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SYNERGISTIC NAIL LACQUER FORMULATION OF CISSUS QUADRANGULARIS AND ITRACONAZOLE FOR ENHANCED ONYCHOMYCOSIS MANAGEMENT

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ABSTRACT

Objective: This study aimed to create an aesthetic nail lacquer containing a natural antifungal agent from the Cissus quadrangularis plant with itraconazole to treat fungal nail infections (onychomycosis). **Methodology**: The researchers extracted antifungal compounds from the Cissus quadrangularis plant and evaluated their effectiveness against Candida albicans, a common fungus causing onychomycosis. We formulated a nail lacquer using this extract in combination with antifungal agent itraconazole. **Results**: The study found that the Cissus quadrangularis extract exhibited enhanced antifungal activity with itraconazole. The formulated nail lacquer demonstrated excellent physical properties, including aesthetically pleasing color, glossiness and faster drying time. Moreover, the nail polish showed high permeability through goat nail, indicating its potential effectiveness in treating onychomycosis. **Conclusion**: This study suggests that a nail lacquer containing Cissus quadrangularis extract with itraconazole could be a promising alternative for treating onychomycosis, offering a potentially safer and more effective solution than existing treatments.

KEYWORDS: Nail Lacquer, Cissus quadragularis Extract, Itraconazole, Onychomycosis, Candida Albicans.

INTRODUCTION

Onychomycosis is a contagious fungal infection affecting approximately 19% of the global population, primarily targeting diabetic and elderly individuals. The infection causes thickening, discoloration, and brittleness of fingernails and toenails, leading to pain, irritation, and surrounding skin tissue erosion.

Various formulations, including solutions, creams, gels, and nail patches, are available to treat onychomycosis. However, these treatments often face challenges in penetrating the nail plate, making it difficult to effectively target the infection. Penetration enhancers, such as keratolytic agents, are used to improve the delivery of antifungal medications.

Cissus quadrangularis, a plant belonging to the ***Vitaceae*** family, has been traditionally used for its antimicrobial and analgesic properties. The plant contains high amounts of vitamin C, carotenes, and anabolic steroid substances, make it a promising natural antifungal agent.

Itraconazole is a widely used antifungal medication that inhibits fungal growth by targeting the cytochrome enzyme 14α-demethylase. However, itraconazole may have limitations in treating onychomycosis due to its poor penetration through the nail plate.

The aim of this research is to develop an antifungal nail lacquer containing Cissus quadrangularis extract in combination with itraconazole, which can effectively penetrate the nail plate and target the fungal infection. The formulation uses dimethyl sulphoxide (DSMO) as a penetration enhancer to improve the delivery of the antifungal agent.

Onychomycosis may be divided into two types. Distal subungual onychomycosis is the first; it harms the nail plate, nail bed, and hyponychium. Diseased nails become thick and dystrophic, and their color changes from yellowish white to brown.

The market has offered a variety of antifungal medicinal products in forms of lotion, cream, ointment, powder, and solutions. Due to these formulations' poor performance, substantial concentrations of active ingredients must be added for therapy to be successful. An efficient method that can distribute the antifungals deeply into the nail bed is required to get around the drawbacks of traditional formulations. However, research is still in its early stages to produce a formulation for topical application that is both safe and effective in treating onychomycosis.

Regarding the choice of solvents, acetone can serve as a solvent in nail lacquers because it has lower toxicity relative to other organic solvents typically used in nail lacquers and can dissolve different active components found in herbal extracts. It proved effective in utilizing salicylic acid as a permeation enhancer and successfully verified its effectiveness in enhancing absorption through the bovine hoof and human nail.

MATERIALS AND METHODS

Extract of Cissus quadrangularis was procured from M/S shamantak enterprises Sinhgad road Pune. Itraconazole was received as a gift sample by Evonik pvt. ltd.

METHOD

Identification Test of Phytoconstituents

The extract was identified for phytoconstituent test such as steroids, phenols, flavonoids, quinones.

- The steroids test was performed by treating the extract with few drops of concentrated sulphuric acid to get red colour.
- To identify of phenols, extract was treated with 3-4 drops of ferric chloride solutions to get in bluish black colour.
- The flavonoids test was performed by treating extract with few drop of lead acetate to get yellow precipitate.
- For the presence of quinines, extract was treated with concentrated HCl to get yellow precipitate.

Evaluation of Extract

S.R NO.	TESTS	OBSERVETION	STANDARD	REMARKS
	GRADE	G/100	G/100	Pass the test
1	Description(sensory evaluation)	Black	Black	Pass the test
2	Odour & Taste	Aromatic	Aromatic	Pass the test
3	Solubility	Miscible	Miscible	Pass the test
4	% Moisture	1.63 % w/w	1-3 % w/w	Pass the test
5	% Ash content(as per IP)	2.35 % w/w	2-7 % w/w	Pass the test
6	Nature	viscous	Viscous	Pass the test

Design of Experiment

FPRMULATIONS	FACTOR 1 (Itraconazole) gm	FACTOR 2 (C.quadragularis) gm	RESPONSE 1 Antifungal action (mm)	RESPONSE 2 Permeability (%)
F1	0.125	0.37	27.3	95.82
F2	0.05	0.37	22.5	90.3
F3	0.05	0.55	25.2	92.61
F4	0.125	0.55	26.5	93.4

The F1 batch was found to be the most effective batch and hence further evaluations were performed on this optimized batch.

Formulation of Nail Lacquer

Ethyl cellulose was dissolved in a sufficient quantity of ethyl acetate to obtain a clear solution. Separately, polyvinylpyrrolidone (PVP) was dissolved in a mixture of dibutyl phthalate and propylene glycol. The extract and acetone were then added to this mixture under continuous stirring at 100 rpm using a magnetic stirrer.

In a separate step, itraconazole was dissolved in dimethyl sulfoxide (DMSO) with the aid of sonication. A small amount of colorant was added to the formulation. Finally, all prepared solutions were combined and transferred into a suitable container for further use.

Actual Photograph of Nail Lacquer.

Formulation Table (F1).

INGREDIENTS	CATEGORY	QUANTITY (FOR 20ml)
Extract	Antifungal	0.375g
Itraconazole	Antifungal	0.125g

Ethyl Cellulose	Film forming	2g
Ethyl Acetate	Solvent	14ml
Acetone	Solvent	1ml
Dibutyl phthalate	Plasticizer	1ml
PVP	Film forming	1g
DMSO	Solvent	0.5ml
Salicylic Acid	Permeation Enhancer	0.04g
Colour	Aesthetic	0.01g

EVALUATION OF NAIL LACQUER

1. Visual Aspects

The samples were analyzed by visual inspection to observe changes in color, visual precipitate formation and nail-lacquer unevenness. There was no precipitate or unevenness found.

2. Colour

Colour comparing with master colour standards by applying on thumbnails, holding them side by side, moving the thumb with the standard first on the right and then on left.

3. Consistency

The consistency was checked by applying on nail.

4. Hardness

Nail lacquer was applied on surface then checked for hardness of the nail paint by applying the pressure by hand and determine the hardness of nail paint.

5. pH

The pH of 1% of sample solution of the formulation was measured by using calibrated pH meter at constant temperature.

6. Spreadability

Spreadability of nail paint was checked by applying of nail paint on glass slide by the nail paint brush.

7. Drug content

Drug content was determined by dissolving 1 ml of nail lacquer in methanol (10ml). After preparing dilutions the absorbance was recorded by using UV-visible spectrophotometer (1800, Shimadzu, Japan) at 236 and 262 nm.

8. Non-volatile content

Non-volatile content was determined to get the weight of formulation that retained on nail plate after application. Nail lacquer (1g) was taken in a glass petri dish of about 6 cm in diameter. Sample was spread equally using brush. The dish was put in an oven at 105°C for 1 hr, cooled and weighed. The difference in weight of sample before and after drying was the non-volatile content present in the nail lacquer.

9. Lacquer film thickness

One ml of formulation was spread equally with an applicator brush in 6 cm diameter petri dish and was allowed to dry at room temperature. After drying nail lacquer film was isolated from the petri dish. The film thickness was measured at three different places using a micrometer screw gauge and average was calculated.

10. Drying time and gloss

An area of 3 x 3 cm^3 was marked on glass petri dish to which a film of nail lacquer formulation and marketed product was applied with the help of brush. The time taken for the film to dry was noted using a stopwatch. The readings were obtained in triplicate.

Glossiness was determined by visual inspection and measured as follows: good (++), very good (+++) and excellent (++++). It was compared with marketed cosmetic product.

11. Smoothness of flow

Formulations were poured on a glass slide on an area of 1.5 inches. It was spread on a glass plate by making glass slide tilt. Smoothness of flow was determined by comparing with marketed nail lacquer.

12. Water resistance test

This test was performed to measure the resistance of nail lacquer towards water permeability of film. A continuous film was applied on the petri dish, dried and then water was poured it to immerse the film, The weight of petri dish was taken before and after immersion and increase in weight was calculated.

13. Peel adhesion test by texture analysis

A peel adhesion test for formulations was performed by Texture Analyzer (Brookfield Engineering Lab,). Nail lacquer (0.1 g) was applied onto a surface of plate with the help of brush and allowed to dry for 10 min at room temperature. An adhesive tape was applied on it.

The other end of tape was fixed at adapter probe. The strength of adhesion between lacquer film and plate became decided via measuring force required to peel lacquer film off the plate the using adhesive tape. Time and load required for peeling off lacquer is recorded.

14. In vitro transungual permeation study

To study the transungual permeation of Cissus quadrangularis and Itraconazole from nail lacquer into the skin through nail bed, the drug permeation study was performed for 24 hr.

A permeation study was conducted using goat hooves as a substitute for human nails. Nail sections were prepared, mounted on a Franz diffusion cell, and treated with 1 ml of nail lacquer. The setup was maintained at 32 ± 0.5°C with stirring for 24 hours. Samples were collected at intervals, replaced with fresh buffer, and analyzed spectrophotometrically at 236 and 262 nm.

15. Antifungal study of formulations

Antifungal activity test was performed by the commonly used agar diffusion method which is designed to determine the smallest amount of the antibiotic needed to inhibit the growth of microorganisms.

Culture Preapration

A loop of mother culture is inoculated into 15 ml sterile nutrient broth and incubated at 37°C for 24 hours. Sterile swabs are dipped in the test organism suspension and spread evenly over agar plates. After drying, 8 mm wells are punched into potato dextrose agar using a sterile cork borer. Test solutions are added to the wells, and plates are incubated at 28°C for 24–48 hours. Microorganisms used – Candida albicans (NCIM 3100)

Minimum Inhibitory Concentration By Broth Dilution Method

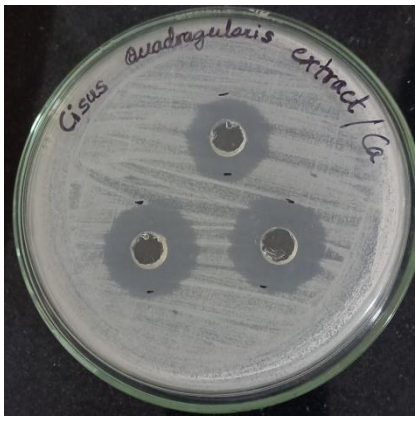
Procedure: In one sterile test tube add 2 ml antibiotic compound to be tested of known concentration. Add 1ml sterile broth to all 6 test tubes(NB for bacteria and PDB for fungus). Add 1ml DMSO in each tubes. Add 500 ul, 250ul, 125ul, 62.5ul, 31.2ul sample respectively in tubes. After that add 50 ul culture in each tubes.Set 1 tube as negative control without adding sample. Incubate at 28^0C for 20 -24 hrs. Note the result. Examine tubes for visible signs of bacterial growth. The highest dilution without growth is the minimal inhibitory conc. Microorganism used – Candida albicans (NCIM 3100)

RESULT AND DISCUSSION

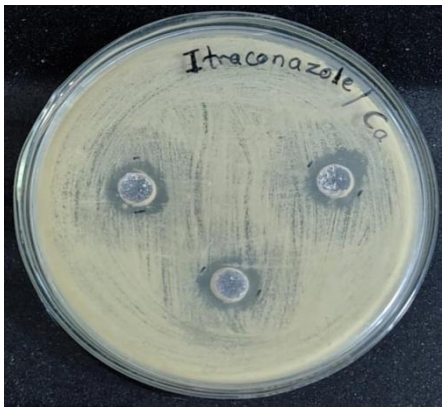
RESULT

SR. NO.	PARAMETERS	RESULTS
1	COLOUR	PURPLE
2	DRYING TIME	70 SEC
3	CONSISTANCY	GOOD
4	FILM THICKNESS (mm)	0.35
5	WATER RESISTANCE (g)	47.19
6	HARDNESS	HARD
7	SPREDABILITY	EASILY SPREADABLE
8	NON-VOLATILE CONTENT	45+/-0.2
9	SMOOTHNESS	SMOOTH
10	pH	6.5

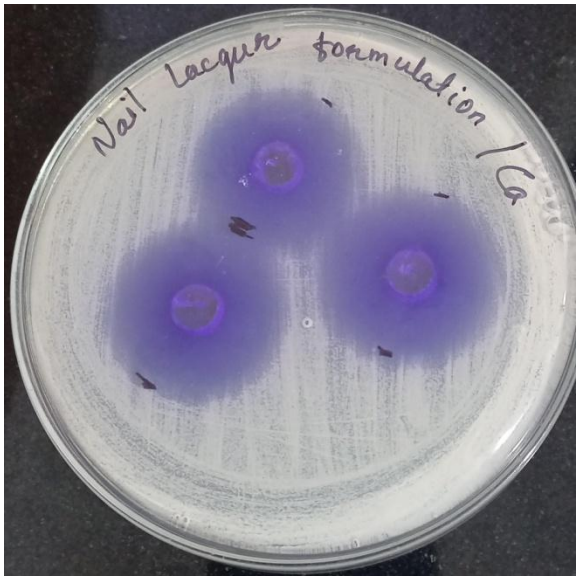
ANTIFUNGAL STUDIES



ZONE OF INHIBITION OF C. Q.



ZONE OF INHIBITION OF ITRACONAZOLE.



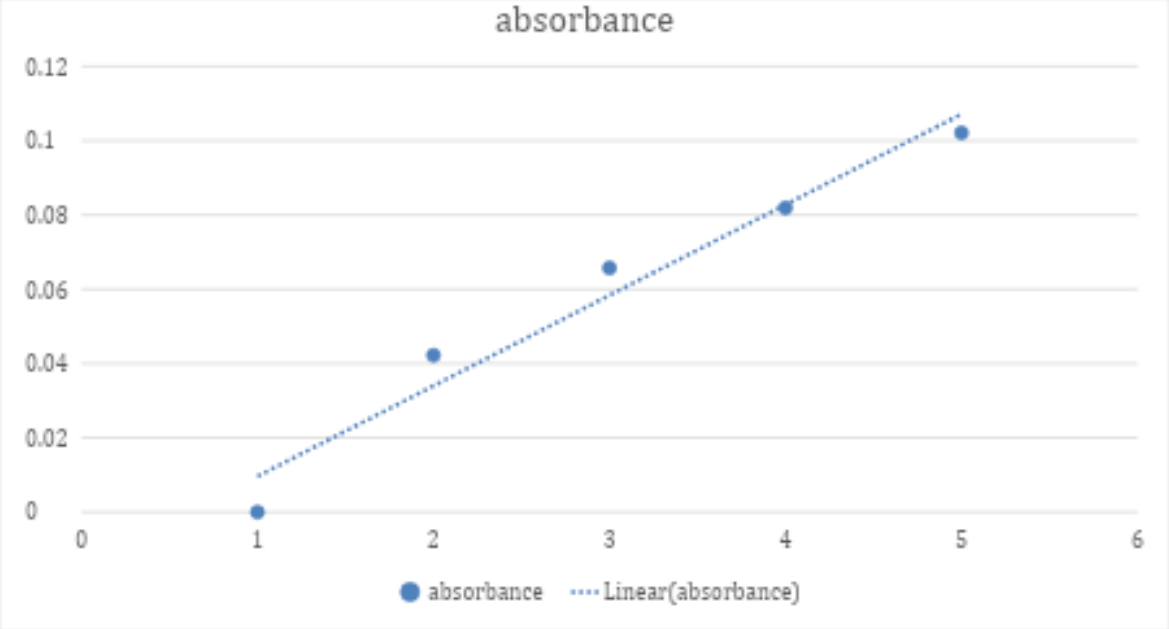
ZONE OF INHIBITION OF ITRACIS LAC.

Zone of Inhibition (mm).

Sample Name	Mean(mm)
Extract	20
Itraconazole	13.6
Formulation	27.3

UV SPECTROSCOPY

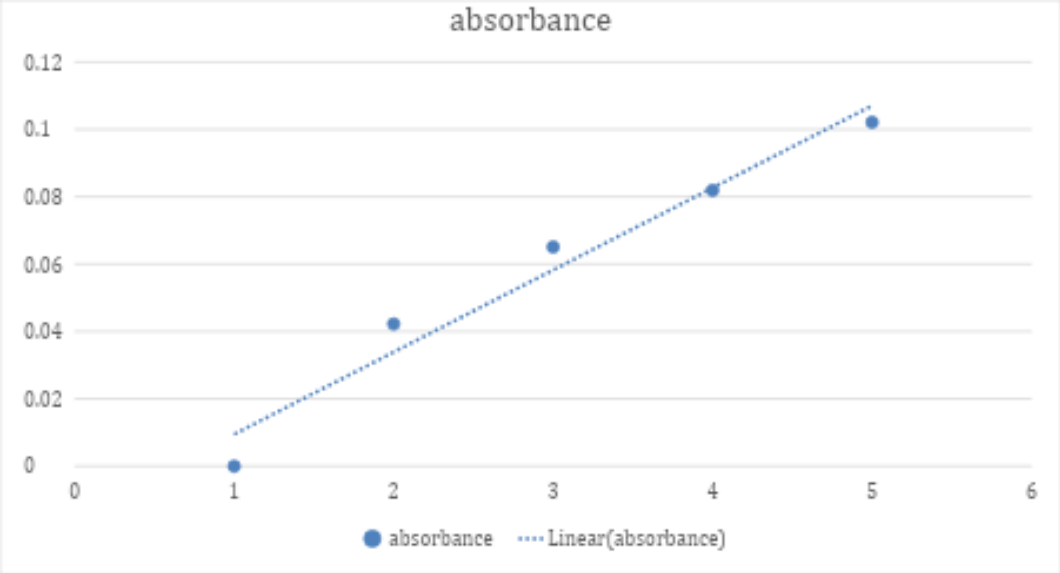
1) UV SPECTROSCOPY OF ITRACONAZOL



UV SPECTROSCOPY OF ITRACONAZOLE.

Concentration ug/ml	Absorbance at 262nm
0.5	0.0247
1.0	0.0459
1.5	0.0638
2.0	0.0861
2.5	0.1063

2) UV. SPECTROSCOPY OF C. QUADRANGULARIS

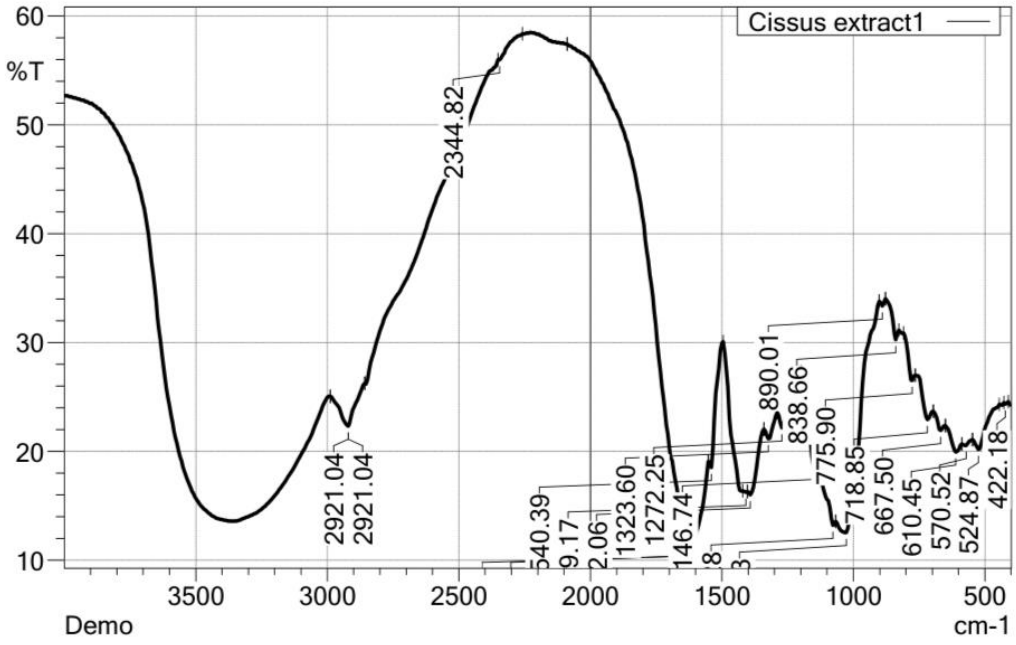


UV SPECTROSCOPY OF C. QUADRANGULARIS

Concentration ug/ml	Absorbance at 236nm
0.5	0.0422
1.0	0.0651
1.5	0.0819
2.0	0.1021
2.5	0.1211

IR SPECTROSCOPY

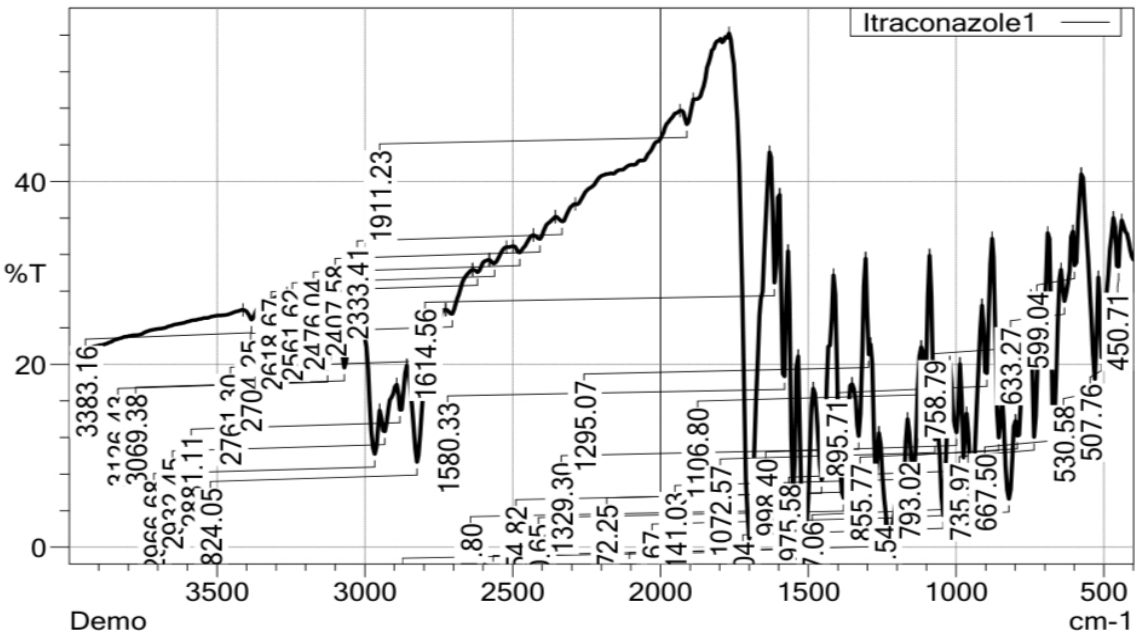
1) IR OF CISSUS QUADRANGULARIS



IR OF CISSUS QUADRANGULARIS.

Frequency Range(cm-1)	Peak(cm-1)	Functional Group
3200-3600	3377	OH(Phenolic group)
1500-1600	1540	C=C(Flavonoid & Tannins)
1000-1300	1146	C-O(Glycosidic group)

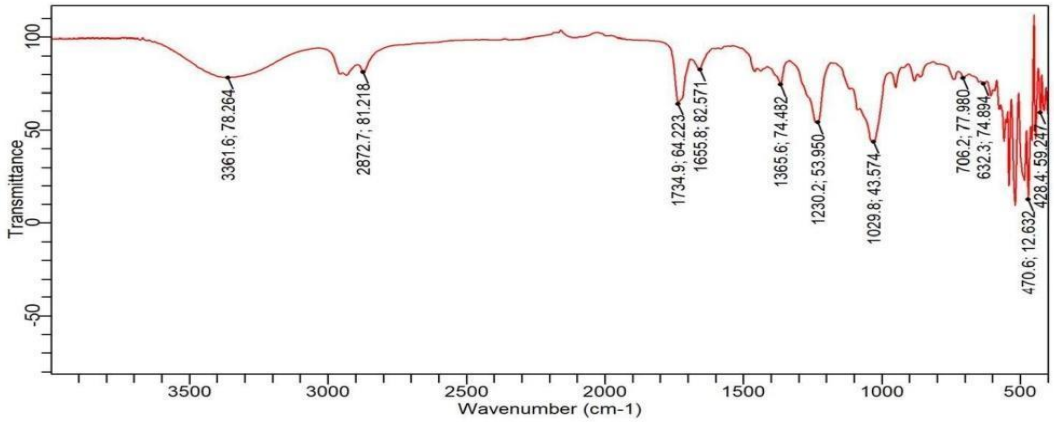
2) IR SPECTROSCOPY OF ITRACONAZOLE



IR OF ITRACONAZOLE.

Frequency Range(cm-1	Peak(cm-1)	Functional Group
1650-1750	1700.14	C=O(Keto group)
1600-1700	1614.56	C=N(Triazole ring)
1000-1400	1141, 1329	C-F(Fluorine atom in triazole ring)

3) IR SPECTROSCOPY OF FORMULATION



IR OF FORMULATION.

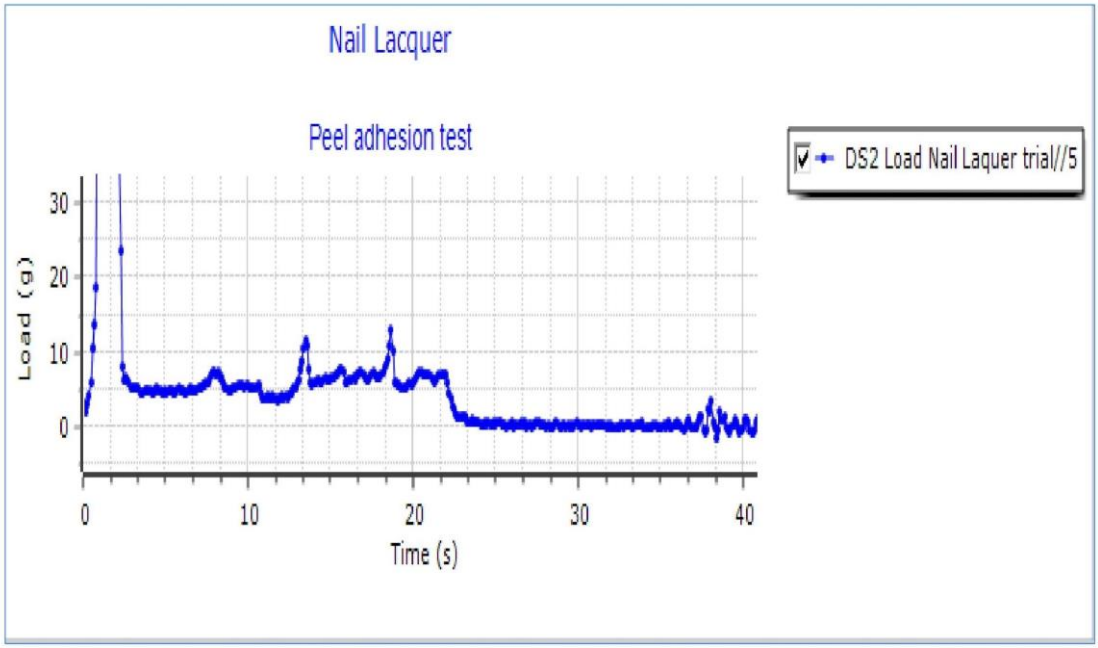
Peak(cm-1)	Functional Group	Assignment
3361	O-H / N-H stretch	Polyphenols(CQ) or NH group (API)
1734	C=O stretch	Ester or Ketone group
1655	C=C / C=O(amide)	Triazole related C=N group
1230	C-O stretch	Ether or Ester
1029	C-O-C / C-N stretch	Ether Linkages

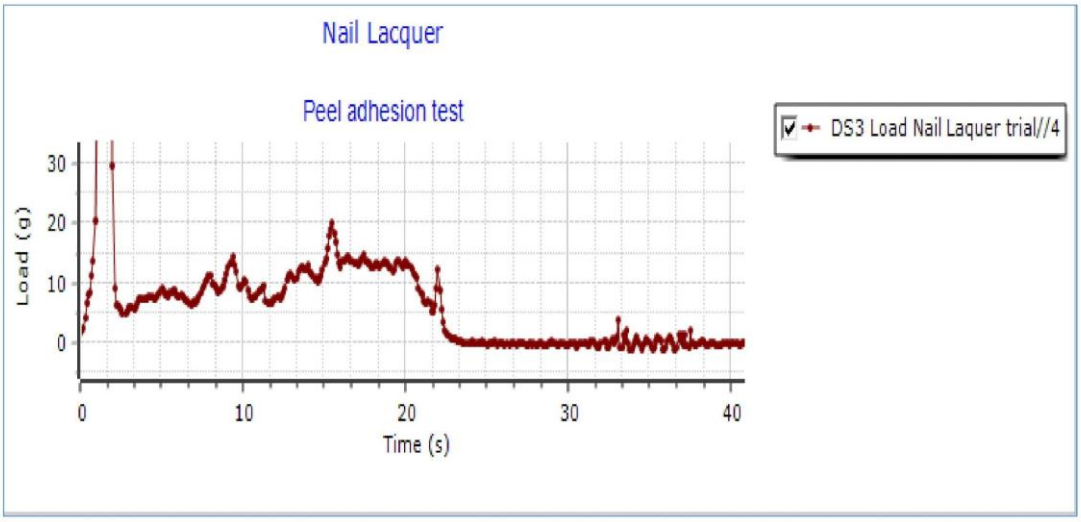
TRANSUNGUAL STUDY

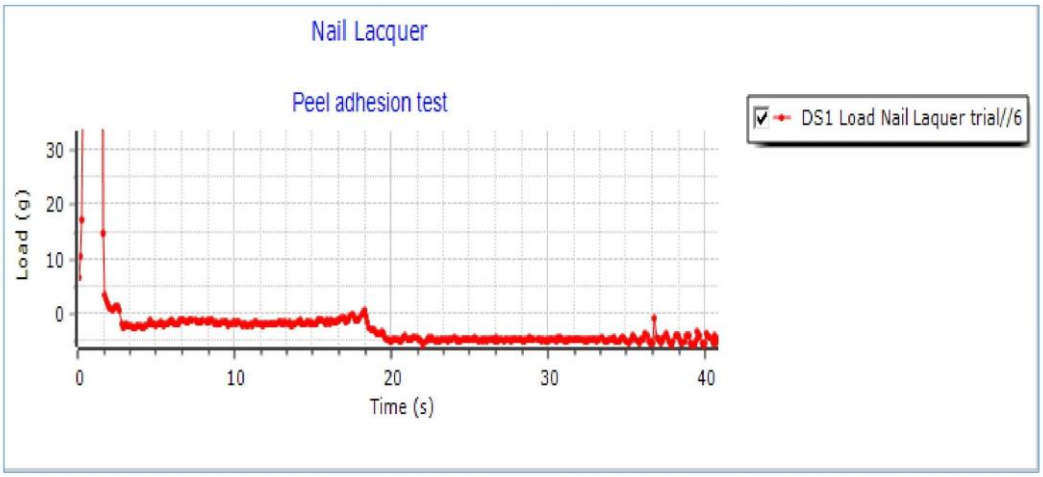
In vitro transungual permeation study of our nail lacquer formulation was performed through goat nail plate. Amount of extract diffused through goat nail was 95.82% in 24 hr. Amount of itraconazole diffused through goat nail was 99.39% in 24 hr. Salicylic acid and DMSO significantly increased the permeation of extract and drug through goat nail.

PEEL ADHESION TEST

Sample	Work(mj)	Deformation At Peak Load (mm)	Mean Load: 1s to 20s (g)
Film 1.1	18.72	**7.83**	18.1
Film 1.2	17.35	7.66	16.4
Film 2.1	16.28	6.72	21.7







STABILITY STUDIES

Temperature	Evaluation Parameters	Observation (days)		
		0	15	30
Room Temperature (25°C RH=60%)	Visual Appearance	Purple	Purple	Purple
	Odour	Characteristic	Characteristic	Characteristic
	Spreadability	Good	Good	Good
40°C±2% RH=75%	Visual Appearance	Purple	Purple	Purple
	Odour	Characteristic	Characteristic	Characteristic
	Spreadability	Good	Good	Good

DISCUSSION

Our evaluation of the Nail Lacquer formulation yielded promising results, demonstrating its potential as a treatment for fungal nail infections. The formulation exhibited desirable characteristics, including color, consistency, smoothness, spredability and film thickness, which are essential for effective application and user acceptance. Additionally, it showcased

excellent water resistance, hardness, and film thickness, ensuring a long-lasting barrier against fungal growth. The formulation also displayed satisfactory spreadability and smoothness, facilitating easy application and uniform coverage. Notably, the Nail Lacquer demonstrated significant antifungal activity, suggesting its potential to effectively combat fungal infections. Furthermore, the non-volatile content met the required standards, indicating a stable and consistent product. While these findings are encouraging, further research is necessary to fully validate the efficacy and safety of the Nail Lacquer formulation considering In vitro studies and clinical trials would provide valuable insights helping to establish its therapeutic potential. By building on these promising results, we can explore the formulation's potential as a topical treatment for fungal nail infections, offering a convenient and effective solution for patients. Ultimately, our study lays the groundwork for further investigation and development of the Nail Lacquer formulation, with the goal of providing a reliable and efficient treatment option for individuals affected by fungal nail infections. With continued research and evaluation, this formulation may emerge as a valuable addition to the treatment of fungal nail infections.

CONCLUSION

The combination formulation of Cissus quadrangularis and Itraconazole in a nail lacquer demonstrated a synergistic antifungal effect, indicating enhanced therapeutic efficacy compared to individual components. This synergistic action suggests that incorporating Cissus quadrangularis with Itraconazole could be a promising approach for the development of more effective topical treatments for fungal nail infections.

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CONFLICT OF INTEREST

Authors do not have conflict of interest.

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