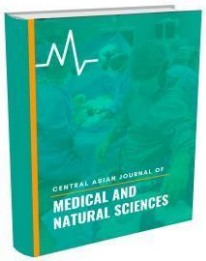

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Article

Emergence of an Aggressive Strain of Dermatophyte Resistant to Conventional Treatments

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Abstract: This study investigates the prevalence and etiology of fungal infections, emphasizing traditional diagnostic methods. A total of 154 samples from skin (75.32%), hair (15.85%), and nails (9%) were analyzed, with a consultant dermatologist's participation at the Turkish Hospital in Nasiriya between February and November 2023. Direct examination using KOH solution revealed a high infection prevalence, with 79% positive results. Females showed a higher infection rate (43.5%) than males (27.92%), and the 11-20 age group exhibited the highest incidence, primarily with ringworm infections. The study identified Trichophyton (54.66%) as the most prevalent genus, followed by T. mentagrophytes (37.33%) and other dermatophytes. Among the five antifungal agents tested—miconazole, ketoconazole, nystatin, fluconazole, and co-trimoxazole—miconazole and nystatin showed the highest inhibition values, whereas co-trimoxazole showed significant resistance. Fungal virulence was also examined through enzyme production (protease, lipase, and keratinase), indicating active infection potential. This study highlights the critical need for effective antifungal treatments and provides insight into the diagnostic and therapeutic challenges of fungal infections in this region.

Keywords: Fungi, Antifungals, Filamentous fungi, Tinea

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1. Introduction

Fungal diseases caused by Dermatophytes impact millions of people every year. Invading keratinized tissues like nails, hair, and skin are filamentous fungus known as dermatologtophytes [1]. Trichophyton, Epidermophyton, and Microsporum are the three genera into which they are traditionally placed [2]. The incorrect diagnosis of morphological mutations has resulted from this taxonomy, which is based on the phenotype of the species. Using nuclear ribosomal internal transcribed spacer (ITS) rDNA sequences, de Hoog et al. (2017) ranked dermatophytes into seven groups: Epidermophyton, Trichophyton, Paraphyton, Lophophyton, Microsporum, and Arthroderma [3]. The three ecological groups that fungi belong to are geophilic, zoophilic, and anthropophilic, based on their host specialization.

Although geophilic dermatophytes are uncommon infective agents in humans and animals, they are present in animal fur. Humans are easy prey for zoophilic dermatophytes, which live in animal fur and can cause symptoms in some people but no symptoms at all in others. Acute inflammatory mycoses are caused by zoophilic and geophilic species that can be transmitted to humans. In most cases, anthropophilic

dermatophytes can be transmitted from host to host. They are responsible for moderate-length infections that do not produce inflammation [4].

Ringworm, often known as tinea, is a common sign of dermatophytosis. The four most prevalent tinea infections are onychomycosis, tinea corporis, tinea cruris, and tinea pedis. Dermatophytosis in humans is mostly caused by three dermatophytes: Trichophyton rubrum, Trichophyton interdigitale, and Trichophyton mentagrophytes [5]. Topical or systemic antifungal medications are used to treat dermatophytosis. Tinea comes in many mild forms, but there are a lot of topical treatments that can help. Commonly used azole derivatives include oxiconazole, econazole, miconazole, and clotrimazole. Additionally, agents belonging to the allylamine class are utilized, including terbinafine and naftifine. In less severe instances of onychomycosis, other topical treatments such ciclopirox or amorolfine might work.

Severe cases of dermatophyte infections typically require oral therapy [6-7]. In 1958, griseofulvin was administered to patients for the first time as an oral medicine to treat dermatophyte infections. This material blocks the assembly of microtubules, which in turn prevents the growth of fungi and the division of cells. Oral administration is the norm for allylamines (often terbinafine) and triazoles (often itraconazole). The cell membrane is the same biological target of allylamines and triazoles. The enzyme sterol 14-α-demethylase is inhibited by triazoles, and ergosterol synthesis is reduced due to allylamines blocking squalene epoxidase. On the other hand, lanosterol, a detrimental step in the ergosterol biosynthesis pathway, accumulates due to allylamines [8-10].

Because of its effectiveness in treating Trichophyton spp., terbinafine is the fungicide of choice [11]. Persistent dermatophytic infections, which can last for years, have been more common in recent years. Rarely, terbinafine-resistant strains of Trichomonas rubrum and Trichomonas mentagrophytes/interdigitale have been found [12]. In most cases, resistance is associated with various point mutations in the gene that targets squalene. This syndrome has been described in several nations since it was initially documented in recalcitrant dermatophytosis in India [13]. It is crucial to establish in vitro antifungal susceptibility testing at reference laboratories to keep an eye on this issue, since there aren't many effective antifungals available for use against dermatophytes, and these agents are becoming more resistant with time.

2. Materials and Methods

Isolation and Identification of Dermatophytes

Clinical sample collection

Clinical samples of different ages and sexes were collected from patients with ringworm disease clinically diagnosed by specialist doctors in the Dermatology Clinic at (Tinea) Hospital. Al-Turki in Dhi Qar Governorate for the period from February to November 2023, Where the study included the collection of 154 samples, including (116 skin scraping samples, 24 hair samples, and 14 samples of Nails (68 samples of females and 86 samples of males, for age groups ranging from one year to 63 years) the samples were distributed to some neighborhoods of the city of Nasiriyah and some villages and surrounding areas. It's done by recording the information of the patients from whom the samples were taken, which included the patient's gender, age, area of infection, and type of ringworm. The affected area was sterilized with 70 ethyl alcohol to reduce contamination; small crusts were removed from the edge.

The injury was done using a sterile blunt blade, hair samples were obtained using sterile forceps, and a cut was taken. SDA prepared from nails is obliquely inoculated with a sterile scalpel directly into tubes containing medium previously in the laboratory, after which the samples were transferred to the graduate studies laboratory in the College of

Education for Pure Sciences, where for four weeks and observing the emergence of fungal growth, the inoculated tubes were placed in an incubator at 28+5 °C.

Direct Microscopic Examination

A small amount of skin scrapings, hair, or thin keratinized residues were taken from the nails with inoculation needles. A sterile Needle drop was added to it (and part of these samples were placed on a clean glass slide.) Or two drops of potassium hydroxide solution at a concentration of 15 , then covered with a slide cover and heated quietly. by moving it over the flame of a Bunsen lamp two or three times, avoiding boiling, as it leads to crystallization of the hydroxide Potassium and left for several minutes until the keratin melted and pressed gently to brush the sample and then examined microscopically [14], and Hyphae 40 conidia to view the filamentous structures x 10 and x under the power of magnification.

Culturing of Samples

After conducting direct microscopy, the isolates were taken and each isolate was cultured in 9 cm diameter Petri dishes referred to in the SDA (the same diameter of the dishes was adopted in all subsequent experiments) containing 55 ml of medium 12 2- 4 weeks for 25±2 °C.

Phenotypic examination of Fungal Colonies

Phenotypic characteristics were utilized to distinguish dermatophytes, encompassing various traits that require consideration. The growth rate, surface characteristics of the fungal colony (flat or with regular or irregular folds), and texture (rusty, smooth, mealy, grainy, velvety, or cottony) are important factors. Additionally, the apparent shape, texture (powdery, cottony, fluffy), color, and the color of the colony's underside are also relevant.

Colonial Microscopy

Microscopic examination was conducted to identify various fungal structures, including fungal filaments, their shapes, and branching patterns. Their shapes, sizes, numbers, and thicknesses (microconidia), as well as small (macroconidia), large conidia (arthrospores), and chlamydospores, were observed. Chlamydial spores were sterilized and placed in a drop of needle dye, using a part of the growing fungal colony. This preparation was examined under a light microscope with LPCB (lacto phenol) on a glass slide, utilizing taxonomic sources at magnifications of x10 and x40, with a lens magnification of 30.

Ethics Approval

This research adhered to the ethical standards outlined in the Declaration of Helsinki. Prior to sample collection, the patient provided informed consent in both written and verbal forms, following the review and approval of the study protocol and participant information by the local ethics committee.

Statistical Analysis

The data were statistically analyzed using the SPSS version 23 software, following a randomized complete block design (RCBD) with three replications, employing the chi-square test at a significance level of $P < 0.05$.

3. Results

Isolation of Fungi

In the current study, the fungus was isolated from 154 samples of skin, hair, and nails obtained from patients with skin infections who were admitted to the Turkish Hospital in Nasiriya during the period from February to November 2023. In total samples, the results of the direct examination in 154 showed that (71%) of the samples positive growth,

whereas the remainder, (29%), showed negative growth, as appeared in Figure 1. The percentage of females was 43.50 compared to 27.92 for males.

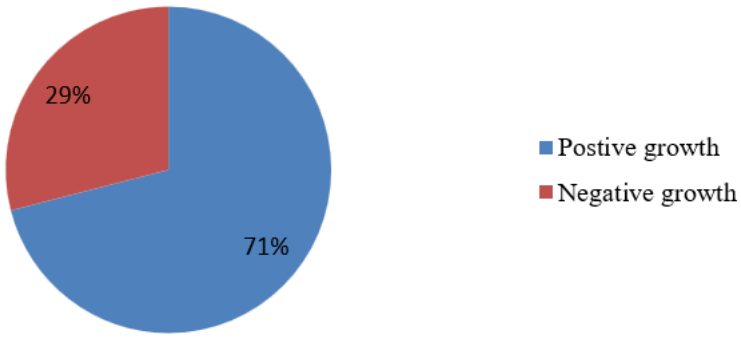

Figure 1. Percentage of growth across all samples

Phenomenal and Microscopic Examination of Fungal Colonies

Fungi were diagnosed based on the phenotypic characteristics of the colonies growing on the media culture, such as the nature of the fungal colonies, their shape, color, texture, pigments they produce, and the shape of the surface. As well as the microscopic characteristics, especially the fungal structures produced, such as large and small spores of in terms of shape, size, number, thickness of the walls, joints, and the number of existing cells, the study included the species following.

T. rubrum

Cottony white or SDA beige developing on the medium of T. rubrum. Phenotypic traits: Fungus colonies appeared light fluffy, slightly raised and flat, may be smooth at first, then becomes velvety The reverse dye is reddish-brown or light yellow to yellow-brown and some isolates did not produce the dye. growth This fungus is slow to moderate in some isolates, as the colony diameter reached between-1 cm through 8-day format (A and B).

Microscopic Characteristics

This fungus is characterized by its abundant production of small, round, teardrop-like conidia Multiple large, smooth-walled, thick-walled conidia are alternately arranged along the hyphae C and D cells are long divided 9 to 1 cells or wide end.

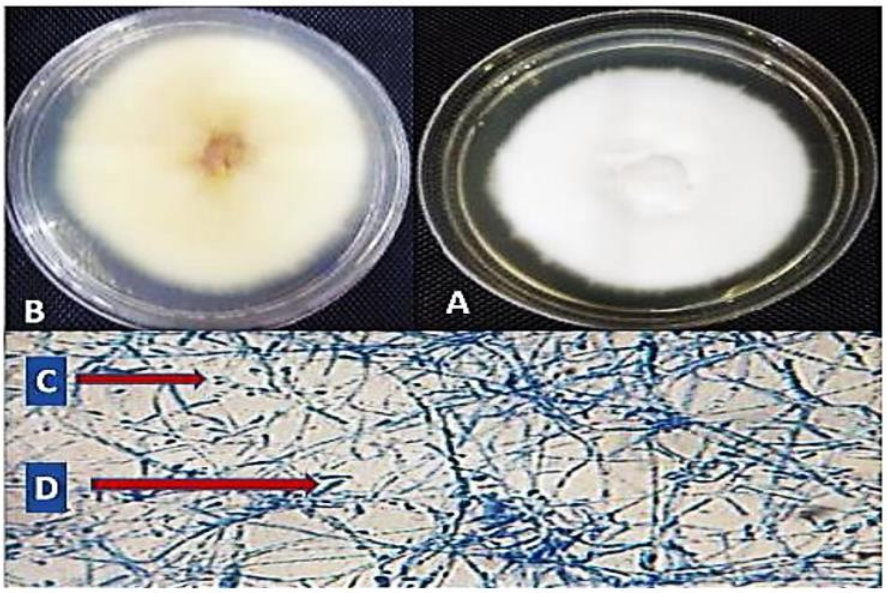

Figure 2. Phenotypic and microscopic characteristics of the fungus growing on T.rubrum nutrient media after 12 SDA days of incubation at 28 °C

Phenotypic and microscopic characteristics of the fungus growing on T.rubrum nutrient media after 12 SDA days of incubation at 28 °C.

A The upper surface of the colony appears white to milky,

B represents the posterior side of the colony, which appears reddish-brown. Microscopic characteristics of mushrooms after staining their compositions,

C. Small conidia that appear on the fungal hyphae in a round and alternate form on the hyphae,

D. Large conidia, cigar-like, segmented, with a thick, smooth wall (40X light microscopy).

T. mentographyte

Appearance characteristics: the results showed that the growth of fungal colonies was rather rapid, and the color of the growing colonies of this fungus appeared on SDA medium in a white to creamy, yellow or pink color, slightly raised and granular in appearance. The posterior side of the colony is yellowish-brown or red-brown (A and B).

Microscopic characteristics

Micro conidia, numerous, single-celled, round and thin-walled, with a circular shape, appearing in groups in the form of grape clusters or single Macro conidia, so they are club- shaped and contain 3-4 septa with a thick smooth wall, and sometimes spiral threads appear (C and D).

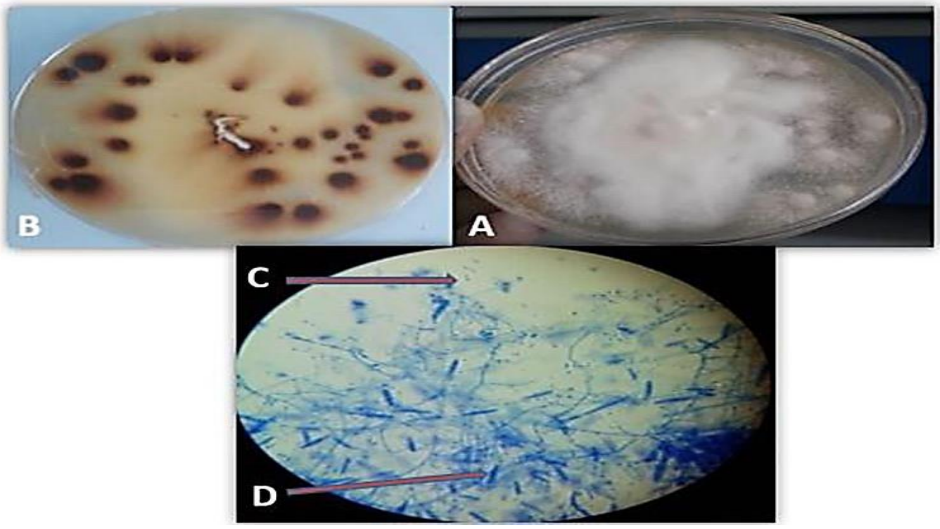

Figure 3. Microscopic phenotypic characteristics of the growth on SDA medium after 12 days of incubation at a temperature of 28 °C

Microscopic phenotypic characteristics of the growth on SDA medium after 12 days of incubation at a temperature of 28 °C. A. represent the upper surface of fungal colonies which appear white to milky. B: The back side of the colonies appears yellowish brown to dark brown. Fungal composition after staining with lacto phenol blue. C1 small conidia that are circular, clustered or sparse, C2 large conidia are sceptical and have thick-walled smooth multicellular (light microscopy imaging x40).

Table 1. Sensitivity of T.rubrum to antibiotics

Antibiotic		Sensitivity		Total
		R%	S%	
Miconazole (Mic)	Count	1	4	5
	within Antibiotic	20.0	80.0	100
	within Sensitivity	7.7	33.3	20.0
	of Total	4.0	16.0	20.0
Ketoconazole (Kt)	Count	1	4	5
	within Antibiotic	20.0	80.0	100
	within Sensitivity	7.7	33.3	20.0
	of Total	4.0	16.0	20.0
Fluconazole (Fle)	Count	5	0	5
	within Antibiotic	100	0.0	100
	within Sensitivity	38.5	0.0	20.0
	of Total	20.0	0.0	20.0
Nystatin (Ns)	Count	1	4	5
	within Antibiotic	20.0	80.0	100
	within Sensitivity	7.7	33.3	20.0
	of Total	4.0	16.0	20.0
Co-Trimoxazole (CoT)	Count	5	0	5
	within Antibiotic	100	0.0	100
	within Sensitivity	38.5	0.0	20.0
	of Total	20.0	0.0	20.0
Total	Count	13	12	25
	within Antibiotic	52.0	48.0	100

	within Sensitivity	100	100	100
	of Total	52.0	48.0	100
Cal.X^2: 15.38	Tab.X^2:13.28	df:4	p:value:0.01	

Table 2. Susceptibility of T. mentographyte to antibiotics

Antibiotic		Sensitivity		Total
		R%	S%	
Miconazole (Mic)	Count	1	9	10
	within Antibiotic	10.0	90.0	100
	within Sensitivity	5.6	28.1	20.0
	of Total	2.0	18.0	20.0
Ketoconazole (Kt)	Count	2	8	10
	within Antibiotic	20.0	80.0	100
	within Sensitivity	11.1	25.0	20.0
	of Total	4.0	16.0	20.0
Fluconazole (Fle)	Count	4	6	10
	within Antibiotic	40.0	60.0	100
	within Sensitivity	22.2	18.8	20.0
	of Total	8.0	12.0	20.0
Nystatine (Ns)	Count	1	9	10
	within Antibiotic	10.0	90.0	100
	within Sensitivity	5.6	28.1	20.0
	of Total	2.0	18.0	20.0
Co-Ttimoxazole (CoT)	Count	10	0	10
	within Antibiotic	100	0.0	100
	within Sensitivity	55.6	0.0	20.0
	of Total	20.0	0.0	20.0
Total	Count	18	32	50
	within Antibiotic	36.0	64.0	100
	within Sensitivity	100	100	100
	of Total	36.0	64.0	100
Cal.X^2:24.82	Tab.X^2:13.28	df:4	p:value:0.01	

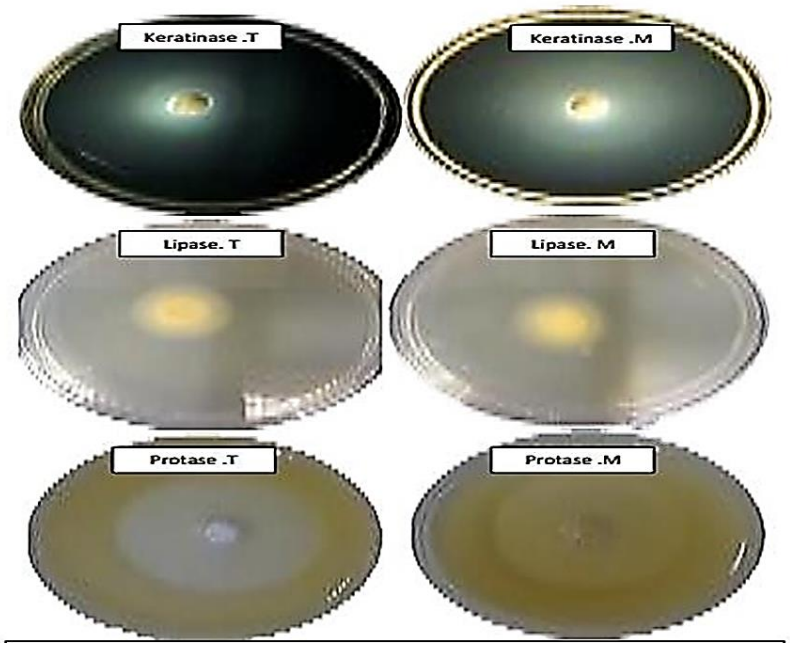

Figure 3. Enzyme production by Trichophyton rubrum and T. mentographyte on suitable culture media for each enzyme at a temperature of 26 °C and 9 days old.

1. Keratinase T = Keratinase production from the fungus Trichophyton rubrum on the medium of the keratin agar
2. Keratinase .M = Keratinase production from T. mentographyte on Keratin Agar Medium. Lipase T= Lipase production from Trichophyton rubrum on Tween 80 Agar medium Lipase. M = Lipase production from T. mentographyte on Tween 80 agar medium
3. Protease. T= production from Trichophyton rubrum on milk skim agar medium Skimmed - milk agar
4. Protease. M= Protease production from the fungus T. mentographyte on the medium of milk skim agar

4. Discussion

The Effectiveness of Antibiotics Against T. rubrum

The susceptibility of T. rubrum to antibiotics The findings presented in Table (1) indicate that T. rubrum. The organism demonstrated resistance to all antibiotics with the exception of Co-trimoxazole, which exhibited a resistance rate of 100 . In contrast, Miconazole and Nystatin showed the highest sensitivity, achieving a rate of 90 , thereby ranking first. Ketoconazole followed in second place with an inhibition rate of 80 , while Fluconazole ranked third with a 60 inhibition rate. The sensitivity of T. rubrum was assessed in this study using the tablet diffusion method, and the results were analyzed in accordance with the criteria established in [15]. In the statistical analysis, no significant differences were observed in the inhibition rates among the four antibiotics Mic, t, Ns, and FLC.

However, significant differences emerged when comparing these four antibiotics with the CoT antibody [16]. The current study aligns with Alhamdani [16], indicating that T. rubrum exhibited sensitivity to the antibiotics Ns and Kt. Additionally, there is concordance with the findings presented by Rudramurthy et al. [17]. Mohamad et al. indicate that all isolates of T. rubrum. Oral isolates exhibited sensitivity to anti-Ns, while demonstrating significant resistance to anti-Kt. The findings of the current study align with

those presented by Alhamdani [16]. It was noted that the sensitivity percentages to the antibiotics Mic and Ns were elevated, while the resistance percentage to the antibiotic CoT in T. rubrum was also significant [18].

Sensitivity of T. mentographyte to Antibiotics

Table (2) demonstrated the presence of T. mentographyte. The organism exhibited sensitivity to antibiotics Mic, Kt, and Ns, while demonstrating complete resistance to antibiotics FLC and CoT, with a resistance rate of 100 , and a susceptibility rate of 80 . Statistical analysis reveals that there are no significant differences in the inhibition rates among the three antibiotics Mic, Kt, and Ns. The current study reveals no differences between the antibiotics FLc and CoT. However, significant differences were identified when comparing the three antibiotics Mic, t, and Ns with the antibodies FLC and CoT.

The results align with [19], which concluded that the Ns antibiotic was among the most effective in inhibiting the growth of 83 isolates from four types of Candida spp., including T. rubrum and Cruise. This was followed by the Kt antibiotic, while the two CoT antigens and FLC demonstrated limited sensitivity against T. mentographyte. Ketoconazole exhibits a broad-spectrum antifungal activity characterized by its fungicidal properties. The mechanism involves the inhibition of the enzyme Cytochrome P450 dependent C-14Xdemethylase (cyp), which plays a crucial role in the conversion of Lanosterol to Ergosterol. Ergosterol is essential for the integrity of the fungal plasma membrane, and its disruption leads to a compromised cell membrane structure [20].

The sensitivity of fungi to synthetic antifungals is influenced by various factors, including type, strain, isolation, growth phase, antibody type and quantity, culture medium components, temperature, incubation duration, and pH levels. The formation of high resistance in certain fungal isolates to various antibiotics may result from the frequent application of these antibiotics, along with the evolution of resistance mechanisms exhibited by these isolates against the majority of administered antibiotics [21]. The present study shown that the antibiotic Ns is among the most efficacious against Candida, likely due to its mechanism of inhibiting the synthesis of Ergosterol, a crucial component in the formation of the cell membrane of T. mentagrophytes [22]. While it contradicted, which demonstrated that all examined isolates exhibited resistance to anti-Ns, the discrepancy may be ascribed to the antigen producers, the concentration employed, and the methodology utilized. In addition to the sample size and location of collection.

Lipase Keratinase

The two fungi exhibited enzymatic activity, specifically Lipase and Keratinase. Trichophyton rubrum and T. mentagrophytes shown susceptibility to pathogenic pathogenicity by producing three enzymes, specifically protease, in growth medium optimized for each enzyme. The quantity of enzyme generated is directly proportional to the average diameter of the areola (mm) around the colony for both fungi concerning the enzymes Keratinase and Lipase, or manifests as a white precipitate around the colony in the case of the protease enzyme. Figure 3 illustrates a triple interaction among the fungus type, enzyme type, and incubation length, as indicated by the diameter of the halo or the white precipitate surrounding the colony. Which totaled 55.67mm, greatly differing from the same The enzyme generated by the Microsporum mushroom, after an incubation period of 9 days, exhibited a significant level below 0.05-0.01.

In contrast, the keratinase enzyme produced by the Microsporum mushroom on the ninth day of incubation demonstrated a superior production rate, averaging 38.67 mm, and showed a significant difference compared to the same enzyme produced by the Trichophyton fungus under identical incubation conditions. T. mentographyte exhibits susceptibility to pathogenic pathogenicity by the synthesis of three enzymes, specifically protease, in growth medium optimized for each enzyme. The quantity of enzyme generated correlates with the average width of the areola (mm) surrounding the colony for both fungus concerning the enzymes Keratinase and Lipase, or manifests as a white precipitate around the colony in the case of the Protease enzyme. Figure 2 illustrates a

triple interaction among the kind of fungus, the type of enzyme, and the time of incubation, as indicated by the diameter of the halo or the white precipitate surrounding the colony. Which totaled 55.67 mm, greatly differing from the same The enzyme generated by the Microsporum mushroom, after an incubation period of 9 days, exhibited a significant level between 0.05 and 0.01. Conversely, the keratinase enzyme produced by the Microsporum mushroom on the ninth day of incubation demonstrated a superior production rate, averaging 38.67 mm, which was significantly different from the same enzyme produced under identical conditions by the Trichophyton fungus.

M. canis mycologist. Its capacity to generate enzymes that cause skin infections enables it to circumvent the host's defense mechanisms and fulfill its nutritional requirements [23]. A study revealed that T. mentographyte secretes proteolytic enzymes (exoantigens), including elastase. Keratinase, catalase, and aminopeptidases. Keratinase is the primary virulence factor of dermatophytes and facilitates the invasion of host tissues by keratinocytes. 30 Numerous studies have detailed the substantial enzyme production by dermatophytes and the hydrolytic activity of these enzymes on various substrates. These enzymes, particularly keratinase, were regarded as virulence agents and hence linked to the clinical manifestation of dermatophytes. Evidence indicates that certain enzymes generated by dermatophytes exhibit hydrolytic activity towards keratin.

According to Lund and Deboer, the results depicted in Figure 3 demonstrate that the optimal incubation period for protease production in the fungus Microsporum canis is the third period, lasting 9 days. The findings align with those of Silva et al. [24], indicating that day 9 is optimal for enzyme synthesis. childcare facility The results obtained were similar to those reported by Farahmand et al, which indicated that maximum protease synthesis by T. rubrum occurred after 8 days of incubation at 30 °C. Conversely, our study's results concurred with those of Sitarek et al. [25], which indicated that the peak length of protease synthesis occurs after 9 days. Furthermore, their findings aligned with those of García-Madrid et al [26]. The optimal incubation duration for enzyme synthesis was determined to be 9 days.

5. Conclusion

Trichophyton rubrum is less sensitive than T.mentographyte most transactions. The fungus Trichophyton rubrum is more resistant than other fungi. This is attributed to the cause of higher infections among the Trichophyton worms. The ability of Trichophyton fungi to produce kinase, protease and lipase enzymes

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