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Review Article

The Causes, Consequences, and Cures of Recurrent External Fungal Infections

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Received: November 30, 2020; **Published:** December 31, 2020

DOI: 10.31080/eccmc.2021.04.00346

Abstract

Superficial fungal infections affect greater than 20% of the global population. Only a few hundred (of the millions of fungi species) are capable of causing human infections. Moreover, superficial infections respond well to various over-the-counter products. However, resistance to specific anti-fungal medicines is developing. The skin surface is an ideal growth environment for dermatophytes, commonly found around public swimming pools, locker rooms, and showers. Transmission occurs through direct person-to-person contact or indirect contact through the handling of contaminated objects. Immunocompromised patients and those with active illnesses and diseases are at a greater risk for fungal and recurrent fungal infections. An individual's genetic design may predispose them to specific fungal infections. Also, specific factors, such as cosmetics, body soaps, and other hygiene products, can alter the skin microbiome, predisposing the host to pathologic fungal infestation. This article reviews the etiology of external fungal infections and recurrent infections, considers susceptibility factors, and describes and evaluates currently available treatment options.

Keywords: *Azole; Dermatophyte Infection; Immune Response; Mannan; Microbiome; Omics; Polyenes; Resistance; Targeted Sequencing*

Abbreviations

OTC: Over-the-Counter; rRNA: Ribosomal RNA

Introduction

Superficial fungal infections (mycosis) are a frequent dermatological condition noted worldwide, affecting > 20% of the population [1]. Fungi are microscopic organisms in plants, soil, and human and animal skin [2]. Among the millions of existing fungal species, only a few

hundred can cause infection in humans [3]. Typically, skin fungi do not cause compllcations in the host unless they multiply rapidly and invade the skin through lesions and abrasions, causing superficial skin and nail mycoses [4]. There are several over-the-counter (OTC) treatments for fungal infections, although increasing resistance to the limited supply of the available antifungal drugs is a severe threat to population health [5]. This article reviews the etiology and sources of external fungal infections. It investigates, especially recurrent infections; why specific individuals are more susceptible than others and provides currently available treatment options.

Etiology of fungal infections

Dermatophytes are filamentous fungi that invade the skin's epidermal layer and areas high in keratin, such as hair and nails [6]. Tinea is a dermatophyte infection, characterized by the infection site: tinea corporis or tinea versicolor (body), tinea pedis (foot), tinea cruris (groin), tinea capitis (scalp), and tinea unguium or onychomycosis (nails) [7]. Among the three genera of dermatophytes (*Trichophyton, Microsporum,* and *Epidermophyton*), the genus *T. rubrum* is the most common cause of tinea and onychomycosis [8]. Superficial skin infections, such as candidiasis of the skin under the breasts, buttocks, and nails, are caused by the yeast *Candida* [9].

Most dermatophytes do not survive at a high environmental temperature of 37°C [10]. The skin's surface temperature is 26°C, which is an ideal growth environment for dermatophytes [11]. As fungi thrive in warm and moist environments, they are often found around public swimming pools, locker rooms, and showers [12]. Transmission occurs through direct person-to-person contact or indirect contact through the handling of contaminated objects [13]. As dermatophytes can survive outside the host environment for extended periods, indirect transmission through clothing and other accessories is common [14].

Sources of and contributing factors in recurrent fungal infections

Most fungal infections do not pose a severe health threat. They can be effectively managed by OTC and prescription medications when treatment is followed through [15]. Prevention is best achieved through good hygiene [16]. Despite good hygiene and treatment, fungal infections are often recurrent or chronic in otherwise healthy patients. Several factors have been implicated in the occurrence of such fungal infections [17].

Dermatophytes can desquamate and survive as spores outside the host environment for extended periods [18]. Their prevalence in the human habitat is associated with an increased possibility of retransmission under favorable conditions [19].

The cell wall of *T. rubrum* is comprised of mannan, a polysaccharide, acting as a robust immunosuppressive agent, protecting the fungus from the host's immune response [20]. The activation of host suppressor T cells during prolonged infections inhibits an adequate host cell-mediated immune response [21]. The human body is assumed to have adapted to the fungus and thus fails to recognize the foreign agent [22]. Overall, host immunologic unresponsiveness and fungal characteristics are responsible for recurrent fungal infections [23].

Patients with underlying diseases are at greater risk for recurrent fungal infections [24]. Conditions such as diabetes, cardiovascular disorders, and the individual's genetic makeup can increase specific patients' vulnerability to fungal infections [25]. Chronic mucocutaneous candidiasis is a hereditary immunodeficiency disorder of T cells, characterized by frequent or chronic recurrent *Candida* infections of the mouth, scalp, skin, and nails [26].

Mechanisms of fungal infections

Dermatophytes' functional characteristic is that they require keratin, found in the outermost skin layer (stratum corneum), for attachment, penetration, and growth [27]. Keratin is also the main constituent of human hair and nails [28], which constitutes additional entry

sites. Thus, dermatophytes rarely invade deeper tissue structures and mucosal membranes [29].

Arthroconidia, a type of fungal spores, is a fungal propagule for disseminating dermatophytes [30]. Once the transmission has occurred, cuts and abrasions promote the arthroconidia's entry into the epidermis in the stratum corneum [31]. Attachment progresses over a 6-h period, during which time germination is initiated [32]. Germination progresses through hyphae extension across the stratum corneum and the upregulation of many fungal genes encoding proteins essential for fungal viability [33], including keratinolytic and lipolytic enzymes that enable the utilization of keratin and lipids as nutritional sources [34-36]. Further, pathogenic factors, especially mannans, inhibit keratinocyte proliferation and prevent dermal sloughing, allowing the fungus to survive [37].

Host immune response

The strength of the host immune response to a particular fungal infection depends on the patient's age, gender, and genetic makeup and can change over the disease course. The host's innate immune response is the first line of defense against fungal pathogens [27]. Keratinocytes are stimulated by recognizing fungal antigens through toll-like receptors to release a plethora of cytokines, including TNF-alpha, interferon-gamma, and interleukins [39]. This process is followed by a cell-mediated delayed-type immune response by T cells and the production of antibodies against the dermatophyte, especially in the case of recurring infections [37].

Role of the epidermal microbiome in maintaining homeostasis

The skin microbiome concept contributing to disease is intriguing and, in light of the current research popularity of the intestinal microbiome, apropos. However, research on the epidermal microbiome has been lagging compared to that of the gut flora [40]. Nevertheless, omics technology has been used to profile the epidermal microbiome to understand disease pathogenesis, study the effect of a particular product, and analyze the efficacy of a potential therapeutic agent [41].

Targeted sequencing of the 16S ribosomal RNA (rRNA) gene is the most commonly used method to profile prokaryotic microbiomes [42]. For fungal classification, the internal transcribed spacer region of ribosomal genes is used as a target. These methods have revealed that healthy skin flora plays a role in host resistance and immune function in microbial dysbiosis associated with exacerbating skin disease [43,44]. However, numerous studies have reported conflicting data on microbiota changes and, hence, the microbiome's impact on disease predisposition [45]. Also, the microbiome profile is influenced by many factors, such as host factors (age, gender, ethnicity, geographic location), environmental factors (temperature, humidity), and skin site and location [46]. Despite these ecological insults, stable microbiota was reported by Oh., *et al*. (2016) in skin samples from 17 sites at 3 different time points in 12 healthy individuals over 2 years [47].

Other possible factors that can alter the skin microbiome are cosmetics, body soaps, and other hygienic products [48]. Frequent hand washing could alter skin barrier function and change the skin microbiome [49]. However, Two., *et al*. (2016) analyzed the effect of washing hands with four different soaps from Softsoap® (lavender and chamomile hand soap, soothing aloe vera moisturizing hand soap, rich shea butter moisturizing hand soap, and aquarium series hand soap) and found no significant changes in the microbiota abundance or diversity [50]. Only the addition of the antimicrobial compound benzalkonium chloride or triclocarban to these soaps helped inhibit bacterial growth. These findings highlight the stability of the epidermal microbiome to external influences and suggest the effect of cosmetic products to be primarily on skin barrier functions.

Although the microbiome may not be predictive of a disease per se, it may reflect disease pathogenesis, especially chronic skin ailments [51]. A recent study, by Stehlikova., *et al*. (2019), on the skin microbiota of patients with psoriasis, a chronic immune-mediated skin disease, revealed disease-specific bacterial and fungal profiles [52]. Metagenomic analysis has demonstrated that *Staphylococcus* and *Corynebacterium* spp colonize the human body's moist areas most prone to fungal infections. [46]. Liu., *et al*. (2019) characterized the

microbiome of patients with tinea pedis and healthy control subjects and demonstrated that the microbial flora was different between the two groups [53]. Healthy subjects presented more fungal diversity, whereas *T. rubrum* dominated in patients with tinea pedis. Interestingly, they found the *Corynebacterium* spp. was decreased in patients with tinea pedis and varied between patients with different forms of the infection, suggesting a microbiome's role in disease development [53]. However, these studies failed to conclude whether a microbial shift predisposes an individual to fungal infection or is secondary to the infection.

Current medical treatment options

Most superficial fungal infections of the skin and nails can be treated successfully with existing antifungal agents in the form of topical drugs [54]. The polyenes, azoles, and allylamines are the most widely used structural classes of drugs in treating infections caused by dermatophytes and *Candida* [55,56]. These drugs target ergosterol, a significant component of the fungal cell membrane.

Polyenes are of historical significance as they were the first antifungal drugs used in the clinical setting [57]. Of the three polyene agents (nystatin, amphotericin B, and candicidin), nystatin—sold under the brand name Mycostatin—is the preferred agent for treating *Candida* infections [58]. Unlike amphotericin B, which requires intravenous administration, nystatin is applied topically [59]. Polyenes display a broad spectrum of antifungal activity [60]. Their mode of action disrupts the cell membrane structure by binding to ergosterol, a sterol specific to the cell membrane of fungi and protozoa [60]. However, due to their weak affinity to cholesterol, polyenes exhibit high toxicity and several side effects [61]. While the extensive development of vehicles and delivery systems has improved therapeutic results and patient tolerance, future research should investigate novel drugs with reduced toxicities and enhanced pharmacokinetic profiles [62,63].

Azoles are the largest group of antifungal agents and can be classified into two groups: imidazoles (ketoconazole, miconazole, clotrimazole) and triazoles (fluconazole, itraconazole, voriconazole, posaconazole, isavuconazole) [64]. They are preferred for their broad-spectrum activity and safety profiles [65].

Ketoconazole, sold under the brand name Nizoral, is effective in treating tinea and candidiasis [66]. The newer series of azoles include efinaconazole, luliconazole, and sertaconazole, along with the recently introduced oxaborole and tavaborole [67]. Among the allylamines, terbinafine is widely used for managing nail infections [68]. Many of these agents are the preferred first-line treatment in children [7].

Among the skin ailments treated by the classes mentioned above, onychomycosis deserves special attention as it is the most common nail infection encountered in the clinical setting [6]. Ricardo and Lipner (2020) reviewed current therapies and their safety, emphasizing the need for individualized treatment because of numerous adverse events and fatal drug-drug interactions [69].

Risk factors for recurrence include familial history, age, diabetes, circulatory disorders, use of public gyms and swimming pools, choice of footwear, and nail trauma [68]. Based on the diagnosis, treatment can be systemic (terbinafine, itraconazole) or topical (efinaconazole, tavaborole). Although these agents' safety and efficacy in the pediatric population have not been established, these agents are nevertheless prescribed [7]. Off-label treatments with fluconazole have also been successful [68]. In contrast to these well-studied drugs and their known mechanisms of action, ciclopirox, a hydroxypyridone with a poorly understood mechanism of action, has also been approved as a nail lacquer formulation for treating onychomycosis [70].

Topical antifungal agents applied once or twice daily are the primary treatment of choice for most superficial mycoses, such as tinea pedis, tinea corporis/tinea cruris, and mild onychomycosis [71]. Therapy often requires prolonged treatment, lasting weeks to months [7,72]. Long-term use of these drugs is associated with the risk of resistance development and adverse effects, such as allergic reactions, burning, itching, rash, eczema, and pain on application [7,71,72]. The frequency of adverse events is generally low: < 0.1% in patients using Nystatin cream [73].

Drug toxicities, on the other hand, can be life-threatening. The association of oral ketoconazole (Nizoral) with increased hepatotoxicity risks and potentially severe adverse effects has led to its removal from some of the markets and restricted use for treating skin and nail fungal infections [74,75]. Toxicity was found to be unrelated to dose, duration, or indication for treatment. It is important to stress that topical formulations of Nizoral (i.e. creams, shampoos, and gels) have not been associated with liver damage, adrenal problems, or drug interactions [66].

Because azoles inhibit cytochrome P450-dependent enzymes, the nature of the interaction between each azole and the type of P540 determines their degree of side effects and toxicities [76]. In this regard, the second-generation triazoles, such as efinaconazole, are deemed safe when used under prescription [56].

As fungi are eukaryotes and many potential drug targets overlap with humans, antifungal agents' central feature is the need for specificity toward the fungus [65]. Thus, antifungal drug development has faced more challenges than antibacterial drug development programs [77].

Many antifungal drugs are often limited by toxicities, drug interactions, drug resistance, and a lack of efficacy in the face of emerging pathogens [77]. The evolution of new pathogens resistant to existing drugs, especially fungistatic agents, such as the azoles, pose new challenges for the prognosis and treatment of these infections with existing drugs [77]. Another major drawback of antifungals is the associated side effects, which lead to premature treatment withdrawal and infection relapse in the long-term [78].

To increase the repertoire of antifungals and avoid limitations of current antifungal agents, several investigational drugs with targets outside the known ergosterol in the fungal cell membrane or 1,3-β-D-glucan in the fungal cell wall are being developed [79]. The advantages of these would be the circumvention of the existing resistance mechanisms the pathogens have explicitly developed against the current antifungal agents [77–79].

Equivocal efficacy of natural antifungal medicaments

Superficial mycosis is rarely a life-threatening condition [80], nevertheless, affected patients look for drug-free alternative therapies. Limited sources on the internet advocate several natural remedies, specifically for fungal infection of the nails; however, their efficacy is uncertain [81]. The advocated natural remedies include the use of apple cider vinegar, tea tree oil, essential oil blends, baking soda, mentholated ointments and mouthwashes, and garlic [82,83]. However, most of these treatments show no significant curative effect and do not compare in efficacy to FDA-approved therapies [82,83].

In a randomized, double-blind trial, 117 patients with onychomycosis were given 100% tea tree oil or 1% clotrimazole solution for a twice-a-day application. Tea tree oil, a well-known natural antifungal with proven effects against dermatophytes, showed no significant benefits in the study [84]. Another small-scale study involving 60 patients found no tea tree oil-effect despite a three-times-a-day application for eight weeks [85]. In the absence of large-scale randomized clinical trials demonstrating efficacy, the use of these remedies cannot be recommended. However, as adverse effects are rare with most natural remedies, they are often believed to be safe to use at the patient's discretion [86].

Conclusion

Superficial mycoses can be treated with several therapeutical options tailored to suit a patient's condition. The patient outcomes depend on the accurate differential diagnosis of the mycosis as symptoms resemble other diseases and bacterial infections. Following the introduction of amphotericin B in the 1950s and ketoconazole in the 1980s, polyenes and azole antifungal agents have been the mainstay of antifungal therapy. However, optimized chemistry and new formulations have significantly improved the limitations of these first-gen-

eration drugs. The increasing rates of mycoses, the high incidence of toxicity of existing drugs, and the emergence of resistant strains have attracted research and drug development in this area, adding to the antifungal pipeline. The premise that fungi are becoming resistant to pharmacological treatment has spurred the search for new antifungal molecular targets and alternative drugs with innovative modes of action. Any novel agents should demonstrate improved pharmacokinetics, pharmacodynamics, and better fungicidal activity, broadening the activity spectrum toward drug-resistant fungi. These inventive antifungals may be needed to tip the balance in the race for dominance against fungal pathogens until medical science further advances, developing an antifungal vaccine.

Conflict of Interest Statement

References

1. Kim SH., *et al*. "Epidemiological Characterization of Skin Fungal Infections Between the Years 2006 and 2010 in Korea". *Osong Public Health and Research Perspectives* 6.6 (2015): 341-345. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4700767/

2. One Health: Fungal Pathogens of Humans, Animals, and Plants: Report on an American Academy of Microbiology Colloquium held in Washington, DC (2017). https://www.ncbi.nlm.nih.gov/books/NBK549988/

3. Hernandez H and Martinez LR. "Relationship of environmental disturbances and the infectious potential of fungi". *Microbiology* 164.3 (2018): 233-241. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5885008/

4. Kobayashi GS. "Disease Mechanisms of Fungi". In: Baron S, editor. Medical Microbiology. 4th edition. Galveston (TX): University of Texas Medical Branch at Galveston (1996). https://www.ncbi.nlm.nih.gov/books/NBK8103/

5. Wiederhold NP. "Antifungal resistance: current trends and future strategies to combat". *Infection and Drug Resistance* 10 (2017): 249-259. https://pubmed.ncbi.nlm.nih.gov/28919789/

6. Elewski BE. "Onychomycosis: pathogenesis, diagnosis, and management". *Clinical Microbiology Reviews* 11.3 (1998): 415-429. https://pubmed.ncbi.nlm.nih.gov/9665975/

7. Gupta AK., *et al*. "Fungal Skin Infections". *Pediatrics in Review* 38.1 (2017): 8-22. https://pedsinreview.aappublications.org/content/38/1/8

8. Kaushik N., *et al*. "Superficial Fungal Infections". *Primary Care* 42.4 (2015): 501-516. https://accessmedicine.mhmedical.com/content.aspx?bookid=2184&sectionid=165459177

9. Metin A., *et al*. "Recurrent candidal intertrigo: challenges and solutions". *Clinical, Cosmetic and Investigational Dermatology* 11 (2018): 175-185. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5909782/

10. Martinez-Rossi NM., *et al*. "Heat Shock Proteins in Dermatophytes: Current Advances and Perspectives". *Current Genomics* 17.2 (2016): 99-111. https://pubmed.ncbi.nlm.nih.gov/27226766/

11. White TC., *et al*. "Fungi on the skin: dermatophytes and Malassezia". *Cold Spring Harbor Perspectives in Medicine* 4.8 (2014): a019802. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4109575/

12. Informed Health.org [Internet]. Cologne, Germany: Institute for Quality and Efficiency in Health Care (IQWiG); 2006-. Athlete's foot: Overview (2015). https://www.ncbi.nlm.nih.gov/books/NBK65083/

13. Richardson MD and Warnock DW. "Fungal Infection: Diagnosis and Management. Wiley (2011). https://www.wiley.com/en-us/Fungal+Infection%3A+Diagnosis+and+Management%2C+4th+Edition-p-9781405170567

14. Tainwala R and Sharma Y. "Pathogenesis of dermatophytosis". *Indian Journal of Dermatology* 56.3 (2011): 259-261. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3132899/

15. McKeny PT., *et al*. "Antifungal Antibiotics (2020). https://pubmed.ncbi.nlm.nih.gov/11831475/

16. Jain A., *et al*. "Emerging fungal infections among children: A review on its clinical manifestations, diagnosis, and prevention". *Journal of Pharmacy and Bioallied Sciences* 2.4 (2010): 314-320. https://pubmed.ncbi.nlm.nih.gov/21180463/

17. Dahl MV and Grando SA. "Chronic dermatophytosis: what is special about Trichophyton rubrum?" *Advances in Dermatology* 9 (1994): 97-109. https://pubmed.ncbi.nlm.nih.gov/8060745/

18. Dogra S and Uprety S. "The menace of chronic and recurrent dermatophytosis in India: Is the problem deeper than we perceive?" *Indian Dermatology Online Journal* 7.2 (2016): 73-76. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4804598/

19. Institute of Medicine (US) Committee on Emerging Microbial Threats to Health in the 21st Century; Smolinski MS, Hamburg MA, Lederberg J, editors. Microbial Threats to Health: Emergence, Detection, and Response. Washington (DC): National Academies Press (US) (2003).

20. Blake JS., *et al*. "An immunoinhibitory cell wall glycoprotein (mannan) from Trichophyton rubrum". *Journal of Investigative Dermatology* 96.5 (1991): 657-661. https://pubmed.ncbi.nlm.nih.gov/2022872/

21. Calich VLG., *et al*. "Regulatory T cells in paracoccidioidomycosis". *Virulence* 10.1 (2019): 810-821. https://pubmed.ncbi.nlm.nih.gov/30067137/

22. Nicholson LB. "The immune system". *Essays Biochem* 60.3 (2016): 275-301. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5091071/

23. Roussey JA., *et al*. "Immunoregulation in Fungal Diseases". *Microorganisms* 4.4 (2016): 47. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5192530/

24. Lanternier F., *et al*. "Primary immunodeficiencies underlying fungal infections". *Current Opinion in Pediatrics* 25.6 (2013): 736-747. https://pubmed.ncbi.nlm.nih.gov/24240293/

25. Klotz SA., *et al*. "Fungal and parasitic infections of the eye". *Clinical Microbiology Reviews* 13.4 (2000): 662-685. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC88956/

26. Okada S. "CMCD: Chronic Mucocutaneous Candidiasis Disease". *Nihon Rinsho Meneki Gakkai Kaishi* 40.2 (2017): 109-117. https://pubmed.ncbi.nlm.nih.gov/28603201/

27. Brasch J. "Current knowledge of host response in human tinea". *Mycoses* 52.4 (2009): 304-312. https://www.researchgate.net/publication/23998355_Current_knowledge_of_host_response_in_human_tinea

28. Bragulla HH and Homberger DG. "Structure and functions of keratin proteins in simple, stratified, keratinized and cornified epithelia". *Journal of Anatomy* 214.4 (2009): 516-559. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2736122/

29. Guarner J and Brandt ME. "Histopathologic diagnosis of fungal infections in the 21st century". *Clinical Microbiology Reviews* 24.2 (2011): 247-280. https://pubmed.ncbi.nlm.nih.gov/21482725/

30. Guarro J., *et al*. "Developments in fungal taxonomy". *Clinical Microbiology Reviews* 12.3 (1999): 454-500. https://cmr.asm.org/content/12/3/454

31. Kim JY and Dao H. "Physiology, Integument (2020).

32. Tsuboi R., *et al*. "Pathogenesis of superficial mycoses". *Journal of Medical and Veterinary Mycology* 32.1 (1994): 91-104. https://academic.oup.com/mmy/article-abstract/32/Supplement_1/91/944259?redirectedFrom=fulltext

33. Yang L., *et al*. "Comparison between gene expression of conidia and germinating phase in Trichophyton rubrum". *Science China Life Sciences* 50.3 (2007): 377-384. https://pubmed.ncbi.nlm.nih.gov/17609895/

34. Ferreira-Nozawa MS., *et al*. "The pH signaling transcription factor PacC mediates the growth of Trichophyton rubrum on human nail *In vitro*". *Medical Mycology* 44.7 (2006): 641-645. https://pubmed.ncbi.nlm.nih.gov/17071558/

35. Hellgren L and Vincent J. "Lipolytic activity of some dermatophytes". *Journal of Medical Microbiology* 13.1 (1980): 155-157. https://pubmed.ncbi.nlm.nih.gov/7359572/

36. Das SK and Banerjee AB. "Lipolytic enzymes of Trichophyton rubrum". *Sabouraudia* 15.3 (1977): 313-323. https://pubmed.ncbi.nlm.nih.gov/23589/

37. Dahl MV. "Dermatophytosis and the immune response". *Journal of the American Academy of Dermatology* 31.3-2 (1994): S34-S41. https://pubmed.ncbi.nlm.nih.gov/8077506/

38. Soll DR. "Mixed Mycotic Infections". In: Brogden KA, Guthmiller JM, editors. Polymicrobial Diseases". Washington (DC): ASM Press (2002). https://www.ncbi.nlm.nih.gov/books/NBK2485/

39. Kany S., *et al*. "Cytokines in Inflammatory Disease". *International Journal of Molecular Sciences* 20.23 (2019): 6008. https://pubmed.ncbi.nlm.nih.gov/31795299/

40. Grice EA and Segre JA. "The skin microbiome". *Nature Reviews Microbiology* 9.4 (2011): 244-253. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3535073/

41. Wang Q., *et al*. "Host and microbiome multi-omics integration: applications and methodologies". *Biophysical Reviews* 11.1 (2019): 55-65. https://pubmed.ncbi.nlm.nih.gov/30627872/

42. Davidson RM and Epperson LE. "Microbiome Sequencing Methods for Studying Human Diseases". *Methods in Molecular Biology* 1706 (2018): 77-90. https://pubmed.ncbi.nlm.nih.gov/29423794/

43. Grice EA and Segre JA. "The skin microbiome". *Nature Reviews Microbiology* 9.4 (2011): 244-253. https://pubmed.ncbi.nlm.nih.gov/21407241/

44. Wanke I., *et al*. "Skin commensals amplify the innate immune response to pathogens by activation of distinct signaling pathways". *Journal of Investigative Dermatology* 131.2 (2011): 382-390. https://www.researchgate.net/publication/47676539_Skin_Commensals_Amplify_the_Innate_Immune_Response_to_Pathogens_by_Activation_of_Distinct_Signaling_Pathways

45. Dreno B., *et al*. "Microbiome in healthy skin, update for dermatologists". *Journal of the European Academy of Dermatology and Venereology* 30.12 (2016): 2038-2047. https://pubmed.ncbi.nlm.nih.gov/27735094/

46. Grice EA., *et al*. "Topographical and temporal diversity of the human skin microbiome". *Science* 324.5931 (2009): 1190-1192. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2805064/

47. Oh J., *et al*. "Temporal Stability of the Human Skin Microbiome". *Cell* 165.4 (2016): 854-866. https://www.cell.com/fulltext/S0092-8674(16)30399-3

48. Bouslimani A., *et al*. "The impact of skin care products on skin chemistry and microbiome dynamics". *BMC Biology* 17.1 (2019): 47. https://bmcbiol.biomedcentral.com/articles/10.1186/s12915-019-0660-6

49. Rocha LA., *et al*. "Changes in hands microbiota associated with skin damage because of hand hygiene procedures on the health care workers". *American Journal of Infection Control* 37.2 (2009): 155-159. https://www.ajicjournal.org/article/S0196-6553(08)00675-5/abstract

50. Two AM., *et al*. "The Cutaneous Microbiome and Aspects of Skin Antimicrobial Defense System Resist Acute Treatment with Topical Skin Cleansers". *Journal of Investigative Dermatology* 136.10 (2016): 1950-1954. https://pubmed.ncbi.nlm.nih.gov/27377698/

51. Blumberg R and Powrie F. "Microbiota, disease, and back to health: a metastable journey". *Science Translational Medicine* 4.137 (2012): 137rv7. https://stm.sciencemag.org/content/4/137/137rv7.full

52. Stehlikova Z., *et al*. "Dysbiosis of Skin Microbiota in Psoriatic Patients: Co-occurrence of Fungal and Bacterial Communities". *Frontiers in Microbiology* 10 (2019): 438. https://pubmed.ncbi.nlm.nih.gov/30949136/

53. Liu X., *et al*. "Characterization of Skin Microbiome in Tinea Pedis". *Indian Journal of Medical Microbiology* 59.4 (2019): 422-427. https://www.researchgate.net/publication/334375350_Characterization_of_Skin_Microbiome_in_Tinea_Pedis

54. Hay R. "Therapy of Skin, Hair and Nail Fungal Infections". *Journal of Fungi* 4.3 (2018): 99. https://pubmed.ncbi.nlm.nih.gov/30127244/

55. Sanglard D. "Clinical relevance of mechanisms of antifungal drug resistance in yeasts". *Enfermedades Infecciosas y Microbiología Clínica* 20.9 (2002): 462-469. https://pubmed.ncbi.nlm.nih.gov/12425880/

56. Campoy S and Adrio JL. "Antifungals". *Biochemical Pharmacology* 133 (2017): 86-96. https://pubmed.ncbi.nlm.nih.gov/27884742/

57. Ghannoum MA and Rice LB. "Antifungal agents: mode of action, mechanisms of resistance, and correlation of these mechanisms with bacterial resistance". *Clinical Microbiology Reviews* 12.4 (1999): 501-517. https://cmr.asm.org/content/12/4/501

58. Liver Tox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases (2012). https://pubmed.ncbi.nlm.nih.gov/31643176/

59. Kovac M., *et al*. "Miconazole and nystatin used as topical antifungal drugs interact equally strongly with warfarin". *Journal of Clinical Pharmacy and Therapeutics* 37.1 (2012): 45-48. https://www.researchgate.net/publication/49846869_Miconazole_and_nystatin_used_as_topical_antifungal_drugs_interact_equally_strongly_with_warfarin

60. Vartak A., *et al*. "Isolation of a new broad spectrum antifungal polyene from Streptomyces sp. MTCC 5680". *Letters in Applied Microbiology* 58.6 (2014): 591-596. https://pubmed.ncbi.nlm.nih.gov/24517845/

61. Lakhani P., *et al*. "Challenges in the Polyene- and Azole-Based Pharmacotherapy of Ocular Fungal Infections". *Journal of Ocular Pharmacology and Therapeutics* 35.1 (2019): 6-22. https://pubmed.ncbi.nlm.nih.gov/30481082/

62. Dupont B. "Overview of the lipid formulations of amphotericin B". *Journal of Antimicrobial Chemotherapy* 49.1 (2002): 31-36. https://www.researchgate.net/publication/11556620_Overview_of_lipid_formulations_of_amphotericin_B

63. Kim HJ., *et al*. "Nystatin-like Pseudonocardia polyene B1, a novel disaccharide-containing antifungal heptaene antibiotic". *Scientific Reports* 8.1 (2018): 13584. https://www.nature.com/articles/s41598-018-31801-y

64. Sheehan DJ., *et al*. "Current and emerging azole antifungal agents". *Clinical Microbiology Reviews* 12.1 (1999): 40-79. https://pubmed.ncbi.nlm.nih.gov/9880474/

65. Perfect JR. "The antifungal pipeline: a reality check". *Nature Reviews Drug Discovery* 16.9 (2017): 603-616. https://pubmed.ncbi.nlm.nih.gov/28496146/

66. National Center for Biotechnology Information. "PubChem Compound Summary for CID 3823, Ketoconazole" PubChem (2020).

67. Gupta AK., *et al*. "New Antifungal Agents and New Formulations Against Dermatophytes". *Mycopathologia* 182.1-2 (2017): 127-141. https://pubmed.ncbi.nlm.nih.gov/27502503/

68. Lipner SR and Scher RK. "Onychomycosis: Treatment and prevention of recurrence". *Journal of the American Academy of Dermatology* 80.4 (2019): 853-867. https://pubmed.ncbi.nlm.nih.gov/29959962/

69. Ricardo JW and Lipner SR. "Safety of current therapies for onychomycosis". *Expert Opinion on Drug Safety* 19.11 (2020): 1395-1408. https://pubmed.ncbi.nlm.nih.gov/32990062/

70. Jinna S and Finch J. "Spotlight on tavaborole for the treatment of onychomycosis". *Drug Design, Development and Therapy* 9 (2015): 6185-6190. https://pubmed.ncbi.nlm.nih.gov/26640371/

71. Dias MF., *et al*. "Treatment of superficial mycoses: review. Part II". *Brazilian Annals of Dermatology* 88.6 (2013): 937-944. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3900345/

72. Dias MF., *et al*. "Update on therapy for superficial mycoses: review article part I". *Brazilian Annals of Dermatology* 88.5 (2013): 764-774. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3798354/

73. Del Rosso JQ and Bhambri S. "Daily application of fluocinonide 0.1% cream for the treatment of atopic dermatitis". *The Journal of Clinical and Aesthetic Dermatology* 2.9 (2009): 24-32. https://pubmed.ncbi.nlm.nih.gov/20729956/

74. Nizoral (Ketoconazole): drug safety communication- potentially fatal liver injury, risk of drug interactions, and adrenal gland problems". *Clinical Infectious Diseases* 57.8 (2013). https://pubmed.ncbi.nlm.nih.gov/24195113/

75. Greenblatt HK and Greenblatt DJ. "Liver injury associated with ketoconazole: review of the published evidence". *The Journal of Clinical Pharmacology* 54.12 (2014): 1321-1329. https://accp1.onlinelibrary.wiley.com/doi/10.1002/jcph.400

76. Hitchcock CA., *et al*. "Interaction of azole antifungal antibiotics with cytochrome P-450-dependent 14 alpha-sterol demethylase purified from Candida albicans". *Biochemical Journal* 266.2 (1990): 475-480. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1131156/

77. Roemer T and Krysan DJ. "Antifungal drug development: challenges, unmet clinical needs, and new approaches". *Cold Spring Harbor Perspectives in Medicine* 4.5 (2014): a019703. https://pubmed.ncbi.nlm.nih.gov/24789878/

78. Johnson MD., *et al*. "Combination antifungal therapy". *Antimicrob Agents Chemother* 48.3 (2004): 693-715. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC353116/

79. Wiederhold NP. "The antifungal arsenal: alternative drugs and future targets". *International Journal of Antimicrobial Agents* 51.3 (2018): 333-339. https://pubmed.ncbi.nlm.nih.gov/28890395/

80. Khadka S., *et al*. "Clinicomycological Characterization of Superficial Mycoses from a Tertiary Care Hospital in Nepal". *Dermatology Research and Practice* (2016): 9509705. https://pubmed.ncbi.nlm.nih.gov/28003819/

81. Ghannoum M and Isham N. "Fungal nail infections (onychomycosis): a never-ending story?" *PLOS Pathogens* 10.6 (2014): e1004105. https://journals.plos.org/plospathogens/article?id=10.1371/journal.ppat.1004105

82. Misner BD. "A novel aromatic oil compound inhibits microbial overgrowth on feet: a case study". *Journal of the International Society of Sports Nutrition* 4 (2007): 3. https://jissn.biomedcentral.com/articles/10.1186/1550-2783-4-3

83. Halteh P., *et al*. "Over-the-counter and natural remedies for onychomycosis: do they really work?" *Cutis* 98.5 (2016): E16-E25. https://pubmed.ncbi.nlm.nih.gov/28040821/

84. Buck DS., *et al*. "Comparison of two topical preparations for the treatment of onychomycosis: Melaleuca alternifolia (tea tree) oil and clotrimazole". *The Journal of Family Practice* 38.6 (1994): 601-605. https://pubmed.ncbi.nlm.nih.gov/8195735/

85. Carson CF., *et al*. "Melaleuca alternifolia (Tea Tree) oil: a review of antimicrobial and other medicinal properties". *Clinical Microbiology Reviews* 19.1 (2006): 50-62. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1360273/

86. Karimi A., *et al*. "Herbal versus synthetic drugs; beliefs and facts". *Journal of Nephropharmacology* 4.1 (2015): 27-30. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5297475/

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