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RECENT ADVANCEMENT IN TRANSUNGUAL THERAPIES: A COMPREHENSIVE APPROACH TO ONYCHOMYCOSIS

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ABSTRACT

Onychomycosis is a prevalent fungal infection of the nail affecting about 14% of the people worldwide, particularly the elderly, diabetics and persons with impaired immune systems. Despite their effectiveness, oral antifungal therapies are constrained by systemic side effects and high recurrence rate. Transungual drug delivery presents a promising substitute, offering a targeted treatment with reduced systemic absorption and fewer adverse effects. Advances in transungual drug delivery such as liposomes, niosomes, transfersomes, ethosomes and different types of nanoparticles, are explored in this review. Additionally, innovative techniques such as electrochemotherapy, mesoscissioning technology, nano patch nail fungus are discussed for their promising results in onychomycosis therapy. These advancements represent a significant leap towards more effective and patient compliant treatments for onychomycosis, addressing the limitations of conventional therapies. This paper highlights the potential of novel drug delivery approaches and techniques in the treatment of onychomycosis and calls for further investigations and clinical studies to ensure the safety, effectiveness and patient compliance.

KEYWORDS: onychomycosis, transungual drug delivery, novel drug delivery, novel techniques.

INTRODUCTION

Onychomycosis or tinea unguium, is a fungal infection of the nail plate or nail bed and characterized by nail plate discolouration, thickening, distortion and detachment. It accounts for about 50% of all nail diseases and affects around 14% of the people world-wide. Cases of onychomycosis have been increasing at a prevalence rate of 14-15% in a 20year time period. The prevalence rate is often determined by age, social class, occupation, and living conditions of the patient, inclining factor and climatic conditions.[1]

Apart from the general population, nail diseases are widespread, particularly in the aged people those who are affected with psoriasis, diabetes, and HIV (Human Immunodeficiency Virus). Onychomycosis is not just a cosmetic problem, if not taken care of can further open to dermatophyte infections, ulceration, osteomyelitis, cellulitis, and tissue necrosis that may lead to the worst-case scenario of amputation.[2,3] Despite not being a life-threatening disease, onychomycosis greatly affects the patient's quality of life due to associated pain and discomfort.[4]

Figure No. 1: Onychomycosis affected nails.

The onychomycosis is caused by various types of fungi, and it greatly affects the toe nails than the fingernails. Investigations shown that more than 90% of onychomycosis are caused by two dermatophytes- the Trichophyton rubrum and Trichophyton mentagrophytes.[1] There are five types of onychomycosis present depending on the mode of fungal invasion of nail bed or nail plate, the most common being the distal and lateral subungual onychomycosis (DLSO).[5,6] Hence, accurate diagnosis is needed before initiating the treatment of onychomycosis. The treatment should be selected based on the severity, number and location of infection, causative agent, comorbidities, antifungal resistance, treatment duration, cost, adverse effects, drug interaction and preference of the patients and physician.[3,7] Drug

therapy for onychomycosis includes oral antifungal therapy for 3-4 months which is effective, but the high recurrence rate, serious side effects, and different drug interactions limit their use.[4,7,8]

When comparing with oral therapy, the topical therapy is the best option for onychomycosis. Topical treatment for onychomycosis provides several superiorities which include targeting the drug to the site of infection, reduction of systemic side effects and drug-drug interactions, and high patient compliance.[9,10]

Types of Onychomycosis

Depending on the mode of fungal invasion of the nail bed or nail plate, the onychomycosis classified into five categories.[1] The types and causative agents of onychomycosis are given in the figure 1.[11]

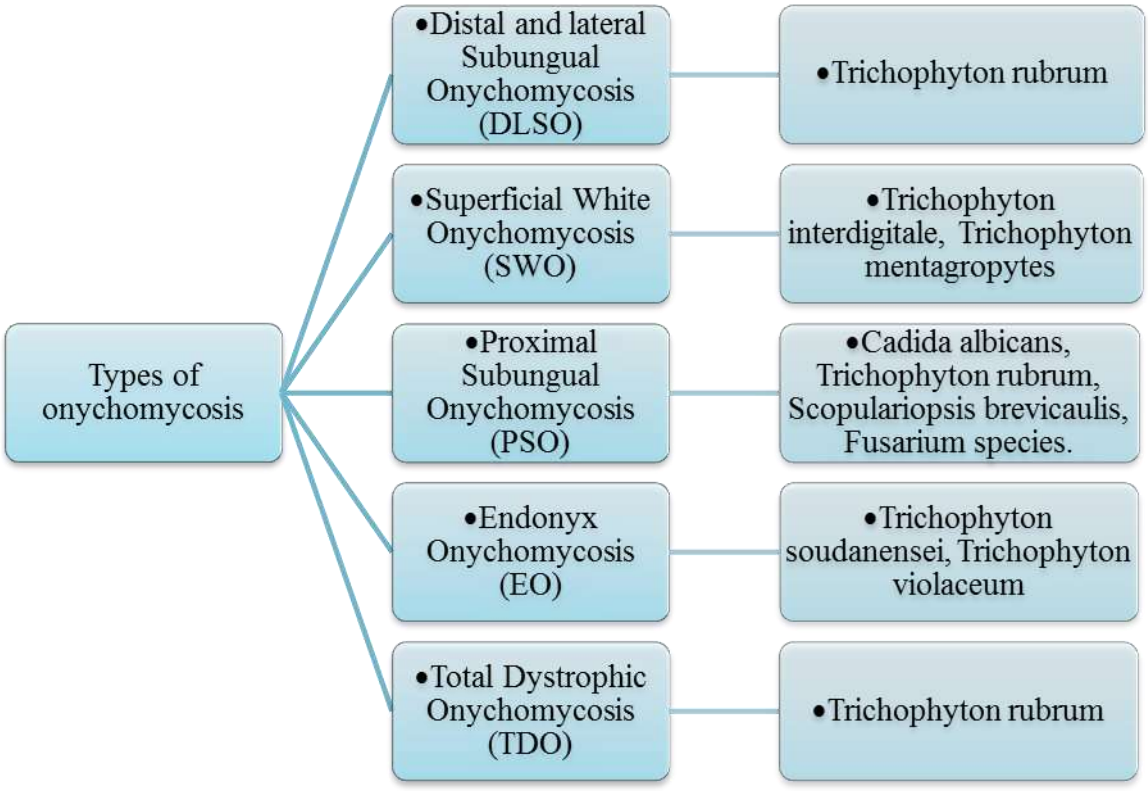

Fig 2. Types and causative agents of onychomycosis.

Etiology of Onychomycosis

The onychomycosis is caused by a variety of fungi, which varies from one geographic area to another depending on the climatic conditions. Dermatophytes, non-dermatophytes and yeasts are various types of fungi, in which dermatophytes are the major causative agent.

Dermatophytes affects approximately 90% of the toe nails and 50% of the fingernails. Trichophyton rubrum is the most common causative agent for the dermatophyte infection. Non-dermatophyte moulds, which greatly affect the toenails and occasionally fingernails. Yeast is now increasingly considered as a pathogenic organism in fingernail infections. The Candida albicans contributes to 70% of the infections, whereas the other Candida species accounts for the remainder.[12]

Transungual Drug Delivery

Topical treatment for onychomycosis provides several superiorities which include targeting the drug to the site of infection, reduction of systemic side effects, high patient compliance, avoids drug interactions, and has fewer local side effects like periungual erythema, which usually diminish over time.[13,14] The systemic absorption is minimal with topical formulation, and it can be easily removed if necessary. This method improves adherence and is suitable for patients, especially the elderly people or those on multiple medications, who cannot take systemic drugs. Most of the conventionally used topical formulations are not specifically adapted to the nails, because they are readily removed by washing and rubbing. The limitations of topical formulations are overcome by the use of transungual drug delivery.[13] "Trans" means "through" and "unguis" means "nails". Transungual drug delivery involves the drug delivery through the nails.[13,14]

A number of characteristics such as the slow growth of nails, restricted vascular supply to the nail bed, and the barrier properties of the nail plate that restrict the passage of drug molecules through it, makes the treatment of onychomycosis as a challenging task. The human nail consists of nearly 25 tightly bound layers of keratinized cells and it is hundred times thicker than the stratum corneum. These factors make the penetration of the drug through the nails ineffective. Moreover, the drug penetration through the nails are influenced by the properties of the nail plate, physical and chemical properties of the drug molecules, characteristics of the formulation, presence of the penetration enhancer and the interaction of the permeating molecule with the keratin network of the nail plate.[15]

NOVEL DRUG DELIVERY APPROACHES FOR IMPROVED ONYCHOMYCOSIS THERAPY

The novel technologies are developed for the successful drug delivery to the targeted site for effective treatment of onychomycosis.[11]

Liposomes

Liposomes are unilamellar or multilamellar spherical vesicles made up of cholesterol and double layer of phospholipid.[11,16] Due to the presence of both hydrophilic and hydrophobic parts, the lipids show amphiphilic characteristics. The liposomes have remarkable value in the drug delivery system due to the ability to encapsulate both hydrophilic and hydrophobic pharmaceutical compounds. The liposomes contain an aqueous core which is enclosed by a phospholipid bilayer. Liposomes offers advantages like sustained drug release, enhancement of therapeutic efficacy and enhance the penetration of drug through the nail.[11]

Liposome containing terbinafine hydrochloride loaded poloxamer gel were developed for transungual delivery and that was found to be a better formulation due to the higher accumulation and easier application.[17] Tanriverdi et al. (2018) prepared caffeine loaded liposomes for transungual drug delivery. The results shown that the caffeine loaded liposomes could enhance the penetration of hydrophilic substances through nail plate, hence it can be used for the topical treatment of nail diseases.[18]

Niosomes

Niosomes are aqueous vesicular structures made up of non-ionic surfactants and phospholipid/cholesterol for targeted drug delivery. They possess lamellar structures, comprising amphiphilic molecules entrapped within aqueous compartment, and are used for the drug delivery of both hydrophilic and hydrophobic compounds. Niosomes are biodegradable, biocompatible, non-toxic and stable under various environmental conditions makes them suitable candidate for the drug delivery.[11,19] Wagh VD et al. (2012) formulated itraconazole niosomes by hydration of proniosome and determined its antimycotic activity against Candida albicans. The formulated niosomes exhibited a higher antimycotic efficacy when compared with marketed formulation, hence it would be a promising carrier for transungual drug delivery.[19]

Transfersomes

Transfersomes are composed of phosphatidylcholine and an edge activator. These vesicles are distinct category of liposomes, which possess a flexible and malleable structure makes them ideal candidate for drug delivery.[11,20,21] The name “transfersome” combines the Latin word “transfere” means “to carry across,” and the Greek word “soma” means “body”.[11,21] These are artificially created vesicles that emulate the characteristics of a cellular vesicle or a cell involved in exocytosis. Transfersomes helps in controlled and targeted delivery of

drugs.[11] They contain hydrophilic surface, hence promotes higher drug absorption.[22] These transfersomes can be characterized as advanced, stress-responsive, and versatile aggregate.[11] Ghannoum M et al. (2012) developed TDT 067 (terbinafine in transfersome) and compared with conventional terbinafine on the morphology of dermatophyte. The transfersomes in TDT 067 may potentiate the antifungal activity of terbinafine by delivering terbinafine more effectively to the fungi in the nail bed. [23]

Ethosomes

Ethosomes are lipid-based vesicles that consist of ethanol, phospholipid and water.[11,24] They consists of higher amounts of ethanol, differentiating them from liposomes.[22] Their unique composition makes them flexible and enables deep penetration into the nails. They are effective in delivering drugs through the dense nail structure, making them a significant advancement in treating onychomycosis. Ethanol acts as a penetration enhancer and solubilizer, facilitating the delivery of both hydrophilic and hydrophobic drugs. Overall, the ethosomes are innovative carriers that improve the transungual delivery, offering benefits for various pharmaceutical substances.[11,24] Tanriverdi et al. (2018) formulated caffeine loaded ethosomes for transungual drug delivery, and the results suggests that the ethosomes could enhance the transungual penetration of hydrophilic substance.[18]

Nanoparticles

In the recent years, nanoparticles gained more attention as a drug delivery system for the treatment of various fungal diseases. The incorporation of nanoparticles enhances drug targeting and increases drug penetration. The nanoparticles can be conveniently applied as a transungual drug delivery system, hence minimizing the side effects of orally administered drugs and reduces the problems associated with conventional formulations.[16] Patel NR et al. (2020) developed itraconazole (ITZ) loaded poly(lactic-co-glycolic) acid (PLGA) nanoparticles by an emulsion-solvent evaporation method for improved antifungal activity. The results revealed that the PLGA-ITZ nanoparticles inhibited the growth of fungi more efficiently than the free ITZ.[25]

Nanocapsules

Nanocapsules comprised of lipid-based core, which contain medication in a dissolved state.[11]The core is usually a lipophilic solvent which is employed for enclosing the hydrophobic or lipophilic drugs.[22] The core is surrounded by a polymeric shell, that controls the drug release from the core.[11,16] Poly(lactic acid) (PLA) and poly (lactide-co-glycolide)

(PLGA) are the synthetic polymers that generally used for the nanocapsule preparation. The incorporation of antifungal drugs in nanocapsules results in sustained release, enhanced penetration and antifungal efficacy.[22]

Nanovesicles

Currently penetration enhancing vesicles or nanovesicles are used to enhance the transungual drug delivery system.[1] Elsherif NI et al. (2016) developed terbinafine hydrochloride loaded spanlastic nanovesicles by a simple ethanol injection method for the transungual delivery of terbinafine. The results showed that they exhibited a good release profile and thus improved permeation through the nail.[26]

Nanoemulsions

Nanoemulsions consist of beads and a combination of surfactants and lipids existing in a size range of 10-500 nm. It possesses all the quality needed for antifungal treatment, including solubility, increased penetration and stability. Nanoemulsions are found to be better choices when compared to less stable liposomes. The drug is dissolved in the nanoglobules, thereby nanoemulsions enhances the antimycotic activity.[1] Yadav U et al. (2013) formulated nanoemulsion gel of clotrimazole using clotrimazole, oil, water, surfactant mixture by water dilution method. The concentration of drug inside the nail increased, hence the effect of drug is prolonged and it raises the cure rate and decreases the time of treatment with fewer side effects.[27]

Solid lipid nanoparticles

Solid lipid nanoparticles (SLNs) were developed in the early 1990s as a potential alternative to emulsions, liposomes and polymeric nanoparticles.[28] Hence, they considered as an effective drug delivery system for hydrophobic drugs. They SLNs contain a solid lipid core surrounded by an emulsifier. The emulsifiers have both hydrophobic and hydrophilic characteristics, it stabilizes the emulsion system by positioning themselves at the oil-water interface.[11,28] The SLNs have several advantages than the traditional drug delivery systems, such as drug protection, enhanced biocompatibility, physical stability, reduced photochemical and oxidative degradation, and scalability for large scale production.[1]

Nanostructured lipid carriers

Nanostructured lipid carriers (NLCs) are the next generation lipid nanoparticles, developed to overcome the limitations of SLNs.[1] They are prepared by using biodegradable lipids in both

solid and liquid states, along with suitable emulsifiers.[11] These NLCs provide entrapment opportunities for the drug within their internal structure based on their physicochemical properties.[29] The inclusion of liquid lipids, produces structural irregularities in the solid lipids, results in a less organized crystalline structure. The design of NLCs minimize the drug leakage and permits a higher drug load.[11] The NLCs enhances entrapment efficiency of lipophilic drugs and improve the melting point issues seen with SLNs.[1] Rocha KA et al. (2017) developed voriconazole loaded NLCs for drug delivery in deeper regions of the nail plate. The results indicate that the NLCs containing drug are promising formulation for the treatment of onychomycosis.[30] The NLCs enhances the drug penetration into the nail layers and making them effective delivery system for onychomycosis treatment.[28]

Lyotropic liquid crystalline nanoparticles

Lyotropic liquid crystalline nanoparticles (LLCNs) or liquid crystal nanoparticles (LCNPs) are used as nanocarriers in targeted drug delivery. LLCNs like cubosomes and hexasomes are gaining attention due to their applications in pharmaceutical field, for the delivery of various bioactive substances such as proteins, peptides, genes etc.[11,31] These are self-assembled mesophases, demonstrating the properties of both ordered solids and isotropic liquids.[20] The LLCNs offer more complex membrane phases than the liposomes. The LLNCs are stable dispersions of liquid crystalline mesophases and highly ordered in their structures. They contain amphiphilic substances, which rearrange into liquid crystalline phases. Cubosomes, cube shaped structures, with their lipid bilayer creating a lattice with two intertwined liquid channels. The hexasomes are soft nanoparticles with hexagonally packed lipid tubules.[11]

Bilayer nail lacquer

Nail lacquers are the most appropriate and recently researched method for the management of onychomycosis.[11] These formulations consist of organic solutions of a polymer that form films and include the medication to be administered with other excipients like plasticizers, resins and dyes.[10,11] Currently, investigations on bilayer nail lacquers have been explored. The bilayers (liposomes, niosomes, ethosomes, etc) promotes the hydrophobic drug delivery and controlled drug release.[11] Kumar BS et al. (2020) formulated bilayer nail lacquer of terbinafine hydrochloride for the treatment of onychomycosis. The results revealed that high permeation rate of nail lacquer helps to reduce the treatment period.[32] The clinical studies also proved that the bilayer nail lacquer provide a higher drug load in the nail on comparison with monolayered lacquer.[33]

Nail patches

The nail patches are another effective method for the transungual drug delivery. They offer benefits over the nail lacquer formulations like sustained and delayed drug release, less frequent administration and short treatment duration, etc. Typically, the nail patches are comprised of a drug impermeable backing layer, membrane reservoir and a release liner. The nail patches are easy to apply, adhere well to the nail plate and easy to remove.[11] The nail patch containing antifungal drug (sertaconazole nitrate) proved the enhanced therapeutic effects in the onychomycosis treatment.[17] Gaddime Sonali B et al. (2018) formulated medicated nail patches containing clotrimazole for the treatment of onychomycosis. The nail patches are used to obtain maximum therapeutic effect along with improved patient compliance.[34]

In situ gel-based delivery system

Recently, in situ gel-based delivery system is gaining more attention for onychomycosis treatment. This system embedded drug molecules within the thermosensitive polymer, present in solution form at lower temperature and converted to gel at body temperature upon application.[11,16] Dhamoon RK et al. (2019) developed luliconazole loaded in situ gelling thermosensitive hydrogel as aqueous based nail lacquer for the management of onychomycosis. The results confirmed that the in situ gel-based delivery system can be used as a novel transungual formulation in the management of onychomycosis.[35]

Hot melt extrusion

Hot melt extrusion (HME) is a well-known method in plastic manufacturing industries and it used for the formulation of amorphous solid dispersions, films, etc in pharmaceutical field.[11,36,37] Mididoddi PK et al. (2007) developed HME films containing ketoconazole (20%) using a Killion extruder (Model KLB-100). These development indicates the relevance of HME films as a potential dosage forms for onychomycosis treatment.[36] The HME technique have several advantages over traditional methods like solvent free process which reduces the risk of residual solvents, ease of scale up, higher drug load, minimized human error due to complete automation, cost effectiveness, fewer processing steps, no requirements for the compressibility of ingredients, intense mixing and agitation during the process results in a more homogenous dispersion and the improvement of bioavailability.[11,36,37]

NOVEL TECHNIQUES FOR IMPROVED ONYCHOMYCOSIS THERAPY

Electrochemotherapy

By using electric current, drugs are directly delivered to the nail plate.[38] The objective of electrochemotherapy is to provide an active drug delivery through the nail plate, which reduces the duration of treatment and enhances the effectiveness of topical monotherapy. The iontophoretic trans-nail delivery approach has been examined recently.[39] It was greatly improved the transport of drug molecules across the nail plate. Electrophoresis and electroosmosis are the main mechanisms that lead to improved drug transport in trans-nail iontophoresis, just like in transdermal iontophoresis. It also improved the patient compliance.[38]

Mesoscissioning technology

Mesoscissioning technology creates a micro-conduit through the nail within a specified depth.[39] This method creates an open channel with a diameter of roughly 300-400 microns that runs throughout the nail without causing any pain. It is intended to deliver drug across the membrane to treat fungal infection of the nail.[38] The painful pressure of subungual hematoma in nails are decreased by the micro conduits.[39]

Nano patch nail fungus

The nano patch nail fungus uses electrochemistry and targeted drug delivery.[39] This technology targets the drug directly into the nail, pushing the drugs to the precise location where the drug's demand should be maximum. The key benefits of this treatment, that it is the first treatment for directly attacking the nail fungus and its source. In another words, it is the preferable treatment.[38]

CONCLUSION

A significant portion of people globally suffer from the onychomycosis. Its influence on quality of life highlights the need for effective therapies, particularly for the elderly, diabetics and immunocompromised persons. The traditional oral antifungal treatments are effective, but the drawbacks like high recurrence rate and systemic side effects limited their use.

On the other hand, transungual drug delivery presents a viable substitute, offering targeted therapy with low systemic absorption and fewer side effects. The field of medicine has greatly advanced as a result of innovations in drug delivery systems, such as liposomes, niosomes, transfersomes, ethosomes and other nanoparticles. Compared to traditional

formulations, these novel carriers enhanced the drug penetration, sustained drug release and improved the therapeutic efficacy and patient compliance. The novel techniques such as electrochemotherapy, mesoscissioning technology, and nano patch nail fungus directly target the infection site, offering more efficient and potentially faster treatment options.

These approaches represent a significant advancement in the management of onychomycosis, addressing the limitations of traditional therapies. The advancement and application of these novel transungual delivery approaches mark a substantial role in the management of onychomycosis. Further research and clinical studies are necessary to ensure that these techniques provide safe, effective, and patient compliant options for controlling this widespread nail disease. By doing so, we can enhance the quality of life for patients suffering from onychomycosis and reduce the burden of this pervasive nail disease.

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Conflicts of Interest

The authors declare that they have no conflict of interest.

ABBREVIATIONS

HIV	Human Immunodeficiency Virus
DLSO	Distal and Lateral Subungual Onychomycosis
SWO	Superficial White Onychomycosis
PSO	Proximal Subungual Onychomycosis
EO	Endonyx Onychomycosis
TDO	Total Dystrophic Onychomycosis
TDT 067	Terbinafine in transfersome
ITZ	Itraconazole
PLGA	Poly(lactic-co-glycolic) acid
PLA	Poly(lactic acid)
SLNs	Solid Lipid Nanoparticles
NLCs	Nanostructured Lipid Carriers
LLCNs	Lyotropic Liquid Crystalline Nanoparticles
LCNPs	Liquid Crystal Nanoparticles

HME Hot Melt Extrusion

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