



## Review

# Review on Onychomycosis due to Non-Dermatophyte Mould: Advance Diagnosis and Treatment Process

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Article history: Received 10 October 2024, Reviewed 27 November 2024, Accepted for publication 02 June 2025

## Abstract

**Background:** Onychomycosis is a chronic infection of the nail. The most common causative agent of onychomycosis due to non dermatophytic mould is *Aspergillus*.

**Objectives:** This review aims to address the various complications of onychomycosis due to non- dermatophyte mould and to provide an update on the diagnosis and treatment of onychomycosis.

**Methods:** Databases including PubMed, Google Scholar were searched to identify the relevant articles. The search strategies included case studies, research articles, and review papers published within the past 20 years.

**Results:** We reviewed all available literature concerning onychomycosis. A literature search revealed 130 studies, for this review paper we included 33 articles evaluating the onychomycosis due to non-dermatophyte mould. Five were case reports, five were research studies, two were cross- sectional studies, one was a randomized controlled trial, and the remaining were review and systematic reviews. In this, 3.03% of included publications have an impact factor more than 15, 6.06% have an impact factor more than 8, 81.81% have an impact factor ranging between 1-5, and 9.09% have an impact factor less than 1. From all the searched data it showed that toenails are more prone to infections than the fingernails.

**Conclusion:** Oral therapies are effective, but one disadvantage is that they have more side effects. Topical treatment is less effective and requires extended treatment because of the slow penetration to the nail plate but it has minimal adverse effects. Now, there are various new techniques that are quite promising like laser, photodynamic, plasma therapy, and oil from ethnomedicinal plants.

**Keywords-** Onychomycosis, Non- dermatophyte mould, Immunocompromised patients, *Aspergillus*



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## How to cite this article

Sahoo M, Mahalik G, Mishra MP, Kar D. Review on Onychomycosis due to Non-Dermatophyte Mould: Advance Diagnosis and Treatment Process. The Nigerian Health Journal 2025; 25(2): 441 – 448.  
<https://doi.org/10.71637/tnhj.v25i2.907>



## Introduction

Onychomycosis is an infection of the nail that primarily affects the toe and fingernails, and it is caused by different types of fungus-like dermatophytes,<sup>1</sup> non-dermatophyte mould (NDM), and yeast, which are associated with nail invasion.<sup>2-4</sup> NDMs are a heterogeneous group of organisms that may cause superficial infection and onychomycosis. It is represented by discoloration of the nail, onycholysis, and nail plate thickening, and it can infect any other part of the nail, such as the nail matrix and nail bed can also be affected.<sup>5-9</sup>

Onychomycosis related to non-dermatophyte mould is rising. The most common non-dermatophytes involved in onychomycosis are *Aspergillus* Species, *Scopulariopsis* Species, *Alternaria* Species, and *Fusarium* Species. Worldwide, *Aspergillus* is reported as the primary causative agent of onychomycosis, approximately 2-25%.<sup>4,10</sup> Among *Aspergillus* Species, most commonly *Aspergillus Fumigatus*, *Aspergillus Flavus*, *Aspergillus Niger*, and *Aspergillus Terrus* are associated with *Aspergillus* onychomycosis.<sup>11</sup> *Aspergillus* species exists as an opportunistic filamentous fungus and are ubiquitous in nature and are found in soil, decaying vegetation, water and are not transmittable from person to person.<sup>4</sup> *Aspergillus* Species are associated with invasive aspergillosis, aspergilloma, sinusitis, otomycosis, and keratitis, which is one of the main causes of morbidity and death in people with impaired immunity. A few *aspergillus* species are related to persistent cavity, fibrosis, and necrotizing pulmonary aspergillosis in individuals with pre-existing illnesses.<sup>11</sup>

Onychomycosis is more prevalent in males and in both genders with increasing age.<sup>12,13</sup> Onychomycosis is very uncommon in children, and the rate of prevalence increases with age, most commonly in people over 60 years of age.<sup>14,15</sup> In adults, toenails are affected more than fingernails due to more exposure to soil, water, and decaying vegetation.<sup>16</sup> Children are most likely to acquire the fungus from their parents, traumatic nail abnormalities, or through environmental contaminants.<sup>12</sup>

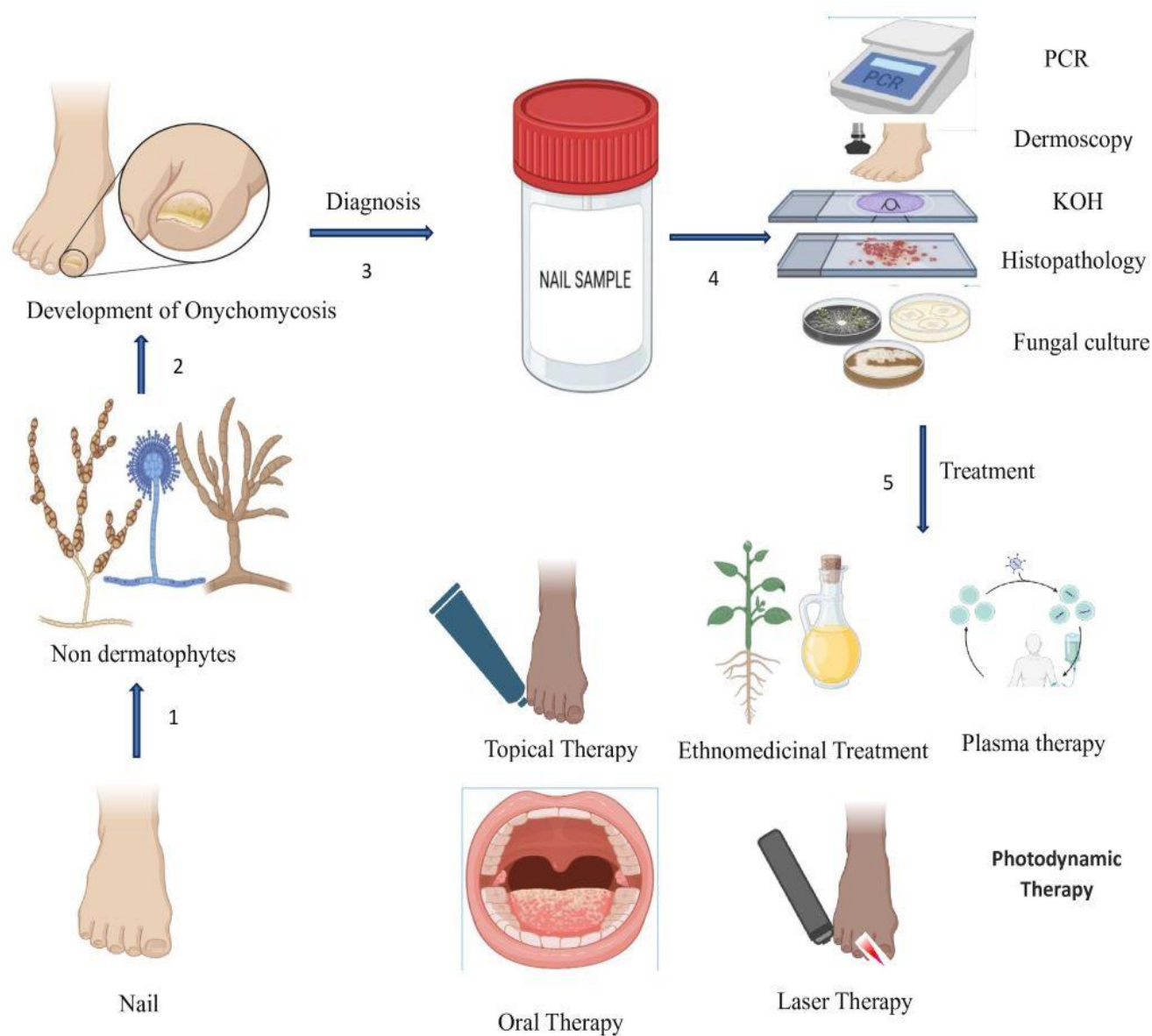
*Aspergillus* onychomycosis is more common among vegetable vendors, coconut breakers, diabetic patients, and elderly persons. Different types of predisposing factors that help to develop onychomycosis are nail trauma, immunodeficiency person, a person with poor

hygiene, different types of occupational exposures like barefoot walking and gardening, a person with increasing age, different types of hormonal imbalances (Cushing's syndrome, hypothyroidism), regular swimming.<sup>4</sup> Onychomycosis affected approximately 33% of the patients with diabetes.<sup>17</sup>

Onychomycosis is asymptomatic, but later, they can develop local pain, difficulty with ambulation, discoloration of the nail, and difficulties in fitting shoes.<sup>18,20</sup> It can also have other negative consequences for patients, like potentially undermining work, and it can also affect the social life of an individual.<sup>21</sup> This review aims to address the various complications of onychomycosis due to *Aspergillus* and to provide an update on the diagnosis and treatment of onychomycosis, like what are the diagnostic challenges and treatment strategies to overcome this fungal infection and what are the new treatment methods for onychomycosis with less side effect. Usually, moulds have been recognized as opportunistic fungi that inhibit the nail and are considered as harmless, but over the past several decades infections due to moulds have been increasing worldwide.<sup>22,23</sup> Onychomycosis is caused by NDM mimicking dermatophyte in clinical features, which makes clinical diagnosis difficult.<sup>4,10</sup>

## PATHOGENESIS OF ONYCHOMYCOSIS

Nails are more susceptible to getting fungal infection because our nail unit does not possess cell mediated immunity, and they are exposed to harsh environments so they are more prone to getting the infection. Individuals can get onychomycosis by direct contact with dermatophytes, non- dermatophyte mould, and yeast.<sup>14</sup> Both mechanical and chemical factors are involved in the fungal invasion of nail. The first step is nail adhesion, followed by the invasion. Fungal elements secrete different types of enzymes that have keratinolytic, proteolytic, and lipolytic activity, which helps in the fungal invasion of the nail plate and helps in degrading the keratin part of the nail, which provides nutrition to the fungus (Fig 1).<sup>24</sup> NDM is usually considered as the secondary invaders of the nail, while the primary is the dermatophytes, because unlike dermatophytes NDM are not keratolytic they mostly lie on un-keratinized extracellular cement or they take advantage of previous keratin destruction caused by dermatophyte otherwise any type of trauma or nail disease.<sup>22,25</sup>



**Fig 1:** Development of Onychomycosis

## CLINICAL PRESENTATION

In onychomycosis, toe nails are most commonly affected as compared to the fingernails, mostly; it affects the big toenail. Some studies have revealed that toe nails are 7-25 times more prone to get the infection as compared to the finger nails because of their more exposure to the harsh environment, water, soil etc.<sup>10,14</sup> Onychomycosis present as changing in the colour of the nail such as yellow-brown, black and green discoloration, onycholysis, onychauxis.<sup>14,15</sup> It is classified into 5 types based on the clinical presentation and route of invasion a) Distal and lateral subungual onychomycosis (DLSO), b) Superficial white onychomycosis (SWO), c) Proximal subungual onychomycosis (PSO) d) Endonyx onychomycosis e) Dystrophic onychomycosis.<sup>26</sup>

### Distal Lateral Subungual Onychomycosis (DLSO)

DLSO is considered as the most prevalent subtype of onychomycosis.<sup>14,15</sup> The fungal invasion takes place from the distal and lateral parts of the nail plate.<sup>15</sup> At first, fungus affects the keratin of hyponychium, and then it affects beneath the nail plate's surface and nail bed. In the starting stage, mild inflammation occurs with focal parakeratosis, onycholysis, and nail plate thickening.<sup>15,24</sup> Another clinical manifestation seen as white-yellow discoloration of the nail, however some other colour changes, such as fungal melanonychia, orange, and brown discoloration has been seen.<sup>15</sup> It affects both toenails and fingernails, but toenails are affected most commonly as compared to the fingernail.<sup>24</sup> It affects one of the big toenails or both the big toenails.<sup>12</sup>

### 1. White Superficial Onychomycosis (WSO)

As compared to distal lateral subungual onychomycosis, white superficial onychomycosis is uncommon. When fungi penetrate the surface layer of the nail plate, it causes white superficial onychomycosis,<sup>12</sup> and it appears as white opaque colonies that can easily be scraped off.<sup>14</sup> WSO is very rare and limited to toenails.<sup>24</sup> The most common etiological agents are *Trichophyton Mentagrophytes*, *Trichophyton interdigitale*.<sup>12</sup> Several non-dermatophyte moulds including *Aspergillus terreus*, *Fusarium oxysporum*, *Acremonium roseogrisum*. Inflammation is usually minimum nail becomes rough, soft, and crumbly.<sup>28</sup>

### 2. Proximal Subungual Onychomycosis (PSO)

It is otherwise known as proximal white subungual onychomycosis.<sup>21</sup> It takes place when organisms invade the inner nail plate, first it takes over the proximal nail fold and then extends distally.<sup>14,15</sup> Clinical features are proximal onycholysis, leukonychia, and hyperkeratosis. It is mainly caused by non-dermatophyte mould such as *Aspergillus sp.* and *Fusarium sp.*<sup>15</sup> It usually affects immunocompromised patients, especially AIDS and HIV patients.<sup>24</sup>

### 3. Endonyx Onychomycosis

It does not affect the nail bed, instead it targets the nail plate directly.<sup>24</sup> It is represented by milky-white discoloration of the nail and lamellar splitting.<sup>15,24</sup> There is no onycholysis or hyperkeratosis.<sup>12</sup> The etiological agents are *Trichophyton Violaceum*, and *Trichophyton Sandanense*.<sup>12,14</sup>

### 4. Total Dystrophic Onychomycosis

It is considered as the last stage of onychomycosis, and the entire nail has been destroyed.<sup>15</sup> There use to be a yellowish discoloration of the nail, nail plate crumbling, and nail thickening.<sup>24</sup> The most common causative agents are *Trichophyton rubrum* and some moulds.<sup>15</sup>

## DIAGNOSIS

Proper Laboratory diagnosis is necessary for onychomycosis to start the treatment, prevent treatment failure, prevent drug-drug interaction, and prevent complications.<sup>10</sup> Onychomycosis affects both the toenail and fingernail but most commonly, it affects the great and second toe nails.<sup>19</sup> Common physical examination includes nail discoloration, thickening of the nail, and hyperkeratosis. There are various methods for diagnosis of onychomycosis: 1) dermoscopy 2) mycological examination.

### Sample Collection

Before collecting the nail sample, clean the surrounding area with alcohol to prevent contamination by the bacteria present in our body and in the surrounding environment.<sup>18,21</sup> Sample collection depends upon the type of onychomycosis; scraping of the affected superficial nail plate is a preferable sample for WSO, PSO proximal nails upper nail plate can be collected, in case of DLSO sample should be collected from the proximal area because this area has the highest concentration of hyphae. After collection of the sample,

it should be transported in a sterile paper without any delay to the laboratory.<sup>14</sup>

### Dermoscopy

Dermoscopy is useful to distinguish onychomycosis from other nail disorders. The most commonly used dermoscopy pattern is spikes in the oncolytic area of the jagged proximal edge. Typical dermoscopic features are leukonychia, chromonychia, dermatophytoma, subungual hyperkeratosis, and white to yellow longitudinal streaks, rarely pseudo-Hutchinson signs, nail plate scale, fungal melanonychia.<sup>14,19</sup>

### Mycological Examination

Mycological examination is differentiated into microscopic examination and culture (Moreno and Arenas 2010). The collected sample should be separated into two parts: one is for microscopic examinations, and another one is for culture.<sup>18</sup>

### KOH and Microscopy

Potassium hydroxide mount is used for direct microscopic examination. Nail scrapings are treated with 40% KOH to digest the keratin and put on a slide,<sup>14</sup> then observed under light microscope to visualize the presence of hyphae, yeast, and spores.<sup>16, 20</sup> KOH mount gives immediate results, but it can't identify the type of fungus.<sup>12</sup>

### Fungal Culture

Fungal cultures are useful to identify the type of fungus; fungal cultures are not that much sensitive. It takes a longer time to give the result, 2-4 weeks and it is expensive. Sabouraud dextrose agar (SDA) is the most commonly used fungal culture media. SDA media with cycloheximide is used to promote dermatophyte growth and SDA media without cycloheximide is used to culture NDMs, and SDA media with gentamicin and chloramphenicol is used to inhibit bacterial growth. Sample is inoculated into two separate SDA media and incubated at 25°C and 37°C. The principal aim of the treatment is the complete eradication of the organism.<sup>14,19</sup> If both the media show growth means the infection is caused by dermatophyte, if cycloheximide-free media show growth means the infection is caused by non-dermatophyte mould.<sup>24</sup>

### Histopathology

Periodic acid-fast stain is the most commonly used staining method for histopathology examination of

onychomycosis;<sup>14</sup> it is performed on nail plate clippings.<sup>19</sup> It can't identify the specific pathogen.<sup>15</sup> It is useful to visualize the hyphae, spores, pseudo hyphae, and yeast.<sup>16</sup> Within 24 hrs it can give results.<sup>14</sup> Other stains that use for histopathology examination are Hematoxylin and eosin stains to visualize fungal elements, Grocott methenamine-silver stain, immunofluorescence, Mayer mucicarmine stain and Fontana-Masson.<sup>19</sup>

### Polymerase Chain Reaction

Polymerase Chain Reaction is a new technique that amplifies the fungal DNA, gives the rapid, and accurate results as compared to the fungal culture technique. It can identify the causative agents behind the infection, such as dermatophyte, non-dermatophyte, and candida spp. It can give results within 24-48 hrs. Sometimes it gives a false-positive reaction because of the contamination and partial treatment.<sup>14,19</sup>

### THERAPY

Onychomycosis is difficult to treat because of its deep involvement and frequent recurrence.<sup>14</sup> The primary aim of the treatment is complete eradication of the organism.<sup>30</sup> Treatment for onychomycosis includes oral treatment, Oral Treatment, Topical treatment, laser therapy, photodynamic therapy, plasma therapy and oil extracted from plants.<sup>31</sup> Treatment of Onychomycosis takes a longer duration, especially in adults.<sup>12</sup> Infected fingernails respond well to the treatment as compared to the toenails. Fingernails infected by Onychomycosis require 3 months of treatment and infected toenails require 6 months of treatment.<sup>10</sup>

### Oral Treatment

It is regarded as the gold standard treatment of onychomycosis due to its low-cost effect, short course duration and high efficiency in the case of both children and adults.<sup>14,19</sup> It is useful for the treatment of all types of onychomycosis, especially when more than one nail is affected. The one disadvantage of oral treatment is it has more side effects.<sup>30</sup> [Currently used oral treatment for the Onychomycosis involves terbinafine, itraconazole, and fluconazole.<sup>4</sup> For second line of treatment, terbinafine plus dosing itraconazole, and fluconazole are used.<sup>15</sup> Griseofulvin is used rarely because of its side effect, longer duration of the treatment and less cure rate. For diabetic people suffering from dermatophyte onychomycosis both terbinafine and



itraconazole therapy is useful. Combination therapy should use for immunocompromised patients, old age group, people suffering from multiple infections or those patients who doesn't respond well to monotherapy.<sup>19</sup> Oral terbinafine shows different types of side effects such as headache, diarrhoea, vomiting, anorexia, disturbance in taste, hepatic dysfunction, neutropenia, steven-Jonson syndrome. Oral itraconazole also have some side effects like headache, upper respiratory tract infection, gastrointestinal upset, hepatic dysfunction, it uses for the patients who can't tolerate terbinafine or for the patients who are suffering from non-dermatophyte mould or yeast. Oral fluconazole is approved by Europe for the treatment of onychomycosis but not by the United States Food and Drug Administration (FDA).<sup>14</sup> Oral ketoconazole has severe side effects like hepatotoxicity, and other side effects include skin rashes, gastrointestinal disturbance, so it should not use for onychomycosis treatment.<sup>30</sup>

### Novel Oral Therapies

Recently novel oral therapies have gain attention for onychomycosis treatment. Patients suffering from oropharyngeal candidiasis and invasive fungal infection posaconazole use as the treatment for onychomycosis.<sup>12,19</sup> Japan has approved fosravuconazole which is a prodrug of ravuconazole for onychomycosis treatment. Oteseconazole is also use for the onychomycosis treatment but it is not yet approved by USA FDA.<sup>16</sup> Albaconazole also use onychomycosis treatment.<sup>12</sup>

### Topical Treatment

Topical treatment is less effective as compare to the oral therapy and requires longer duration of treatment course because of the slow penetration to the nail plate due to thick nail, hardening of the nail plate and presence of keratin.<sup>14,19</sup> It can be useful the patients who are intolerance to the oral treatment or people who are suffering with superficial onychomycosis and early DLSO because of lower drug-drug interactions.<sup>14</sup> Topical agents must reach trans ungual space as cream and other topical agents are not effective for treatment,<sup>14,19</sup> so nail lacquer is use for onychomycosis treatment because nails are more permeable to aqueous vehicle.<sup>30</sup> Currently use nail lacquers are efinaconazole, tavaborole, ciclopirox, terbinafine and amorolfine.<sup>21,14</sup> Amorolfine is effective against Mold, yeast, dermatophyte, non-dermatophyte and *Candida Spp.*

Ciclopirox has fungicidal and anti-inflammatory effect it is active against dermatophyte, non-dermatophyte, gram-negative, gram -positive bacteria and *candida spp.* Efinaconazole and tavaborole is effective against dermatophyte onychomycosis and useful for the treatment of toenail onychomycosis and it is active against dermatophyte, non-dermatophyte and *Candida Spp.* Luliconazole has both fungicidal and fungistatic activity.<sup>12,19</sup> Some of the nail lacquers shows adverse effects, discoloration of the nail and development of erythema were reported in patients using ciclopirox, efinaconazole and tavaborole.<sup>19</sup> Itching, burning, and erythema has been reported in patients using amorolfine cream. Burning, pruritus, vesicles and pain around the nail has been reported in the patients using 5% amorolfine lacquer.<sup>30</sup>

### Novel Topical Therapy

Ciclopirox hydro lacquer most commonly used in Europe for onychomycosis treatment and approved by more than 40 countries but is not approved by USA for onychomycosis treatment. Topical terbinafine is also use as novel therapy.<sup>19</sup>

### Laser Therapies

Laser therapy is useful to improve the appearance of the nail but it has less mycological cure rate. Several types of laser treatments are available like carbon dioxide, diode 870-nm leaser, neodymium-doped yttrium aluminium garnet (Nd: YAZ), 930-nm laser.<sup>12,14</sup> To penetrate the nail laser wave length should be between 750-1300 nm.<sup>9</sup> Laser treatment works in the principle of photothermolysis, where nail absorbs the radiation, it increases the temperature in fungal mycelium which cause fungal cell death.<sup>14</sup> During the laser treatment surrounding area is not affected. The oldest laser treatment is the carbon dioxide laser.<sup>12</sup> Laser treatment has some disadvantages it requires more treatment session and high-cost effect.<sup>19</sup>

## NEW TREATMENT OPTIONS

### Photodynamic Therapy

Photodynamic therapy is a device-based treatment and it is nondamaging in nature.<sup>30</sup> It is a light base therapy which causes photoactivation of photosensitizer. The energy which was generated during photoactivation in the tissue it reacts with the dissolve oxygen and releases free radicals which cause cytotoxic. It causes necrosis and apoptosis and It is useful for off-label treatment and actinic keratosis.<sup>19</sup> There are different types of

photosensitizers such as toluidine blue, Methyl Aminolevulinate, Porphyrins, 5- Aminolevulinic Acid, rose Bengal and Aluminium Phthalocyanine. There are some disadvantages of using photodynamic therapy like pretreatment with urea, pain, nail avulsion. Some side effects include burning sensation, erythema, pain, and blisters.<sup>14,19</sup>

### Plasma Therapy

Low temperature plasma or non-thermal plasma is used for the treatment of onychomycosis. It is created from pulses of strong electric field that generates ozone, nitric oxide, ions and hydroxy radicals. Which provides limited tissue heating and it has anti-fungal properties.<sup>9,19</sup>

### Treatment of Onychomycosis Using Oil from Plant Extract

Tea tree oil used for the treatment of Tinea pedis. Nutmeg oil, Lavandula angustifolia oil, Cedar leaf oil, Camphor, Turpentine oil, Eucalyptus oil has some anti-fungal activity. Against impetigo and tinea pedis ozonized sun flower oil shown some anti-fungal activity.<sup>24</sup> Vitamin E, oil of bitter orange also has some activity against fungus.<sup>32,33</sup>

### CONCLUSION

Onychomycosis, a common nail disorder, is often caused by *Aspergillus* spp., an opportunistic fungus affecting older adults, diabetics, and immunocompromised patients. It presents with nail discoloration, onycholysis, and onychia, causing pain and difficulty walking. Diagnosis is confirmed with KOH, fungal culture, histopathology and PCR, while dermoscopy helps differentiate it from other conditions. Treatment typically includes oral antifungals (terbinafine, itraconazole, and fluconazole) and topical treatments like nail lacquers (efinaconazole, tavaborole, ciclopirox, terbinafine and amorolfine). However, these treatments can cause effects like nail discoloration and erythema, and resistance is a concern. Novel therapies, such as laser therapy, photodynamic therapy, and plant-based oils, show promise in overcoming these challenges.

### Statements and Declarations

**Conflict of Interests:** Authors declare that they have no conflict of interest among themselves.

**Funding Source:** The Authors declare that the study has not been funded by any external or internal sources.

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