

# *Senna alata* (akapulko) Extract versus Topical Antifungals for Treatment of Superficial Fungal Skin Infections: a Systematic Review and Meta-analysis

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## ABSTRACT

**Objective.** The study aimed to assess the efficacy and safety of *Senna alata* (akapulko) plant extracts compared with topical antifungals in the treatment of superficial fungal skin infections.

**Methods.** A systematic review and meta-analysis of randomized controlled trials that studied patients with diagnosed cutaneous tinea or dermatophytosis (excluding hair and nail), tinea versicolor, or cutaneous candidiasis, via microscopy or culture, and compared the efficacy and safety of *S. alata* (akapulko) extract versus topical antifungals. Two authors independently screened titles and abstracts of merged search results from electronic databases (The Cochrane Skin Group Specialized Register, CENTRAL, MEDLINE, EMBASE (January 1990 to December 2011), Health Research and Development Information Network (HERDIN), and reference lists of articles), assessed eligibility, assessed the risk of bias using the domains in the Cochrane Risk Bias tool and collected data using a pretested Data extraction form (DEF). Meta-analyses were performed when feasible.

**Results.** We included seven RCTs in the review. There is low certainty of evidence that *S. alata* 50% lotion is as efficacious as sodium thiosulfate 25% lotion (RR 0.91, 95% CI, 0.79 to 1.04; 4 RCTs, n=216; p=0.15; I<sup>2</sup>=52%) and high quality evidence that *S. alata* cream is as efficacious as ketoconazole (RR 0.95, 95% CI, 0.82 to 1.09; 1 RCT, n=40; p=0.44) and terbinafine cream (RR 0.93, 95% CI, 0.86 to 1.01; 1 RCT, n=150; p=0.09) in mycologic cure. For adverse effects, there is very low certainty of evidence of increased harm with *S. alata* 50% lotion compared to sodium thiosulfate 25% lotion (RR 1.26, 95% CI, 0.46, 3.44; 2 RCTs, n=120; p=0.65; I<sup>2</sup>=19%). Adverse effects were few and mild.

**Conclusion.** *S. Alata* 50% lotion may be as efficacious as sodium thiosulfate 25% lotion and is as efficacious as ketoconazole 2% and terbinafine 1% creams. There is insufficient evidence to compare the safety of *S. alata* 50% lotion with sodium thiosulfate 25% lotion.

**Key Words:** *Senna alata*, *Cassia alata*, akapulko, skin fungal infections, dermatophytosis, tinea versicolor, pityriasis versicolor, candidiasis, systematic review, meta-analysis.

## INTRODUCTION

Superficial fungal skin infections are prevalent in tropical countries, and are commonly caused by pathogenic dermatophytes (*Trichophyton* spp., *Epidermophyton* spp., and *Microsporum* spp.), and normal skin commensals such as *Malassezia* spp. and *Candida albicans*. Dermatophytes are keratinase-producing fungi that are capable of invading and reproducing within the keratinized tissue of hair, nails, and skin.<sup>1</sup> These may be transmitted via contact with infected

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humans, animals, or through exposure with contaminated soil.<sup>2</sup> *Tinea versicolor* (also known as pityriasis versicolor) is caused by lipophilic *Malassezia* yeasts, which are normal skin commensals.<sup>3</sup> *Candida albicans* is also part of the normal flora of the skin, but may cause cutaneous candidiasis particularly in immunocompromised individuals.<sup>4</sup>

Dermatophytosis, particularly tinea corporis, is one of the 10 most common skin conditions at the Philippine General Hospital's Section of Dermatology. Based on the Health Information System of the Philippine Dermatological Society last 2017, dermatophytosis is the 2<sup>nd</sup> most common diagnosis seen among both new and old patients.<sup>5</sup> It is extremely pruritic, highly contagious, and the treatment can be lengthy and costly. *Tinea versicolor* is usually asymptomatic; however, the skin discoloration and highly recurrent course pose cosmetic concerns for the patient. Lastly, although candidiasis is rarely associated with significant morbidity in healthy hosts, it may become persistent and disseminate systemically in immunocompromised individuals.<sup>6</sup>

There are several treatment options for tinea versicolor and dermatophytosis. These include keratolytic agents like selenium sulfide, propylene glycol, and salicylic acid, which act by facilitating removal of affected skin.<sup>7</sup> Drugs that work by inhibiting the cytochrome p450-dependent conversion of lanosterol to ergosterol, such as sodium thiosulfate and ketoconazole, disrupt fungal cell membrane and subsequent leakage of cellular contents.<sup>8</sup> Terbinafine, an allylamine, inhibits squalene epoxidase, the enzyme necessary for the conversion of squalene to lanosterol, thus preventing synthesis of ergosterol.<sup>2</sup>

*Senna alata* (L.) Roxb. (syn. *Cassia alata*) (family Leguminosae/Fabaceae) or candle bush is an indigenous plant of central America and known in the Philippines as akapulko.<sup>9</sup> *S. alata* has long been purported to have antifungal property and has been studied in several clinical trials regarding its effect on superficial fungal infections such as dermatophytosis and tinea versicolor.<sup>10-14</sup> *In vitro* studies showed that crude methanol and ethanol extracts of *S. alata*, inhibit growth of *Trichophyton rubrum*, *Microsporum canis*, and *Candida albicans*.<sup>15,16</sup> According to an *in vitro* study, anthraquinone aglycones and anthraquinone aglycosides, identified through thin layer chromatography of crude ethanol extracts, are responsible for *S. alata*'s antifungal activity.<sup>17</sup>

*S. alata* is one of the ten medicinal plants approved for use by the Philippines' Department of Health. The plant is readily accessible throughout the Philippines, commonly known to the layperson as a household treatment for skin fungal diseases, and a cheaper alternative to the more costly azoles and allylamines (leading drugstore, 93 php per 15 gram tube).<sup>18,19</sup> Although there are numerous studies available, treatment effects are uncertain. A systematic review was done in order to collate existing data regarding efficacy and safety of *S. alata* as an antifungal.

## OBJECTIVE

This review aimed to assess *S. alata*'s efficacy and safety compared with other topical antifungal drugs as treatment for superficial fungal infections.

## METHODS

The Cochrane Collaboration methods<sup>20</sup> and the PRISMA<sup>21</sup> statement were followed in this systematic review.

### Data Sources

The authors conducted a search of electronic databases (from inception to September 2014), namely: Cochrane Skin Group Specialized Register, Cochrane Central Register of Controlled Trials (CENTRAL), EMBASE, MEDLINE, and Health Research and Development Information Network (HERDIN). We searched for unpublished trials and ongoing trials using ClinicalTrials.gov and contacted authors and organizations. We also searched grey literature, references of included studies, and hand-searched relevant journals (Journal of the Philippine Dermatological Society 1992-2013) for potential studies. The following search terms were used "*Senna alata*," "*Cassia alata*," "*senna*," "*cassia*," "*akapulko*," dermatophyt\*, tinea, candidiasis, moniliasis, and *candida*. All relevant randomized controlled trials regardless of language and status of publication were included.

Two authors (RG, ET) independently assessed the titles and abstracts of retrieved trials from the search for eligibility for inclusion in the review. When the titles and abstracts were not enough to decide on eligibility of the trial, the full report was retrieved to make a decision. If information in full report is still not complete, the author was contacted to clarify unclear items. A single failed eligibility criterion was enough to exclude the trial. Disagreements were resolved by discussion.

### Study Selection

We included all relevant RCTs regardless of language, and status of publication that compared *S. alata* extract, from any part of the plant, with allylamines, azoles, or non-specific antifungals as treatment for patients with diagnosed dermatophytosis, cutaneous candidiasis or tinea versicolor via direct microscopy. Only the first phase of cross-over RCTs was included. We excluded studies involving other species of *Senna* and studies with other components combined with *S. alata* extract. Trials were included if they reported the following primary outcomes: percentage of participants with mycologic clearance defined as a negative KOH mount, and percentage of participants who develop adverse/side effects to treatment. Secondary outcome measures were percentage of participants with clinical resolution of lesions as evaluated by outcome assessor, and percentage of participants who reported clinical resolution of symptoms.

## Data Extraction and Quality Assessment

Two reviewers independently extracted data using a pretested data extraction form, and assessed risk of bias using the Cochrane Collaboration Risk of Bias tool<sup>20</sup> from the included studies. Disagreements between the two authors were resolved through discussion or a third author. Original authors of study reports were contacted to ask details of missing data or items needing clarification.

Data was pooled for studies which were clinically homogenous. RevMan 5 was used to generate summary tables and graphs. For dichotomous outcomes, risk ratio and 95% confidence intervals were used, while for continuous outcomes, mean difference and SD were used. We attempted to do intent-to-treat analysis by analyzing non-compliant participants or protocol violators in the group they were randomized to, regardless of how the original authors analyzed them. Missing data (e.g., participants lost to follow-up who did not have any outcome assessments at relevant time points) were excluded from the main analysis (available case analysis).

Heterogeneity was assessed using visual inspection of the forest plots to check for overlapping confidence intervals. We also computed for chi-square test for heterogeneity at 10% level of significance, and  $I^2$  statistic was also computed. If  $I^2$  value was  $>50\%$ , heterogeneity was assessed to be significant, and if  $>75\%$ , it was assessed to be substantial. If significant heterogeneity existed, random effects model was used; otherwise, fixed effects model was used. When significant heterogeneity existed, subgroup analysis was done to determine the possible cause of heterogeneity.

## RESULTS

Out of 119 records via database searching and 3 additional records via hand searching, 59 duplicates were excluded, leaving 63 records for screening of titles and abstracts. After assessing full reports and abstracts of nine potentially relevant studies for eligibility, two studies were excluded (Appendix 1) and seven studies were included in qualitative and quantitative analyses (Figure 1).

The seven included studies are described in Appendix 2. Four RCTs (461 patients) compared *S. alata* 50% lotion versus sodium thiosulfate (STS) 25% lotion as treatment for tinea versicolor.<sup>10,11,14,22</sup> One study (150 patients) compared *S. alata* cream of unknown concentration against 1% terbinafine cream as treatment for tinea versicolor.<sup>23</sup> One study (48 patients) investigated an unknown concentration of *S. alata* cream against ketoconazole cream as treatment for cutaneous fungal infections and tinea versicolor.<sup>13</sup> One study was conducted in a prison (67 inmates) and compared 3 different kinds of herbal soaps with antifungal properties (3% *S. alata* soap; 5% *Erythrophloeum guineense*; 5% *Aframomum melegueta* + *Pipers guineense* + *Xylopiã aethiopicã*) to treat tinea versicolor, tinea corporis, scabies, and acne/m bump.<sup>24</sup> We did not identify any trials on *S. alata* for cutaneous candidiasis.

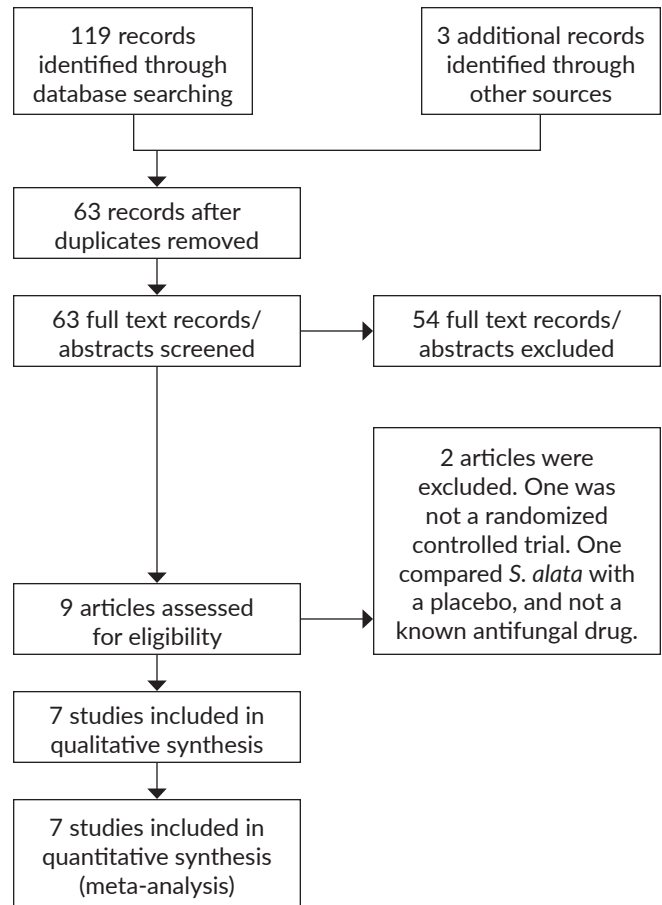


Figure 1. Study flowchart.

Overall quality assessment shows that majority of studies were low risk for bias for all domains except for selective reporting domain where majority were moderate to high risk of reporting bias due to unclear or different definition of cure outcomes (Figure 2).

Only three studies had at least one domain with high risk of bias (Figure 3).

## Primary Outcome Measures

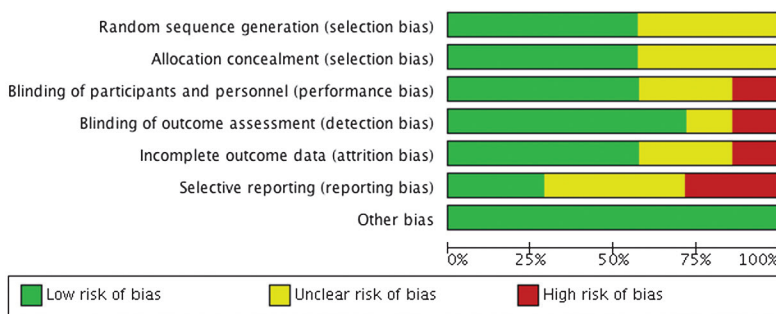
### Mycologic cure

Four trials that compared *S. alata* 50% lotion with STS 25% lotion showed that the two treatments were equally efficacious for mycologic cure in tinea versicolor (RR 0.91, 95% CI, 0.79, 1.04;  $p=0.15$ ) (Figure 4).<sup>10,11,14,22</sup> The presence of significant heterogeneity ( $I^2=52\%$ ) may be attributed to a longer treatment period, and significant number of dropouts in one study.<sup>22</sup>

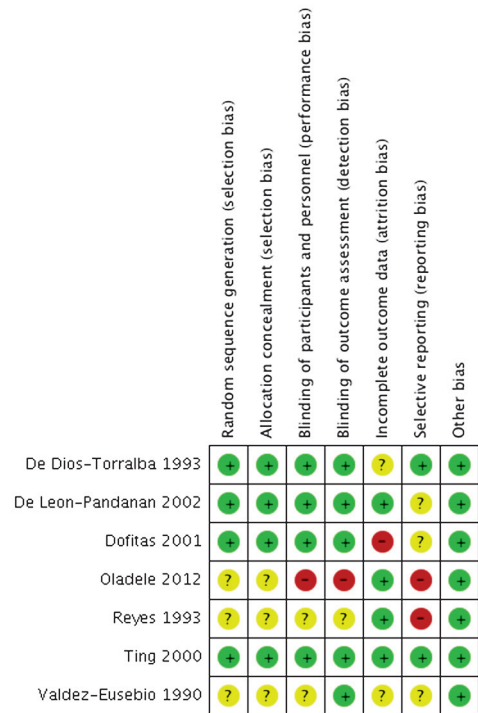
Two individual studies noted no significant difference in mycologic cure comparing *S. alata* cream with ketoconazole cream as treatment for dermatophytosis or tinea versicolor (RR 0.95, 95% CI 0.82, 1.09;  $n=40$ ;  $p=0.44$ )<sup>13</sup> and terbinafine 1% cream when applied twice daily for two weeks (RR 0.93, 95% CI, 0.86, 1.01;  $n=150$ ;  $p=0.09$ ).<sup>23</sup>

**Adverse effects**

Only two studies that compared *S. alata* 50% lotion with STS 25% lotion as treatment for tinea versicolor noted adverse effects.<sup>10,14</sup> We were uncertain if *S. alata* lotion had more adverse effects than STS lotion (RR 1.26, 95% CI 0.46, 3.44; 2n=120; p=0.65; I<sup>2</sup>=19%) (Figure 5).<sup>10,14</sup> The most common adverse effect for both treatments was pruritus. No adverse effects were reported by participants in the study which compared *S. alata* cream with ketoconazole cream as treatment for dermatophytosis or tinea versicolor, and in the study comparing *S. alata* cream with 1% terbinafine cream as treatment for tinea versicolor.<sup>13,23</sup>

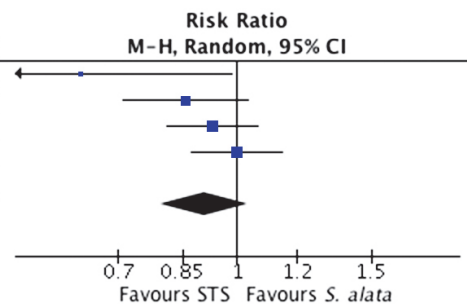


**Figure 2.** Risk of bias graph showing authors' judgments about risk of bias item across all included studies.



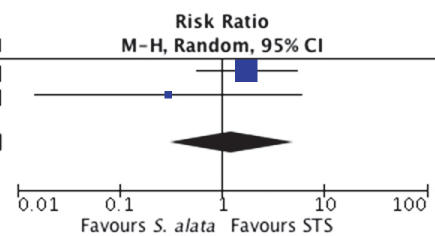
**Figure 3.** Risk of bias summary showing authors' judgments about each risk of bias item for each included study.

Study or Subgroup	<i>S. alata</i>		STS		Weight	Risk Ratio M-H, Random, 95% CI
	Events	Total	Events	Total		
Valdez-Eusebio 1990	9	16	18	20	7.3%	0.63 [0.40, 0.99]
Dofitas 2001	20	24	35	36	25.5%	0.86 [0.71, 1.03]
Reyes 1993	27	30	29	30	33.5%	0.93 [0.81, 1.07]
De Dios-Torralba 1993	28	30	28	30	33.7%	1.00 [0.87, 1.14]
<b>Total (95% CI)</b>	<b>100</b>	<b>116</b>	<b>100.0%</b>			<b>0.91 [0.79, 1.04]</b>
Total events	84		110			
Heterogeneity: Tau <sup>2</sup> = 0.01; Chi <sup>2</sup> = 6.25, df = 3 (P = 0.10); I <sup>2</sup> = 52%						
Test for overall effect: Z = 1.44 (P = 0.15)						



**Figure 4.** *S. alata* 50% lotion versus STS 25% lotion, Outcome: Mycologic cure.

Study or Subgroup	<i>S. alata</i>		Sodium Thiosulfate		Weight	Risk Ratio M-H, Random, 95% CI
	Events	Total	Events	Total		
De Dios-Torralba 1993 (1)	7	30	4	30	80.7%	1.75 [0.57, 5.36]
Dofitas 2001 (2)	0	24	2	36	19.3%	0.30 [0.01, 5.91]
<b>Total (95% CI)</b>	<b>54</b>	<b>66</b>	<b>100.0%</b>			<b>1.24 [0.31, 5.03]</b>
Total events	7		6			
Heterogeneity: Tau <sup>2</sup> = 0.30; Chi <sup>2</sup> = 1.23, df = 1 (P = 0.27); I <sup>2</sup> = 19%						
Test for overall effect: Z = 0.30 (P = 0.76)						



**Footnotes**  
 (1) Akapulko – 6 w/ pruritus, 1 w/ transient burning sensation; STS – 4 w/ pruritus  
 (2) STS – 2 w/ transient erythema and pruritus

**Figure 5.** *S. alata* lotion versus STS 25% lotion, Outcome: Adverse effects.

## Secondary Outcomes

### Clinical resolution (as reported by outcome assessors)

One study (n=36) noted *S. alata* 50% lotion to be less efficacious in clinical resolution of tinea versicolor than STS 25% lotion (RR 0.63, 95% CI 0.40, 0.99; p=0.04).<sup>10</sup> In one other study, it was uncertain whether *S. alata* cream was less efficacious than ketoconazole cream (RR 0.37, 95% CI 0.02, 8.5; n=40; p=0.53) in achieving complete clearance of lesions of dermatophytosis and tinea versicolor.<sup>13</sup>

One study compared *S. alata* soap with two antifungal soaps (*Erythrophleum* soap and *Aframomum* soap) in patients diagnosed with either tinea versicolor or tinea corporis. It was uncertain whether *S. alata* soap was more efficacious than *Erythrophleum* soap (RR 1.15, 95% CI 0.65, 2.06; n=35; p=0.63), but there was a trend that it was more efficacious than *Aframomum* soap (RR 1.94, 95% CI 0.91, 4.13; n=37; p=0.09).<sup>24</sup>

## DISCUSSION

This review included seven RCTs with 460 participants, mostly patients with tinea versicolor, done in the Philippines (5/7), medium-sized (median sample size=98), and conducted in the 1990s to 2000s (6/7). The paucity of RCTs using *S. alata* is quite striking considering that it is one of the ten medicinal plants recommended by the Department of Health in the Philippines. Four of the seven included trials used STS lotion as control. The World Health Organization lists sodium thiosulfate as one of the topical treatments for tinea versicolor.<sup>25</sup> It acts as a keratolytic, enabling the removal of stratum corneum affected by dermatophytes, and as a fungistatic, particularly against *Malassezia furfur*, but its mechanism is unknown.<sup>26,27</sup> Of note, current guidelines (NICE, UpToDate) and textbooks recommend topical antifungals such as azoles, allylamines, selenium sulfide, and zinc pyrithione as treatment for superficial fungal infections.<sup>2,28,29</sup> Although the goal of this review is to determine the efficacy of *S. alata* against superficial fungal infections, majority of the studies focused on tinea versicolor, which is caused by yeasts. In addition, only two, small-sized studies compared *S. alata* with established antifungals: ketoconazole and terbinafine.

There is low certainty of evidence that *S. alata* is as effective as STS 25% lotion for mycologic cure (RR 0.91, 95% CI 0.79 to 1.04; 4 RCTs, n=216) but less effective for clinical cure (RR 0.63, 95% CI 0.40 to 0.99, 1 RCT, n=36) (Appendix 3: Summary of Findings Table 1). The evidence was downgraded due to a high risk for attrition bias, as well as high heterogeneity between studies probably since one study had a longer treatment period. In terms of adverse effects, there is very low certainty of evidence that *S. alata* has greater risk of harm than STS 25% lotion (RR 1.26, 95% CI 0.46 to 3.44; 2 RCTs, n=120; I<sup>2</sup>=19%). The evidence was downgraded twice due to the high risk of bias

(because of high attrition rate) and imprecision due to small sample size.

There is high certainty of evidence that *S. alata* is as efficacious as terbinafine for mycologic cure (RR 0.93, 95% CI 0.86 to 1.01; 1 RCT, n=150) (Appendix 3: Summary of Findings Table 2) There is high certainty of evidence that *S. alata* is as efficacious as ketoconazole for mycologic cure (RR 0.95, 95% CI 0.82 to 1.09, 1 RCT, n=40) but low certainty of evidence that it is less efficacious for clinical cure (RR 0.37, 95% CI 0.02 to 8.5; 1 RCT, n=40) (Appendix 3: Summary of Findings Table 3).

Lastly, there is very low certainty of evidence that *S. alata* soap is as efficacious as *Erythrophleum* soap (RR 1.15, 95% CI 0.65 to 2.06; 1 RCT, n=35), and more efficacious than *Aframomum* soap (RR 1.94, 95% CI 0.91 to 4.13; 1 RCT, n=37) for mycologic cure. The evidence was downgraded twice due to significant risk of bias from lack of blinding of participants and personnel, lack of pre-specified objectives or outcomes, and a high number of dropouts.

## CONCLUSIONS

This review suggests that *S. alata* lotion may be as efficacious as STS 25% lotion in the treatment of tinea versicolor. Adverse effects were few and mild for both treatments and it is unclear whether there is a risk for greater adverse effects due to *S. alata* lotion. Based on single studies, *S. alata* lotion may be as efficacious as terbinafine and ketoconazole creams.

### Implications for research

There is a need for more adequately-sized RCTs with good follow-up comparing *S. alata* with standard topical antifungal drugs in the treatment of tinea versicolor, cutaneous dermatophyte infections, and candidiasis.

### Ethics review approval

University of the Philippines-Philippine General Hospital (UP-PGH) Expanded Hospital Research Office (EHRO), October 2015 (2015-10-07-058)

### Study registration

UP Manila-Research Grants Administration Office, January 2018 (RGAO-2018-0014)

### Statement of Authorship

All authors participated in data collection and analysis, and approved the final version submitted.

### Author Disclosure

All authors declared no conflict of interest.

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## APPENDICES

## Appendix 1. Characteristics of excluded studies

Study ID	Reason for exclusion
Damodaran 1994 <sup>30</sup>	Not an RCT
Oladele 2010 <sup>31</sup>	Comparator was placebo

## Appendix 2. Characteristics of included studies

Study ID	Participants	Intervention	Control	Outcome/s
Valdez-Eusebio, 1990 <sup>22</sup>	98 patients with tinea versicolor; dermatology clinic; Philippines	<i>S. alata</i> 50% lotion BID for 6 wks.	(+) Control: STS 25% lotion (-) Control: placebo BID for 6 wks.	Mycologic cure on KOH mount; Clinical activity: scaling and erythema were assessed separately; Adverse effects
De Dios-Torralba, 1993 <sup>14</sup>	60 patients with tinea versicolor; dermatology clinic; Philippines	<i>S. alata</i> 50% lotion BID for 4 wks.	STS 25% lotion BID for 4 wks.	Mycologic cure on KOH mount; Clinical activity: scaling and erythema were assessed separately; Cure (negative KOH mount and disappearance of scaling+erythema); Adverse effects
Reyes, 1993 <sup>11</sup>	174 patients with tinea versicolor; dermatology clinic, Philippines	<i>S. alata</i> 50% lotion BID for 4 wks.	(+) Control: STS 25% solution (-) Control: placebo BID for 4 wks.	Mycologic cure on KOH mount; Clinical activity: scaling and erythema were assessed separately; Adverse effects
Dofitas, 2001 <sup>10</sup>	129 patients with tinea versicolor; dermatology clinic, Philippines	<i>S. alata</i> 50% lotion BID for 4 wks.	STS 25% lotion BID for 4 wks.	Mycologic cure on KOH mount; Clinical activity: scaling and erythema were assessed separately; Adverse effects
De Leon-Pandan, 2002 <sup>23</sup>	150 patients with tinea versicolor; dermatology clinic, Philippines	<i>S. alata</i> cream BID for two wks.	1% Terbinafine cream BID for two wks.	KOH examination recorded as (+) or (-) mycologic cure
Ting, 2000 <sup>13</sup>	48 patients with "cutaneous fungal infection", Upper Dicapay Relocation Site, Dipolog City, Zamboanga del Norte	<i>S. alata</i> cream Applied BID for 15 days	Ketoconazole cream Applied BID for 15 days	Clinical resolution of lesions (no clearing, partial clearing, complete clearing); adverse reaction; KOH smear
Oladele, 2012 <sup>24</sup>	67 patients with "superficial fungal skin infections" Ilesa Prison, Nigeria	<i>S. alata</i> soap Lather and bathe with soap BID for 4 wks.	Control 1: <i>Erythrophleum</i> 5% w/w soap Control 2: <i>Xylopi</i> a 5% w/w soap Control 3: placebo soap Lather and bathe with soap BID for 4 wks.	Did not specify any outcome measure

STS – Sodium thiosulfate; BID – Twice daily

## Appendix 3. Summary of Findings Table 1

50% *Senna alata* lotion compared to 25% Sodium Thiosulfate lotion for tinea versicolor

Patient or population: tinea versicolor

Setting: Dermatology clinic

Intervention: 50% *Senna alata* lotion

Comparison: 25% Sodium Thiosulfate lotion

Outcome	Anticipated absolute effect* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with 25% Sodium Thiosulfate lotion	Risk with 50% <i>Senna alata</i> lotion				
Mycologic Cure assessed with: Potassium hydroxide (KOH) smear	95 per 100	86 per 100 (75 to 99)	RR 0.91 (0.79 to 1.04)	216 (4 RCTs) <sup>1,2,3,4</sup>	⊕⊕○○ LOW <sup>4,a,b</sup>	
Adverse Effects	9 per 100	11 per 100 (4 to 31)	RR 1.26 (0.46 to 3.44)	120 (2 RCTs) <sup>1,3</sup>	⊕○○○ VERY LOW <sup>c,d</sup>	
Clinical Cure	90 per 100	57 per 100 (36 to 89)	RR 0.63 (0.40 to 0.99)	36 (1 RCT) <sup>4</sup>	⊕⊕○○ LOW <sup>4,e,f</sup>	

\*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: Confidence interval; RR: Risk ratio

## GRADE Working Group grades of evidence

**High certainty:** We are very confident that the true effect lies close to that of the estimate of the effect

**Moderate certainty:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

**Low certainty:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

**Very low certainty:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

## Explanations:

- High risk for attrition bias. Sensitivity analyses revealed a soft conclusion for three studies. One study did not indicate number of dropouts per treatment arm.
  - High heterogeneity due to one study with longer treatment period and significant number of dropouts.
  - Sensitivity analysis of one study reveals a soft conclusion, while another study only indicated the number of participants who completed the trial, hence a sensitivity analysis cannot be performed.
  - Confidence intervals are very wide and crossed both significant benefit (RR>1.25) and harm (RR<0.75).
  - High risk for attrition bias. Sensitivity analysis reveals a soft conclusion.
  - Confidence interval is wide and crossed harm (RR<0.75).
- De Dios-Torralba, 1993
  - Reyes, 1996
  - Dofitas, 2001
  - Valdez-Eusebio, 1996



**Appendix 3. Summary of Findings Table 2**

**Senna alata cream compared to Ketoconazole cream for tinea versicolor**

**Patient or population:** tinea versicolor

**Setting:** Dermatology clinic

**Intervention:** Senna alata cream

**Comparison:** Ketoconazole cream

Outcome	Anticipated absolute effect* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Ketoconazole cream	Risk with Senna alata cream				
Mycologic Cure	100 per 100	95 per 100 (82 to 100)	RR 0.95 (0.82 to 1.09)	40 (1 RCT) <sup>1</sup>	⊕⊕⊕⊕ HIGH	
Clinical Cure	5 per 100	2 per 100 (0 to 40)	RR 0.37 (0.02 to 8.50)	40 (1 RCT) <sup>1</sup>	⊕⊕○○ LOW <sup>a</sup>	

\*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: Confidence interval; RR: Risk ratio

**GRADE Working Group grades of evidence**

**High certainty:** We are very confident that the true effect lies close to that of the estimate of the effect

**Moderate certainty:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

**Low certainty:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

**Very low certainty:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

**Explanations:**

a. Confidence intervals are very wide and crossed both significant benefit (RR>1.25) and harm (RR<0.75).

1. Ting, 2000

**Appendix 3. Summary of Findings Table 3**

**Senna alata cream compared to 1% Terbinafine cream for dermatophytosis or tinea versicolor**

**Patient or population:** dermatophytosis or tinea versicolor

**Setting:** Dermatology clinic

**Intervention:** Senna alata cream

**Comparison:** 1% Terbinafine cream

Outcome	Anticipated absolute effect* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with 1% Terbinafine cream	Risk with Senna alata cream				
Mycologic Cure	97 per 100	91 per 100 (84 to 98)	RR 0.93 (0.86 to 1.01)	150 (1 RCT) <sup>1</sup>	⊕⊕⊕⊕ HIGH	

\*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: Confidence interval; RR: Risk ratio

**GRADE Working Group grades of evidence**

**High certainty:** We are very confident that the true effect lies close to that of the estimate of the effect

**Moderate certainty:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

**Low certainty:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

**Very low certainty:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

**Explanations:**

1. De Leon-Pandanan, 2002