A Randomized, Double-blind, Controlled Trial on the Efficacy and Safety of 1.5% Carica Papaya Latex Cream Compared to 1% Terbinafine Cream in the Treatment of Localized Tinea Corporis and/or Tinea Cruris*

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ABSTRACT

Background: Tinea corporis and cruris are superficial fungal infections mainly caused by dermatophytes. The antifungal effect of carica papaya latex cream has been demonstrated in clinical studies, however, larger population and comparative studies to standard antifungal agents are needed to further strengthen this conclusion. This study determined the efficacy and safety of 1.5% carica papaya latex in cream base as treatment for tinea corporis and/or cruris compared to 1% terbinafine cream.

Methods: This is a randomized, double-blind controlled trial wherein subjects with a clinical diagnosis of tinea corporis or cruris confirmed by microscopy applied terbinafine or carica papaya latex cream twice daily for 6 weeks. The efficacy and safety were assessed 2, 4, and 6 weeks using clinical and mycological cure parameters. The incidence of adverse effects was likewise evaluated.

Results: 90 subjects were randomized, 45 in carica papaya group and 45 in the terbinafine group. Both groups had statistically comparable improvements based on symptoms and mycological cure rates. Adverse events are significantly higher in the papaya latex cream group.

Conclusion: Carica papaya latex cream is as effective as terbinafine cream in the treatment of tinea corporis and/or cruris, but it has a higher incidence of adverse events.

Key words: tinea corporis, tinea cruris, carica papaya latex cream, terbinafine cream

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INTRODUCTION

"Tinea" refers exclusively to dermatophyte infections and are among the most common skin diseases affecting millions of people throughout the world. It is seen commonly in typically hot humid climates and the classic presentation also known as "ringworm" is a lesion with central clearing surrounded by an advancing, red, scaly, elevated border. Its estimated lifetime risk is between 10 and 20 percent. In the epidemiologic surveillance of cutaneous fungal infections in the United States from 1999 to 2002, dermatophytes remain the most commonly isolated fungal organisms.[1] A local study in 2005 revealed that fungal infections ranked as the second leading cause of consultation with a prevalence of 12.98% and among these, tinea corporis comprised 22.63%.[2] From 1995 to 2004, an analysis of a cross sectional study revealed an estimated 51 million visits for superficial fungal infections of the skin, of which tinea corporis represented 17.4% of the total cases.[3] In our institution (Jose R. Reyes Memorial Medical Center, Department of Dermatology), tinea corporis together with tinea cruris consistently played part of the top 15 most common dermatologic diseases from 2001-2012 with an average incidence of 7.6%.

Topical antifungals in the treatment of tinea corporis include most commonly the imidazoles, allymines and the benzylamines. Terbinafine 1% cream is an antimycotic with a broad-spectrum of anti-fungal activity belonging to the allylamine group. This product interferes with fungal sterol biosynthesis by the inhibition of squalene epoxidase in the fungal cell membrane, which leads to an intracellular accumulation of squalene, resulting in fungal cell death. Twice daily applications of terbinafine 1% cream for one week (followed by three weeks of placebo) was significantly superior, both in terms of mycological cure and effective treatment, to twice daily applications for four weeks of clotrimazole 1% cream when compared six weeks after starting treatment. The cure rates with terbinafine 1% cream were high, with 97% of patients mycologically cured and 90% of patients effectively treated.[4]

Carica papaya tree (from the family Caricaceace) have shown great potential against a number of health problems. A study in in 2009 demonstrated that treatment with papaya preparation accelerated wound healing and reduced the severity of local inflammation in rats with burn wounds.[5] The fungistatic effect is the result of degradation of the polysaccharide constituents of the fungal cell walls. It is the latex from unripe fruits that showed full activity towards both proteins and peptones.[6-7]

Two years ago, a randomized, double-blind, controlled trial in the efficacy and safety of 1.5% carica papaya latex cream compared to 2% ketoconazole cream and vehicle in the treatment of tinea corporis revealed complete resolution which occurred within 14 days with the carica papaya group compared to 21 and 28 days for the ketoconazole and placebo group, respectively[8]. A hundred percent therapeutic response (or treatment success) was achieved. A quasi-experiment also revealed that carica papaya latex cream exhibits antifungal properties and is a safe and cost-effective alternative as treatment for tinea corporis and/or cruris.

Carica papaya is used as food in most parts of the world. No health hazards have been noted in conjunction with designated therapeutic dosages. The leaves contains tannins and both leaves and roots contain cyanogenic glucosides which form cyanide. Together, at high concentration can cause adverse reactions. Allergic reaction have also been documented. However, in this study latex was extracted from the stems and the fruit itself.[9-14]

The general objective of this study is to evaluate the efficacy and safety of 1.5% carica papaya latex cream compared to 1% terbinafine cream in patients with tinea corporis and/or cruris. Specifically, it determined the differences in clinical and mycological cure, incidence of adverse effects and overall efficacy of both topical antifungal medications in comparison.

METHODOLOGY

Patient and Study Design

This study was a randomized, double-blind controlled trial conducted at Jose R. Reyes Memorial Medical Center Department of Dermatology from July 2012 to August 2013. The Institutional Review Board of the hospital approved the trial protocol prior to commencement. This clinical trial was conducted in compliance with Good Clinical Practice and in accordance with the ethical principles of the Declaration of Helsinki.

Eligible patients included male or female aged 18 years old and above with clinical diagnosis of tinea corporis and/or cruris confirmed by microscopy

detection of fungal hyphae on potassium hydroxide (KOH) smear. A clinical diagnosis of tinea corporis was based on the presence of pruritic annular patch with erythematous border, may be topped with scales, papules, pustules and or vesicles. The lesions were localized on areas of the body except the scalp, palms and soles.

The following criteria excluded patients from the study (1) Subjects who took systemic antifungals or corticosteroid therapy during the past month (2) Subjects who applied topical antifungals and corticosteroids during the past 2 weeks (3) Subjects who took or applied other medications like antibacterial and antiviral agents within the past 2 weeks 4) Subjects with associated dermatophytosis of hands, feet, scalp and nails (5) Subjects with extensive lesions not suitable for topical treatment (6) Subjects with known hypersensitivity reactions to carica papaya or allyamines (7) Pregnant or lactating women (8) Immunocompromised patients (9) Unreliable subjects as assessed by the investigator (10) Patients participating in any other investigational drug study during the 4 weeks before the trial begun.

The subjects were oriented and primed on the study's objectives, procedures and outcome measures. Written informed consent forms were provided and signed by the subjects before admission to the study. Appropriate measures were done in taking photographs to conceal patients' identities.

Study Medications

The carica papaya latex creams were prepared at the Department of Industrial Pharmacy, College of Pharmacy, University of the Philippines, Manila. (Appendix 5) The test creams [1.5% carica papaya latex cream and 1% terbinafine cream were stored in identical opaque 15 g containers. The containers are of the same size, color and shape. The creams are also of the same color and consistency without any pertinent, characteristic smell. The containers were labeled A or B by the pharmacist. The same mild soaps were provided by the investigator and were the only ones used by the subjects throughout the duration of the study. Instructions were given to all patients not to apply any other creams, lotions or powder to areas under active treatment and not to use any oral antifungal medications and antihistamines.

Randomization, treatment allocation and blinding

The primary investigator provided a computer generated table of random numbers. The second investigator (a resident doctor) who was blinded to the codes allocated the labeled creams randomly. All were blinded to the treatment allocations.

Clinical Assessment

Demographic data (Appendix 1) were collected and clinical examinations of the patients were done by the primary investigator. The location and size of each lesion were noted and photographs were taken. From the border of each test site, skin scrapings were obtained for potassium hydroxide (KOH) examination. Patients were instructed to apply the cream twice daily for 6 weeks. They were asked to follow up after every 2 weeks for 6 weeks, and were required to bring the container on each follow up visit to check for compliance. During every visit, photographs were taken under standardized settings, skin scrapings were obtained for KOH examination and the patients were assessed by the third investigator (another resident doctor) blinded to the treatment allocation. Adverse reactions such as erythema, burning sensation, stinging or pain, exacerbation of pruritus were recorded by investigators. The codes were only disclosed to the investigators at the end of the study

The primary outcome in this study were the therapeutic response rate at six weeks based on clinical and mycologic scores. Clinical assessment scores were based on the following clinical parameters: scaling, erythema, and pruritus. (Appendix 2) Mycologic scores were based on mycological examination (KOH) done at baseline, every 2 weeks and follow up. Scales were obtained using the blunt side of a blade from an advancing border of the lesion. Ten percent (10%) KOH was used to determine the presence or absence of branched, septated hyphae. (Appendix 3)

Secondary outcomes measured were the patient's assessment of efficacy and adverse events. The efficacy of study medication at the end of the study were assessed by each patient and was scored 0-3, 0 = not effective, 1 = slightly effective, 2 = moderately effective, 3 = markedly effective (Appendix 4). The ultimate response or complete resolution of tinea corporis/cruris was based on the complete mycological clearance until the disappearance of hyphae on repeat KOH examination.

Stopping guidelines

The study was stopped in patients who experienced adverse reactions to the test creams, who had worsening of the skin lesions, if the patient became pregnant, or if the patient voluntarily withdrew from the study. These patients were considered as withdrawals from the study. Those who did not comply to the twice-daily application of the test creams, or those who used other topical or oral medications were also withdrawn from the study. Likewise, both test creams were given 2 weeks maximum for the observation of improvement on the lesions for the study to continue. Dropouts were defined as those who did not follow up within two weeks and whose outcome was unknown by the end of the study period.

Sample Size

The sample size was computed based on frequency in a population. Population size (for finite population correction factor or fpc) (*N*):3000. Hypothesized % frequency of outcome factor in the population (*p*):7.5%+/-5 and design effect (for cluster surveys-*DEFF*):1. We aimed at 45 study patients per arm to achieve at least 80% confidence interval.

Data processing and analysis

Statistical analysis was done using Stata v10. Descriptive analysis was done by computing the frequency and central tendency measures of the demographic variables. The association between the proportion of "improved" tests was analyzed using Pearson chi-squared test and Fisher's exact test. Comparison of means using Student's t-test and paired t test were also used for the comparisons of results between monitoring. Tests below 0.05 were regarded as statistically significant.

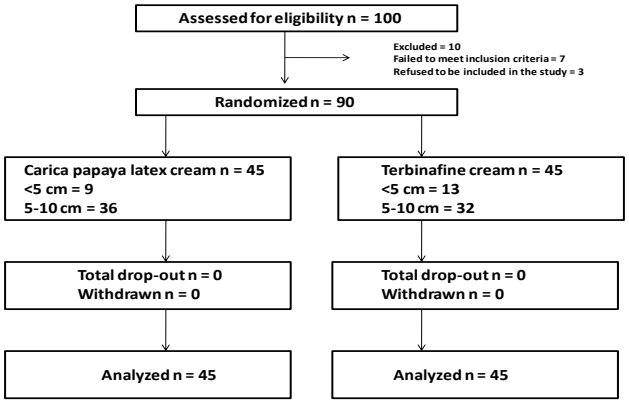

Figure 1. Trial profile showing patient populations

RESULTS

Study Population

One hundred patients were screened and 90 met the inclusion criteria. They were randomized to treatment (carica papaya, n=45) and (terbinafine, n=45) groups. (Figure 1) There were no dropouts nor withdrawals in the study. All 90 patients were included in the full analysis. The baseline characteristics showed no statistically significant differences between the 2 groups based on gender, duration, location and size of lesions. A difference was noted based on age. (Table 1)

There is an increase in reduction rates of all clinical parameters of carica papaya group and terbinafine group throughout 6 weeks of treatment. (Table 2) The adverse events of carica papaya group are higher than terbinafine group. (Table 3) Overall efficacy was shown after 6 weeks of treatment. (Table 4)

Table 1. Demographic profile

VARIABLE	CARICA PAPAYA (N=45)	TERBINAFINE (N=45)	P-VALUE
Age in years (mean ± sd)	40.73±13.78	29.27±13.62	P=0.0001
Sex			
Female	31 (68.89%)	26 (57.78%)	P=0.105
Male	14 (31.11%)	19(42.22%)	
Duration of lesions in months	4.98± 3.50	4.94±5.18	P= 0.9673
Number of lesions	2.20±1.47	2.31±0.70	P=0.6485
Widest diameter in cm			
< 5 cm	9 (20%)	13 (28.89%)	P = 0.327
5 – 10 cm	36 (80%)	32 (71.11%	
Positive koh	45 (100%)	45 (100%)	P= 1
Baseline scaling	2.18±0.72	2.44±0.50	p=0.0439
Baseline erythema	2.18±0.58	2.07±0.54	p=0.3473
Baseline pruritus	1.96±0.74	2.51±0.55	p=0.0001

Table 2. *Reduction rates throughout 6 weeks of treatment between both groups*

Clinical Parameters	Mean Carica papaya	Mean Terbinafine	P value
Scaling			
2 weeks	26±55.15 %	41.10±55.15 %	p<0.0001
4 weeks	44.08±44.97 %	74.45±22.36%	p=0.0001
6 weeks	90.37±23.97 %	100±0 %	p=.0084
Erythema			
2 weeks	20.36±48.31 %	55.18±31.35%	p=0.0001
4 weeks	48.52±50.98 %	88.52±22.42%	p<0.0001
6 weeks	91.48±20.61 %	100.0±0%	p=0.0068
Pruritus			
2 weeks	37.40±39.11 %	79.63±27.51%	p<0.0001
4 weeks	45.93±60.53 %	100±0%	p<0.0001
6 weeks	77.78±34.08 %	100±0%	p<0.0001

Table 3. *Adverse events throughout 6 weeks of treatment*

Adverse events	Mean Carica papaya	Mean Terbinafine	P value
Pruritus			
2 weeks	1.47±0.84	1.29±0.76	p=0.2953
4 weeks	1.33±0.90	1.53±0.16	p=0.2953
6 weeks	0.23±0.52	0	p=0.0045
Burning			
2 weeks	1.16±0.93	0.60±0.69	p=0.0018
4 weeks	0.96±0.90	0.84±0.77	p=0.5311
6 weeks	0.2±0.59	0	p=0.0249
Erythema			
2 weeks	1.40±0.99	0.76±1.03	p=0.0031
4 weeks	1.07±0.81	0.38±0.53	p<0.0001
6 weeks	0.15±0.52	0	p=0.0480

Table 4. *Efficacy scoring by patients after 6 weeks of treatment*

Efficacy scoring	Mean Carica papaya	Mean Terbinafine	P value
6 weeks	2.71±0.63	2.84±0.37	p=0.2209

Both groups showed decline in the mean scaling scores post treatment but the terbinafine reduction rate (100%) is statistically higher (p=.0084) than the carica papaya group (90.37±23.97 %). (*Figure 2)*

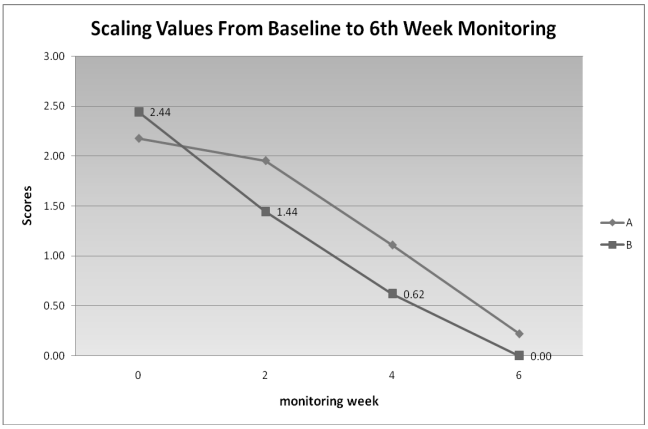

Figure 2. *Comparison of changes in mean score for scaling for carica papaya and terbinafine group from baseline to week 6*

Similarly, both groups showed decline in the mean erythema scores post treatment but the terbinafine reduction rate (100%) is statistically higher (p=0.0068) than the carica papaya group (91.48±20.61 %). (*Figure 3)*

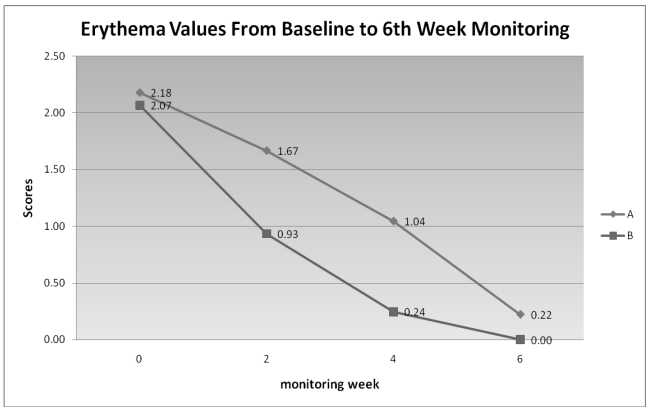

Figure 3. *Comparison of changes in mean score for erythema for carica papaya and terbinafine group from baseline to week 6*

Both groups showed decline in the mean pruritus scores post treatment but the terbinafine reduction rate (100%) is statistically higher ($p<0.0001$) than the carica papaya group (77.78±34.08 %). (*Figure 4)*

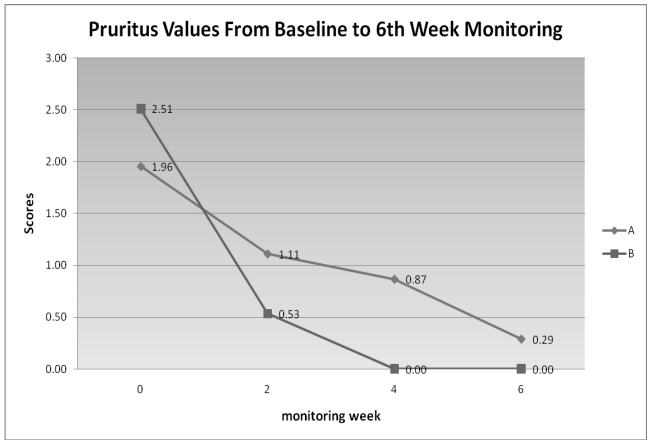

Figure 4. *Comparison of changes in mean score for pruritus for carica papaya and terbinafine group from baseline to week 6*

Post treatment, mycological cure rates are comparable (p=0.315) in both groups. *(Figure 5)*

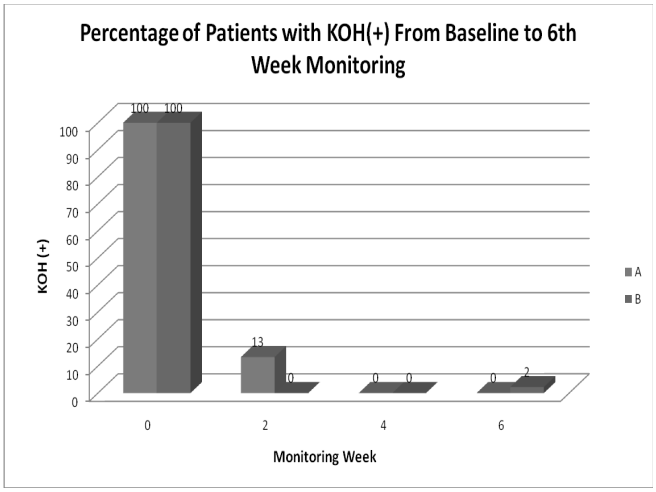

Figure 5. Mycological cure rates for both groups characterized by a negative KOH smear.

The mean scores of adverse events (pruritus, burning and erythema) after 6 weeks of treatment showed statistically higher in the carica papaya group. (p=0.0045, p=0.0249, p=0.0480, respectively). *(Figure 6, 7, 8)*

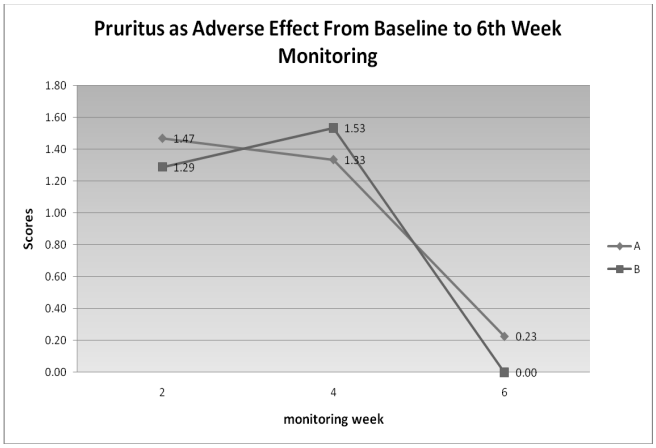

Figure 6. *Incidence of adverse effect, specifically pruritus from both groups.*

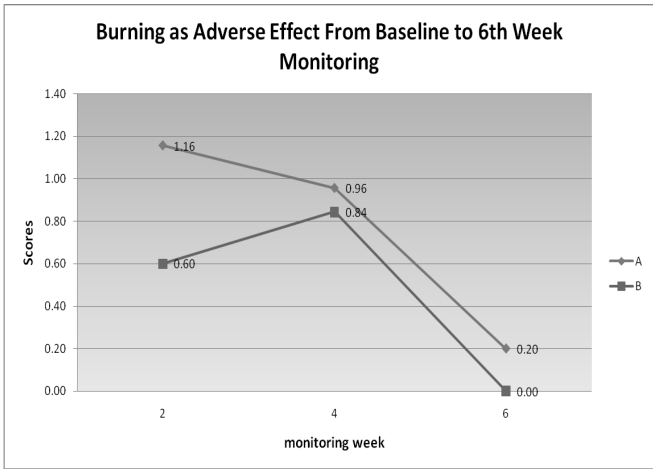

Figure 7. *Incidence of adverse effect, specifically burning from both groups.*

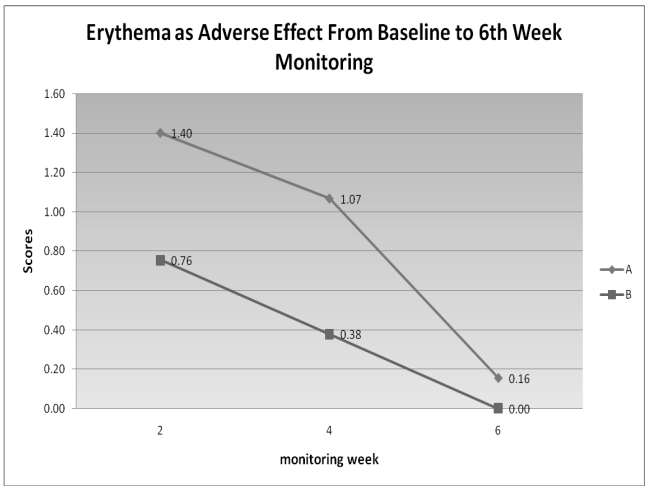

Figure 8. *Incidence of adverse effect, specifically erythema from both groups.*

DISCUSSION

Mycological cure rates are comparable for both groups, but clinical parameters of improvement were significantly better in the terbinafine group. The terbinafine group showed significant decreases in scaling, erythema and pruritus at two and four weeks, however the carica papaya group achieved maximal and almost comparable improvement of these parameters at the sixth week of treatment. This suggests that terbinafine has a faster onset of action, and better clinical cure which may be attributed to its fungicidal action and inherent anti-inflammatory actions, as compared to carica papaya having more of a fungistatic effect. The decrease in these clinical parameters may be attributable not only to carica papaya latex' ability to degrade polysaccharide component of the fungal cell wall (fungistatic effect) but also to its inhibitory effect on chronic inflammation.[6-8] Also, the adverse effects of erythema, burning and pruritus were significantly higher in the carica papaya group, which may mask the clinical improvement of this intervention. These events are attributable to the tannin and cyanogenic glucoside contents of papaya that were reduced in this study by using the stems and fruit itself compared to the leaves and roots which contains more of those harmful elements.[9-14] After 6 weeks, mycological cure rates are comparable and clinical parameters of improvement more similar, suggesting that the adverse effects have resolved and the anti-mycotic activity of carica papaya becomes more obvious.

Limitations of the study are the locations of lesions that should be more uniform in both groups for better comparison in future studies. The difference in age as baseline characteristic was noted. However, this may not be a confounding variable because the efficacy of topical antifungals is not influenced by age. In this study, mycological cure based on the KOH results was used as the primary outcome efficacy measure instead of clinical cure. Fungal culture is the undisputable gold standard of diagnosis but the discordance between fungal culture and KOH examination results is too great.[15] KOH examinations were true positives in spite of negative culture. It was found that the a low percentage of patients presenting with a clinical diagnosis of tinea that had skin cultures positive for fungus, raising a question as to whether culture is the optimal gold standard by which to evaluate diagnostic tests for tinea infections. It concluded that clinical tinea infection with positive KOH is equivalent to clinical tinea with positive fungal culture in accurately diagnosing fungal infections. Examples of how culture may miss a diagnosis include sampling error from the affected area, using defective culture medium, and mishandling of the culture medium.[16-18]

Recurrence rates were not investigated after discontinuation of treatment, thereby recommending considerations of prolonged investigations should this study be done in the future. A decrease in the concentration of carica papaya latex cream, a change of vehicle used and a longer time of treatment and observation should likewise be considered.

CONCLUSION

Carica papaya latex cream has comparable mycological cure rates as terbinafine cream in the treatment of tinea corporis and/or cruris. However, clinical improvement is significantly faster in the terbinafine group, and higher incidence of adverse events is seen with carica papaya latex cream use.

***Appendix 1** : Demographic data of study patients*

Characteristics	Carica Papaya	Terbinafine 1% cream	P value
Age			
Sex			
Duration of lesions			
Number of lesions			
Size of lesions			

***Appendix 2**: Clinical assessment score based on degree of scaling, erythema, and pruritus*

Score	Scaling	Erythema	Pruritus
0	none	none	none
1	minimal scaling	slightly erythematous	1-3
2	moderate scaling	erythematous	4-6
3	severe scaling	Brightly erythematous	7-10

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