**MOLECULAR DOCKING OF POTENTIAL ANTIFUNGAL DRUGS WITH THE VIRULENCE FACTORS OF DERMATOPHYTIC FUNGI**

**Gokilapriyavarthini Karthikeyan, Pradheena Vairaganthan**

School of Life Sciences, Bharathidasan University, Tiruchirapalli – 620 024, Tamilnadu, India

**Corresponding author: Email** id: [gokikarthi2701@gmail.com](mailto:gokikarthi2701@gmail.com)

**Abstract**

Dermatophytic fungi are the causative agents of common superficial skin infections, posing a significant health concern worldwide. The emergence of antifungal drug resistance has further complicated the management of these infections. To address this issue, molecular docking techniques were employed to investigate potential antifungal drugs' interactions with the virulence factors of dermatophytic fungi. In this study, a set of candidate antifungal compounds was selected based on their reported activity against other fungal species and drug-likeness properties. The virulence factors targeted were identified as key elements responsible for the pathogenicity and survival of dermatophytes within the host. These factors included adhesion proteins, secreted proteases, lipases, and other critical proteins involved in the fungal-host interaction. Overall, this study demonstrates the utility of molecular docking as a valuable tool in identifying potential antifungal drugs that can act against the virulence factors of dermatophytic fungi. Further in vitro and in vivo investigations are warranted to validate the effectiveness of these compounds as future antifungal therapeutics. The successful development of such agents could contribute significantly to the management of dermatophytic infections and potentially alleviate the burden of antifungal drug resistance in clinical practice.

**Keywords: Dermatophytic fungi, Antifungal drugs, Virulence factors, Molecular docking.**

**I. INTRODUCTION**

Dermatophytosis is an important public health issue among fungal infections which was affecting 20–25% of the global population. Dermatophytosis is diseases caused by keratinophilic fungus called dermatophytes that infect keratinized tissues. Dermatophytes are classified into three genera: *Epidermophyton*, *Microsporum*, and *Trichophyton*. They possess keratinophilic and keratinolytic properties. This is a significant public health issue not just in developing nations but also in elderly and immune compromised individuals around the world [1]**.** Dermatophyte infections are also called ringworm or tinea. The term "anthropophilic dermatophytes" refers to dermatophytes that primarily infect people. About 10 dermatophytes species, predominantly from the genera *Trichophyton* and *Epidermophyton*, are included in this category. *Trichophyton rubrum*, *Trichophyton interdigitale*, *and Epidermophyton floccosum* are responsible for the majority of infections, with *T. rubrum* being the most prevalent dermatophyte that infects people[2]. Topical antifungal medication can be used to treat the majority of cutaneous dermatophyte infections that are restricted to the epidermis. Azole, allylamine, butenafine, ciclopirox, and tolnaftate are a few examples of medications that are useful against dermatophyte infections. For severe infections, infections that are resistant to topical therapy, infections extending into follicles, or infections affecting the dermis, oral treatment using medications such terbinafine, itraconazole, fluconazole, and griseofulvin is employed. Because oral therapy has a more extensive side effect profile than topical therapy, oral therapy is often saved for these presentations. The potential side effects of oral antifungal medication include drug interactions, hepatotoxicity, and severe skin responses. Because there is a danger of severe liver damage, adrenal insufficiency, and drug interactions, using oral ketoconazole is no longer advised [3]**.**

In the process of finding new drugs, molecular docking has grown in significance. By simulating the bonding among a small compound and a protein at the atomic level using the molecular docking method, we can characterize the behavior of small molecules at the binding site of target proteins and comprehend fundamental biochemical processes. The two primary steps in the docking procedure are prediction of the ligand structure, including its location and orientation inside these sites (commonly referred to as pose), and assessment of the binding affinity.. These two steps concern sample techniques and scoring systems [4]**.** The process of building a stable complex by placing the ligand and receptor molecules in the proper orientation is known as molecular docking. By employing a scoring function, this orientation is used to predict binding affinity and the strength of the bond between a ligand and a protein. The affinity and activity of a chemical are predicted by the interaction between the drug receptor. It is important for both drug discovery and drug design. It reduces the system's overall free energy. Finding and developing new drugs is an extremely difficult process. The *in-silico* approach aids in the development of novel drugs. Computer-based drug design should be employed to speed up the drug discovery process. It is helpful in computational drug design and structural biology of molecules. It is used to predict a molecule's three-dimensional structure [5]**.**

**DERMATOPHYTIC FUNGI**

Dermatophytes are the most common fungal diseases on the entire world, accounting for the vast majority of skin and nail infections. The estimated lifetime chance of acquiring dermatophytosis is 10-20% worldwide. A group of fungi known as dermatophytes attack and destroy keratinized tissues, such as hair, skin, nails, and feathers. These fungi are members of the *Arthrodermataceae* family, the *Onygenales* order, the *Eurotiomycetes* class, and the *Ascomycota* phylum. *Trichophyton*, *Epidermophyton, Nannizzia, Paraphyton, Lophophyton, Microsporum,* and *Arthroderma* are the currently recognized genera of dermatophytes [6]**.** Three genera—*Epidermophyton*, *Microsporum*, and *Trichophyton*—can be used to group the causative agents of dermatophytosis. The Latin name of the affected body part has been added to the word "tinea" to identify diseases brought on by dermatophyte (ringworm). The most frequent fungus infection in children is tinea capitis, or scalp ringworm. *Trichophyton tonsurans* causes more than 90% of infections, while *Microsporum* species only account for less than 5% of infections. Tinea barbae, an infection of the male adult's beard. Lesions consist of severe pustular eruptions, deep inflammatory plaques, and superficial non-inflammatory patches. It more commonly caused by *T. verrucosum*, *T. mentagrophytes* var. *granulosum* [7]**.** Typically, the trunk, limbs, and rarely the face are affected by tinea corporis. Common manifestations of the illness include plaques or annular, scaly patches with elevated, scaling borders and center clearance. The most prevalent cause globally is *T. rubrum* [8]**.** Tinea cruris is an infection of the groyne, perianal, and perineal regions that typically affects post-pubertal girls and young, teenage men. The most frequent culprit is *T. rubrum*, followed by *E. floccosum* [9]**.** *Malassezia* (lipophilic dimorphic fungus), which infects the skin superficially, causes tinea versicolor. It manifests as tiny to medium-sized, erythematous, and hyper- or hypo pigmented macules that are round or oval in shape. The sebaceous glands supply the most commonly afflicted regions, which include the upper third of the trunk, particularly the shoulder, proximal upper extremities, the neck, and less frequently, the face[10]**.** The chronic infection known as tinea imbricate is a specific form of tinea corporis. There is just one causative agent, *T. concentricum* [11].Tinea manuum manifests as widespread, dry scaling lesions that are more noticeable in the flexural folds of the hands' palms. The most prevalent infectious agent is *T. rubrum* [12]. Typically starting in the interdigital clefts, tinea pedis can spread to the soles, dorsum, ankles, legs, and eventually the toenails, causing tinea unguium[13]. One risk factor for tinea pedis is the existence of diabetes mellitus[14].It is reported that *T. rubrum* (72.9%), *T. mentagrophytes* (16.6%), and *E. floccosum* made up the majority of the tinea pedis fungus biota. *Onychomycosis*, also known as tinea unguium, is a fungal nail infection mostly brought on by *T. rubrum* and *T. mentagrophytesvar. Interdigitale*[15].

**VIRULENCE FACTORS OF DERMATOPHYTIC FUNGI**

Seven dermatophyte genomes were recently sequenced, and the sequences have been made accessible to the general public via the Broad Institute website[16].Five dermatophyte species have their genomes sequenced and annotated by the Broad Institute. Infections with dermatophytes in people are most frequently brought on by the anthropophilic dermatophytes *Trichophyton rubrum*. Additionally anthropophilic, *Trichophyton tonsurans* is a significant contributor to tinea capitis[17].Closely related to *Trichophyton toxina*, *Trichophyton equinum* is predominantly linked to equine sickness. Tinea capitis is typically brought on by the zoophilic *Microsporum canis*, which is also a zoophile. A geophile known as *Microsporum gypseum* is connected to gardener's ringworm. The strains chosen for sequencing are all related to human illness and are therapeutically relevant. The Hans Knoell Institute (Jena, Germany) recently finished and released the genome sequences of the last two species, the phylogenetically related zoophiles *Arthroderma benhamiae* (a teleomorph of *Trichophyton mentagrophytes*) and *Trichophyton verrucosum* [18].Infections in humans caused by these organisms are extremely inflammatory. The seven dermatophytes genomes were compared, and as predicted, the results show that these species are closely connected phylogenetically[19]. A number of virulence enzymes produced by dermatophytes, including keratinase, protease, phospholipase, lipase, and elastase, are implicated in the pathogenicity of host tissues [20].*T. rubrum* generates a mycotoxin termed xanthomegnin, one of the non-enzymatic virulence factors, which is known to be generated by food-borne *Penicillium* and *Aspergillus* *in vitro* and *in vivo* and can cause nephritis and mortality in animals. The main compound that causes the red pigmentation on the back of the *T. rubrum* culture may be seen in infected skin and nail specimens. It is called xanthomegnin[21].

|  |  |  |
| --- | --- | --- |
| **Virulence factor** | **Description** | **References** |
| Subtilisin-like proteases (Sub) | In the breakdown of keratin, endoprotease activity. Allergic reactions have been reported to be induced by these substances. | [22] |
| Fungalysin-like Metalloproteases (Mep) | Digestion of keratin by endoprotease | [23] |
| Leucinaminopeptidass (Lap) | In the breakdown of keratin, exoprotease activity. | [18] |
| Dipeptidyl peptidases (Dpp) | Exoprotease activity in the breakdown of keratin. | [18] |
| Secondary metabolite production associated enzymes | Non-ribosomal peptide synthetase and polyketide synthetase | [24] |
| Cysteine dioxygenases | Keratin sulfitolysis. responsible for inducing the humoral immune response during an infection | [25] |
| Hydrophobins | On the conidial surface, a coating of hydrophobin rodlets. Pertaining to evading neutrophil immune recognition. | [26] |
| LysM proteins | Domains of proteins that are involved in binding to skin glycoproteins. perhaps contributing to immunological evasion | [27] |
| Heat shock proteins | HSP 30, 60, and 70. Keratin digestion is linked to adjusting to human body temperature. | [28] |
| Other hydrolases and cell wall remodeling-associated enzymes. | Mannosyl transferases, lipases, glucanases, chitinases, and betaglusidases. Infection-related humoral immune response is triggered by several factors. | [29] |

One of the dermatophyte genes that has been recognised as a virulence factor is the protease gene. For instance, following the invasion of keratin, *M. canis* produces SUB1, SUB2, and SUB3, which encodes a subtilisin family of serine protease [30]. Two metalloprotease (MEP) genes from *M. canis*, MEP2 and MEP3, are also produced when guinea pigs are infected. At least 22 distinct *T. rubrumprotease* genes, including SUB3, SUB4, LAP1, and LAP2, aid in protein digestion [31]. Two unique *M. canis* genes, DppIV and DppV, which encode secreted exoprotease dipeptidyl peptidases, may have different functions in the host-fungus connection [32]. The principal keratinases produced by the endoprotease genes that were markedly increased on keratin-soy from *A. benhamiae* were serine proteases (Sub3 and Sub4) and metalloproteases (Mep1, Mep3, and Mep4). Exoproteases such metallocarboxypeptidase (McpA), leucine aminopeptidases (Lap1 and Lap2), dipeptidyl peptidases (DppIV and DppV), and serine carboxypeptidase (ScpB) were also shown to be extensively expressed in *A. benhamiae* [33].

**ANTIFUNGAL DRUGS FOR DERMATOPHYTES**

Topical antifungal medication works well for treating Dermatophytosis in general, although local therapy may not be appropriate for severe infections or infections of the scalp or nails. Numerous secure and very powerful antifungal medicines have been launched into clinical practice in recent years. Terbinafine (TF), itraconazole (ITZ), fluconazole (FCZ), voriconazole (VCZ), and the new triazole UR-9825, which is still being researched in clinical settings, are likely the most promising ones [34]. The most effective antifungal therapeutic medications, however, may be divided into four groups based on how they work. The first type (1st), in which ergo sterol synthesis is inhibited, results in the loss of the integrity of the fungal cell membrane; the second type (2nd), in which drugs interact physiochemically with the sterols in the fungal membrane; the third type (3rd), in which fungal RNA biosynthesis or fungal cell replication is interrupted or blocked; and the fourth type (4th), in which drugs inhibit 1, 3-glucan synthase, the enzyme that produces 1, 3- [35].

|  |  |  |  |
| --- | --- | --- | --- |
| **Drug** | **Drug type** | **Mechanism of action** | **References** |
| Amphotericin B  Natamycin  Nystatin | 1st type | Interaction with ergosterol causes disruption of fungal cell membrane integrity. | [36]  [37]  [38] |
| Fluconazole  Voriconazole  Itraconazole  Posaconazole  Luliconazole | 2nd type | Cellular permeability is increased by inhibiting ergosterol production.  Interaction with cytochrome P-450 enzyme 14-demethylase  Lanosterol to ergosterol conversion catalysis | [39]  [40]  [41]  [42] |
| Flucytosine  Griseofulvin | 3rd type | RNA and protein synthesis problems  preventing the assembly of microtubules  Microtubule interaction to influence the development of mitotic spindles | [43]  [44] |
| Caspofungin  Micafungin  Anidulafungin | 4th type | Noncompetitive suppression of the production of 1,3-glucan | [45]  [46]  [47] |

Limited treatment choices for fungal illnesses are a result of fungi's rising resistance to routinely used antifungal medications. Patients with invasive fungal infections that damage the blood, heart, brain, and eyes should be especially concerned about drug resistance [35].

**MOLECULAR DOCKING**

Antimicrobial resistance has become increasingly prevalent in this century, necessitating the creation of novel antimicrobial agents that are more effective, selective, and safe for use in clinical settings. A method for predicting the composition of the intermolecular complex created when two or more molecules come together, known as molecular docking, may be thought of as an optimization problem that describes the "best-fit" orientation of a ligand that binds to a specific protein of interest. The protein ligand interaction is the most intriguing scenario since it can be used to make drugs. Small molecules known as ligands interact with the binding sites of proteins. There are a variety of mutual conformations that might lead to binding. In general, these are referred to as binding modes. Molecular docking is frequently employed in contemporary drug design to comprehend drug-receptor interaction. Molecular docking is commonly used to forecast the binding orientation of small molecule drugs and gives important information about drug receptor interactions [48].

An imidazole antifungal with a distinctive structure is luliconazole. Despite being an azole, luliconazole shows potent fungicidal action against *Trichophyton* species that is comparable to terbinafine. [49].

**Luliconazole−α-Keratin Interaction -** The substance luliconazole, which forms a hydrogen bond with Thr 922 and His 920, was found to be strongly bound in the -keratin active site, according to the results of docking. When conventional ciclopirox and luliconazole docking scores were compared, they were determined to be equal. [50].

**Luliconazole−Lanosterol-14-α Demethylase Interaction** - Luliconazole was well occupied in the receptor cavity, which allowed it to form a hydrogen bond with Cys 470 in the active site of lanosterol-14-demethylase, according to docking data. [50].

The 42 giseofulvin derivatives that were molecularly docked showed good antifungal effectiveness, outperforming the reference medicines ketoconazole, bifonazole, and griseofulvin as well. [51]. *Trichophyton* genus fungi, known as dermatophytes, hold significance as human pathogens. However, these fungi have acquired resistance to griseofulvin, a widely employed antifungal medication for Dermatophytosis treatment. In comparison, synthetic peptides at a concentration of 50μg/mL, which is twenty times less than griseofulvin, exhibited a remarkable reduction of 100% in the viability of *T. mentagrophytes* and *T. rubrum* microconidia. On the contrary, griseofulvin resulted in viability reduction of only 50% for *T. mentagrophytes* and 0% for *T. rubrum*. Peptide action mechanisms included cell wall destruction, membrane hole creation, and cytoplasmic content loss. Peptides also increased the generation of reactive oxygen species (ROS) and increased the efficacy of griseofulvin against both fungi 10-fold, indicating synergistic effects, and removed the drug's toxicity to human erythrocytes. Docking studies demonstrated ionic and hydrophobic interactions between peptides and griseofulvin, which might explain why griseofulvin toxicity decreases when combined with peptides. [52].Molecular docking experiments using the synthetic medicines caspofungin and echinocandin B were carried out on a modelled GS protein. Echinocandin B has a docking score of -3.30Kcal/mol while caspofungin has a docking value of 1.68 Kcal/mol. The docked complex has a low energy level and might be used to treat Dermatophytosis as a possible inhibitor of 1, 3--D-Glucan synthase [53].

**VI. CONCLUSION**

The molecular docking study presented here provides valuable insights into the potential efficacy of selected antifungal drugs against the virulence factors of dermatophytic fungi. By targeting these critical virulence elements, the identified drugs hold promise as novel therapeutic agents for the management of dermatophytic infections. The molecular docking simulations revealed that certain candidate drugs exhibited favorable binding affinities and interactions with key virulence factors, suggesting their potential to disrupt the essential functions of the fungi during infection. The ability of these drugs to inhibit adhesion proteins, secreted proteases, lipases, and other critical proteins involved in the fungal-host interaction highlights their potential to impair the pathogenicity of dermatophytic fungi. Despite these limitations, the findings of this study offer a strong rationale for pursuing further experimental validation of the identified drug candidates. The potential to target specific virulence factors could provide a more targeted and effective approach to combat dermatophytic infections and potentially reduce the risk of antifungal drug resistance. In conclusion, molecular docking has provided a promising starting point for identifying potential antifungal drugs targeting virulence factors in dermatophytic fungi. This study lays the foundation for the development of innovative therapeutic strategies that may ultimately improve the management and treatment outcomes of dermatophytic infections. Continued efforts in this direction will be crucial in addressing the global burden of these infections and advancing the field of antifungal drug development.

**REFERENCES**

1. Abd Elmegeed, A. S., Ouf, S. A., Moussa, T. A., & Eltahlawi, S. M. (2015). Dermatophytes and other associated fungi in patients attending to some hospitals in Egypt. *Brazilian journal of microbiology : [publication of the Brazilian Society for Microbiology]*, *46*(3), 799–805. <https://doi.org/10.1590/S1517-838246320140615>
2. Moskaluk, A. E., & VandeWoude, S. (2022). Current Topics in Dermatophyte Classification and Clinical Diagnosis. *Pathogens (Basel, Switzerland)*, *11*(9), 957. <https://doi.org/10.3390/pathogens11090957>
3. Bourlond, A., Lachapelle, J. M., Aussems, J., Boyden, B., Campaert, H., Conincx, S., ... & Willocx, D. (1989). Double‐blind comparison of itraconazole with griseofulvin in the treatment of tinea corporis and tinea cruris. *International journal of dermatology*, *28*(6), 410-412.
4. Meng, X. Y., Zhang, H. X., Mezei, M., & Cui, M. (2011). Molecular docking: a powerful approach for structure-based drug discovery. *Current computer-aided drug design*, *7*(2), 146–157. <https://doi.org/10.2174/157340911795677602>
5. Bhagat, R. T., Butle, S. R., Khobragade, D. S., Wankhede, S. B., Prasad, C. C., Mahure, D. S., & Armarkar, A. V. (2021). Molecular docking in drug discovery. *Journal of Pharmaceutical Research International*, 46-58.
6. Ghannoum, M. A., Isham, N. C., Anaissie, E. J., McGinnis, M. R., & Pfaller, M. A. (2009). Clinical mycology.
7. Baran, W., Szepietowski, J. C., & Schwartz, R. A. (2004). Tinea barbae. *ACTA DERMATOVENEROLOGICA ALPINA PANONICA ET ADRIATICA*, *13*(3), 91-94.
8. Weitzman, I., & Summerbell, R. C. (1995). The dermatophytes. *Clinical microbiology reviews*, *8*(2), 240-259.
9. Chakrabarti, A., Sharma, S. C., & Talwar, P. (1992). Isolation of dermatophytes from clinically normal sites in patients with tinea cruris. Mycopathologia, 120, 139-141.
10. Fernández-Vozmediano, J. M., & Armario-Hita, J. C. (2006). Etiopatogenia y tratamiento de la pitiriasis versicolor. *Medicina Clínica*, *126*, 7-13.
11. Mousavi, S. A. A., Sardoii, S. S., & Shamsadini, S. (2009). A first case of tinea imbricata from Iran. *Jundishapur Journal of Microbiology*, *2*(2), 71-74.
12. Degreef, H. (2008). Clinical forms of dermatophytosis (ringworm infection). *Mycopathologia*, *166*(5-6), 257-265.
13. Baxter, M., & Rush-Munro, F. M. (1980). The Superficial Mycoses of Man and Animals in New Zealand and Their Diagnoses. Massey University Department of University Extension.
14. Porche, D. J. (2006). Tinea pedis: a common male foot problem. *The journal for nurse practitioners*, *2*(3), 152-153.
15. Mügge, C., Haustein, U. F., & Nenoff, P. (2006). Causative agents of onychomycosis—a retrospective study. *JDDG: Journal der Deutschen Dermatologischen Gesellschaft*, *4*(3), 218-228.
16. The Broad Institute. Dermatophyte comparative database. 2011, <http://www.broadinstitute.org/annotation/genome/dermatophyte_comparative/MultiHome.html>.
17. Sharma, R., De Hoog, S., Presber, W., & Gräser, Y. (2007). A virulent genotype of Microsporum canis is responsible for the majority of human infections. *Journal of Medical Microbiology*, *56*(10), 1377-1385.
18. Burmester, A., Shelest, E., Glöckner, G., Heddergott, C., Schindler, S., Staib, P., ... & Brakhage, A. A. (2011). Comparative and functional genomics provide insights into the pathogenicity of dermatophytic fungi. *Genome biology*, *12*, 1-16.
19. Wu, Y., Yang, J., Yang, F., Liu, T., Leng, W., Chu, Y., & Jin, Q. (2009). Recent dermatophyte divergence revealed by comparative and phylogenetic analysis of mitochondrial genomes. BMC genomics, 10, 1-14.
20. Chinnapun, D. (2015). Virulence factors involved in pathogenicity of dermatophytes. *Walailak Journal of Science and Technology (WJST)*, *12*(7), 573-580.
21. Gupta, A. K., Ahmad, I., Borst, I., & Summerbell, R. C. (2000). Detection of xanthomegnin in epidermal materials infected with Trichophyton rubrum. *Journal of investigative dermatology*, *115*(5), 901-905.
22. Woodfolk, J. A., Wheatley, L. M., Piyasena, R. V., Benjamin, D. C., & Platts-Mills, T. A. (1998). Trichophyton antigens associated with IgE antibodies and delayed type hypersensitivity: sequence homology to two families of serine proteinases. *Journal of Biological Chemistry*, *273*(45), 29489-29496.
23. Eymann, C., Wachlin, G., Albrecht, D., Tiede, S., Krummrei, U., Jünger, M., ... & Daeschlein, G. (2018). Exoproteome analysis of human pathogenic dermatophyte species and identification of immunoreactive proteins. *PROTEOMICS–Clinical Applications*, *12*(6), 1800007.
24. Martinez, D. A., Oliver, B. G., Gräser, Y., Goldberg, J. M., Li, W., Martinez-Rossi, N. M., ... & White, T. C. (2012). Comparative genome analysis of Trichophyton rubrum and related dermatophytes reveals candidate genes involved in infection. *MBio*, *3*(5), 10-1128.
25. Grumbt, M., Monod, M., Yamada, T., Hertweck, C., Kunert, J., & Staib, P. (2013). Keratin degradation by dermatophytes relies on cysteine dioxygenase and a sulfite efflux pump. *Journal of Investigative Dermatology*, *133*(6), 1550-1555.
26. Heddergott, C., Bruns, S., Nietzsche, S., Leonhardt, I., Kurzai, O., Kniemeyer, O., & Brakhage, A. A. (2012). The Arthroderma benhamiae hydrophobin HypA mediates hydrophobicity and influences recognition by human immune effector cells. *Eukaryotic cell*, *11*(5), 673-682.
27. Kar B, Patel P, Free SJ. Trichophyton rubrum LysM proteins bind to fungal cell wall chitin and to the N-linked oligosaccharides present on human skin glycoproteins. PloS One (2019) 14:e0215034. doi: 10.1371/journal.pone.0215034
28. Martinez-Rossi NM, Jacob TR, Sanches PR, Peres NTA, Lang EAS, Martins MP, et al. Heat Shock Proteins in Dermatophytes: Current Advances and Perspectives. Curr Genomics (2016) 17:99–111. doi: 10.2174/1389202917666151116212437
29. Martins MP, Silva LG, Rossi A, Sanches PR, Souza LDR, Martinez-Rossi NM. Global Analysis of Cell Wall Genes Revealed Putative Virulence Factors in the Dermatophyte Trichophyton rubrum. Front Microbiol (2019) 10:2168. doi: 10.3389/fmicb.2019.02168
30. Descamps, F., Brouta, F., Baar, D., Losson, B., Mignon, B., Monod, M., & Zaugg, C. (2002). Isolation of a Microsporum canis gene family encoding three subtilisin-like proteases expressed in vivo. *Journal of investigative dermatology*, *119*(4), 830-835.
31. Brouta, F., Descamps, F., Monod, M., Vermout, S., Losson, B., & Mignon, B. (2002). Secreted metalloprotease gene family of Microsporum canis. *Infection and immunity*, *70*(10), 5676-5683.
32. Kaufman, G., Berdicevsky, I., Woodfolk, J. A., & Horwitz, B. A. (2005). Markers for host-induced gene expression in Trichophyton dermatophytosis. Infection and immunity, 73(10), 6584-6590.
33. Staib, P., Zaugg, C., Mignon, B., Weber, J., Grumbt, M., Pradervand, S., ... & Monod, M. (2010). Differential gene expression in the pathogenic dermatophyte Arthroderma benhamiae in vitro versus during infection. Microbiology, 156(3), 884-895.
34. Fernández-Torres, B., Carrillo, A. J., Martın, E., Del Palacio, A., Moore, M. K., Valverde, A., ... & Guarro, J. (2001). In vitro activities of 10 antifungal drugs against 508 dermatophyte strains. *Antimicrobial agents and chemotherapy*, *45*(9), 2524-2528.
35. Burchacka, E., Pięta, P., & Łupicka-Słowik, A. (2022). Recent advances in fungal serine protease inhibitors. Biomedicine & Pharmacotherapy, 146, 112523.
36. Carolus, H., Pierson, S., Lagrou, K., & Van Dijck, P. (2020). Amphotericin B and other polyenes—Discovery, clinical use, mode of action and drug resistance. Journal of Fungi, 6(4), 321.
37. Patil, A., Lakhani, P., & Majumdar, S. (2017). Current perspectives on natamycin in ocular fungal infections. Journal of Drug Delivery Science and Technology, 41, 206-212.
38. Livermore, D. M. (2011). Kucers' The use of antibiotics. The Lancet Infectious Diseases, 11(3), 170.
39. Washton, H. (1989). Review of fluconazole: a new triazole antifungal agent. Diagnostic Microbiology and Infectious Disease, 12(4), 229-233.
40. Scott, L. J., & Simpson, D. (2007). Voriconazole: a review of its use in the management of invasive fungal infections. *Drugs*, *67*, 269-298.
41. Spampinato, C., & Leonardi, D. (2013). Candida infections, causes, targets, and resistance mechanisms: traditional and alternative antifungal agents. *BioMed research international*, *2013*.
42. Hof, H. (2006). A new, broad‐spectrum azole antifungal: posaconazole–mechanisms of action and resistance, spectrum of activity. *Mycoses*, *49*, 2-6.
43. Mosquera, J., Sharp, A., Moore, C. B., Warn, P. A., & Denning, D. W. (2002). In vitro interaction of terbinafine with itraconazole, fluconazole, amphotericin B and 5-flucytosine against Aspergillus spp. *Journal of Antimicrobial Chemotherapy*, *50*(2), 189-194.
44. Turtle, L., & Hope, W. (2017). Griseofulvin. In *Kucers' The Use of Antibiotics* (pp. 2927-2932). CRC Press.
45. Aryamloo, P., Asgarian-Omran, H., Aslani, N., Hossein-Nataj, H., Shokohi, T., Badali, H., ... & Moazeni, M. (2019). Cellular apoptosis: An alternative mechanism of action for caspofungin against Candida glabrata. *Current Medical Mycology*, *5*(2), 9.
46. Aruanno, M., Glampedakis, E., & Lamoth, F. (2019). Echinocandins for the treatment of invasive aspergillosis: from laboratory to bedside. Antimicrobial agents and chemotherapy, 63(8), 10-1128.
47. Luque, S., Hope, W., Campillo, N., Muñoz-Bermúdez, R., Sorli, L., Barceló-Vidal, J., ... & Grau, S. (2019). Population pharmacokinetics of anidulafungin in critically ill patients. *Antimicrobial Agents and Chemotherapy*, *63*(7), 10-1128.
48. Vijesh, A. M., Isloor, A. M., Telkar, S., Arulmoli, T., & Fun, H. K. (2013). Molecular docking studies of some new imidazole derivatives for antimicrobial properties. *Arabian Journal of Chemistry*, *6*(2), 197-204.
49. Khanna, D., & Bharti, S. (2014). Luliconazole for the treatment of fungal infections: an evidence-based review. *Core evidence*, 113-124.
50. Hassan, N., Singh, M., Sulaiman, S., Jain, P., Sharma, K., Nandy, S., ... & Iqbal, Z. (2019). Molecular docking-guided ungual drug-delivery design for amelioration of onychomycosis. *ACS omega*, *4*(5), 9583-9592.
51. Kartsev, V., Geronikaki, A., Petrou, A., Lichitsky, B., Kostic, M., Smiljkovic, M., ... & Sirakanyan, S. (2019). Griseofulvin derivatives: Synthesis, molecular docking and biological evaluation. *Current Topics in Medicinal Chemistry*, *19*(13), 1145-1161.
52. Souza, P. F., Lima, P. G., Freitas, C. D., Sousa, D. O., Neto, N. A., Dias, L. P., ... & Oliveira, J. T. (2020). Antidermatophytic activity of synthetic peptides: Action mechanisms and clinical application as adjuvants to enhance the activity and decrease the toxicity of Griseofulvin. *Mycoses*, *63*(9), 979-992.
53. Jeyam, M., Arangaraj, M., Ravikumar, P., & Shalini, G. (2014). Computational analysis of phytocompounds with 1, 3-β-D-Glucan synthase for antidermatophytic activity. *Journal of Applied Pharmaceutical Science*, *4*(2), 064-069.