Original Article

Antifungal Nail Lacquer Loaded with Extract of *Cissus quadrangularis* for Treatment of Onychomycosis

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ABSTRACT

Objectives: An attempt was made to prepare transparent nail lacquer containing natural antifungal agent obtained from extract of whole plant of *Cissus quadrangularis* for the treatment of onychomycosis. **Methods:** The extract of *C. quadrangularis* was evaluated for antifungal study against *Candida albicans*. Minimum inhibitory concentration of extract against *C. albicans* was performed to get the amount of extract to be loaded in the nail lacquer. Extract was further evaluated for phytochemical study such as test for steroids, glycoside and flavonoids. Nail lacquer was prepared by using nitrocellulose, ethyl cellulose, ethyl acetate, salicylic acid, dibutyl phthalate, extract of *C. quadrangularis* and acetone with continuous stirring. The nail lacquer of fluconazole was prepared and compared with formulation. Formulations of nail lacquer were evaluated for drying time, gloss, non-volatile content, water resistance, viscosity, smoothness of flow. *In-vitro* transungual permeation study was performed through goat nail. **Results:** Phytoconstituents such as flavonoid and quinine were found present in the extract. Antifungal activity of nail lacquer and fluconazole formulation against *C. albicans* was found good (zone of inhibition of 20 ± 2mm at 50mg/ml, 16 ± 1mm for 40mg/ml respectively). Drying time of formulation was 62-70 s with visually seen glossiness of formulation. Formulation of nail lacquer showed good non-volatile content, water resistance and viscosity with smoothness of flow. *In-vitro* permeation of F7 formulation showed 90.9% of permeation which was faster within 24 hr. **Conclusion:** Thus, *C. quadrangularis* extract loaded antifungal nail lacquer could be a good choice for treatment of onchomycosis rather than fluconazole.

Key words: Onychomycosis, *Cissus quadrangularis,* Transungual, Nail lacquer, Antifungal.

INTRODUCTION

Onychomycosis is a contagious contamination of fingernails and toenails which influences around 19% of world population.[1] This infection occurs mainly in diabetic and elderly patients. The most common cause is dermatophytes, non-dermatophytes, moulds and yeast mainly *Candida albicans*.[2] About 80% cases of onychomycosis, mostly toenails are affected.[3] In diabetic patients, onychomycosis is prevalent than non-diabetic patients. Diseased nail of patient have thick sharp edges infect surrounding skin tissue due to pressure that leads to erosion of nail bed.[4]

The infection of the nail folds is associated with proximal subungual onychomycosis, distal and lateral subungual onychomycosis and primary total dystrophic onychomycosis. Yellow-brown patches appear at lateral border of nail.[5,6]

The masses of horny debris disperse and nail plate rapidly becomes thickened and broken. The irritation, pain and pressure also are the secondary effects.[7] To treat various fungal infections of nail, variety of formulations are available either by oral or topical route like solution, cream, gel and nail patch.[8] Penetration enhancers are generally utilized in the nail formulations which work by a few mechanisms. Some

Submission Date: 11-07-2019;
Revision Date: 06-02-2020;
Accepted Date: 18-03-2020

DOI: 10.5530/ijper.54.2s.83

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penetration enhancers act as keratolytic operator which breaks the disulfide bonds of keratin protein and a few enhancers work by changing the cooperation among the keratin fibers by hydrating the filaments.[9] Two primary factors to consider for better penetration are porousness and binding of medication to keratin inside the nail. Binding of medication to keratin decreases accessibility of active or free medication, concentration gradient and thus restricts deep penetration of medication in the nail.[10]

Currently, health care system is more inclined to nutraceuticals in line of this, *Cissus quadrangularis* L., belong to family *Vitaceae* is used as an antidyspeptic, digestive tonic, analgesic and has antimicrobial activity.[11,12] *C. quadrangularis* is a tendril climbing shrub with shoot found throughout the India. The leaf portion constitutes only 5-8% of aerial plant parts; the fleshy green steam is the major portion. The plant contains high amounts of Vitamin C, cartotene, anabolic steroid substance.[13]

At the present, various synthetic drugs are used to treat Onychomycosis. Fluconazole is one of the broad-spectrum antifungal agent.[14] Fluconazole is the first generation triazole derivative. It inhibits the fungal cytochrome enzyme 14α-demethylase, which is responsible for conversion of lanosterol to ergosterol.[15] Drug binds to ergosterol, a major component of fungal cell membrane, forms pores in the membrane causing potassium leakage and death of the fungus.[16]

The recent work on the medicated nail lacquer include improved permeation of apremilast using salicylic acid and dexpanthenol nail lacquer for nail psoriasis.[17] Antifungal sensitivity of fluconazole medicated nail lacquer against *Candida albicans* was studied at various concentrations of ethyl cellulose, thioglycolic acid and dimethyl sulfoxide for treatment of onychomycosis.[18] Medicated nail lacquer of isotretinoin was developed using thioglycolic acid as penetration enhancer and successfully tested for effectiveness for increase the permeation across bovine hoof and human nail.[19]

The aim of the present research was to develop antifungal nail lacquer containing extract of *C. quandrangularis* for treatment of onychomycosis. Biomaterial *Cissus quadrangularis* extract was used with penetration enhancer salicylic acid. This activity was performed using *ex-vivo* drug diffusion study through goat nail plate.

MATERIALS AND METHODS

Material

Fluconazole was gifted generously by Glenmark Pharmaceuticals Limited, Mumbai, India. *Cissus quadrangularis* extract (CQE) of whole plant was gifted by Kisalaya Herbals Limited, Indore, India.

Methods

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 color. To identify of phenols, extract was treated with 3-4 drops of ferric chloride solutions to get in bluish black color. 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.[20]

Antifungal activity of Cissus quadrangularis extract

Antifungal activity of CQE was determined against *Candida albicans* by cup plate method, evaluated. The sterilized sabouraud dextrose media was poured to the sterilized petri plates and allowed to set. *C. albicans* was inoculated on the media in aseptic condition. Wells were prepared aseptically with sterilized cork borer and filled with each 0.5ml solution of DMSO containing extract of CQE ranging from 10mg/ml to 50mg/ml. Plates were kept for pre-diffusion in refrigerator for 15 min. After normalized room temperature, all plated were incubated at 30°C for 48 hr and zone of inhibition (diameter in mm) was measured.[19-21]

Formulation of nail lacquer

Nitrocellulose and ethyl cellulose were dissolved in sufficient quantity of ethyl acetate to get clear solution. Salicylic acid was dissolved in above mixture and dibutyl phthalate was added. Then extract of *C. quadrangularis* and acetone were added with continuous stirring at 100 rpm on magnetic stirrer. The formulations were coded as F1 to F4. Formulations containing fluconazole were prepared and coded as F5 to F7 (Table 1). Finally, sufficient quantity of ethyl acetate was added to get proper consistency to nail lacquer (Figure 1).[22]

Evaluation of Nail Lacquer

Drug content

Drug content of F5 and F7 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 260 nm.

Table 1: Formulation of nail lacquer.

Ingredient	F1	F2	F3	F4	F5	F6	F7
C. quandrangularis extract (%)	0.05	0.05	0.05	0.05	-	-	-
Fluconazole (%)	-	-	-	-	0.04	0.04	0.04
Nitrocellulose (%)	2	2	2	2	2	2	2
Ethyl cellulose (%)	1	1	1	1	1	1	1
Salicylic acid (%)	0.35	0.50	0.60	0.70	0.50	0.60	0.70
Ethyl acetate (%)	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Dibutyl phthalate (%)	0.2	0.2	0.2	0.2	0.2	0.2	0.2
Acetone (%)	0.1	0.1	0.1	0.1	0.1	0.1	0.1

Figure 1: Actual Photograph of nail lacquer.

Non-volatile content

Non-volatile content of F1 to F7 was determined to get the weight of formulation that retained on nail plate after application. Nail lacquer (1 g) was taken in a glass petri dish of about 8 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.[23]

Lacquer film thickness

One ml of formulation was spread equally with an applicator brush in 8 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 guage and average was calculated.[24]

Drying time and gloss

An area of 4 × 4.5 cm^2 was marked on glass petri dish to which a film of nail lacquer formulation (F1 to F7) 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.[25]

Glossiness (F1 to F7) was determined by visual inspection and measured as follows: good (++), very good (+++) and excellent (++++). It was compared with marketed cosmetic product.[26]

Smoothness of flow

Formulations (F1 to F7) 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.[27]

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 on it to immerse the film. The weight of petri dish was taken before and after immersion and increase in weight was calculated.[28]

Peel adhesion test by texture analysis

A peel adhesion test for formulations was performed by Texture Analyzer (Brookfield Engineering Ltd,). 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 of adhesive tape. Time and load required for peeling off lacquer is recorded.[29]

In vitro transungual permeation study

To study the transungual permeation of fluconazole from nail lacquer into the skin through nail bed, the

drug permeation study was performed for 24 hr. The permeation study was performed using animal hooves as an alternative to human nail. The goat finger nail was collected from the slaughter house and stored in a -20°C freezer until further use. Before the use the nail softened at room temperature in phosphate buffer pH 7.4 solutions. The nail were rinsed with phosphate buffer solution and dried. The thin section of soften nail was cut and dried. The cut section act as nail membrane and was mounted between donor and receptor compartment with nail portion facing donor compartment of Franz diffusion cell. The nail lacquer was applied (1ml) on surface of nail section to cover the entire area of receptor compartment. The assembly was maintained at 32±0.5°C with constant stirring at 600 rpm for 24 hr. The sample was withdrawn (5ml) at predetermined time intervals and replaced with fresh solution to maintain the sink condition. The sample was analysed spectrophotometrically at 260nm.[30,31]

Milling test

Following the permeation of fluconazole through nail plate, the amount retained on the nail bed was determined by washing the nail three to four times with phosphate buffer solution of pH 7.4. The solution was filtered through 0.22µm filter paper and was analysed spectrophotometrically. To determine the amount of fluconazole retained inside the nail bed, after 7 h and 24h, nail was cut into small pieces and was kept in methanol for 24 hr, then sonicated for 10 min followed by vortex mixing for 15 min. Then the sample was centrifuged at 6000 rpm for 15min. The supernatant was filtered through 0.22 µm filter and was analysed by UV spectrophotometer at 260nm for Fluconazole.[25]

Antifungal study of formulations

Antifungal activity of *C. quadrangularis* extract nail lacquer and fluconazole nail lacquer was evaluated by cup plate method against *Candida albicans*. The sterilized sabouraud dextrose media was poured to the sterilized petri plates and allowed to set. Bacterial culture was inoculated on the media in aseptic condition. Wells were prepared aseptically with sterilized cork borer.[21] Wells were filled with each 0.8ml (50mg/ml) following solution in DMSO: A: *Cissus quadrangularis* extract loaded formulation (0.8ml), B: Fluconazole loaded formulation 0.8ml (40mg/ml). Plates were kept for pre-diffusion in refrigerator for15 min. After normalized room temperature, all plated were incubated at 30°C for 48 hr. Zone of inhibition (diameter in mm) was measured.[22]

RESULTS

Onychomycosis need targeted drug delivery. The treatment of onychomycosis is difficult because of barrier properties of nail plate. They can inhibit entrance of antifungal drugs in required concentration to treat fungal infection, beneath the nail plate. Therefore, selection of good penetration enhancer was required to pass maximum more amount of active constituent through the nail plate.

Identification test of phytoconstituents

The extract turned red color, which indicated presence of steroids. For the presence of phenolic test, the extract turned into bluish black color, which confirmed the presence of phenol. For the flavonoids test, the extract turned into yellow precipitate, which confirmed presence of flavonoids. For the presence of quinones, extract turned into yellow precipitate that indicated the presence of quinones.

Antifungal activity

The antifungal activity of extract was performed against *C. albicans*. The extract 10mg/ml showed the less zone of inhibition (12±2mm), while 50mg/ml showed highest zone of inhibition 18±2 mm (Figure 2).

Formulation of nail lacquer

Formulation of nail lacquer F1-F4 and fluconazole nail lacquer F5-F7 were prepared using penetration enhancer salicylic acid.

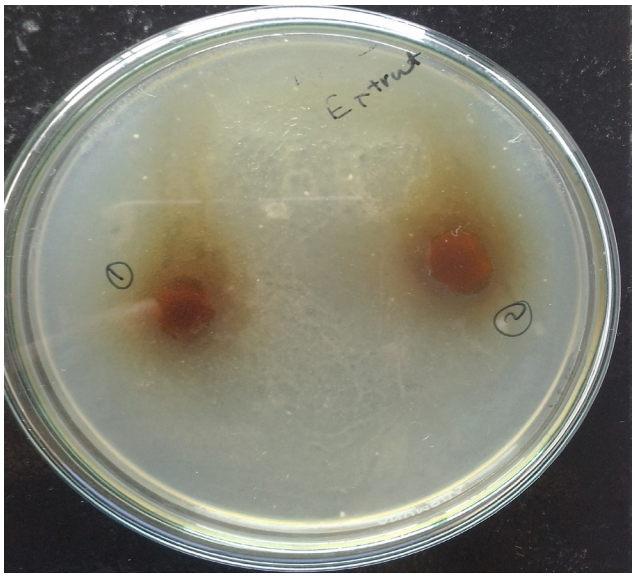

Figure 2: Antifungal activity of extract of *Cissus quadrangularis*.

Table 2: Evaluation of Formulated nail lacquer.

Batches	Drug Content (%)	Non-volatile content (%)	Lacquer Film Thickness (mm)	Drying time (s)	Water resistance (%)	DrugDiffusion (%)	Milling test (%)	Zone of inhibition (mm)
F1	-	33±0.5	0.17±0.2	62±2	90	-	-	18±1
F2	-	35±0.2	0.17±0.5	64±1	89	-	-	16±2
F3	-	36±0.4	0.18±0.1	62±6	90	-	-	14±1
F4	-	37±0.3	0.19±0.3	65±3	98	-	-	20±2
F5	95.3	34±0.5	0.18±0.1	66±1	90	85.6	1.2	16±2
F6	96.7	37±0.2	0.19±0.4	65±3	35	88.1	6.4	14±1
F7	98.03	38±0.1	0.20±0.2	70±2	97	90.9	12.5	16±1

Evaluation of nail lacquer

Drug content

Drug content of F5 to F7 and was found to be 95.3, 96.7 and 98.03% respectively (Table 2). The drug content uniformity in formulation suggested batch to batch uniformity in the formulation.

Non-volatile content

Non-volatile content of F1 to F7 was observed to be in range of 33±0.5% to 38±0.1% (Table 2). Formulation F4 and F7 showed, 37±0.3 and 38±0.1% of non-volatile content, respectively. Non-volatile content, thus confirmed the uniformity in preparation of all batches.

Lacquer film thickness

After drying, the thickness of the film was found to range between 0.17±0.1mm to 0.20±0.2mm (Table 2). The thickness of lacquer was found to be uniform in all formulation.

Drying time and gloss

Drying time of F1 to F7 was found to be in the range of 62±2 to 70±4 s (Table 2). There was no significant difference in all batches. Drying time of F4 and F7 was observed to be 65±3 and 70±2 s, individually. The glossiness of nail lacquer was evaluated by comparing with the marketed product. Nail lacquer applied on the nail and gloss was visually seen and there was no significant difference in all batches. Glossiness of F4 and F7 was good (++) and very good (+++). It was found to be satisfactory when compared to the marketed product.

Smoothness of flow

Smoothness of flow of all batches (F1 to F7) was compared with marketed product and found to be good.

Water resistance test

Higher was the increase in weight, lower was the water resistance of nail lacquer. Formulation F1 and F5 showed very high permeation as compared to F4 and F7. Formulations F4 and F7 showed 98 and 97% water resistance.

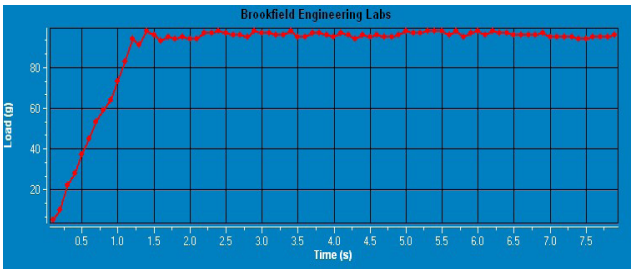

Figure 3: Peel adhesion of nail lacquer.

Peel adhesion test

Peel adhesion test showed deformation of film from the substrate for formulation at 90s (Figure 3).

In vitro transungual permeation study

In vitro transungual permeation study of F1 to F7 was performed through goat nail plate. Amount of drug diffused through nail of batches F5, F6 and F7 was 85.6, 88.1 and 90.9 % respectively in 24 hr (Figure 4). As the concentration of salicylic acid was increased, the penetration capacity of formulation was also increased. F7 showed highest amount of drug permeated within 24h due to highest amount of salicylic acid (0.7%) than F5 and F6. Thus, salicylic acid was found to enhance the permeation of fluconazole.

Milling test

Amount of drug retained on nail bed was found to be 1.2% (F5), 6.4% (F6) and 12.5% (F7). Formulation F7 showed high amount of drug retained inside the nail till 7 hr. It was necessary to retain the drug inside the nail to diffuse the drug slowly after 24hr.

Antifungal study

Formulation F4 and F7 exhibited highest zone of inhibition. F4 and F7 showed 20±2mm and 16±1mm

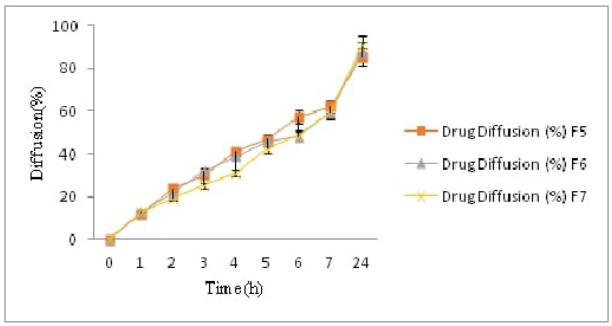

Figure 4: *In-vitro* transungual permeation of fluconazole nail lacquer.

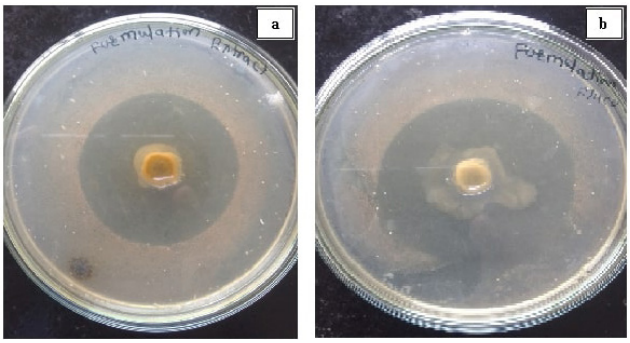

Figure 5: Zone of inhibition of (a) *Cissus quadrangularis* extract loaded nail Lacquer (b) Fluconazole loaded nail lacquer.

zone of inhibition (Figure 5a and b). Extract exhibited good antifungal action against *C. albicans*. Therefore, formulation F4 containing extract of *Cissus quadrangularis* could be considered as good antifungal medicated nail lacquer.

From the above evaluation tests, F4 and F7 formulations of nail lacquer were found good against *C. albicans* to treat onychomycosis. F4 batch containing *Cissus quadrangularis* extract loaded nail lacquer showed good water non-volatile content, drying time, water resistance than other formulation of nail lacquer. Zone of inhibition also showed good result than other formulation. Therefore, F4 batch was considered as best batch of medicated nail lacquer.

DISCUSSION

The dried powder extract was green in colour. A phyto-constituent tests confirmed presence of steroids, phenol, flavonoids, quinone in the extract. The quinine has antimicrobial activity.[20] However, antifungal activity of *Cissus quadrangularis* extract against *C. albicans* was due to presence of quinine.[22] As the concentration of extract increased the antifungal activity also found to be increased.

The drug content uniformity in formulation suggested batch to batch consistency in the formulation. In non-volatile content test the F4 and F7 showed good non-volatile content, which was similar to earlier work. The F4 formulation containing *Cissus quadrangularis* extract showed good non-volatile content than the F7 formulation.[24] The non-volatile content was helped for film making by evaporation of volatile content. The thickness of lacquer was found to be uniform in all formulation. The thickness of lacquer film was found increased with increases in concentration of salicylic acid.[25]

F4 formulation showed faster drying time as compared to other formulation, which was convenient for patient to have the nail wet with nail lacquer for less time.[26] Glossiness was visually seen required to accept medicated nail lacquer by patient as cosmetically asthetic.[27] There was no significant difference in all batches, thus confirmed uniformity in preparation of all batches. The smoothness of flow of F4 and F7 batches confirmed satisfactory compared to marked product.[28]

In the water resistance test, higher was the water permeation increase in weight of lacquer. Both batch F4 and F7 showed very less increase in weight after immersing in water. It concluded that nail lacquer has less permeability and thus high resistance towards water.[7] Formulations did not show clean removal of film from the plate by using pulling the probe at peel adhesion test. Therefore, confirmed adhesive nature of lacquer to the nail, required to retain on the nail to diffuse slowly through it.[31]

In vitro transungual permeation study was performed to compare penetration capability of fluconazole with salicylic acid as penetration enhancer. F5 to F7 as the concentration of salicylic acid was increased in formulation, the permeation of formulation also increased. Salicylic acid acts as good penetration enhancer due to rapid drug release. Salicylic acid, a keratolytic substance, causes softening of nail plate. F7 formulation showed faster permeation than the F5 and F6 formulations within 24 hr.[30,31] However the retention of drug in nail plate was required for slow diffusion of drug to kill microorganism.[25] The antifungal activity of extract was found to be effective in killing *C. albicans*.[22] Petri plate with F4 formulation loaded with extract showed good antifungal activity compared with F7 formulation with fluconazole.[22]

Thus, *C. quadrangularis* extract was considered as good antifungal agent to be used in the medicated nail lacquer. F4 and F7 showed good non-volatile content and gloss, water resistance and less drying time, high drug retention in nail plate and better permeation. Nail lacquer F4 and

F7 did not show any change in color thus confirmed the physical stability of formulations. No microbial growth was observed in F4 formulation.

CONCLUSION

Cissus quadrangularis extract loaded nail lacquer was successfully delivered through nail plate. The incorporation of penetration enhancer salicylic acid proved to enhance transungual delivery. *Cissus quadrangularis* extract showed good antifungal activity than fluconazole. Thus, *Cissus quadrangularis* extract loaded nail lacquer. *Cissus quadrangularis* extract loaded nail lacquer could be accepted by patient due to its natural appeal. Thus, *Cissus quadrangularis* extract considered as good choice of as antifungal agent to cure onychomycosis.

ACKNOWLEDGEMENT

Author would like to thank to Glenmark Pharmaceuticals Limited, Mumbai, India for providing fluconazole and Kisalaya Herbals Limited, Indore, India for providing *Cissus quadrangularis* extract.

CONFLICT OF INTEREST

Authors do not have conflict of interest.

ABBREVIATIONS

C. quadrangularis: *Cissus quadrangularis*; **CQE:** *Cissus quadrangularis* extract; ***C. albicans*:** *Candida albicans*; **DMSO:** Dimethyl sulfoxide.

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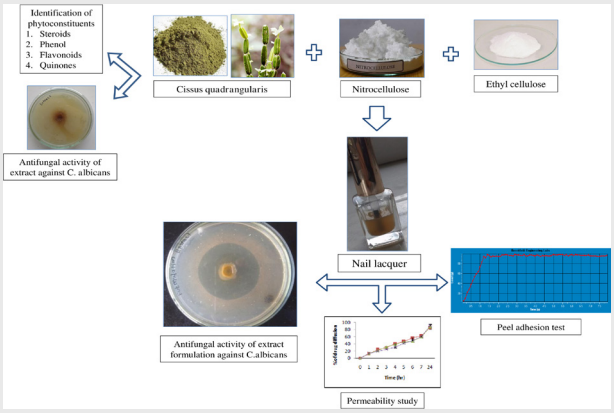
PICTORIAL ABSTRACT



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SUMMARY

The antifungal nail lacquer was formulated using extract *Cissus quadrangularis* and fluconazole separately to treat onychomycosis. The extract was tested for presence of phytoconstituents steroids, flavonoids, quinone and phenols. Antifungal activity of nail lacquer and fluconazole formulation against *C. albicans* was found good (zone of inhibition of 20±2mm at 50mg/ml, 16±1mm for 40mg/ml, respectively). Transparent nail lacquer was prepared by mixing nitrocellulose, ethyl cellulose, ethyl acetate, salicylic acid and dibutyl phthalate. The formulation good non-volatile content and gloss, water resistance and less drying time, high drug retention in nail plate and better permeation. In conclusion, *Cissus quadrangularis* extract considered as a good choice as antifungal agent to cure onychomycosis and an alternative to synthetic medicines.

Cite this article: Pandit AP, Kedar AA, Ranaware SV, Khandelwal KR. Antifungal Nail Lacquer Loaded with Extract of *Cissus quadrangularis* for Treatment of Onychomycosis. Indian J of Pharmaceutical Education and Research. 2020;54(2s):s269-s276.