Original Article

Nail Drug Delivery System for Terbinafine

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Abstract

The nail has a structure of horns. The nail plate is to blame for drug penetration across it. Because it is hard enough, only a small amount of topical medication can get through it. As a result, the therapeutic concentration that is effective is not reached. Due to a lack of glow, the nail plate may appear abnormal. It involves the nail bed, reduces blood flow, or has chemical or physical characteristics of the nail bed. Consequently, a variety of diseases emerge. Topical therapies are limited by their low rate of penetration through the nail plate, whereas oral therapies are accompanied by systemic side effects and drug interactions. By using a nail drug delivery system, the desired therapeutic concentration of a drug can be achieved, curing these diseases .In addition to their protective and ornamental functions, human nails can be considered an alternative route for drug delivery, particularly in nail diseases like onychomycosis and psoriasis. The most prevalent nail disorder seen in clinical practice is onychomycosis, a fungal nail infection caused by yeast, dermatophytes, and nondermatophytes. Onychomycosis recurrence prevention strategies and new treatments are also discussed.

Keywords: Nail drug delivery ,Onychomycosis, Photodynamic therapy, Plasma therapy

INTRODUCTION

The structure of the nail is horny. The nail plate is to blame for drug permeation across it. It is difficult enough as it is. Only a fraction of the topical medication penetrates the skin. reaches it through it.. As a result, the successful therapy has no concentration. The nail plate may be seen. It is the diminished light. It is the involvement of reduction in blood flow, physical or chemical. As a result, a wide variety of disorders appear.[1]

These disorders can be cured by using a nail drug delivery system to get the desired therapeutic concentration of medication Human nails can be used for more than just protection and decoration; they can also be used as an alternate route for medicine delivery, particularly in nail illnesses. such onychomycosis and psoriasis These nail infections are called widely prevalent in the population, especially among the elderly. For people with weakened immune systems.[2]

Oral medicines are accompanied by systemic side effects and drug interactions, whereas topical therapies are limited by the nail plate's low penetration rate. To be effective in treating nail illnesses, the active medicine must penetrate the dense keratinized nail plate and reach deeper levels, such as the nail bed and the nail matrix. The aim of this study is to better understand the physicochemical parameters that affect medication absorption through the nail plate in order to treat not only topical nail disorders but also to evaluate the possibility of medication entering systemic circulation and neighbouring target sites. The objective of this study is to investigate the problems in drug absorption over the nail plate as well as the increase in antifungal drug bioavailability. Current topical therapies have low therapeutic efficacy, probably because to their inability to penetrate the nail plate sufficiently to deliver a therapeutically proper quantity of antifungal medicine to the target locations to eliminate the protection. It's also difficult to analyse the drug's permeation. Topical therapy for nail infections, particularly onychomycosis and, to a lesser extent, nail psoriasis, is desirable in order to prevent the side effects linked with systemic medication, enhance patient compliance, and lower treatment costs. Due to the limited permeability of the nail plate to topical therapy medicines, systemic therapy is the cornerstone of treatment. Fungal medication permeability must be improved for effective topical therapy. Topical therapy for nail infections, particularly onychomycosis and, to a lesser extent, nail psoriasis, is desirable in order to prevent the side effects linked with systemic medication, enhance patient compliance, and lower treatment costs. Due to the limited permeability of the nail plate to topical therapy medicines, systemic therapy is the cornerstone of treatment. Fungal medication permeability must be improved for effective topical therapy.[3]This can be accomplished by physically or chemically damaging the nail plate.

Alternatively, drug permeation into the intact nail plate can be aided by iontophoresis or by encapsulating the drug in a vehicle that allows for high drug partition out of the vehicle and into the nail plate. Physical techniques (manual and electrical nail abrasion, acid etching, laser ablation, microporation, use of low-frequency ultrasonic and electric currents) and chemicals (thiols, sulphites, hydrogen peroxide, urea, water, enzymes) have been found to increase reactivity. Several diseases can affect the human nail, including paronychia, psoriasis, and infections caused by bacteria, viruses, or fungi.

While these are rarely life-threatening, they do cause self-consciousness and psychological stress.[4]The most frequent treatment strategy comprises oral dosage with antifungal drugs such as terbinafine or itraconazole. Experiments on the penetration and distribution of chemicals into and through the nail plate demonstrated that drugs can be delivered to the nail following topical application, leading to the development of newer, more effective topical products and regimens for the treatment of onychomycoses and other nail diseases. A novel ultrasound-mediated drug delivery method for the treatment of a nail fungal illness (onychomycosis) has been created by improving delivery to the nail bed by increasing the permeability of the nail.

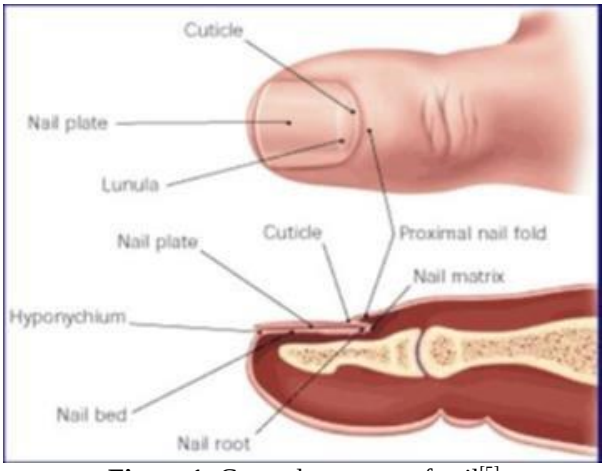

Figure 1: General structure of nail[5]

Anatomy of a Nail

Human nails are composed of the following parts:

1. the nail matrix or the nail's root
2. eponychium or cuticle-living skin covers approximately 20 percent of the nail plate.
3. Paronychium: The perionychium is the skin that overlies the nail plate on its sides.
4. Hyponychium: The nail unit's most distal or farthest edge.
5. Nail plate: The nail plate is mostly made of keratin, which is a special protein that creates the bulk of the nail plate.
6. The nail bed is a pinkish tissue area that supports the entire nail plate.
7. Lunula: The half-moon-shaped, opaque, bluish-white nail plate.[6]

COMMON DISEASE OF THE NAIL:

1.Paronychia:

Bacteria, fungi, and some viruses can cause paronychia infections of the nail fold. This infection is distinguished by discomfort, redness, and swelling of the nail folds. This condition can develop in people who put their hands in water for a lengthy period of time, and it is extremely infectious.

Figure 2: Paronychia infection[7]

2.Pseudomonas bacterial infection :

It can happen between the native nail plate and the nail bed, as well as between a synthetic nail coating and the natural nail plate. People have been misled into thinking that the distinctive "green" colouring of this type of sickness is caused by mould. Mold, in fact, is not a human pathogen.[8] Pseudomonas grows in damp environments; it feeds on dead tissue and bacteria in the nail plate and grows due to the moisture levels. The infection's aftereffects will cause the nail plate to

discolour and soften beneath an artificial coating. The darker the discolouration, the deeper the bacteria has penetrated into the nail plate layers.

Figure 3: Pseudomonas bacterial infection

3. A fungal or yeast infection:

Onychomycosis can be caused by a fungal or yeast infection that enters through a tear in the proximal and lateral nail folds, as well as the eponychium. This infection is distinguished by onycholysis (nail plate detachment) and visible debris beneath the nail plate. It is usually white or yellowish in colour and can affect the texture and shape of the nail. The fungus digests the keratin protein that makes up the nail plate.

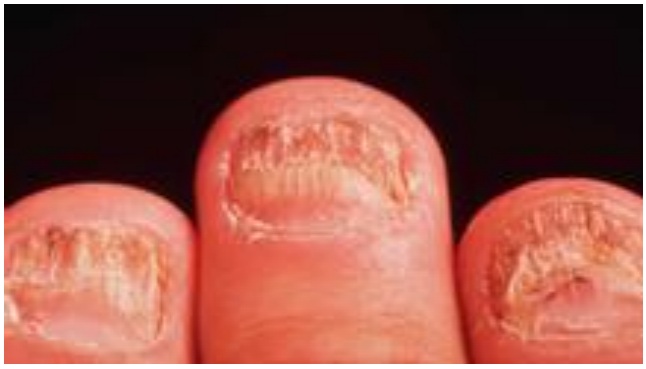

Figure 4: A fungal or yeast infection[9]

4.Onychatrophia:

It is the wasting away of the nail plate that causes it to lose its lustre, shrink, and sometimes shed totally. This abnormality could be explained by injury or sickness.

Figure 5: Onychatrophia

5.Onychogryposis:

Onychogryposis is a condition characterised by claw-like nails with a thicker nail plate that is commonly the result of trauma. This form of nail plate will bend inward, squeezing the nail bed and occasionally necessitating surgical treatment to relieve the pain.

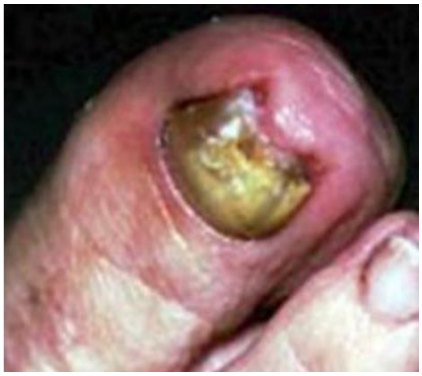

Figure 6: Onychogryposis

6. Psoriasis:

Psoriasis of the nails is distinguished by rough, scaly skin and is sometimes confused with dermatitis. When it assaults the nail plate, it leaves it scarred, dry, and crumbling. The plate may become detached from the nail bed and appear red, orange, or brown, with red patches in the lunula.

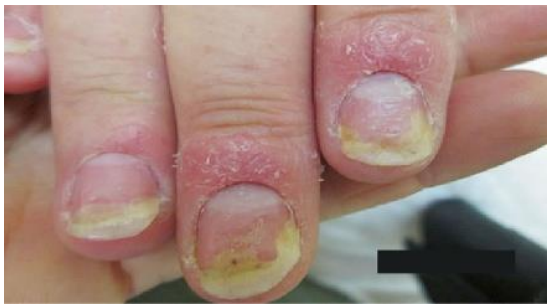

Figure 8: Psoriasis[10-14]

7.Obychorrhexis:

Onychorrhexis commonly known as brittle nails, is characterised by the nail plate splitting vertically, peeling, and/or having vertical ridges. It could be inherited or caused by excessive use of harsh soaps, water exposure, or nail polish remover.

Figure 9: Obychorrhexis

8. Leukonychia:

It's identified by white lines or dots on the nail plate. Injury to the nail matrix is the most common cause. It could be caused by trauma-induced entrapment of microscopic air bubbles in the nail plate layers, or it could be hereditary.

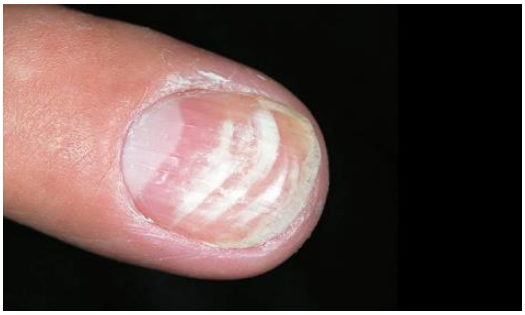

Figure 10: Leukonychia

9. Melanonychia:

It is distinguished by vertical black or brown pigmented bands, sometimes referred to as "nail moles," which typically occur in the nail matrix. It could be the result of trauma.

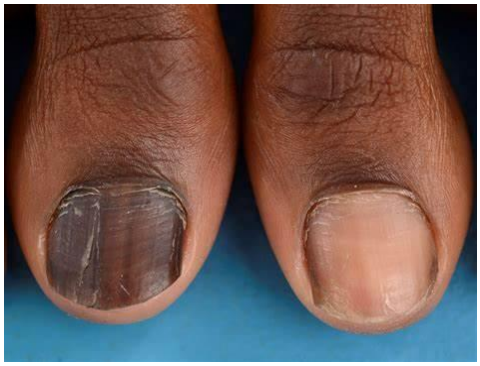

Figure11: Melanonychia

10. Onychomycosis:

It is a fungal nail infection caused by dermatophytes, yeasts, or moulds that are not dermatophytes. Age, occupation, social class, climate, and living environment all influence the prevalence of onychomycosis.

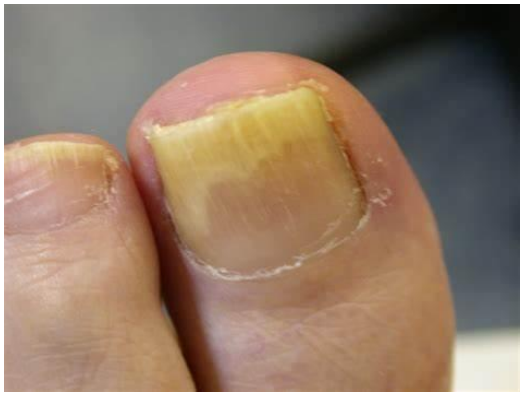

Figure 12: Onychomycosis

11. Beau's lines:

Beau's lines are deep, circular, parallel lines of darkened cells on the fingernail that run from side to side. It can be caused by an injury, illness, malnutrition, or a major metabolic condition, or it can be caused by chemotherapy. It could be caused by any disruption in the protein synthesis of the nail plate.

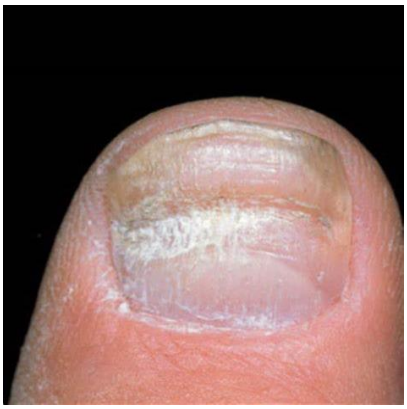

Figure 13: Beau's lines[15-18]

Onychomycosis (a fungal infection of the nail plate and/or nail bed) and nail psoriasis are the two most prevalent infectious illnesses that affect the nail apparatus.

ONYCHOMYCOSIS:

The term "onychomycosis" is derived from the Greek word's "onyx" meaning nail and "mykes" meaning fungus.[22]Any component of the nail unit can be impacted, including the nail plate, nail matrix, and nail bed.[23] Onychomycosis is the most common nail condition, accounting for at least half of all nail illnesses.[24,25,26] Onychomycosis (Tinea unguium) is a fungal nail infection that causes approximately half of all nail diseases. It affects about 5% of the world's population [19-

[20] its causes thickening, detachment, discolouration, and deformation. The rate of onychomycosis prevalence is frequently determined by the person's age, social class, inclining factor, occupation, living arrangements, and climatic conditions, as well as the patient's recurrence incidence.[21] The majority of infections (90-95%) are caused by dermatophytes, with the remainder caused by yeast and moulds. Toenails are more affected than fingernails.[27] Onychomycosis has been reported to be more common in older persons and diabetics.[28] Immunosuppression, as in Human Immunodeficiency Virus (HIV) infection and malignancy, and atopic diseases are two further risk factors for onychomycosis. As a result, the incidence of onychomycosis appears to be increasing due to an ageing population and widespread use of immunosuppressive drugs in HIV infections. [29,30,31] Onychomycosis treatment is recognised to be difficult; failure to attain "disease-free nail" with one course of medication is very usual.[32] and a high relapse rate (22.2%) is reported by Tosti et al. [33]
Onychomycosis is classified based on the region of infection, side effects of treatment, and clinical symptoms. Onychomycosis can be classified as primary or secondary based on its origin. Primary onychomycosis affects the entire nail, whereas secondary onychomycosis develops into disease-affected areas of the nail.[34]

Onychomycosis can be classified :
Distal subungual onychomycosis (DSO), Proximal subungual onychomycosis (PSO), Superficial white onychomycosis (SWO), Endonyx onychomycosis (EO) and Total dystrophic onychomycosis (TDO).[35,36]

Table 1: Types of Onychomycosis[37-40]

	Frequency	Evolution	Appearance
DSO	Common clinical form	The invasion location is the hyponychium, which is the distal region of the nail that disturbs the onychodermal band and infects the nail bottom to the nail bed.	Onycholysis (nail bed separates from nail plate) and subungual area thickens
PSO	Uncommon	Proximal nail bed and cuticle intrusion	Nail unit destructs, hyperkeratosis, and proximal onycholysis
SWO	10% of cases	Dorsal nail plate intrusion	White islands on the external nail plate
EO	Uncommon	Invades superficial surface and deeper into the nail plate	Nail plate lamellar splitting and appears milky white

Onychomycosis is tough to treat due to a difficult diagnosis, but a definitive method of diagnosis is required to distinguish it from other nail illnesses. Onychomycosis diagnostic procedures include laboratory methods[41-43], microscopy[41,43], fungal culture[41], and biopsy[44]. Fungal culture and microscopy are regarded conventional diagnostic procedures for identifying and determining dermatological agents, however a biopsy is required to detect disorders similar to onychomycosis, such as psoriasis. [41]

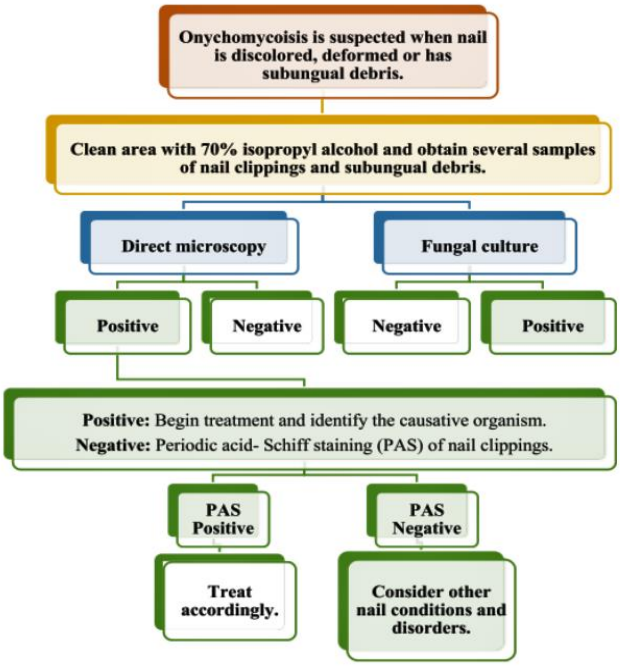

Figure 14: An outline of the diagnostic strategy for onychomycosis

Onychomycosis treatment is problematic due to a lack of understanding of the underlying pathophysiology and other factors such as the pattern of fungal growth and the patient's vulnerability to the condition. Topical and oral treatments are currently available for onychomycosis. Although oral antifungal medication has a high cure rate, it has some drawbacks, including a lengthy therapy duration and adverse effects such as liver toxicity and cardiac abnormalities.[45] Topical antifungals, on the other hand, have less adverse effects and are more patient-friendly, but they have low efficacy. To achieve optimum therapeutic efficacy, there is a need for combination therapy as well as methods to improve topical distribution.[46]

Drug	Mechanism	Dose	Side effect	Reference
Terbinafine	Inhibits squalene epoxidase in the pathway of ergosterol biosynthesis	250 mg daily for 6–8 months and 12 months for finger and toe nails respectively	Headache, gastrointestinal symptoms, rash, liver enzyme abnormalities, taste disturbance, and visual disturbance	[53,54,56]
Itraconazole	Inhibits the ergosterol biosynthesis pathway's lanosterol 14a-demethylase.	200 mg daily for 12 weeks and 6 weeks for toe and finger nails respectively	Headache, rhinitis, upper respiratory tract infection, diarrhoea, abdominal pain, hypertriglyceridemia, and elevated liver function enzymes	[55,56,57]
Griseofulvin	It results in the inhibition of the fungal synthesis of nucleic acid and cell wall production	500 mg/day in adults for 6–8 months and 12– 18 months for finger and toe nails respectively	Headache, nausea, rash, Blistering, peeling, or loosening of the skin, chills,	[49,50]
Ketoconazole	Inhibits lanosterol 14a-demethylase in ergosterol biosynthesis pathway	200 mg daily	Nausea, vomiting Allergic rash Hormone imbalance, menstrual disturbances Fluid retention ,Hepatitis Teratogenic	[49,52,58,59]
Fluconazole	Inhibits lanosterol 14a-demethylase in ergosterol biosynthesis pathway	450 mg one in a week for period of 6–9 months and 9–18 months for finger and toenails respectively	Headache, nausea, vomiting, rash, abdominal pain, diarrhoea, and elevation of transaminases	[51,60,61]

Table 2: Mechanism, Dose, Side effect of oral drug which used in treatment of onychomycosis

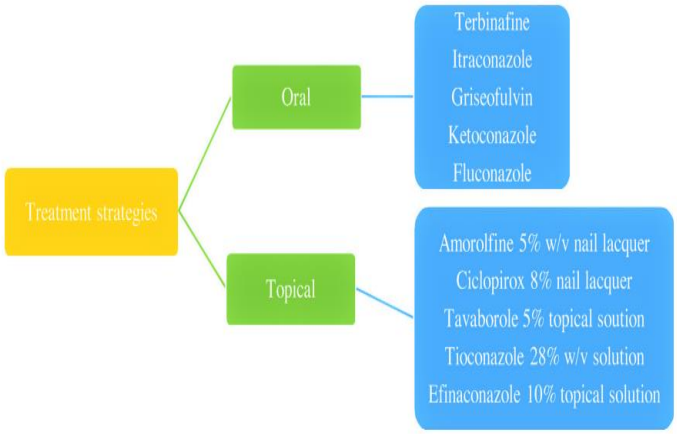

Figure15: Onychomycosis management strategies

ORAL TREATMENT:

When fungus affects 50% or more of the nails, this is the oldest therapeutic option.[47] Antifungal medications are used in the oral treatment of onychomycosis.[48] Because nail development is slow, treatment with oral antifungals takes a long time and hence does not satisfy the patient. Longer treatment duration results in significant adverse effects and drug interactions. Table shows the mechanism of action, spectrum of activity, and dose of various antifungals

Terbinafine: Terbinafine, an allylamine, inhibits squalene epoxidase and has broad-spectrum antidermatophyte activity, as well as moderate effectiveness against NDMs and Candida spp. [70,71] It is FDA-approved for the treatment of onychomycosis caused by dermatophytes and is administered orally at a dose of 250 mg daily for 6 weeks for fingernails and 12 weeks for toenails. Package insert mycologic cure rates are 79% and 70%, respectively, and complete cure rates are 59% and 38% for fingernails and toenails. The most common adverse effects are headache, stomach problems, and rash, which seldom need prescription withdrawal. Liver enzyme problems and taste impairments are less common· There are a limited number of drug - drug interactions with terbinafine and It also inhibits the CYP450 2D6 isozyme.[56] Laboratory testing with terbinafine therapy is controversial.[72] Laboratory monitoring with terbinafine therapy should be customised based on the patient's medical history and concomitant drugs.[56] Terbinafine dosage in pulses. The FDA has not approved pulse-dose terbinafine therapy for the treatment of onychomycosis, but it has been examined in clinical studies and may be used off-label for this purpose. Some physicians and patients may choose it to reduce costs and side effects.[73] A number of pulsed regimens have been demonstrated to be as effective in achieving complete cure as continuous terbinafine regimens. For example, 1 intermittent regimend2 cycles of 250 mg per day terbinafine for 4 weeks on and 4 weeks off had the highest efficacy of the pulse regimens, with mycologic and full cure rates equivalent to that of 12 continuous weeks of 250 mg per day terbinafine.

TREATMENTS IN DEVELOPMENT:

Photodynamic and plasma therapies have been explored for the treatment of onychomycosis, but larger randomized trials are needed to determine their efficacy and practicality in the clinical setting.

1. Photodynamic therapy : PDT is a non-invasive treatment that combines light-based techniques with photosensitizers. It is FDA-approved for the treatment of actinic keratoses and has been used off-label for the treatment of onychomycosis.[62,63] A topically applied photosensitizing compound is excited by laser or visible light,[64] resulting

in the formation of reactive oxygen species and free radicals that are deadly to growing cells and have antibacterial characteristics. [66-67]

2. Plasma therapy : Plasma therapy is also being researched as a treatment for onychomycosis (fig. A)

Figure A: Plasma patch application treated the left great toenail.

Device-based treatments in development for onychomycosis. [65]Plasma is formed in air by powerful electric field pulses that ionise air molecules, producing ozone, hydroxyl radicals, and nitric oxide, all of which have antifungal effects.[68] Thermal plasma creates substantial tissue heating, which can result in significant pain and nail unit destruction. Nonthermal plasma, on the other hand, does not create significant tissue heating due to its low current and duration.[69] A pilot research on 19 patients with toenail onychomycosis found that nonthermal plasma had a clinical cure rate of 53. 8% and a 15.4% rate of mycological cure.

CONCLUSION :

Ungual medication delivery is a significant difficulty, with a lack of understanding of both the barrier qualities of the nail and formulations to enable better ungual delivery limiting the efficacy of topical treatments for nail disorders. The benefits of topical delivery of systemic medicines outweigh the technical challenges. Nail illnesses such as onychomycosis, nail psoriasis, yellow nail syndrome, paronychia, and others are successfully treated with medicinal lacquers. This avoids antifungal drug oral toxicity and allows for more interaction time at the site of action. This systemic review discusses the architecture of a human nail, disorders connected to the nail plate, nail formulations, and various approaches used to improve the topical bioavailability of medications across the nail, as well as the most recent advancements in drug administration across the nail.

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