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Onychomycosis Novel Treatment Updates : An Overview

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ABSTRACT

Onychomycosis, a chronic fungal infection of the nail, poses a significant challenge in terms of treatment. However, recent advancements in novel technologies and formulations have improved treatment outcomes. This overview provides an update on the latest developments in onychomycosis treatment, including topical therapies, laser and photodynamic therapies, nanoparticle-mediated delivery, transungual drug delivery systems, prodrug approaches and chemical modifications. These innovative approaches enhance drug efficacy, improve nail penetration, and offer alternative treatment options. This abstract highlights the progress made in the field and provides a glimpse into the future of onychomycosis treatment.

INTRODUCTION

"Onychomycosis" originated from the Greek phrases "onyx" (meaning nail) and "mykes" (meaning fungus). It is a chronic fungal infection of the fingernails or toenails brought on by non-dermatophytic moulds, yeast, or dermatophytes, which is the most prevalent nail condition. There are many predisposing factors for onychomycosis like diabetes, HIV virus infection, obesity, smoking, age, etc. The majority of cases of onychomycosis occur in adults, while it can also strike youngsters. Common clinical symptoms include nail discoloration, subungual hyperkeratosis, onycholysis, nail plate cracking, and nail plate disintegration. An estimated 19% of people worldwide are thought to be affected by it, and it causes around half of all nail infections. It was once mostly thought to be a cosmetic problem, but recently, because to its persistence and difficulty in curing due to relapses, attention has been focused on it [1,2].

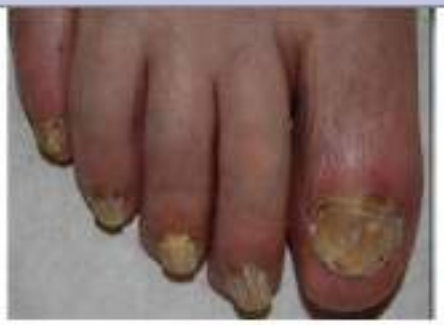
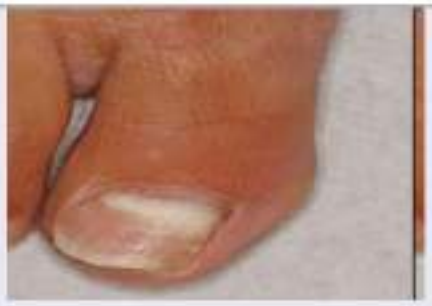
In addition to being difficult to cure, onychomycosis has a high likelihood of treatment failure and recurrence. Since the nails are tightly packed with 80% keratin and disulphide linkages, the nail plate serves as the strongest barrier against drug penetration. While topical therapy is associated with fewer side effects and patient compliance, its main drawback is its poor penetration into the rigid structure of the nails. In contrast, oral therapy is associated with adverse effects, including hepatotoxicity, drug interactions, and a longer treatment duration. A large number of studies conducted in the past few years have demonstrated the use of topical therapy in conjunction with physical and chemical procedures; however,

these approaches come with their own set of problems and are not even commercially available [3]. Therefore, the development of innovative medicines that enhance patient compliance and yield effective outcomes is imperative. The treatment strategies and several novel therapies for onychomycosis are outlined in this review.

Clinical manifestation

Onychomycosis typically manifests as a yellow-brown or white nail discolouration. There have also been reports of violaceous, green, and black discolorations on the nail plate. Subungual hyperkeratosis, onycholysis (the separation of the nail from the nail bed) and onychauxis (the thickening of the nail plate) are additional clinical symptoms [4]. The location of the infection in respect to the nail structure allows for the classification of onychomycosis into distinct subgroups (Table 1)

Table 1 : Classification of Onychomycosis

Type	Description	Figure
Distal lateral subungual onychomycosis (DLSO)	characterized by a thick, opaque nail plate, thickening and hardening of the nail bed beneath the nail (nail bed hyperkeratosis), and separation of the nail from the bed underneath (onycholysis).	
Endonyx onychomycosis (EO)	nail plate shows a milky white staining and there is no onycholysis.	
WSO (white superficial onychomycosis)	Little patches of white that appear powdery or speckled appear on the nail plate's surface. The nail becomes hard and easily breaks off.	
Proximal subungual onychomycosis (PSO)	White spots, streaking, or staining (leukonychia) around the nail fold may spread to deeper layers of the nail	

DIAGNOSIS

The diagnostic gold standard remains the isolation of fungus in the laboratory, as clinical symptoms alone cannot usually provide a reliable diagnosis. Periodic acid-Schiff (PAS) stains and other fungal stains, along with nail clippings delivered in formalin for histology, are sensitive tests for onychomycosis. Fungal culture is a useful tool for pathogen identification, but it has a low sensitivity and can produce contaminated findings that are falsely positive. Although false positives are frequently observed, polymerase chain reaction (PCR) testing is a highly sensitive and good diagnostic

Table 2 : Different diagnostic technique for Onychomycosis

Diagnostic technique	Sensitivity	Specificity	Benefits	Shortcomings
KOH testing	61% (44-100%)	95% (75-100%)	Inexpensive; easy to conduct	Cannot identify pathogen subtypes; accuracy depends on assessor's skill
Fungal culture	56% (29-82%)	99% (83-100%)	Can recognize pathogen subtype	Low sensitivity; may require 1 month for results
Histopathology	84% (61-93%)	89% (44-100%)	Conventional mycological test; most sensitive	Expensive
Nail dermoscopy	Jagged onycholytic edge with spikes: 86.4%, 100% longitudinal striae: 25%, 86.5% ruins aspect: 59.1%% homogenous opacity: 34.1%	Jagged onycholytic edge with spikes: 58.3%, 100% longitudinal striae: 83.3%,100%ruins aspect: 91.7% homogenous opacity: 83.3%	Bedside tool; non-invasive;quick results; inexpensive	-
Reflectance confocal microscopy	52.9%, 79.5%, 91.67%	57.58%, 81%, 90.2%	Bedside tool; non-invasive	Modest sensitivity and specificity; not suitable for thick nails
PCR	85% 87.3% 100% pandermatophyte assay: 90% panfungal assay: 47%	94%94.3%100% pandermatophyte and pangungal assays: NR	Can categorize pathogen; high sensitivity; lesser specimen needed to produce results	Assays still under development ; risk of false positives
Flow cytometry and mass spectrometry	NR	NR	Can hypothetically recognize subtype of disease-causing agent	Under investigation
Artificial intelligence	70.2%, 82.7%-96%	72.7%, 69.3-96.7%	Inexpensive; patients themselves can cause for highly doubtful nails.	Under investigation: updating in dataset and considering technique of distribution are needed to practitioners; not confirmatory techniques

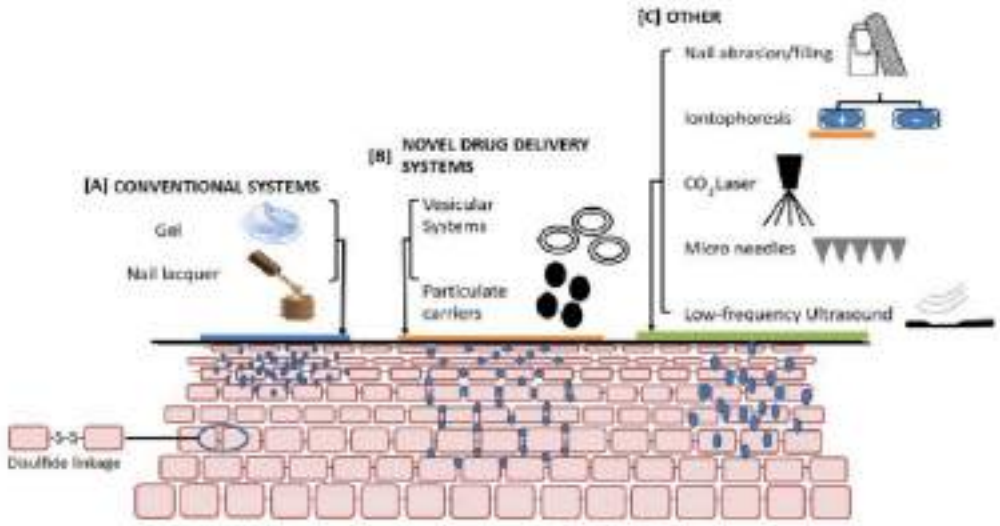


Figure 3. Various system/technologies for transungual drug delivery: (A) Conventional systems comprising (i) Gels and (ii) Nail Lacquer; (B) Novel drug delivery systems comprising (i) Vesicular systems and (ii) Nanoparticulate systems; and (C) other approaches (i) Filing, (ii) Iontophoresis, (iii) CO2 Lasers, (iv) Micro needles and (v) Low-frequency Ultrasound

Figure 1 : Various systems / technologies for transungual drug delivery systems

technique. Molecular diagnostics can help choose the right antifungal treatment, since mixed onychomycosis and non-dermatophyte infections are becoming more common [5]. The various diagnostic techniques are listed in the table 2.

TREATMENT

Oral treatment, topical treatment, or combination therapy are the three primary pharmacologic approaches to onychomycosis treatment. Treatment for onychomycosis is influenced by the clinical type of the condition, the quantity of affected nails, and the degree of nail involvement.

ORAL TREATMENT

Because oral antifungal therapy requires fewer courses of treatment and has a greater cure rate than topical antifungal therapy, it is regarded as the gold standard for treating onychomycosis in both adults and children. Oral treatment is readily available and has a relatively cheap cost. Although oral antifungals show very good results, their prolonged treatment duration, low absorption, hepatotoxic effects, and medication interactions have caused a significant halt in their market share [5].

TOPICAL TREATMENT

Transungual drug delivery is a technique that delivers medication through the nails to treat a variety of nail conditions and achieve the desired drug distribution. There are numerous nail lacquers and remedies on the market right now for the treatment of nail problems. The application of topical therapy is effective in treating superficial onychomycosis and yields encouraging outcomes when combined with oral antifungals. Nonetheless, the main obstacle to medication administration is the nail plate's low penetration. A variety of physical and chemical techniques are employed to improve efficacy and get around the obstacles of nail delivery because topical medications used to treat onychomycosis have a poor cure rate and a high relapse rate [6]. This is shown in the Figure 1.

Strategies to improve transungual drug delivery

The various strategies to improve transungual drug delivery are shown in the Figure 2.

Chemical Strategies

The chemical enhancers target the polar, hydrogen, peptide, and disulfide bond cleavage of the nail plate in order to maintain its structural integrity. The chemical enhancer can be put to the nail's surface before or after formulation. By hydrolyzing the nail plate's keratin layer, keratinolytic enzymes like papain change the barrier and improve drug penetration. The permeability of the medication increased when nail clippings were soaked in a salicylic acid solution for ten days after being cultured for one day in a papain solution. Sulfites function by rupturing the disulfide bond found in the nails, increasing drug flow and

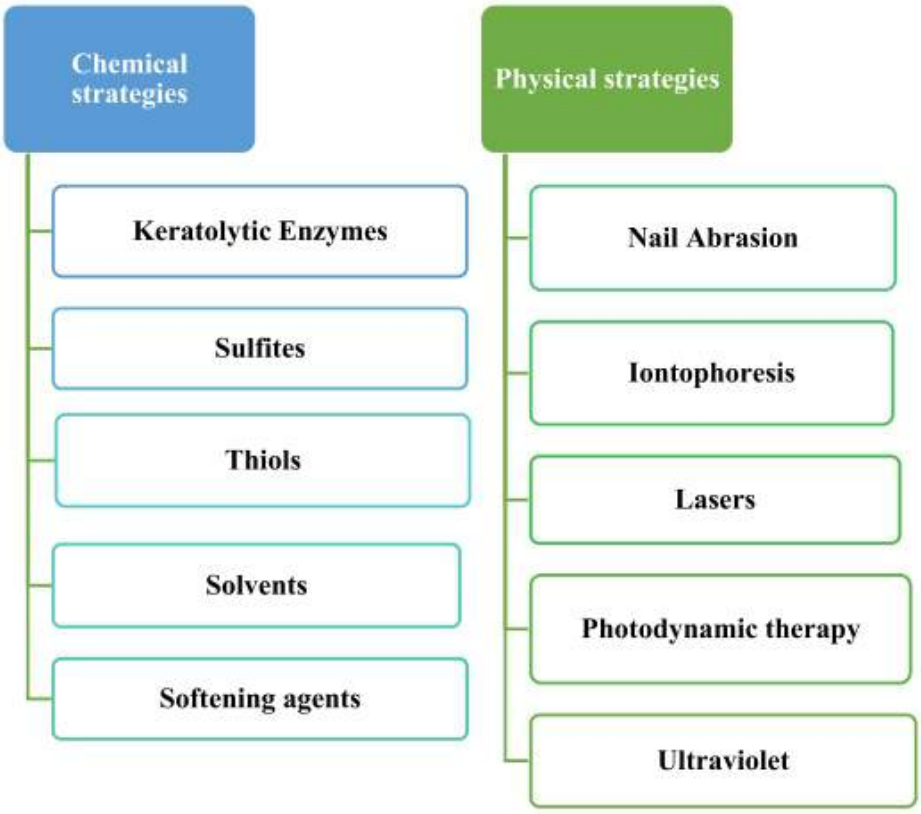


Figure 2 : Strategies to improve transungual drug delivery

lowering the nail plate barrier. When employed as an enhancer, sodium sulfite increased 5,6-carboxyflurosceine's penetrability. Thiols work by lowering the disulfides in the keratin of the nail plate, such as thioglycolic acid, pyrithone, mercaptoethanol, and N acetyl-L-cysteine. Since this reduction is irreversible, nails can either be included in the formulation or pretreated with these enhancers prior to formulation administration. Similarly, thioglycolic acid was used as an enhancer to boost caffeine flow. The drug's penetration was enhanced when voriconazole nail lacquer was mixed with 5% thioglycolic acid. The transungual permeability is also improved by the use of several solvents during the formulation's production. When used as a solvent, dimethyl sulfoxide (DMSO) alters the concentration of lipids in the nails and causes alterations to the keratin's structure. Water as a solvent causes the nails to swell and become hydrated, which has an impact on the structure of the nails as well. Water cannot be regarded as a significant factor for improving penetration, though, as evidenced by the fact that drug penetration in another trial did not increase with increasing water content. When used in the formulation (20%), the epidermal enhancer ethanol was unable to affect the drug's flow. Salicylic acid and urea belong to the category of nail softening agents. They cause keratin denaturation and solubilization, which breaks and destroys the nail's structure. This breaks down the disulphides and encourages the medication to penetrate. When N-(2-mercaptopropionyl) and urea were combined, there was an increase in permeability. [7].

Physical strategies

The term "physical strategies" describes a variety of methods or approaches that entail making bodily gestures or movements in order to accomplish a goal. The use of physical techniques for topical and transdermal medication delivery has been extensively studied[8] . The various physical strategies are listed in Table 3.

Challenges in Transungual Delivery

In earlier times, fungal infections in nails were treated with surgery, which was a severe and unpleasant procedure. As an alternative, systemic treatment with several antifungal agents, such as fluconazole, itraconazole, terbinafine, griseofulvin, etc., can be used to cure onychomycosis. Systemic therapy does, however, come with drawbacks, including long-term medication administration, drug

Table 3 : Physical strategies

Physical method	Specifications	Advantages	Disadvantages
Nail abrasion	Well established method, It involves abrading the surface of the nail with the help of sandpaper which leads to nail plate thinning and slowing of fungicidal activity of onychomycosis.	Patient complaint, not expensive, less time consuming.	Pain, Success rate is low.
Iontophoresis	technique is non-invasive and works by applying a mild electric field to help molecules move across bio-layers.The counter-electrode is placed outside of the body and is in contact with the ionised medicinal ingredient and an electrode of equal charge.	Patient compliant, affordable, no impact on the structure of nail.	Adverse effects, long-term safety not determined.
Laser	The laser sources utilized to manage onychomycosis can differ, encompassing neodymium-doped yttrium aluminium garnet (Nd:YAG), titanium sapphire, and diode rays	No discomfort, no effect on tissues surrounding the nails, high efficacy.	High cost, photo ageing, long-term microbiological and clinical effects needs to be determined
Photo-dynamic	Light source is used to agitate photosensitizer to generate oxygen species leading to destruction of fungus. Example: Combinational delivery with 5-aminolevulinic acid	No drug-drug interaction, High selectivity and efficiency.	Erythema, burning, pain.
Ultrasound	Sonic waves form micro-pores in nails which enhance penetration. Ultraviolet radiation ranging from 100 to 400 nm is used.	Non-invasive, Prevents reinfection.	Costly, efficacy and safety need to be determined.
Microporation	microporation entails making precise holes in the nail plate without compromising the integrity of the nail bed	Non-invasive, enhanced absorption, precise drug delivery.	Pain and discomfort, risk of infection

combinations, and negative effects on other body organs (nausea, vomiting, upset stomach, hepatic issues). With the drawbacks of systemic and surgical therapy, topical therapy with antifungal drugs is much sought after and does not have these drawbacks. However, there are some challenges that must be addressed before effective topical treatment may be sold.

For transungual medication delivery, the human nail plate serves as a strong biological barrier that needs to be overcome. The formation of cysteine disulfide bonds between keratin fibres is what gives the nail plate its strength. Therefore, a medication molecule finds it extremely difficult to get through this highly keratinized nail plate. Therefore, for a greater transungual permeability, the molecule or formulation should have certain physicochemical properties, such as small size, high diffusion rate, and presence of penetration enhancer. The therapeutic molecule needs to be integrated or coupled with an appropriate drug delivery vehicle in order to accomplish these qualities. In order to reduce the local fungal growth, the medicine should be concentrated enough in the vehicle to surpass the minimum inhibitory concentration (MIC) and carry enough drug molecules over the nail plate.

Because of this, nail lacquers make up the majority of topical nail preparations. They consist of plasticizers, suspending agents, organic solvents, and polymers that create films. As soon as the nail lacquer

is applied to the affected area, the solvent evaporates and a polymeric film coating is applied to the surface. The medication diffuses through the nail plate after being progressively liberated from the polymeric layer and eventually comes into contact with the nail bed .

The strong keratinized barrier of the nail plate is not the only element that influences nail permeability; additional aspects include the size and molecular weight of the bioactive, the molecules' lipophilicity, their affinity for the keratinized membrane, the formulation's pH, the ionisation of drug molecules, etc. Therefore, while creating new formulations or technologies for improved bioactive permeability, formulation scientists must consider these variables[9].

Novel technological discoveries for onychomycosis treatment

The development and utilisation of functional devices at the nanometric scale, usually about 100 nm, is the main goal of nanotechnology, an interdisciplinary subject of applied science . Recent years have seen a notable surge in the use of nanostructured drug delivery technologies, especially for topical and transdermal applications[10,11,12].

Future perspectives

Onychomycosis is the subject of extensive study, with several novel formulations being created and put through pre-clinical and clinical testing. As was previously said, creating animal models of the illness is difficult, but with further work in this area, reliable and real animal models for testing will be established. At the moment, nail lacquers which are made of organic solventsare among the various topical dose forms that are accessible. But if used over an extended period of time, these solvents can reach the nail plate and enter it, and their negative consequences are unavoidable. As a result, scientists all over the world are developing aqueous-based formulations with a low concentration of hazardous organic compounds. Additionally, as the field of nanotechnology grows, scientists from all over the world are becoming interested in it. As a result, dosage forms based on different nanocarrierssuch as liposomes, lipidic/polymeric nanocarriers, nanosuspension, nanoemulgel, microemulsion, nanovesicles, etc.are being developed and their efficacy assessed. Good clinical trials and ongoing research in this field will provide some positive results, and before long, these

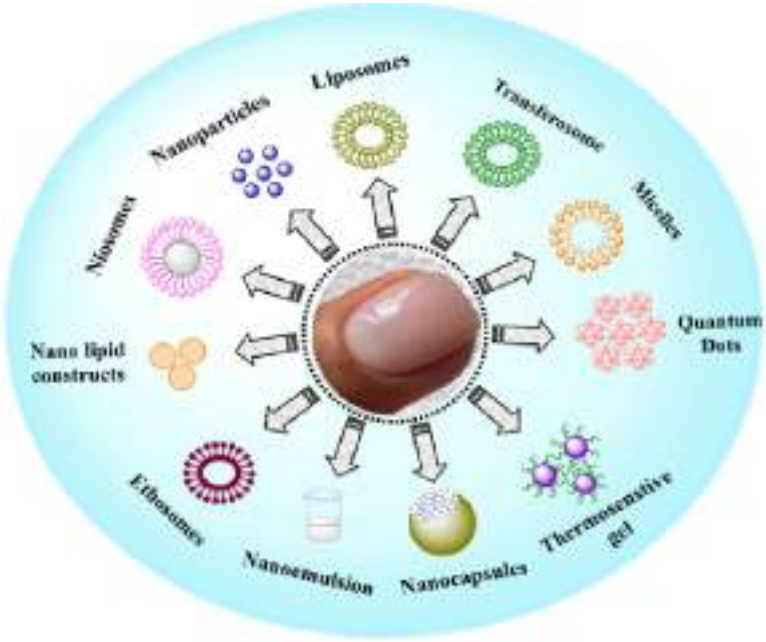


Figure 3 : Various drug nanocarriers used for the transungual delivery of drugs

Table 4 :

Liposomes	These spherical structures, known as liposomes, are made up of two layers of phospholipids. They are useful in drug delivery systems because they can encapsulate pharmaceutical compounds that are hydrophilic or hydrophobic. Liposomes have an aqueous core that is surrounded by a bilayer of phospholipids. This allows for controlled and sustained release of the drug, improved therapeutic efficacy, and improved skin penetration.
Transferosomes	The Greek word "soma," which implies a physiological "body," and the Latin verb "transfere," which means "to carry across," are the sources of the word "transference." A synthetically produced vesicle that resembles a biological vesicle or a cell engaged in exocytosis is called a transferosome carrier. Because they include an edge activator and phosphatidylcholine, these liposomes belong to a different class. These vesicles have a pliable, flexible structure that was created especially to maximise the transfer of active medications.
Niosomes	They are aqueous vesicular structures made of cholesterol or phospholipids and nonionic surfactants that act as carriers for the administration of certain medications.These vesicular systems are made up of lamellar structures with an aqueous compartment enclosing molecules that are amphiphilic. They could be used to deliver drugs that are both hydrophilic and hydrophobic.
Solid lipid nanoparticles (SLNs)	SLNs are becoming more and more popular as a potential hydrophobic medication delivery system. Emulsifiers are hydrophobic and hydrophilic in nature, a trait known as amphiphilic qualities. Because they are positioned near the oil-water (o/w) interface, these molecules play a critical role in stabilising emulsion systems. Effective delivery methods for SLNs include oral, parenteral, dermal, transdermal, ocular, and pulmonary. A solid lipid core surrounded by an emulsifier border, which acts to stabilise the particle, is the characteristic structural makeup of SLNs.
Polymeric nanoparticles	The small size of polymeric nanoparticles (NPs) gives them their distinctive characteristics. NPs provide a number of benefits to pharmaceutical companies as medication carriers. These benefits include the possibility that they may be used to regulate the release of medications, the ability to protect medications and other physiologically active compounds from external influences, and the possibility that they could improve the bioavailability and therapeutic index of these substances. Reservoir systems refer to two different types of polymeric nanoparticles: nanospheres and nanocapsules.
In situ gel - based delivery system	Onychomycosis is currently being treated with in-situ gel-based delivery of bioactives. This type of delivery system is designed to incorporate drug molecules inside thermosensitive polymers, which at lower temperatures are present in solution form but develop into gel form at body temperature. Previously, this type of delivery system has been explored for topical administration of drugs, such as skin and intranasal delivery. This approach is also being explored for transungual delivery of drug.

efforts will pay off and innovative technologies-based dosage forms will be available for purchase[13].

CONCLUSION

Onychomycosis, a fungal infection affecting millions worldwide, requires effective treatment options. Recent advancements in novel technologies and formulations have improved treatment outcomes. Topical therapies, such as nail lacquers and creams, have shown promise, while laser and photodynamic therapies offer alternative approaches. Nanoparticle-medicated delivery and transungual drug delivery systems enhance drug efficacy. Prodrug approaches and chemical modifications improve drug affinity and penetration. Penetration enhancers and ionotrophoresis facilitate drug delivery. These updates offer hope for improved treatment outcomes and enhanced quality of life for patients with onychomycosis. Ongoing research and development will continue to shape the future of onychomycosis treatment.

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