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

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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. The three genera of dermatophytes are *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. We can characterize the behavior of small molecules at the binding site of target proteins and understand basic biochemical processes by using the molecular docking approach to mimic the interaction between a small molecule and a protein at the atomic level. Prediction of the ligand structure as well as its placement and orientation within these sites (often referred to as pose) and evaluation of the binding affinity are the two fundamental processes in the docking process. 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 have been recognized as a virulence factor is the protease gene. For instance, *M. canis* produces SUB1, SUB2, and SUB3 during the invasion of keratin, which encodes a subtilisin family of serine protease [30]. In addition, during the infection of guinea pigs, two metalloprotease (MEP) genes, MEP2 and MEP3, of *M. canis* are also generated. Protein digestion is facilitated by at least 22 different *T. rubrumprotease* genes, including SUB3, SUB4, LAP1, and LAP2 [31]. DppIV and DppV, two isolated *M. canis* genes that code for secreted dipeptidyl peptidases of exoproteases, may play specific roles in the host-fungus connection [32]. Serine proteases (Sub3 and Sub4) and metalloproteases (Mep1, Mep3, and Mep4) were the primary keratinases encoded by the endoprotease genes that were strongly elevated on keratin-soy from *A. benhamiae*. Exoproteases such leucine aminopeptidases (Lap1 and Lap2), dipeptidyl peptidases (DppIV and DppV), metallocarboxypeptidase (McpA), and serine carboxypeptidase (ScpB) were also found to be expressed significantly 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. The most promising ones are probably terbinafine (TF), itraconazole (ITZ), fluconazole (FCZ), and more recently voriconazole (VCZ) and the novel triazole UR-9825, which is still being studied in clinical settings [34]. The most effective antifungal therapeutic medications, however, may be divided into four groups based on how they work. The integrity of the fungal cell membrane is lost in the first type (1st) when ergo sterol synthesis is inhibited; in the second type (2nd), drugs interact physiochemically with the sterols in the fungal membrane; in the third type (3rd), fungal RNA biosynthesis or fungal cell replication is interrupted or blocked; and in the fourth type (4th), drugs inhibit 1, 3-glucan synthase, the enzyme that produces 1, 3-glucans [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 structure of the intermolecular complex formed between two or more molecules, 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].

Luliconazole is an imidazole antifungal agent with a unique structure. Luliconazole, although belonging to the azole group, has strong fungicidal activity against *Trichophyton spp*., similar to that of terbinafine [49].

Luliconazole−α-Keratin Interaction - Docking results reveal that the compound luliconazole bound tightly in the active site of α-keratin, as it was well occupied in the receptor cavity and

makes hydrogen bond with Thr 922 and His 920. The docking scores of standard ciclopirox and luliconazole were compared and found to be same [50].

Luliconazole−Lanosterol-14-α Demethylase Interaction - Docking results reveal that the compound luliconazole bound tightly in the active site of lanosterol-14-α demethylase as it was well occupied in the receptor cavity thereby forming hydrogen bond with Cys 470 [50].

Molecular docking of the Forty-two giseofulvin derivatives revealed good antifungal activity, better than reference drugs ketoconazole, bifonazole, and griseofulvin as well [51]. Dermatophytes belonging to the *Trichophyton* genus are important human pathogens, but they have developed resistance to griseofulvin, the most common antifungal drug used to treat Dermatophytosis synthetic peptides at 50 μg/mL, a concentration 20-fold lower than griseofulvin, reduced the microconidia viability of *T. mentagrophytes* and *T. rubrum* by 100%, whereas griseofulvin decreased their viability by only 50% and 0%, respectively. The action mechanism of peptides involved cell wall damage, membrane pore formation and loss of cytoplasmic content. Peptides also induced overproduction of reactive oxygen species (ROS) and enhanced the activity of griseofulvin 10-fold against both fungi, suggesting synergistic effects, and eliminated the toxicity of this drug to human erythrocytes. Docking analysis revealed ionic and hydrophobic interactions between peptides and griseofulvin, which may explain the decline of griseofulvin toxicity when mixed with peptides [52]. Molecular docking studies were performed for modeled GS protein with the synthetic drugs caspofungin and echinocandin B. The docking score of echinocandin B is -3.30Kcal/mol and caspofungin, is 1.68 Kcal/mol. The docked complex had low energy level and can be considered as potential inhibitor for 1, 3-β-D-Glucan synthase to treat Dermatophytosis [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.

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