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CONVENTIONAL METHODS AND NATURAL THERAPEUTIC OPTIONS IN THE TREATMENT OF ONYCHOMYCOSIS

Metody konwencjonalne i naturalne możliwości terapeutyczne w leczeniu grzybicy paznokci

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A - Koncepcja i projekt badania, B - Gromadzenie i/lub zestawianie danych, C - Analiza i interpretacja danych, D - Napisanie artykułu, E - Krytyczne zrecenzowanie artykułu, F - Zatwierdzenie ostatecznej wersji artykułu

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Abstract (in Polish):
Wprowadzenie i cel pracy
Grzybica paznokci (OM - onychomycosis) jest najczęściej spotykaną chorobą paznokci w praktyce klinicznej na całym świecie. Bez skutecznego leczenia grzybica paznokci staje się przewlekłym i uciążliwym schorzeniem. Konwencjonalne leczenie grzybicy paznokci obejmuje terapię doustną i miejscową. Doustne środki przeciwgrzybicze, choć dość skuteczne, są toksyczne dla wątroby i powodują

interakcje między lekami. W pracy przedstawiono najczęściej występujące rodzaje OM oraz przegląd dostępnych metod leczenia grzybicy paznokci w obrębie stóp.

Metody przeglądu

Niniejsza praca jest przeglądem literatury dotyczącej dotychczasowej wiedzy i najnowszych doniesień naukowych na temat konwencjonalnych metod leczniczych i naturalnych środków w terapiach grzybicy płytek paznokciowych. Poszukując informacji do artykułu, uwzględniono aktualne publikacje oraz literaturę anglojęzyczną w bazie PubMed. Opcje leczenia OM obejmują doustne leki przeciwgrzybicze, miejscowe terapie, chirurgiczne usunięcie paznokcia oraz laserereroterapię. Leczenie grzybicy paznokci musi być zindywidualizowane w oparciu o badanie mikologiczne, skuteczność leku, obraz kliniczny, preferencje i co najważniejsze, bezpieczeństwo pacjenta. Atutem olejków eterycznych jest posiadanie wysokiej aktywności przeciwgrzybiczej względem patogenów wywołujących grzybicę skóry i jej przydatków.

Podsumowanie

Ograniczony zakres konwencjonalnych i skutecznych środków przeciwgrzybiczych a także możliwe pojawienie się nieprzyjemnych działań niepożądanych pobudziły zapotrzebowanie na bezpieczniejsze terapie, prowadząc do zwiększonego zainteresowania terapiami miejscowymi. Olejki eteryczne mogą stać się źródłem nowych terapeutycznych związków, a włączenie ich do preparatów miejscowych stanowi ciekawą, skuteczną i bezpieczną alternatywę w leczeniu OM.

Abstract (in English):

Introduction and aim of the paper

OM - onychomycosis is the most common nail plate disease in dermatological clinical practice. Onychomycosis becomes a chronic and troublesome condition with no effective treatment. Conventional treatment of onychomycosis includes topical and oral therapy. Oral antifungal agents, although quite effective, are hepatotoxic and cause drug interactions. This paper presents the most common types of OM and a review of the available treatments for onychomycosis of the toenails.

Methods of review

This paper constitutes a literature review of current expertise and recent scientific reports on conventional treatment methods and natural agents used in the course of onychomycosis. In search for information to be included in the article, current publications and English-language literature in the PubMed database were taken into consideration. Treatment options for OM include oral antifungals, topical therapies, surgical removal of the nail and laser therapy. Treatment of onychomycosis must be individualised based on the mycological examination, medication efficacy, the clinical picture, preferences and, most importantly, patient's safety. The advantage of essential oils is that they show high antifungal activity against pathogens causing dermatophytosis and skin-related infections.

Summary

The limited range of conventional and effective antifungal agents and the possible occurrence of unpleasant side effects caused a demand for safer therapies, leading to an increased interest in topical therapies.

Essential oils have the potential to become a source of new therapeutic compounds, and their use in topical preparations offers an interesting, effective and safe alternative in the treatment of OM.

Keywords (in Polish): Onychomycosis, grzybica stóp, inwazyjne zakażenia grzybicze, inwazyjne grzybice, leczenie inwazyjne.

Keywords (in English): Onychomycosis, Tinea Pedis, Invasive Fungal Infections, Invasive Mycoses, Involuntary Treatment.

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Short title
Metody konwencjonalne w leczeniu grzybicy paznokci

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Introduction

OM - onychomycosis is the most common nail plate disease in the global dermatological clinical practice and it is becoming a major social and epidemiological problem. Despite the availability of advanced medical care for most conditions, the high prevalence of nail mycoses suggests that either currently available treatments are ineffective or patients are unaware of their condition. Consequently, they serve as a reservoir of fungi and a source of infection for the environment and themselves, leading to self-infection. Without effective treatment, OM becomes a chronic and troublesome condition that can be accompanied by discomfort when walking, thus significantly reducing the quality of life of the patients [1-5].

The aim of this study was to review the most commonly used various treatments for nail plate onychomycosis.

Methods of review

This paper focuses on the treatment and available therapies for onychomycosis. A search was made in PubMed using the key term "onychomycosis treatment". Data on conventional treatment solutions were collected and analysed, and attention was also paid to the side effects of the commonly used drugs and natural therapies for onychomycosis. The search strategy included meta-analyses, randomised controlled trials, clinical trials, observational studies and reviews published within the last 5 years.

Treatment methods for OM - Onychomycosis

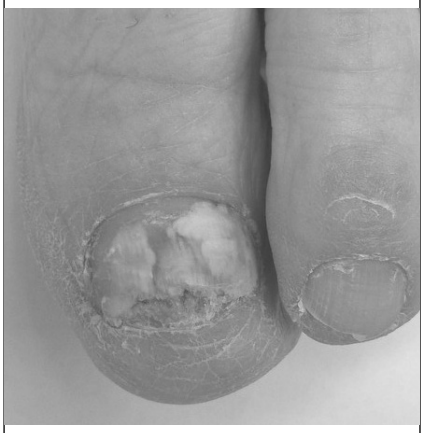
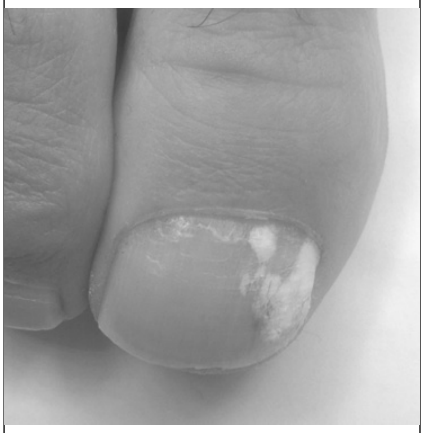
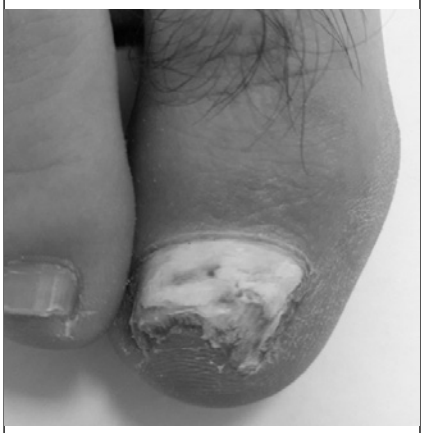
Although OM can cause pain in the NA (nail apparatus), patients most often report because of cosmetic problems involving the appearance of their nails. Treatment is important, especially in the elderly and diabetics, as onychomycosis can lead to cellulitis and foot ulcers in these populations [4]. Treatment options for OM include oral antifungals, topical therapies, surgical removal of the nail and FDA (Food and Drug Administration) approved lasers, as device-based therapies for temporary nail removal and/or improvement [5-7].

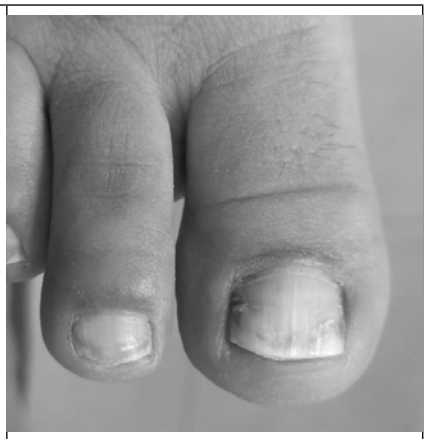
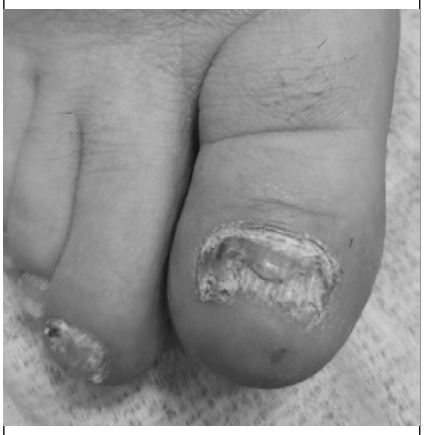
Prior to choosing a proper therapy for the patient, it is important to correctly diagnose the disease. The clinical picture alone can never be the basis for the diagnosis and commencing a treatment for onychomycosis. Confirmation of the initial diagnosis should always be sought by detecting the presence of a pathogenic fungus in the altered nail plates. To this end, a correct diagnosis based on history, thorough physical examination and diagnostic mycological tests should be performed. When taking the history, attention should be paid to: duration of infection, previous antifungal treatment, general health status of the patient including medical conditions (diabetes, kidney and liver disease, chronic venous insufficiency, atopy), antibiotic therapy, recent immunosuppressive medication, occupational exposures (farmers, veterinarians, laboratory employees) or pet ownership, environmental exposures (working in mines, staying in boarding houses or barracks, frequent use of swimming pools, sports and leisure facilities, spa stays). Mycological examination involves proper collection of diagnostic material in the form of scrapings from the pathologically altered nail together with subungual keratosis masses in the hard-to-access part of the nail plate adjacent to the nail bed. Mycological examination includes microscopic examination of the preparation appropriately made with the use of the clinical material (direct examination), and a culture. A positive microscopic examination is the only sure diagnosis of OM, while the characteristic morphological features of the culture allow the evaluation of the pathogen's species affiliation. Fungal identification is carried out in microscopic preparations from the culture and by evaluating their biochemical properties with the use of specific reagents. Culture for dermatophytes takes approximately 3-4 weeks [1, 5, 8-11].

Traditional oral antifungal drugs are the most commonly chosen by physicians as they have a high efficacy rate [16, 17]. However, they can be associated with systemic toxicity and numerous drug interactions causing serious side effects: chronic or active liver disease, congestive heart failure and renal dysfunction [17]. Taste and/or odour disorders are one of the most common adverse effects in patients taking terbinafine and can be persistent. Azole antifungals are associated with many drug interactions, including QT interval prolongation, torsade de pointes (TdP) and death, heart failure and rhabdomyolysis (dangerous muscle breakdown), leading to only 35-65% of physicians prescribing oral therapy to cure onychomycosis [1, 18]. Laboratory tests on terbinafine therapy are controversial. In a review of the National Institutes of Health Livertox database, PubMed and EMBASE, 69 patients had symptomatic drug-induced liver injury, with an average of 30.2 days of therapy (range 5-84 days) [18, 19]. With the view to reports of mild and severe liver damage, clinicians often perform liver enzyme tests, while the FDA recommends determination of serum transaminases when starting the therapy [20, 21].

Despite their promising efficacy (~60%) in the treatment of fungal nail infections, oral antifungal agents (terbinafine hydrochloride, itraconazole) have a high recurrence rate, ranging from 25-50%. Particular caution should therefore be exercised when treating the elderly, immunocompromised patients, patients on multiple medications, dialysis or organ transplant patients and those with comorbidities [1, 22].

Table 1. Types of onychomycosis [2, 8, 10-16].

Mycosis type, clinical type and type of pathogen	Main symptoms and infection site	Clinical picture confirmed by mycological examination
DLSO – distal and lateral subungual onychomycosis ***Dermatophytic*** *caused by:* Trichophyton rubrum, *more rarely by* Trichophyton mentagrophytes ***Non-dermatophytic*** *caused by:* Scopulariopsis brevicaulis, Fusarium sp., Acremonium sp., Aspergillus species, Scytalidium dimidiatum *and* Acremonium sp., *as well Tritirachium oryzae reported in recent years.*	The infection starts from the hyponychium and then progresses to involve the nail bed and raises the distal part of the nail plate. **Clinical features:** • onycholysis • subungual hyperkeratosis • yellowish, whitish or brownish discolouration of the distal corner of the nail • dermatophytoma: yellow-orange area of onycholysis in the central part of the nail • frayed proximal edge of the nail plate • distal chipping of the nail plate	 *Fig. 1.* ***DLSO*** *infection caused by T. mentagrophytes - own archive*
WSO - white superficial onychomycosis ***Dermatophytic*** *caused by:* Trichophyton mentagrophytes var. interdigitale ***Non-dermatophytic*** *caused by:* Fusarium sp., Acremonium sp., Aspergillus species,	The infection occurs in the dorsal part of the nail plate; due to keratolytic enzymes generated by the fungi the hard keratin is decomposed, resulting in a white matting of the plate. This condition may accompany interdigital tinea pedis. **Clinical features:** • white powdery spots on the nail surface • no dystrophic changes in the nail plate	 *Fig. 2.* ***WSO*** *infection caused by Fusarium oxysporum - own archive*
PSO – proximal subungual onychomycosis ***Dermatophytic*** *caused by:* Trichophyton rubrum ***Non-dermatophytic*** *caused by:* Fusarium sp., Aspergillus species	An infection in which fungi penetrate through the proximal nail shaft to the ventral portion of the nail plate. It usually occurs in patients with immunodeficiencies, especially with acquired immunodeficiency syndrome (AIDS). **Clinical features:** • vitiligo (leukonychia) from the proximal part of the nail which extends distally with nail growth (dermatophytic mycosis) • rapid progression of the infection involving entire nail plate (non-dermatophyte mycosis) • pus may collect under the nail plate	 *Fig. 3. PSO infection caused by Fusarium solani - own archive*

EO - endonyx onychomycosis ***Dermatophytic*** *caused by:* Trichophyton soundanense and Trichophyton violaceum	The infection is characterised by pathogens penetrating directly into the nail plate without infecting the nail bed. **Clinical features:** • dull, non-glossy nail plate with milky colouring • dents and splitting of the nail plates may occur • no onycholysis (nail plate firmly attached to nail bed) • no subungual hyperkeratosis	 *Fig. 4.* ***EO*** *infection caused by T. soundanense - own archive*
TDO - total distrophic onychomycosis	The infection is characterised by complete destruction of the entire nail apparatus and is often the final stage of onychomycosis, which can occur after any of the other subtypes. **Clinical features:** • severe dystrophy with crumbling and fragmented nail plate that is yellowish, diffuse, thickened, resembling a "rotten tree"	 *Fig. 5.* ***TDO*** *infection caused by T. rubrum - own archive*

Overexposure to conventional systemic antifungal drugs may contribute to resistance to terbinafine and azoles. Case reports of OM with reported failure after terbinafine therapy are increasingly reported in the literature. Treatment of onychomycosis must be individualised based on the medication efficacy, the clinical picture, preferences and, most importantly, the patient's safety, and special attention should be given to comorbidities and concomitant medications [18, 23].

Topical treatment is usually used if fungal lesions affect no more than three nails and do not exceed half of the nail surface or in cases where oral treatment is not recommended [11, 23]. Topical medications approved by the FDA for the treatment of OM include ciclopirox, efinaconazole and tavaborol. These therapies generally have incomplete efficacy compared to systemic agents and also involve long treatment cycles [24]. Topical pharmacological agents often show low penetration through the nail and are associated with potential local side effects, e.g. efinaconazole can cause allergic contact dermatitis [18, 21, 26, 27].

Nail polishes with amorolfine and ciclopirox are popular on the market. The use of an 8% solution of ciclopirox once daily for 48 weeks has been shown to cure only 2-3% of OM in various stages in controlled clinical trials. Topical nail polish containing ciclopirox was found to be most effective in the treatment of superficial and mild distal-lateral OM. Furthermore, topical antifungal agents have limited efficacy, but may show synergistic effects when used in combination with oral antifungal drugs [1, 11, 21].

According to Gupta et al. (2018), efinaconazole and tavaborol, unlike varnishes, are formulated as solutions. For topical treatment to be effective, the antifungal agent must reach the nail bed and matrix

and should accumulate in the nail plate. The solution-based formulation allows the drug to be applied to the stratum corneum and the subungual space (subungual administration). Due to the poor permeability of the nail plate, removal and cleansing of infected diseased areas can significantly reduce the fungal load and complement topical therapy [22].

Global research is strongly emphasising new drug application systems such as nanoparticles, microemulsions, polymer films to increase the penetration of topical therapy drugs. [21]. Bseiso et al. (2016) and Abobakr et al. (2021) developed lipid nanoparticle formulations with various substances to enhance penetration through the nail plate (N-acetyl-L-cysteine, thioglycolic acid, thiourea and ethanol). In vitro microbiological studies showed significantly higher hydration and increased absorption of the drug with sertaconazole [28] and terbinafine [29] in nail scrapings compared to the market product. Furthermore, both experiments showed significantly higher inhibition of *Trichophyton rubrum* growth than the market cream. These formulations represent a very promising option, worthy of clinical experimentation in patients with OM [28, 29].

Alqahtani et al. (2022), on the other hand, demonstrated that novel self-emulsifying itraconazole (ITZ) nanoparticles loaded into a carboxymethyl fenugreek gum (CMFG) gel, increase drug permeability and extend retention at the site of action. The prepared CMGF-ITZ-nPEVs gel showed greater antifungal activity than the commercially available gel. Clinical trials to determine the efficacy of ITZ-nPEVs in patients with OM are currently ongoing [30].

All currently available systemic and topical treatments for onychomycosis should be avoided during pregnancy and breastfeeding [17, 26].

Other new methods that are still in the clinical trial phase, such as lasers, photodynamic therapy or iontophoresis, are more are more frequent[19, 28].

In Japan, favourable results have been reported in patients with onychomycosis who receive combined treatment involving a dioxide laser and topical antifungal medication, photodynamic therapy and Nd:YAG laser treatment [30]. One of the advantages of laser therapies is their capability to concentrate the energy beam on the affected tissue, thus reducing possible side effects, when compared with oral therapies. This makes it safe for use during pregnancy and lactation [17, 26]. However, the conditions and number of irradiation sessions and methods of assessing efficacy vary between centres and clinical trials, so there is no established evidence supporting these results [31].

Photodynamic therapy (aPDT) is a non-invasive alternative suitable for the treatment of superficial fungal infections. However, successful treatment depends on the correct selection of a photosensitiser and substances improving the properties of the final preparation. In their study, Valkov et al. (2022) proved the antifungal activity of rose bengal (RB) in their study. IN order to find a formulation suitable for the treatment of onychomycosis, urea and thiourea were added to RB as agents that potentially increase the nail plate permeability. The most effective preparation to inhibit the growth of T*richophyton rubrum* and *Candida albicans* under light contained 150 μM RB, 5% urea and 0.5% thiourea in a glycerol/water solution (70/30%, w/w). The formulation was stable for at least one month of storage at 30°C [32, 33].

Ma et al. (2022) investigated the photodynamic inactivation efficiency and action of aloe-emodin (AE), a natural photosensitiser (PS), against *T. rubrum* microconidia in vitro. After irradiation, AE showed an effective therapeutic effect against *T. rubrum*-induced mycobacteriosis in a guinea pig model and tinea pedis in an ex vivo model. The results suggest that AE is a potential PS for the photodynamic treatment of dermatophytosis caused by *T. rubrum*, but its penetration in the skin and nails needs to be improved [32].

In their study, Nair et al. (2021) used a constant voltage iontophoresis technique for the transdermal administration of terbinafine. A Box-Behnken statistical design was conducted to optimise formulation

development. Preliminary studies suggest that PEG 400, voltage and application time can affect both penetration of terbinafine through the nail plate and accumulation of the drug in the nail tissue. The data obtained represent a new approach to the effective treatment of OM but require confirmation in clinical trials [34].

For several decades, efforts have been made to increase the efficacy of topical drug application for the effective treatment of OM. Mechanical, physical and chemical methods have been used. Despite all these attempts, the problem of preparations application into the nails has not yet been solved [21].

In recent years, there has been a significant increase in interest in therapeutics of plant origin. Many micro-organisms have acquired resistance to known and usually used medication, e.g. *Candida* yeasts. Research on medicinal plants confirms the wide range of pharmacological effects of essential oils and their constituents [35]. They consist of a variety of organic compounds, mainly low-molecular-weight terpenes, which readily penetrate an adequately cleaned nail plate, finding fragments or mycelial strands. Chemically, they are mixtures of monoterpene and sesquiterpene compounds or their derivatives with features of alcohols, ketones, aldehydes, hydrocarbons, esters or ethers. The complex mixture of these compounds imparts a broad spectrum of antifungal activity by interacting with biological membranes, interfering with radical and enzymatic reactions of fungal cells [36-38]. The advantage of essential oils is that they show high antifungal activity against pathogens causing dermatophytosis and skin-related infections. They also show anti-inflammatory, antibacterial, antiviral and antiparasitic effects, as well as stimulate the immune system. Most oils have tremendous medicinal properties, and many are valued for their remarkable cosmetic effects. Both plants or their parts have beneficial effects, but the essential oils derived from them show much more powerful benefits [35].

Tea tree oil (TTO) extracted from the Australian plant *melaleuca alternifolia* is considered one of the most potent antiseptics, thanks to its main constituent terpinen-4-ol [34]. In infections caused by dermatophytes and yeast-like fungi, studies have shown that after six months of treatment with preparations containing TTO, the majority of patients were cured, and in other cases, a marked regression of the fungal lesions was observed [39]. A high cure rate was achieved: 55% of patients treated with TTO at a concentration of 25% and 64% of patients treated with TTO at a concentration of 50% [40]. In vitro studies have also been conducted using combination therapy consisting of oral fluconazole or terbinafine and topical preparations containing TTO in their formulation. Combined therapy improved treatment efficacy when compared to monotherapy from 55.9% to 87.9% [41] Furthermore, in an in vitro study by Marcos-Tejedora et al. (2021), TTO showed fungistatic activity against *T. rubrum* fungi at concentrations greater than or equal to 0.04%. In contrast, it was effective against *T. mentagrophytes* at a concentration of 0.02% and showed a potentially inhibitory effect against these pathogens at a concentration of 0.07% [42]. For deep subungual mycosis, the use of TTO is more effective than the often recommended clotrimazole [35].

Lavender oil (*Lavandula Angustifolia Oil*) has shown antifungal properties against two clinical isolates of onychomycosis (*Scopulariopsis brevicaulis* and *Fusarium oxysporum*) and against other 42 strains, including dermatophyte fungi. The authors attribute the antifungal activity to the main components: linalool, linalyl acetate, b-caryophyllene and terpinen-4-ol. In addition, the oil has been shown to be active against *Candida albicans, Aspergillus fumigatus* and *Trichophyton mentagrophytes* species [35, 36]. The results of the study indicate a broad spectrum of antimicrobial activity of lavender oil. This raises great hopes for plant-derived substances that may in future be important in the treatment and control of antibiotic-resistant microorganisms that are dangerous to human health [43].

Oil of oregano, rich in carvacrol and thymol, also known as wild thyme (*Thymus Capitatus Herb Oil*), also shows antifungal activity. Sahin et al.(2004) verified its effective action on 15 fungal strains,

including C. albicans, *F. oxysporum, T. rubrum and T. mentagrophytes*, as well as on other clinical isolates [44]. Inouye et al. (2006), on the other hand, found that oregano oil was most active against *T. mentagrophytes* compared to TTO and lavender oils [45]. A huge advantage is that the microorganisms do not acquire resistance with prolonged use of the oil, as with artificial chemicals [46].

Rosemary oil (*Rosmarinus Officinalis Leaf Oil*) is active against *Candida* and *Trichophyton*. Moreover, it shows antimicrobial properties by inhibiting the growth of many Gram-positive as well as Gram-negative bacteria. Phytoncides - contained in rosemary cause damage to cell walls and cytoplasmic membranes of bacteria and fungi [36].

Clove oil (*Eugenia Caryophyllus Leaf Oil*) can also be counted among the oils with high fungicidal activity due to its eugenol content [35]. In a study by Kędzia et al. (2014), it has high activity against all *Candida* and yeast-like fungal strains tested. A low concentration of the oil of 0.25 mg/ml inhibited the growth of 33% and a concentration of 0.5 mg/ml inhibited the growth of a further 64% of strains, suggests the potential for practical use in prevention and therapy [47].

Conclusions

The limited range of conventional and effective antifungal agents and the possible occurrence of unpleasant side effects caused a demand for safer therapies, leading to an increased interest in topical therapies. As the application is easy and the risk is minimal to the patient, a new, effective combination of a broad-spectrum medicine and natural antifungal agents is being sought.

Essential oils have the potential to become a source of new therapeutic compounds, and their use in topical preparations offers an interesting, effective and safe alternative in the treatment of OM. Active ingredients in oils, rich in low molecular weight molecules, may provide better penetration into the fungal elements inside the nail plate.

Although many natural agents show promising antifungal activity in vitro, further studies are required to prove the penetration of active compounds into the nail plate and their efficacy in vivo for the treatment of OM.

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