolated, tiny, oval cells. Some fungi have the ability to change their appearance (known as dimorphic) depending on their surroundings, becoming either yeasts or molds [10]. Fungi are predominantly distributed across diverse ecosystems and are capable of reproducing autonomously in their natural environments, without requiring assistance from humans or animals. However, some species infect humans and cause systemic, superficial, or subcutaneous diseases. Most fungi that cause deep-seated or systemic infections enter the body through an infected wound site or straight through the lungs. Other fungi (like *Candida albicans*) are naturally occurring organisms that live on the skin and gastrointestinal system and may grow and move into the bloodstream under specific circumstances. Some fungi can cause infections in people who are generally healthy, but many species only become harmful when the host is weak, such as when the immune system is impaired [11].

2.1. Superficial fungal infections

The term “superficial fungal infections” refers to infections brought on by pathogenic fungi that only affect human skin (epidermis), hair, nails, and mucosa (Fig. 1).

These diseases are significant because of their widespread distribution, person-to-person transmission, frequency, and morbidity, even though they are rarely harmful or life-threatening. In cases where infections are particularly severe or resistant to treatment may be the first sign of an underlying immunodeficiency [13]. Dermatophytes, which infect keratinized epithelium, nails and hair follicles, are among these superficial fungal infections [14]. The most prevalent dermatophytes that infect nonviable, keratinized epidermal structures (including skin stratum corneum, hair and nails) are *Candida* species, *Malassezia* species, *Trichosporon*species, *and Hortaes*pesies [9]. Other superficial fungal infections can also affect the mouth, genitalia, esophagus, or moist skin areas. Around 50 % of healthy adults have oral colonization of *Candida species* [15] whereas 21 % of women have vaginal colonization [16]. *Candida* overgrowth may result in an opportunistic infection when the local ecology is altered or when there is an immunological disorder. The oral cavity, esophagus, and genitals (producing balanitis in males and vulvovaginitis in females) are the mucosal surfaces most commonly affected by candidiasis [17].

2.2. Subcutaneous fungal infections

Because these fungal infections frequently have high rates of morbidity and death, it is crucial to identify and treat invasive subcutaneous fungal infections. They are often limited to the dermis and subcutaneous tissues, and the microbes that cause them are typically found only in tropical and subtropical regions of the world. Chromoblastomycosis, mycetoma, and sporotrichosis are three prominent subcutaneous mycoses [18]. Sporotrichosis, the most frequent subcutaneous fungal infection (particularly widespread in portions of Latin America), is caused by the dimorphic fungus *Sporothrix schenckii* [19]. The first sign of infection is a lesion (an ulcerated nodule), which can then spread to other subcutaneous areas by means of the lymphatic system. The development of lymphocutaneous sporotrichosis, although serious, is generally not fatal [20]. Members of the *Dematiaceae* family, including *Fonsecaea compacta, Cladosporium carrionii, Rhinocladiella aquaspersa, Fonsecaea pedrosoi* and *Phialophora verrucosa,* cause the chronic fungal infection known as chromoblastomycosis. The primary sign of chromoblastomycosis is the development of verrucous or nodular lesions on the skin. These lesions typically start as small bumps or nodular growths that may resemble warts or keloids. Over time, the lesions can become more wart-like and may ooze or ulcerate. They often have a dark, pigmented appearance due to the presence of fungal cells (sclerotic bodies or muriform cells) within the tissues. These lesions can be pruritic (itchy) and can gradually spread, particularly if left untreated [21]. Chronic subcutaneous infection, mycetoma, known by other names such as “Madura foot” or “Maduromycosis”, is a localized, and often progressive infection of the skin and underlying tissues, usually involving the feet or hands. It is distinguished by the development of grains or granules, sinus tracts, and localized edema. Most likely, bacteria or fungi are traumatized into the subcutaneous tissue and then inoculated, causing infection. Over 70 different bacteria and fungi have been identified as potential causal agents, including *Madurella mycetomatis, Actinomadura madurae, Fusarium* species, *Aspergillus* species, among others [22].

2.3. Systemic fungal infections

2.3.1. Opportunistic systemic fungal infections (OSFIs)

Fungal infections in immunocompromised hosts are caused by opportunistic fungal pathogens. Such infections are severe and potentially life-threatening, especially among immunocompromised individuals. Patients at risk include those with HIV/AIDS, cancer, organ transplants, or those going through prolonged corticosteroid therapy. Fungi can enter the body through the lungs, paranasal sinuses, gut, or skin if the right circumstances/conditions are met [23]. The most prevalent pathogens that cause these infections include species of *Aspergillus, Cryptococcus, Histoplasma,* and *Candida* [23].

Candida species are the most common cause of OSFIs, leading to candidiasis. Oropharyngeal, esophageal, and invasive candidiasis are among the different ways that candidiasis can appear. Invasive candidiasis, or candidemia, is particularly severe, affecting the bloodstream and potentially spreading to the bones, brain, heart, eyes and other organs [24]. *Aspergillus* species cause aspergillosis, which predominantly affects the lungs. Invasive aspergillosis can happen to those who are seriously immunocompromised, such as those receiving chemotherapy

for hematologic cancers or hematopoietic stem cell transplantation [25]. *Cryptococcus* species, particularly *Cryptococcus neoformans* and *Cryptococcus gattii,* cause cryptococcosis. Cryptococcosis is primarily a central nervous system infection, leading to meningoencephalitis. Immunocompromised patients, especially those with HIV/AIDS, are at significant risk [26].

2.3.2. Endemic systemic fungal infections

Fungi that are indigenous to a particular geographic area are the source of endemic systemic fungal infections, which can afflict both immunocompetent and immunocompromised people. Notable examples include histoplasmosis, blastomycosis, coccidioidomycosis, and paracoccidioidomycosis. *Histoplasma capsulatum* is the fungus responsible for histoplasmosis, a disease commonly found in the Mississippi and Ohio River valleys of the United States, as well as in certain areas of Central and South America [27]. Blastomycosis, resulting from *Blastomyces dermatitidis*, occurs in areas such as the southeastern and south-central United States [28]. Coccidioidomycosis, or Valley Fever, is frequently found in the southwestern United States, along with certain regions of Mexico, Central America, and South America. It is caused by *Coccidioides immitis* and *Coccidioides posadasii*. In South America, particularly Brazil, *Paracoccidioides brasiliensis* is the primary causative agent of paracoccidioidomycosis, a systemic fungal infection that predominantly affects the lungs and can disseminate to other organs [29]. These infections can manifest as acute or chronic pulmonary infections and may disseminate to other organs, leading to severe systemic disease [29].

Endemic systemic fungal infections exhibit distinct pathological features depending on the causative fungus, infection route, and host immune response. In histoplasmosis, caused by *Histoplasma capsulatum*, the infection begins when airborne spores are inhaled and reach the alveoli in the lungs, where alveolar macrophages phagocytose them. The fungi then convert to their yeast form, triggering granuloma formation and potentially disseminating to other organs [30]. Blastomycosis, due to *Blastomyces dermatitidis*, starts similarly with inhaling the spores that transform into yeast in the lungs, causing pyogranulomatous inflammation and possibly spreading to the skin, bones, and genitourinary system [31]. Coccidioidomycosis, caused by *Coccidioides immitis* and *Coccidioides posadasii*, involves inhaled arthroconidia that develop into spherules filled with endospores in the lungs, resulting in a mixed inflammatory response and potential dissemination to the bones, central nervous system and skin [32]. Paracoccidioidomycosis, due to *Paracoccidioides brasiliensis*, features inhaled conidia transforming into yeast in the lungs, causing granulomatous inflammation and dissemination to the lymph nodes, mucous membranes and other organs [33]. These infections can manifest as acute or chronic pulmonary diseases and may disseminate, leading to severe systemic conditions.

2.4. Treatment with antifungal drugs

Fungal infections are treated by the use of antifungal agents that selectively eradicate fungal pathogens from a host. Considering their mode of action, antifungal drugs can be used topically and systemically and fall into the following categories.

2.4.1. Polyenes

Antifungal polyenes function by binding to ergosterol, a vital component of fungal cell membranes. The primary mechanism of action involves forming complexes with ergosterol, causing the fungal cell membrane to develop pores or channels. Fungal cell death is the final result of this disruption, which also increases membrane permeability and allows cellular contents to leak out. This has fungicidal effects. Examples are Amphotericin, nystatin, and pimaricin [34]. Systemic fungal infections, especially those caused by fungi like *Candida, Aspergillus, Cryptococcus*, and other molds and yeasts, are the main conditions for which polyenes are used. They are often reserved for severe infections or cases where other antifungal classes are ineffective or contraindicated.

2.4.2. Azoles

Because of their broad-spectrum ability to combat a variety of fungal infections, azoles are frequently utilized. They show antifungal effects by preventing the production of ergosterol, which is a crucial part of the fungal cell membrane. Azoles inhibit lanosterol 14α-demethylase enzyme (part of the cytochrome P_{450} family), which plays a key role in converting lanosterol to ergosterol, which leads to increased permeability of the cell membrane and ultimately, fungal cell death [35]. They have a wide spectrum and can be applied topically or taken orally. Ketoconazole, Fluconazole, Itraconazole, Voriconazole, and Posaconazole are examples of antifungal azoles.

2.4.3. Allylamines

Allylamines, a class of antifungal agents effective in treating dermatophyte infections [36]. The most well-known allylamine antifungals are terbinafine and naftifine. Allylamines function by blocking squalene epoxidase, an enzyme essential to the synthesis of ergosterol. By inhibiting squalene epoxidase, allylamines cause an accumulation of squalene within the fungal cell, which is toxic and adversely impacts the integrity of the cell membrane. This causes cell death and eradication of the fungal infection [37]. Unlike azoles, which also inhibit ergosterol synthesis but at a different step, allylamines specifically target squalene epoxidase early in the ergosterol biosynthesis pathway. This specificity contributes to their effectiveness against dermatophytes and some other fungi.

The main indication for allylamines (like terbinafine) is dermatophyte infections, which impact the hair, skin and nails. They are available in different formulations, including oral tablets and topical creams, gels, and sprays. Because topical administration reduces the risk of systemic adverse effects and provides a focused impact with limited systemic absorption, it is especially helpful in treating localized fungal infections, including tinea pedis, tinea cruris, and tinea corporis [38].

2.4.4. Antimetabolites

Antimetabolites cause fungal cells to die by interfering with the metabolic processes of fungi. Antifungal drug 5-fluorocytosine comes in this category. Antimetabolites function by mimicking naturally occurring molecules within fungal cells, thereby disrupting essential cellular processes. For example, within the fungal cell, flucytosine is transformed into 5-fluorouracil, which interferes with the synthesis of DNA and RNA [39].

The enzyme cytosine deaminase (an enzyme not found in human cells, which makes this drug selectively toxic to fungi), transforms flucytosine into 5-fluorouracil once it is absorbed by fungal cells via cytosine permease [39]. 5-fluorouracil disrupts the synthesis of both DNA and RNA inside the fungal cell. It undergoes further metabolism to 5-fluorodeoxyuridine monophosphate, which prevents the production of DNA by inhibiting the enzyme thymidylate synthase. DNA replication is essentially stopped by this inhibition, which depletes thymidine triphosphate, an essential DNA precursor. Another byproduct of 5-fluorouracil is 5-fluorouridine triphosphate, which replaces uridine triphosphate in RNA. The incorporation of 5-fluorouridine triphosphate into RNA disrupts RNA processing and protein synthesis, ultimately leading to fungal cell death [39].

2.4.5. Echinocandins

It is highly effective semi-synthetic antifungals with a sophisticated cyclic lipopeptide structure. By blocking β-1,3-D-glucan synthase enzyme, which is necessary for the production of β-1,3-D-glucan (a crucial structural polysaccharide in cell wall of fungus), echinocandins affect the fungal cell wall. Fungal cell lysis and death result from this inhibition, which weakens the cell wall structure and increases osmotic instability [40]. Caspofungin, micafungin, and anidulafungin are typical

echinocandins. Echinocandins are administered efficiently via intravenous administration because of their low oral bioavailability [41]. Prompt and appropriate treatment is necessary for fungal infections to get satisfying beneficial clinical outcomes. Despite the availability of several antifungal drugs on the market, their effectiveness is debatable, and their adverse effects must be taken into consideration. Conventional dosage forms have several drawbacks, including insufficient drug concentration at infection/target areas, exposure to natural flora, rapid breakdown and removal, frequent administration, serious side effects, and poor patient compliance [42]. These elements contribute to less-than-ideal therapeutic outcomes, which fuels the current dilemma of worldwide antifungal resistance, especially in immunocompromised patients or those with chronic diseases [43]. In light of this, it has become critical to develop novel and innovative drug carriers for these drugs to battle fungal infections and avoid the emergence of drug-resistant strains.

3. Nanotherapeutic approaches to treat fungal infections

Treating infectious fungal infections is still challenging despite the availability of numerous antifungal drugs. This is primarily due to the rising incidence of fungal resistance, poor drug absorption, significant toxicity, and limited therapeutic efficacy [44]. The clinical development of novel antifungals is currently stagnant [45]. Fungal infections are increasingly becoming a global health concern, particularly due to the rise of resistant strains. Traditional antifungal therapies often fall short due to various resistance mechanisms such as efflux pump overexpression and biofilm formation.

Biofilm formation is a key mechanism by which fungi protect themselves from antifungal agents and the host immune system. It is a structured community of fungal cells encased in a self-produced matrix of extracellular polymeric substances. This matrix is composed of polysaccharides, proteins, lipids, and extracellular DNA, creating a barrier that is highly resistant to conventional treatments [46]. Nanotechnology offers a novel solution to this barrier due to its nanoscale size, which allows it to penetrate deep into biofilm layers where conventional drugs often fail. The intrinsic characteristics of some nanoparticles (NPs), like lipid-based or silver NPs, cause the extracellular matrix to be disrupted, increasing the exposure of fungal cells to antifungal agents. Additionally, NPs can be functionalized with anti-biofilm peptides or enzymes that degrade the matrix, further improving drug access.

Efflux pumps are transport membrane proteins that actively expel antifungal agents from fungal cells inner to the exterior environment, significantly reducing the antifungal efficacy of the drug. The effectiveness of antifungal drugs is greatly diminished by efflux pumps, which are transport membrane proteins that aggressively remove antifungal molecules from the intracellular environment to the outside. The ATP-binding cassette proteins and the major facilitator superfamily transporters are the two primary families of efflux pump proteins found in fungi. These pumps identify and eliminate antifungal substances before they can reach their intracellular targets, which leads to multidrug resistance [46]. Nanotechnology-based therapies provide a promising strategy to bypass this resistance through two primary mechanisms. First, NPs can act as a "Trojan horse," encapsulating antifungal agents and delivering them intracellularly via endocytosis, a pathway that efflux pumps cannot easily counteract. Second, certain NPs can interact directly with efflux pumps, leading to their irreversible blockage and preventing the expulsion of therapeutic agents. A recent study demonstrated that combining fluconazole with fusidic acid, an efflux pump inhibitor, significantly enhanced the antifungal activity of fluconazole in resistant *Candida albicans* isolates, effectively restoring its therapeutic efficacy against these resistant strains [47].

Incorporating antifungal drugs into nanocarriers to develop nanotherapeutics has the potential to enhance the therapeutic efficacy of existing antifungal treatments. Nanocarriers offer several benefits, including enhancing the solubility and stability of active ingredients, prolonging antifungal effects, improving drug absorption, and adjusting their hydrophilicity/lipophilicity balance [48]. According to the literature, nanotherapeutics have been effective in treating fungi and may be effective in minimizing the emergence of drug resistance [48,49]. To provide a clearer understanding of the advantages offered by nanotechnology-based antifungal systems over traditional therapies, a side-by-side comparison is presented in Table 1. This comparison highlights key parameters such as efficacy, toxicity, delivery challenges, patient compliance, and formulation aspects. The insights demonstrate how nano-formulations can potentially overcome several limitations associated with conventional antifungal treatments. NPs have submicron particle sizes [50] and the most relevant in this area can be divided into polymeric, lipidic, vesicular, micellar, and metallic NPs.

Table 1
Comparison between nanotechnology-based antifungal systems and conventional antifungal therapies across various important parameters.

Parameter	Conventional Antifungal Therapies	Nanotechnology-Based Antifungal Systems	References
Efficacy	Require higher doses due to poor solubility or absorption	Enhanced efficacy due to targeted delivery and improved bioavailability	[1,44]
Drug Solubility	Limited by intrinsic solubility of the drug	Can improve solubility of poorly water-soluble antifungal drugs	[51]
Targeting Ability	Non-specific distribution	Active/passive targeting to infection site, reducing systemic exposure	[52]
Toxicity	Higher systemic toxicity (e.g., nephrotoxicity with Amphotericin B)	Reduced systemic toxicity due to localized delivery	[1,44]
Resistance Management	Increasing risk of resistance development	Can bypass or overcome some resistance mechanisms	[53]
Stability	Some antifungals are unstable in biological environments	Enhanced stability with encapsulation or surface modifications	[54]
Controlled Release	Usually immediate or short-duration release	Allows sustained and controlled drug release	[1,51]
Delivery Challenges	Easier to formulate and scale-up; well-established pathways	Requires complex formulation and characterization; regulatory barriers	[55]
Cost of Production	Relatively lower	Generally higher due to advanced materials and processes	[1,55]
Clinical Translation	Multiple approved and widely used agents	Limited products approved; many are still in preclinical/clinical stages	[55]
Administration Routes	Mostly limited to conventional routes (oral/topical/IV)	Can be tailored for oral, topical, transdermal, intravenous, etc.	[1,49]
Patient Compliance	May require multiple doses; risk of side effects lowers adherence	Improved due to lower dosing frequency and fewer side effects	[50,56]

3.1. Polymeric nanoparticles

A broad class of materials made up of monomer-repeating units is called polymers and is an essential component of drug delivery. In recent years, polymeric nanoparticles (PNPs) have attracted a lot of attention because of their distinct properties and behavior depending on their small size [56]. PNPs are extremely tiny particles that range in size from 1 to 1000 nm. They may include active ingredients that are trapped

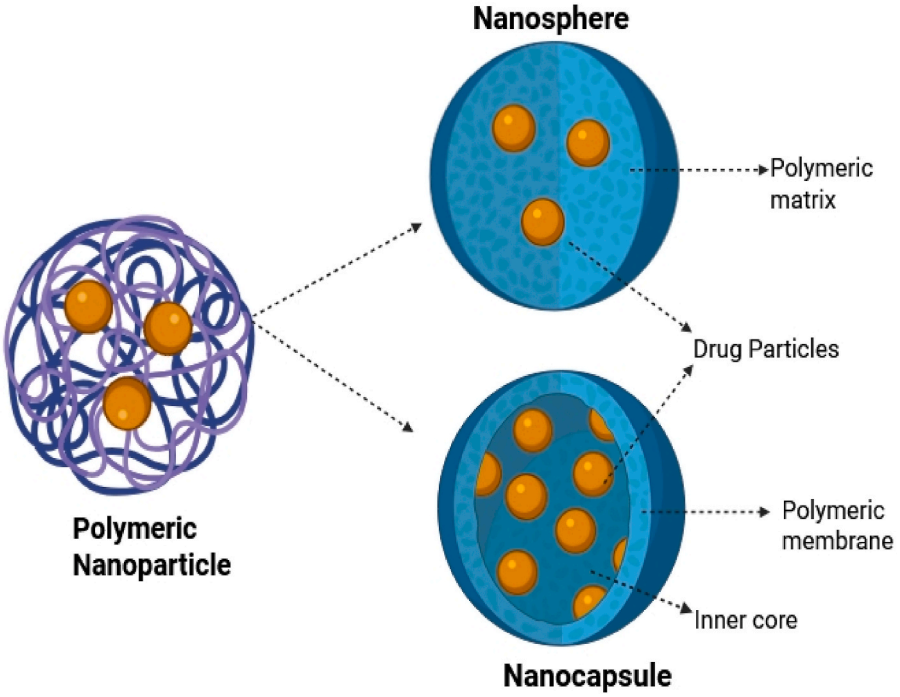

Fig. 2. Structural differences between nanocapsule and nanosphere.

inside of them or surface-adsorbed onto the polymeric core [57]. Using PNPs carriers has several advantages, such as controlled drug release, shielding drugs from the external environment, and boosting bioavailability. PNPs primarily exist in two distinct morphologies: nanospheres, which are matrix systems, and nanocapsules, which are reservoir systems. Nanospheres contain a continuous polymeric network that permits drugs to be enclosed within the matrix or adsorbed onto their surface. On the other hand, nanocapsules consist of a polymeric shell that encloses the drug, which is often dissolved within the core (Fig. 2).

The polymers utilized to prepare PNPs should be non-antigenic, non-toxic, and biocompatible with the host cells. PNPs should also biodegrade within the human body. There are two types of polymers that are most frequently utilized to prepare PNPs: natural and synthetic [58]. Polysaccharides (like cellulose, chitosan, dextran, guar gum, hyaluronic acid, etc.) and proteins/polypeptides (including albumin, transferrin, elastin, gliadin, gelatine, legumin, etc.) are examples of natural polymers [59]. Polylactides, polyglycolides, polyethylene glycol, polycaprolactone, polyacrylic acid derivatives and copolymers like poly (lactide co-glycolides), among others, are examples of synthetic polymers [60,61]. The main advantage of employing natural polymers is that they contain hydrophilic groups (such as carboxyl, hydroxyl, and amino) that control their water solubility and allow them to create non-covalent interactions with mucosal membranes and biological tissues [62]. Additionally, this characteristic offers the chance to chemically alter the particle surface in order to immobilize the drug [63]. The drug release from PNPs at the site of action typically occurs through three general physicochemical mechanisms: (i) hydration-induced swelling of the PNPs; (ii) enzymatic cleavage of bonds leading to polymer degradation at the delivery site; (iii) De-adsorption of the drug from the swollen PNPs [64].

PNPs have certain qualities that make them ideal for delivering antimicrobial drugs. Passive or active targeting may be used by PNPs to interact with the fungal cell wall. Passive targeting is based on particle size and PNPs ability to produce pores that interfere with the membrane structure of the pathogen. Other homing molecules, including specific antibodies and aptamer bacteriophage proteins, have been used for PNP surface functionalization in active targeting, yielding tailored delivery platforms that are effective against various fungal infections [65].

One study found that miconazole-containing chitosan NPs were effective at preventing fungus growth and had antifungal potential against *Candida albicans* [66]. The work focused on developing a novel therapeutic strategy for vulvovaginal candidiasis caused primarily by *Candida albicans*, a fungus notorious for its virulence in transitioning from yeast to hyphae forms. The researchers aimed to harness the inhibitory properties of miconazole and farnesol within a mucoadhesive nanostructured system using chitosan NPs. Farnesol successfully blocked the yeast-to-hyphae transition at doses $\geq$300 μM, whereas miconazole demonstrated strong antifungal action against *Candida albicans* with a minimum inhibitory concentration (MIC) of 1 μg/ml. Miconazole's MIC remained unchanged when farnesol and miconazole were co-encapsulated in chitosan NPs, preserving their respective efficacies. Overall, the study indicates that chitosan NPs containing farnesol and miconazole offer a promising therapy option for vulvovaginal candidiasis, addressing both virulence attenuation and fungal growth inhibition [66].

According to a different study, itraconazole-encapsulated NPs by using monomethoxypoly(ethylene glycol)-b-poly(lactic acid) (mPEG-b-PLA) as a polymer were reported to improve antifungal activity, decrease systemic toxicity, and serve as a possible intravenous formulation of itraconazole for effective antifungal therapy [67]. *In vitro* results demonstrated that itraconazole-NPs exhibited significantly prolonged drug release profiles compared to free itraconazole and effectively inhibited fungal growth. Additionally, compared to commercially available cyclodextrin formulations of itraconazole, the NPs demonstrated greater biocompatibility with low haemolysis and minor venous irritation. An *in vivo* biodistribution analysis following intravenous administration demonstrated that itraconazole-loaded NPs exhibited efficient retention in the bloodstream and specific accumulation in organs abundant in the reticuloendothelial system when contrasted with conventional cyclodextrin injection [67].

Antifungal topical therapy is also important. Various studies have shown its effectiveness in rapidly alleviating symptoms and reducing fungal load. Gamil et al. examined the antifungal effects of miconazole and miconazole-loaded chitosan NPs gels in diabetic patients with oral candidiasis. In order to treat oral candidiasis in diabetics, this study sought to assess the topical administration of miconazole and

miconazole-encapsulated chitosan NPs. Eighty diabetic individuals with symptomatic oral candidiasis were randomly assigned to one of two therapy groups: miconazole or miconazole-loaded chitosan NPs. For 28 days, the patients underwent therapy. Both treatment modalities demonstrated similar effectiveness in lowering *Candida* colonization and managing oral candidiasis symptoms. Results showed that, from the beginning to the completion of the investigation, the group that received miconazole-loaded chitosan NPs demonstrated a notable decrease in the quantity of *Candida albicans* colonies forming units [68]. Ocular mycoses can lead to serious health complications that could progress to visual impairment and loss of vision. Sertaconazole (STZ) is a commonly utilized antifungal agent for these diseases. Nevertheless, its limited solubility in water hinders its effectiveness when administered topically to treat ocular fungal keratitis. A research study investigates the development of STZ-loaded Poly(lactic-co-glycolic acid) (PLGA) nanoparticles as a delivery system designed to improve the ophthalmic bioavailability of STZ. A research investigation focuses on the development of STZ-loaded NPs as delivery systems aimed at enhancing the ophthalmic bioavailability of STZ for the treatment of fungal keratitis. The drug was formulated into solid dispersions with PEG 2000 and subsequently integrated into PLGA NPs (STZ-PEG2000-laden PLGA NPs). STZ-PEG2000-laden PLGA NPs led to an increase in the rate of drug dissolution during the early stages, leading to a sustained release of the drug over a period of 24 h. The incorporation of STZ-PEG2000 into PLGA NPs significantly improved the permeability across rabbit corneas, showing a 2.5-fold increase compared to STZ-loaded PLGA NPs. Additionally, the antifungal efficacy of the formulated NPs was evaluated against *Candida albicans*, revealing a fourfold decrease in the minimum inhibitory concentration when using the NPs containing STZ solid dispersion, in contrast to those with the free drug [69]. Amphotericin-B (AmB) ophthalmic preparations that are ready to use have also been investigated in one study. This was achieved by developing a combination system of AmB-encapsulated silk fibroin NPs integrated in thermosensitive in situ hydrogel (AmB-FNPs ISG) for the treatment of fungal keratitis. Compared to commercial AmB, AmB-FNPs ISG demonstrated much less toxicity to HCE cells and good antifungal efficacy. AmB-FNPs ISG showed an improved ability to adhere to the ocular surface for longer than 6 h in both *in vitro* and *ex vivo* mucoadhesive tests. This would lengthen the time that AmB is retained in the eye and decrease the frequency of administration during the course of treatment. Furthermore, AmB-FNPs ISG demonstrated strong chemical and physical stability [70].

3.2. Nanostructured lipid carriers (NLCs)

Lipid carriers are very popular nowadays because they can increase the solubility and bioavailability of drugs that are poorly soluble in water. NLCs contain a solid lipid matrix embedded within a liquid lipid

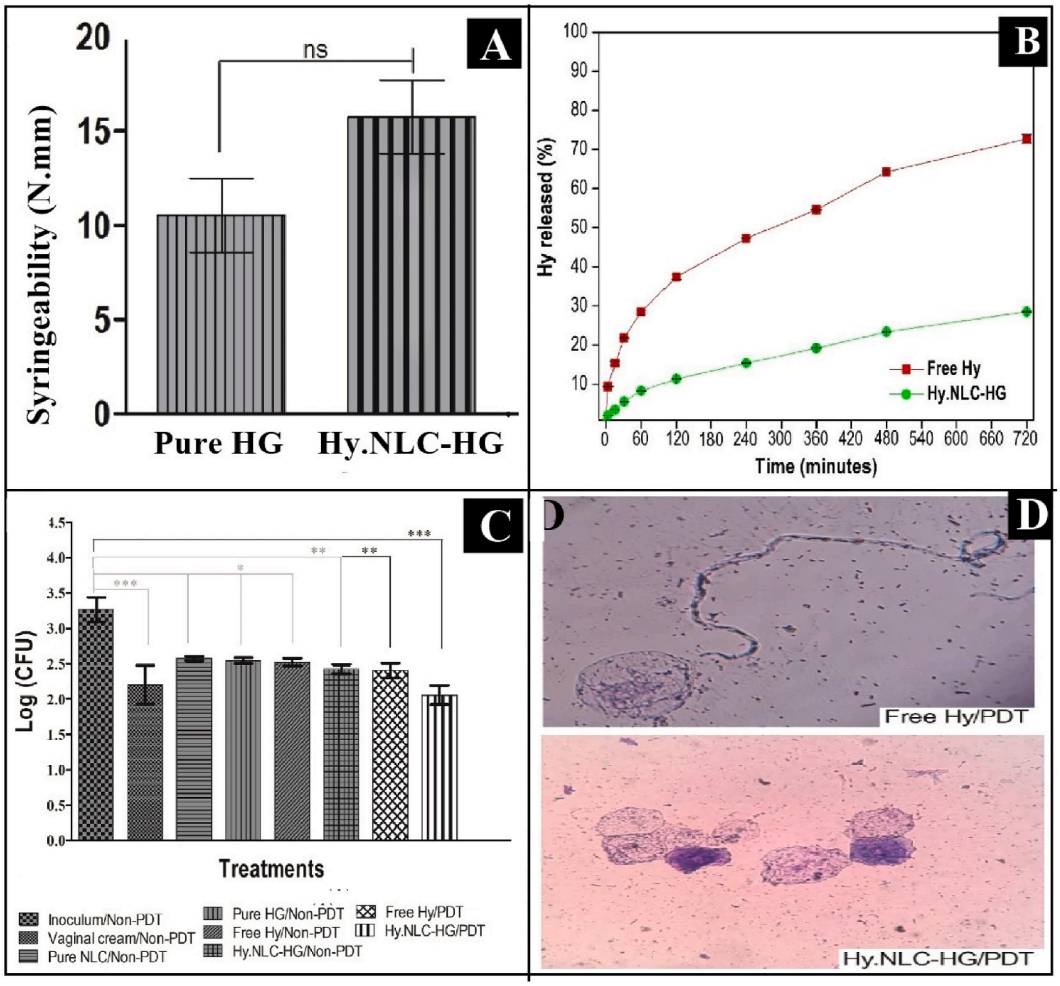

Fig. 3. A) Syringeability assessment of the pure hydrogel and the hypericin.NLC-hydrogel, shown as a mean ± SD (n = 6; ns = not statistically significant, $p > 0.05$); **B)** *In vitro* release profiles comparing free hypericin with hypericin.NLC-hydrogel; **C)** Logarithmic count of *Candida albicans* colonies isolated from the vaginal fluid of female C57BL/6 mice, treated either without light (non-PDT) or with photodynamic therapy (PDT using LED light at 113 J.cm−2 for 5 min). Data are presented as mean ± SD over four treatment days (days 1, 3, 5, and 7 post-inoculation); **D)** Microscopic images (40 × magnification) showing the morphology of *Candida albicans* in the vaginal tissue of PDT-treated animals. Adapted from Ref. [78].

matrix. A combination of solid and liquid lipids (ideally in a 70:30 ratio) with a 95 % solid content in the solid matrix structure restricts the NPs from coalescence [71]. NLCs are designed or developed using a wide range of biocompatible lipids and surfactants as a delivery mechanism for both hydrophobic and hydrophilic drugs. Solid lipids like stearic acid, glyceryl tridecanoate, glyceryl monostearate, glyceryl distearate (Precirolfi ATO 5), glyceryl tripalmitate; liquid lipids like oleic acid, alpha-tocopheryl acetate, squalene, medium chain triglycerides (MCT)/caprylic and capric triglycerides, soy lecithin (Epikuron™200), propylene glycol dicaprylocaprate (LabrafacTM PG), among others, are used in the formulation of NLCs.

The NLC provides significant potential for drug delivery while improving their therapeutic effectiveness, and enhancing their physical stability. They are less expensive than liposomes and simple to scale up and produce [67]. Numerous intriguing properties of NLCs include their capacity to: (i) increase drug stability; (ii) maintain hydration of skin; (iii) prolong drug release; (iv) achieve greater encapsulation efficiency for lipophilic drugs through the inclusion of liquid lipids in their matrix; and (v) ensure are biocompatibility and biodegradability owing to their composition of solid lipids combined with a portion of liquid lipids sourced from natural origins [72]. In a study, after being administered intravenously to rats, the tissue distribution of radiolabelled NLCs was assessed. Authors reported that the radiolabelled nanocarriers showed a long circulation time in the blood, even 24 h after injection [73]. Another study indicates that gels formulated with itraconazole-NLC markedly improved itraconazole retention in excised human skin compared to conventional itraconazole gel. An encapsulation efficacy of more than 98 % was observed across many experiments and kept its integrity even after six months of storage. *In vivo* studies showed that the itraconazole NLC gel successfully treated cutaneous candidiasis in rats [74]. In a study, the authors aimed to enhance the dermal bioavailability and effectiveness of luliconazole (LCZ), by addressing its limitations, such as low water solubility, low skin retention, and low skin penetration. To achieve this, they formulated luliconazole-encapsulated NLCs (LCZ-NLCs) using a modified emulsification-solvent evaporation method. The findings showed that the LCZ-NLCs had a favorable zeta potential, uniform dispersion, nanoscale dimensions, and an encapsulation effectiveness of almost 90 %. The *in vitro* drug release experiments suggested a higher dissolution rate of the drug with the LCZ-NLCs. Additionally, the developed LCZ-NLCs formulation may be a promising topical treatment for superficial fungal infections, especially in resistant cases, as the *in vitro* antifungal susceptibility tests demonstrated strong antifungal activity of both LCZ and LCZ-NLCs against resistant fungal isolates [75]. Chilamakuri et al., developed hydrogel-containing NLCs that were encapsulated with ketoconazole (KTZ) to efficiently treat candidiasis. The hydrogel loaded with NLCs demonstrated optimal spreadability and displayed shear-thinning characteristics, highlighting the formulation's ease of application. The transdermal flux (Jss) for KTZ was found to be 6.41 times greater from KTZ-NLC compared to coarse-KTZ, underscoring the advantages of using NLCs. Furthermore, KTZ-NLCs demonstrated impressive retention rates in the stratum corneum and viable epidermis, which were 2.58 and 6.35 times higher, respectively. Cytotoxicity assessments conducted on human dermal fibroblast cells (HDFS) lines illustrated the effectiveness of NLCs in minimizing cell toxicity associated with KTZ. With a MIC-50 value of 0.39 μg/mL, the KTZ-NLCs showed a greater zone of inhibition against *Candida albicans* strains and successfully inhibited planktonic development and hyphal transformation. These results demonstrate the antifungal activity against *Candida albicans* that is obtained by encapsulating KTZ in the NLC matrix [76].

A study aimed at improving voriconazole ocular penetration was carried out, using the formation of NLCs to overcome the difficulties related to voriconazole (VCZ) solubility. The optimized formulation VCZF5-NLCs demonstrated superior characteristics such as 126.6 nm size, 33.5 mV Zeta potential, 97.38 ± 0.210 drug content, 88.01 ± 0.272 encapsulation efficiency, and sustained drug release. The in-situ gel (VCZ-NLC-IG) was prepared using the optimized formulation. According to the *ex vivo* corneal diffusion study findings, VCZ-NLC-IG3 showed 74.2 % drug entrapment and 88.25 % drug content. The zone of inhibition data showed that VCZ-NLC-IG3 was more effective than AmB. The enhanced VCZ-loaded NLCs offer a potential therapy for fungal infections of the eyes [77].

Vulvovaginal candidiasis (VVC) is a significant worldwide health issue primarily attributed to *Candida albicans*, an opportunistic fungus known for its morphological adaptability. To improve the effectiveness of photodynamic therapy (PDT) in treating VVC caused by *Candida albicans*, a potent photosensitizer named hypericin was combined with an NLC and dispersed within a hydrogel. The hydrogel system underwent thorough physical and chemical characterization, with evaluations conducted on its photodynamic and antifungal effects both *in vitro* and *in vivo*. These hydrogels demonstrated remarkable mucoadhesive properties and the ability to be easily extruded from a delivery device, highlighting their user-friendly administration and their capacity to remain effective in the vaginal environment (Fig. 3A). Free hypericin exhibited a controlled release pattern of 21.86 ± 0.23 % after 30 min and 72.67 ± 1.13 % after 720 min during the *in vitro* drug release testing. As demonstrated in Fig. 3B, hypericin.NLC-hydrogel, in contrast, demonstrated a controlled and continuous release of around 5.62 ± 0.15 % and 28.55 ± 0.15 % after 30 and 720 min, respectively. Hypericin's antifungal efficacy against vaginal Candida albicans infection was evaluated *in vivo* by administering hydrogel systems to female mice both under photodynamic therapy (PDT) and without light. Furthermore, as shown in Fig. 3C, the cell morphology in vaginal fluid was investigated under a microscope. As shown in Fig. 3C, the Candida albicans inoculation in the infected group persisted throughout the trial. Among female mice infected and treated without light using pure systems, NLCs and hydrogel, and hypericin in the free condition, the mean number of colonies varied significantly ($p < 0.05$) over the course of the four treatment days. When comparing the animals given vaginal cream/non-PDT to the inoculation group, where the average colony count was 2.20 (log), a significant improvement was noted ($p < 0.001$). Analysis of the morphological forms (Fig. 3D) revealed a decrease in the growth of Candida albicans hyphae in the vaginal fluids of animals infected with *Candida albicans* and treated with both free hypericin/PDT and hypericin.NLC-hydrogel/PDT [78].

3.3. Vesicular nanoparticles

Traditional creams, lotions, and gels containing free antifungal drugs are utilized to address skin fungal infections. However, as side effects, they could cause erythema, stinging, burning, and skin redness [79]. Hydrophilic antifungal drugs have a poor skin penetration rate and conventional antifungal formulations require high doses or frequent dosing, which reduces their efficacy against skin fungus pathogens [80]. Vesicular NPs possess the capability to address the limitations of traditional antifungal treatments, as they can effectively penetrate hair follicles and may accumulate within the spaces between corneocytes, integrate with the lipid layer, and engage robustly with the lipids present in the epidermis. Innovative systems based on vesicular nanoparticles for the treatment of fungal infections comprise liposomes, ethosomes, and transferosomes.

3.3.1. Liposomes

For effective/improved drug delivery, liposomes are the most widely utilized phospholipid-based nanocarrier system. These are closed, spherical lipid bilayer that generates an interior cavity with the capacity to transport drugs. Two sheets of phospholipids (with a hydrophobic tail and a hydrophilic head) that are closely packed together make up a lipid bilayer. Liposomes have emerged as the leading nanocarriers for antifungal drugs due to their exceptional biocompatibility, biodegradability, and low immunogenicity. These liposome-based drug delivery systems have the capability to effectively address the issue of drug resistance by

ensuring that sufficient medication reaches the site of infection [81]. In a promising recent study, researchers took significant steps to combat infections caused by the multidrug-resistant yeast *Candida auris* by developing an innovative antifungal agent, PQA-Az-13. This compound combines indazole, pyrrolidine, and arylpiperazine scaffolds with a trifluoromethyl group, demonstrating remarkable antifungal activity against biofilms from 10 different clinical isolates of *Candida auris*, representing all four known geographical clades. To further enhance its solubility and stability, PQA-Az-13 encapsulated cationic liposomes were formulated from soybean phosphatidylcholine (SPC), 1,2-dioleoyloxy-3-trimethylammonium-propane chloride (DOTAP), and DSPE-PEG 2000. The resulting liposomal formulation showed improved antifungal activity in both *in vitro* biofilm models and *ex vivo* skin colonization models. These findings suggest that PQA-Az-13 has significant potential for further development as an effective antifungal therapy [82]. Given that the local management of oral candidiasis typically necessitates prolonged use of antifungal medication, an optimal dosage form should be capable of sustaining drug release over an extended duration, thereby ensuring sufficient concentration at the site of infection. In a research, scientists explored the potential of mucoadhesive polymeric matrices for the effective buccal administration of miconazole nitrate (MN). By leveraging the amphiphilic characteristics of liposomes, MN was successfully incorporated into a hydrophilic matrix. The liposomes were expertly crafted using a thin film evaporation technique paired with extrusion, while solid matrices emerged from the freeze-drying of a liposomal suspension in a carefully formulated polymer solution containing chitosan, sodium hyaluronate, or hydroxypropyl methylcellulose. Remarkably, even though the sodium hyaluronate-based formulation released a higher quantity of the drug, both chitosan and sodium hyaluronate formulations demonstrated the ability to nearly eliminate *Candida albicans* growth within just 24 h. Notably, the chitosan-based liposomes exhibited superior mucoadhesive properties, positioning it as the most promising candidate for the localized treatment of oral candidiasis [83].

As a result of a nationwide shortage of amphotericin B deoxycholate, the protocols at a neurosurgical center in the southwestern region were updated in the spring of 2023. The revised guidelines suggest an initial intrathecal dose of 0.125–0.5 mg of liposomal amphotericin B, contingent on the type of insertion device utilized. This dose should be slowly increased by 0.125–0.25 mg every 48 h, with a maximum daily dose of up to 2 mg.

Intrathecal amphotericin B is an essential component of treatment for severe fungal meningitis. Although traditional formulations often rely on amphotericin B deoxycholate, liposomal amphotericin B emerges as a compelling alternative, delivering superior clinical outcomes in systemic treatment. A thorough review was performed on four cases of fungal meningitis that received supplementary intrathecal treatment using a liposomal formulation of amphotericin B. This included one case of suspected *Fusarium solani* meningitis that arose after an outbreak, as well as three cases of coccidioidal meningitis. Following the initiation of intrathecal amphotericin B, all patients showed significant early improvement in their condition and were able to tolerate long-term therapy. This study clearly demonstrates that intrathecal administration of liposomal amphotericin B represents a promising and viable supplementary therapeutic option for managing severe fungal meningitis [84].

3.3.2. Niosomes

Niosomes are bilayer, spherical, nanostructure lipid-based vesicles that are prepared with the help of non-ionic surfactants. Niosomes provide an added benefit over liposomes, such as greater reproducibility using inexpensive raw materials (non-ionic surfactant), stability, and storage [85]. Furthermore, when it comes to prolonged or controlled release applications, the superior encapsulation of drugs, combined with their inert, biodegradable, and non-immunogenic properties, offers a compelling advantage over alternative vesicles [86]. In a study, niosomes loaded with fluconazole were synthesized using the film hydration process, utilizing distinct surfactants, and were subsequently assessed for many parameters. The most effective niosomes were formulated using Span 40, Span 60, and Brij 72, demonstrating superior stability. Their sizes measured at 0.378 ± 0.022 μm, 0.343 ± 0.063 μm, and 0.287 ± 0.012 μm, all of which contributed to a remarkable entrapment efficiency. *In vitro* studies on skin penetration and retention clearly indicated that both vesicle size and surfactant properties play crucial roles in enhancing cutaneous accumulation, making these niosomes a compelling choice for advanced skin delivery systems. The findings demonstrated that niosomes appear to concentrate and create localized drug depots in the skin, which can significantly improve cutaneous retention of fluconazole by releasing its contents over time [87]. Clotrimazole, a BCS class II antifungal drug, is used to treat oral thrush caused by *Candida albicans*. Clotrimazole's high permeability but low water solubility, along with its current lozenge formulation, leads to uneven drug distribution in saliva, requiring frequent dosing and resulting in poor patient compliance. To enhance drug efficacy and patient adherence, the researchers developed a niosomal-based subgingival film formulation of clotrimazole. This formulation aimed to improve drug solubilization and prolong drug release at the targeted site, thus reducing dose frequency. The niosomal films demonstrated good entrapment efficiency and significant antifungal activity. Additionally, the release pattern of the niosomal film was superior to that of a traditional drug-loaded film, suggesting enhanced therapeutic potential for localized oral treatment of *Candida albicans* infections [88].

Conventional methods of administering fluconazole, such as eye drops, often have limited effectiveness due to poor bioavailability. To overcome this issue, researchers developed fluconazole niosome-loaded contact lenses to improve drug release control and enhance bioavailability. Two techniques were used to create fluconazole niosomes: the solvent injection method and the thin film hydration method, which incorporated a combination of Span 60 and cholesterol. The optimized niosomes were then integrated into contact lenses using the soaking method. The lenses were evaluated based on their *in vitro* release patterns and antimicrobial properties. Fluconazole was gradually released from the niosome-laden contact lenses over 48–72 h, achieving a total release of 79.62 %. Statistical analysis showed that the fluconazole niosome-laden contact lenses significantly reduced fungal adhesion compared to standard fluconazole-loaded contact lenses [89].

In light of the alarming rise in drug resistance among Candida species, a pivotal study was conducted to uncover the antifungal potential of crocin (Cro) and evaluate the effectiveness of its niosomal formulation (N-Cro). This research also explored the synergistic effects of combining these formulations with fluconazole against both susceptible and resistant *Candida albicans* isolates. Remarkably, the N-Cro formulation achieved an astonishing entrapment efficiency of up to 99.73 ± 0.54 % and an average size of 5.224 ± 0.618 μm (mean ± SD, n = 3). Both Cro formulations displayed strong anticandidiasis activity against the isolates. Notably, the synergistic effect of N-Cro combined with fluconazole closely matched that of Cro alone, with a significant P-value of 0.03. These compelling results underscore the profound antifungal effect of N-Cro when paired with fluconazole, highlighting its potential as a powerful therapeutic option [90].

3.3.3. Ethosomes

Ethosomes are hydroalcoholic phospholipid-based nano-vesicular carriers with high alcohol content. In addition to water, alcohol, and propylene glycol, ethosomes may also contain various phospholipids (such as phosphatidylcholine, phosphatidylinositol, phosphatidylglycerol, phosphatidylethanolamine, hydrogenated phosphatidylcholine, phosphatidylserine, and phosphatidic acid) [91]. Due to their remarkable flexibility, ethosomes have been shown in studies to have a significant ability to penetrate human skin. Because they can more effectively transport many types of drugs through the skin barrier, ethosomes are typically applied topically [92]. According to Lin et al.,

luliconazole ethosomes exhibit greater skin penetration and antifungal efficacy [93]. Prepared using thin-film hydration with optimized conditions, these ethosomes exhibit small, uniform particle sizes and high entrapment efficiency (~70 %). Antifungal efficacy against *Trichoderma* was notable, with minimal skin irritation observed in rat models, highlighting their potential for clinical use in dermatology [43].

In a recent study, researchers developed a promising local treatment for oral candidiasis by ingeniously combining Fluconazole (FLC) and Etoricoxib (ET) into an innovative mucoadhesive bilayer film designed for buccal use. Utilizing a 3^2-full factorial design, the team optimized the formulation of FLC-loaded niosomes (FLC-NSs) by carefully selecting the type of surfactant and the surfactant-to-cholesterol ratio. These optimized FLC niosomes were then seamlessly integrated into a mucoadhesive film and paired with a second ET layer, resulting in the creation of the FLC NSs/ET film. Remarkably, this novel film exhibited a slower release profile compared to existing treatments like F3, Diflucan®, and Arcoxia®. *In vivo* studies in animals demonstrated that the FLC NSs/ET film not only restored normal tissue histology in the rat tongue but also significantly normalized levels of nuclear factor-kappa B (NF-κB) and interleukin-36 (IL-36). Additionally, it achieved a remarkable 70 % reduction in interleukin-1 beta (IL-1β) levels compared to Diflucan®/Arcoxia®. These compelling results highlight the immense potential of the FLC NSs/ET film as a revolutionary treatment option for oral candidiasis [94].

3.4. Micellar systems

Nanomicelles represent a remarkable development in colloidal chemistry, characterized by their unique hydrophobic core structure encased in a hydrophilic shell. With particle sizes typically ranging from 10 to 100 nm, these self-assembling nanocarriers offer incredible potential for various applications, including drug delivery and nanotechnology [95]. Amphiphilic molecules are self-assembled into organized supramolecular structures that generate nanomicelles in water. Hydrophobic tails and hydrophilic heads make up the core and shell of amphiphilic molecules, respectively. This unique nanostructure makes the efficient encapsulation and delivery of hydrophobic drugs to particular body targets possible. Nanomicelles exhibit some distinctive or novel properties due to their size, solubility, customized surface, or exposure to the environment, making them multifunctional. Nanomicelles are effective at locating and eliminating fungal cells due to their high bioavailability and low toxicity to healthy cells, thus minimizing harm to normal cells. Polymeric micelles are advantageous for topical drug delivery due to several factors, including enhanced drug solubility, improved drug partitioning within the skin, and increased drug accumulation in the skin and hair follicles. These micellar systems have been acknowledged as effective delivery mechanisms for topical antifungal medications (95,96).

A serious corneal infection that can cause blindness is called fungal keratitis. Because of its low absorption and poor water solubility, butenafine (BTF), an allylamine drug with strong antifungal effects, has limited practical utility in ophthalmology. To tackle these hurdles, the authors have innovatively encapsulated butenafine within polymeric nanomicelles (NM), effectively enhancing both its solubility and corneal permeability. The BTF-NM not only exhibited high stability but also displayed a typical biphasic release pattern during *in vitro* drug release studies. Moreover, this formulation demonstrated excellent cellular and ocular tolerance in rabbit models, significantly boosting its *in vitro* antifungal activity. Crucially, *in vivo* assessments revealed marked improvements in corneal permeation when compared to a BTF suspension formulation. The *in vivo* antifungal activity studies confirm that the BTF-NM formulation offers therapeutic effectiveness against fungal keratitis, rivaling the efficacy of commercial natamycin suspension eye drops [97]. This invention has enormous potential to combat this dangerous eye infection and improve treatment results.

Noshi et al. (2022) successfully focused on enhancing the ocular delivery of miconazole nitrate (MN), a broad-spectrum antifungal agent recognized for its poor solubility and limited permeability to ocular tissues. This approach is particularly crucial for effectively treating fungal keratitis. To accomplish their goal, they strategically harnessed polymeric mixed nano-micelles and implemented a 3^3 full factorial design, skillfully varying the ratios of Pluronic® F127, Pluronic® P123, and Tetronic® T701 for optimal results. The *in vivo* evaluation using a rabbit model of induced ocular candidiasis demonstrated that the Soluplus®-MPM formula had superior antifungal efficacy against *Candida albicans* compared to a 0.2 % MN suspension. Following seven days of treatment, a histopathological analysis of the rabbits' eyes verified that the ocular tissues had not undergone any degenerative changes. In order to treat ocular infections safely and effectively, the results indicate that SP-pluronic mixed nano-micelles provide a stable and successful platform for delivering MN to the eyes [98].

3.5. Metallic nanoparticles

A class of inorganic nanomaterials known as metallic NPs (MNPs) is a strong candidate for the delivery of antifungal medications due to their stability, site-targeting capabilities, and sustained/controlled drug delivery. In addition to their simple surface functionalization and low dispersity index, they are also readily producible in a range of sizes [99]. Numerous studies have already established that MNPs do not cause drug resistance, are more selective for the infection site, and have fewer side effects [100]. Inorganic NPs are widely recognized for their antibacterial and antifungal properties, enabling them to effectively interact with microorganisms [101]. Applications of MNPs, such as those involving platinum, zinc, silver, gold, copper, iron, and many others, are generating increasing attention.

3.5.1. Gold nanoparticles

Gold NPs are small gold particles with a diameter ranging from 1 to 100 nm. These NPs have garnered significant research interest due to their remarkable optical, electronic, and chemical properties that make them valuable in various scientific and medical applications [102]. The potential antifungal effects of gold NPs in *Candida albicans* biofilm cells have been studied. This is because, when combined with a photosensitizer, gold NPs were found to boost the effectiveness of photodynamic therapy. By interacting with the lipids and proteins of the fungal cell, gold NPs can damage the fungal cellular membranes [103]. In one study, the anticandidal properties of indolicidin in combination with gold NPs were tested using clinical isolates of *Candida albicans* that are resistant to fluconazole. The nanocomplex was innocuous to fibroblasts and erythrocytes, but it drastically decreased *Candida albicans's* ERG11 gene expression and the iNOS gene in macrophages. Higher antifungal activity against the clinical isolates was demonstrated by conjugates that had lower minimum inhibitory concentrations against Candida isolates (fluconazole-resistant) and fewer cytotoxic effects on eukaryotic cells. Clinical isolates of *Candida albicans* were found to be more susceptible to the indolicidin-gold NPs conjugates than to either free indolicidin or fluconazole, according to qRT-PCR experiments [104].

Another investigation has proposed a novel approach to boost the effectiveness of antifungal treatments by creating multifunctional metal nanozymes, specifically using Amphotericin B (AmB). The synthesis of AmB-gold nanoparticles (AmB@AuNPs) was carried out through a simple one-pot reaction process. These NPs displayed an impressive increase in peroxidase (POD) like enzymatic activity, with their maximum reaction rates for the catalytic breakdown of hydrogen peroxide being 3.4 times greater than those of standard gold NPs. The antifungal efficacy of AmB was significantly enhanced due to the enzyme-like properties of the gold NPs; the minimum inhibitory concentration (MIC) of AmB@AuNPs against *Candida albicans* and *Saccharomyces cerevisiae* was reduced to 1.6 and 50 times lower levels, respectively, compared to AmB alone. Furthermore, *in vivo* studies conducted on mice with fungal-infected wounds showed that

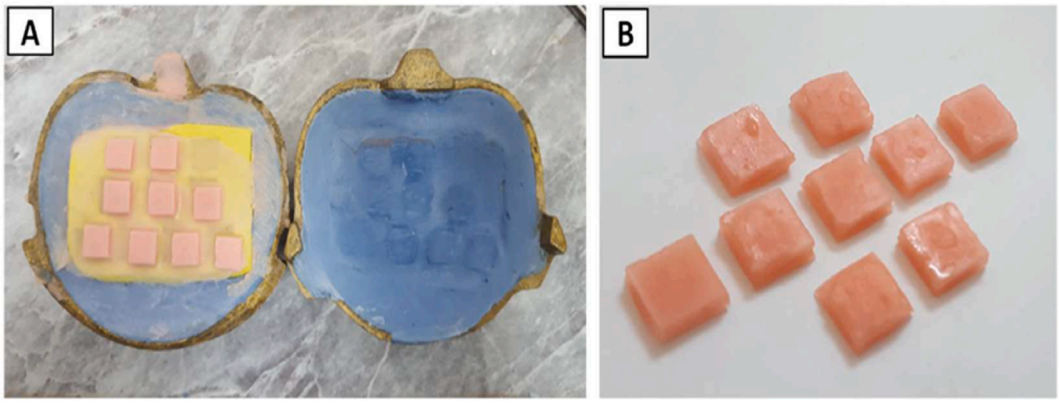

Fig. 4. Soft liner samples following the curing process: **A)** positioned inside the molds; **B)** removed from the molds. Adapted from Ref. [113].

AmB@AuNPs demonstrated significantly improved antifungal effectiveness and biosafety [105].

3.5.2. Silver nanoparticles

The most extensively studied inorganic NPs for antifungal uses, especially as antifungal agents, are silver NPs. Silver NPs drastically modify the crucial processes that are carried out by fungal cells by modulating their transcriptome, epigenome, and metabolome. It has been demonstrated that structural alterations, mostly at the level of biological membranes, result from the down-regulation of genes linked to the tricarboxylic acid cycle, ergosterol synthesis, and lipid metabolism [106]. Curcumin-coated silver nanoparticles (Cur-Ag NPs) were evaluated recently for their antifungal capabilities against a variety of *Candida* and *Aspergillus* species. This study was motivated by the well-known broad-spectrum antimicrobial effects of both curcumin and silver. The researchers evaluated the efficacy of Cur-Ag NPs on 30 fungal isolates from *Aspergillus* and *Candida*, also examining their susceptibility to antifungals such as fluconazole and itraconazole. The assessments were conducted using the broth microdilution technique, both individually and in combination. Cur-Ag NPs showed encouraging antifungal activity, especially against different species of Candida. For every fungus species examined, the geometric mean of the MIC for Cur-AgNPs was substantially lower than that of fluconazole. Furthermore, it was lower than the MIC for itraconazole in both *Candida albicans* and *Aspergillus fumigatus*. While the minimum fungicidal concentrations (MFC) of Cur-Ag NPs were notably higher than those of fluconazole, they remained below those of itraconazole. The researchers concluded that Cur-Ag NPs demonstrated clear antifungal properties and hold considerable promise for use in combating fungal infections, particularly those caused by azole-resistant strains of *Aspergillus* and *Candida* [107].

AgNPs and fluconazole have been shown in a study to work together in the fight against fluconazole-resistant *Candida albicans*. Two clinically isolated strains of fluconazole-resistant *Candida albicans* were used by the researchers to conduct a more thorough investigation of the possible synergistic effect and underlying mechanisms of the AgNPs-fluconazole combination. AgNP treatment was followed by the observation of cellular and molecular targets associated with fluconazole resistance. The antifungal properties of the AgNPs fluconazole combination were also examined *in vivo* using a rodent model of disseminated candidiasis. Analysis was done on tissue burden and survival rate. The outcomes showed that AgNPs and fluconazole combined to effectively combat both the planktonic cells of *Candida albicans* that were resistant to fluconazole and the biofilms that formed within 12 h. AgNP treatment reduced membrane fluidity and ergosterol levels. It also downregulated CDR2, ERG1, ERG11, and ERG25, which in turn reduced efflux pump activity. Additionally, it reduced Cdr1p and Cdr2p's membrane composition. The increased production of ROS most likely contributed to the synergistic effect as well. AgNPs and fluconazole together significantly decreased the fungal burden and raised the *in vivo* survival rate of infected mice. These results lend credence to the idea that combining fluconazole and AgNPs to treat fluconazole-resistant fungal infections is a promising therapeutic strategy [108].

3.5.3. Copper nanoparticles

Copper NPs are a viable and less expensive alternative to traditional fungicides since they have demonstrated strong antifungal action against phytopathogenic fungi [109]. Due to its unique properties, copper oxide (CuO) is a significant transition metal oxide. One study examined the structural and antidermatophytic characteristics of CuO-NPs synthesized through a precipitation process. CuO-NPs with a flower-shaped appearance were seen using SEM, and their crystalline nature was revealed by an XRD pattern. Using the broth microdilution method, these NPs were assessed against two common dermatophyte species, namely *Trichophyton rubrum* and *Trichophyton mentagrophytes*. Moreover, a comparison was made between the activity of NPs and synthetic sertaconazole. The findings indicated that compared to *Trichophyton rubrum*, *Trichophyton mentagrophytes* were more vulnerable to CuO-NPs [110]. Copper Iodide (CuI) nanomaterials were developed and thoroughly described in a work to develop effective antifungal agents. *Sporothrix schenckii* and *Candida albicans* were used to assess the bioactivity of CuI-nanomaterials. Colloidal suspensions and powders of CuI nanomaterials have been successfully developed. To enhance the antifungal properties of these CuI materials and control their particle size, biopolymers such as chitosan and gum arabic were utilized as surfactants. The nanomaterials exhibited exceptional antifungal effectiveness against pathogenic fungal strains, utilizing a range of diverse and simultaneous mechanisms of fungal defense provided by the composites. After 5 h of exposure, CuI-arabic gum and CuI-Chitosan exhibited MIC and MFC of less than 50 μg/mL. Atomic force microscopy further illustrates the capacity of the materials to attach to and infiltrate fungal cells, leading to their subsequent lysis and demise. In line with the crucial principle of safety by design, we thoroughly evaluated the biocompatibility of these materials. Our assessment included an examination of hemolytic activity using red blood cells, ensuring their safety and efficacy for use. The study findings suggest that the materials exhibit remarkable antifungal efficacy at reduced levels of hemolytic disruption [111].

3.5.4. Iron oxide nanoparticles

Iron oxide NPs are poised to transform antifungal therapy due to their remarkable and unparalleled properties, including enhanced drug delivery, biofilm disruption, and reduced resistance development. Their versatility and biocompatibility make them an important tool in combating fungal infections, especially those resistant to conventional treatments. A study examined the antifungal efficacy of iron oxide NPs against different Candida species compared with fluconazole. The iron

Table 2
Presentation of the main characteristics of the different NPs and their most effective applications in antifungal therapy.

Nanotherapeutic System	Composition	Specific Features	Route of Administration	Effective Applications	Reference
Polymeric Nanoparticles	Biodegradable polymers (natural or synthetic)	1–1000 nm; positive/neutral charge; Biocompatible with the host cells	Oral, IV, topical	Controlled drug release, systemic fungal infections	[68–70]
Nanostructured Lipid Carriers	Solid & liquid lipids with surfactants	High drug loading; Improved stability	Topical, oral	Cutaneous and mucosal fungal infections	[74–76]
Liposomes	Phospholipids and cholesterol	Biocompatible; Low immunogenicity	IV, topical, inhalation	Amphotericin B delivery, systemic & pulmonary fungal infections	[82–84]
Niosomes	Non-ionic surfactants + cholesterol	Sstable; Enhanced skin penetration	Topical, transdermal	Dermal candidiasis, skin infections	[87–89]
Ethosomes	Phospholipids + ethanol	Enhanced skin permeation due to ethanol	Topical, transdermal	Deep skin fungal infections	[43]
Micellar Systems	Amphiphilic surfactants	<100 nm; hydrophobic core; Solubilizing ability	Oral, topical	Poorly soluble antifungal drug delivery, ocular drug delivery	[97,98]
Gold Nanoparticles	Metallic gold with stabilizers	Remarkable optical, electronic, and chemical properties; Surface modifiable; Biocompatible	Topical, IV	Antifungal coatings, biofilm inhibition, and drug delivery platforms	[102,103]
Silver Nanoparticles	Metallic silver	<100 nm; Strong antifungal activity; Reactive	Topical	Wound healing, antifungal dressings	[106–108]
Copper Nanoparticles	Metallic copper or copper oxide	ROS generation; Cytotoxic at high doses	Topical	Broad-spectrum antifungal and antimicrobial coatings	[109–111]
Iron Oxide Nanoparticles	Fe_3O_4 or γ-Fe_2O_3, often coated	10–100 nm; Magnetic; Surface functionalization possible	IV, topical	Magnetic targeting, theranostic antifungal delivery	[112]
Titanium Dioxide Nanoparticles	Crystalline TiO_2 forms	Photocatalytic; Stable	Topical, IV	Antifungal surface treatments and photodynamic therapy	[113]

oxide NPs exhibited a spherical morphology, measuring between 30 and 40 nm in diameter. The MIC and MFC for these NPs were found to be in the range of 62.5–500 μg/ml and 500–1000 μg/ml, respectively. In comparison, fluconazole demonstrated values of 16–128 μg/ml and 64–512 μg/ml, respectively. The results of the growth inhibition showed that iron oxide NPs were particularly harmful to *Candida tropicalis, Candida albicans, and Candida glabrata*. According to Seddighi et al. (2017), this observation implies that iron oxide NPs have antifungal qualities against harmful *Candida* species and can inhibit the growth of every *Candida* species examined.

In an innovative study, superparamagnetic iron oxide nanoparticles (SPIONPs) were synthesized using FeCl3 and FeCl2. These NPs were effectively reduced to iron oxides through a precise chemical co-precipitation process involving NaOH and ammonia solution. The naked SPIONPs were then deliberately functionalized with oleic acid and tagged with the antifungal drug itraconazole. To enhance their efficacy, these NPs were encapsulated in a microbial-derived polyester, polyhydroxybutyrate, resulting in a robust core-shell structure specifically designed for controlled drug release. The resultant core-shells demonstrated a slow drug release profile and significant antibacterial activity against *Pseudomonas aeruginosa* and *Brevibacillus brevis*, as well as antifungal activity against *Candida albicans*, confirmed via diffusion method [112].

3.5.5. Titanium dioxide nanoparticles

Titanium dioxide NPs are highly regarded for their exceptional antifungal properties, stemming from their unique physicochemical characteristics. The antifungal effectiveness of adding titanium dioxide NPs to a soft denture liner (Fig. 4) to lower microbial activity, specifically, *Candida albicans*, was assessed by Ahmed et al. in a study. By analyzing the viable count of *Candida albicans*, antifungal resistance was examined. The results showed mean counts of 139.80 (control), 12.00 (1.0 wt%), 6.20 (1.5 wt%), and 1.00 (2 wt%), indicating a substantial decrease in fungal colonization with greater concentrations of titanium dioxide NPs ($p < 0.05$). The results show that adding titanium dioxide NPs to the denture liner improves its antifungal qualities and that higher concentrations of NPs are associated with higher antifungal activity [113].

3.5.6. Zinc oxide nanoparticles

Zinc oxide NPs are appealing as potential antifungals because of their distinct physicochemical and biological characteristics. It has been found that zinc oxide NPs interfere with cellular functions, which causes fungal hyphae to distort and restrict the growth of the fungus *B. cinerea.* Additionally, ZNPs have been connected to the inhibition of conidiophore and conidial development in *P. expansum*, which ultimately led to the mortality of hyphae [114]. In a recent study, ketoconazole-coated zinc oxide NPs were innovatively prepared using green synthesis with green tea extract, enhancing their antifungal efficacy against *Malassezia furfur*. The NPs exhibited superior antifungal activity compared to standard ketoconazole, highlighting their potential as a more effective treatment option for dandruff. Incorporating these NPs into a novel shampoo formulation further demonstrated promising results, suggesting a viable alternative to existing anti-dandruff shampoos with improved therapeutic benefits [115].

To provide a clearer understanding, we present a comparative Table 2, summarizing key characteristics and targeted applications of different nanoparticles.

4. Mycology for nanoparticle development

In recent years, the biosynthesis of NPs using biological entities such as fungi has emerged as a crucial focus of research. This method is not only eco-friendly but also offers substantial potential for large-scale production. Mycology has significantly contributed to nanoparticle development through innovative approaches such as green synthesis using fungal species like *Fusarium, Aspergillus,* and *Candida* [116,117]. This biogenic approach typically involves exposing fungal cultures to metal salts, where enzymes and biomolecules secreted by the fungi mediate the reduction and stabilization of NPs. These fungi utilize their enzymatic and metabolic pathways to reduce metal ions and stabilize NPs, yielding products with controlled size, shape, and surface properties [118,119]. The mechanisms underlying fungal nanoparticle biosynthesis involve enzymatic reduction, extracellular metabolite-mediated reduction, and intracellular sequestration. Enzymes like nitrate reductase, laccase, and reductases play crucial roles in reducing metal ions to NPs. Several variables, such as pH, temperature, incubation duration, and metal ion concentration, affect the process and together define the size, form, and stability of the resulting NPs [120]. Fungal cell wall components, including polysaccharides and proteins, further enhance nanoparticle stability and biocompatibility [120]. These fungal-derived NPs exhibit potent antifungal properties due to

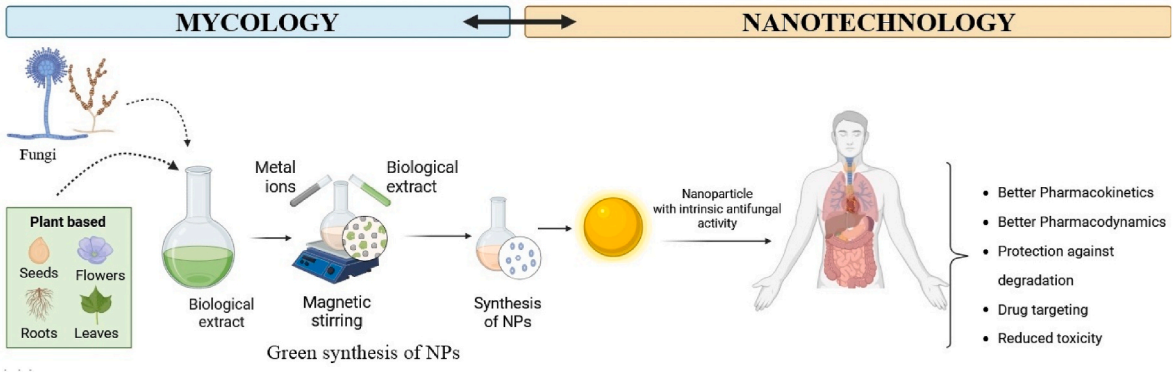

Fig. 5. The Two-Way Interaction Between NPs and Mycology: Nanoparticles can enhance the performance and delivery of antifungal treatments, while various fungal species play a significant role in the green synthesis of nanoparticles. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

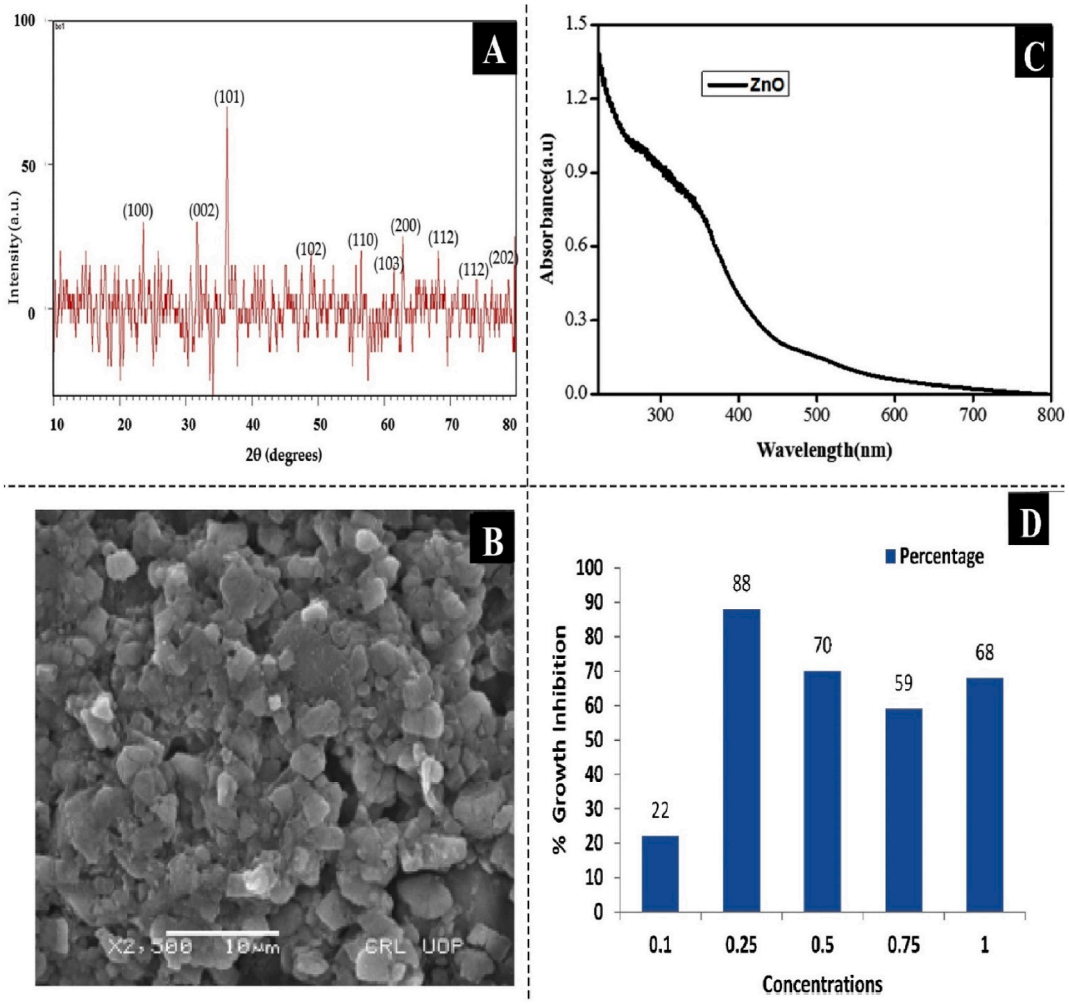

Fig. 6. A) X-ray diffraction profile of zinc oxide NPs; **B)** UV absorption of zinc oxide NPs; **C)** SEM image captured at 2500x magnification; **D)** Evaluation of the antifungal activity of zinc oxide NPs against *Aspergillus* species. Adapted from Ref. [124].

their composition and structure. They can effectively target fungal pathogens, including *Candida* species and dermatophytes, which are known causes of skin infections, nail infections, and systemic fungal diseases [121]. Furthermore, research on mycology-driven NPs has the potential to address issues like drug resistance and adverse effects linked to traditional antifungal therapies. By harnessing the natural abilities of fungi to produce NPs, researchers are advancing sustainable and innovative solutions for managing fungal infections, consequently making a substantial contribution to the fields of nanotechnology and medical mycology. Since nanotechnology enables the targeted delivery of drugs, which can lower toxicity and treatment costs, it is a potential path that is currently being studied for the development of novel antifungal therapeutics [122,123] (Fig. 5).

Due to the presence of various physiologically active compounds,

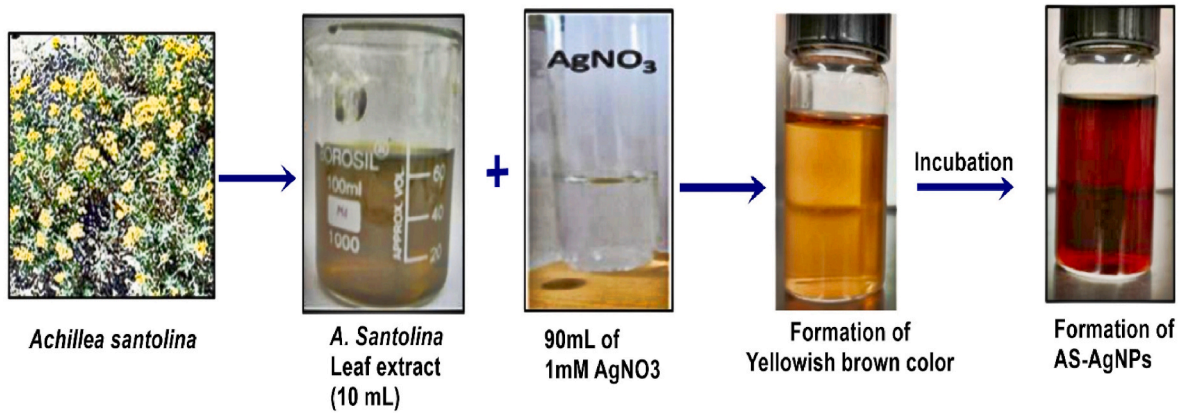

Fig. 7. Green synthesis of AS-AgNPs: a visible color shift from yellow-brown to dark brown occurs following the incubation of the *Artemisia santolina* leaf extract with silver nitrate at room temperature in the absence of light. Adapted from Ref. [129]. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

mushroom extracts serve as a key method for the mycosynthesis of NPs. In a study, zinc oxide NPs were synthesized using the extract from *Daedalea* sp. The resulting NPs displayed an irregular shape and had an average size of 14.58 nm, highlighting their distinct characteristics. For the synthesis process, 10 g of the mushroom were combined with 100 ml of purified water. Following this, 100 ml of zinc solution was gradually added to the mushroom extract. The mixture was kept at a steady temperature of 100 °C on a heated plate and stirred magnetically at 250 rpm for 6 h. Throughout this process, the color of the zinc oxide solution remained constant, with a measured pH of 1.9. After centrifugation at 15,000 rpm for 15 min, the supernatant was removed, and the nanoparticles were then washed, placed into a Petri dish, and dried at 300 °C. Once the NPs were ground into a fine powder, they were stored safely. The crystallinity of the synthesized NPs was evaluated using X-ray diffraction analysis (Fig. 6A). The zinc oxide NPs primarily exhibited absorption peaks around 370 nm, indicating successful synthesis (Fig. 6B). Infrared (IR) analysis of the mycosynthesized zinc oxide NPs showed the presence of phenolic OH groups, supporting the synthesis process. The sticky nature of the wild mushroom extract on the surface of the zinc oxide NPs led to aggregation and agglomeration, as illustrated in Fig. 6C. Antifungal activity was assessed using the agar well diffusion method against the pathogenic fungus *Aspergillus niger,* with observations made at various concentrations of the zinc oxide NPs. At a concentration of 0.25 mg/mL, 88 % of fungal growth was observed, while a 0.5 mg/mL concentration inhibited growth by 70 %. At 0.75 mg/mL, a significant growth inhibition of 75 % was recorded. These results indicate a strong inhibitory effect of the NPs at the higher concentration of 0.75 mg (Fig. 6D) [124].

A study by Baskar et al. investigated the synthesis and antifungal properties of zinc oxide NPs derived from fungal sources. The NPs were produced outside the cell using the culture filtrate from *Aspergillus terreus*, leading to the formation of white clusters that indicated their successful synthesis. X-ray diffraction analysis revealed a 2θ value of 29.8, while the UV absorption spectrum showed a peak at 340 nm, indicating the presence of crystalline zinc NPs. The scanning electron microscopy analysis revealed that the NPs were spherical, with dimensions varying between 54.8 nm and 82.6 nm. Importantly, the zinc oxide NPs exhibited significant antifungal activity against multiple fungal species [125].

Enain et al. explored actinomycetes, a varied group of microorganisms found in diverse environments, which can be harnessed for the biosynthesis of NPs with promising biomedical applications. The primary goal of the work was to investigate the antifungal effectiveness of AgNPs produced through this process against *Candida albicans* sourced from semen and to evaluate their anticancer properties using the $CaCO_2$ cell line. The isolate identified as *Streptomyces griseus* was responsible for the production of AgNPs, which were characterized using various analytical techniques. The biosynthesized NPs demonstrated significant antifungal activity against *Candida albicans*, with a MIC of 125 ± 0.8 μg/ml, and they also enhanced the apoptotic rate in $CaCO_2$ cells, exhibiting an IC_{50} value of 7.30 ± 0.54 μg/ml, while showing minimal toxicity (CC50 = 142.74 ± 4.71 μg/ml) towards Vero cells. The research indicates that specific actinomycetes have the potential to be effective for the production of NPs with significant antifungal and anticancer properties, highlighting the need for additional *in vivo* research [126].

Arthroderma fulvum was shown to be the most effective fungal strain for AgNP production. AgNPs had an average size of 15.5 ± 2.5 nm, confirming their crystalline structure. Furthermore, research indicated that the biosynthesized AgNPs exhibited excellent homogeneity and stability, along with significant antifungal activity against various species, including *Candida, Aspergillus,* and *Fusarium* [127].

A compelling research study explored the remarkable potential of titanium oxide and AgNPs, both derived from the mycelial extract of *Penicillium chrysogenum* AUMC 6092, to combat pathogenic microorganisms when used in combination with tioconazole. The effectiveness of these NPs was assessed against twelve different human pathogenic fungal strains, which included dermatophytes like *Trichophyton rubrum, Microsporum canis, Epidermophyton floccosum* and *Trichophyton mentagrophytes* as well as several strains of multidrug-resistant yeast. The synthesized NPs were characterized as being round and uniform. The study highlighted the enhanced antifungal activity of the NPs combined with tioconazole [128].

In another study, researchers studied the antifungal effects of silver nanoparticles (AgNPs) developed from *Achillea santolina* extract, called AS-AgNPs (see Fig. 7), against the fungus *Trichophyton rubrum.* They used both lab tests and a rat model for their study. The eco-friendly AS-AgNPs, were evaluated through various analytical approaches. The findings revealed that AS-AgNPs effectively inhibited *Trichophyton rubrum* growth, with a minimum inhibitory concentration of 128 μg/mL, and significantly hindered conidial germination and hyphal progression by 55.3 % and 84.6 %, respectively. Fungal cell wall destruction, mycelial structural changes, and enhanced membrane permeability were among the consequences of AS-AgNPs. This increase in permeability was linked to a decrease in ergosterol production. Additionally, AS-AgNP treatment induced apoptosis and increased intracellular ROS levels. The decrease in activities of β-(1,3)-d-glucan synthase and chitin synthase suggested that AS-AgNPs compromised the cell wall integrity. When tested on human skin cells, AS-AgNPs showed very low toxicity. In the rat model, applying AS-AgNPs to infected skin resulted in a significant decrease in the fungus within 7 days. By the end of the treatment, all fungal spores had been cleared. After 14 days, the skin structure in the treated rats improved more than in the control group. AS-AgNPs also

Table 3
Overview of nanotherapeutic systems for fungal infections.

Nanotherapeutic system	Formulation	Main advantages	Method of production	Toxicology		Targeted use	Reference
				Human	Environmental		
Polymeric nanoparticles (PNPs)	Miconazole and farnesol co-encapsulated within chitosan NPs	• ↑ Antifungal efficacy • Sustained release • ↑ Bioavailability • ↑ Treatment of vulvovaginal candidiasis	Ionic gelation	NA	NA	Vulvovaginal candidiasis – enhanced efficacy through mucoadhesive delivery	[66]
	Itraconazole-loaded nanoparticles	• Sustained release • ↑ Bioavailability • ↑ Biocompatibility • ↑ Antifungal activity • ↑ Targeting ability to Reticuloendothelial System-rich organs • Promising NPs for intravenous delivery of Itraconazole	Simple film hydration method.	NA	NA	Systemic fungal infections – IV delivery with Reticuloendothelial System organ targeting (e.g., liver, spleen)	[67]
	Miconazole-loaded chitosan NPs gel	• Randomized controlled clinical trial • Treatment of oral candidiasis in diabetic patients • ↓ Adverse effects	Ionotropic gelation process	NA	NA	Oral candidiasis – especially effective in diabetic patients	[68]
	STZ- Poly(lactic-co-glycolic acid) (PLGA) polymeric nanoparticles	• ↑ Permeability across the corneas of rabbits. • Controlled drug delivery	Nanoprecipitation technology	NA	NA	Fungal keratitis – ocular delivery for localized treatment	[69]
	Amphotericin-B -encapsulated silk fibroin NPs	• ↑ Ocular drug delivery • Ready to use eye drops for the treatment of fungal keratitis	Desolvation method	Significantly reduced toxicity on HCE cells compared to commercially available Amphotericin B.	NA	Fungal keratitis – safer topical ocular formulation	[70]
Nanostructured lipid carriers (NLCs)	Itraconazole-loaded NLCs in gel	• ↑ Drug encapsulation efficiency • ↑ Dermal retention of Itraconazole • ↑ Stability • ↑ Topical antifungal efficacy	Microemulsion method	NA	NA	Topical treatment of dermatomycoses – improved skin retention	[74]
	Luliconazole-loaded NLCs	• ↑ Solubility, permeability, and bioavailability of luliconazole • ↑ Encapsulation efficiency • ↑ Stability • Antifungal activity against resistant fungal isolates.	Modified emulsification-solvent evaporation method	No toxic effects observed	NA	Skin and nail infections – effective against resistant dermatophytes	[75]
	NLCs loaded with ketoconazole	• ↑ Retention in the skin's viable epidermis and stratum corneum • ↑ Spreadability and ease of application • ↑ Antifungal activity • ↓ Toxicity	High-energy processes	Reduced cell (Human dermal fibroblast cell lines) toxicity	NA	Topical use for superficial mycoses – enhanced skin distribution	[76]
	Voriconazole-loaded NLCs	• Improved ocular penetration				Ocular fungal infections – improved eye penetration	[77]
	Hypericin incorporated NLC	• Significant reduction in *C. albicans* colonies • Potential vaginal drug delivery	Sonication process	NA	NA	Vaginal candidiasis – potential local delivery system	
Liposomes	Novel antifungal agent, PQA-Az-13, liposomes	• ↑ Drug encapsulation efficiency • ↑ Stability	Thin film hydration method	Nontoxic to normal human dermal fibroblasts.	NA	Systemic fungal infections – high stability formulation for potential parenteral use	[82]

(*continued on next page*)

Table 3 (*continued*)

Nanotherapeutic system	Formulation	Main advantages	Method of production	Toxicology		Targeted use	Reference
				Human	Environmental		
	Miconazole nitrate-loaded liposomes	• ↑ Encapsulation efficiency • ↑ Mucoadhesive capacity • ↑ Local treatment of oral candidiasis	Thin film evaporation method	NA	NA	Oral candidiasis – enhanced mucosal adhesion and local delivery	[83]
	Amphotericin B Liposomes for intrathecal administration	• Efficacious treatment of fungal meningitis • ↓ Side effects		NA	NA	Fungal meningitis – Central Nervous System delivery with reduced toxicity	[84]
Niosomes	Clotrimazole-loaded niosomes	• ↑ Drug efficacy • Improving drug solubilization capacity • ↑ Entrapment efficiency • ↑ Patient compliance • Target drug delivery		NA	NA	Topical candidiasis – improved patient compliance and efficacy	[85]
	Fluconazole-loaded niosomes	• ↑ entrapment efficiency • ↑ *In vitro* skin permeation • ↑ Retention	Film hydration method	NA	NA	Cutaneous fungal infections – higher retention and skin permeation	[87]
	Clotrimazole encapsulated niosomes-based subgingival film	• ↑ Drug efficacy • ↑ Patient compliance • Drug targeting • Prolonged drug release	Thin film Hydration method	NA	NA	Oral cavity fungal infections – sustained local release (e.g., periodontal candidiasis)	[88]
	Fluconazole niosome-loaded contact lenses	• ↑ Bioavailability • ↑ Therapeutic efficacy	Solvent injection and thin film hydration	Cytotoxicity; The Test showed no harmful impact on normal mouse endothelial cells	NA	Ocular candidiasis – prolonged drug release via contact lenses	[89]
	Crocin encapsulated in niosomes alone and in combination with fluconazole	• ↑ Antifungal effect of crocin loaded in niosomes combined with fluconazole	Heating method	NA	NA	Systemic or mucosal candidiasis – enhanced synergistic antifungal action	[90]
Ethosomes	Luliconazole encapsulated ethosomes	• ↑ Entrapment efficiency • ↑ Skin penetration • ↑ Antifungal efficacy • No skin irritation	Thin-film hydration	NA	NA	Topical treatment, especially for tinea infections, with enhanced skin penetration	[93]
	Fluconazole-loaded niosomes	• ↓ Minimum inhibitory concentration • ↑ Storage stability • An effective treatment option for oral candidiasis.	Ethanol injection method	NA	NA	Oral candidiasis – high mucosal permeation and retention	[94]
Micellar systems	Butenafine-loaded polymeric nanomicelles	• ↑ Storage stability • ↑ Corneal permeation • ↑ Cellular and ocular tolerance in rabbits		HCECs were exposed to a BTF-NM dilution of more than 50 % for more than 4 h. This exposure may have been harmful to the cells due to the TPGS excipient.	NA	Ocular fungal infections – improved delivery and tolerance	[97]
	Miconazole Nitrate loaded Soluplus®-Pluronic® nano-micelles	• Sustained release • Efficacious treatment of Ocular candidiasis and susceptibility to *C. albicans*	Direct equilibrium technique	Histopathological examination showed no degenerative effect on the ocular tissue.	NA	Ocular candidiasis – controlled release and enhanced susceptibility to *C. albicans*	[98]
Gold Nanoparticles	Gold nanoparticles conjugated with indolicidin	• ↑ Antifungal activity against candidiasis in burn patients. • ↓ Drug adverse effects	Chemical synthesis and conjugation	The nanocomplex exhibited no toxicity towards erythrocytes or fibroblast cells.	Concerns about gold nanoparticle accumulation, need for further environmental impact studies.	Candidiasis in burn patients – targeted delivery with reduced side effects	[104]
	Gold nanozymes conjugated with Amphotericin B	• ↑ Antifungal activity • ↓Toxicity • ↑ Therapeutic outcomes	Chemical synthesis and conjugation	NA	NA	Systemic fungal infections – increased efficacy with lower toxicity	[105]

(*continued on next page*)

Table 3 (*continued*)

Nanotherapeutic system	Formulation	Main advantages	Method of production	Toxicology		Targeted use	Reference
				Human	Environmental		
Silver Nanoparticles	Curcumin-coated silver nanoparticles	• ↑ Antifungal activity • Synergistic effects with fluconazole and itraconazole	Green synthesis using plant extracts	NA	NA	Adjunct therapy for resistant *Candida* spp. – synergistic potential	[107]
	Silver nanoparticles combined with fluconazole	• Synergistic antifungal effect of silver NPs and fluconazole • Effective against fluconazole-resistant fungal infections.	Chemical synthesis	NA	NA	Treatment of azole-resistant infections – synergy and improved outcomes	[108]
Copper Nanoparticles	Copper oxide nanoparticles	• Strong antifungal activity against *Trichophyton* spp.,	Precipitation technique	NA	NA	Topical treatment of dermatophytosis (*Trichophyton* spp.) – strong direct antifungal effect	[110]
	Copper Iodide nanomaterials	• The capacity to cling to and enter fungal cells, after which the cells lyse and die. • Biocompatible	Precipitation technique	NA	NA	Systemic and mucosal infections – potential for cellular internalization and direct fungal lysis	[111]
Iron oxide Nanoparticles	Iron-oxide nanoparticles	• Ability to combat pathogenic *Candida* spp. with antifungal properties.	Precipitation technique	NA	NA	Systemic candidiasis – experimental use against *Candida* spp.	[132]
	Super Paramagnetic Iron Oxide NPs Coated with Itraconazole	• Controlled drug release • Drug tagging • ↑ Antifungal activity	Chemical co-precipitation	NA	NA	Targeted systemic therapy – potential magnetically guided delivery for deep fungal infections	[112]
Titanium dioxide Nanoparticles	Soft denture liner embedded with Titanium dioxide NPs	• ↓ Fungal colonization • ↑ Antifungal activity	Incorporation of NPs into the liner material during fabrication	NA	NA	Oral candidiasis prevention in denture wearers – sustained antifungal surface	[113]
Mycology for Nanoparticle Development	Ketoconazole-coated Zinc oxide NPs	• Eco-friendly synthesis process • ↑ Antifungal activity compared to standard ketoconazole • Effective treatment option for dandruff	Mycosynthesis using green tea extract	NA	NA	Dandruff treatment – enhanced antifungal efficacy for topical scalp application	[115]
	Zinc oxide nanoparticles	• Eco-friendly synthesis process • ↑ Antifungal activity	Mycosynthesis using *Daedalea* sp. mushroom extract.	NA	NA	Broad-spectrum topical antifungal – potential in skin and scalp infections	[124]
	Zinc oxide nanoparticles	• Eco-friendly synthesis process • ↑ Antifungal activity	Mycosynthesis using the culture filtrate of *Aspergillus terreus*	NA	NA	Topical antifungal therapy – eco-friendly formulation targeting superficial mycoses	[125]
	Silver nanoparticles	• Eco-friendly synthesis process • ↑ Antifungal activity in semen candidiasis • Anticancer activity • Minimal toxicity	17 isolated actinomycetes for the biosynthesis of AgNPs	Nontoxic	NA	Male genital candidiasis – a biocompatible alternative with minimal toxicity	[124]
	Silver nanoparticles	• Eco-friendly synthesis process • ↑ Antifungal activity	Mycosynthesis using *Arthroderma fulvum*	NA	NA	Topical treatment – promising against dermatophytes and superficial infections	[127]
	Titanium oxide and silver nanoparticles	• Eco-friendly synthesis process • ↑ Antifungal activity against 12 human pathogenic fungal strains	Mycosynthesis using mycelial extract of Penicillium chrysogenum AUMC 6092	NA	NA	Broad-spectrum topical application – effective against multiple human pathogenic fungi	[128]
	Silver nanoparticles	• ↑ Antifungal therapy against *Trichophyton rubrum* dermatophytosis	Mycosynthesis using *Achillea santolina* extract	NA	NA	Dermatophytosis (*T. rubrum*) – potential for enhanced topical therapy	[129]

notably reduced the level of inflammatory cells and pro-inflammatory substances (like TNF-α, IL-1, IL-6, MOP, and IL-17) [129].

Overall, it was observed that the antifungal activity of mycosynthesized NPs is typically observed against other fungal pathogens, not against the same fungal strain used in their synthesis. This is because the fungus acts primarily as a biological factory, reducing metal ions and stabilizing the NPs through secreted enzymes, proteins, and other biomolecules [130,131]. These capping agents often coat the NPs,

Table 4
Nanotechnology-based antifungal formulations available in the market.

Brand name	Nanotechnology system	Dosage form	Drug	Indication
AmBisome®	Liposomes	Injection	Amphotericin B	Treats severe fungal infections, including cryptococcal meningitis, leishmaniasis, and aspergillosis.
Abelcet®	Lipid Complex	Suspension for injection	Amphotericin B	Used to treat severe fungal infections, especially in patients who cannot tolerate conventional Amphotericin B.
Fungizone®	Conventional nanodispersion	Intravenous infusion	Amphotericin B	Broad-spectrum antifungal for severe infections.
Noxafil®	Nanocrystal formulation	Delayed-release tablets, oral suspension, and injection	Posaconazole	Prophylaxis and treatment of invasive infections caused by *Aspergillus* and *Candida*.
Nanotect®	Topical Nano-Silver Formulation	Topical cream or ointment	Silver NPs	Used topically to treat fungal infections, including those that don't respond to traditional treatments.
Amphotec®	Amphotericin B Cholesteryl Sulfate Complex	Injection	Amphotericin B	Used to treat individuals who are either intolerant of or do not react to traditional antifungal medication for severe systemic fungal infections, such as aspergillosis and other potentially fatal fungal infections.

modulating their surface reactivity and reducing toxicity toward the producing fungus itself. Moreover, the biosynthesizing fungus may possess innate defense mechanisms, such as antioxidant enzymes or stress-response pathways, which help neutralize the reactive species or membrane-disruptive effects caused by the NPs. In contrast, other fungal pathogens, lacking these specific protective mechanisms, are more vulnerable to the antimicrobial effects of the NPs [54]. Therefore, the selective antifungal activity is a result of both the protective role of fungal metabolites during NP synthesis and inter-species variability in susceptibility.

5. Overview of nanotherapeutics for fungal infections: insights and concerns

Nanotherapeutics for fungal infections represent a promising advancement in antifungal therapy, offering improved efficacy, target drug delivery, and low toxicity compared to conventional antifungal treatments. These nanoscale formulations enable the sustained release of antifungal agents, improving therapeutic outcomes. They can also overcome challenges such as poor bioavailability and drug resistance, which are common in traditional antifungal therapies. However, concerns remain regarding the potential cytotoxicity, environmental impact, and the extended safety of nanomaterials over time. The development of biocompatible and biodegradable nanocarriers is essential to address these concerns and ensure the safe and effective use of nanotherapeutics in treating fungal infections. Table 3 presents an overview of various nanotherapeutic systems for fungal infections, highlighting their formulations, advantages, limitations, production methods, scale-up potential, toxicological concerns and targeted use. Some of the nano-based antifungal formulations available in the market are presented in Table 4.

6. Nanoparticle performance and safety in immunocompromised patients: influence of immune status and nanoparticle type

The growing use of NPs in medicine has also raised concerns regarding their biocompatibility and immunogenicity. The clinical success of these systems hinges on a thorough understanding of their biocompatibility and immunological profile. Understanding how various NPs behave in biological environments, particularly how they interact with immune cells and tissues, is essential for their safe and effective clinical translation. Biocompatibility refers to the ability of a material to perform its desired function in the body without eliciting any undesirable local or systemic effects. For NPs, this includes not only their direct toxicity to cells and tissues but also how they influence immune responses. The immune system's reaction to NPs can range from negligible to highly inflammatory, depending on several parameters, including composition, size, shape, surface charge, hydrophobicity, and route of administration. Each class of NPs offers distinct advantages and challenges concerning biocompatibility and immunogenicity. A recent investigation assessed the antifungal efficacy and immunomodulatory potential of itraconazole encapsulated in PLGA NPs, administered via oral and intraperitoneal routes in an *in vivo* model of histoplasmosis. Researchers assessed fungal load, biodistribution, immune modulation, and histopathological changes. The findings revealed a synergistic therapeutic benefit from the NP-encapsulated drug, which not only enhanced infection control but also helped prevent fungal dissemination. Notably, itraconazole-NP treatment significantly decreased pulmonary levels of key cytokines and markers, including IFN-γ, GM-CSF, IL-2, IL-12, IL-6, IL-18, IL-1β, IL-4, IL-5, IL-13, T-bet, and Arg-1. These results highlight the immunomodulatory role of NPs in managing *Histoplasma capsulatum* infection [133]. Lipid-based NPs, including liposomes and solid lipid NPs, are among the most extensively studied for antifungal delivery. Liposomal amphotericin B (AmBisome®) is an FDA-approved and encapsulation of amphotericin B within liposomes that significantly reduces its nephrotoxicity while maintaining or even enhancing its antifungal efficacy [134]. Polymeric NPs can elicit immune responses depending on their surface charge and degradation products. For instance, chitosan's cationic nature facilitates cellular uptake but may also trigger membrane destabilization and mild cytotoxicity. PEGylation and surface functionalization with ligands or sugars can improve biocompatibility and reduce unwanted immune recognition [135].

Metallic NPs require more careful design to balance efficacy with biocompatibility. At high concentrations or prolonged exposure, they may induce oxidative stress, mitochondrial dysfunction, and inflammatory responses in human cells [136]. Gold NPs, on the other hand, are more chemically inert and have been employed as drug carriers or diagnostic agents. When functionalized properly, gold NPs exhibit relatively low immunogenicity, although their accumulation in organs like the liver and spleen raises concerns for long-term systemic use [137]. Future research must continue to focus on optimizing formulations to minimize immune activation while maximizing antifungal activity. Standardized protocols for immunotoxicity testing, alongside regulatory guidance, are essential to accelerate the translation of nanoparticle-based antifungal therapies from bench to bedside. Table 5 presents a summary of the main pharmacokinetic features, therapeutic efficacy, and biocompatibility profiles of selected nanoparticle types in immunocompromised individuals. The table highlights how altered immune responses can influence nanoparticle distribution, accumulation, and systemic toxicity.

7. Conclusion and future perspectives

Fungal infections are becoming more and more important in today's society as a result of both the rising yearly frequencies and the death rate they cause. The therapy of fungal infections has made significant strides in recent years, although they are still challenging to manage. Early detection, ongoing evaluation, and follow-up are necessary for an

Table 5
Comparative characteristics of different nanoparticle types in the context of immunocompromised patients.

Type of Nanoparticle	Main Characteristics	Pharmacokinetics in Immunocompromised Patients	Therapeutic Efficacy	Biocompatibility	Systemic Toxicity	References
Liposomes	• Phospholipid bilayer vesicles • Encapsulate hydrophilic and lipophilic drugs • Modifiable surface (e.g., PEGylation)	• Altered RES clearance • PEGylation enhances half-life • Safer biodistribution in immune-compromised	• High efficacy, especially for antifungal (e.g., liposomal amphotericin B) and anticancer drugs	• Excellent • Mimics biological membranes	• Low • Reduces drug-associated toxicities like nephrotoxicity	[82–84]
Solid Lipid Nanoparticles	• Solid lipid core • Physical stability • Controlled release • Scalable	• May accumulate in the liver/spleen • Offers sustained release • Reduced metabolic burden	• Effective for sustained topical and systemic delivery • Stable in inflammatory environments	• Excellent • Composed of GRAS-status lipids	• Low • Reduced burst release limits toxicity	[67,72]
Polymeric Nanoparticles	• Biodegradable • Controlled release • Tunable size and drug loading • Surface functionalization	• Prolonged drug release • Slower clearance • Less immune response • PEGylation improves PK	• High • Modifiable for targeting	• High • PLGA and PLA are FDA-approved	• Minimal • Degradation into lactic and glycolic acid	[52,54,57, 138]
Metallic Nanoparticles	• High surface area • Intrinsic antimicrobial effects (Ag) • Easy to functionalize	• May be rapidly sequestered by RES • Bioaccumulation risk in liver/spleen	• Moderate to high in topical antimicrobial therapy • Promising for diagnostics	• Variable • Surface coating (e.g., PEG, PVP) improves safety	• Potential cytotoxicity • ROS generation • size- and dose-dependent	[99–101]
Micellar systems	• Amphiphilic block copolymers • Encapsulate hydrophobic drugs; size <100 nm	• Enhanced permeability and retention (EPR) • Improved circulation time	• Effective for poorly soluble drugs • Enhances stability and delivery	• Polymer selection affects compatibility	• Low • Degradation products are usually non-toxic	[95,96]

effective antifungal treatment. Additionally, it is required to optimize the course of treatment, which includes the antifungal drug, the course of treatment, and the mode of administration. Even though many novel antifungal agents have recently been discovered, fungal infections still don't seem to be adequately controlled. This is caused by the toxicity and side effects of antifungal medications, as well as the emergence of resistance to particular antifungal treatments. Conversely, the majority of antifungal drugs have low bioavailability and efficacy due to their physicochemical characteristics. Advances in nanotechnology over the past few decades have opened up more rare chances to treat fungal infections. Nanotechnology may offer solutions to the issues that hinder the effectiveness of antifungal medications. NPs can penetrate cellular membranes and significantly damage cytoplasmic contents, leading to fungal cell dysfunction and death. This action is a key factor in their effective antifungal properties, positioning NPs as a promising solution against fungal infections. The safety profile, clinical efficacy, methods for scaling up production, and the potential role of NPs in antifungal treatments are critical issues that researchers are currently examining. Understanding these factors is essential for the advancement of effective therapies and could revolutionize the way we combat fungal infections. Despite these challenges, there is still a large window of opportunity to develop and discover better therapeutic options. Many drugs remain untested, and a wide variety of nanosystems offer potential as strategies for their incorporation.

Among the variety of NPs, metal NPs have shown considerable promise in the field of antifungal treatment, yet there are relatively few reported studies on their use with antifungal drugs. While this review focuses on providing an overview of current nanoparticle-based antifungal formulations, a systematic comparison of different nanoparticle platforms developed for the same antifungal agent remains an important yet underexplored area. Equally important is the need to analyze how specific physicochemical characteristics of different nanocarrier systems, such as size, surface charge, and material composition, affect their clinical performance in various fungal infection contexts. Establishing clearer correlations between nanoparticle properties and therapeutic outcomes could inform the rational design of more effective and targeted antifungal nanotherapies. Such analysis could offer valuable insights into formulation-specific advantages and should be considered a priority for future research.

An additional promising avenue involves the development and evaluation of untapped drugs and nanosystems, focusing on strategies that can be transposed to an industrial scale and have a diminished toxicological risk to both humans and the environment. Moreover, it is crucial to invest in "green" techniques for synthesizing these nanotherapeutics. Sustainable and eco-friendly techniques for the synthesis of NPs can reduce toxic effects and lead to safer, more scalable antifungal treatments. A multidisciplinary approach and collaboration between academia and industry will be essential to drive innovation and make these advancements a reality.

CRediT authorship contribution statement

Alka Lohani: Writing – review & editing, Writing – original draft, Validation, Supervision, Methodology, Investigation, Conceptualization. **Ritika Saxena:** Writing – original draft, Methodology, Investigation, Conceptualization. **Shahbaz Khan:** Writing – original draft, Methodology, Investigation, Conceptualization. **Ana Figueiras:** Writing – review & editing, Visualization. **Filipa Mascarenhas-Melo:** Writing – review & editing, Writing – original draft, Validation, Supervision, Conceptualization.

Funding

The authors declare that no funds, grants, or other support were received during the preparation of this manuscript.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

The authors acknowledge the support from the Biotechnology Research, Innovation and Design for Health Products (BRIDGES) and Amity Institute of Pharmacy, Amity University Uttar Pradesh, Noida, India.

Data availability

No data was used for the research described in the article.

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