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REVIEW ARTICLE

Innovative Approaches for Onychomycosis Treatment: An Insight Into Natural Remedies and Novel Pharmaceutical Formulations

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Abstract

Onychomycosis, commonly referred to as nail fungus, is a persistent and difficult-to-treat condition that affects both toes and fingernails. Even though traditional treatments such as antifungal medications and topical ointments are effective in some cases, they are often associated with significant side effects and a high recurrence rate. There has been a growing interest in alternative and complementary treatments in recent years, including natural remedies and new pharmaceutical formulations, which are becoming increasingly popular. This review aims to explore the current state of knowledge surrounding onychomycosis treatment and its challenges, with a particular focus on the benefits and limitations of the current therapeutic options. Also, light is shed on the prospects available as treatment options.

Key words: Onychomycosis; Fungus; Formulations; Natural; Antifungal.

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Introduction

Onychomycosis, often known as a fungal infection of the nail, accounts for over half of all nail illnesses. Its frequency is estimated to be around 5.5 %.[1] The elderly (those over the age of 65), those with diabetes, people with impaired immune systems (particularly those with HIV) and sportsmen are more at risk for developing onychomycosis.[2] Both environmental variables and autosomal inheritance (HLA-DR8) have a role in the prevalence of onychomycosis in families. The first toenail is the most common nail on which onychomycosis manifests, yet it can affect any nail. It can spread to the skin around it, although systemic effects are extremely rare. Toenail fungus infections are often minor and easy to treat. Nails infected with fungus may change colour, become thick, brittle, or crack.

Depending on the clinical subtype, many factors contribute to developing onychomycosis. The most frequent kind of onychomycosis, known as distal lateral subungual onychomycosis, involves the migration of fungus from the plantar surface to the nail bed through the hyponychium. Distal lateral subungual onychomycosis manifests itself clinically by inflammation of the nail apparatus.[3, 4] On the other hand, white superficial onychomycosis is a less common presentation produced by

the invasion of the nail plate's surface.[5, 6] Fungi infiltrate the nail matrix through the proximal nail fold and populate the deep section of the proximal nail plate in the rare condition known as proximal subungual onychomycosis.[7, 8] "End-onyx" onychomycosis is a kind of distal lateral subungual onychomycosis in which the fungus infects the nail *via* the epidermis and enters the nail plate.[9, 10] Onychomycosis that affects the entire nail bed is called total dystrophic onychomycosis. Candida invasion of the nails is uncommon because the yeast requires a compromised immune response as a predisposing factor to get under the nail plate. *Candida* is only a secondary coloniser in individuals with chronic *paronychia* or onycholysis, although it is frequently isolated from the proximal nail fold or the subungual region of these patients.

Nail as a barrier to drug permeation

Mammal claws and nails are epidermal derivatives that serve as armour for the digits and toes and as implements and weapons. About 25 layers of dead, keratinised, flattened cells make up the nail plate, which is thin (0.25 mm – 0.6 mm for fingernails and up to 1.3 mm for toes), rigid, but somewhat elastic, transparent, convex in shape and protected by a nail bed.[11] Cell structures called desmosomes, randomly distributed on the lateral surfaces of plasma membranes and specialised for cell-to-cell adhesion are responsible for the strong bonds between these cells.[12] Compared to the epidermis, the permeability parameters of the human nail plate are substantially different because of the nail plate's unique physicochemical attributes.[13] Nail plate behaviour is comparable to that of a hydrogel with high ionic strength and the structure of human nails has been compared to a hydrophilic gel membrane, while the SC acts as a lipid barrier to the absorption of low molecular weight substances.[14] The nail, which has a lipid content of just 0.1 %, loses water faster than the lipid-rich epidermis around it. Hydrophobic chemicals have been proven to permeate into and through the nail despite its purported hydrophilic characteristics.[15] For instance, long-chain alcohols can penetrate the nail through a lipid pathway, as described by Walters and colleagues.[16]

Increasing penetration is crucial for the success of transungual medications. To do this, the nail plate might be damaged mechanically or chemically. Iontophoresis and drug formulations inside vehicles that provide high drug partition into the nail plate are two further options for increasing medication penetration into the intact nail plate.[17, 18]

Current therapeutic options for treatment

The severity, number of nails damaged and kind of onychomycosis present all play a role in determining the best course of treatment.[19, 20] Proximal subungual onychomycosis, as well as distal lateral subungual onychomycosis affecting the lunula area, invariably necessitate systemic therapy. It is possible to use topical medication to treat white superficial onychomycosis and distal lateral subungual onychomycosis that is confined to the distal nail. The success rate of therapy rises when systemic and local approaches are used together. Lasers and photodynamic therapy are promising future therapeutic options.[21, 22] Figure 1 describes the common ways for the treatment of nail psoriasis.

Topical medications should only be used when the affected area is less than half of the distal nail plate or when the patient cannot tolerate systemic therapy. Nail treatments like ciclopiroxolamine 8 % and efinaconazole 10 % are commercially available in the USA. Topical therapies often fall short when it comes to onychomycosis since they cannot get deep enough under the nail plate to do the trick. Both ciclopirox and amorolfine solutions are said to be able to permeate all layers of the nail but only work somewhat when applied alone.[23] They could help prevent relapse in individuals treated with systemic medicines or as an adjuvant to oral therapy. Efinaconazole and ciclopirox require daily application and are used for an extended period (48 weeks) to be effective.[24, 25] Toenail onychomycosis treatment has been effective with efinaconazole.[26] Efinaconazole was associated with considerably higher mycologic cure rates than the drug vehicle.[27, 28]

When used topically, tavaborole (aboron-containing antifungal) is effective against *Trichophy-*

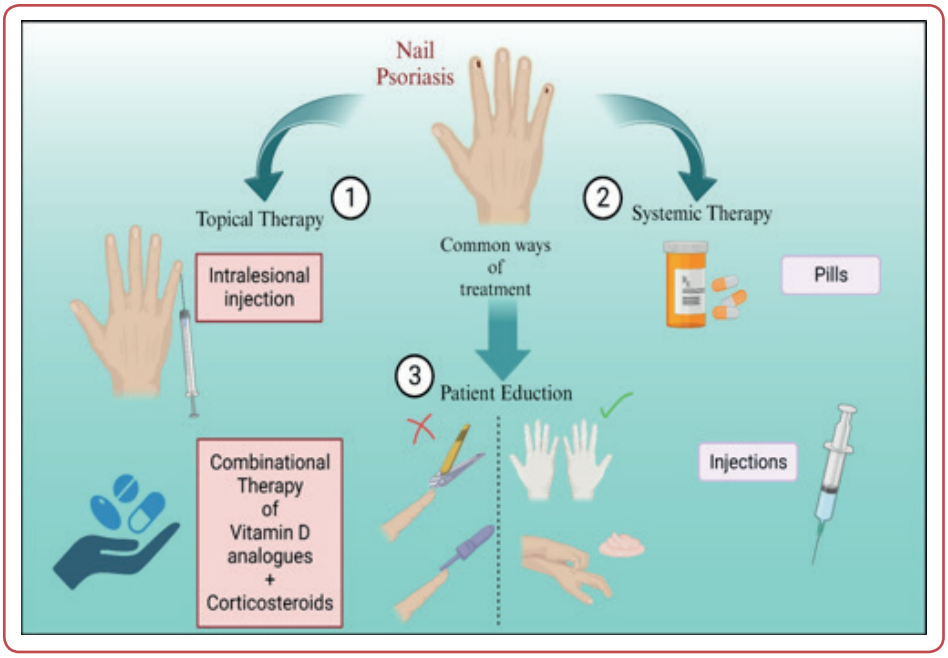

Figure 1: Common ways for the treatment of nail psoriasis

ton rubrum and *Trichophyton mentagrophytes*, the causative agents of toenail onychomycosis.[29] It was accepted after 1194 participants in two randomised, double-blind, placebo-controlled studies at many locations. Complete remission was observed in 6.5 % and 9.1 % of tavaborole-treated patients after 48 weeks of therapy, compared to 0.5 % and 1.5 %, respectively, of patients treated with the vehicle alone.[30] Effective treatment for onychomycosis has been found with fluconazole, 150–450 mg once weekly for adults; this may be especially helpful for patients with complex prescription regimens.[31, 32] However, contrasting once-weekly fluconazole with itraconazole and terbinafine has not shown comparable efficacy or cost-effectiveness.[33, 34]

Onychomycosis can be treated with griseofulvin. Low-quality evidence suggests that terbinafine is more effective than griseofulvin for these endpoints, while moderate-quality evidence suggests that azoles are just as effective as griseofulvin.[35] It is important to note that albaconazole, a broad range of oral antifungal medication, is not currently available on the market. Albaconazole may be a potential therapy option for onychomycosis since it was reported to be more effective than a placebo in a phase II randomised study for distal subungual onychomycosis.[36] As an example of a new generation (tetrazole antifungal) agent, VT-1161 inhibits lanosterol 14-alpha demethylase (CYP 51), which has the potential to be effective in the treatment of onychomycosis.[37]

Uncontrolled trials showing clinical improvement in a percentage of patients are largely the only evidence supporting the benefit of laser devices. Treatment with a dual-wavelength near-infrared diode laser for onychomycosis showed positive results in a small, randomised experiment.[38] Results from randomised controlled studies of Nd:YAG lasers for onychomycosis have been disappointing. After three months, there was no statistically significant difference between the groups in terms of the proportion of patients who had a mycologic clearance of all affected nails in a randomised trial in which 27 patients with onychomycosis involving 125 nails were randomly assigned to two treatments with 1064 nm Nd:YAG laser (17 patients) or no treatment (10 patients).[39, 40]

Several mechanisms of action have been proposed for laser therapy for onychomycosis. These include direct fungicidal effects, inhibition of fungus by laser-induced changes in the tissue environment and laser-induced immunologic effects.[41] Patients who do not respond to pharmacological treatment alone may have surgical excision of the nail (nail avulsion).[42] The use of iontophoretic drug delivery, in which a mild electrical current is applied to a topical medicament to increase its absorption, shows promise for enhancing the efficacy of topical antifungal therapy.[43, 44] Combination therapy appears to enhance the chance for new healthy nail development in a small, unblinded, randomised study comparing

the treatment of toenail onychomycosis with topical terbinafine and iontophoresis with the sole topical terbinafine.[45]

Natural remedies

Natural products have been proven to be beneficial in various other diseases for ages. Due to the poor permeation characteristic of topical products and poor oral bioavailability of antifungal drugs, there has been a steep rise in interest in natural remedies for the treatment of onychomycosis. Based on data available through various sources the following products were found to possess anti-onychomycosis activity.

Tea tree oil

Before modern antimicrobials were developed, essential oils were often used. Tea tree oil has been shown to have beneficial effects against bacteria, fungi, viruses and inflammation.[46, 47] Tea tree oil has been found in many trials to have antifungal effects.[48] For the most part, studies including tea tree oil have concentrated on its potential to cure *Candida* infections.[49, 50] Tea tree oil has also been demonstrated to be an effective therapy for dermatitis, ringworm (*T equinum*) and stomatitis, according to studies.[51, 52]

Essential oils have also improved the skin's ability to absorb and hold onto medications.[53, 54] Furthermore, this suggests that tea tree oil may be useful as a delivery vehicle for other antifungal drugs. Tea tree oil has been proven in many tests when used with antifungal drugs to have a synergistic impact.[55] Tea tree oil is effective against *T rubrum*, the most prevalent cause of onychomycosis, in *in vitro* antifungal assays.[56] Misner discovered that a blend of essential oils applied topically to the feet and containing tea tree oil blocked the growth of aerobic bacteria, yeast and fungus on the foot when enclosed in shoes.[57] Tea tree oil and clotrimazole are both used to treat onychomycosis, but Buck and coworkers compared how well they work. Treatment with clotrimazole resulted in an 11 % cure rate, whereas treatment with tea tree oil resulted in an 18 % cure rate in this randomised, controlled study of 117 patients.[58]

Flores and colleagues recently assessed the antifungal effectiveness of tea tree oil in an onychomycosis model. Results showed that *T rubrum* growth was inhibited when the oil was encapsulated in nanocapsules and then suspended. A model-based study was performed and it was found that the diameters of the fungal colony were 2.88 ± 2.08 mm^2, 14.59 ± 2.01 mm^2, 40.98 ± 2.76 mm^2 and 38.72 ± 1.22 mm^2. Based on the data it can be said that oil in nanocapsules was found to be best for onychomycotitic treatment.[59]

Ageratina pichinchensis

Using ciclopirox (8 %) as a positive control, researchers created a standardised 10 % lacquer with a depigmented extract of the aerial portions of *A pichinchensis* and tested it in a randomised, double-blind clinical trial on patients with cutaneous mycosis with less than 50 % fungal infection. The therapeutic and mycological effectiveness of the group treated with the standardised extract was 71.1 % and 59.1 %, respectively, whereas the control group's results were 80.9 % and 63.8 %, respectively, with no adverse effects. Since encecalin was the most abundant component, the authors reasoned that it must be responsible for the desired pharmacological action.[60]

Romero-Cerecero et al prepared two types of lacquer using either 12.6 % or 16.8 % extracts and tested them agains*t T mentagrophytes*. Patients with mild and severe onychomycosis, defined as having between one and ten infected nails, were followed for six months while receiving one of these therapies. No fungi were detected in mycological microscopic tests and patients treated with lacquer (16.8 % extract) exhibited a statistically significant improvement over those treated with lacquer containing 12.6 % extract.[61]

Coniferous resin lacquer

Natural coniferous resin from the Norway spruce (*Picea abies*) is highly effective against all dermatophytes responsible for onychomycosis in humans.[62, 63] Sipponen et al conducted a study using natural coniferous resin to treat onychomycosis.[64] Thirty-seven people having a clinical diagnosis of onychomycosis were included in the research. During the study, all participants applied a topical resin lacquer treatment once daily. Nail samples were processed at the start and finish of the investigation using a mycological culture and a potassium hydroxide (KOH) stain. Twenty patients with positive mycological cultures or KOH stains for dermatophytes at study enrolment. Only 6 patients had positive results towards the end of the research. There was a clinical success

with resin lacquer therapy, as reported by 14 patients who followed all instructions. There is some proof that the natural coniferous resin used topically for onychomycosis works clinically, as shown by the findings. Although this is only preliminary observational research, it does provide some evidence that coniferous resin applied topically over an extended period (30 days) in the form of lacquer at a concentration of 30 % may aid in the healing of onychomycosis.[65, 66]

Novel treatment options

Emulsions

An emulsion is a mixture of two or more liquids normally immiscible (unmixable or unblendable) owing to liquid-liquid phase separation. Emulsions may be made using a variety of liquids, although water and oil are the most frequent. However, nanoemulsions are granted kinetic stability due to the lower attraction between the small-sized droplets, which prevents the droplets from gravitationally separating and aggregating.[67] In contrast to microemulsions, nanoemulsions are not sensitive to changes in physical and chemical conditions like temperature and pH. They can be prepared using a lesser quantity of surfactants. The optical quality and stability of a nanoemulsion are not the only concerns affected by the droplet size; the nanoemulsion's rheological and release behaviour are, too. Therefore, nanoemulsions are superior to microemulsions in several settings.[68]

An additional non-invasive local treatment for onychomycosis is photodynamic therapy (PDT). Photosensitiser drugs are used in PDT and these medications must be "photoactivated" by certain wavelengths of light. Also, PDT does not cause any systemic negative effects and may be used repeatedly without developing resistance in the fungus.[69] There have been many published clinical trials using PDT to treat onychomycosis. Aluminium chloride phthalocyanine nanoemulsions were used by Morgado et al for the treatment of onychomycosis. This combination of photosensitiser and nanoemulsion known as a third-generation photosensitiser. This generation of photosensitisers offers several benefits over earlier generations, including photoactivation at longer wavelengths, which makes it possible to treat deeper nail layers, ease of distribution throughout the nail and skin and absence of staining due to methylene blue.[70, 71]

Emulsions are often stabilised by surfactants.[72] Pickering emulsions are particle-stabilised emulsions that provide various benefits over traditional emulsions.[73, 74] Due to the increased adsorption energy of solid particles compared to surfactants at oil-water interfaces,[75] this adsorption can be deemed irreversible, allowing Pickering emulsions to be as stable as traditional emulsions. The size of emulsion droplets is also a crucial factor in developing and administering emulsion-based pharmaceuticals and medical treatments. On this basis, Horváth et al created tea tree essential oil-based Pickering emulsions.[76] *In vitro* studies showed that Pickering emulsion formulation showed better drug permeation in agar gel membranes. The Pickering emulsion with the smallest droplet size of about 1.85 µm could deliver 89.9 % of actives through the agar membrane.[77]

Agrawal et al formulated a microemulsion based on efinaconazole for the transungual route to treat onychomycosis. The microemulsion formulations of efinaconazole showed enhanced penetration compared to the reference formulation in *ex vivo* permeation and nail clipping experiments without noting any delay in drug release from the nail plate. Microemulsion formulations showed higher antifungal efficacy than the reference formulation in an *in vitro* examination of three fungal species (*Trichophytonrubrum, Trichophytonmentagrophytes* and yeast *Candida albicans*).[78]

Pal et al developed a microemulsion-containing gel using benzyl alcohol and isopropyl myristate was added as an oil, Pluronic F68 as a surfactant and ethanol as a co-surfactant, in double-distilled water and loading itraconazole as the model antifungal drug for the treatment of onychomycosis. Because of itraconazole hydrophobicity, it prefers to stay in an intermediate location, ie at the palisade layer inside the surfactant molecules of the microemulsion structure, rather than in the oil phase or the aqueous phase. Keratolytic ingredients such as salicylic acid, which regulates the formulation's pH and urea are thought to improve the nail's ability to retain water significantly.[79] Nails, it is thought, respond well to water as a plasticiser. The rate at which molecules can diffuse through the nail plate grows in tandem with the nail's moisture content. The formulation's pH, the molecular weight of the penetration molecule, etc are all crucial considerations.[80]

Hydrogels

Hydrogels are a three-dimensional polymer matrix that swells when exposed to the water phase. They have been reported in various applications such as wound healing, drug delivery, imaging, etc.[81, 82] Kesharwani et al developed an itraconazole and difluorinated-curcumin-based nanoparticle entrapped hydrogel system to treat onychomycosis. The drugs were loaded into chitosan nanoparticles using the ionic gelation method and they were dispersed in Carbopol 940-based hydrogels. The hydrogels provide a good residence time in the fungal-affected region. As a result, this increases the permeation due to hydration, enhances drug delivery and reduces the burden of higher drug dosing. *In vitro* data showed a significant decrease in the colony-forming units compared to free drug molecules applied. This can be due to nano-sized formulation, which causes the slow release of drugs but at a steady rate from the polymer matrix.[83]

Amra et al developed a ketoconazole-based microemulsion loaded in hydrogel using nigella oil as a permeation enhancer and various polymers such as HPMC K100, HPMC K4M, HPMC K100M, Carbopol 971, Carbopol 974, Carbopol 980, xanthan gum, sodium alginate and sodium CMC.[84] The optimised formulation containing alginate and HPMC (1:1), was further evaluated for drug release study. A sustained-release formulation is favoured over the currently available cream for treating fungal infections since it requires fewer applications.[85]

Nanoparticles and nanocapsules

Gaballah et al developed nanocapsules to deliver ciclopirox using Poly lactide-co-glycolide *via* nanoprecipitation technique and to incorporate them into hydroxypropyl chitosan-based nail lacquer.[86] The placebo lacquer exhibited antifungal activity and a zone of inhibition at 15.80 ± 0.14 mm, while medicated nail lacquer showed a significantly higher zone of inhibition of a mean diameter of 62.60 ± 13.32 mm.[87]

Nail polishes with water-soluble film-forming agents solve the issues with water-insoluble nail varnishes by ensuring strong adhesion to the nail and facilitating the partition and/or release of the active substance to the nail. Penetration enhancers containing vesicles (PEVs) have been reported to have a good permeation effect on the skin barrier. PEVs are quite similar to liposomes but are distinguished by possessing many permeation enhancers, such as oleic acid, labrasol and transcutol. Bseiso et al developed PEVs of sertaconazole skin fungal disease treatment.[88] The same authors later developed PEVs, including nail permeation enhancers such as N-acetyl-L-cysteine, thioglycolic acid, thiourea and ethanol and sertaconazole as a model drug for the onychomycosis treatment. Microbial testing showed a zone of inhibition for control formulation of 5.3 ± 0.58 mm due to the presence of permeation enhancers such as cysteine and its derivative. The formulation showed (20.9 ± 0.25 mm) a significant increase in the zone of inhibition compared to the model (11.6 ± 0.44 mm). This was primarily due to the synergistic effect of sertaconazole and permeation enhancers.[89]

Vesicular drug delivery systems or carriers

Researchers proposed several liposomal-based formulations for treating onychomycosis, including those loaded with terbinafine as a model drug. Phospholipon 90 G and Lipoid S 100, as phospholipids for the liposomal layer and pullulan and Eudragit L100, as plasticisers for the liposomes, were used in the preparation of the newly acquired film formulations. The liposomes were dispersed in a gel to facilitate their use on fingernails. The proportion of medication released *in vitro* from liposome-loaded films ranged from 46.0 to 71.6 %. Nail plate accumulation of the various film formulations was within the therapeutic range, measuring between 8.17 to 31.16. As observed previously, all nail thicknesses dropped after the experiments due to the experimental settings. The transonychial water loss (TOWL) of nails was measured to demonstrate the nail plate's efflux of water. The nail plate expands when submerged in water because it acts like a hydrophilic gel membrane. Swelling causes the intercellular spaces between keratin structures to enlarge, allowing more water to permeate through them. The swelling was present throughout the experiment, the TOWL of the nails rose in each casen.[90] Similar results were reported by Shah et al, they also formulated the based liposomes of terbinafine HCl using a quality by design (QbD) approach and reported similar outcomes.[91]

Novel and investigational treatments for onychomycosis

ME1111

Meiji Seika Pharma Co, Ltd (Tokyo, Japan) recently discovered ME1111 [2-(3,5-dimethyl-1H-pyrazol-1-yl)-5-methylphenol], a new agent with potent *in vitro* antifungal activity against dermatophytes like *T rubrum* and *T mentagrophytes*, which are common etiologic agents of onychomycosis.[92] It has been suggested that a compound's molecular weight plays a crucial role in its capacity to penetrate nails.[93] ME1111's molecular weight of 202.25 makes it easily able to pierce human nails. The prior *in vitro* experiments showed that ME1111 penetrates nails more deeply than ciclopirox (the active ingredient in *Penlac* nail lacquer).[94, 95] There was no safety problems found in GLP-compliant general toxicity studies, including ME1111. These investigations included repeated-dose toxicity, safety pharmacology and genotoxicity. It was found that the succinate dehydrogenase (complex II) of the mitochondrial electron transport system is the molecular target of the new antifungal drug ME1111.[96, 97] Missense mutations in the genes encoding SdhB, SdhC and SdhD were found in ME1111-resistant *T mentagrophytes* mutants produced *in vitro.* Cross-resistance to carboxin and boscalid, which have been reported to bind to the ubiquinone-binding region surrounded by SdhB, SdhC and SdhD, was observed for most ME1111-resistant mutants. These data point to ME1111's binding site being the same as or very close to, the ubiquinone-binding site.[98]

NP213

NP213 (*Novetexatine*) is a topical antifungal medication for onychomycosis. NP213 is a cyclic antimicrobial peptide that is synthetic, water-soluble and very efficient in penetrating human nails.[99] NP213 was inspired by HDPs (host-defence peptides). The skin and nails are the primary sites of HDP expression and production[100] and they play a crucial role in the innate immune response to infection.[101, 102] At concentrations of 4-7 ppm, NP213 is quickly fungicidal in a water-based topical formulation and it has shown superior effectiveness to known antifungal drugs under *in vitro* circumstances mimicking those of the human nail. Unlike the comparative topical onychomycosis treatments ciclopirox and amorolfine, NP213 efficiently eliminated distinct strains of *T rubrum* from diseased nails in *ex vivo* human nails after just 28 days of daily administration. Unlike other topical onychomycosis therapeutics, NP213 can effectively penetrate the human nail *via* transungual and subungual routes thanks to its water-based film-forming vehicle, which eliminates the need for penetration enhancers,[103, 104] optical brighteners[105, 106] and the use of organic solvents.[107, 108]

Clinical trials

An extensive literature search has revealed the completion of 31 interventional clinical trials related to onychomycosis. The findings of these trials provide valuable insight into the current state of knowledge surrounding the treatment of onychomycosis. To make this information accessible and easy to understand, the details of these trials have been summarised and presented in Table 1.

Table 1: Summary of interventional clinical trials on onychomycosis

NCT number	Interventions	Study size	Phase
NCT01278394	Drug: AN2690 solution, 5.0 %	29	Phase 2
NCT00791219	Drug: SUBA-itraconazole, itraconazole, placebo	175	Phase 2
NCT01851590	Device: resin lacquer Drug: amorolfine, terbinafine	129	Phase 4
NCT03168841	Drug: Efinaconazole topical	40	Phase 3

NCT02812771	Drug: Efinaconazole	62	Phase 4
NCT02588599	Device: Erchonia LUNULA	54	Not applicable
NCT00730405	Drug: albaconazole 100 mg, albaconazole 200 mg, albaconazole 400 mg, placebo 400 mg	584	Phase 2
NCT01666002	Device: laser treatment (pulsed Nd:YAG 1064 nm laser)	27	Not applicable
NCT02267356	Drug: VT-1161, placebo	259	Phase 2
NCT00871728	Drug: itraconazole	132	Phase 4
NCT00356915	Drug: itraconazole 100 mg capsules, itraconazole 200 mg tablets, placebo tablets	1381	Phase 3
NCT03110029	Drug: Efinaconazole 10 % topical application solution [JUBLIA] Other: application of nail polish	13	Phase 4
NCT03216200	Device: plasma treatment	5	Not applicable
NCT00459537	Drug: terbinafine hydrogen chloride, amorolfine nail lacquer	1029	Phase 3
NCT01302119	Drug: AN2690 topical solution, 5 %, solution vehicle	604	Phase 3
NCT01270971	Drug: AN2690 topical solution, 5 %, solution vehicle	594	Phase 3
NCT00491764	Drug: SCH 56592, terbinafine, placebo	218	Phase 2
NCT03072550	Device: RenewalNail™ plasma treatment system	26	Not applicable
NCT00935649	Device: PinPointeFootLaser	134	Phase 2/3
NCT02933879	Drug: NVXT topical, placebo (vehicle) topical	184	Phase 2
NCT02798380	Drug: HTS-519 insert	30	Phase 2
NCT02242019	Device: erchonia LUNULA	109	Not applicable
NCT01534689	Device: erchonia FX-405™ laser	105	Not applicable
NCT00443898	Drug: terbinafine, placebo	518	Phase 3
NCT00443820	Drug: terbinafine, placebo	526	Phase 3
NCT03405818	Drug: tavaborole 5 % topical solution	55	Phase 4
NCT03098615	Drug: Jublia (efinaconazole 10 % topical solution)	19	Phase 4
NCT02343627	Drug: NVXT solution, vehicle of the test product	47	Phase 2
NCT02679911	Drug: loceryl NL, ciclopirox NL	20	Phase 4
NCT02714504	Drug: voriconazole or posaconazole	239	Not applicable
NCT02321098	Drug: loceryl NL + cosmetic varnish, loceryl NL 12 weeks, loceryl NL 15 months	50	Phase 4

Conclusion

Nail fungus is a complicated and long-lasting medical illness and this study has summarised the current therapy options for onychomycosis. Although antifungal drugs and topical ointments are the mainstays of traditional therapy, they can have certain side effects. There has to be a change in treatment approaches because of the serious side effects and high recurrence rates of these current options. As part of a larger movement in medicine towards more integrative and patient-centred methods, they include novel pharmaceutical formulations and natural cures. The rising desire for therapies that are effective, safe and tolerated over the long term is reflected in the popularity of these options. Additional clinical studies and research are needed to confirm the effectiveness of alternative therapies, but some show promise. There is hope for the future of onychomycosis therapy in the scientific community. New insights into the pathophysiology of the illness, together with developments in me-

dicinal research and pharmaceutical development, have the potential to completely alter current approaches to therapy. Reducing the burden of side effects and recurrence, personalised medicine and targeted treatments have the potential to deliver more effective and individualised treatment alternatives. To sum up, onychomycosis therapy has come a long way, but there's still a long way to go. The existing limits must be overcame *via* ongoing research and innovation so that patients may have access to safer, more effective and more personalised treatment alternatives in the future. Both academics and healthcare providers face new obstacles in the treatment of onychomycosis, but patients with this persistent and agonising ailment have reason to be hopeful about the future.

Ethics

This study was a secondary analysis based on the currently existing data and did not directly involve with human participants or experimental animals. Therefore, the ethics approval was not required in this paper

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Conflicts of interest

The authors declare that there is no conflict of interest.

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Data access

The data that support the findings of this study are available from the corresponding author upon reasonable individual request.

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