International Journal of Current Science Research and Review
ISSN: 2581-8341
Volume 06 Issue 06 June 2023
DOI: 10.47191/ijcsrr/V6-i6-09, Impact Factor: 6.789
IJCSRR @ 2023

www.ijcsrr.org

Super Glue Production by Dermatophytes: Review

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ABSTRACT: Dermatophytosis can be caused on by the invasion and infection of keratinized tissues in people and animals via a group of filamentous fungus known as dermatophytes. About a quarter of the world's population is affected by it which is one of the most prevalent superficial fungal diseases. Some of these fungi have the capacity to develop complex 3-D biofilm structures, or "biofilm," which are distinguished by the creation of extracellular polymeric molecules and a heightened drug resistance. The assessment of biofilm now relies on a variety of different methods, which frequently results in various evaluations of the microbial strains' capacity to create biofilms.

It has only recently been discovered the architecture and growth features of dermatophytic biofilms (Trichophyton spp., Microsporum spp.). Additionally, the structural complexity and lack of research on filamentous fungal biofilms make therapy challenging. Therefore, there is a demand for newer antifungals or methods for treating resistant dermatophytosis to offer an efficient, original, and safe substitute to current treatments. Therefore, this review highlighted on the significance, characterization and evaluation of biofilm that produced from dermatophytes.

KEY WORDS: Antifungal therapy, Biofilm**,** Dermatophytes, virulence factors.

INTRODUCTION

Trichophyton spp., *Microsporum* spp., and *Epidermophyton* spp. are three genera of Dermatophytes which are filamentous keratinophilic and keratinolytic fungi that are highly related to one another and have evolved to colonize and invade the keratinized tissues of both animals and people [1]. Dermatophytes can be categorized ecologically as geophilic, zoophilic, or anthropophilic depending on where they get their keratin from. Additionally, the majority of human infections are caused by anthropophilic species, and dermatophytes are the most prevalent aetiological agents of superficial mycoses [2].

According to estimates, dermatophytes afflict 25% of the world's population, with 30–70% of people acting as carriers who do not show any clinical symptoms [3].

In response to environmental changes, fungi may develop a variety of adaption mechanisms. A promising antifungal target is the fungal cell wall, which allows fungi to interact dynamically with their surroundings. Additionally, the pathogen's structural integrity, which is actively modified in response to stress conditions, is necessary for adhesion, signaling, and colonization [4].

Numerous instances of antifungal resistance have also been recorded, in addition to time-consuming and expensive therapies [5]. Skin peeling, a drop in humidity, a rise in skin pH, an increase in body temperature, and fatty acids are among the host's main defense mechanisms. Fungi, on the other hand, create adaptable responses to get around these difficulties [6]. In order to tolerate or resist the effects of antifungals, fungi set off a number of mechanisms including overexpression of drug efflux pumps, detoxification of enzymes, and modification of drug targets [7].

According to Brilhantea et al. (2019)[8], the development of a fungal biofilm makes treatment more challenging because it produces an extracellular polymeric matrix, which functions as a physical barrier to inhibit the entry of antifungal drugs and promotes the growth of cells that are resistant to antimicrobials. Additionally, biofilm development enhances the production of efflux pumps and the secretion of proteins that result in filamentation while decreasing the contact between fungi and the human immune system (Wang et al. 2021)[9].

The existence of biofilm is thought to be a significant contributing element to the chronic dermatophytic infection's resistance to traditional antifungal regimens.[10] In addition, giving critically ill patients excessive doses of antifungals frequently results in other complications. The rise of biofilm-based infections signals the need for biofilm-specific medications as well as fresh approaches to finding more effective therapeutic targets [11].

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Significance of Biofilms in Dermatophytes

It has been demonstrated over the past few decades that many fungus have the capacity to produce biofilms, much like how bacteria do. Microbial colonies that are attached to biotic or abiotic surfaces and embedded in an exopolymeric matrix produce biofilms. By offering protection against environmental stresses, the host immune system, and antimicrobial substances, this structure improves the conditions for fungal survival both in the environment and within the host, facilitating host colonization and infection. Based on these features, the capacity of fungi to build biofilms is seen as a crucial component of their pathogenicity [2], and although the majority of research on fungal biofilms has focused on yeasts, it is known that filamentous and dimorphic fungus may also produce similar structures [12,13]

Burkhart *et al.*[14] initially described the potential of dermatophytes to form biofilm in vivo in dermatophytoma in conjunction with tinea unguium. Due to their strong adhesion to the nail plate and capacity to build biofilms, living fungi like hyphae and arthroconidia present in dermatophytoma instances make them resistant to conventional treatments and more challenging to surgically remove. Few research have examined the treatment failures of dermatophytosis, continuing the original report [15,16] The principal virulence mechanism in human nail infections caused by dermatophytes, which promotes chronicity and clinical relapses of infection, is thought to be biofilm development [17].

Characterizations of Biofilm

A colony of microorganisms creates tight structures called biofilms in which they are immersed in an extracellular matrix made of polymeric materials such proteins, extracellular nucleic acids, membrane vesicles, and polysaccharides.[18] Fungal cells called conidia initially attach to biotic and abiotic surfaces in order to form a biofilm. After being produced, the hyphal fragments, individual conidia, and mycelia enclose themselves in an extracellular matrix that strengthens the resulting biofilm [19]. The benefits of establishing a biofilm for an organism include environmental protection, resistance to physical and chemical stress, metabolic cooperation, and community-based gene expression regulation. Contributory factors include nutrients, quorum-sensing molecules, and surface contact [20] These defenses safeguard microbial pathogens from the immune system of the host and outside influences. Additionally, the development of biofilms led to the potential development of antimicrobial agent resistance, which raises significant issues for the treatment of microbial infections that require up to 100 times the amount of antimicrobials than planktonic cells do[21-23].

Steps of Biofilm formation:

According to Gonzalez-Ramrez et al. (2016)[24], there are four stages in the creation of a biofilm.

1) The first stage of biofilm formation, adhesion, occurs within the first four hours after cell aggregation and ECM production. During this stage, contact between the conidia and the surface as well as between conidia was formed. ECM structures were also visible, and conidial early co-aggregation was present. ECM tightens its bond with the cell in order to accelerate the growth of a fungal colony. The first surface attachment is influenced by a range of environmental parameters, including as the flow of the surrounding media (urine, blood, saliva, and mucus), pH, temperature, osmolarity, bacteria, the presence of antimicrobial agents, and host immunological components.[25].

2) Reproduction Conidia into hyphae with the development of the biofilm was a phase that needed 8–12 hours. Conidia developed in a variety of branching hyphae before anastomosis started. The effective cell accumulation created cellular organization (micro-colonies). Biofilm development requires 16 to 20 hours, during which time the hyphae grew and formed networks. Initially, channel perforation was observed while the ECM was squeezed and stretched between the hyphae. Last but not least, the isolate strain showed aberrant fungal structures resembling micro-hyphae with tiny.

3) A 24-hour period of biofilm growth. this stage entails The processes of mycelia creation, development, and propagation were more pronounced and involved hypha-hypha adhesion, condensed hyphal layering networks, and the performance of channels, a widespread formation of ECM, and high structural arrangement.

4) Cell separation and newly formed conidia were observed as a result of cell dispersion, which was predominantly noticed during the 24-hour mark of biofilm formation.

On the other hand, Costa-Orlandi et al., (2017)[26] described the steps of biofilm formation in six phases as following:

(I) Propagule adsorption, which involves spores, hyphal fragments, or sporangia coming into contact with a surface. (II) Active adhesion, in which spores produce adhesins throughout germination and other reproductive processes. (II) Active adhesion, in which

spores produce adhesins throughout germination and other reproductive processes. (III) First microcolony formation, which entails hyphal branching and extension, generating a monolayer and producing extracellular matrix. (IV) The creation of the second microcolony or the primary maturation, during which dense hyphae networks take shape in three dimensions and are covered by an extracellular matrix and water channels. (V) Final maturation, during which fruiting bodies and other surviving structures develop in accordance with the fungus; and, **(VI)** The release of conidia and/or hyphae fragments, which marks the start of a new cycle, occurs during the dispersion or planktonic phase, which comes last.

Approaches for Evaluation of dermatophytic Biofilm

Currently, there are numerous methods and procedures used to quantify biofilms, which frequently results in varying assessments of the examined microbial strains' propensity to produce biofilms and each method based on a specific reaction of the cells or of the extracellular matrix.[27]

One of the most often used dyes is crystal violet (CV), which is based on its capacity to color the polysaccharidic matrix, This technique is commonly used to quantify the biofilm since it is affordable, readily available, and provides accurate data. One drawback of this approach is the inability to distinguish between live and dead cells in biofilm biomass[17].

In studies of the growth of biofilms and their receptivity to antifungal medications, colorimetric tests are frequently employed. Such as employing the methyltetrazolium assay (MTT (3-[4,5-dimethylthiazol-2-yl]-2,5-iphenyltetrazolium bromide)) MTT is a yellow soluble salt that, when exposed to metabolic activity, transforms into a purple formazan crystal that is insoluble. The metabolic activity of various fungi in planktonic and biofilm forms can be ascertained using this technique. Additionally, this technique exhibits high concordance with dry weight biomass determination.It is quick and practical [28]. The inability to distinguish between each microorganism's contribution to the MTT compound decrease when mixed biofilms were assessed, This was a disadvantage of this method [29].

XTT is a derivative of 2,3-bis(2-methoxy-4-nitro-5-sulfophenyl)-5-[(phenylamino)carbonyl].Another tetrazolium salt used to study medication susceptibility and biofilm development. This Tetrazolium salt (yellow) is converted to formazan salt (orange), which is linked with cell survival, by the action of fungal mitochondrial dehydrogenase. Additionally, it is employed in antifungal susceptibility testing and biofilm growth phases to measure metabolic activity [30]. The XTT approach has an advantage over MTT since formazan produced as a result can be quantified immediately in the supernatant, whereas MTT requires an additional step involving cell lysis, in which cells must be treated with dimethyl sulfoxide before optical density measurement [31]
Other microtiter plate assays for biofilm characterization and susceptibility testing have been investigated, including Alamar blue/resazurin, safranin, Alician blue and DMMB (1,9–dimethyl methylene blue) [26].

Biofilm analysis is frequently carried out by morphologically characterizing the biofilm or by measuring its mass. Some studies used optical microscopy, stereomicroscopy, confocal laser scanning microscopy (CLSM), and scanning electron microscopy (SEM) techniques to examine the morphology of biofilms in vitro and ex vivo [32]. The most basic type of optical microscopy is used for morphological study. The presence of the extracellular matrix of the biofilm and the fungus's mycelium (hyphae and conidia) indicates that the procedure was successful. Optical microscopy can be helpful for visual assessment of biofilm production, but it becomes more pertinent when used in conjunction with other advanced techniques (like SEM) to assess the structure and matrix of the biofilm [33].

By using the scanning electron microscopy (SEM) technique, a sample is fixed, dehydrated, and dried before being coated with a conductor like gold or carbon and being processed under a high vacuum. However, due to ECM collapse, drying and dehydration can modify biofilm morphology. The photos may also be changed by artifacts. As an alternative, environmental SEM has become a popular technique since the biofilm may be seen without fixation or dehydration, and the mild vacuum maintains the morphology and structures of the surfaces.[34].

The architecture of biofilms is also visualized using transmission electron microscopy (TEM). Similar to SEM preparation in some steps, In contrast to SEM, this approach embeds the biofilm in a resin, which keeps the ECM stable. One drawback of TEM is that the configuration of the biofilm cannot be seen [26].

Another tool for examining the three-dimensional (3D) architecture and thickness of biofilms is confocal laser scanning microscopy (CLSM). Additionally, macromolecular substances like polysaccharides, proteins, nucleic acids, and lipids can be confirmed to be present. CLSM (LIVE/DEAD staining) is regarded as one of the most significant and adaptable techniques for

understanding the spatial structure of the biofilm and its associated functions [35], despite the fact that SEM is the favored technique for seeing the three-dimensional biofilm structure. The biofilm roughness coefficient, its total biomass, average thickness, and surface-to-volume ratio can all be measured using image analysis [34].

CONCLUSION

The majority of fungal infections that result in dermatophytosis in people and other vertebrates are caused by dermatophytes. Treatment failures are frequently linked to biofilm formation. Biofilms are extremely resistant to most clinically used antimicrobials, requiring inhibitory concentrations 100 times higher than those required to stop planktonic cells from growing. Also, Over any other method of proliferation, biofilm offers fungi a number of advantages. Therefore, biofilms represent a growing issue in the context of human health. There are several ways to analyze the development of microbial biofilms, which most of them rely on automatic readers. Additional descriptors for fungi that produce biofilms may be added in future studies to improve their description and to discover more about the procedures involved in the production and make up of dermatophyte biofilms, more research on various dermatophytes is required. On the other hand, study and analysis of the biofilms produced by dermatophytes may help in the hunt for new medications to treat these mycoses as well as guide future adjustments to the dosage and course of action of already existing antifungals.

REFERENCES

1. Pir M., Budak F. and Metiner K. (2022). In vitro antifungal activity of heterocyclic organoboron compounds against Trichophyton mentagrophytes and Microsporum canis obtained from clinical isolates.Brazilian Journal of Microbiology .https://doi.org/10.1007/s42770-022-00777-3
2. Brilhante RSN., Correia EEM., Guedes GM., Pereira VS., Oliveira JS., Bandeira SP., Alencar LP., Andrade ARC., Castelo-Branco DACM., Cordeiro RA., Pinheiro AQ., Chaves LJQ., Neto WAP., Sidrim JJC. and Rocha MFG. 2019. Quantitative and structural analyses of the in vitro and ex vivo biofilm-forming ability of dermatophytes. Journal of Medical Microbiology;66:1045–1052. DOI 10.1099/jmm.0.000528.
3. Gnat S, Łagowski D, Nowakiewicz A. Major challenges and perspectives in the diagnostics and treatment of dermatophyte infections. J Appl Microbiol. 2020; 129: 212–232.
4. Martins, M.P.; Silva, L.G.; Rossi, A.; Sanches, P.R.; Souza, L.D.R.; Martinez-Rossi, N.M. Global Analysis of Cell Wall Genes Revealed Putative Virulence Factors in the Dermatophyte Trichophyton rubrum. Front. Microbiol. 2019, 10, 2168.
5. Martinez-Rossi, N.M.; Bitencourt, T.A.; Peres, N.T.; Lang, E.A.; Gomes, E.V.; Quaresemin, N.R.; Martins, M.P.; Lopes, L.; Rossi, A. Dermatophyte resistance to antifungal drugs: Mechanisms and prospectus. Front. Microbiol. 2018, 9, 1108.
6. Mendes, N.S.; Bitencourt, T.A.; Sanches, P.R.; Silva-Rocha, R.; Martinez-Rossi, N.M.; Rossi, A. Transcriptome-wide survey of gene expression changes and alternative splicing in Trichophyton rubrum in response to undecanoic acid. Sci. Rep. 2018, 8, 2520.
7. Yamada, T.; Yaguchi, T.; Tamura, T.; Pich, C.; Salamin, K.; Feuermann, M.; Monod, M. Itraconazole resistance of Trichophyton rubrum mediated by the ABC transporter TruMDR2. Mycoses 2021, 64, 936–946.
8. Brilhantea RSN., Aguiarb L., Salesb JA., Araujo GS., Pereiraa VS., Pereira-Netoa WA., Pinheirob AQ. , Paix~aoa GC., Cordeiroa RA., Sidrim JJC., Bersanob PRO., Rochaa MFG. and Castelo-Brancoa DSC. (2019). Ex vivo biofilm-forming ability of dermatophytes using dog and cat hair: an ethically viable approach for an infection model. BIOFOULING 2019, VOL. 35, NO. 4, 392–400.
9. Wang, Y.; Lu, C.; Zhao, X.;Wang, D.; Liu, Y.; Sun, S. Antifungal activity and potential mechanism of Asiatic acid alone and in combination with fluconazole against Candida albicans. Biomed. Pharmacother. 2021, 139, 111568.
10. Chen B, Sun Y, Zhang J, Chen R, Zhong X, Wu X, Zheng L and Zhao J (2019) In vitro Evaluation of Photodynamic Effects Against Biofilms of Dermatophytes Involved in Onychomycosis. Front. Microbiol. 10:1228.
11. Alim D., Sircaik S. and Panwar Sl. 2018. The Significance of Lipids to Biofilm Formation in Candida albicans: An Emerging Perspective. J. Fungi 2018, 4, 140.
12. Brilhante RS, de Lima RA, Marques FJ, Silva NF, Caetano ÉP et al. *Histoplasma capsulatum* in planktonic and biofilm forms: in vitro susceptibility to amphotericin B, itraconazole and farnesol. J Med Microbiol 2015;64:394–399.

13. Gao L, Jiang S, Sun Y, Deng M, Wu Q et al. Evaluation of the effects of photodynamic therapy alone and combined with standard antifungal therapy on planktonic cells and biofilms of Fusarium spp. and Exophiala spp. Front Microbiol 2016;7:617.
14. Burkharta CN, Burkhart CG, Gupta AK. Dermatophytoma: recalcitrance to treatment because of existence of fungal biofilm. J Am Acad Dermatol. 2002; 47(4): 629–31.
15. Chen B, Sun Y, Zhang J, Chen R, Zhong X, Wu X, et al. In vitro evaluation of photodynamic effects against biofilms of dermatophytes involved in onychomycosis. Front Microbiol. 2019; 10: 1228.
16. Sen S, Borah SN, Kandimalla R, Bora A, Deka S. Sophorolipid biosurfactant can control cutaneous dermatophytosis caused by Trichophyton mentagrophytes. Front Microbiol. 2020; 11: 329.
17. Yazdanpanah S., Sasanipoor F., Khodadadi H., Rezaei-Matehkolaei A., Jowkar F., Zomorodian K., Kharazi M., Mohammadi T., Nouripour-Sisakht S., Nasr R.and Motamedi M. (2023). Quantitative analysis of in vitro biofilm formation by clinical isolates of dermatophyte and antibiofilm activity of common antifungal drugs. *International Journal of Dermatology*.62(1):120-127
18. Azeredo, J.; Azevedo, N.F.; Briandet, R.; Cerca, N.; Coenye, T.; Costa, A.R.; Desvaux, M.; Di Bonaventura, G.; Hébraud, M.; Jaglic, Z.; et al. Critical review on biofilm methods. Crit. Rev. Microbiol. 2017, 43, 313–351.
19. Castelo-Branco D SCM, de Aguiar L, Araujo G S et al. in vitro and ex vivo biofilms of dermatophytes: a new panorama for the study of antifungal drugs. Biofouling. 2020; 36: 783–791.
20. Fanning S, Mitchell AP (2012) Fungal Biofilms. PLoS Pathog 8(4):e1002585.
21. Borghi E, Borgo F, Morace G. Fungal biofilms: update on resistance. Fungal Biofilms and Related Infections. 2016; 3: 37–47.
22. Liu S., Mauff FL., Sheppard DC. and Zhang S. 2022. Filamentous fungal biofilms: Conserved and unique aspects of extracellular matrix composition, mechanisms of drug resistance and regulatory networks in Aspergillus fumigatus. npj Biofilms and Microbiomes (2022) 8:83.
23. Sena S. , Boraha SN., Borac A. and Deka S. (2020). Rhamnolipid exhibits anti-biofilm activity against the dermatophytic fungi Trichophyton rubrum and Trichophyton mentagrophytes. Biotechnology Reports 27 (2020) e00516
24. González-Ramírez, A. I., Ramírez-Granillo, A., Medina-Canales, M. G., Rodríguez-Tovar, A. V., & Martínez-Rivera, M. A. (2016). Analysis and description of the stages of Aspergillus fumigatus biofilm formation using scanning electron microscopy. BMC microbiology, 16(1), 1-13.
25. Ramage G., Rajendran R., Sherry L. and Williams C.2012. Fungal Biofilm Resistance. Hindawi Publishing Corporation .International Journal of Microbiology.2012: 14.
26. Costa-Orlandi, C. B., Sardi, J. C., Pitangui, N. S., De Oliveira, H. C., Scorzoni, L., Galeane, M. C., ... & Mendes-Giannini, M. J. S. (2017). Fungal biofilms and polymicrobial diseases. J. Fungi, 3(2), 22.
27. Corte L., Pierantoni DC., Tascini C., Roscini L. and Cardinali G.(2019). Biofilm Specific Activity: A Measure to Quantify Microbial Biofilm. Microorganisms 2019, 7, 73.
28. Trafny, E.A.; Lewandowski, R.; Zawistowska-Marciniak, I.; Stepinska, M. Use of MTT assay for determination of the biofilm formation capacity of microorganisms in metalworking fluids. World J. Microbiol. Biotechnol. 2013, 29, 1635–1643.
29. Manavathu, E.K.; Vager, D.L.; Vazquez, J.A. Development and antimicrobial susceptibility studies of in vitro monomicrobial and polymicrobial biofilm models with Aspergillus fumigatus and Pseudomonas aeruginosa. BMC Microbiol. 2014, 14, 53.
30. Trafny, E.A.; Lewandowski, R.; Zawistowska-Marciniak, I.; Stepinska, M. Use of MTT assay for determination of the biofilm formation capacity of microorganisms in metalworking fluids. World J. Microbiol. Biotechnol. 2013, 29, 1635–1643
31. Casagrande Pierantoni, D.; Corte, L.; Roscini, L.; Cardinali, G. High-Throughput Rapid and Inexpensive Assay for Quantitative Determination of Low Cell-Density Yeast Cultures. Microorganisms 2019, 7, 32.
32. Pereira FO. A review of recent research on antifungal agents against dermatophyte biofilms. Medical Mycology, 2021, 59, 313–326.

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IJCSRR @ 2023

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33. Azeredo J, Azevedo NF, Briandet R et al. Critical review on biofilm methods. Crit Rev Microbiol. 2017; 43: 313–351.
34. Bridier, A.; Meylheuc, T.; Briandet, R. Realistic representation of Bacillus subtilis biofilms architecture using combined microscopy (CLSM, ESEM and FESEM). Micron 2013, 48, 65–69.
35. Karim MT., Ghosh SJ., Chougale RA., Vatkar VS., Deshkar DW. And Narute JV. (2017). Study of Dermatophytes and their Biofilm Production. Journal of Advanced Medical and Dental Sciences Research; 5(11):56-59.

Cite this Article: Shaimaa Nabhan Yassein (2023). Super Glue Production by Dermatophytes: Review. International Journal of Current Science Research and Review, 6(6), 3154-3159