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Understanding onychomycosis - a neglected form of cutaneous mycosis

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ABSTRACT

Onychomycosis refers to the chronic fungal infection of toenails and fingernails that may involve any component of the nail unit. It is the most common nail disorder experienced worldwide and is usually caused by different species of dermatophytes, saprophytic moulds, yeast and yeast-like fungi. Approximately 50-70 percent of the nail disorders are caused by fungal pathogens, which affect the quality of life by causing pain, discomfort and physical impairment. Moreover, onychomycosis cause psychological and social limitations, which can undermine work and social life of a person. Onychomycosis is mostly caused by keratinophilic fungi, which have the unique ability of degrading keratin that forms the nail apparatus. Structurally, the nail apparatus has certain protective layers, such as, the cuticle and the distal solehorn but it is exposed to the harsh environments and is thus prone to damage and invasion by various keratinophiles through the distal and proximal nail folds. Management of onychomycosis is quite challenging since the infection is embedded within the nail and is difficult to reach. Synthetic antifungal agents are commonly used to control them but they are non-biodegradable, have various side effects due to residual toxicity, long duration of treatment, recurrence of infection and development of resistance to fungal pathogens. All these reasons have led to the exploration of some naturally occurring fungitoxicants like essential oils of higher plants for the management of onychomycotic pathogens

Keywords: Onychomycosis, Nail dystrophies, Dermatophytes, Non-dermatophytic filamentous fungi, Yeast-like fungi

INTRODUCTION

Onychomycosis is the fungal infection of nails, which may even affect the adjacent skin. Typically, it manifests as nail discoloration, nail plate thickening, brittleness and onycholysis (Vlahovic, 2016). Onychomycosis accounts for approximately half of the nail disorders and about one third of the cutaneous fungal infections (Elewski, 2000). It is known to be the most common nail pathology, which accounts for about 90% of toenail infections worldwide (Vlahovic, 2016). Affected population presents several problems like local pain, paresthesia and reduced quality of life as its appearance may impair social interactions and daily activities of individuals (Lipner and Scher, 2019). Generally, onychomycosis is known to be caused by dermatophytes such as *Trichophyton rubrum, T. mentagrophytes,* and *Epidermophyton* (Welsh *et al.,* 2010). In many cases, infections initiate from tinea pedis, a fungal infection on the surrounding skin of the feet (Welsh *et al.,* 2010). Common factors that contribute to disease progression are humid environments, occlusive footwear, nail trauma, genetic predisposition, etc. (Adams *et al.,* 2015; Gupta *et al.,* 2019). Patients with poor peripheral circulation, diabetes mellitus, HIV, immuno-suppression, smokers, etc., are also more susceptible, as are elderly patients. It can occur in any age group though it is seen more in the later life and its prevalence continues to increase with age (Vasconcellos *et al.,* 2013; Gupta *et al.,* 2016). Two common infections i.e., tinea pedis plantaris and tinea pedis interdigitalis are risk factors, which commonly co-occur with onychomycosis (Gupta, 2000; Pierard, 2001; Klaassen *et al.,* 2014). These factors may lead to recurrence of onychomycosis after treatment, which makes it a challenging disease to treat.

The fungal organisms by grouping together form biofilms in the nail rather than acting as independent hyphae and spores (Gupta and Foley, 2019). These biofilms are sessile microbial communities (fungi or bacteria) that are attached to a surface such as nail plate. Most of the microbes are able to form biofilms. Fungi, if not deeply penetrating a substrate, alternate between free-floating planktonic forms and members of a surface biofilm (Ramage *et al.,* 2009; Gupta *et al.,* 2016). These characteristics of biofilms provide some advantages for growth and survival to the fungus as they are surrounded by extracellular matrix (ECM). The extracellular matrix protects them from the host's immune response as well as antifungal drugs and physical and chemical removal strategies. It enables fungi to diffuse nutrients to the elements of the biofilm (Ramage *et al.,* 2009; Kernien *et al.,* 2017). The biofilm formation may be a reason for the treatment resistance observed in onychomycosis and for the inability to completely eradicate fungal spores in cases of chronic infection (Borghi *et al.,* 2016). It has also been reported that the presence of onychomycosis is common among related family members and may be autosomal dominantly inherited (Bodman and Krishnamurthy, 2022). Human leukocyte antigene DR8 is more common in people with onychomycosis than normal controls (Garcia-Romero and Arenas, 2015).

PREVALENCE OF ONYCHOMYCOSIS AND PATHOGENS INVOLVED

Prevalence of onychomycosis usually differs according to geographical, racial, environmental, economic and cultural variations. For instance, in North America, the prevalence rate ranges from 8.7-13.8% (Elewski and Charif, 1997; Ghannoum *et al.,* 2000) and it is likely due to the immigration of dermatophytes from other parts of the world (Gupta *et al.,* 2019). In Europe, its range is broader and has been reported between 0.5% and 24% (Sergeev *et al.,* 2002; Ioannidou *et al.,* 2006). In Western countries, onychomycosis is predominantly reported to be caused by dermatophytes, which make up to 72% of cases (Gupta *et al.,* 2016). Yeasts and yeast-like fungi account for up to 19% (Ghannoum *et al.,* 2000), whereas non-dermatophytic moulds account for 10% (Welsh *et al.,* 2010). Wide variation in the prevalence rates have also been reported from Brazil (28.3%), Tehran (56.4%) and Ethiopia (60.4%) by Chiacchio *et al.* (2013), Soltani *et al.* (2015), and Bitew and Wolde (2019) respectively.

Earlier, dermatophytes were thought to be the sole infectious organisms causing onychomycosis, but these days non-dermatophytic moulds are being reported more frequently, especially in the warmer climates (Raghavendra *et al.,* 2015; Ranawaka *et al.,* 2016; Rafat *et al.,* 2019). Mixed infections by dermatophytes and non-dermatophytes represent around 3-11% of the onychomycotic cases but it could be even higher (Moreno and Arenas, 2010; Salakshna *et al.,* 2018). The role of non-dermatophytes in mixed infections with dermatophytes is not well understood (Ebihara *et al.,* 2009; Gupta and Nakrieko, 2014). Historically, non-dermatophytes have often been ignored as nail contaminants, especially if a dermatophyte was also present (Gupta *et al.,* 2012). Up to 70% of the mixed infections are usually caused by the dermatophytes, predominantly by *Trichophyton rubrum* (50%) and *T. mentagrophytes* (about 20%), with remaining infections caused by *Epidermophyton floccosum*, *Microsporum* spp., *Trichophyton verrucosum*, *T. violaceum*, *T. krajdenii*, and *Arthroderma* spp. (Gupta *et al.,* 2016).

Non-dermatophytic moulds are responsible for more than 50% of the fungal nail infections and the most common organisms are *Aspergillus niger*, *A. sydowii, Alternaria alternata, Curvularia lunata, Sarocladium subulatum, Nigrospora sphaerica, Scopulariopsis* spp., *Acremonium* spp., *Fusarium* spp., and *Chaetomium* spp. (Jandial and Sumbali, 2012; Bhou and Sumbali, 2015a,b; Sharma and Sumbali, 2020). Yeasts and yeast-like fungi account for up to 20 percent of the cases of onychomycosis and are represented by *Candida* spp., *Trichosporon* spp., *Rhodotorula* spp., and *Aureobasidium* spp., (Gupta *et al.,* 2016; Kotwal *et al.,* 2018, 2019; Sharma and Sumbali, 2021). It has been reported that foot and toenail infections are common even among the members of the same household, and the transmission risk from the affected member to other family members is variable (Ghannoum *et al.,* 2013; Kotwal *et al.,* 2018). According to Klaassen *et al.* (2014), onychomycosis is also more prevalent in the psoriatic patients and it is estimated that they have 50% more chances of developing onychomycosis in comparison to the non-psoriatics. In a retrospective study of 8331 patients, the prevalence of onychomycosis was 20.7% in adults of more than 60 years of age (Pappini *et al.,* 2015). Similarly, Chetana *et al.* (2019) from Puducherry, south India reported 15-20% prevalence in patients aged 40-60 years and the frequency rose over 60 years of age. However, in a study conducted at San Diego among children between the ages of 12 and 18 years, prevalence of onychomycosis was reported to be only 1.1% (Totri *et al.,* 2017). Recently, Tyagi *et al.* (2021) studied the etiology and epidemiology of onychomycosis from a tertiary care hospital in north India and prevalence of onychomycosis was confirmed in 57.02% samples analysed.

SCENARIO OF ONYCHOMYCOSIS IN JAMMU AND KASHMIR

Survey of literature shows few reports of isolated cases of onychomycosis from UT of Jammu and Kashmir (Ahmad *et al.,* 2010; Jandial and Sumbali, 2012; Bhou and Sumbali, 2015a,b; Kanth *et al.,* 2016). However, district wise survey for the prevalence of onychomycosis has been done for the residents of Jammu (Bhou, 2017), Doda (Kotwal, 2018) and Rajouri districts (Sharma, 2021) (**Fig.1 & 2**). Some of the fungal pathogens recovered from the dystrophied nails of the population belonging to these three districts of Jammu and Kashmir have been shown in **fig. 3** and tabulated below:



Fig. 1: Dystrophied fingernails caused by fungal infection



Fig. 2: Dystrophied toenails caused by fungal infection.

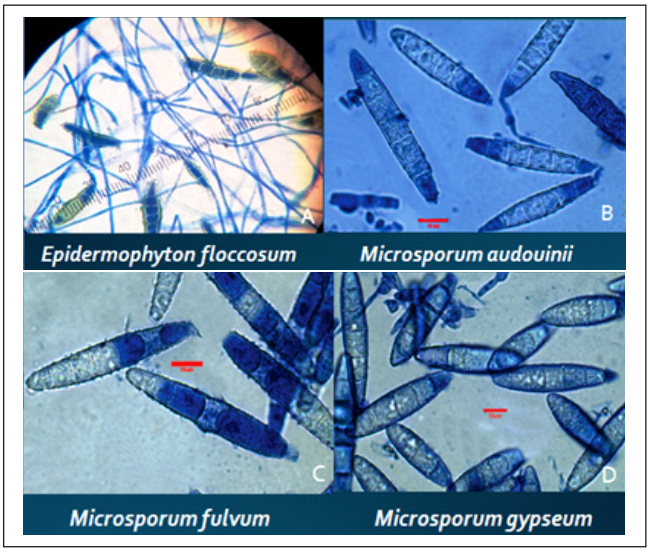


Fig. 3: A-D. Dermatophytes causing onychomycosis from Jammu and Doda districts.

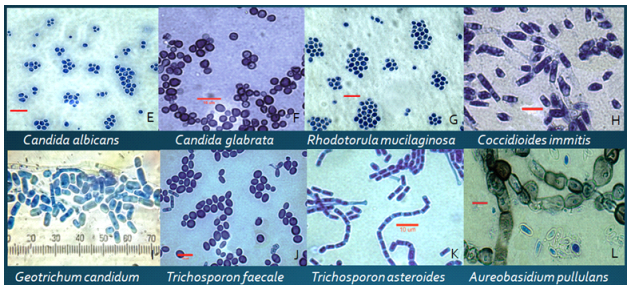


Fig. 3: E-L. Some non-dermatophytes (yeast-like fungi) detected to cause onychomycosis from Jammu, Doda, and Rajouri districts.

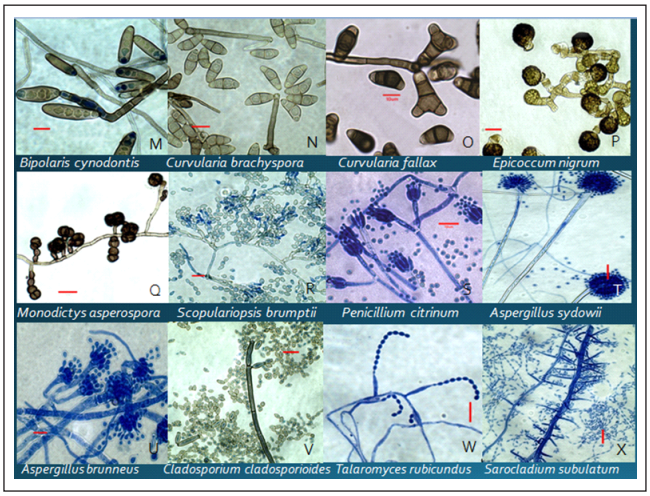


Fig. 3. M-X. Some non-dermatophytes (filamentous fungi) detected to cause onychomycosis from Jammu, Doda and Rajouri districts

CLINICAL MANIFESTATIONS OF ONYCHOMYCOSIS

Patients with onychomycosis often complain of nail discoloration, nail separation, brittleness or thickenings, which often worsen with time (Lipner and Scher, 2015). A history of tinea pedis or hyperhidrosis of the feet is common (Pierard, 2001; Walling and Sniezek, 2007; Augustin *et al.,* 2013). Nails affected by onychomycosis may cause social embarrassment, local pain, difficulty in fitting shoes and in the employed persons it may have a negative impact on the quality of life (Lipner and Scher, 2014).

On the basis of pattern of fungal invasion, onychomycosis is divided into different subtypes (**Fig. 4**). Distal lateral subungual onychomycosis (DLSO) is the most frequent type characterized by distal onycholysis with subungual hyperkeratosis, nail plate thickening and yellow to brown discoloration. When the infecting organisms invade the upper surface of the nail plate and are most often seen as superficial white patches that can be easily scraped off, it is known as superficial onychomycosis (Baran *et al.,* 2004). Less common presentations are black patches, transverse striations and invasive patterns (Piraccini and Tosti, 2004). It is oftenly seen in immunosuppressed patients, particularly in HIV

Table 1: Fungal pathogens recovered from the infected nails of patients residing in some districts of UT of Jammu and Kashmir

Onychomycotic species recovered from the sampled diseased nails	Districts to which the patients belonged
A. Dermatophytes	
Epidermophyton spp. (1)	Doda and Jammu
Microsporum spp. (3)	Doda and Jammu
B. Non-dermatophytic filamentous fungi	
Alternaria spp. (3)	Doda, Rajouri and Jammu
Acremonium spp. (3)	Doda and Jammu
Arthrinium spp. (1)	Doda
Bipolaris spp. (2)	Rajouri
Eurotium spp. (1)	Doda
Exserohilum spp. (1)	Rajouri
Curvularia spp.(6)	Doda, Rajouri and Jammu
Cladosporium spp. (2)	Doda, Rajouri and Jammu
Chaetomidium spp. (1)	Doda
Chaetomium spp. (2)	Rajouri and Jammu
Punctularia spp. (1)	Doda
Epicoccum spp.(2)	Doda and Rajouri
Isaria spp. (1)	Doda
Humicola spp.(1)	Rajouri
Gilmaniella spp.(1)	Rajouri
Apiospora spp.(1)	Rajouri
Monodictys spp.(1)	Rajouri
Nigrospora spp.(2)	Doda, Rajouri and Jammu
Trichothecium spp. (1)	Doda and Jammu
Scopulariopsis spp.(4)	Doda, Rajouri and Jammu
Rhizopus spp.(4)	Doda, Rajouri and Jammu
Aspergillus spp.(13)	Doda, Rajouri and Jammu
Emericella spp. (1)	Rajouri
Corynascus spp. (2)	Doda and Jammu
Monoascus spp. (1)	Doda
Mucor spp. (4)	Doda and Jammu
Lichthemia spp. (1)	Doda
Fusarium spp.(5)	Doda, Rajouri and Jammu
Syncephalastrum spp. (1)	Doda and Jammu
Sphaerostilbella spp. (1)	Jammu
Absidia spp. (1)	Jammu
Talaromyces spp. (1)	Rajouri
Nodulisporium spp.(1)	Rajouri
Paecilomyces spp. (3)	Doda, Rajouri and Jammu
Phialemonium spp. (1)	Rajouri
Sarocladium spp.(3)	Doda, Rajouri and Jammu
Penicillium spp.(10)	Doda and Rajouri
Purpureocillium spp. (1)	Jammu
Preussia spp.(1)	Rajouri
C. **Yeast-like fungi**	
Aureobasidium spp. (1)	Doda and Rajouri
Candida spp. (6)	Doda, Rajouri and Jammu
Trichosporon spp. (3)	Doda and Rajouri
Rhodotorula spp. (1)	Rajouri and Jammu
Geotrichum spp. (1)	Doda
Coccidioides spp. (1)	Doda
Naganishia spp. (1)	Jammu

patients (Baran *et al.,* 2007). When the fungus invades from the undersurface of the proximal nail fold and then progresses distally, it is known as proximal subungual onychomycosis (PSO). When PSO progresses quickly, it may be associated with immunosuppression (Hay and Baran, 2011). Endonyx onychomycosis (EO) is usually caused by the invasion of the nail plate without infection of the nail bed. While the other subtypes are most commonly caused by *Trichophyton rubrum*, EO is frequently caused by *T. soudanense* and *T. violaceum*. EO causes lamellar nail splitting and milky patches of the nail plate (Hay and Baran, 2011). In mixed pattern onychomycosis (MPO), there is more than one type of nail plate infection within the same nail; most commonly PSO or distal lateral subungual onychomycosis combined with SO (Hay and Baran, 2011). Total dystrophic onychomycosis (TDO) is the end stage of onychomycosis and presents with a severely dystrophic and crumbled nail plate (Hay and Baran, 2011). Secondary onychomycosis is defined as fungal



Fig. 4: Clinical types of onychomycosis

invasion following another non-fungal nail condition, such as psoriasis or previous trauma. Clinically, it resembles both the fungal and non-fungal nail conditions (Hay and Baran, 2011).

COLLECTION OF DISEASED NAIL SAMPLES AND DIAGNOSIS

Proper method of specimen collection is essential to avoid false negative results and to eliminate contaminants present in the sample. Separate samples should be obtained from fingernails and toenails, associated tinea pedis, or manuum (Baran *et al.,* 2006). The specimen should be obtained when the patient is not using any topical and systemic antifungal drugs for 24 weeks. Fine shavings/scrapings or minute clippings are usually preferred. Collected specimens must not be kept in moist place to avoid rapid multiplication of bacterial and fungal spores and should be processed within a week (Kaur *et al.,* 2008). For collection of diseased nail, the entire nail unit should be thoroughly cleaned with 70% alcohol. The affected nail bed should be exposed by removing the onycholytic nail plate with a nail cutter and scraping the hyperkeratotic nail with a disposable scalpel and outermost debris should be discarded (Baran *et al.,* 2006).

To diagnose onychomycosis, confirmatory mycological testing is very essential step. Different clinical presentations of onychomycosis may provide clues to the infecting organism, but usually appearance caused by different fungal species may be indistinguishable. Therefore, it is crucial to identify the causative fungus before initiating treatment, because some therapies are more effective against certain organisms than others. Some effective techniques used for diagnosis include:

(i) Direct potassium hydroxide (KOH) testing, which is a simple, quick and inexpensive technique and is integral to dermatological practice for identifying fungal pathogens (Dasgupta and Sahu, 2012). It involves two steps i.e., retrieving the specimen from the nail bed and underneath the nail plate and then dissolving it in KOH (Velasquez-Agudelo and Cardona-Areas, 2017). KOH dissolves the keratin, allowing microscopic visualization of the fungal hyphae or spores (Velasquez-Agudelo and Cardona-Areas, 2017). Further, the specimens can be treated with stains, such as, Calcofluor White, Gram, India ink, Evans Blue, and Giemsa (Gupta and Simpson, 2013; Ghannoum *et al.,* 2018). Direct microscopy establishes the presence or absence of fungi but it cannot identify the specific fungus or differentiate the viable from non-viable fungi. Therefore, fungal culturing on specific media is very important for the identification purpose.

(ii) Culturing and PCR techniques are required to identify the causal agents of infection. These techniques are also useful in determining the source of infection in atypical cases or when one suspects a primary saprophytic infection (Bodman and Krishnamurthy, 2022). To confirm this suspicion, two to three subsequent cultures of the same saprophytic mould should be obtained before concluding that the saprophyte is the primary pathogen and not a contaminant. Further, PCR improves the species-specific detection of dermatophytes up to 20% over fungal cultures alone (Bodman and Krishnamurthy, 2022). Culture allows the isolation and detection of the etiological agents and in most cases allows differentiating species. With this technique, it also becomes essential to use a combination of different culture media to show growth of the etiological agent (Mendoza *et al.,* 2012).

(iii) Dermoscopy is a technique that can clinically diagnose onychomycosis. It readily differentiates between nail

dystrophy and onychomycosis. The presence of subungual short spikes and longitudinal striations indicates onychomycosis, whereas transverse onycholysis is consistent with micro traumatic nail dystrophy (Bodman and Krishnamurthy, 2022).

IMPACT OF ONYCHOMYCOSIS ON THE QUALITY OF LIFE

Onychomycosis is a condition that can significantly affect one's quality of life (Chacon *et al.,* 2013; Jacobsen and Tosti, 2017). Onychomycosis is a common, chronic disease with a substantial negative effect on the quality of life of those who suffer from it (Drake *et al.,* 1998). Nevertheless, the perception still persists in the minds of many physicians that onychomycosis is more of a cosmetic nuisance than a significant disease (Scher, 1994).

Patients with nail infections are commonly reported to have feeling of low self-esteem and embarrassment. Nail disorders are often visible and long-lasting and may even result in modification of patient's everyday activities such as avoiding public facilities like gyms, swimming pools, public bathing, etc., to minimize the potential of someone seeing their affected nails (Chacon *et al.,* 2013). Many patients experience pain and difficulty in walking caused by the infected nails (Chacon *et al.,* 2013; Adams *et al.,* 2015; Jacobsen and Tosti, 2017).

MANAGEMENT OF ONYCHOMYCOSIS

Currently, several treatments for onychomycosis are used, namely, laser treatment, surgery, debridement, and pharmacological interventions (Hay, 2005; Bhatta *et al.,* 2016; Gupta *et al.,* 2020). The gold standard pharmacological treatment for onychomycosis is a continuous or intermittent therapeutic scheme including amorolfine, terbinafne, ciclopirox, and itraconazole (Westerberg and Voyack, 2013; Ameen *et al.,* 2014; Sigurgeirsson, 2016). Despite the multiple approaches and treatments available, the success rate remains relatively low, with infection recurrence rates ranging from 40-70% (Ameen *et al.,* 2014).

Some of the important topical agents that have been widely used include amorolfine, ciclopirox, tioconazole, efinaconazole, butenafine, bifonazole, salicylic acid, ionized sunflower oil, etc. (Derby *et al.,* 2011; Menendez *et al.,* 2011) but there are limited reports to support their use for the management of onychomycosis. Apart from these topical agents, some of the systemic drugs that are widely used for the treatment of nail infections include ketoconazole, griseofulvin, itraconazole, terbinafine and fluconazole. However, these systemic drugs have been reported to show adverse effects and often result in the development of microbial resistance against anti-microbial agents (Murdan, 2008; Gupta and Simpson, 2015). Additionally, the treatment process is generally long, being approximately more than six months for fingernails and 12-18 months for toenails (Scher *et al.,* 2013). In view of the side effects, high cost and long duration of treatment, systemic drug treatments have not been successful in many cases (Phongpaichit *et al.,* 2004; Gupta and Tu, 2006).

In recent years, some of the developed as well as developing countries have revived an interest to use products of aromatic medicinal plants as they are safe and without adverse side effects (Jain and Sharma, 2003; Ekwealor *et al.,* 2012). Some plant products have been shown to be effective sources of chemotherapeutic agents with strong fungicidal activity and without any undesirable effect (Flores *et al.,* 2016). Most of the plants contain essential oils, which are potentially effective against several microorganisms including pathogenic fungi causing superficial infections (Viollon and Chaumont, 1994; Williams *et al.,* 1998; Manohar *et al.,* 2001; Chuang *et al.,* 2007). Essential oils are concentrated hydrophobic liquids, natural, volatile, complex and multi-component products, which are usually extracted from various parts of the plant such as, leaves, flowers, buds, seeds, twigs, bark, woods, fruits and roots (Chen *et al.,* 2004; Raut and Karuppayil, 2014). They are composed of monoterpenes, sesquiterpenes and non-terpenaceous components, which have the advantage of being resistant to microbial adaptation by providing a broad spectrum of action against fungi, bacteria, and viruses (Bakkali *et al.,* 2008; Hammer and Carson, 2011). Moreover, some studies have also showed synergism among the different compounds (Pinto *et al.,* 2006; Yahyazadeh *et al.,* 2008). Nevertheless, their prominent action seems to be due to their interaction with biological membranes, which leads to an alteration on cell selection permeability (Bakkali *et al.,* 2008). Terpenaceous compounds, such as, monoterpenes are able to act through ergosterol-binding leading to destabilization of fungal membranes and suppression of spore formation (Inouye *et al.,* 2009; Miron *et al.,* 2014). Some components may interfere differently by reducing the activity of mitochondrial enzymes (Pinto *et al.,* 2013). It also produces an enzymatic reaction with the cell wall and inhibits other cellular metabolism (Yahyazadeh *et al.,* 2008; Zuzarte *et al.,* 2011).

For treatment of onychomycosis, it is important to have mycological confirmation first and then clinical diagnosis of onychomycosis. In some cases of treatment failures and suspected antifungal resistance, antifungal susceptibility testing and investigation into environmental and patient-related factors may assist in determining the most appropriate antifungal agents for targeted therapy. It has been observed that different essential oils show variable inhibitory activity against same onychomycotic agents and vice-versa (Kotwal, 2018; Sharma, 2021). Further, disinfection of shoes and socks and use of prophylactic antifungal therapy for the affected nails and surrounding skin may reduce the spread of fungal organisms, which will help to achieve successful long-term management of onychomycosis.

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