The Promising Role Of Nanotechnology In Dermatophytosis Treatment In The Era Of Antifungal Resistance and AI: A Narrative Review

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ABSTRACT

Dermatophytosis is a common superficial infection that causes an inflammatory response in humans. In immunocompromised patients, the disease becomes more severe. In recent years, there have been increased challenges in treating dermatophyte infections. These include antifungal resistance to available antifungal drugs, side effects, and lengthy treatment processes. Moreover, the emergence of terbinafine-resistant Trichophyton indotinea isolates worldwide has made dermatophytosis treatment more difficult. These obstacles highlight the need for novel treatment strategies. Although several approaches have been investigated, such as drug repurposing, lasers, and novel antifungals, we mainly focus on the role of nanotechnologies in the development of potential treatments for dermatophytosis. The nanformulation of antifungal drugs like terbinafine, fluconazole, and griseofulvin shows promising results and leads to improved antifungal drug activity. Moreover, nanoformulations of metals, such as copper, silver, and gold, have yielded encouraging results in improving treatment outcomes. Furthermore, nanoformulations of essential oils alone or combined with metals, such as silver, demonstrate better antifungal activity and improve penetration for onychomycosis treatment. Nanotechnology is a promising field for the development of novel antifungal treatments and improving the efficacy of available antifungal drugs in the era of antifungal resistance. However, more clinical trials and Further investigations are needed to guarantee and evaluate the side effects and toxicity of these nanomaterials. Artificial Intelligence (AI) can accelerate and optimize nanoformulated drug development, but model optimization and further research based on integrating AI into the drug development of nanobased antifungal treatment are needed.

Keywords: **Dermatophytosis, nanoformulation, antifungal resistance, Liposome, drug delivery, *Trichophyton indotinea, Artificial intelligence***

1. *INTRODUCTION*

Dermatophytosis is a prevalent superficial fungal infection that affects people worldwide (1). Dermatophytes are keratophilic filamentous fungal species that cause dermatophytosis infections in different parts of the body, which are enriched with keratin (1-3). Dermatophytosis can become more severe in immunocomprised patients with more severe manifestations (4-6). The rise in prevalence of dermatophytosis and antifungal resistance to the limited number of available drugs underscores the need to develop novel treatment approaches. The discovery and development of novel antifungals is time-consuming and costly, so other approaches should be considered (2, 3, 7, 8). Nanoformulation of the antifungal drugs is one of the promising

approaches for developing antifungal treatments for dermatophytosis(9-14). The nanoformulation improves the drug's penetration, bioavailability, and maintenance of slow and targeted drug release, and it can reduce the drug side effects and improve the antifungal efficacy (14-18). Some studies have investigated the nanoformulation of antifungal drugs in recent years, which have shown promising results in dermatophytosis treatment. Fluconazole, griseofulvin, and terbinafine have been nanoformulated, and the nanoformulated terbinafine has shown promising efficacy and safety in treating dermatophytosis (9, 13, 16, 19). Nanoformulated terbinafine showed efficacy and safety in a phase 1/2 clinical trial for onycomycosis treatment (12). These results raise hope for treating dermatophytosis with reformulated antifungal drugs and improving the treatment of onycomycosis and tinea pedis. However, there is some consideration in terms of producing nanoformulated drugs in safety and efficacy (20, 21). Other challenges are the costly production process and regulatory barriers, and an appropriate manufacturing process (17, 21). Moreover, the development of these drugs requires more clinical trials to optimize drug penetration and evaluate the toxicity profiles (17).

2. *Dermatophytosis:*

Dermatophytosis is a worldwide superficial fungal infection that has gained more attention since the rising incidence and antifungal resistance among dermatophyte species (1, 3, 7, 22). Dermatophytosis can pose an economic and psychological burden on society (23). Dermatophytes can be classified based on different features, such as host specificity (zeophilic, geophilic, and anthrophilic), and it has seven species (*Trichophyton, Epidermophyton, Nannizzia, Paraphyton, Lophophyton, Microsporum,* and *Arthroderma*) in this group that can cause infection in humans and different animals (24).

Different parts of the body that are enriched with keratins can be affected by dermatophyte species, and the disease manifestations are called ‘ringworm’ due to the structure of the lesion (25). The misdiagnosis of dermatophytosis can complicate the treatment process (26). The dermatophytosis can lead to deep mycosis and become invasive in high-risk groups such as immunocomprised individuals (4-6). The dermatophytosis is a prevalent infection, and appropriate identification and treatment are crucial.

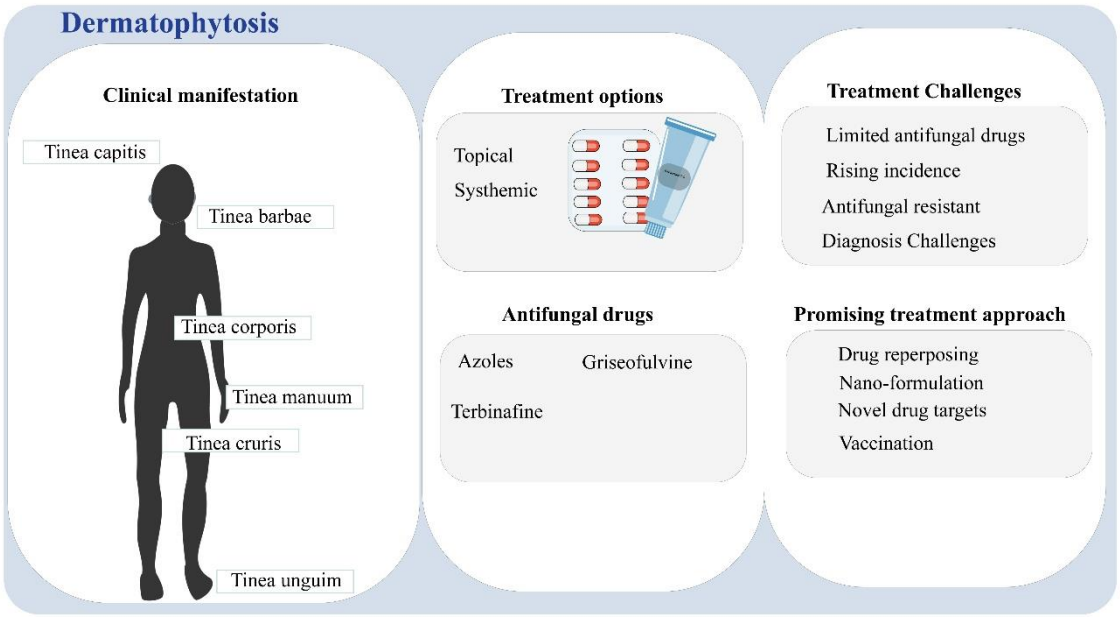

Figure 1*The Dermatophytosis treatment, treatment challenges, and promising approach for dermatophytosis treatment*

3. Conventional Treatment For Dermatophytosis:

The treatment for dermatophyosis is mainly based on the site and the severity of the infection. In mild to moderate cases, topical antifungal drugs are usually preferred; however, in more severe manifestations, systemic antifungal alone or in combination with antifungal will be prescribed (27). The systemic treatment comprises allylamine, azole, griseofulvin, and echinocandins. The terbinafine is the most preferred allylamine, and topical treatments include amorolfine, ciclopirox, and luliconazole (2). During these years, the novel antifungal groups were approved, such as Ravuconazole and Oteseconazole, which have shown promising results for dermatophytosis treatment. Conventional treatments for dermatophytosis face challenges, which are discussed in the next section.

Table 1 The dermatophytosis conventional antifungal drugs

Antifungal drugs	Classes	Disadvantages/Advantages	Refrence
Terbinafine	allylamine	Rising resistant isolates, possible side effects	(28)

Itraconazole	Azole	Rising resistance isolates, possible side effects, variable bioavailability based on host factors, and foods taken	(29)
Fluconazole	Azole	Rising resistance isolates, possible side effects	(27)
Efinaconazole	Azole	Lower resistance rate, better penetration for onycomycosis treatment	(30, 31)
Sertaconazole	Azole	Side effects Improving drug delivery*	(32)
Posaconazole	Azole	Side effects Promising performance on dermatophytosis treatment*	(33)
Oteseconazole	Azole	Should not be utilized by women of reproductive potential	(34)
Griseofulvin		Forbidden during pregnancy, Interaction with other drugs (Warfarin,…), Increase the rate of the resistant isolates	(35)
Tavaborole	oxaboroles	Side effects Good results on onycomycosis treatment, limited side effects*	(36)
SUBA-ITZ	Azole	Improving the bioavailibiltity*	(37)

SUBA-ITZ: Super Bioavailable Itraconazole, *: the advantages of novel antifungal were listed

4. Challenges In Dermatophytosis Treatment:

There are several obstacles to successful dermatophytosis treatment (3). The limited antifungal drugs with side effects, the antifungal resistance to available drugs, and the long-term treatment with the risk of recurrence(1, 3, 38). The Trichophyton indotinea is the emerging antifungal resistance species that has been detected in the world, which can be resistant to terbinafine, sometimes to itraconazole, and also multidrug resistant has been reported (8, 39, 40). The challenges in dermatophytosis treatment highlight the need for a novel treatment approach (1, 7). Poor antifungal penetration and solubility are other problems related to topical antifungal drugs, especially in the treatment of nail infections, which are more challenging (41-43). The topical treatments have some limitations, such as poor penetration through the skin layer that affects their efficacy, and nanoformulations of conventional drugs have gained attention since their super penetration, targeted treatment, controlled drug release, and tolerance for superficial infection treatments (9-

11, 15). Although there are several promising ways for dermatophytosis treatment, such as drug repurposing, antifungal drug combination, and vaccination, we discuss the role of nanotechnology in dermatophytosis treatment.

5. Nanotechnology In Dermatophytosis Treatments:

The challenges in dermatophyte treatments underscore the necessity of finding novel or complementary treatment approaches (44). The nanotechnologies have shown promising results that raise hope for the future of dermatophytes treatment with nanoformulation of conventional antifungal drugs and compounds, such as ionic and essential oils with antifungal activity (14, 16, 19, 45, 46). These drugs have shown promising results in dermatophytosis treatment by improving the efficacy and penetration of antidermatophyte drugs.

5.1 Different Types of Nanoformulation:

Various nanoformulations have shown promising results for fungal infections (10). The nanostructure delivery systems can be classified based on several factors, such as size and component, and each of them has its advantages and limitations (18, 47-49). The list of common nanocarriers for drug delivery is shown in Table 2. In categories, a nanostructured material can be divided into three subclasses (polymer-based, Lipid-based, and non-polymeric-based) (50) . The liposomal, SNEDDS (self-nano-emulsifying hydrogel), ionic nanomaterial, Transethosomal, nanoemulsion, nanohydrogel, and niosomal have been utilized as a nanodelivery system for antifungal drugs and essential oils.

Table 2 Advantages and disadvantages of different nanocarriers for delivering drugs

Nanocarrier	Advantages	Disadvantages
Liposome	Appropriate for loading hydrophilic and hydrophobic drugs Simple formulation Bioavailability Non-toxic	Low encapsulation efficiency Poor stability
SLN	Appropriate for lipophilic substances Lower toxicity Increase penetration through skin layers	Low drug loading efficiency High manufacturing costs

Niosome	High drug enterapment rate Biodegradable Increase drug penetration Low toxicity	High production cost Poor solubility
Nanoemulsion	Controlled drug release Non-toxic Appropriate for loading hydrophilic and hydrophobic drugs	Poor stability High manufacturing costs Poor solubility A large amount of non-toxic surfactant is needed
Dendrimers	Biocompatible Soluble in water Encapsulation of different biomolecules High drug encapsulation efficiency	The possibility of toxicity and immunogenicity Rapid clearance Non-biodegradable
Polymeric Micelles	Biocompatibility Increase drug solubility Lower toxicity	Low encapsulation efficacy Appropriate only for lipophilic drugs
Inorganic nanoparticles	Stability Small size and flexibility	Toxicity and side effects concerns Nanoparticle aggregation
Transethosome	Increase transdermal drug delivery Controlled drug release Improve vioavailibity	Possible skin reactions
Carbon Nanotubes	Sustainable drug release Encapsulation of different biomolecules	Non-biodegradable Low solubility in water
SNEDDS	Improve drug penetration Improve drug bioavailability Simple preparation method High drug loading efficiency	Expenxive manufacturing process Toxicity Susceptible to environmental factors High concentration of surfactant

Different nanodrug delivery systems have their limitation and advantages, and choosing the carrier depends on the research goal and research facilities.

5.2 Advantages Of Nanotechnology And Dermatophytosis Treatment:

Nanotechnology by nanostructure delivery systems can improve the treatment of superficial infections. Nanotechnology can lead to targeted treatment, improve the drug solubility, and control the drug release at

the site of infection while minimizing the safety concerns (51, 52). Several nanotechnology-based carriers have been utilized to nanoformulate the antifungal drugs to improve their efficacy and the drug penetration (1).

Table 3 The nano formulation advances in dermatophytosis treatment

Nanomaterial	Dermatophytes species	Year	Result	Refrence
Griseofulvin nanoparticles+zinc oxide	*Trichophyton mentagrophytes Trichophyton verrucosum*	2022	GF-ZnO NPs showed better inhibitory effect than griseofulvin alone	(9)
Griseofulvin zinc nanohybrid emulsion	*Trichophyton rubrum*	2024	Better antifungal activity and dermatophytes treatment	(46)
Liposomal Fluconazole	*Trichophyton interdigitale*, *T. rubrum*, *Epidermophyton floccosum*	2020	The liposomal fluconazole performs better than conventional fluconazole	(16)
Terbinafine-Loaded Nanoemulgel (TH-NE)	____	2023	Enhance the drug penetration with optimized safety and efficacy in the mouse model.	(19)
BB2603 (Nano-formulated Terbinafine with the polymer polyhexamethylene biguanide (PHMB)	Tinea pedis and onychomycosis	2022	In a Phase 1/2 clinical trial as a topical treatment of Tinea pedis and onychomycosis.	(12)

LiposomalFluconazole and liposomal terbinafine	*Trichophyton mentagrophytes in a guinea pig*	2021	Nano-formulation leads to better treatment outcomes in an animal model.	(13)
F-OEO, F-OEO/bioAgNPs	*Onycomycosis*	2024	Nail Lacquer containing essential oils and silver nanoparticles has shown promising results in treating an ex vivo model of onycomycosis	(45)
Green niosomal piperlongumine	*Trichophyton indotinea in the guinea pig*	2025	The topical treatment showed better efficacy and safety, and is effective on resistant T.indotinea	(53)
Silver and gold nanoparticles	*Microsporum, Trichophyton isolates*	2018	Safe and effective treatment in treatment of dermatophytosis in the skin cell line.	(14)
Copper oxide nanoparticles	*Microsporum canis*	2025	Promising *in vitro* results for inhibiting *Microsporum canis* isolates.	(54)
Berberine Hydrochloride-loaded Transethosomal	*Trichophyton rubrum*	2024	The nanostructured formulation improves the antifungal activity and penetration of Berberine Hydrochloride *in vitro* and *in vivo.*	(55)
Gallic acid loaded in SNEDDS	Onycomycosis *Trichophyton mentagrophytes*		Good results on onycomycosis treatment and can be utilized instead of conventional drugs.	(56)

F-OEO Formulation- oregano essential oil, bioAgNPs: Biogenic Silver Nanoparticles, SNEDDS: self-nano-emulsifying hydrogel

5.2.1 The Advantages Over Conventional Drugs:

The nanoformulation can bring several advantages in dermatophytosis treatment by enhancing the drug penetration, improving drug bioavailability, decreasing the side effects, and targeted and controlled drug release(9, 10, 20, 57). The advantages of nanotechnology over conventional drugs were illustrated in Figure 2. These advantages improve the treatment efficacy and safety that underscore the role of nanotechnology in the future of dermatophytosis treatment(1, 50, 54).

Moreover design and development of novel antifungal drugs is costly and time-consuming, and the development of novel formulations of antifungal drugs can be one of the promising ways in the era of antifungal resistance (13, 15, 16, 18, 46, 54, 56, 58). The nanoformulated fluconazole and terbinafine lead to improving and accelerating the improvement of dermatophytosis clinical manifestation in comparison to conventional antifungal drugs(12, 13, 19).

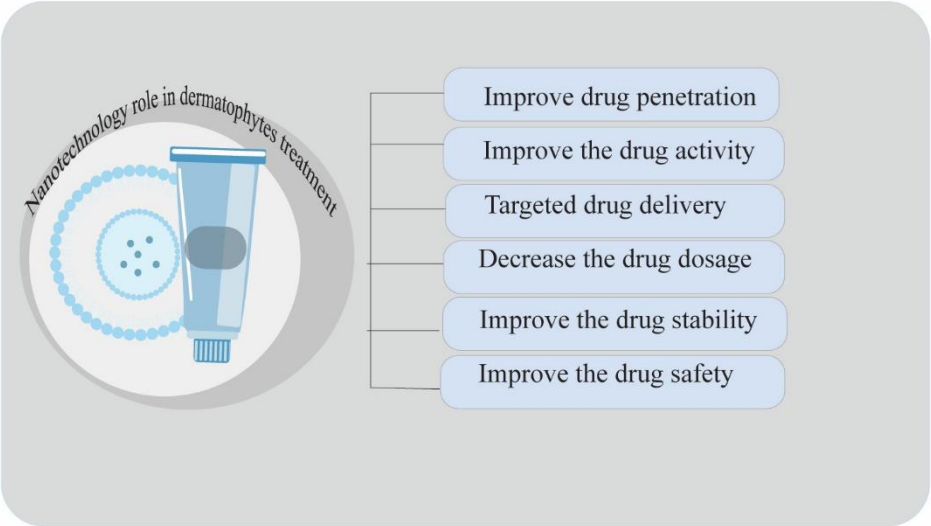

Figure 2 The advantages of nanotechnology over conventional drugs

6. Challenges In Nanotechnology Application In Treatment:

Besides the advantages of nanotechnology in antifungal drug nanoformulation, several challenges hinder the development of these nanoformulated drugs (59, 60). Each drug formulation should be approved by the Food and Drug Administration (FDA) or the European Medicines Agency (EMA) to ensure the safety and efficacy(17, 20, 61, 62). Most available studies on nanoformulated antifungal drugs for dermatophytosis lack investigation of the toxicity profile and evaluation of possible side effects. Furthermore, limited clinical

trials, manufacturing limitations, and the high cost of production can hinder the development of nanoformulated antifungal drugs (20, 63). The nanodrug cytotoxicity evaluation is one of the most concerning challenges, since available *in vivo* tests can examine short-term side effects, not chronic side effects (20, 60). The nanoparticles' toxicity relies on several factors, such as size, charge, and the route of administration (20). The optimal toxicity test should simulate the human body's physicochemical environment(64). Moreover, there is no standard toxicity test for nanodrugs, which makes the evaluation more challenging (20). Large-scale production is another major concern in nanodrug development, and several factors should be optimized during the process (PH, temperature, drug concentration,..), which can affect the nanodrug efficacy and safety (20).

All in all, there is a need to investigate the safety of these nanostructured drugs and to control the dosage and release (20, 57). Although the nanoformulation led to an increase in the drug's penetration, the side effects and the disposal of these nanomaterials should be evaluated to improve the safety (57, 62, 65). Although nanotechnologies are a promising field in the development of novel antifungal formulations, some areas need investigation. We refer to AI as a promising way to optimize the design and development process.

7. Role Of AI In Nanotechnology Drug Development:

Artificial intelligence (AI) integration in drug design in recent years has brought a lot of advantages in drug development (66). Moreover, AI can optimize and accelerate the nanoformulated drug development. AI advances can be utilized in this field to improve the nanostructure formulation, improve the drug release rate, and optimize the drug loading (67). The AI models can process large datasets and investigate hidden patterns between different datasets to build a predictive model (68). AI algorithms such as machine learning (ML) and deep learning (DL) can optimise nanodrug formulation by predicting the formulation stability and performance under different physiological environments. This leads to designing more controlled and slow drug release in an optimized concentration (69, 70) AI algorithms can be utilized to predict nanoformulated drug features such as the toxicity, stability, and solubility. Moreover, AI can be utilized to improve other features of nanoparticles that can affect their efficacy and safety (66). By improving the nanoformulated drugs, the efficacy and targeted drug release can be optimized, which leads to decreasing the toxicity (66, 71). These advantages can lead to designing a more effective and safe nanodelivery system.

The use of AI can pave the way for personalized medicine by analyzing the genetic profile of the patient and optimizing dosage optimization (66). Besides all the advantages, utilizing AI has some challenges, such as data quality, data size, ethical concerns, and interpretation of the AI models which can be challenging (72) . These challenges hinder the utilization of AI models in nanotechnology. The more studies that utilize AI algorithms in the design of nanoformulated antidermatophytes drugs can accelerate the design and optimize the safety and efficacy of the drugs.

8. Conclusion:

Dermatophytosis, a superficial fungal infection, is a common disease worldwide. The treatment of dermatophytosis is becoming increasingly challenging because of the rise in recurrent infections and antifungal resistance to available antifungal drugs. Moreover, topical antifungal penetration is another challenge that makes treatment more demanding. Several promising strategies for dermatophytosis treatment such as drug repurposing, vaccines, and the design of novel antifungal drugs. Here, we explore the promising role of nanoformulation and nanotechnology in dermatophytosis treatment. Some studies have utilized different nanocarriers for antifungal agents such as terbinafine, fluconazole, and griseofulvin. These studies have shown promising results in decreasing the disease manifestation in animal models and somewhat lower MIC for nanoformulated antifungal drugs. Furthermore, there are several studies that evaluate the antifungal efficacy of irons such as silver and gold in nanoformulation that illustrate promising antidermatophytosis activity. Moreover, essential oils and compounds that are effective against fungal infections, but have low penetration by nanoformulation, and their penetration and treatment efficacy. Although nanotechnology has shown promise in drug development, some obstacles require more attention. These challenges include toxicity and safety concerns, regulatory approval challenges, and the manufacturing process, which make the clinical application of nanotechnology-based drugs more challenging. AI can optimize the nanoformulated drug feature and predict the efficacy of these drugs in a physicochemical environment and improve their safety and efficacy. The more studies that utilize AI algorithms in the design of nanoformulated antidermatophytes drugs can accelerate the design and optimize the safety and efficacy of the drugs.

More focused and standardized protocols for toxicity evaluation, integrating AI in design and development process, and the development of cost-effective and appropriate manufacturing processes for large-scale production can bring hope for the future of nanodeveloped antidermatophytosis treatments.

Author contribution

R.S.A. conceived, designed the study, wrote the manuscript, and illustrated the study figure by Adobe Illustrator.

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Conflict of interest

The authors declare they have no conflict of interest.

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