

A Comprehensive Review On Onychomycosis

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Abstract

The nail is the permanent protect of the nail matrix. Human nails not only have protective & decorative role, but also used as drug delivery pathway especially nail diseases like onychomycosis or psoriasis. Onychomycosis is a fungal infection, most commonly affecting on nail by dermatophytes, non dermatophytes, molds and yeast. One-third of integumentary fungal infections and half of all nail diseases have been linked to onychomycosis. The major causative organisms of onychomycosis are dermatophytes like *Trichophyton mentagrophytes*, *Trichophyton rubrum*, *Epidermophyton floccosum* and *Tinea unguium*. Onychomycosis infection with Non dermatophytes cases about 10% of world wide, the most common organisms *Acremonium*, *Alternaria* species, *Aspergillus* species etc. Yeast caused onychomycosis infection up to 10 to 20% cases, with pathogenic organisms like *Candida* species. Treatment of onychomycosis is Antibiotic and antifungal drug resistance has grown during the last few years. The oral administration of terbinafine, itraconazole, fluconazole, ketoconazole, and griseofulvin are first-line onychomycosis therapy techniques. Treatment of topical onychomycosis includes ciclopirox and amorolfine nail polish. Side effect of already existed treatment of onychomycosis like Hepatotoxicity, Leukopenia, Thrombocytopenia or anemia, Photosensitivity. To overcome this side effect to prepare the topical formulation containing medicinal plant like *Aristolochia bracteolata*, *Lawsonia inermis* and *Calotropis procera*.

Keywords: Onychomycosis, Nail disease, Fungal nail infection, Management, Treatment, Medicinal plants.

INTRODUCTION

Onychomycosis is a fungal infection, most commonly affecting on nail by dermatophytes, non dermatophytes, molds and yeast.^[1] The term onychomycosis is derived from the Greek word “onyx” meaning nail and mykes meaning fungus.^[2,3] Various factors contributing to this are damage of the nail surface during nail grinding or manicuring use of artificial nail advanced age occlusive foot wear, nail trauma, peripheral vascular disease, diabetes, smoking, HIV, immunosuppression regular swimming as are more susceptible as are elderly patient.^[4,5] Genetics may predispose to developing infection and transmission risk increase when members of the same household are infected.^[1] Typically, it manifests discoloration of the nail pathology and accounts for about 90% of toenail infections worldwide.^[5] Although onychomycosis is not a life-threatening disease, it can significantly reduce patients' quality of life. It's associated with a negative impact with regard to patients physical, social & emotional wellbeing.^[6,7]

NAIL

The nail is the permanent protect of the nail matrix. Its normal appearance and growth depend on the integrity of several components: the surrounding tissues and the bonyl phalase that are contributing to the nail apparatus.^[8] Finger nails and toenails are made of a tough protein called keratin.^[9] Human nails not only have protective & decorative role, but also used as drug delivery pathway especially nail diseases like onychomycosis or psoriasis for the benefit treatment of nail diseases applied active drug must penetrate through the dense keratinized nail plate to reach deeper layer, nail bed & nail matrix. But due to the composition & construction of the nail plate critically restricts the permeation of medication & only a small amount of topical medication permeates across the nail, at the same time oral therapies are accomposied by systemic side effects, tonicity, drug interaction, low patient compliance, long treatment period up to 4-8 months.^[10] The challenges of the drug delivery to the nail, with lack of the understanding the barrier properties of nail formulation. Enlarge more effective methods for nail drug delivery is an important aim for the pharmaceutical industry.^[12]

STRUCTURE OF NAIL

The human nail consists of various parts like:

- The matrix or root of the nail
- Nail bed
- Eponychium or cuticle
- Paronychium

- Hyponychium
- Lunula

Nail matrix

The nail matrix is also called as nail root, the area where your finger nails and toenail start to grow. Its new cells are added to the root and by their constant addition nail plate is pushed slowly forward over nail bed about 0.5mm/week. Root of fingernails is also known as germinal matrix. It is thickened part of nail bed & is composed of 3-20 layers of actively dividing cells of stratum germinativum.^[9,10]

Nail bed

Nail bed (sterile matrix) is the part of the nail matrix. Its pinkish-colored soft tissue underneath nail plate, thin, soft, non-cornfield epithelium connected with ventral layer and underlying papillary dermis & contains blood vessels, nerves, melanocytes or melanin producing cells. It extends from edge of the germinal matrix to the hyponychium.

Nail plate

The nail plate is a thin, hard, yet slightly elastic, translucent, convex structure & made up of approximately 25 layer of dead keratinized flattened cells.^[9]

Eponychium or cuticle

It is situated between the skin of the finger and nail plate. It fuses these structures together, providing a waterproof barrier. It forms the seal between the nail and the digit to prevent foreign matter from entering.^[9]

Paronychium

The paronychium is the skin that overlies the nail plate on its sides. It is also known as the paronychial edge. The perionychium is the site of hangnails, ingrown nails, and an infection of the skin called paronychia.^[12]

Hyponychium

It is the area between the nail plate and the fingertip. It is the junction between the free edge of the nail and the skin of the fingertip, providing a waterproof barrier and prevents the penetration of foreign bodies, dirt and invasion of pathogens that cannot digest keratin. It is composed of tough keratin layer that seals the subungual space.^[9, 12]

Lunula

The lunula is the visible portion of the distal nail matrix that extends beyond the proximal nailfold. It is white, half-moonshaped. The opacity of lunula is probably caused by considerable thickness of nail Matrix.^[9]

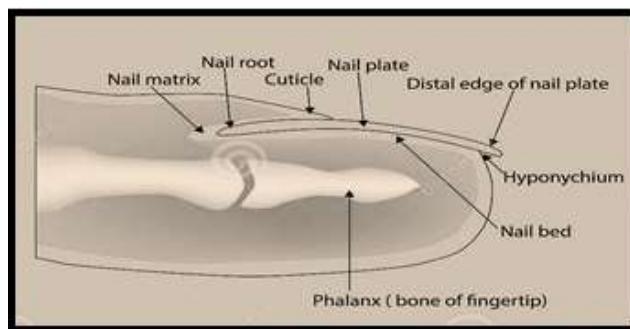


Fig No: 01 Anatomy of nail

NAIL ANATOMY

The finger nail has a three-layer structure (outer to inner) –

1. Dorsal layer (superficial) - is derived from the matrix.
2. Intermediate layer (middle) - it also derived from the matrix.
3. Ventral layer (deep)-is derived from the nail bed.

With a thickness ratio of approximately 3:5:2, respectively.^[10] The ventral layer consists of soft hyponychial in which many pathological changes occur.^[12]

Although the dorsal upper layer of the nail is only a few cells thick, it is composed of strong keratin with a high sulphur content, primarily in the form of the amino acid cysteine, which accounts for 94% of the nail's weight. The growth of nails is at its peak throughout childhood and gradually slows with age. The posterior nail fold's pressure causes the growth to shift from upward to forward. Localized nail fold disruptions or aberrant nail plate keratinization might potentially have an impact on nail growth. It is possible for general or local factors to cause the nail to thicken, ridge, pit, discolour, become brittle, split, or even separate from its bed.^[11] Severe illness can leave a transverse groove in the body. White

spots on the nail plate, which are present in 62% of healthy individuals, are caused by imperfect keratinization and the retention of nuclear material.^[12]

FUNCTION OF NAIL

- Your fingernails actually act as a form of defense. The tips of your fingers would become severely scraped if they weren't there. They also seem to assist us in grabbing onto things.
- The distal phalanx, the fingertip, and the nearby soft tissues are all shielded from harm by a healthy finger nail. Through counterpressure applied to the finger pulp, it also helps to improve the fine, accurate movements of the distal fingers.
- When the tip of the finger touches an object, the nail then serves as a counterforce, increasing the sensitivity of the fingertip.^[14]

ONYCHOMYCOSIS

One-third of integumentary fungal infections and half of all nail diseases have been linked to onychomycosis. The fungus that has infected your nail can potentially spread to other parts of your body and possibly to other people. Onychomycosis is more than just a cosmetic issue, despite the fact that those who have it are typically ashamed of their disfigured nails. Due to their limitations on mobility, these infections may impede peripheral blood flow, aggravating already severe diseases including venous stasis and diabetic foot ulcers.^[12]



Fig No: 02 onychomycosis

CAUSATIVE ORGANISM OF ONYCHOMYCOSIS

The word 'dermatophytes' is used to describe infection by members of the genus *Trichophyton*, *Epidermophyton* and *Microsporum*. The major causative organisms of onychomycosis are dermatophytes: *Trichophyton mentagrophytes*, *Trichophyton rubrum* and *Epidermophyton floccosum*. In some cases, the causative agents like *Trichophyton verrucosum*, *Trichophyton violaceum*, *Trichophyton kraidenii* and *Arthroderma spp.* are also responsible for onychomycosis. The secondary dermatophyte infection caused by *Tinea unguium*. Onychomycosis infection with Non dermatophytes cases about 10% of world wide, the most common organisms *Acremonium*, *Alternaria* species, *Aspergillus* species, *Botryodiplodia theobromae*, *Fusarium* species, *Onychochola canadensis*, *Pyrenochaeta unguis-hominis*, *Scytalidium dimidiatum* scopulariopsis species, *Scytalidium hyalimum*, *Neoscytalidium spp* and *Scopulariopsis brevicaulis*. Yeast caused onychomycosis infection up to 10 to 20% cases, with pathogenic organisms like *Candida albicans*, *Candida krusei*, *Candida parapsilosis*, *Candida glabrata* and *Candida tropicalis*.^[1,7,16]

TYPES OF ONYCHOMYCOSIS

The most common types of onychomycosis are:

1. Distal and lateral subungual onychomycosis
2. White superficial onychomycosis
3. Proximal subungual onychomycosis
4. Total dystrophic onychomycosis
5. Endonyx onychomycosis

ALREADY EXISTED TREATMENT OF ONYCHOMYCOSIS

Onychomycosis treatment is tough due to the infection's propensity to be buried within the nail, which makes it difficult for a medicine to penetrate, as well as the condition's high cost, unfavourable drug effects, need for prolonged therapy, and antifungal resistant (fungal) strains.^[19] Antibiotic and antifungal drug resistance has grown during the last few years. It's likely that using antifungal medications incorrectly or, more often than not, using topical antifungal medications without a prescription to treat fungal diseases has increased the chance of developing resistance or will result in the development of an antifungal resistance mechanism. Medical mycologists predict that as resistance spreads more widely, medication selection pressure will rise.^[3,20] Onychomycosis has a number of therapeutic options, including oral and topical antifungals, laser therapy, device-based therapies, surgical nail avulsion, nail debridement, and combination therapies.^[1]

ORAL ANTIFUNGAL AGENTS

Among the several treatment options for onychomycosis that are currently available, oral antifungal medications are thought to be the most efficient ones. Ketoconazole and fluconazole are frequently given for the treatment of onychomycosis; however, only griseofulvin, itraconazole, and terbinafine are now licenced for the treatment of this condition in the US and the UK by the US Food and Drug Administration (FDA). The oral administration of terbinafine, itraconazole, fluconazole, ketoconazole, and griseofulvin are first-line onychomycosis therapy techniques.^[17]

TOPICAL ANTIFUNGAL AGENT

Due to their potential to penetrate biofilms and lower likelihood of drug-drug interactions, topical medicines for the treatment of onychomycosis are growing in popularity. There are obstacles to penetration, such as the nail's slow development and thickness, its hard nail plate, which serves as a concentrated hydrogel, its dense, impenetrable network of keratin fibres, and nails that are sick. The more recent topicals are pricey, and patients with poor dexterity or mobility may have trouble adhering to treatment regimens due to their length.^[1] The most recent advancements in the treatment of topical onychomycosis include ciclopirox and amorolfine nail polish.^[17] An antifungal cream such as Tavaborole, Efinaconazole, or Ciclopirox.^[5]

SIDE EFFECT OF ALREADY EXISTED TREATMENT OF ONYCHOMYCOSIS

- Hepatotoxicity
- Leukopenia
- Thrombocytopenia or anemia
- Headache
- Nausea
- Photosensitivity
- Vomiting
- Abdominal pain
- Pruritus
- Fever
- Hypersensitivity reactions

REMEDIES

One of the safer, less expensive, frequently accessible, and deemed safe alternatives to synthetic medications is the use of medicinal plants and herbal items to treat fungus infections. The thick fungal cell wall, which is made of chitin and other polysaccharides like -glucans, makes it more challenging to find antifungal drugs than it is for bacteria. In fact, many reports from throughout the world have occasionally mentioned the antifungal activity of plant extracts and essential oils from plants, including their effects on dermatophytes and NDMs. Due to its ability to treat diseases and lack of negative side effects, medicinal plants have attracted more attention in recent years. Researchers found that using plant-based solutions to combat fungus infections has also been proven to be a successful strategy. Some plants, including ginger, neem, cilantro, garlic, tulsi, henna, aadu thinna paalai, Erik, aloe vera, and others, have been shown to have antifungal properties against fungi. Some of the bioactive substances included in these plants include 1,4-naphthoquinone, saponins, glycosides, carbohydrates, Flavonoids, alkaloids, tannins, citronellol, geraniol, thymoquinone, and phenolic compounds.^[3]

DIFFERENT FORMULATION FOR NAIL

The most widely formulated dosage forms for nails are:

- Nail lacquer
- Enamel remover
- Nail moisturizers
- Powder polish
- Nail cream
- Nail bleach
- Cuticle remover
- Cuticle softener

NAIL LACQUER

A viscous lacquer known as nail enamel, nail varnish, or nail paint is used to beautify and protect the nail plate on the surface of fingernails or toenails. Since a longer time, conventional nail lacquer has been used as cosmetics to beautify and protect nails. Topical nail care products like lacquer, enamel, and varnish enhance and maximise the colour, lustre, and glow of nails.^[12,22,23]

CONSTITUENTS OF NAIL LACQUER

1. Film forming polymers

Nail polish that has been applied to a solvent evaporates, leaving a coating of polymer on the nail. Examples include vinyl polymers, nitro cellulose, ethyl cellulose, cellulose acetate, methacrylic acid, and cellulose.

2. Adhesive polymer resin

To ensure the nitrocellulose stick on the nail plate surface. Example: Benzoin, Modified tosylamide formaldehyde, Shellac, Polyvinyl and Polystyrene.

3. Plasticiser

To increase the flexibility of nail polish after it dries and extend the lifespan of nail polish. Example: Camphor, Castor oil, d-butyl phthalate, n-butyl phthalate, Glycol ester.

4. Glitter

To add glittery or shimmer look. Example: Aluminium powder, natural pearls mica and bismuth oxychloride.

5. Solvent

Evaporation characteristics are important of nail lacquer, but rapid rate of evaporation causes poor flow of enamel resulting in uneven and streaky application.

Example: Ether, Ethyl acetate, Amyl acetate, Ethyl alcohol, Butyl alcohol and Acetone.

6. Stabilizers

Resist colour changes when the dry film is exposed to sunlight. Example: Benzophenone-1

7. Thickening agent

To maintain the sparkling particles in suspension while in the bottle. Example: Stearalkonium hectorite.^[10, 12, 22]

Advantage of nail lacquer

- prevent the nail from scratches
- It's used to beautify of hands
- Improve strength and thin of nails
- It's not damage to the nail
- Nail polish looks natural on the nail
- It used to prevent growth of fungus and bacteria
- It's no smudge

Disadvantages of nail lacquer

- Not easily removable without use of nail lacquer remover
- Nail become weak and brittle
- Its cause cancer
- Gaps develop between polished nails and cuticles
- Its mask the nail bed
- Flammability
- Sometimes small ingestion of nail polish cause irritation of stomach throat when eat food.^[10]

CONCLUSION

Onychomycosis is a fungal infection, most commonly affecting on nail by dermatophytes, non dermatophytes, molds and yeast. In this review discussed on the causative organism of onychomycosis, different diseases affecting nail, nail anatomy and structure, already existed treatment of onychomycosis. Treatment of onychomycosis is antibiotic and antifungal drug resistance has grown during the last few years. The challenges of the drug delivery to the nail, to understanding the barrier properties of nail formulation. The oral administration (like terbinafine, itraconazole, fluconazole, ketoconazole and griseofulvin) and topical onychomycosis (like ciclopirox and amorolfine) nail polish. Side effect of already existed treatment of onychomycosis like Hepatotoxicity, Leukopenia, Thrombocytopenia or anemia, Photosensitivity. To overcome this side effect to prepare the topical formulation containing medicinal plant like *Aristolochia bracteolata*, *Lawsonia inermis* and *Calotropis procera*.

REFERENCE

1. Falotico JM, Lipner SR. Updated perspectives on the diagnosis and management of onychomycosis. *Clinical, Cosmetic and Investigational Dermatology*. 2022 Jan 1;1933-57.
2. Leung AK, Lam JM, Leong KF, Hon KL, Barankin B, Leung AA, Wong AH. Onychomycosis: an updated review. *Recent patents on inflammation & allergy drug discovery*. 2020 May 1;14(1):32-45.
3. Borgohain P, Saikia LR, Mahanta J. Herbal medicine as an alternative for the treatment of onychomycosis. 2022 Feb 7:29-34
4. Baran R, Hay RJ, Tosti A, Haneke E. A new classification of onychomycosis. *British Journal of Dermatology*. 1998 Oct 1; 139(4):567-71.
5. Gupta AK, Stec N. Recent advances in therapies for onychomycosis and its management. *F1000Research*. 2019;8.
6. Runyoro DK, Ngassapa OD, Nondo RS, Melkiory P. Antifungal activity against onychomycosis causative fungi and brine shrimp lethality of a Tanzanian ornamental plant *Euphorbia cotinifolia* L. (Euphorbiaceae). *Journal of Pharmaceutical Sciences and Research*. 2017;9(1):63.
7. Elewski BE. Onychomycosis: pathogenesis, diagnosis, and management. *Clinical microbiology reviews*. 1998 Jul 1; 11(3):415-29.
8. De Berker DA, André J, Baran R. Nail biology and nail science. *International journal of cosmetic science*. 2007 Aug; 29(4):241-75.
9. Neelam N. Mangtani, Tanishka Gupta, Swati Gajbhiye A review of antifungal herbs in nail lacquer for the treatment of onychomycosis. 2019 May 4
10. Mohite MS, Kharat J, Deshmukh S, Kashid G. Formulation and Evaluation of Herbal Based Nail Polish. homepage: <https://www.easpublisher.com/>. 2022;4(2):20-8.

11. Abdullah L, Abbas O. Common nail changes and disorders in older people: Diagnosis and management. *Canadian Family Physician*. 2011 Feb 1;57(2):173-81.
12. Aswani VM. Formulation and Evaluation of a Medicated Nail Lacquer for the Treatment of Onychomycosis 2015. (Doctoral dissertation, RVS College of Pharmaceutical Sciences, Coimbatore).
13. Daniel CR, Tosti A, Iorizzo M, Piraccini BM. The disappearing nail bed: a possible outcome of onycholysis. *CUTIS-NEW YORK-*. 2005 Nov 1;76(5):325.
14. Bhapkar PH, Puttewar TY, Patil RY. Topic name–nail lacquers in nail diseases. *IOSR Journal of Pharmacy*. 2013 Oct;3(9):24-48.
15. Sarkar M, Mahesh DM, Madabhavi I. Digital clubbing. *Lung India: Official Organ of Indian Chest Society*. 2012 Oct;29(4):354.
16. Chadeganipour M, Mohammadi R. Causative agents of onychomycosis: a 7-year study. *Journal of clinical laboratory analysis*. 2016 Nov;30(6):1013-20.
17. Thomas J, Jacobson GA, Narkowicz CK, Peterson GM, Burnet H, Sharpe C. Toenail onychomycosis: an important global disease burden. *Journal of clinical pharmacy and therapeutics*. 2010 Oct;35(5):497-519.
18. Westerberg DP, Voyack MJ. Onychomycosis: current trends in diagnosis and treatment. *American family physician*. 2013 Dec 1;88(11):762-70.
19. Morah FN, Okoi WW. Euphorbia Sanguinea stem sap as antifungal agent against Onychomycosis. *Int. J. Adv. Sci. Res*. 2016; 1:8-9.
20. Hudson MM. Antifungal resistance and over-the-counter availability in the UK: a current perspective. *Journal of Antimicrobial Chemotherapy*. 2001 Sep 1;48(3):345-50.
21. Borgohain P, Barua P, Das D, Mahanta J, Saikia B, Dutta P, Saikia LR. Antifungal Activity of Selected Medicinal Plants Used by Indigenous People of Assam in India to Treat Onychomycosis. *Journal of Herbs, Spices & Medicinal Plants*. 2022 Apr 3;28(2):160-78.
22. Chandra S, Das A. The science of nail polish, nail polish remover, and nail moisturizers. In *Nail Disorders 2019* Feb 4 (pp. 497-501). CRC Press.
23. Yadav K. A review article on anti-fungal nail lacquer using treatment of onychomycosis. *International Journal of Scientific and Research Publications*. 2019;9(4):352-7.