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**Review Article.....!!!**

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## **PREUNGUAL DELIVERY SYSTEM - A REVIEW**

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### **ABSTRACT**

Transungual drug delivery system is associated with the drug delivery through the hard keratinized nail plate to treat the diseases of nail itself in conditions like onychomycosis and nail psoriasis, this review is focusing mainly on nail lacquers which have been used as cosmetics since a long time for beautification and protection of nails. These can also be used as a drug delivery system. Medicated nail lacquers are the formulations that are used for transungual drug delivery for maximal antifungal efficacy. The factors, which affect the drug uptake and permeation of drug through the nail plate, are solute molecular size, hydrophilicity / hydrophobicity, charge, and the nature of the vehicle, followed by ways of enhancing drug transport into and through the nail plate. The film formed after application of nail lacquer on the nail surface acts as a drug depot that permits optimized and sustained diffusion across the nail and leads to continuous penetration of active principle to high tissue concentration required for its efficacy. The present review concluded that the medicated nail lacquers in the optimised form are the efficacious dosage forms for treating nail disorders. Some natural agents are also effective in the treatment of onychomycosis.

## INTRODUCTION

“Trans” means “through” and “Unguis” means “Nail”, So transungual or preungual drug delivery system is nothing but a system associated with drug delivery through the nail to achieve a targeted drug delivery system of the nail to treat diseases of nail itself. The hardness and impermeability of the nail makes it an unpromising route for drug delivery. However improvement in the topical delivery of compounds for the treatment of nail fungal diseases (onychomycosis and nail psoriasis) would reduce the need for systemic administration of drugs with its associated side effects. In addition, it may reduce the length of time required for treatment and help to prevent relapse. Medicated nail lacquers are the formulations that are used for transungual drug delivery for maximal antifungal efficacy now days <sup>[1]</sup>. The preungual delivery system is used to treat the fungal infection of nail plate Onychomycosis.

Onychomycosis (tineaunguium) is a fungal infection of the nail bed or nail plate caused by the organism *Trychophyton rubrum*. It accounts for approximately 50% of all nail diseases and is the most common disorder in adults.



**Fig. 1. Onychomycosis in fingers.**

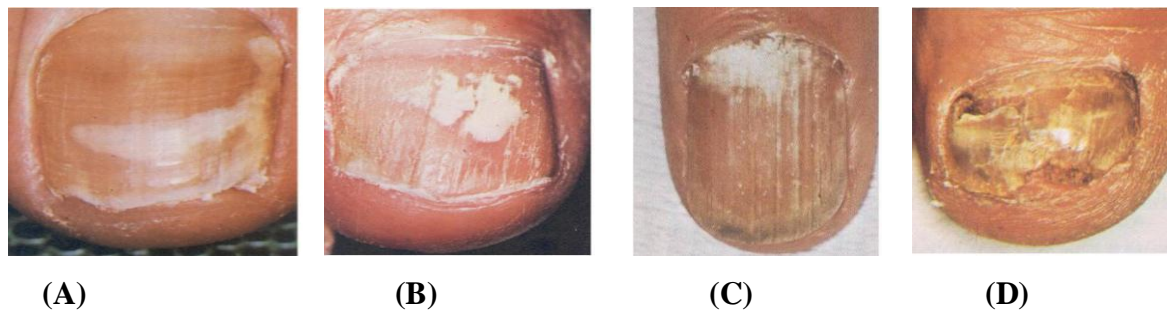
It is classified clinically as

(I) *Distal and lateral subungual onychomycosis* is the most common type of onychomycosis. The organisms access to the nail unit from the hyponychium and invade first distal nail bed, but then usually spread to proximal nail bed (Fig.A).

(II) *Superficial white onychomycosis* is developed when the surface of the nail plate is the initial site of invasion. Small superficial white patches with distinct edges can be distinguished in the nail plate, which can spread as the disease progresses. This type of onychomycosis can be treated with topical antifungal drugs alone (Fig.B).

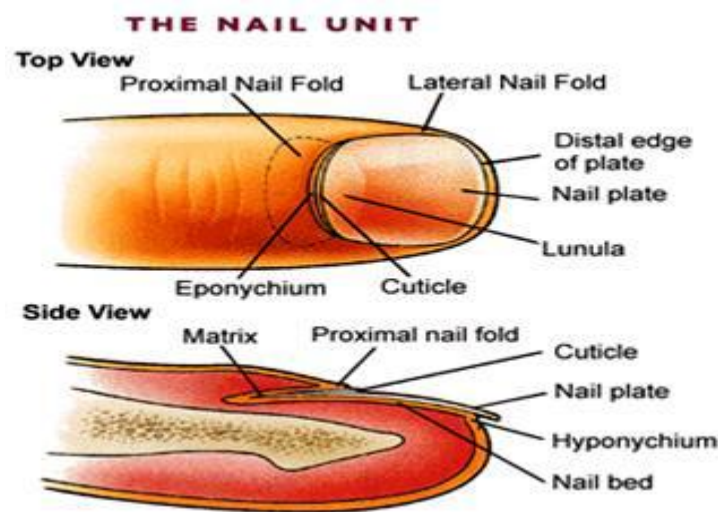
(III) *Proximal subungual onychomycosis* starts when causative agent penetrates through the proximal nail fold, where the stratum corneum is the primary site of the fungal invasion. This type of onychomycosis is less common (Fig. C).

(IV) *Total dystrophic onychomycosis* is an advanced form of the previously described types. It is characterized by total destruction of the nail plate. (Fig. D) <sup>[2]</sup>



**Fig 2. Types of onychomycosis**

### STRUCTURE OF HUMAN NAIL



**Fig. 3 Structure of human nail.**

The nail consists of the nail plate, the nail matrix and the nail bed below it, and the grooves surrounding it <sup>[3]</sup>.

**Matrix** (matrix *unguis*, keratogenous membrane, nail matrix, onychostroma) <sup>[4]</sup>

It is the tissue (or germinal matrix) upon which the nail rests <sup>[5]</sup>, the part of the nail bed that extends beneath the nail root and contains nerves, lymph and blood vessels. The matrix is responsible for the production of the cells that become the nail plate. The width and thickness of the nail plate is determined by the size, length, and thickness of the matrix.

The shape of the fingertip itself determines if the nail plate is flat, arched, or hooked. <sup>[7]</sup> The matrix will continue to grow as long as it receives nutrition and remains in a healthy condition. <sup>[6]</sup>

As new nail plate cells are incubated, they emerge from the matrix round and white to push older nail plate cells forward; and in this way yet older cells become compressed, flat, and translucent, making the pink colour of the capillaries in the nail bed below visible. <sup>[8]</sup>

**Lunula** ("the moon"):

It is the visible part of the matrix, the whitish crescent-shaped base of the visible nail. <sup>[9]</sup> The lunula is largest in the thumb and often absent in the little finger.

**Nail bed:**

It is the skin beneath the nail plate. <sup>[14]</sup> Like all skin, it is composed of two types of tissues.

1. The deeper dermis - the living tissue fixed to the bone which contains capillaries and glands <sup>[10]</sup>.
2. The superficial epidermis - the layer just beneath the nail plate which moves forward with the plate.

The epidermis is attached to the dermis by tiny longitudinal "grooves" <sup>[7]</sup> known as the matrix crests or crests of nail matrix (*cristae matricis unguis*) <sup>[5,10]</sup>. With the age, the plate grows thinner and these ridges become evident in the plate itself <sup>[7]</sup>.

**Nail sinus** (*sinus unguis*):

It is the deep furrow into which the nail root is inserted <sup>[5]</sup>.

**Nail root** (*radix unguis*):

It is the part of nail situated in the nail sinus <sup>[5]</sup> i.e. the base of the nail embedded underneath the skin. It originates from the actively growing tissue below, the matrix. <sup>[6]</sup>

**Nail plate** (*corpus unguis*). <sup>[5]</sup>

It is the actual nail, made of translucent keratin protein made of amino acids. In the nail it forms a strong flexible material made of several layers of dead, flattened cells. <sup>[7]</sup> The plate appears pink because of the underlying capillaries. <sup>[14]</sup> Its transversal shape is determined by the form of the underlying bone <sup>[7]</sup>

**Free margin** (*margo liber*):

It is the anterior margin of the nail plate corresponding to the abrasive or cutting edge of the nail <sup>[5]</sup>

**Hyponychium** ("quick") <sup>[11]</sup>

It is the epithelium located beneath the nail plate at the junction between the free edge and the skin of the fingertip. It forms a seal that protects the nail bed <sup>[6]</sup>

**Onychodermal band:**

It is the seal between the nail plate and the hyponychium. It is found just under the free edge, in that portion of the nail where the nail bed ends and can be recognized by its glassy, greyish colour (in fair-skinned people). It is not perceptible in some individuals, it is highly on others. <sup>[7]</sup>

**Eponychium:**

It is the small band of epithelium that extends from the posterior nail wall onto the base of the nail <sup>[5]</sup>. Often and erroneously called the "proximal fold" or "cuticle", the eponychium is *the end of*

the proximal fold that folds back upon itself to shed an epidermal layer of skin onto the newly formed nail plate. This layer of non-living, almost invisible skin is the cuticle that "rides out" on the surface of the nail plate. Together, the eponychium and the cuticle form a protective seal. The cuticle on the nail plate is dead cells and is often removed during manicure, but the eponychium is living cells and should not be touched <sup>[8]</sup>.

### **Perionyx:**

It is the projecting edge of the eponychium covering the proximal strip of the lunula. <sup>[5]</sup>

### **Nail wall (*vallum unguis*):**

It is the cutaneous fold overlapping the sides and proximal end of the nail.

### **Lateral margin (*margo lateralis*):**

It is lying beneath the nail wall on the sides of the nail and the nail groove or fold (*sulcus matricis unguis*) are the cutaneous slits into which the lateral margins are embedded. <sup>[5]</sup>

### **Paronychium:**

It is the border tissue around the nail <sup>[12]</sup> and paronychia is an infection in this area.

### **Function:**

A healthy nail protects the distal phalanx, the fingertip, and the surrounding soft tissues from injuries. It also serves to enhance precise delicate movements of the distal digits through counter-pressure exerted on the pulp of the finger. <sup>[3]</sup> The nail acts as a counterforce when the end of the finger touches an object, thereby enhancing the sensitivity of the fingertip even though there are no nerve endings in the nail itself.

### **Growth:**

The growing part of the nail is the part still under the skin at the nail's proximal end under the epidermis, which is the only living part of a nail. In mammals, the length and growth rate of nails is related to the length of the terminal phalanges. Thus, in humans, the nail of the index finger grows faster than that of the little finger; and fingernails grow up to four times faster than toe nails <sup>[14]</sup>. In humans, nails grow at an average rate of 3 mm (0.12 in) a month (as they are a form of hair) <sup>[15]</sup>. Finger nails require 3 to 6 months to regrow completely, and toenails require 12 to 18 months. Actual growth rate is dependent upon age, gender, season, exercise level, diet, and hereditary factors. Nails grow faster in the summer than in any other season <sup>[16]</sup>. Nails do not continue to grow after death; skin dehydrates and tightens, making the nails appear to grow <sup>[17]</sup>.

## **FACTORS AFFECTING DRUGS TRANSPORT INTO/ACROSS THE NAIL**

Topical application of a drug formulation onto the nail plate, the drug has to enter the nail plate and diffuse into the deeper nail layers and possibly into the nail bed. Walters et al. found that the nail plate behaves like a concentrated hydrogel rather than a lipophilic membrane. Drug delivery into and through the nail plate is influenced by:

- Physicochemical properties of a drug molecule to be applied,
- Type and nature of formulations
- Presence of permeability enhancers in the formulations
- Properties of nail and
- Interactions between the permeant and the keratin network of the nail plate.

### **Molecular size of drug**

The larger the molecular size, the harder it is for drug to diffuse through the keratin network and lower the drug permeation. Mertin and Lippold demonstrated the decreasing permeability coefficients through human nail plate and through bovine hoof membrane with increasing molecular size of a series of alkyl nicotines<sup>[18]</sup>

### **Hydrophilicity / lipophilicity of drug**

Walters et al. studied the permeation of a series of homologous alcohols (C1–C12), diluted in saline, through avulsed human nail plates. Increasing the chain length from one carbon to eight carbon atoms resulted in a decrease in permeability coefficient, after which, increasing chain length (>C12) resulted in increased permeability coefficient. The study by Walters et al. concluded that the nail plate is characterized as a hydrophilic gel membrane.

### **Nature of Vehicle used in formulation**

The permeability coefficients of alcohols diluted in saline through nail plates was five times greater than the permeability coefficients of neat alcohols. Water hydrates the nail plate which consequently swells. Considering the nail plate to be a hydrogel, swelling results in increased distance between the keratin fibers, larger pores through which permeating molecules can diffuse and hence, increased permeation of the molecules. Replacing water with a non-polar solvent, which does not hydrate the nail, is therefore expected to reduce drug permeation into nail plate.

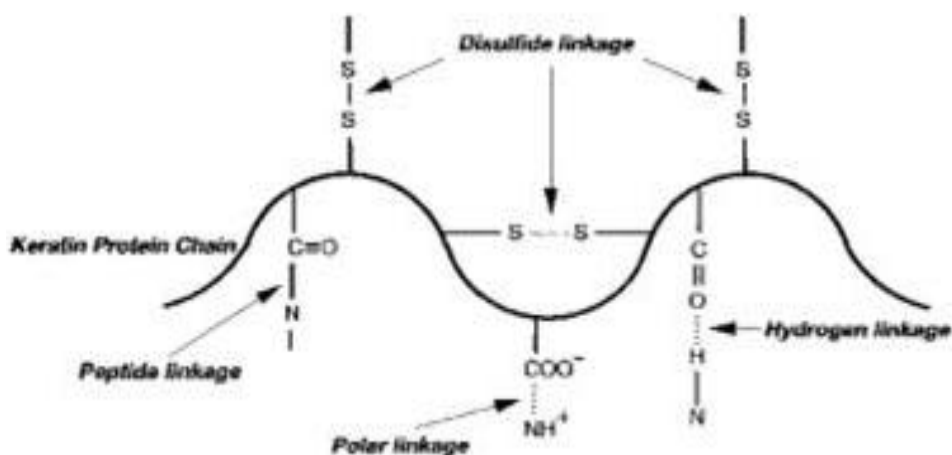
### **pH of vehicle and solute charge**

The pH of aqueous formulations affect the ionization of weakly acidic/basic drugs, which in turn influences the drug's Hydrophilicity / hydrophobicity, solubility in the drug, formulation, solubility in the nail plate and its interactions with the keratin matrix. It seems that the pH of the formulation has a distinct effect on drug permeation through the nail plate.[19]



### physicochemical properties of nail

The entire nail fabric is hard keratin. The hardness of the nail plate not only depends on the junctions between the cells and the transverse orientation of the keratin filaments with respect to the axis of the nail growth. Moreover, the multiplicity of the lateral bonds between keratin fibers (disulfide bridges, hydrogen bonds, acid- base bonds, electrostatic bonds) also account for high resistance. The keratin of nails has been classified as “hard trichocyte keratins”. It contains significant amount of phospholipids, mainly in the dorsal and intermediate layers, which contribute to its flexibility



**Fig. 4. Chemical bonds involved in a nail keratin chain**

#### Properties of the chemical:

Among the other physicochemical properties of chemicals, these are the important set of properties which affect the most, the drug absorption through nail.

#### Solute molecular size:

As the nail plate is produced mainly by differentiation of cells in the nail matrix, and it comprises three horizontal layers: a thin dorsal lamina, the thicker intermediate lamina, and a ventral layer from the nail bed. Because the nail plate is composed of many strands of keratin held together through disulfide bonds, the space between the strands must have a finite size causing the nail plate to act like a molecular sieve. Small molecules can weave through these spaces while larger molecules are unable to pass.

The molecular weight of most antifungal agents is >300Da. accordingly, these drugs will have difficulty penetrating the nail plate, a likely reason for low clinical efficacy observed. So, the optimum small particle size of the drug is the foremost prerequisite for formulation point of view.

**Hydrophilicity / hydrophobicity**

There is a marked difference between the permeability characteristics of the nail plate and the epidermis. These observed differences have been largely attributed to the relative amounts of lipid and protein regulation within the structures and the possible differences in the physicochemical nature of the respective phases. The lipid levels in the nail plate are near 1%, which combined with lower water levels of about only 10% affords the nail plate. Studies using DMSO, homologous alcohols of different molecular weights have shown that, the nail plate was permeable to dilute aqueous solutions of low molecular weight.

**ENHANCEMENT OF NAIL PERMEATION**

Physical, chemical and mechanical methods have been used to decrease the nail barrier. Within each of these broad categories, many techniques exist to enhance penetration. Mechanical modes of penetration enhancement are typically straight forward, and have the most *in vivo* experience associated with them. In contrast, many of the chemical and physical methods discussed are still in the *in vitro* stages of development; laboratory studies are currently examining these techniques using human nail samples. The goal of topical therapy for onychomycosis is drug penetration into deep nail stratum at amounts above the minimal inhibitory concentration (MIC). Effective penetration remains challenging as the nail is believed by some to be composed of approximately 25 layers of tightly bound keratinized cells, 100-fold thicker than the stratum corneum (SC). It increases in toe nail thickness along the nail. Mean nail plate thickness increased progressively along the entire length of the nail ranging between 590µm and 1080µm. While there is disagreement on the exact thickness of the nail there is consensus that the nail structure is difficult to penetrate.

In addition, poor permeability and prolonged transport lag time contribute to disappointing topical efficacy in nail disease. Chemical and physical modes of penetration enhancement may improve topical efficacy. There are two main factors to consider: physicochemical properties of the drug (polar compounds are more permeable) and binding of the drug to keratin within the nail. Binding to keratin reduces availability of the active (free) drug, weakens concentration gradient, and limits deep penetration<sup>[20 - 24]</sup>

**Nail avulsion:** Total nail avulsion and partial nail avulsion involve surgical removal of the entire nail plate or partial removal of the affected nail plate, and under local anesthesia. Keratolytic agents such as urea and salicylic acid soften the nail plate for avulsion. Urea or a combination of urea and salicylic acid have been used for nonsurgical avulsion (chemical avulsion) in clinical studies, prior to topical treatment of onychomycosis<sup>[25]</sup>



**Nail abrasion:** Nail abrasion involves sanding of the nail plate to reduce thickness or destroy it completely. Sandpaper number 150 or 180 can be utilized, depending on required intensity. Sanding must be done on nail edges and should not cause discom. An efficient instrument for this procedure is a high-speed (350,000 rpm) sanding hand piece. Additionally, dentist's drills have been used to make small holes in the nail plate, enhancing topical medication penetration. Nail abrasion thins the nail plate, decreasing the fungal mass of onychomycosis, and exposing the infected nail bed. In doing so, it may enhance the action of antifungal nail lacquer.<sup>[26]</sup>

**Chemical methods to Enhance Nail Penetration:** the high disulfide bond content of nail has been found to be responsible for the hardness of the nail. In recent years, the ability of compounds that possess –SH groups to increase nail permeation has been documented. Promising enhancers include papain, sulfhydryl containing endopeptidase enzyme, 2mercaptoethanol, 1, 4-Dithiothreitol, which contains 2-SH groups and various reducing sulfites and bisulfites. These increase the ability of the nail to hydrate. As well as nail softening agents (keratolytic agents) like urea and salicylic acid can be used in the formulation for enhancing the drug permeation through chemical-means.

**2-n-nonyl-1, 3-dioxolane:** 2-n-nonyl-1,3-dioxolane (SEPA®) enhances penetration of econazole (from a lacquer formulation) into the human nail. They demonstrated that econazole penetrates the nail six times more effectively in a lacquer containing 2-n-nonyl-1,3-dioxolane than in an identical lacquer without enhancer. Concentrations of econazole in the deep nail layer and nail bed were significantly higher in the 'enhancer' group than in the control group. Furthermore, in the 'enhancer' econazole concentration in the deep nail layer was 14,000 times greater than the MIC necessary to inhibit fungal growth.<sup>[27]</sup>

**N-acetyl-L-cysteine and Mercaptan compounds:** N-acetyl-L-cysteine and 2- mercaptoethanol, in combination, enhanced permeability of the antifungal drug tolnaftate into nail samples. They suggested that these compounds may be generally useful in enhancing drug permeation across the nail plate. The penetration-enhancing properties of N-acetyl-L-cysteine with the antifungal drug oxiconazole in vivo. N-acetyl-L-cysteine promoted oxiconazole retention in upper nail layers.<sup>[28]</sup>

**Keratolytic Enhancers:** Keratolytic agents (papain, urea, and salicylic acid) on the permeability of three imidazole antifungal drugs (miconazole, ketoconazole, and itraconazole). In the absence of keratolytic agents, no transungual antifungal permeation was detected over a period of 60 days. Despite these findings, it is likely that the spectrophotometric method of analysis was insufficiently sensitive to accurately measure drug concentrations. Permeation of these agents did not improve by pre-treatment with 20% salicylic acid (for 10 days) and the addition of 40% urea

to the donor solution. However, pre-treatment with both 15% papain (for 1 day) followed by 20% salicylic acid (for 10 days), enhanced antimycotic permeation. Presence of ethanol (as a co-solvent) did not promote flux. Although ethanol is an effective skin permeation enhancer, it does not have a similar effect on the nail. Ethanol acts on the SC by altering intercellular lipids; however, the lipid content of the nail comprises just 0.15–0.76% of its total weight <sup>[29]</sup>

**PHYSICAL MEANS of enhancing drug permeation:** The composition of the nail plate suggests that, the use agents that effect by delipidization or fluidization of the intracellular lipids can help in drug permeation <sup>[30-31]</sup>

Many approaches have been used to resolve these barriers to drug delivery. These include:

**Iontophoresis:** Iontophoresis involves delivery of a compound across a membrane using an electric field (electromotive force). The principle has been applied clinically for cutaneous anesthesia, hyperhidrosis management, antibiotic penetration, and herpes simplex treatment. Currently both LidoSite® (lidocaine HCl/epinephrine topical iontophoretic patch) and GlucoWatch® (iontophoretic measurement of glucose in diabetics) are FDA approved. Iontophoresis has been used for various applications different from transdermal ophthalmic, dental, orthopaedic, etc. Drug diffusion through the hydrated keratin of a nail may be enhanced by iontophoresis. Several factors contribute to this enhancement: electrorepulsion/ electrophoresis, interaction between the electric field and the charge of the ionic permeant; electroosmosis, convective solvent flow in preexisting and newly created charged pathways; and permeabilization/electroporation, electric field-induced pore induction. The effects of electric current on nails are reversible in vitro; nail plates will return to normal after iontophoresis treatment. In vitro transport studies were performed using specifically-designed diffusion cells. Compared to passive transport, iontophoresis significantly enhanced drug penetration through the nail. Iontophoretic trans-nail flux improved with higher SA concentrations (up to 2mg/ml), higher current density (up to 0.5mA/cm<sup>2</sup>), higher buffer ionic strength (optimal strength at 50–100 mM), and higher pH. pH dependent transport due to cathodal iontophoresis followed the opposite trend (i.e. lower pH correlated with increased flux). Griseofulvin transport was enhanced ≈8-fold with iontophoresis.

**Etching:** “Etching” results from surface-modifying chemical (e.g. phosphoric acid) exposure, resulting in formation of profuse microporosities. These microporosities increase wettability and surface area, and decrease contact angle; they provide an ideal surface for bonding material. Presence of microporosities improves “interpenetration and bonding of a polymeric delivery system and facilitation of inter diffusion of a therapeutic agent”. Once a nail plate has been

“etched,” a sustained-release, hydrophilic, polymer film drug delivery system may be applied. Bioadhesion, “a phenomenon related to the ability of biological or synthetic material to adhere to biological substrate,” must be considered improved bioadhesion results in superior application of a transungual bioadhesive drug delivery system.<sup>[30]</sup>

**Ultraviolet Light:** A recently submitted patent discusses use of heat and/or ultraviolet (UV) light to treat onychomycosis; several different instruments and methodologies are discussed which may effectively provide exposure. One method involves heating the nail, exposing it to UV light, and subsequently treating with topical antifungal therapy.<sup>[32]</sup>

**Phonophoresis:** Phonophoresis describes the process by which ultrasound waves are transferred through a coupling medium onto a tissue surface. The induction of thermal, chemical, and mechanical alterations in this tissue may explain drug delivery enhancement. At a gross level, phonophoresis may result in improved penetration through the SC transcellularly or via increased pore size; at a cellular level, pores in the cell membrane (secondary to lipid bilayer alteration) may enhance drug diffusion. It has been used to enhance percutaneous penetration to joints, muscle, and nerves. Enhanced penetration of anesthetics, fluocinolone acetonide, and amphotericin B is recorded. Advantages of phonophoresis include: enhanced drug penetration, strict control of penetration rates, and rapid termination of drug delivery, intact diseased surface, and lack of immune sensitization.<sup>[33]</sup>

**Electroporation** is a method in which, with the application of an electric pulse of about 100–1,000 V/cm creates transient aqueous pores in the lipid bilayers making the solute particles permeable through it.

**Microneedle** enhanced delivery systems, a method using arrays of microscopic needles to open pores in the SC directly to the skin capillaries; also has the advantage of being too short to stimulate the pain fibers, thus facilitating drug permeation.

**Carbon dioxide Laser:** CO<sub>2</sub> laser may result in positive, but unpredictable, results. One method involves avulsion of the affected nail portion followed by laser treatment at 5000W/cm<sup>2</sup>. Thus, underlying tissue is exposed to direct laser therapy. Another method involves penetrating the nail plate with CO<sub>2</sub> laser beam. This method is followed with daily topical antifungal treatment, penetrating laser-induced puncture holes

**Hydration and Occlusion:** Hydration may increase the pore size of nail matrix, enhancing transungual penetration. Additionally, hydrated nails are more elastic and permeable. Iontophoresis studies have utilized this property to further enhance penetration. Solution pH and ionic strength have demonstrated no significant effect on nail hydration. Diffusivity of water and

other materials (i.e. drugs) increases as human skin becomes more hydrated. Human stratum corneum retains up to ~300% of its weight in water; when SC is saturated, diffusivity increases several-fold.

**Photodynamic therapy of Onychomycosis with Aminolevulinic acid:** Photodynamic therapy (PDT) is a medical treatment based on the combination of a sensitizing drug and a visible light used together for destruction of cells. PDT based on topical application of aminolevulinic acid (ALA) acid is used in oncological field. Topical PDT is being evaluated and modified to provide a once-off curative treatment for onychomycosis. This would negate the need for prolonged topical or systemic treatment regimens, with their associated poor success rates and potential for drug resistance, side effects, drug–drug interactions, and increased morbidity.<sup>[34]</sup>

**Lasers:** A patent has been filed for a microsurgical laser apparatus which makes holes in nails; topical antifungals can be applied in these holes for onychomycosis treatment. Further work remains to characterize this new invention, termed the ‘onycholaser’.<sup>[35]</sup>

#### **TOPICAL THERAPIES AVAILABLE:**

Topical drug delivery is especially suitable for onychomycosis and nail psoriasis, which affect 2 - 13 and 1 - 3% of the general population, respectively, and make up the bulk of nail disorders. Topical therapy would avoid the adverse events and drug interactions of systemic antifungal agents and the pain of injection when antipsoriatic agents are injected into affected nail folds. Moreover, the target sites for the treatment of onychomycosis and other nail disorders reside in the nail plate, nail bed and nail matrix.

Various topical therapies for nail disorders, which have been studied so far are:

Lacquers, Gels / Solutions, Creams / Pastes, Colloidal systems / Liposomes, Powders, Aerosols / Foams / Sprays.

A Bandage is adapted comprising a T-shaped adhesive backing, and a flexible pad having an impervious backing and a nail-shaped cavity (containing active solute along with other additives). Nail Lacquer of Ciclopirox distributed commercially under the trade name PENLAC.TM. by Dermik Laboratories, Inc.), as an 8% topical solution and 5% amorolfine, a morpholine derivative, and is manufactured by Roche Laboratories under the trade name LOCERYL.TM. containing a water-insoluble, film-forming polymer.<sup>[36-37]</sup>

#### **Commercially available drug-containing nail varnish**

The first drug-containing nail varnish seems to be one that was used to treat nail mycoses, where the drug was the anti-mycotic, sulbentine and the film-forming polymer was nitrocellulose. This nail varnish was not universally accepted however, due to the fact that only mild nail mycoses

could be treated, possibly as a result of poor drug bioavailability in the nail plate. Recent advances have resulted in more effective products, namely Loceryl and Penlac, both of which are indicated for mild to moderate onychomycosis. Loceryl – first marketed in 1992 - is a clear, colourless liquid and comprises the antifungal amorolfine (5%), Eudragit RL 100, glycerol triacetate, butyl acetate, ethyl acetate and ethanol. The lacquer is applied 1-2 times weekly to infected nail plates for up to 6 months for fingernails or 9-12 months for toenails. Penlac<sup>7</sup> was approved by the FDA in 1999. A clear, colourless liquid, it is composed of the antifungal agent ciclopirox (8%), ethyl acetate, isopropanol and butylmonoester of poly(methylvinyl ether/maleic acid). Penlac<sup>7</sup> is applied once daily, for up to 48 weeks. The film is removed every 7 days with alcohol before re-application of the lacquer<sup>[38]</sup>

Following application of Loceryl and Penlac (which contain 5% amorolfine and 8% ciclopirox respectively) to the nail plate, the solvents evaporate and a polymer film with a higher drug concentration (approximately 25% amorolfine or 35% ciclopirox) is left on the nail plate<sup>[39-40]</sup>

This creates a high diffusion gradient for drug permeation into the nail plate. Formation of a film on the nail plate also reduces water loss from the nail surface to the atmosphere; this results in hyperhydration of the upper nail plate layers which can also assist drug diffusion<sup>2</sup>. Following application of the lacquers, amorolfine and ciclopirox were found to reach fungicidal concentrations in the nail plate and were found to be effective at treating the disease.<sup>[41-43]</sup>

The nail lacquers are also well-tolerated; adverse effects are rare and usually comprise mild irritation localised to the application site. Although Loceryl and Penlac are not usually used on their own for severe onychomycosis, there is a large body of literature showing the benefits of combining the nail lacquers with conventional oral anti-fungal therapy in severe disease states. These include a more effective treatment of the disease, a reduction in oral drug intake and reduced cost of treatment. The nail lacquers could also be used to treat severe disease in special populations where oral therapy is contra-indicated, for example in children, in pregnant and in breastfeeding women, in patients with hepatic and/or renal impairment and in those who perceive nail infection to be too trivial for systemic therapy<sup>[44-45]</sup>

**Table 1. DEVELOPED FORMULATIONS FOR NAIL DISORDERS**

Sr. No.	Name of product	Name of drug	Uses/Indications	Name of company
1	Eco-Nail Nail lacquer	5% econazole +18% SEPA nail lacquer	Promotes the release of econazole from dried lacquer film, creating a large chemical gradient at the lacquer nail interface, to drive econazole into the deep nail plate SEPA acts as a percutaneous penetration enhancer which itself has no effect on nail and do not penetrate nail.	MacroChem Corporation
2	Loceryl nail Film	Antifungal drug, amorolfine	A non-water-soluble film of amorolfine formed on the nail plate, and this film remains in place for 1 week. The film contains a high concentration of amorolfine and forms a depot from which the drug is delivered and which allows the drug to permeate the nail plate.	Galderma Australia Pty Ltd
3	Umecta nail Film	Urea 40%	Psoriatic nails, brittle and thick nails, and calluses.	JSJ Pharmaceuticals
4	Tazorac 0.1% Gel	Tazarotene	Used in the treatment of Fingernail psoriasis.	Allergan Inc
5	Zalain nail Patch	Setaconazol Nitrate	Once-a-week nail patch for treatment of onychomycosis & onychodystrophy.	Labtec
6	Penlac nail Lacquer	Ciclopirox topical solution	A broad-spectrum antifungal medication that also has antibacterial and anti-inflammatory properties.	

***The future***

The future for manufacturers of drug-containing lacquers, especially of anti-fungal containing lacquers is bright, given the increasing prevalence of onychomycosis, and a large number of patents covering anti-fungal nail lacquers have been filed. A review of the patent literature reveals that future pharmaceutical lacquer formulations could include, among others:

- Ungula permeation enhancers, such as, oxacyclohexadecan-2-one, which could increase drug flux into the nail (e.g. US 2003049307, US 2003232070, US 6224887)
- Keratolytic agents such as urea, salicylic acid, enzymes, which could also increase drug flux into the nail (e.g. US 5264206, US 5346692),
- Acidified formulations (acidification was found to enhance drug uptake into nail, probably via increased drug solubilisation in the nail lacquer (WO 9949835),
- Drug combinations e.g. anti-mycotic and a steroidal anti-inflammatory agent (it has been suggested that the overall effectiveness of antimycotic agents may be improved by combining an anti-fungal with a steroidal anti-inflammatory agent (US 6224887),
- Vitamins which are thought to possess therapeutic activities against keratinic disorders



- Colorants, included to hide unsightly manifestations of nail disorders (US 2003232070),
- Water -based nail lacquers, which would be environmentally-friendly and whose manufacture would be cheaper and safer, given the avoidance of flammable organic solvents. <sup>[41-43]</sup>

#### **SOME PLANT REMEDIES EFFECTIVE IN THE TREATMENT OF ONYCHOMYCOSIS**

1. *Psidium sartorianum* : The methanol extract of the fruit of *Psidium sartorianum* was evaluated against 7 *Candida* species and 9 other fungal strains. The extract show significant activity against 7 trichophyton species.
2. *Nigella sativa* : Antifungal activity of ether extract of the *Nigella sativa* seed and its active principle thymoquinone was tested against *Trychophyton rubrum* and other species.
3. *Moringa oleifera* : Ethanol extract of seeds and leaves showed antifungal activity against *Trychophyton rubrum* and *Trychophyton mentagrophytes*.
4. *Eugenia caryophyllata* : essential oil active against trychophyton species.
5. *Lawsonia inermis* (henna). Lawsone, the principal constituent active against Trychophyton species. <sup>[46]</sup>
6. The methanol extract of the fruit pulp of *Psidium sartorianum* was evaluated against 5 species of Trychophyton and found to be effective in the treatment of onychomycosis.
7. Antifungal activity of ether extract of *Nigella sativa* seeds and its active principle thymoquinone was tested against 8 species of dermatophyte (4 species of *T. rubrum*).
8. Ethanol extracts of seeds and leaves showed antifungal activities against *T. rubrum* and *T. mentagraphytes*.
9. Essential oil from *Eugenia caryophyllata* showed antifungal activity against Trychophyton species.
10. Lawsone from *Lawsonia inermis* was found to be effective in the treatment of onychomycosis.
11. *Ocimum gratissimum* (Ram Tulsi) due to the presence of eugenol used in the treatment of onychomycosis.
12. Garlic: This is frequently touted as being beneficial to those suffering from heart disease. However, it is a powerful fungus fighter as well. In addition to eating it, you can juice the garlic and apply a little bit of it to the affected fingernail using a cotton ball. Do this three times per day to maximize the antifungal properties of this herb.
13. Chamomile: Frequently enjoyed as tea, this plant has antibacterial and antifungal properties. It has been shown to inhibit the growth of bacteria and fungus. Like garlic, you can consume chamomile as a tea. The tea can also be applied directly to the nail up to three times per day.

14. Thymol: Derived from the herb thyme, this is a powerful antifungal herb has antiseptic, antimicrobial and antibacterial properties that damage the cell membranes of the fungus.
15. Green tea: Among its other health benefits, green tea is an antifungal agent that can be used to fight nail fungus. After steeping the tea, apply a few drops onto the affected nail. Drink the rest to boost the body's fungus fighting processes.
16. Ginger root: This herb has been known to reduce inflammation, blood clots, and alleviate cardiovascular conditions. It is also a natural immune system booster which can provide the body with the strength it needs to fight the fungal infection in its system.
17. Cayenne: Probably better known as the pepper used to make pepper sprays and similar self-defense products, cayenne peppers are immensely useful for improving blood circulation. This is particularly helpful for people suffering from medical conditions that result in poor circulation like diabetes. Good circulation makes it easier for the body to deliver nutrients and white blood cells to the site of the nail fungus infection.
18. Echinacea: A member of the daisy flower family, Echinacea is another immune system booster. It is most effective at treating upper respiratory tract infections, but also provides general support to the body
19. Although not herb, tea tree oil is a good medicine for nail fungus. It is an essential oil extracted from the *melaleuca alternifolia* tree. Among other things, it is a powerful antifungal agent that has been shown to kill nail fungus dead. It's pretty strong, though, so you may have to dilute it with another oil – such as lavender oil – before applying it directly onto the nail. You can also use apple cider vinegar for nail fungus infections. It comes as a liquid and as a dietary supplement. It is a good idea to use both to fight your nail infection. Apply the vinegar directly to the affected nail twice per day. You can also combine it with equal parts water and soak your foot in it once per day for 30 minutes until the infection clears. <sup>[47-52]</sup>

The above mentioned remedies don't show significant results in moderate to severe infection. But there are a number of natural products that use a combination of tea tree oil and nail fungus killers to provide quick relief from the infection that is moderate or severe.

## CONCLUSION

Topical therapy is worth pursuing however, as local action is required in many nail disorders. Drug transport into the nail plate can be assisted by filing the nail plate before topical application of drug formulations as well as by the use of chemical enhancers. The permeability of the compact, highly keratinized nail plate to topically applied drugs is poor and drug uptake into the nail apparatus is extremely low. A review of the literature has revealed that research aimed at

enhancing ungual drug uptake following topical application may be divided into three approaches: first understanding the physico-chemical factors that influence drug permeation into the nail plate; second the use of chemical enhancers which cause alterations in the nail plate, thus assisting drug permeation; and third the use of drug-containing nail lacquers which are brushed onto nail plates and which act as a drug depot from which drug can be continuously released into the nail. The nail plate behaves like a concentrated hydrogel to permeating molecules and diffusion of molecules through the nail plate has been compared to the diffusion of non-electrolytes through polymer gels. Thus, for optimal ungual permeation and uptake, drug molecules must be of small size and be uncharged. The natural remedies may become popular in the future because of lesser side effects. So that area require the research works to develop new formulations as preungual delivery system.

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