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Current Insights on Antifungal Therapy: Novel Nanotechnology Approaches for Drug Delivery Systems and New Drugs from Natural Sources

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Abstract: The high incidence of fungal infections has become a worrisome public health issue, having been aggravated by an increase in host predisposition factors. Despite all the drugs availableon the market to treat these diseases, their efficiency is questionable, and their side effects cannot be neglected. Bearing that in mind, it is of upmost importance to synthetize new and innovative carriers for these medicines not only to fight emerging fungal infections but also to avert the increasein drug-resistant strains. Although it has revealed to be a difficult job, new nano-based drug delivery systems and even new cellular targets and compounds with antifungal potential are now being investigated. This article will provide a summary of the state-of-the-art strategies that have been studied in order to improve antifungal therapy and reduce adverse effects of conventional drugs. The bidirectional relationship between Mycology and Nanotechnology will be also explained. Furthermore, the article will focus on new compounds from the marine environment which have a proven antifungal potential and may act as platforms to discover drug-like characteristics, highlighting the challenges of the translation of these natural compounds into the clinical pipeline.

Keywords: Nanoparticles; Fungi; Drug Delivery Systems; Marine; Biological Synthesis; Myconanotechnology

1. Introduction

Fungi infections range in severity from small skin infections to systemic infections affecting vital organs [1]. Fungus affects millions of people every year all around the world. More than 1.5 million people are affected by invasive fungal infections, which necessitate extensive treatment and hospitalisation. Candida, Cryptococcus, Aspergillus, and Pneumocystis species, which cause cryptococcosis, candidiasis, aspergillosis, and pneumocystis pneumonia, are the most common causes of disseminated infections [2].

Although superficial fungal infections are rarely fatal, they can cause serious illness if they spread to other regions of the body. They can also infect others, causing secondary bacterial skin infections and a lower quality of life. The three forms of skin mycoses identified by the causative fungal agents are dermatophytosis, yeast infections, and mould infections [1].

Invasive fungal infections are a leading cause of morbidity and mortality in hospitals. These findings are especially concerning for immunocompromised persons who are more vulnerable to opportunistic infections, such as AIDS patients and transplant recipients who have had their immune systems suppressed to prevent organ rejection.

Immunosuppressive therapy includes immunosuppressive therapy for autoimmune patients, immunosuppressive chemotherapy for cancer patients, and immunosuppressive chemotherapy for cancer patients [2,3].

According to their mechanism of action (Table 1), the four main classes of currently available drugs for treating invasive

fungal infections are polyenes, azoles, allylamines, and echinocandins [4]. In terms of range of activity, drug–drug interactions, pharmacokinetics and pharmacodynamics, resistance mechanisms, and chemical toxicity, they all have drawbacks. Furthermore, due to their physical-chemical characteristics, such as their hydrophobic nature, which results in limited water solubility, and selectivity concerns arising from the similarities between fungal and human cells [3,5], there are some limitations in terms of clinical efficacy and efficiency.

Table 1. Targets of each group of antifungals [6,7].

Class	Target (Mechanism of Action)	Antifungal
Azoles	Ergosterol (inhibition of lanosterol 14-α-demethylase)	Imidazoles: Miconazole, Econazole, Ketoconazole, Clotrimazole
		Triazoles: Itraconazole, Fluconazole, Voriconazole
Allylamines	Ergosterol (inhibition of squalene epoxidase)	Terbinafine, Naftifine, Butenafine
Polyenes	Cell membrane (production of ROS)	Amphotericin B
	Ergosterol (inhibition of lanosterol 14-α-demethylase)	Nystatin
Echinocandines	Cell wall (block of β-1,3 glucan synthesis)	Caspofungin, Micafungin, Anidulafungin
Other antifungals	Chelation of polyvalent metal cations	Ciclopirox
	Microtubules (prevention of the formation of the mitotic spindle)	Griseofulvin
	Ergosterol (inhibition of D14 reductase and D7-D8 isomerase)	Amorolfine

Nonetheless, due to the following facts [8,] the design and development of new drug delivery systems, as well as new antifungals, is becoming increasingly necessary.

- As a result of the increased number of patients undergoing long-term antifungal treatment, pharmacokinetics and pharmacodynamics can still be improved in order to minimise medicine usage frequency;
- Invasive mycoses demand further study.

• Antifungal resistance is increasing at an alarming rate across the board [8]

. Existing medications can be paired with new ones to improve outcomes, but new therapy groups with separate mechanisms of action are needed.

Nanotechnology is a relatively recent field of study that has already demonstrated its adaptability, leading in medicinal breakthroughs, faster detection, cellular regeneration, and drug delivery [9,10]. Polymers, lipids, and metals are the three main materials used to make nanoparticles, each of which creates a different form of nanoparticle [11]. Figure 1 depicts the major representations of each of these three distinct types of nanoparticles.

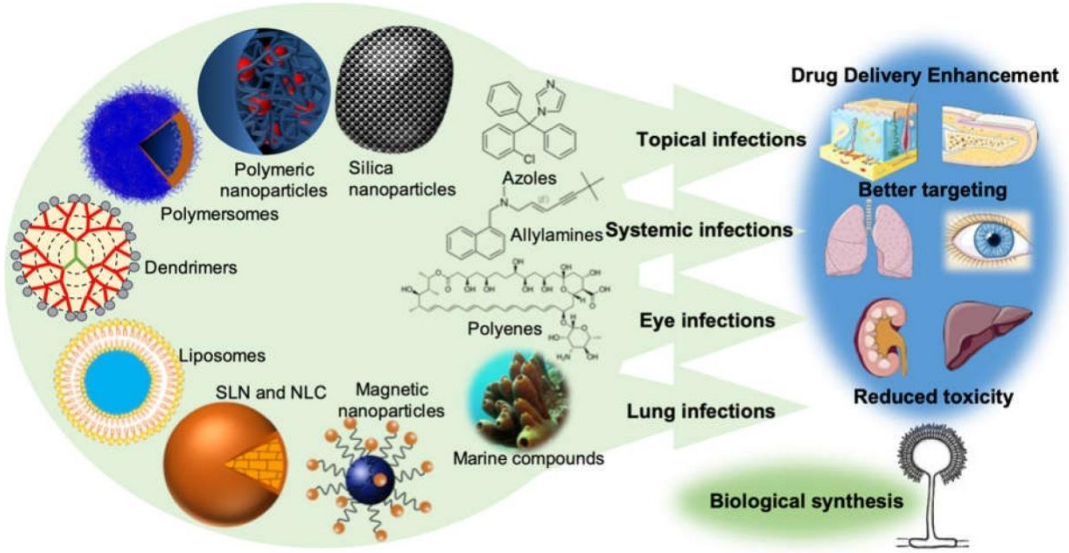

Figure 1. The new drug delivery systems based on nanotechnology that are currently being employed in order to enhance drug delivery, promote a better targeting, and reduce the toxicity of conventional antifungal drugs. It is also important to point out the importance of the production of nanoparticles by fungi (biological synthesis) and the undeniable potential of the sea as a source of new molecules with antifungal activity.

Because of their ability to influence and improve the pharmacokinetic and pharmacodynamic characteristics of medications, nanoparticles have been used in pharmaceutical formulations. This is due to their capacity to improve drug solubility and stability, allow for regulated release, and have biocompatibility with tissues and cells, all of which contribute to improved therapeutic efficiency [11,12]. It may also be delivered intravenously due to its subcellular size, and its large surface area can be modified to personalise drug release, lowering the standard dose and frequency of administration while improving treatment compliance [13,14].

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Table 2. Some of the novel drug delivery systems already developed for each antifungal drug.

Antifungal Drugs	Novel Drug Delivery Systems	Routes of Administration	Dosage Forms	References
Miconazole	Niosomes	Transdermal	Gel	[18]
	SLN	Oral	N.A.	[19]
		Topical	Gel	[20]
	Microemulsion	Topical	N.A.	[21]
	Liposomes	Topical	Gel	[22]
	Nanoemulsion	Topical	N.A.	[23]
	Nanosponges	Vaginal	Gel	[24]
	Transfersomes	Topical	Gel	[25]
Econazole	Microemulsion	Percutaneous	N.A.	[26]
		Topical	Gel	[27]
	SLN	Topical	Gel	[28]
	NLC	Topical	Gel	[29]
	Liposomes	Topical	Gel	[30]
	Ethosomes	Topical	Gel	[31]
	Transethosomes	Transdermal	Gel	[32]
	Nanosponges	Topical	Hydrogel	[33]
	Niosomes	Transdermal	Gel	[34]
	Polymeric micelles	Topical	N.A.	[35]
	Nanoemulsion	Topical	N.A.	[36]
Ketoconazole	SLN/NLC	Topical	Gel	[37]
	Niosomes	Topical	Gel	[38]
	Microemulsion	Oral	N.A.	[39]
	Spanlastics	Ocular	N.A.	[40]
	Dendrimers	Topical	Hydrogel	[41]
	Liposomes	Topical	N.A.	[42]
Clotrimazole	Liposomes	Topical	Gel	[43]
	Nanosponges	Topical	Hydrogel	[44]
	Ethosomes	Topical	Gel	[45]
	Niosomes	Topical	Gel	[46]
	Polymeric emulgel	Topical	Gel	[47]
	Polymeric micelles	Topical	N.A.	[35]
	SLN/NLC	Topical	N.A.	[48]
	Microemulsion	Buccal	Gel	[49]
		Vaginal	Gel	[50]
	Transfersomes	Transdermal/Topical	N.A.	[51]
Itraconazole	Transfersomes	Transdermal	N.A.	[52]
	SLN	Ocular	N.A.	[53]
	NLC	Inhalation	N.A.	[54]
	Niosomes	Topical	N.A.	[55]

Table 2. *Cont.*

Antifungal Drugs	Novel Drug Delivery Systems	Routes of Administration	Dosage Forms	References
	Microemulsion	Transdermal	N.A.	[56]
	Liposomes	Topical	N.A.	[57]

	Polymeri	Oral	N.A.	[58]
		Polymersome	Intravenous	N.A.	[54]
		Spanlastics	Ocular	N.A.	[59]
		Silica nanoparticles	Oral	N.A.	[60]
Fluconazole		Microemulsion	Vaginal	Gel	[61]
		Niosomes	Ocular	Gel	[62]
		Liposomes	Intravitral	N.A.	[63]
		SLN	Topical	Gel	[64]
		NLC	Oral	N.A.	[65]
		Microsponges	Topical	Gel	[66]
		Ethosomes	Topical	Gel	[67]
		Spanlastics	Ocular	N.A.	[68]
		Polymeric amphiphilogel	Topical	Gel	[69]
		Polymeric micelles	Topical	N.A.	[35]
Voriconazole		Microemulsion	Ocular	N.A.	[70]
		Polymeric nanoparticles	Ocular	N.A.	[71]
			Pulmonar	N.A.	[72]
		SLN	Topical	Gel	[73]
		Transethosome	Topical	N.A.	[74]
		Ethosome	Topical	N.A.	[75]
Terbinafine		Liposomes	Topical	Gel	[76]
		SLN	Topical	N.A.	[77]
		Transfersomes	Topical	N.A.	[78]
		Spanlastics	Transungual	N.A.	[79]
		Polymeric chitosan nanoparticles	Topical	Hydrogel	[80]
Naftifine		Microemulsion	Topical	N.A.	[81]
		Niosomes	Topical	Gel	[82]
Butenafine		Microemulsion	Topical	Hydrogel	[83]
Amphotericin B		Liposomes	Intravenous	N.A.	[84]
		SLN/NLC	Oral	N.A.	[85]
			Topical	N.A.	[86]
		Magnetic nanoparticles	Nasal instilation	N.A.	[87]
		Nanoemulsion	Topical	N.A.	[88]
		Polymeric nanoparticles	Intravenous	N.A.	[89]
			Oral	N.A.	[90]

Table 2. *Cont.*

Antifungal Drugs	Novel Drug Delivery Systems	Routes of Administration	Dosage Forms	References
	Polymersomes	Oral	N.A.	[91,92]
	Transfersomes	Topical	N.A.	[93]
	Micelles	Intravenous	N.A.	[94]
	Silica nanoparticles	Intravenous	N.A.	[95]
Nystatin	SLN	Topical	N.A.	[96]
	Nanoemulsion	Topical	N.A.	[97]
	Liposomes	Intravenous	N.A.	[98]
	Niosomes	Parenteral	N.A.	[99]
Griseofulvin	Niosomes	Oral	N.A.	[100]
Ciclopirox	Niosomes	Topical	Gel	[101]
Caspofungin, Micafungin, Anidulafungin, Amorolfine	No nano-tech studies yet released			

N.A.: the dosage form is not mentioned in the reference cited; SLN: Solid Lipid Nanoparticles; NLC: NanostructuredLipid Carriers.

The overwhelming body of published evidence, on the other hand, raises doubt on the efficacy and human safety of these novel medications. They usually lack controlled clinical studies when compared to recognised treatments, and the recommended delivery systems are either impossible to implement or unreasonably expensive. The converse is true in some circumstances, and some drugs have the potential to become first-line therapies [102]. As a result of widespread use of antifungal drugs and limited treatment options, fungi have developed resistance mechanisms such as efflux pump protein overexpression and biofilm formation. These procedures may result in medication modifications and subexpression, as well as a decrease in the medicine's effective concentration. Metabolic bypass and targeting [6]. As a result, lowering antifungal resistance may be viewed as a precondition for developing antifungal infection treatment techniques [2,103].

Nanoparticles can bypass antifungal resistance systems in a variety of ways, despite the growth of antifungal resistance mechanisms:

• The emergence of resistance is a once-in-a-lifetime event (for example, due to the chemical characteristics of nitric oxide, chitosan, and metallic nanoparticles, as well as the simultaneous application of numerous mechanisms)

- • Because numerous gene alterations in the same cell are uncommon, antimicrobial resistance can be decreased by combining antimicrobial medicines into a single nanoparticle. Some nanoparticles, such as liposomes and dendrimers, can overcome the resistance mechanisms of decreased absorption and rapid efflux of drug from the microbial cell by encapsulating antifungal drugs in chitosan or silver nanoparticles, reducing the likelihood of drug resistance [104,106].
- Liposomes can quickly merge with a microbial cell's plasma membrane and release a large amount of energy
- • drug concentration in plasma membrane or cytoplasm, avoiding resistance's reduced absorption mechanism. As a result, there are fewer transmembrane pumps in use, resulting in improved drug efflux and faster drug delivery. Dendrimers, on the other hand, are branching molecules with positively charged quaternary ammonium compounds on their surfaces, which bind to negatively charged microbial cell envelopes and allow more fluid to pass through. As a result, there is a possibility that additional dendrimers will enter the system.
- The microbial cell's cytoplasmic contents migrate to the cell's outside, and the cell's membrane disintegrates. Dendrimers can thus get beyond drug resistance's poor absorption mechanism [107]. Reactive oxygen species produced by other nanoparticles, such as silica-based nitric oxide nanoparticles and zinc oxide nanoparticles, kill or prevent biofilm formation [108,109].

• Nanoparticles have been used to target antifungal medications, allowing high concentrations of drug to be administered locally while keeping the total amount of drug delivered low. This high local dose can kill the pathogenic fungus before it develops resistance, treat the illness, and decrease the likelihood of side effects in the patient [104].

However, it's critical that research focuses not only on building these systems, but also on overcoming the most significant commercialization barriers, such as nanoparticle physical instability, drug loading capacity, cytotoxicity/immunogenicity, and so on. Furthermore, due to the intricacy of the equations, as well as the high production and standardisation costs. Furthermore, due to the difficulties in attaining the therapeutic range required, in vivo research is limited. This is because certain circumstances are required for drug release, nanoparticle aggregation and precipitation, and accumulation in non-target tissues.

Nanotechnology and Mycology

Mycology and nanotechnology have a long-standing symbiotic relationship. To describe the dynamic interaction between mycology and nanotechnology, the term "myconanotechnology" [110] was coined. According to positive in vitro studies, nanotechnology has the potential to improve the potency and effectiveness of existing antifungals while lowering toxicity and cost, preventing anticipated degradation, increasing circulation time and enhancing pharmacokinetics, and improving drug targeting. in addition to in vivo data [5]. Furthermore, several metallic nanoparticles have been used against human and plant pathogenic fungus due to their natural antifungal properties, and a wide spectrum of fungi can biosynthesize nanoelemental particles [110].

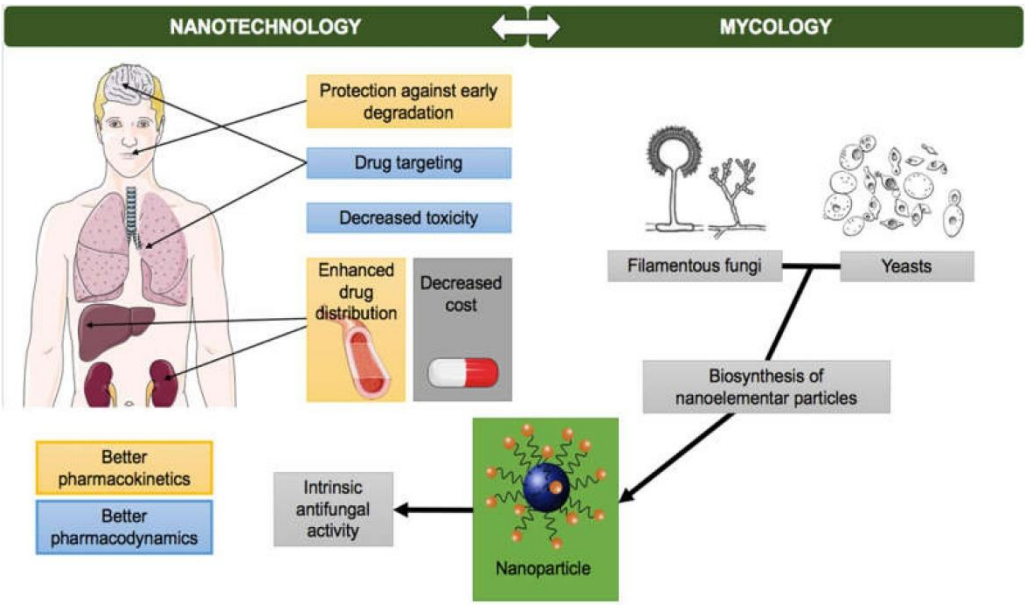

Figure 2. Bidirectional relationship of Nanoparticles and Mycology: nanotechnology has proven to be useful in improving antifungals pharmacokinetics and pharmacodynamics and many fungi have beenused to biologically synthetize nanoparticles.

Antifungal Potential of Nanoparticles

2. Metallic nanoparticles have been used to eradicate pathogenic fungus in humans and plants due to their natural antibacterial properties [110]. Although the precise mechanisms behind this activity are unknown, three main pathways have been proposed: (1) direct nanoparticle uptake, (2) indirect nanoparticle activity via reactive oxygen species (ROS), and (3) nanoparticle buildup resulting in cell wall/membrane damage [111]. Antimicrobial activity is almost always the outcome of combining these pathways [112]. Dissolving processes are caused by nanoparticles' electrochemical potential [113]. In the microbial fluid or culture media, this leads them to split into ions. These ions have the potential to jam microtubules on the inside or outside, causing them to malfunction. Outside of microtubules, nanoparticles form layers that obstruct the cellular respiratory chain and destroy microtubules [111].
3. The electrical charge of a nanoparticle affects its interaction with the drug it carries. Silver nanoparticles were the first to display antibacterial activity due to the electrostatic mechanism. The mechanism of antibacterial activity is assumed to be electrostatic contact between bacteria's negatively charged cellular membrane and nanoparticles' positively charged membrane [111]. Ag+ uncouples adenosine triphosphate synthesis because it has a strong affinity for thiol groups in cysteine in respiratory chain enzymes (ATP). Ag+ binds to a wide range of proteins. As a result of this transfer, protons leak out of the respiratory chain, lowering the proton motive force. Furthermore, Ag+ inhibits phosphate uptake, leading to an increase in intracellular phosphate outflow [113].
4. At dosages of 1–7 g/mL, silver nanoparticles were antifungal against clinical isolates and ATCC Trichophyton mentagrophytes strains, with a Candida albicans MIC of 25 g/mL [114]. Silver nanoparticles show antifungal efficacy against Aspergillus niger when coupled with simvastatin, reducing spore germination and biofilm growth, resulting in an additive and synergistic effect that improves treatment efficiency Simvastatin, an ergosterol production inhibitor (see Table 1), allows nanoparticles to pass through the fungal cell membrane [115].
5. When exposed to the acidic environment of lysosomes or when interacting with oxidative organelles, metals present in nanoparticles can act as catalysts, reacting with biomolecules and causing the direct creation of free radicals [112,113].
6. Byproducts such as superoxide anions, hydroxyl radicals, and hydrogen peroxide are formed when a chemical is exposed to an oxygenated atmosphere. Biomolecules interact with one another on a daily basis. As a result, they may disrupt the biological system's ability to detoxify reactive intermediates and repair damage, as well as reactive species [111]. Excessive ROS production can result in oxidative stress and lipid peroxidation, resulting in membrane degradation, mitochondrial

dysfunction, and DNA damage. Cytotoxicity studies on nanoparticles whose antibacterial activity is connected to the formation of reactive oxygen species (ROS) should be done to minimise interactions and unfavourable responses in individuals [111].

7. Because of their biocompatibility, biodegradability, and mucoadhesivity, chitosan and its chemical derivates have been used as building blocks for drug delivery nanoformulations, with benefits such as in situ gelling, mucoadhesive properties, and the ability to prolong the release of low-molecular-weight compounds to macromolecular drugs [116]. Antimicrobial efficacy of chitosan nanoparticles against Candida infections has been demonstrated [1]. This antimicrobial activity is caused by positively charged amino groups reacting with negatively charged groups of lipopolysaccharides and proteins on the surface of microbial cells, resulting in cell membrane breakdown, according to the literature and previous study. Nanoparticles can bind to DNA molecules, preventing the production of mRNA and proteins.
8. Chitosan inhibits the action of growth-promoting enzymes in fungi, reducing sporulation and spore germination [1,117].
9. Antifungal activity of zinc oxide nanoparticles (ZnONPs) has been demonstrated against dermatophytes as well as other pathogenic fungi such as Candida and Aspergillus [1]. Meanwhile, antifungal medications were found to enhance the inhibitory action of ZnONPs, potentially lowering overuse, toxicity, and improving antifungal activity [118]. Additionally, these nanoparticles have the potential to eventually replace conventional cosmetic preservatives [119].

10. In addition to the nanoparticles mentioned above, dendrimers have antifungal properties, allowing for complex therapies in which dendrimers act as both a drug carrier and an adjuvant component of the dose form [41].*Synthesis of Nanoparticles by Fungi*

Due to their metal tolerance and ability to bioaccumulate metals, fungi play an essential role in the biological synthesis of metallic nanoparticles (Table 3) [10]. They can be used to make nanomaterials for nanosystem coatings and to move nanomaterials about the nanosystem. As a result, innovative solvent and chemical waste reduction solutions that are environmentally friendly are being developed. Biosynthesis technologies are more convenient to use and provide more exact control over nanoparticle size and shape. In addition to fungus, other species are used to generate. Bacteria, plants, or plant extracts, for example, are nanoparticles [110]. Fungi produce more enzymes than bacteria, resulting in a better yield in the production of nanoparticles. Furthermore, in the lab and on a large scale, their growth is easier to manage [110].

Table 3. Some examples of metallic nanoparticles produced by fungi and their method of synthesis [10,120].

Fungal Species	**Nanoparticles Type**	**Method of Synthesis**
Phoma sp.	Silver	Extracellular
Fusarium oxysporum	Gold; Magnetite	Extracellular
Verticillium sp.	Silver	Intracellular
Aspergillus fumigatus	Silver	Extracellular
Aspergillus niger	Silver	Extracellular
Fusarium semitectum	Silver	Extracellular
Trichoderma asperellum	Silver	Extracellular
Phaenerochaete chrysosporium	Silver	Extracellular

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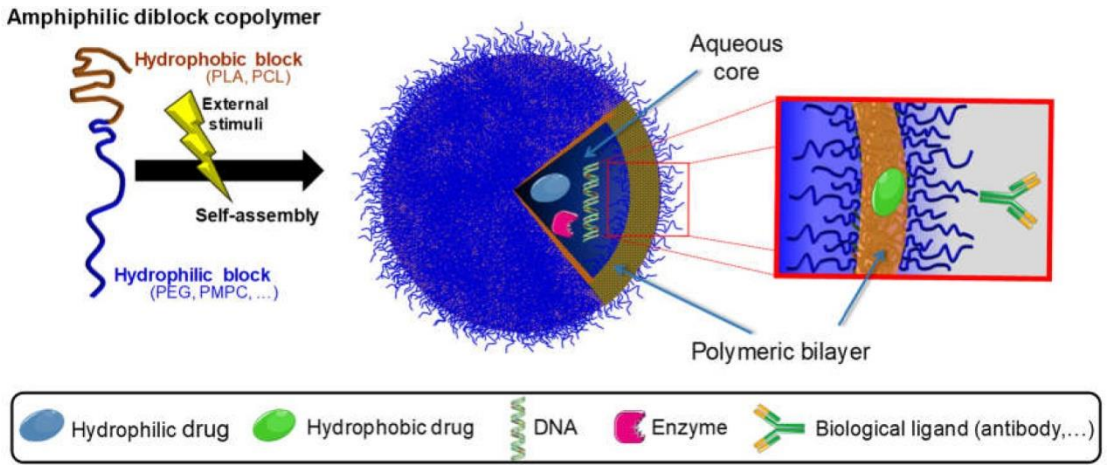

Figure 3. Schematic representation of the formation of a polymersome and its versatile properties. Polymersomes are generally self-assembled from block copolymers, presenting a unique structure that is able to encapsulate different biological molecules.

A study team produced an amphotericin B-loaded polymersome using the solvent injection method and (PEG)3-PLA as a co-polymer. This formulation was compared to two commercial formulations (Fungizone® and Ambisome®) in terms of release, molecular organisation of amphotericin B, and hemolysis. More in vivo testing may be required because the results were comparable to commercial versions.

Dendrimers [161–163] are three-dimensional homogeneous polymeric nanoarchitectures having a central core (a single atom or group of atoms), generations (ejected repeating unit building blocks), and a dense surface coating of water-soluble functional groups (terminal group). The components are added to the central core by a series of chemical reactions, and the gaps between the voids aid in the encapsulation of active molecules within the dendritic structure.

The efficiency of nucleic acid complexation or drug entrapment is determined by the terminal functional groups [164]. They are particularly appropriate as drug delivery vehicles due to their tiny and homogenous size structure (2–10 nm in diameter), high degree of branching, and water solubility.

Despite the fact that dendrimers come in a variety of forms and sizes, polyamidoamine (PAMAM) and polypropylene imine (PPI) dendrimers are the most commonly utilised antifungal medicines [163]. Drug solubility, in vitro release, and antifungal activity have all been demonstrated to improve with PAMAM dendrimers containing ketoconazole [41]. A type of nanoparticle is metal nanoparticles.

Antifungal drugs can be vectorized using metallic nanoparticles such as gold, silver, and magnetic nanoparticles.

Chemically, physically, and therapeutically, metallic nanoparticles can be created. Biological synthesis is becoming more popular [166] due to a number of unfavourable side effects associated with chemical synthesis, such as toxic chemical particle absorption on nanoparticle surfaces [10].

In immunochemical research, gold nanoparticles are used to identify protein interactions, and DNA fingerprinting is utilised to detect DNA in a sample. Streptomycin, gentamicin, and neomycin are aminoglycosides that they can recognise [10].

Because of their antibacterial qualities, silver nanoparticles are the most effective antibacterial agents against bacteria, viruses, and other eukaryotic organisms. The most often utilised chemicals are antimicrobial agents, which are employed in the textile sector, water treatment, solar protection, and other purposes [10].

Superparamagnetic iron oxide nanoparticles with high magnetic susceptibility include magnetite (Fe3O4), hematite (-Fe2O3), and maghemite (-Fe2O3) (-Fe2O3)

This type of nanoparticle has received special attention by virtue of their capacity to be influenced by magnetic fields, therefore being easily directed and released in a specific site of the organism [10,167]. Superparamagnetic iron oxide

nanoparticles present other unique properties, for instance:

low toxicity, biocompatibility, potent magnetic targeting capacity, and chemical inertia, thus, they have many biomedical applications, for example in the cancer research field, steam cells, tissue repair, drug release, genetic therapy, DNA analysis, and clinical diagnosis through magnetic resonance [10,167].

The reactivity of superparamagnetic iron oxide nanoparticles to an external magnetic field has improved, making them more suitable as drug carriers [5]. These Fe3O4 magnetic nanoparticles must be coated with DMSA (meso-2,3-dimercaptosuccinic acid) to avoid cytotoxic effects; this is an important procedure not only for increasing cell internalisation and biocompatibility, but also for transporting active molecules to the nanoparticle's surface, which is required for drug delivery [168].

Other Methods of Drug Administration

Niosomes are non-phospholipid vesicles made up of non-ionic surfactants that work as drug depots in the body, delivering medication slowly and gently through bilayers. In topical therapy, they can also increase skin permeability, shield the active substance from side effects, and improve chemical stability [169].

The use of niosomes to encapsulate nistatin resulted in a parenteral formulation that was both safe and efficacious. This formulation reduced nephrotoxicity and hepatotoxicity in female Wistar rats while also exhibiting good anti-Candida albicans action and a higher drug level in key organs [99].

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These systems can enter the cell through tighter fenestrations without squashing the vesicles since they are exceedingly adaptive [138].

Ketoconazole-loaded spanlastics were first developed for ocular drug administration [40], followed by terbinafine hydrochloride-loaded spanlastics for onychomycosis treatment [79].

Microemulsions are colloidal carriers made composed of a liquid dispersion of oil and water with a surfactant interfacial layer that stabilises it. As a result, a variety of lipophilicity medications are now available [170]. They could be employed as colloidal carriers because of their transparency, ease of production, and long-term stability [171].

Microemulsions are highly beneficial for delivering medicines through the stratum corneum because the oils and surfactants in them can act as skin penetration enhancers [170,172]. They're also fascinating candidates for oral delivery of pharmaceuticals that aren't particularly water soluble because they can improve medicine solubilization.

When terbinafine hydrochloride, a moderately water-soluble medication, was blended into a microemulsion, it showed improved solubility, dissolving rate, and efficacy [170,171]. Voriconazole microemulsions significantly increased antifungal effectiveness and medication skin penetration in Candida albicans [173].

Nanoemulsions have been examined as colloidal carriers to improve the efficacy and acceptance of a number of antifungal medications because they are more thermodynamically and kinetically stable than emulsions. Nanoemulsions are effective drug delivery vectors because of their ability to dissolve large amounts of low solubility medications, their compatibility, their ability to shield drugs from enzymatic degradation and hydrolysis, and their ability to permeate deeper epidermal layers [143,174].

In terms of antifungal efficacy, a topical nystatin nanoemulsion was found to be more effective than nystatin alone [97].

[95,175] Nanoparticles have the ability to store large amounts of medicines.

- Because of their biodegradability, low toxicity, ability to activate macrophages, and simplicity of synthetization and customisation, silicon dioxide nanoparticles have been examined as drug carriers to improve the antibacterial efficacy of a variety of therapies. The ability to load huge amounts of medications onto these nanoparticles is its key advantage [95,175].

- There are four basic forms of silica nanoparticles, however in some circumstances, their antifungal potential has yet to be investigated:

• Anti-biofilm characteristics of nitric oxide-silica nanoparticles [108];

• Silver or copper-modified silica nanoparticles [177,178], which occur as a result of cell membrane and DNA damage, thiol group interactions with enzymes, or the generation of hydrogen peroxide.

Because of its homogeneous mesoporous tunnels and narrow pore size distribution, mesoporous silica nanoparticles have emerged as the most appealing options for a variety of therapeutic reasons, including antifungal therapy.

They're biocompatible and chemically stable, as well as fast soluble and degradable. These features enable a higher dose of medicine to be administered while reducing particle-induced toxicity [95,180].

According to one study, mice with Candida albicans-induced candidiasis were given amphotericin B-functionalized silica nanoparticles, while mice with Candida albicans-induced candidiasis were given officinal amphotericin B. The first group's survival rates had significantly improved [95]. According to recent studies [177,178], silica nanoparticles coated with quaternary ammonium surfactants had a stronger antifungicidal and antifungistatic effect on Candida albicans than colloidal silver.

Itraconazole, a water-insoluble antifungal medication, was mixed with mesoporous silica particles to increase its oral bioavailability. Because it improves the oral bioavailability of extremely low water-soluble medicines, ordered mesoporous silica has been identified as a candidate carrier [60].

Because metals quickly concentrate in soil and then enter the food chain, combining Ag+ ions with silica lowers metal production and toxicity [176]. As a result, silica nanoparticles have been investigated as a safe and effective alternative to fungicides for treating tomato early blight in agriculture [180].

11. Hidden Potential and Challenges of Natural Antifungal Compounds

Between 1981 and 2014, 32 new chemical entities for treating fungal infections were approved: one was derived from a biological source (interferon gamma-n1), a peptide created through a biotechnological procedure; three were derived from a semisynthetically modified natural product (anidulafungin, caspofungin, and micafungin); and 25 were completely synthetic (fluconazole, itraconazole, ketoconazole).
During this time, synthetic antifungal drugs accounted for almost 90% of all antifungal prescriptions dispensed. Natural elements are still in limited supply in modern medicine, and 1950s medications like amphotericin and griseofulvin are still widely used [181].

Pennyroyal, or Mentha pulegium L., is a flowering herb that is antitussive, carminative, and antibacterial. It was employed in the production of nanoparticles. This plant has been used to make antifungal stable colloidal silver nanoparticles against Candida albicans [182].

The marine environment, on the other hand, offers a promising and underutilised platform for the discovery of novel chemicals [183]. Antifungal action has been demonstrated in vitro and in vivo in natural products isolated from a number of marine taxa, including microorganisms (bacteria and fungus), invertebrates (sponges, corals, and sea cucumbers), and marine algae.

Table 4. Overview of antifungal natural compounds produced by marine organisms [183,184].

Marine Organism	Source Organism	Type of Compound	Compound Name	Spectrum of Activity
Bacteria (30% of total)	*Bacillus licheniformis*	Glycolipid	Ledoglucomide C, Iedoglycolipid	*Aspergillus niger, Rhizoctonia solani, Botrytis cinerea, and Colletotrichum acutatum, Candida albicans*
	Bacillus subtilis	Lipopeptide	Gageopeptides A-D	*R. solani, P. capsici, B. cinerea, C. acutatum*
	Actinoalloteichus sp. NPS702	Macrolide	Neomaclafungins A-I	*Trichophyton mentagrophytes*
	Streptomyces sp.	Peptide	Mohangamide A	*C. albicans*
	Bacillus marinus	Macrolide	Macrolactins T and B	*Pyricularia oryzae, A. solani*
	Tolypothrix	Lipopeptide	Hassallidin A	*A. fumigatus and C. albicans*
	Chondromyces pediculatus	Peptide	Pedein A	*Rhodotorula glutinis*
Fungi (15% of total)	*Stagonosporopsis cucurbitacearum*	Alkaloid	Didymellamide A	*C. neoformans, C. albicans, C. glabrata*
	Aspergillus sclerotiorum	Peptide	Sclerotide B	*C. albicans*
	Penicillium bilaiae MA-267	Sesquiterpene	Penicibilaenes A and B	*C. gloeosporioides*

Table 4. *Cont.*

Marine Organism	Source Organism	Type of Compound	Compound Name	Spectrum of Activity
Sponge (35%)	*Theonella swinhoei*	Peptide	Theonegramide, Theonellamide G, Cyclolithistide A	*C. albicans*
	Halichondria cylindrata	Peptide	Halicylindramide D and E	*Mortierella ramanniana*
	Siliquariaspongia mirabilis,	Peptide	Theopapuamide A; B and C	*C. albicans*
	Jaspis johnstoni *Theonella swinhoei*	Peptide	Jasplakinolide	*C. albicans, C. pseidrotropicalis, C. parapsilosis*
	Monanchora arbuscular	Alkaloid	Batzelladine L	*A. flavus*
	Xestospongia muta	Furan	Mutafuran D	*Cryptococcus neoformans var.grubii*
Corals (5%)	*Clavelina oblonga*	Alkanol	(2S,3R)-2-aminododecan-3-ol	*C. albicans ATCC 10231, C. glabrata*
Sea cucumbers (6%)	*Stichopus variegates*	Triterpene glycoside	Variegatuside D	*C. albicans, C. pseudo- tropicalis, C. parapsilosis, and M. gypseum*
Algae (9%)	*Caulerpa racemos*	Xylene	Caulerprenylol B	*T. rubrum*

Sponge antimicrobial compounds with unusual properties have long piqued the interest of pharmacologists, chemists, and biologists. These sessile colonial organisms must produce chemicals to protect themselves, communicate, and regulate their biological activity [184].

Because of their vast variety of bioactivity, peptides offer a lot of potential as medications. In the sponge genus Theonella, antibacterial, antifungal, and anti-HIV peptides have been discovered. Some of these peptides show antifungal activity that is superior to that of other commercial formulations, as evidenced by their diffusion zone in the agar diffusion method [184].

There is no evidence that marine-based formulations are useful against fungal infections, despite clinical trials [183].

Theopapuamide A, a cyclic depsipeptide (a peptide containing one or more amides substituted by an ester group), is found in theonella swinhoei, a Papua New Guinea sponge [183]. This molecule's isolation, structural elucidation, and stereochemical characterisation have all been well documented [185]. It stops Candida albicans wild strains and amphotericin B-resistant strains from growing [186]. It also exhibits anti-HIV activity due to the 3,4-dimethyl-L-glutamine residue in its chemical makeup [183,184].

In addition to the marine environment, medicinal plants and alternative substances such as secondary metabolites, phenolic compounds, essential oils, and extracts have all been researched. Some plant extracts have antifungal properties against Candida species, whereas others have antifungal properties against filamentous fungus (Asteraceae, Euphorbiaceae, Rubiaceae, and Solanaceae). Even if the technique is simple, biological activity found through plant extract screening may not be repeatable in the lab. Chemical alterations in crude extracts, extraction solvent degradation, and chemical composition modifications according on growth stage are all possibilities.

Some essential oil compounds, like eugenol, camphor, curcumin, geraniol, and linalol, are antifungal, whereas others, like clemateol and citral, aren't. Propolis has been shown to be resistant against Candida spp., dermatophytes, and onychomycosis. When bees eat resinous substances present in flowers, they produce it. Paracoccidioidomycosis and Fusarium spp. infections have been shown to benefit from ajoene, a garlic-derived compound. Saponins, alkaloids, flavonoids, coumarins, xanthones, lignans, and tannins all have antifungal action [187].

In reality, there is a growing awareness of existing compound libraries' limited structural diversity, as well as the numerous benefits of using natural compounds, which have a vast chemical diversity and great biological activity. These chemical compounds can also be utilised as platforms.

[188] to create new molecules with drug-like characteristics As a result, natural antifungal compounds are a feasible alternative to currently available antifungals, and encapsulating them in nanocarriers represents a significant advance in nanoformulation as well as a more sustainable method due to the use of marine resources [183].

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[188] to create new molecules with drug-like characteristics As a result, natural antifungal compounds are a feasible alternative to currently available antifungals, and encapsulating them in nanocarriers represents a significant advance in nanoformulation as well as a more sustainable method due to the use of marine resources [183].

Natural commodities, despite being a valuable and finite resource, face a number of challenges in a variety of industries, placing their inclusion in the therapeutic pipeline in peril.

Natural compounds are scarce, demanding time-consuming, costly, and difficult extraction and purifying procedures, particularly for small quantities of extract [190]. Furthermore, there is no standard technique, and research organisations are continually revising established techniques, resulting in results that are inconsistent and inaccurate [187].

Because the chemical may be obtained from an endangered species, overexploitation could result in habitat damage [188], environmental concerns are a major roadblock to medicine discovery and development.

12. Regulatory criteria for natural-constituent-containing substances (medicines, nutraceuticals, and cosmeceuticals) vary by region and are overseen by several organisations [188].

13. Ongoing Clinical Trials on Myconanotechnology

A number of pharmaceutical companies and writers have done clinical trials on antifungal nanomedicines. Only a few of these nanomedicines have achieved FDA approval for clinical use, despite breakthroughs in the application of nanotechnology in pharmaceutical research. Clinical studies have a variety of disadvantages, including the time it takes to complete them and the difficulty in finding and analysing data on prior nanomedicine trends. The active ingredient in the majority of currently available nanomedicines is amphotericin-B, which is found in lipid-based formulations such as Amphotec® (Three Rivers Pharmaceuticals, approved in 1992), Abelcet® (Sigma-Tau, approved in 1995), and Ambisome® (Gilead Sciences, approved in 1997) [191,192]. Econazole (Pevaryllipogel®) is also available in a liposomal form [193]. A list of ongoing clinical studies can be found in the table below.

Table 5. Some examples of ongoing clinical trials on myconanotechnology [194].

Trade Name/Sponsor	ClinicalTrials.gov Identifier	Antifungal	Nanoformulation	Clinical Phase	Disease
Sara Botros, Minia University	NCT04110834	Itraconazole	Nanoemulsion gel	II	*Tinea versicolor*
Sara Botros, Minia University	NCT04110860	Voriconazol	Nanoemulsion gel	II	*Tinea versicolor*
Matinas BioPharma	NCT02971007	Amphotericin B	Cochleate lipid-crystal nanoparticle	II	Vulvovaginal candidiasis
Matinas BioPharma	NCT02629419	Amphotericin B	Cochleate lipid-crystal nanoparticle	II	Mucocutaneous candidiasis

Table 5. *Cont.*

Trade Name/Sponsor	ClinicalTrials.gov Identifier	Antifungal	Nanoformulation	Clinical Phase	Disease
Ahmed Abdellatif, Al-Azhar University	NCT03752424	-	Silver nanoparticle gel	I	Mycosis
Mona Badran, Cairo University	NCT03666195	-	Titanium dioxide nanoparticles	Recruiting	Candidiasis
Rasha Hamed, Assiut University	NCT04431804	-	Silver nanoparticle	Recruiting	Invasive aspergillosis
Celtic Pharma Development Services	NCT01145807	Terbinafine (TDT067)	Transfersome	III	Onychomycosis

14. Conclusions

All of these characteristics could lead to lower doses, more pleasurable regimens, better absorption, and fewer serious side effects.

Magnetic nanoparticles that can directly limit fungal proliferation and ultradeformable vesicles (transethosomes) that are easy to scale up have recently attracted interest due to their unique features.

c) biocompatible PAMAM dendrimers, d) polymersomes capable of transporting both hydrophobic and hydrophilic molecules while responding to environmental stimuli, and e) mesoporous silica nanoparticles with high drug loading capacity.

Natural substances, such as chitosan, are clearly less harmful to the environment and provide nanotechnological solutions that benefit both the environment and pharmacokinetics. Despite their obvious potential, little is understood about sea-derived compounds' methods of action and toxicity.

Nanoparticles have been pushed as viable treatments due to their capacity to target specific fungi-infested regions and their potential to improve the pharmacological efficacy of drugs by optimising their physiochemical properties. Dealing with the administrative process has so become more pleasurable. All of these qualities may result in lower doses, more enjoyable regimens, improved absorption, and fewer major side effects.

Magnetic nanoparticles that can directly influence fungal growth and ultradeformable vesicles (transethosomes) that are easy to scale up have recently received attention due to their unique features.

c) biocompatible PAMAM dendrimers, d) polymersomes that can retain both hydrophobic and hydrophilic molecules while also responding to environmental signals, and e) mesoporous silica nanoparticles that can hold a huge number of drugs Future antifungal medicines will very certainly be based on these five types of nanoparticles, given existing knowledge of how to use nanoparticles for various purposes (for instance, as anticancer agents). These novel nanotechnological systems should be able to overcome the aforementioned concerns as well as provide a significant improvement over standard antifungal therapies in terms of antifungal resistance. They should also be able to be mass-produced industrially, with a wide range of activities, an emphasis on increasing potency, and low host toxicity.

Interdisciplinary collaboration may be the key to nanomedicine and nanotechnology's long-term success, as well as the efficient use of natural therapeutic resources. Complementary knowledge from physicists, health-care researchers, and clinical specialists can be combined. to develop nanoparticles that are more effective, practical, and safe This would boost patient satisfaction while also increasing the likelihood of commercial investment and, eventually, a reconsideration of the current antifungal arsenal.

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