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EVALUATION AND FORMULATION OF ANTIFUNGAL ACTIVITY OF DRAGON BLOOD EXTRACT AND INORGANIC SALTS ON DERMATOPHYTOSIS AND CANDIDIASIS

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ABSTRACT

Introduction: Fungal infections, particularly dermatophytosis and candidiasis, pose significant challenges, especially in tropical and subtropical regions. Aim: This study aimed to assess the antifungal activity of Dragon's blood extract and inorganic salts and develop an effective and affordable pharmaceutical formulation for treating these infections. **Methods:** A study at the National Center of Public Health Laboratories in Sana'a from December 2021 to May 2022 collected clinical samples aseptically. It identified dermatophytes and C. albicans through KOH microscopic examination and culture on SDA. Antifungal susceptibility testing of Dragon blood extract, inorganic salts solutions, and formulation cream showed strong activity against Candida albicans and dermatophyte strains. Positive controls (Miconazole, Ketoconazole, Fluconazole, and Nystatin) also exhibited significant antifungal activity. **Results:** The Dragon blood extract and inorganic salts showed significant antifungal activity at different concentrations against M. audouinii, M. canis, T. violaceum and C. albicans with inhibition zone ranging from 14mm to >30mm. An oil in water (O/W) emulsion based cream was formulated. These results suggest the potential of Dragon's blood extract and inorganic salts as effective antifungal agents for dermatophytosis and candidiasis. Previous research has also highlighted the antimicrobial and antioxidant properties of the resin extracts, reaffirming their potential for pharmaceutical applications. **Conclusion:** The study indicates that Dragon's blood extract, inorganic salts, and the formulated cream have strong antifungal activity, making them potential candidates for alternative antifungal agents. The findings support the potential therapeutic and pharmaceutical applications of these natural compounds for combating fungal infections.

KEYWORDS: Evaluation, Formulation, Antifungal Activity, Dragon Blood Extract, Inorganic Salts, Dermatophytosis, Candidiasis.

1. INTRODUCTION

Dermatophytes and Candida spp. are highlighted as the most common pathogens causing such infections, particularly in tropical and subtropical developing countries. The excerpt emphasizes the need for newer antifungal compounds due to the limitations associated with existing drugs, including lack of efficacy, side effects, and resistance.[1] The Dracaena cinnabari is threatened due to the collection of its resin, known as Damm Al-akhwain in Yemen. Dragon's blood is a deep red resin, which has been used as a famous traditional medicine since ancient times by many cultures. Dragon's blood has been used for its medicinal properties by various cultures throughout history.[2,3] Previous research has highlighted the antimicrobial properties of the resin extracts from D. cinnabari showed greater susceptibility of human pathogenic fungi compared to bacterial strains, the antifungal activities of D. cinnabari resin against different species, including Candida albicans, Aspergillus flavus, and A. nige[4-7] Fungal disease suppression by inorganic salts, simple inorganic salts, offer an effective, safe, and affordable solution. such as zinc sulfate, used in treatment of Tinea Corporis.[8,9] Furthermore, sulfur-based compounds known as sulfites are extensively utilized in industries such as cosmetics, pharmaceuticals, and food, like sodium sulfite, sodium bisulfite, and sodium metabisulfite are commonly employed in the treatment of tinea versicolor,. Additionally, Aluminum sulfate (alum) is sometimes called alum has shown promising antimicrobial effects against various skin diseases and fungal infections.[10-13] Aim: The aim of this study was to investigate the antifungal activity of Dragon blood extract and inorganic salts and develop a new, affordable, effective, and safe pharmaceutical formulation for the treatment of candidiasis caused by Candida albicans and

dermatophytosis (tinea) caused by Microsporum audouinii, Microsporum canis, and Trichophyton violaceum.

2. MATERIAL AND METHOD

2.1. Collection of plants

The *Dracaena cinnabari* plant was collected in its natural habitat on Soqotra Island. The botanical name of this endemic wild tree is *Dracaena cinnabari* Balf. f. (Dracaenaceae). The English common name for both the tree and its resin is dragon's blood. The Arabic name "Dam Alakhwin" means "Brother's blood" and is also used for both the tree and its resin. The Soqotri resin (dragon's blood = Dam Alakhwin) is a high-quality, pure red blood resin that is known on the island as "Emzoloh." It is collected from the incision of the young stem bark of the female tree. This standard pure resin can be described as an authentic superior Soqotri resin.[14]

The resin of *D. cinnabari* was collected from a young fresh stem female tree on Soqatra Island, Yemen. Dragon's blood resin was purchased from a wholesale supplier of traditional Unani medicine in March 2022. The plant samples were identified and authenticated by the Environmental Protection Authority of Yemen and have been deposited at the herbarium of the Department of Pharmacognosy, Faculty of Pharmacy, Sana'a University, Yemen.

2.2. Preparation of Dracaena cinnabari resin methanol extract

The powdered resin of *D. cinnabari* (50g) was extracted with methanol in a 1:10 ratio. The mixture was shaken at room temperature for 3 days, then sonicated at 45°C for 30 minutes to enhance the extraction. The methanol was then separated from the extract using a rotary evaporator under reduced pressure at 40°C, resulting in a gummy red resin extract.[14,15]

2.3 Collection of specimens

For dermatophytes specimens: the suspected lesions were cleaned with 70% ethyl alcohol to remove any dirt and contaminating bacteria. Skin scales and crusts were collected from the erythematous, peripheral, actively growing margins of the lesions by scraping across the inflamed margin of the lesion into the apparently healthy tissue using the blunt edge of a sterile surgical blade onto sterile dry Petri dishes. The samples were divided into two parts: one for microscopic examination and one for culture.[16]

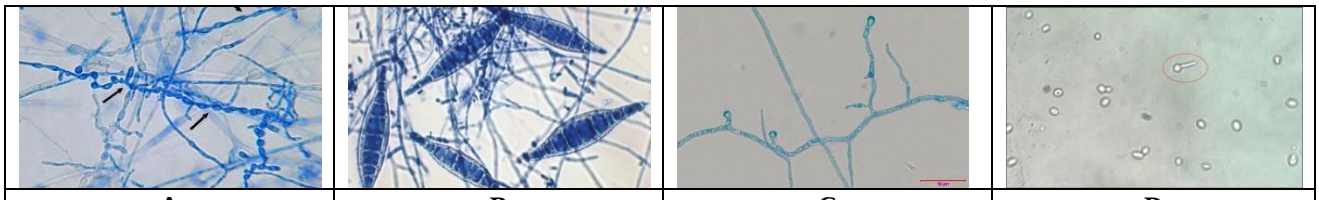
For candida specimen: oral swabs were collected by swabbing the dorsum of the tongue with the help of a dry sterile cotton stick. Swab cultures were immediately inoculated on Sabouraud dextrose agar.[17]

2.4: Methods for identification of dermatophytes and C. albicans

There are different methods used for identification of dermatophytes and C. albicans includes the microscopically method, macroscopically method (culture method), and PCR methods …etc. Two methods used in this study explained below.

2.4.1 Microscopic examination

After specimen's collection it was divided into two parts. The first part of the scales was examined directly unstained under microscope. One drop of 10% potassium hydroxide solution was taken and put on a sterile glass slide then small piece of sample was smear and the slide was covered. The slide was examines either directly under the microscope or after gentle heating for better fixation according to a method reported by Berman (2006). The result was recorded and a photograph was taken in figure (1).



A	B	C	D

Figure 1: Microscopic morphology of dermatophytes and C. albicans: (A) *M. Audouinii,* (B) *M. Canis,* (C) *T. Violaceum* and (D) *C. albicans.*

2.4.2 Macroscopic examination (Culture method)

The second part of the scale and a swab of a lesions site which was collected from the patients as previously mentioned was cultured in a media. The medium which was used for the culture of dermatophytes and C. albicans is Sabouraud dextrose agar.

The medium was prepared by weighing 66g of the Sabouraud dextrose agar and dissolved in 1000 ml of distilled water then sterilized by steam sterilization using autoclave at 121˚C for 15 min, shows cultural and microscopic characteristics of dermatophytes and C. albicans in figure (2).[18,19]

A	B	C	D

Figure 2: Macroscopic morphology of dermatophytes and C. albicans: (A) *M. Audouinii,* (B) *M. Canis,* (C) *T. Violaceum* and (D) *C. albicans.*

2.5. Antifungal Activity and Minimal Inhibitory Concentration Evaluation

Agar well diffusion method was carried out for the assessment of the Dracaena cinnabari extract and inorganic salts study. One hundred microliters of inoculums (10^6 CFU/ml; 0.5 McFarland) of each test fungi evenly was spread using a sterile swab spreader onto Sabouraud dextrose agar plates. The plates have been kept to dry and a sterile tip (8 mm in diameter) was then used to punch wells in the agar medium. Subsequently, wells were filled with 100µl of the Dracaena cinnabari extract and inorganic salts solution at concentration of 100-5mg/ml and allowed to diffuse at room temperature for 2h. The plates were incubated at 25-30°C from 2 days to 2 weeks. The minimum inhibitory concentration (MIC) is regarded as the lowest concentration of the Dracaena cinnabari extract and inorganic salts that inhibit the growth of the test organisms. Sterile distilled water used as negative control. Fluconazole 25µg, ketoconazole 10µg, miconazole 50µg, and nystatin 50µg disks were used in the assay as positive control. The antifungal activity was evaluated to determine the inhibition zone. The inhibition zone of Dracaena cinnabari extract and inorganic salts solutions against tested fungi showed in tables.[20,21]

2.6. Preparation of Cream Formulation

An oil in water (o/w) emulsion-based cream was formulated. The ingredients of oil phase (stearic acid, cetyl alcohol and paraffin) were mixed together by melting at 70 °C on a water bath with constant stirring. The components of the aqueous phase (glycerine, Tween 20, water, sodium benzoate and the therapeutically active 1% of Dracaena cinnabari extract and inorganic salts; Zinc sulfate, Dracaena cinnabari extract, Sodium thiosulfate, Sodium metabisulfate) were dissolved together in a beaker and heated about the same temperature as of the oil phase (70 °C) on a water bath. The aqueous phase was added to the oil phase drop by drop with continuous stirring using an emulsifier until formation of cream. Four formulations were prepared using substances shown in Table 1.

Table 1: Pharmaceutical Ingredients Used for Cream Preparation.

	Ingredients	**F1 % w/w**
Oily phase	**Steric acid**	10
	Cetyl alcohol	5
	Liquid Paraffin	10
Water phase	**Dracaena cinnabari extract and inorganic salts (**Zinc sulfate**,** Aluminum sulfate (alum), Sodium thiosulfate, Sodium metabisulfate	4
	Glycerine	10
	Carbabol	0.5
	Tween 20	2
	Methylparaben	0.02
	Water	Up to 100

2.6.1 Evaluation of antifungal Cream[22-23]

Evaluation Parameters for Anti-fungal Cream Viscosity: The viscosity of the anti-fungal cream was determined using a Brookfield viscometer at 100 rpm with spindle number 7.

Determination of Type of Emulsion (Dye Method): A scarlet red dye was mixed with the cream. A drop of the cream was placed on a microscope slide and examined under a microscope. If the dispersed globules appear red and the continuous phase is colorless, the cream is classified as a water-in-oil (w/o) type. Conversely, if the dispersed globules appear colorless and the continuous phase is red, the cream is classified as an oil-in-water (o/w) type.

pH of the Cream: The pH of the cream was measured using a pH meter. Firstly, the pH meter was calibrated using a standard buffer solution. Then, 0.5 g of the cream was weighed and dissolved in 50 mL of distilled water. The pH of the resulting solution was then measured.

Homogeneity: The homogeneity of the cream was assessed through visual inspection and tactile examination by touch.

Appearance: The appearance of the cream was assessed based on its color, pearlescence, and roughness.

After-Feel: The cream was evaluated for its emolliency, slipperiness, and the amount of residue left on the skin after application.

Type of Smear: The type of film or smear formed on the skin after the cream was applied was assessed.

Removal: The ease of removal of the cream after application was examined by washing the applied area with tap water.

Table 2: Physiochemical Evaluation of Formulated Cream.

Parameter	Formulation
Homogenity	**Good**
Appearance	**No change in color**
Odour	**Good**
Color	**yellow**
Feel	**Smooth**
Type of smear	**Emollient**
Spreadability	**Non greasy**
Removal	**Easy**
Stability	**one month**

Table 7: Data for Stability Studies of Cream Formulation.

Storage condition	Time period	pH	Appearance	Color	Odour
4^0C	0 day	3.5	No change in color	yellow	Good
	1st Week	3.4	No change in color	yellow	Good
	2nd Week	3.4	No change in color	yellow	Good
	3rd Week	3.4	No change in color	yellow	Good
	4th Week	3.4	No change in color	yellow	Good
40°C	0 day	3.5	No change in color	yellow	Good
	1st Week	3.4	No change in color	yellow	Good
	2nd Week	3.4	No change in color	yellow	Good
	3rd Week	3.3	No change in color	yellow	Good
	4th Week	3.2	No change in color	yellow	Good

2.7. Antioxidant assay iodometrictitration[24]

Transfer about 1 gm of cream, accurately weighed, to a glass-stoppered conical flask. Add a mixture of 5 mL of water and 0.3 mL of hydrochloric acid, and swirl to dissolve. Add 0.17 g of potassium iodide in 2ml water, insert the stopper into the flask, and allow to stand in the dark for 30 minutes. Then add 2 mL of water, and titrate the liberated iodine with 0.1 M sodium thiosulfate VS, adding starch TS as the endpoint. The solution become pale yellow colour is approached**.**

3. RESULTS

3.1 Antifungal activity of Dracaena cinnabari extract and inorganic salts against *Microsporum audouinii.*

Table 2: Zone of inhibition and MIC of Cream formula, Dracaena cinnabari extract and inorganic salts against *Microsporum audouinii.*

Name	Zone of inhibition (mm) concentration (mg/ml)				MIC (µg/ml)
	100	50	25	5	
Cream formula	>30	>30	28	26	500
Zinc sulfate	>30	>30	22	0	500
Dracaena cinnabari extract	>30	24	0	0	5000
Sodium Thiosulfate	30	20	0	0	5000
Sodium metabisulfite	>30	16	0	0	5000
Ammonium ferric sulfate	19	0	0	0	10000
Ferrous ammonium sulfate	0	0	0	0	-

Table (2) and figure (3) show the inhibition zone and MIC of Cream formula, Dracaena cinnabari extract and inorganic salts solutions against *Microsporum audouinii.* The Cream formula exhibited the strongest activity against *Microsporum audouinii* with MIC values 500-10000µg/ml and inhibition zone of 26 to >30mm. The

Zinc sulfate also exhibited strong activity against *Microsporum audouinii* with MIC values 5000µg/ml and inhibition zone of 22 to >30mm. The Ferrous ammonium sulfate salts have less antifungal activity. The Ammonium ferric sulfate show only activity in the concentration of 10000µg/ml with an inhibition zone of 19mm. Ferrous ammonium sulfate salts did not show any activity against *Microsporum audouinii.*

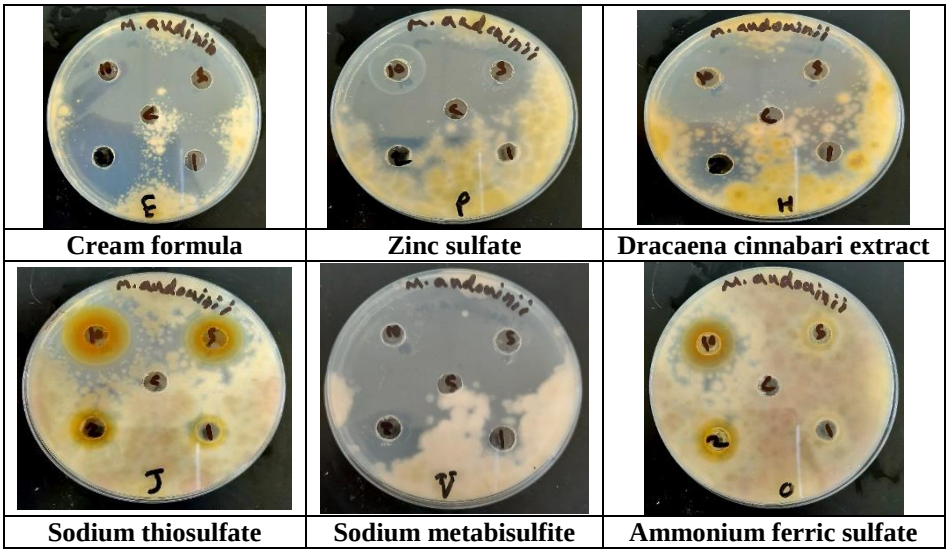


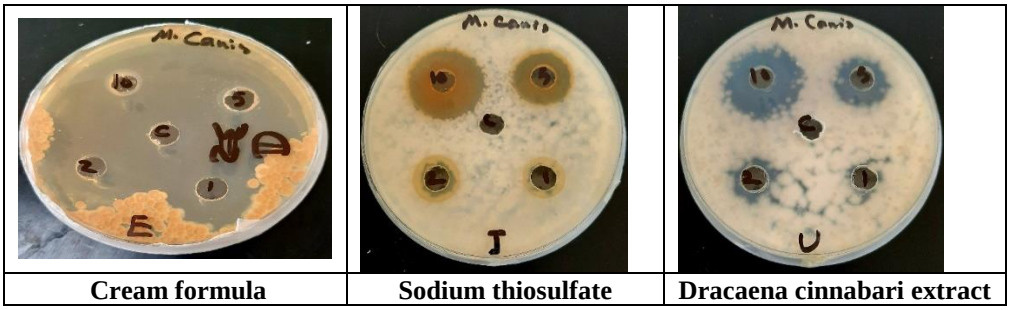
Figure 3: Zone of inhibition of Cream formula Dracaena cinnabari extract and inorganic salts against *Microsporum audouinii.*

3.2 Antifungal activity of Cream formula Dracaena cinnabari extract and inorganic salts against *Microsporum canis*

Table 3: Zone of inhibition and MIC of Dracaena cinnabari extract and inorganic salts against *Microsporum canis.*

Name	Zone of inhibition (mm) concentration (mg/ml)				MIC (µg/ml)
	100	50	25	5	
Cream formula	>30	>30	>30	25	500
Sodium thiosulfate	25	20	15	0	2500
Dracaena cinnabari extract	29	23	0	0	5000
Aluminum sulfate (alum)	28	20	0	0	5000
Ammonium ferric sulfate	19	16	0	0	5000
Ferrous ammonium sulfate	0	0	0	0	-
Sodium metabisulfite	0	0	0	0	-
Zinc sulfate	0	0	0	0	-

Table (3) and fifure (4) showthe inhibition zone and MIC of cream formula Dracaena cinnabari extract and inorganic salts solutions against *Microsporum canis.* The cream formula exhibited the strongest activity against *Microsporum canis* with MIC values 500-10000µg/ml and inhibition zone of 25 to >30mm. The Ferrous ammonium sulfate, Sodium metabisulfite salts and Zinc sulfate did not show any activity against *Microsporum canis.*



Aluminum sulfate (alum)	Ammonium ferric sulfate	Ferrous ammonium sulfate

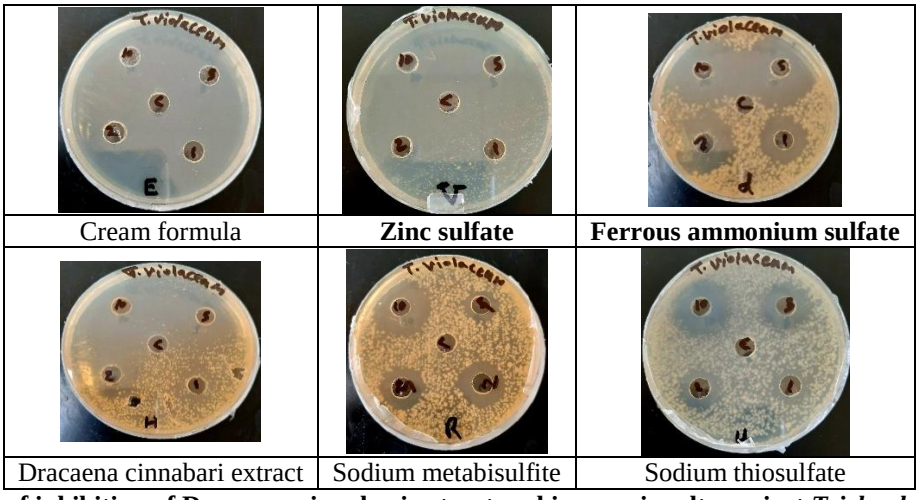
Figure 4: Zone of inhibition of cream formula, Dracaena cinnabari extract and inorganic salts against *Microsporum canis.*

3.3 Antifungal activity of cream formula Dracaena cinnabari extract and inorganic salts against *Trichophyton violaceum*

Table 4: Zone of inhibition and MIC of cream formula Dracaena cinnabari extract and inorganic salts against *Trichophyton violaceum.*

Name	Zone of inhibition (mm) concentration (mg/ml)				MIC (µg/ml)
	100	50	25	5	
Cream formula	>30	>30	>30	>30	500
Zinc sulfate	>30	>30	>30	>30	500
Ferrous ammonium sulfate	>30	>30	23	20	500
Dracaena cinnabari extract	30	25	0	0	5000
Sodium metabisulfite	22	16	14	0	2500
Sodium thiosulfate	>30	0	0	0	10000
Ammonium ferric sulfate	28	16	0	0	5000
Aluminum sulfate (alum)	0	0	0	0	-

Table (4) and figure (5) show the inhibition zone and MIC of Dracaena cinnabari extract and inorganic salts solutions against *Trichophyton violaceum.* cream, zinc sulfate and Dracaena cinnabari extract exhibited the strongest activity against *Trichophyton violaceum* with MIC values 500-10000µg/ml and inhibition zone of >30mm. The Ammonium ferric sulfate with MIC values of 5000 µg/ml and inhibition zone of 16. The Aluminum sulfate (alum) show resistance against *Trichophyton violaceum.*



Cream formula	Zinc sulfate	Ferrous ammonium sulfate
Dracaena cinnabari extract	Sodium metabisulfite	Sodium thiosulfate

Figure 5: Zone of inhibition of Dracaena cinnabari extract and inorganic salts against *Trichophyton violaceum.*

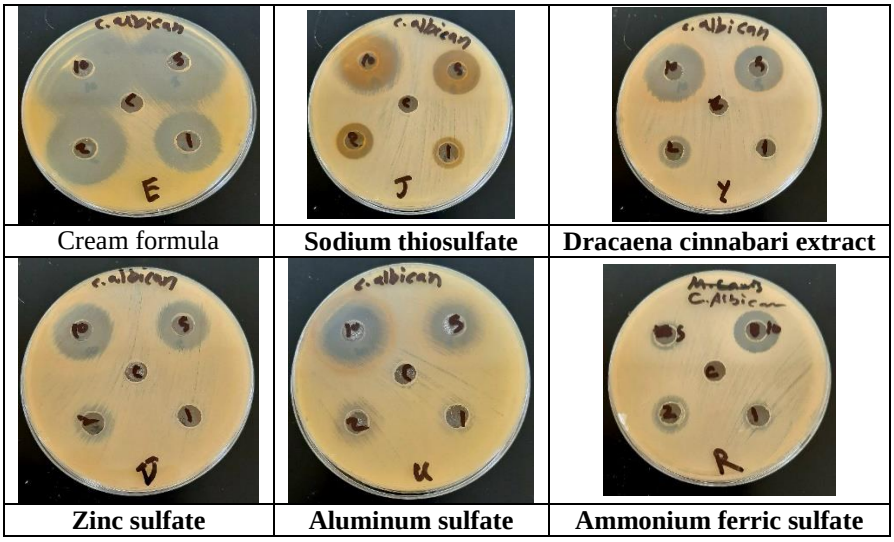
3.4 Antifungal activity of Dracaena cinnabari extract and inorganic salts against *Candida albicans*

Table 5: Zone of inhibition and MIC of Dracaena cinnabari extract and Dracaena cinnabari extract and inorganic salts against *Candida albicans.*

Name	Zone of inhibition (mm) concentration (mg/ml)				MIC (µg/ml)
	100	50	25	5	
Cream formula	>30	>30	28	25	500
Sodium thiosulfate	25	20	15	0	5000
Dracaena cinnabari extract	26	20	0	0	5000
Zinc sulfate	24	18	0	0	5000

Aluminum sulfate (alum)	21	15	0	0	5000
Ammonium ferric sulfate	0	0	0	0	-
Ferrous ammonium sulfate	0	0	0	0	-
Sodium metabisulfite	0	0	0	0	-

Table (5) and figure (6) show the inhibition zone and MIC of Dracaena cinnabari extract and inorganic salts solutions against *Candida albicans.* The cream formula exhibited the strongest activity against *Candida albicans* with MIC values 500-10000µg/ml and inhibition zone of 25 to >30mm. The Dracaena cinnabari extract, Zinc sulfate, Aluminum sulfate (alum) and Sodium thiosulfate also exhibited strong activity against *Candida albicans* with MIC values 2500-10000µg/ml and inhibition zone of 15 to 25mm. The rest of the tested inorganic salts did not show any activity against *Candida albicans.*



Cream formula	**Sodium thiosulfate**	**Dracaena cinnabari extract**
Zinc sulfate	**Aluminum sulfate**	**Ammonium ferric sulfate**

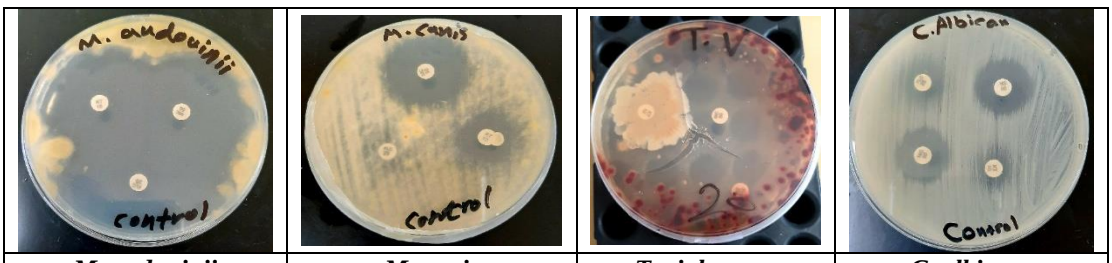
Figure 6: Zone of inhibition of Dracaena cinnabari extract and Dracaena cinnabari extract and inorganic salts against *Candida albicans.*

3.5 Antifungal activity of positive controls against Dermatophytes and C. albicans

Table 6: Antifungal activity of positive controls against Dermatophytes and C. albicans.

Organisms	**Zone of inhibition (mm)**			
	Miconazole 50µg	**Ketoconazole 10µg**	**Fluconazole 25µg**	**Nystatin 50µg**
M. audouinii	>30	>30	>30	-
M. canis	>30	16	0	-
T. violaceum	>30	-	0	-
C. albicans	0	0	0	16

In the current study, the positive controls; Miconazole and Ketoconazole showed antifungal activity against *M. audouinii, M. canis* and *T. violaceum* with inhibition zone of 16 to >30mm. Fluconazole showed antifungal activity only against *M. audouinii* with inhibition zone of >30mm. Nystatin showed antifungal activity only against *C. albicans* with inhibition zone of 16mm (Table 6 and figure 7).



M. audouinii	***M. canis***	***T. violaceum***	***C. albicans***

Figure 7: Antifungal activity of positive controls against Dermatophytes and C. albicans.

3.6 Stability Studies of Cream Formulation: The dye test demonstrated that all the formulations were oil-in-water (o/w) emulsion creams. The pH of the formulated cream was found to be between 3.2 and 3.5, which is a

good and recommended pH for the skin. The formulated antifungal creams were evaluated using several physicochemical tests, and the results are shown in Table 7. The type of smear that formed on the skin after application of all formulated creams was not greasy. The formulated creams could be easily removed by washing with water. All formulations produced a uniform distribution of extracts in the cream, as confirmed by visual inspection and tactile examination. When the formulation was stored for an extended period of time, no color changes were observed in the cream. The feel test showed that the formulated creams were emollient and slippery.

4. DISCUSSION

The results of this study indicate that both the Cream formula has strong antifungal activity against various fungal strains, including Microsporum audouinii, Microsporum canis, Trichophyton violaceum, and Candida albicans. The MIC values indicate that they effectively inhibit the growth of these fungi. The inhibition zones further demonstrate their potency as antifungal agents. Among the inorganic salts tested, Zinc sulfate showed strong activity against Microsporum audouinii, while Ferrous ammonium sulfate salts showed less activity. None of the tested salts showed activity against Microsporum canis. When it comes to Trichophyton violaceum, the Cream formula, Zinc sulfate, and Dracaena cinnabari extract showed the strongest activity. However, Ammonium ferric sulfate exhibited activity only at a high concentration. The complexation of flavonoids with iron can enhance their antioxidant properties, making them more effective at neutralizing free radicals and protecting our cells from oxidative damage. Aluminum sulfate showed resistance against Trichophyton violaceum. For Candida albicans, the Cream formula showed the strongest activity, while Dracaena cinnabari extract, Zinc sulfate, Aluminum sulfate (alum), and Sodium thiosulfate also exhibited strong activity. The other tested inorganic salts did not show any activity against Candida albicans. Positive controls Miconazole and Ketoconazole consistently showed antifungal activity against M. audouinii, M. canis, and T. violaceum. Fluconazole showed activity only against M. audouinii, while Nystatin showed activity only against C. albicans. Overall, the findings suggest that both the Cream formula has potential as effective antifungal agents. Previous studies have shown that resin extracts have strong antioxidant effects, which could be used in tooth whitening products.[25] The previous research has emphasized the antimicrobial characteristics of the resin extracts from D. cinnabari, demonstrating a higher susceptibility of human pathogenic fungi in comparison to bacterial strains. Specifically, the antifungal activities of D. cinnabari resin have been studied against various species, such as Candida albicans, Aspergillus flavus, and A. niger. These findings underscore the potential of D. cinnabari resin as a source of natural antifungal compounds with implications for therapeutic and pharmaceutical applications.[4-7] Mohamed Al-Fatimi's research showed The methanolic solution exhibited potent antifungal, antioxidant, and cytotoxic properties, validating its traditional medicinal uses.[14] Pona, Adrian, et al. research showed C. lechleri's extracts, particularly C. urucurana, exhibited significant antifungal activity against dermatophytes. Additionally, has antiviral properties, originally observed against cytomegalovirus, indicate its potential for diverse therapeutic applications beyond antifungal effects.[26] These findings suggest C. lechleri as a promising source of natural compounds for pharmaceutical and medicinal use. The optimized formulated cream was evaluated for stability over a period of one month. The pH of the formulation were measured. The results are shown in Table 7. The results showed that the formulation was stable under both accelerated stability conditions and refrigerated conditions (8°C). The pH of the formulation remained within the acceptable range of 3.2-3.5 throughout the study period, all physicochemical parameters were maintained. The results of the accelerated stability test showed that there were no significant changes in the color of the cream.

5. CONCLUSION

The Cream formula and Dracaena cinnabari extract demonstrated strong antifungal activity against various fungal strains. These findings suggest that they could be potentially used as alternative antifungal agents.

6. ACKNOWLEDGEMENTS

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7. Conflicts of Interest The authors declare that there are no conflicts of interest regarding the publication of this paper.

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