Benha Journal of Applied Sciences (BJAS) **print: ISSN 2356–9751**
Vol. (9) Issue (10) (2024), (31- 36) **online: ISSN 2356–976x**

http://bjas.bu.edu.eg
Medical and Health Science

Photodynamic Therapy in treatment of Onychmyosis

Ghady F. El Bakly[1], Ahmed A. Saleh[1], Aliaa E. Daifalla[1] and Asmaa M. Elbakry[2]
[1]Dermatology, Venereology and Andrology Department, Faculty of Medicine, Benha University, Benha, Egypt
[2]Pharmaceutics and Pharmaceutical Technology Department, Faculty of Pharmacy, Al-Azhar University, Heliopolis University, Cairo, Egypt
E-mail: ghadyfoad@icloud.com

Abstract

Context: Onychomycosis is among the most prevalent fungal infections, accounting for as much as 50% of nail illnesses. Even though there are systemic and topical antifungal medications available, treatment hurdles such inadequate penetration, drug resistance, and adverse effects still exist. A targeted and non-invasive approach to treating onychomycosis that has become resistant to other treatments is photodynamic therapy (PDT).. It uses light-activated photosensitizers to produce reactive oxygen species. Objective: To what extent is photodynamic therapy safe and effective in treating onychomycosis? That is the goal of this narrative evaluation. Methods: In order to determine the effectiveness, safety, and mechanisms of PDT in treating onychomycosis, a systematic literature review was performed. The study also looked at how well PDT may work to improve patient compliance and decrease the development of fungal biofilms. In summary: As an alternative to conventional antifungal treatments, photodynamic therapy shows promise in the treatment of onychomycosis. Fewer side effects, less likelihood of medication resistance, and increased antifungal efficacy when combined with other treatments are some of its benefits. For patients who are resistant to other treatments or have side effects from them, PDT is a good alternative because of its safety record and its capacity to target fungal biofilms.

Keywords: Photodynamic, onychomycosis.

Introduction

Half of all nail abnormalities are caused by onychomycosis, making it one of the most common fungal infections. With a treatment failure rate of 10–53%, it is among the most therapeutically difficult superficial mycoses. There are a number of pharmacological shortcomings with the antifungal terbinafine, such as its low penetration capacity and the development of resistance [1]. Despite its best cure rates, however, it needs extended administration, may induce unpleasant effects, and suffers from these issues.

Onychomycosis occurs in a range of 2–13% of North American populations. Adults are thirty times more likely to be affected than children, and it disproportionately affects men. Age, immunodeficiency, aberrant nail morphology, and hereditary variables are among the risk factors that raise the disease's prevalence [2].

The symptoms of onychomycosis include coloring, thickness, splitting, and roughening of the nails. It may cause secondary bacterial infections like cellulitis in addition to pain, discomfort, and mobility issues with everyday tasks. Even minor occurrences of onychomycosis may cause substantial anguish to patients due to its psychological effects, such as lowered self-esteem and humiliation. A major health concern is onychomycosis. Onychomycosis may impair social and occupational life due to its psychological and social restrictions [3].

Traditional methods of treating onychomycosis often include the use of either systemic or topical antifungal medications; however, there are some limits to both of these treatments. Although they are effective, oral antifungals include side effects such medication interactions and damage to the liver. However, since they can't get past the nail plate and into the infection site, topical antifungals don't work very well [4].

One potential alternative to traditional methods of treating superficial skin infections, such as onychomycosis, is photodynamic treatment (PDT). Short treatment duration promotes adherence; low probability of resistance development implies a multitarget mechanism of action; lack of drug interaction allows for possible combination with antifungals; easy reproducibility; mild adverse effects with an acceptable risk-benefit profile; and last but not least, this modality has a lack of drug interaction.

This narrative review aims to assess how well and how safely Patients with onychomycosis who are unable to tolerate systemic medications or who are at risk for side effects may benefit from photodynamic therapy, which has the ability to be used as either a primary or supplementary treatment.

The Fungus Nails

The nail unit—the nail plate, matrix, and bed—is infected with fungus in the most prevalent nail condition, known as onychomycosis. It usually manifests as thickening, discolouration, and onycholysis in nails and is caused by yeasts, non-dermatophyte molds, and dermatophytes. Over half of all nail illnesses are caused by this, so getting a proper diagnosis—and treatment that doesn't break the bank—requires testing in a lab. The management of onychomycosis has been greatly enhanced by recent developments in diagnostic tools and therapy choices, providing more accurate and sensitive approaches to care [6].

The origin:

Yeasts, molds, and dermatophytes are all potential culprits in the development of onychomycosis. For over 90% of toenail infections and 75% of fingernail infections, the dermatophytes to blame are Trichophyton mentagrophytes and Trichophyton rubrum. Epidermophyton floccosum, Microsporum, and a number of Trichophyton species are among the less frequent dermatophyte species. Around 10% of cases worldwide are caused by molds that aren't dermatophytes, such as Aspergillus, Scopulariopsis, and Fusarium. Onychomycosis caused by yeast, most often Candida albicans, is uncommon but more common in those with impaired immune systems, particularly in the fingernails [7].

Epidemiology: Onychomycosis has an estimated 5.5% worldwide prevalence, with increasing rates linked to variables including urbanization, obesity, and longer life expectancy. While children have a frequency of 0.4%, adults, especially those over the age of 65, have a prevalence of up to 35%. While females are more likely to have Candida infections in their fingernails, men are more likely to get onychomycosis in their toenails. Tinea pedis, persistent paronychia, occlusive shoes, nail damage, immunodeficiency, diabetes, obesity, psoriasis, peripheral vascular disease, and other disorders are risk factors [8].

The nail unit does not have good cell-mediated immunity, therefore it is susceptible to infection by dermatophytes, non-dermatophyte molds, or yeasts, which may lead to onychomycosis. In order for fungi to invade a nail, fungal enzymes that are proteolytic, keratinolytic, and lipolytic break down the nail's keratin. Infection is more likely to occur if the nail's protective barriers are compromised. The different varieties of onychomycosis are based on where the fungus invaded and how it spread. Fungi may also become resistant to antifungal treatments by forming biofilms, which they use to avoid being treated [9].

Clinical Signs and Symptoms:

The most common nail discolorations caused by onychomycosis are white or yellow-brown, but violaceous, green, and black discolorations may also happen. Subungual hyperkeratosis, onychauxis, or the separation of the nail from its bed, are further symptoms. The unique skin condition known as dermatoma, with its characteristic bands of white, yellow, orange, or brown, is exclusive to onychomycosis. Tinea pedis is more often linked to toenails than fingernails; it most typically affects the large toes. It is common for many toenails to be affected, but individual fingernails to be unaffected unless the patient has impaired immunity or a history of trauma (Figure 1) [10].

Patients may exhibit symptoms from more than one clinical subtype of onychomycosis, which is depending on the pattern of fungal invasion. A typical kind of onychomycosis is distal lateral subungual onychomycosis, which manifests as discolouration, hyperkeratosis, and onycholysis. This infection begins in the hyponychium and spreads across the nail plate (Fig 2-A). Easily scraped white spots are the hallmark of white superficial onychomycosis, which affects the surface of the nail (Fig 2-B). In immunocompromised individuals, proximal subungual onychomycosis begins close to the cuticle and spreads outward (Fig 2-C). The nail bed is unaffected by Endonyx onychomycosis, which affects just the nail plate and causes cracking and milky spots. At last, the nail is entirely destroyed in total dystrophic onychomycosis (Fig 2-D). Species of the fungus Trichophyton are the most prevalent culprits [13].

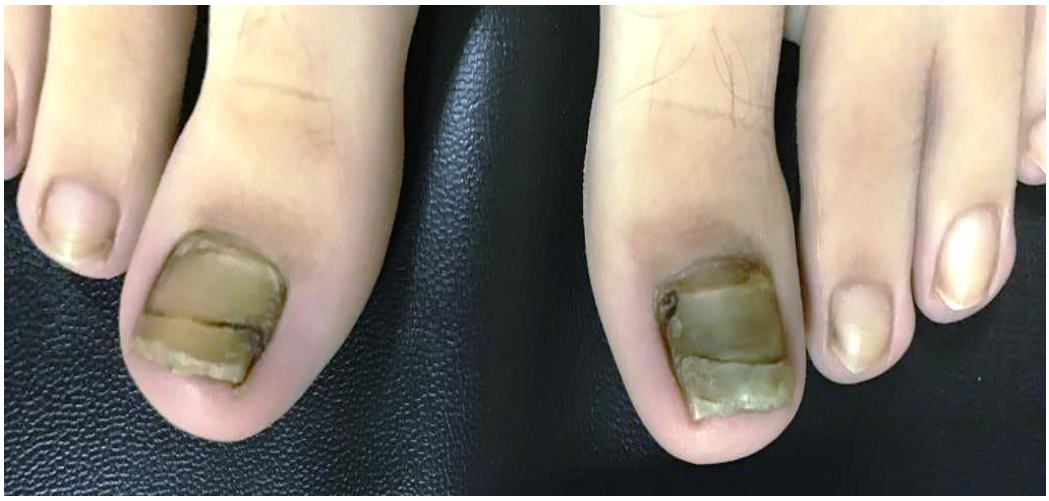

Fig. (1) A. The nail plate of the right big toe displays a linear, yellow band in a patient with distal lateral subungual onychomycosis, which is known as a dermatophytoma [11]. Onychomycosis with tinea pedis in the same patient [12].

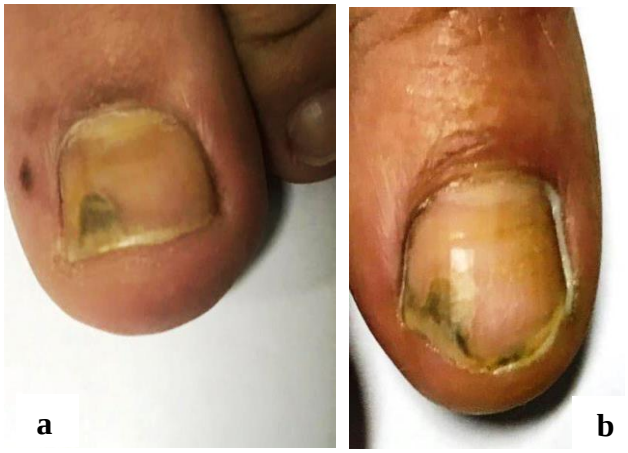

Fig. 2: Distal lateral subungual onychomycosis in right big toe (a) and right thumb (b) of same patient. [13].

Diagnosis:

1. The Nail discolouration, hyperkeratosis, onycholysis, and thickness are the main clinical signs used to diagnose onychomycosis. Dermoscopy is a useful non-invasive diagnostic method that may separate it from other nail illnesses. Transverse onycholysis points to a different diagnosis, but common dermoscopy patterns include dermatophytoma, longitudinal streaks, and jagged proximal margins. For cost-effective and tailored therapy, laboratory confirmation is required prior to treatment, even though dermatologists and non-dermatologists have different levels of clinical diagnostic accuracy [14].
2. Fungal cultures, PCR tests, histopathologic evaluation using PAS staining, and potassium hydroxide (KOH) wet-mount preparation are all examples of laboratory procedures. Although KOH is an inexpensive and easy way to find fungal hyphae, it isn't very sensitive or good for identifying species. Unfortunately, PAS stain is not able to detect fungal species or viability, despite its increased sensitivity. Although laborious, fungal cultures are useful for identifying species and directing therapy; nevertheless, they are not very sensitive. PCR tests are costly and not often used, yet they provide fast and accurate findings. To ensure that viable fungal components are acquired from the most active infection locations, it is necessary to use sample collection procedures that are guided by clinical presentation and dermoscopy [15]. This will allow for an accurate diagnosis.
3. Possible Alternative Diagnoses:
4. Onychomycosis has several possible causes, including other nail disorders such psoriasis, chronic dermatitis, alopecia areata, lichen planus, and onychogryphosis. Pityriasis rubra pilaris, subungual melanoma, chronic paronychia, autoimmune illnesses such as lupus erythematosus and pemphigus vulgaris, trachyonychia, melanonychia striata, and pachyonychia congenita are among the other potential causes. The differential diagnosis also takes into account subungual warts, keratoacanthoma, traumatic onychodystrophy, yellow nail syndrome, and a variety of cancers such squamous cell carcinoma, fibroma, and myxoid cysts [16].
5. Other issues:
6. Another cutaneous fungal infection that onychomycosis may harbor and disseminate to other nails is tinea pedis, tinea corporis, and tinea cruris. In those with impaired immune systems, such as diabetics, it heightens the likelihood of bacterial infections, such as cellulitis and paronychia. In extreme circumstances, it may cause discomfort, numbness, abnormalities in the nails, and problems with normal tasks including walking, standing, and cutting nails. In the absence of treatment, it may lead to pain, trouble fitting shoes, and a decline in self-esteem and quality of life as a result of its humiliating and ugly look [14].
7. Methods Currently Used to Treat Onychomycosis
8. Drugs for Fungal Overgrowth:
9. Onychomycosis is often treated with systemic antifungal medications such as fluconazole, terbinafine, and itraconazole. A fungicidal agent like terbinafine may break down fungal cell walls by blocking the production of ergosterol, but a fungistatic agent like itraconazole or fluconazole can slow the development of fungi without really killing them. In more serious instances, oral antifungals are usually used as a first line of defense. Due to their increased risk of adverse effects, such as hepatotoxicity, and decreased effectiveness, glimepiride and ketoconazole are currently seldom used [17].
10. When systemic treatment is not an option or when the nail infection is mild to severe, a topical antifungal agent such as efinaconazole, amorolfine, or ciclopirox may be used. Although these chemicals are applied directly to the nail

and the skin around it, their effectiveness is often hindered due to the lack of penetration into the nail. Patients who are unable to receive systemic therapies, or who have conditions such white superficial onychomycosis, may benefit from a combination of oral and topical antifungals to increase the likelihood of a cure [17].

11. Treatment with Lasers: Lasers, such fractional CO_2 and long-pulsed Nd:YAG lasers, kill fungus cells via selective photothermolysis. They are localized to the affected region, reducing the likelihood of systemic adverse effects that are common with oral antifungal drugs. When systemic treatments are either not appropriate or have not worked, laser therapy is often used as an additional therapeutic option [18].
12. In photodynamic treatment, photosensitizers like methylene blue, 5-aminolevulinic acid (5-ALA), or methylaminolevulinate (MAL) are used to activate photosensitizers. Light at specified wavelengths then produces reactive oxygen species (ROS), which kill the cells of the fungus. Patients who are unable to take systemic antifungal therapy or who have resistant onychomycosis may find PDT to be a viable option [19].
13. In addition to the methods already mentioned, keratolytic drugs and surgical avulsion may be helpful in treating thickened nails [20].
14. Photodynamic treatment
15. Effect Mechanism:
16. There are three stages to the process of photodynamic therapy:
17. Use of a Photosensitizer: The affected nail or tissues are treated with a photosensitizing agent, such as 5-ALA or MAL. As the photosensitizer builds up within the fungal cells, it ensures focused therapy since healthy tissues absorb very little of it [21].
18. After photosensitizer absorption, it is activated by exposure to light of a certain wavelength, often in the red, blue, or green spectrum. The photosensitizer employed determines the activation wavelength [21].
19. The photosensitizer enters an excited state when exposed to light, transferring energy to the oxygen molecules around it. This process generates reactive oxygen species (ROS) such superoxide anions, hydroxyl radicals, and singlet oxygen. Cell death by necrosis or apoptosis results from oxidative damage caused by these ROS to fungal cell components, including membranes, mitochondria, and proteins. Even fungal biofilms, which are notoriously difficult to cure, may be broken up by PDT in some instances. Because biofilms may develop on the nail plate and cause onychomycosis to reoccur, this is a very essential consideration [22].

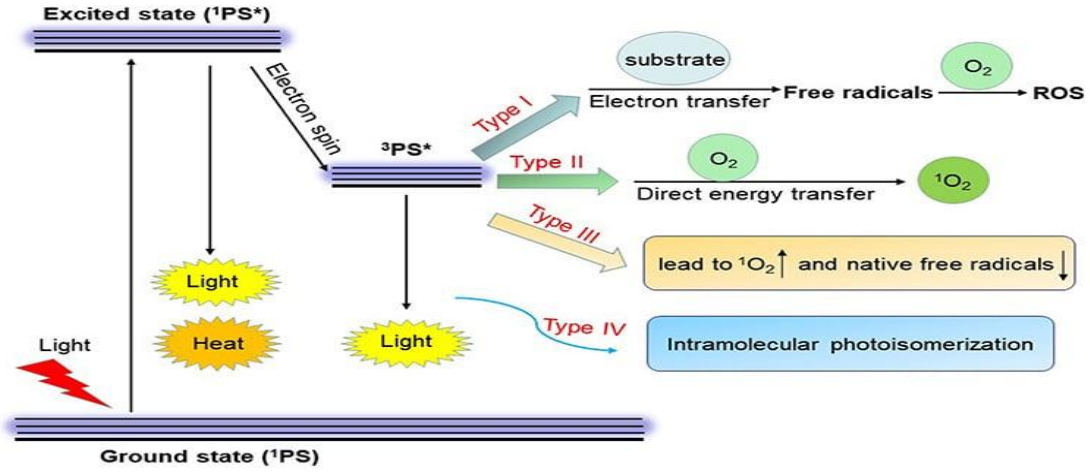

Fig. (3) Photodynamic therapy's mechanism of action. [21].

Potential Benefits:

PDT is able to selectively target diseased tissues, which is one of its main benefits over conventional antifungal treatments. By being so exact, the danger of adverse effects is reduced and harm to healthy skin and nails around the area is minimized. In comparison to oral antifungal drugs, PDT has very low systemic absorption, which greatly reduces the likelihood of side effects such liver damage and drug interactions. One problem with conventional antifungal therapies is that fungal infections may evolve resistance. This medication works by generating reactive oxygen species (ROS), which targets several pathways and reduces the risk of this happening [22].

The fact that PDT is not intrusive means that it may be performed as an outpatient operation without the need for general anesthesia or systemic medicine; this is particularly helpful for individuals who have problems responding to systemic treatments. In situations of persistent onychomycosis, it is possible to enhance results by combining PDT with oral or topical antifungal medications. When opposed to patients who get systemic medications, those who

undergo PDT often recover faster and have faster nail regeneration. A helpful therapeutic alternative in controlling onychomycosis is PDT because of its tailored therapy, safety, and increased recovery [23].

Disclaimers & CAUTIONS:

Although PDT has many advantages, it is not without its drawbacks. Patients may experience an increase in treatment costs and burden due to the need of many PDT treatments (generally weekly or bi-weekly) for maximum effectiveness. Even though photodynamic therapy (PDT) works in most situations, the degree to which it works depends on the kind of fungus, how much of the nail is affected, and the photosensitizer that is employed. Depending on the photosensitizer and light source, cure rates may range from 50% to 100%, according to certain studies [24].

Compared to more conventional methods of treating fungal infections, such as topical or oral antifungal treatments, PDT may be somewhat expensive. This makes it harder for people to use, particularly in areas with little resources. Patients with hyperkeratotic or dystrophic nails may also find that some photosensitizers are less effective due to the nail plate's thick keratin structure, which limits their penetration. If you want better penetration, you may need to use keratolytic agents (like urea) or shave your nails beforehand. Pain, redness, or burning may occur at the treatment site during or after photodynamic therapy (PDT) sessions; however, this is usually well-tolerated. Typically, these side effects won't last more than a few days until they go away [24].

Practical Considerations:

For individuals with onychomycosis who have not had success with conventional therapies or who are unable to use systemic antifungals, photodynamic therapy holds great promise. When deeper nail penetration is not required, it may be used as a first-line treatment for mild to moderate instances, including white superficial onychomycosis. To improve cure rates and reduce systemic treatment time, PDT may be coupled with systemic antifungals such as terbinafine for more severe patients. Particularly helpful in treating biofilm-associated onychomycosis, it reduces recurrence and improves results by disrupting fungal biofilms. Additionally, PDT provides a less hazardous option for individuals who are more likely to have side effects from oral antifungals, including the elderly and those with several medical conditions. After more testing, PDT has the potential to replace more intrusive methods as a standard part of onychomycosis treatment plans.

Conclusions

Ultimately, photodynamic therapy stands as a worthwhile substitute for traditional methods of treating onychomycosis. Whether administered alone or in conjunction with systemic or topical treatments, it can lessen the dosage of systemic antifungals needed, lessen the chances of side effects and interactions, and achieve even better cure rates, particularly in cases where the infection is caused by dermatophytes.

References

[1] A. Navarro-Bielsa, T. Gracia-Cazaña, P. Robres, C. Lopez, M.D. Calvo-Priego, C. Aspiroz, et al. Combination of Photodynamic Therapy and Oral Antifungals for the Treatment of Onychomycosis. Pharmaceuticals (Basel);vol,15. 2022

[2] S. Hanna, A. Andriessen, J. Beecker, M. Gilbert, E. Goldstein, S. Kalia, et al. Clinical Insights About Onychomycosis and Its Treatment: A Consensus. J Drugs Dermatol;vol,17:pp:253-62. 2018

[3] A.K.C. Leung, J.M. Lam, K.F. Leong, K.L. Hon, B. Barankin, A.A.M. Leung, et al. Onychomycosis: An Updated Review. Recent Pat Inflamm Allergy Drug Discov;vol,14:pp.32-45. 2020

[4] Alexandra Y. Zhang, William L. Camp, Boni E. Elewski,: Advances in Topical and Systemic Antifungals, Dermatologic Clinics, vol,25,pp. 2:165-183, 2007

[5] P. Robres, C. Aspiroz, A. Rezusta, Y. Gilaberte. Usefulness of Photodynamic Therapy in the Management of Onychomycosis. Actas dermo-sifiliograficas;vol,106. 2015

[6] A. Gupta, N. Stec, R. Summerbell, N. Shear, V. Piguet, A. Tosti, et al. Onychomycosis: a review. J Eur Acad Dermatol Venereol;vol,34:pp:1972-90. 2020

[7] A.K. Leung, J.M. Lam, K.F. Leong, K.L. Hon, B. Barankin, A.A. Leung, et al. Onychomycosis: an updated review. Recent Pat Inflamm Allergy Drug Discov;vol,14:pp:32-45. 2020

[8] A.K. Gupta, H.J. Renaud, E.M. Quinlan, N.H. Shear, V. Piguet. The growing problem of antifungal resistance in onychomycosis and other superficial mycoses. Am J Clin Dermatol;vol:22:pp:149-57. 2021

[9] J.K. Christenson, G.M. Peterson, M. Naunton, M. Bushell, S. Kosari, K.E. Baby, et al. Challenges and opportunities in the management of onychomycosis. J Fungi;vol,4:pp:87-91. 2018

[10] R. Aggarwal, M. Targhotra, B. Kumar, P. Sahoo, M. Chauhan. Treatment and management strategies of onychomycosis. J Mycol Med;vol,30:pp:10-6. 2020

[11] V. Silva-Neves, V. Hugo, P. Alves, J.C. Amado, C. Pais-Vieira, F. Sousa, et al. Quality of life and therapeutic regimen management in onychomycosis patients and in vitro study of antiseptic solutions. Scientific Reports;vol,11:pp:140-9. 2021

[12] S. Halvaee, R. Daie-Ghazvini, S.J. Hashemi, S. Khodavaisy, A. Rahimi-Foroushani, H.

Bakhshi, et al. A mycological and molecular epidemiologic study on onychomycosis and determination in vitro susceptibilities of isolated fungal strains to conventional and new antifungals. Front Cell Infect Microbiol;vol,11:pp:150-6. 2021

[13] C.R. Stewart, L. Algu, R. Kamran, C.F. Leveille, K. Abid, C. Rae, et al. Effect of onychomycosis and treatment on patient-reported quality-of-life outcomes: A systematic review. J Am Acad Dermatol vol,85:pp:1227-39. 2021

[14] A. Jazdarehee, L. Malekafzali, J. Lee, R. Lewis, I. Mukovozov. Transmission of onychomycosis and dermatophytosis between household members: a scoping review. J Fungi;vol,8:pp:60-77. 2022

[15] A. Valkov, M. Zinigrad, A. Sobolev, M. Nisnevitch. Keratin biomembranes as a model for studying onychomycosis. Int J Mol Sci;vol,21:pp:3512-9. 2020

[16] C. Daggett, R.T. Brodell, C.R. Daniel, J. Jackson. Onychomycosis in athletes. Am J Clin Dermatol;vol,20:pp:691-8. 2019

[17] M. Ivanov, A. Ćirić, D. Stojković. Emerging Antifungal Targets and Strategies. Int J Mol Sci;vol,23. 2022

[18] W. Ma, C. Si, L.M. Kasyanju Carrero, H.F. Liu, X.F. Yin, J. Liu, et al. Laser treatment for onychomycosis: A systematic review and meta-analysis. Medicine (Baltimore);vol,98:pp:e17948. 2019

[19] J.H. Correia, J.A. Rodrigues, S. Pimenta, T. Dong, Z. Yang. Photodynamic Therapy Review: Principles, Photosensitizers, Applications, and Future Directions. Pharmaceutics;vol,13. 2021

[20] E. Caliskan, M. Tunca, H. Erbil, A. Akar. Phenol application to distal nail matrix for the treatment of nail thickening. Indian Journal of Dermatology, Venereology and Leprology;vol,77:pp:344. 2011

[21] J. Ghorbani, D. Rahban, S. Aghamiri, A. Teymouri, A. Bahador. Photosensitizers in antibacterial photodynamic therapy: an overview. Laser Ther;vol,27:pp:293-302. 2018

[22] M. Przygoda, D. Bartusik-Aebisher, K. Dynarowicz, G. Cieślar, A. Kawczyk-Krupka, D. Aebisher. Cellular Mechanisms of Singlet Oxygen in Photodynamic Therapy. Int J Mol Sci;vol,24. 2023

[23] S.A. Al-Maweri, M.N. Alhajj, L. Anweigi, S. Ashraf, E. Halboub, N.M. Salleh, et al. Efficacy of photodynamic therapy on candida colonization and clinical symptoms in denture stomatitis: a systematic review and meta-analysis. BMC Oral Health;vol,24:pp:84. 2024

[24] J.F. Algorri, M. Ochoa, P. Roldán-Varona, L. Rodríguez-Cobo, J.M. López-Higuera. Light Technology for Efficient and Effective Photodynamic Therapy: A Critical Review. Cancers (Basel);vol,13. 2021