Efficacy and Safety of *Gliricidia sepium*, *Senna alata*, and *Tinospora rumphii* in the Treatment of Filipino Patients with Scabies: A Systematic Review and Meta-analysis

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ABSTRACT

Background. Scabies is a highly contagious neglected tropical disease and a persistent challenge globally, particularly in regions like the Philippines, where it remains endemic. With conventional treatments facing limitations such as resistance and adverse effects, exploring the potential of traditional medicinal plants offers a promising avenue for novel therapeutics. However, evidence of their comparative efficacy and safety is still lacking.

Objectives. To determine the efficacy and safety of *Gliricidia sepium* (kakawati), *Senna alata* (akapulko), and *Tinospora rumphii* (makabuhay) compared to topical scabicides or placebo in the treatment of Filipino patients with scabies using a systematic review.

Methods. We searched the following databases from inception to March 2024: MEDLINE via PubMed, CENTRAL, EMBASE, EBSCO, HERDIN, ClinicalTrials.gov, WHO-ICRTP, and PHRR. We included all randomized controlled trials involving Filipino patients diagnosed with scabies where preparations containing one of three plants (*G. sepium*, *S. alata*, or *T. rumphii*) were compared with a topical scabicide or placebo for treatment. Two review authors independently applied eligibility criteria, assessed risk of bias (using Risk of Bias 2.0), and extracted data from the included studies. Primary outcomes were complete clearance of skin lesions, reduction of pruritus, and the presence of serious adverse events. Secondary outcomes were recurrence, any adverse events, adverse events requiring withdrawal, and patient-reported outcomes. We used RevMan 5.4 to pool dichotomous outcomes using risk ratios and continuous outcomes using mean difference and applied random-effects meta-analysis. We tested for statistical heterogeneity using both the Chi^2 test and the I^2 statistic. We presented the results using forest plots with 95% confidence intervals. We intended to conduct a funnel plot analysis to check for reporting bias but were unable to because of the limited number of studies. Quality of evidence was assessed using the GRADE approach, and a Summary of Findings table was created using GRADEpro GDT for the primary outcomes.

Results. We included nine RCTs (N=607 participants) that compared various dosage forms (ointments, lotions, poultice, soap, aqueous extract) containing one of the three plants (*G. sepium*, three studies; *S. alata*, two studies; *T. rumphii*, four studies) versus placebo or existing topical scabicides (permethrin, sulfur, crotamiton). Pooled analyses showed that there is probably no difference in complete clearance of lesions between *G. sepium* and 5% sulfur (RR 0.92 [0.79, 1.07], 2 RCTs, N=85, moderate certainty of evidence). We are uncertain about the difference in complete clearance of lesions between *S. alata* lotion and placebo (RR 4.94 [1.67, 14.62], 2 RCTs, N=157, very low certainty of evidence), *T. rumphii* and crotamiton (RR 1.02 [0.76, 1.37], 2 RCTs, N=131,

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very low certainty of evidence), and *T. rumphii* lotion and placebo (RR 5.28 [0.76, 36.43], 2 RCTs, N=71, very low certainty of evidence). Data could not be pooled for reduction in pruritus scores due to limited studies for each intervention. No serious adverse events were reported across all studies.

Conclusion. *Gliricidia sepium* (kakawati) is probably as effective and safe as 5% sulfur in the management of patients with scabies and may be a promising alternative herbal treatment. Future RCTs should compare it with scabicides recommended by the Philippine Department of Health and World Health Organization, such as permethrin, benzyl benzoate or oral ivermectin. *T. rumphii* and *S. alata* may also be investigated using RCTs that should be adequately powered and with good methodologic quality.

Keywords: scabies, herbal medicine, Gliricidia sepium, Senna alata, Tinospora rumphii, kakawati, akapulko, makabuhay

INTRODUCTION

Scabies is a highly contagious infestation caused by the obligate ectoparasite, *Sarcoptes scabiei* var. *hominis*, and represents a multifaceted and persistent challenge in global public health.[1] It is transmitted primarily through direct, prolonged skin-to-skin contact with an infested individual.[2] The clinical presentation may vary depending on several factors, but this infestation classically presents as severe pruritus, papular eruptions, and linear burrows in common sites such as the wrists, elbows, interdigital areas, nipples, pelvis, buttocks, and the male genitalia.

Globally, scabies is estimated to affect 300 million individuals yearly, greatly affecting vulnerable populations such as children, the elderly, immunocompromised individuals, and institutionalized persons.[1,3] Epidemiological studies have highlighted its prevalence in low-income tropical countries, with the burden being higher in the following geographic regions: east Asia, southeast Asia, Oceania, tropical Latin America, south Asia, and Africa.[4,5] It was declared a "neglected tropical disease" by the World Health Organization (WHO) in 2017 because of the disproportionate burden it places on populations living in poverty, emphasizing the necessity for innovative disease management strategies.[6] In the Philippines, scabies is the second most common cause of disability due to skin disease with a national prevalence estimated to be between 2 and 10%. True to its pattern of transmission, local institution-based surveys report even higher proportions, affecting 39 to 45% of their residents.[7]

Effective management of scabies involves a combination of pharmacological interventions, environmental measures, and community-based approaches.[3] Scabies necessitates a systematic treatment approach as outlined in the 2017 European Guidelines for the Management of Scabies. Among the primary recommendations are permethrin cream, oral ivermectin, and benzyl benzoate lotion.[8] Scabies, a disease which disproportionately affects populations living in poverty, warrants the integration of cheap, acceptable, and locally available alternatives into these guidelines.

Recent literature highlights a concerning trend of increasing treatment failure rates, attributed to various factors including improper application techniques, reinfection risks, and emerging mite resistance to conventional therapies like permethrin and ivermectin.[9,10] A recent meta-analysis revealed a significant increase over time in overall and permethrin treatment failure as well as higher rates of ivermectin treatment failure in studies published in 2011 or later.[11] Other available scabicides also present with health and environmental safety concerns or administration issues: the use of lindane is strongly discouraged due to its neurotoxic and environmental risks, and crotamiton cream, although low in toxicity, necessitates multiple applications for satisfactory results.[8,12] Moreover, treatment choices may also be limited due to cost and availability, especially in low-income countries, which disproportionately bear the burden of scabies. These trends underscore the urgency for ongoing research endeavors aimed at developing novel and alternative therapeutic options and addressing evolving resistance patterns.

Herbal medicines, defined by the Philippine Food and Drug Administration as "finished, labeled medicinal products that contain as active ingredient(s) aerial or underground part(s) of plants or any other plant material, or combination thereof, whether in the crude state or as plant preparations… intended for use in the diagnosis, alleviation, cure or treatment of disease," are widely used and accepted, especially in less developed countries where access to conventional healthcare is challenging.[13] These plant-based products offer several advantages, including safety, patient acceptability, low cost, and reduced likelihood of resistance development.[14] In 2023, the WHO released a technical document calling for the integration of evidence-based traditional medicine into national health systems, particularly at the level of primary health care.[15] Scabies is a disease that disproportionately affects people living in poverty and is currently managed using drugs that may not be inexpensive to these patients. In the Philippines, the Department of Health (DOH) endorsed a list of ten 'scientifically-validated' medicinal plants for various indications, signaling the integration of herbal medicines into mainstream treatment protocols.[16] Building an evidence based on several local medicinal plants led to the development and inclusion in the national formulary of lagundi (*Vitex negundo*) and sambong (*Lagerstroemia speciosa*).[17] Included in this DOH-sanctioned list is akapulko (*Senna alata*), which is indicated as an external treatment for superficial fungal infections. Additionally, its leaves find folkloric use as a decoction in the management of scabies. Other local medicinal plants that are notable for their purported efficacy in the treatment of scabies are kakawati/kakawate/madre de cacao (*Gliricidia sepium*) and makabuhay (*Tinospora rumphii*).[18]

Gliricidia sepium or kakawati contains saponins, flavonoids, and volatile oils, and exhibits notable insecticidal and ovicidal activity against *Anopheles stephensi*, a vector for malaria, highlighting its potential role in vector control efforts.[19,20] In the Philippines, kakawati is traditionally used in the management of scabies as leaf juice or decoctions and bark decoctions.[17,19] A local randomized controlled trial demonstrated the comparative efficacy of a kakawati poultice with sulfur lotion in treating scabies, thus validating its traditional use in the management of this parasitic infestation.[21] *Senna alata* has garnered attention for its potent antifungal activity, substantiated by numerous in vitro and clinical studies showing comparable mycologic cure rates with conventional antifungal treatment.[22] It holds a diverse array of pharmacological activities attributed to its rich composition of secondary metabolites, such as various tannins, alkaloids, flavonoids, terpenes, volatile oils, and many more throughout its various plant parts, the most used of which in traditional medicine are its leaves, bark, stem, roots, pods, and seeds.[23,24] In fact, in China, Thailand, and the Philippines, decoctions derived from its stem, bark, and leaves have been traditionally used in the management of other skin infestations, such as scabies.[17,25] Clinical trials in the Philippines used the lotion preparation for the treatment of scabies.[26–29] *Tinospora rumphii* is a deciduous climbing plant native to Africa and Southeast Asia that contains alkaloids, flavonoids, terpenoids, and phenolic compounds.[30,31] Its leaves, stems, seeds, rhizomes, and roots are used in ethnomedicine predominantly in Southeast Asia for various ailments such as hypertension, diabetes, rheumatism, jaundice, inflammation, fever, malaria, loss of appetite, fractures, scabies, and urinary disorders.[17,30] In the context of scabies, various studies comparing *T. rumphii* lotion preparations with standard treatments have demonstrated its efficacy in managing this ectoparasitosis.[27,28,31]

To date, while there are several local randomized controlled trials on the use of these plants for scabies, there have been no attempts to give a complete assessment of the present evidence by synthesizing data from these relevant studies among Filipinos. Validating the effectiveness of these herbal medicines in scabies management is a step towards incorporating complementary and alternative therapies to mainstream treatment protocols, addressing gaps in accessibility and affordability.[17,20] Thus, there is a need to systematically evaluate the efficacy and safety of these medicinal plants in the treatment of Filipino patients with scabies.

OBJECTIVES

This study aimed to determine the efficacy and safety of preparations containing *Gliricidia sepium, Senna alata*, and *Tinospora rumphii* in the treatment of Filipino patients with scabies.

METHODS

The systematic review protocol was registered in the University of the Philippines (UP) Manila Research Grants Administration Office (RGAO-2024-0328) and the UP College of Medicine Research Implementation Development Office (RIDO-2024-096) and is available upon request from the authors. The study was considered REB-exempt (UPMREB 2024-0325-EX). We followed the Cochrane Collaboration methods and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 checklist.[32,33] This study was conducted from May 4 - July 30, 2024 through online search and data extraction. There were no protocol amendments.

Eligibility Criteria

Types of studies

We included randomized controlled trials conducted in the Philippines which determined the efficacy and safety of *Gliricidia sepium, Senna alata,* or *Tinospora rumphii* in the treatment of scabies in people of all ages.

Types of participants

We included studies with Filipino participants clinically diagnosed with scabies by a physician or a trained healthcare professional, either through history taking and physical examination or microscopic examination using skin scrapings.

Types of interventions

We included studies whose interventions are preparations that contain as active ingredient/s any part (e.g., stems, leaves, roots, fruits) of one of three plants, whether in the crude state or as prepared dosage forms: *Gliricidia sepium, Senna alata*, or *Tinospora rumphii*. We excluded studies if their interventions (1) contained more than one of the three plant species; (2) were combined with chemically defined, therapeutically active substances; or (3) included chemically defined, isolated constituents of plants or preparations of compound/s isolated from any of these plants. We excluded the first two criteria to isolate the efficacy of each plant alone, without any possible contributions of other plants or chemicals. We excluded the third criterion since these are already considered conventional, and not herbal, medicine.

Types of comparator

We included studies that used the following comparator/s: topical scabicidal agents (e.g., permethrin, benzyl benzoate, crotamiton, topical ivermectin, lindane, sulfur, malathion, other pyrethrins), placebo, or no treatment. Studies were excluded if they used as comparator the same intervention as the treatment group but with a different dose/concentration, formulation, frequency, or mode of delivery.

Types of outcome measures

The primary outcomes included in this study were complete clearance of skin lesions, reduction of pruritus, and the presence of serious adverse events, all determined by using the definition of each original study; while the secondary outcomes include recurrence, any adverse events, adverse events requiring withdrawal, and patient-reported outcomes (e.g., quality of life, satisfaction, acceptability).The outcome measures reported in the studies screened were not used as part of the eligibility criteria.

Search Strategies

Electronic searches

We searched the following databases from inception until March 2024: MEDLINE via PubMed, The Cochrane Library for Clinical Trials in CENTRAL, EBSCO, and HERDIN (Health Research and Development Information Network) using the search strategies detailed in Appendix A. No language restrictions were applied.

Trial registers

We searched for study protocols and reports up to March 2024 using the search word, "scabies," in the following trial registries: ClinicalTrials.gov, WHO-ICRTP, and the Philippine Health Research Registry (www.registry.healthresearch.ph).

Supplementary searches

We manually checked the reference lists of all trials retrieved by the search and utilized the 'similar articles' feature of databases. We also performed hand searching of relevant local journals as well as thesis/dissertation collections from the College of Medicine, College of Pharmacy, and College of Public Health of the University of the Philippines Manila.

Data Collection and Analysis

Selection of studies

The titles and abstracts from the search were screened by two authors for potential relevance based on the eligibility criteria. Independent screening was ensured by utilizing Rayyan, an artificial intelligence software.[34] These two authors were not blinded as to the identifiers of the studies (names of authors, institutions, journal of publication, and results) when they applied the eligibility criteria.

Full texts of all potentially relevant studies were assessed for eligibility. Discrepancies in the inclusion and exclusion of articles were resolved by discussion or by referring to the third author. When studies were excluded, an explanation was provided (Appendix B).

Data extraction and management

Two authors independently extracted data from the included studies using a piloted standardized data extraction form. Any discrepancy was resolved by discussion or by referring to the third author. The following data items were extracted:

- **Identifiers:** Study title, authors, publication year, country in which the study was conducted, funding sources, any conflicts of interest
- **Methods:** Study design, duration of participation, inclusive dates
- **Participants:** number, age (range and mean), sex distribution, setting, diagnostic criteria, severity of scabies, inclusion/exclusion criteria, comorbidities
- **Interventions and comparators:** description, method of preparation, dose, timing, mode of delivery, blinding, co-intervention, simultaneous treatment of close contacts, integrity of intervention
- **Outcomes:** Primary outcomes (complete clearance of skin lesions, reduction of pruritus, and the presence of serious adverse events); Secondary outcomes (recurrence, any adverse events, adverse events requiring withdrawal, and patient-reported outcomes [e.g., quality of life, satisfaction, acceptability]).

Assessment of risk of bias in included studies

Two review authors independently assessed the risk of bias for every outcome of all included studies using the Cochrane Risk of Bias 2.0 tool in five domains: randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result.[35] Overall risk of bias was assessed as "low risk," "some concerns," or "high risk." Any discrepancy was resolved by discussion or by referring to the third author. Traffic light plots and summary plots were generated using the Risk-of-bias VISualization software (https://mcguinlu.shinyapps.io/robvis/).[36]

Data synthesis

We pooled studies that compared the same herb to the same comparator, at any dose/concentration,dosage, or preparation. Although varying concentrations or preparations of the same plant may potentially cause heterogeneity, we planned to do subgroup analysis if there were enough studies. Overall intervention effect was calculated using RevMan 5.4.[32] For dichotomous outcomes (complete clearance of lesions, any adverse events), risk ratio (RR) and 95% confidence intervals were used, while mean difference (MD) and standard deviation (SD) were obtained for continuous outcomes (reduction in pruritus scores). Data was pooled only for studies which were clinically homogeneous (same intervention, comparator, and outcomes measured). Direct meta-analysis of each comparison was performed by pooling RRs if there were at least two studies. We constructed forest plots with risk of bias per individual study.

Unit of analysis

The unit of analysis in this review was the individual/participant.

Dealing with missing data

We planned to do intent-to-treat analysis by analyzing participants in the group they were originally randomized to, regardless of how the study authors analyzed them. If there were missing data, such as from participants who did not have any outcome assessments at relevant timepoints, we excluded them from the main analysis.

Assessment of heterogeneity

For the pooled studies, we assessed heterogeneity using visual inspection of the forest plots to check for overlapping confidence intervals. Using RevMan 5.4, a chi-squared test was automatically performed at 10% level of significance and the I^2 statistic was obtained.[32] If the I^2 value is >50%, heterogeneity was assessed to be significant, and it was substantial if I^2 was >75%. If significant heterogeneity exists, a random-effects model was used; otherwise, a fixed-effects model was used. We planned to do subgroup analysis if there were enough studies to try to explain heterogeneity if it existed.

Sensitivity analyses

We compared fixed effects vs random effects meta-analysis as well as worst- and best-case analysis based on dropouts to determine the robustness of our main analysis.

Assessment of reporting bias

We planned to identify potential publication bias by constructing funnel plots where necessary, but we were unable to due to few studies.

Assessment of quality of evidence

We assessed the quality of evidence using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach to facilitate interpretation and inform recommendations. With this, we evaluated the effect measures per outcome, taking into consideration risk of bias, inconsistency, imprecision, indirectness, and publication bias. Imprecision was assessed using a minimally contextualized approach proposed by Zeng and colleagues.[37] We used the GRADEpro GDT (Guideline Development Tool) software (V. 2021: http://www.gradepro.org/) to create the 'summary of findings' tables for the primary outcomes (Appendix C).[38]

RESULTS

We identified 337 records from the databases and two from secondary sources. From 339 records, we removed 59 duplicates and screened 280 titles and abstracts. Out of 14 potentially relevant records, only 11 full-text articles were retrieved for assessment of eligibility criteria, and two were excluded (Appendix B). Nine RCTs were included in the review.[21,26–29,31,39–41] Seven studies were included in the meta-analyses (Figure 1).

Description of Included Studies

The nine RCTs included in this review included data from 607 participants: 135 from RCTs studying *G. sepium*, 220 for *S. alata*, and 252 for *T. rumphii*. Five were 2-arm studies while four were 3-arm studies.[28,29,39,41] One study was a cluster-RCT, however, the number of households and average household size were not stated and effective sample size was not computed.[26] Sample sizes ranged from 40 to 120 with a median of 55.[26,28] There was a wide range of ages among participants, from two months to over 60 years, but most of the studies included children. All RCTs had both male and female participants except Yoro 2005, which was conducted in a female-only institution. Median male/female ratio for the six studies that reported sex distribution was 1.48. Diagnosis of scabies was done clinically for all studies, however, one also included microscopic examination of skin scrapings in their diagnostic criteria.[41]

All RCTs were conducted in the Philippines, specifically in the National Capital Region and Region IV-A (CALABARZON). Five were done in residential institutions such as orphanages, detention centers, or correctional facilities, three in community-based health centers, and one in a residential village. Publication date was sparsely distributed from 1983 to 2013 (two in the 1980s, two in the 1990s, four in the 2000s, and one in the 2010s).

Three studies used *G. sepium* in various dosage forms as their intervention.[21,39,40] All RCTs used the leaves of *G. sepium* as their active component. Two studies both followed similar unspecified standardized instructions for the preparation of their ointment and poultice, respectively, while one study hired a private company for the manufacture of their soap.[21,39,40] Two of these did not have any co-interventions; one study, however, also included *G. sepium* ointment as an adjunct treatment to the intervention (i.e., soap) in both treatment arms.[21,39,40] 5% sulfur was used as the comparator for two studies, while one study had ordinary soap as placebo.[21,39,40]

Two studies used *S. alata* as their intervention, both being prepared as lotions but in different dosages.[26,41] They were prepared similarly, boiling dried leaves in water and mixing a vehicle into the resulting decoction. One study had three treatment arms, comparing 50% lotion to 10% crotamiton and placebo, while the other compared 80% lotion with placebo.[26,41]

The remaining four RCTs used *T. rumphii* in their experimental arm.[27–29,31] All studies used the plant stems in preparing their dosage forms, three of which were lotions while one used the aqueous extract.[27–29,31] One study compared *T. rumphii* against 5% permethrin lotion, two studies against crotamiton, and one study against 5% sulfur.[27–29,31] A placebo was also used as a third treatment arm in two studies.[28,29]

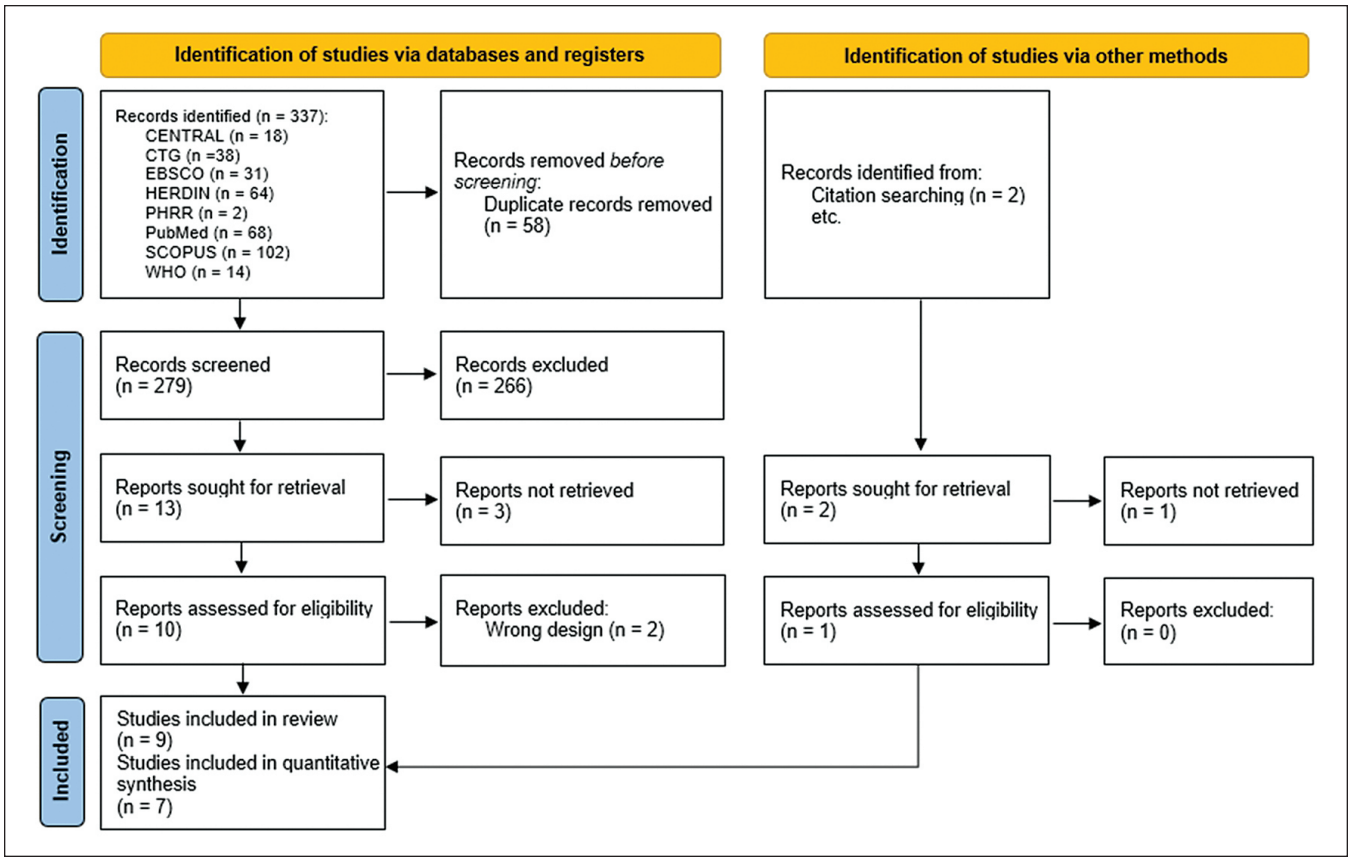

Figure 1. PRISMA study flow diagram.

The experimental treatment was applied topically in all studies, with all being left on the skin for 12-24 hours after a bath, except for one study wherein the participants used the soap in bathing. The duration of administration varied across studies, ranging from three consecutive days to weekly administration. All RCTs reported cure, which they defined as complete clearance of scabies lesions. Seven studies intended to report adverse events, but only three were able to record such, with the rest posting zero events.[31,40,41] Four measured pruritus scores and their reduction thereof, two reported acceptability, while one also measured cost-effectiveness.[26,29,31,40,41]

The characteristics of the included studies are detailed in Table 1.

Risk of Bias in Included Studies

Majority of the studies that measured complete clearance of lesions had either high overall risk of bias (four studies) or some concerns (two studies).[26-29,39,40] These assessments were made mostly on the basis of problems with the randomization process, such as the non-reporting of allocation sequence generation and/or allocation concealment and the presence of substantial differences in the baseline characteristics of the treatment arms.[27,28] High risk of bias was also detected due to deviations from intended interventions, non-blinding of outcome assessors, or the inappropriate selection of reported results (Figure 2).[26,39]

Meanwhile, there was low overall risk of bias for the two studies that measured reduction in pruritus scores (Figure 3).[29,31] As for the three studies that reported adverse events, there were some concerns regarding the risk of bias for one study arising from the randomization process and deviations from intended interventions (Figure 4).

The forest plots in Figures 5 to 9 contains the risk of bias assessments per domain per individual study for each comparison/outcome.

Effects of Interventions

Gliricidia sepium versus placebo

We are uncertain whether *G. sepium* soap as an adjunct to *G. sepium* ointment differs in clearance of lesions when compared to placebo soap as an adjunct to *G. sepium* ointment (RR 0.86 [0.63, 1.18], 1 RCT, N=49, very low certainty of evidence) (Appendix C.1). We downgraded the evidence rating by two levels for risk of bias due to outcome measurement and selection of reported results, and by one level for imprecision due to lower limit of the confidence interval crossing important benefit for placebo.

Table 1. Characteristics of Included Studies (n = 9)

Author (Year Published)	Methods	Participants	Intervention	Comparator	Outcomes
***Gliciridia sepium* (k = 3)**					
Ancheta (2003) [26]	Design: randomized controlled trial (3-arm) Allocation: randomized using draw lots Blinding: not stated	Children with scabies Age: 3-18 years Sex: male and female Setting: two institutions (Marikina City and Quezon City) housing orphans, street children, and juvenile delinquents Inclusion criteria: children aged 3-18; clinical diagnosis of scabies; no previous treatment received for scabies N=49	*Gliricidia sepium* soap Plant part: Fresh leaves Other ingredients: refined coconut oil (Baguio Oil), and melted paraffin wax Timing: daily, during bathing Delivery: applied by caretakers Duration: seven days Co-interventions: *G. sepium* ointment N=27	Placebo 1. Ordinary soap A (Safeguard) N=15 2. Ordinary soap B (Palmolive) N=7 Timing: daily, during bathing Delivery: applied by caretakers Duration: seven days Co-interventions: *G. sepium* ointment *The two ordinary soap groups were combined into placebo group	Cure
Bañez (1999) [27]	Design: randomized controlled trial (2-arm) Allocation: randomized using draw lots Blinding: double-blind (participants and investigators)	Patients with scabies Age: all ages Sex: male and female Setting: CBHP (community-based health program) in Bagong Nayon II, Antipolo, Rizal Inclusion criteria: clinical diagnosis of scabies; residents of six months; not receiving any treatment for scabies N=44	*Gliricidia sepium* poultice Plant part: Not stated Timing: daily; left on skin for 24 hours before rinsing Delivery: self-application from neck down Duration: five days Co-interventions: none N=20	5% sulfur lotion Timing: daily; left on skin for 24 hours before rinsing Delivery: self-application from neck down Duration: five days Co-interventions: none N=24	Cure Adverse events
Felicen (2002) [28]	Design: randomized controlled trial (2-arm) Allocation: allocation sequence generation not stated Blinding: double-blind (participants and investigators)	Patients with scabies Age: 5-60 years Sex: male and female Setting: Area III, Payatas, Quezon City Inclusion criteria: resident of Area III; aged 5 and older; clinical diagnosis of scabies; no use of ectoparasiticide in the previous three weeks; no allergy to sulfur; no signs of systemic infection or other diseases N=42	*Gliricidia sepium* ointment (50%) Plant part: Not stated Timing: daily after bathing in the evening, left on the body overnight for 12 hours Delivery: self-applied from neck down Duration: five days Co-interventions: none N=21	5% sulfur ointment Timing: daily after bathing in the evening, left on the body overnight for 12 hours Delivery: self-applied from neck down Duration: five days Co-interventions: none N=21	Cure, effectiveness (improvement in quality of life), cost-effectiveness, Adverse events
***Senna alata* (k = 2)**					
Alayon (2002) [29]	Design: randomized controlled trial (2-arm) Allocation: cluster randomization Blinding: double-blind (participants and investigators)	Patients with scabies Age: all ages Sex: male and female Setting: rural health units of Dasmariñas, Cavite Inclusion criteria: clinical diagnosis of scabies Exclusion criteria: pregnancy; very young age; infected lesions; absence of typical lesions N=120	*Senna alata* lotion (80%) Plant part: Dried leaves - boiled in water Other ingredients: Propyl and methyl paraben. Tragacanth, and liquid petrolatum Timing: daily after bathing in the evening, then washed off using one brand of soap in the morning Delivery: self-application from neck down to feet Duration: three days Co-interventions: none N=78	Placebo (same components as the vehicle without the *S. alata* decoction) Timing: daily after bathing in the evening, then washed off using one brand of soap in the morning Delivery: self-application from neck down to feet Duration: three days Co-interventions: none N=42	1. Cure (Complete = 80% reduction in lesion count; Partial = 70% reduction in lesion count with a decrease in pruritus; Failure = <70% reduction in lesion count and no change or aggravating pruritus), 2. Itch resolution (VAS, scale 0 to 10), 3. Acceptability (odor, suitability, convenience), 4. Adverse events Others: benefit rate, failure rate

Table 1. Characteristics of Included Studies (n = 9) *(continued)*

Author (Year Published)	Methods	Participants	Intervention	Comparator	Outcomes
Concepcion (1998) [30]	Design: randomized controlled trial (3-arm) Allocation: block randomization Blinding: double-blind (participants and investigators)	Patients with scabies Age: 7-30 years Sex: male and female Setting: community health centers served by the De La Salle University Medical Center in Cavite Inclusion criteria: aged 7-30 years; male or female; positive for scabies eggs or fecal pellets from skin scrapings based on microscopic examination; with at least one member of the family with typical signs and symptoms of scabies Exclusion criteria: presence of infected skin lesions; prior use of scabicide or other topical medication within the last 14 days; presence of other skin diseases; pregnancy or lactating mothers; presence of systemic diseases N=100	*Senna alata* lotion (50%) Plant part: Dried leaves - boiled in water Other ingredients: unspecified "Vehicle" Timing: daily after bathing in the evening, then washed off using one brand of soap in the morning Delivery: self-application from neck down to feet Duration: three days Co-interventions: none N=39	2 comparator arms 1. 10% crotamiton lotion (N=25) 2. Placebo (N=36): same component as vehicle, without the *S. alata* decoction Timing: daily after bathing in the evening, then washed off using one brand of soap in the morning Delivery: self-application from neck down to feet Duration: three days Co-interventions: none	Cure, itch resolution, acceptability, adverse events, benefit rate
***Tinospora rumphii* (k = 4)**					
Castillo (2013) [31]	Design: randomized controlled trial (2-arm) Allocation: randomization using Microsoft Excel Blinding: single-blind (participants)	Patients with scabies Age: 2-22 years Sex: male and female Setting: Manila Youth Reception Center, Reception Action Center and Tanglao Detention Center in Malolos, Bulacan, Philippines Inclusion criteria: aged 2-22 years; clinical diagnosis of scabies Exclusion criteria: use of topical or oral scabicide or corticosteroid four weeks before trial; presence of concomitant secondary bacterial infections with systemic manifestations like fever, malaise, chills; enrollment in other clinical study N=66	*Tinospora rumphii* lotion Plant part: Fresh mature stems – air-dried and powdered (from Angat, Bulacan) – 80% ethanolic extract Other ingredients: water phase (methyl paraben and water) + creamy phase (stearic acid, tween 80, lanolin, propyl paraben) Timing: daily for three consecutive days per week, after a night bath using a mild soap Delivery: self-application from neck down to feet, especially on the sites of predilection Duration: 14 days Co-interventions: none N=34	5% Permethrin lotion Timing: daily for three consecutive days per week, after a night bath using a mild soap Delivery: self-application from neck down to feet, especially on the sites of predilection Duration: 14 days Co-interventions: none N=32	Cure, itch resolution, adverse events, resolution of other signs and symptoms of scabies (erythema, secondary lesions)
Rivera (1983) [32]	Design: randomized controlled trial (2-arm) Allocation: allocation sequence generation not stated Blinding: not stated	Children with scabies Age: 2 months to 8 years Sex: male and female Setting: Reception and Study Center for Children in Quezon City Inclusion criteria: clinical diagnosis of scabies Exclusion criteria: presence of secondary infection; clinical or laboratory evidence of kidney problem; drug or food allergy; fever N=91	*Tinospora rumphii* Plant part: Fresh stems - powdered/pounded into aqueous extract Timing: after bath on first night; applied similarly on second and third night without bathing Delivery: applied by caretaker from scalp down, with special attention to creases and folds Duration: three days Co-interventions: none N=33	10% Crotamiton (Eurax) Timing: after bath on first night; applied similarly on second and third night without bathing Delivery: applied by caretaker from scalp down, with special attention to creases and folds Duration: three days Co-interventions: none N=53	Cure, partial cure, adverse events

Table 1. Characteristics of Included Studies (n = 9) *(continued)*

Author (Year Published)	Methods	Participants	Intervention	Comparator	Outcomes
Salazar (1987)[33]	Design: randomized controlled trial (3-arm) Allocation: allocation sequence generation not stated Blinding: not stated	Patient with scabies Age: all ages Sex: male and female Setting: Elsie Gaches Village (residential care center for individuals with mental disability) Inclusion criteria: clinical diagnosis of scabies N=40	*Tinospora rumphii* lotion Plant part: Macerated stems Other ingredients: Vegetable oil Timing: once a day for three days, usually each morning after bathing; followed by a rest period of 7-14 days, then by a regimen change to 5-day application and 5-day rest Delivery: self-application Duration: 26-33 days Co-interventions: none N=26	2 comparator arms 1. 5% sulfur ointment (N=9) Timing: once a day for three days, usually each morning after bathing; followed by a rest period of seven days; repeated for another cycle (3-7-3) Delivery: self-application Duration: 26 days Co-interventions: none 2. Placebo (N=5) Contains refined vegetable oil Timing, delivery, and duration same as *T. rumphii* lotion Co-interventions: none	Cure Recurrence
Yoro (2005)[34]	Design: randomized controlled trial (3-arm) Allocation: allocation sequence generation not stated Blinding: double-blind (participants and investigators)	Female children with scabies Age: 2-17 years Setting: Manila Boystown Complex Girls' Home Inclusion criteria: clinical diagnosis of scabies Exclusion criteria: use of scabicide within the past two weeks; secondary bacterial and/or fungal infection N=55	*Tinospora rumphii* lotion Plant part: Not stated Other ingredients: stearic acid lanolin, Tween 80 and propyl paraben, and methyparaben Timing: five consecutive days of application (after bathing on the first night, then without bathing on the succeeding nights), followed by a rest period of five days, and another five consecutive days of application Delivery: self-application from scalp down with special attention to creases and folds Duration: two weeks Co-interventions: none N=30	2 comparator arms 1. 10% crotamiton lotion (N=15) 2. Placebo (N=10) Timing: five consecutive days of application (after bathing on the first night, then without bathing on the succeeding nights), followed by a rest period of five days, and another five consecutive days of application Delivery: self-application from scalp down with special attention to creases and folds Duration: two weeks Co-interventions: none	Cure, itch resolution, adverse events, resolution of other signs and symptoms of scabies (erythema, secondary lesions)

Gliricidia sepium (kakawati) versus 5% sulfur

There were two RCTs (N=85) with low to moderate risk of bias in this comparison. The intervention was kakawati 50% ointment in one study while the other used poultice, whereas the comparator was 5% sulfur ointment or lotion, respectively; all interventions were applied daily for five days.[21,40] There is probably little or no difference between *G. sepium* and 5% sulfur in the complete clearance of scabies lesions (RR 0.92 [0.79, 1.07]; moderate certainty of evidence) (Figure 5) (Appendix C.2). Despite using different dosage forms for the treatment arm (ointment and poultice), there was no significant heterogeneity (I^2 = 0%) between the studies. Certainty of evidence was rated moderate because we downgraded one level for imprecision.

Likewise, there may be more adverse events (2/20 with rashes) when using *G. sepium* versus 5% sulfur (1/21 with intense itching and rashes), as reported by one study (RR 2.10 [0.21, 21.39], N=41, low certainty of evidence).[40] Evidence was downgraded by two levels due to imprecision.

One study also reported that the *G. sepium* poultice was associated with ease of application, acceptable odor, and a tolerable amount of stickiness, whereas those who used 5% sulfur noted ease of application but also unacceptable odor and relative stickiness.[21]

Senna alata versus placebo

We are uncertain whether *S. alata* lotion differs in clearance of lesions when compared to placebo (RR 4.94 [1.67, 14.62], 2 RCTs, N=157; very low certainty of evidence) (Figure 6) (Appendix C.3). The evidence was downgraded by two levels for imprecision and one level for high risk of bias in one study.

With only one small study reporting any adverse events, it suggests that *S. alata* may lead to more adverse events compared to placebo (RR 12.03 [0.70, 206.12], N=75; low certainty of evidence).[41]

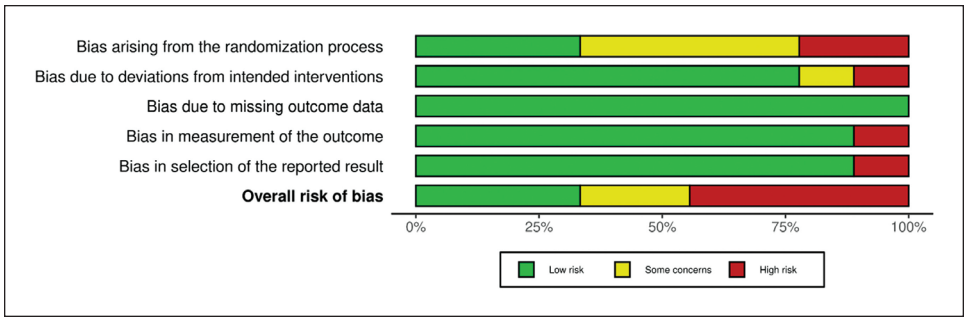

Figure 2. Risk of bias summary plot for studies reporting 'complete clearance of lesions' (n=9).

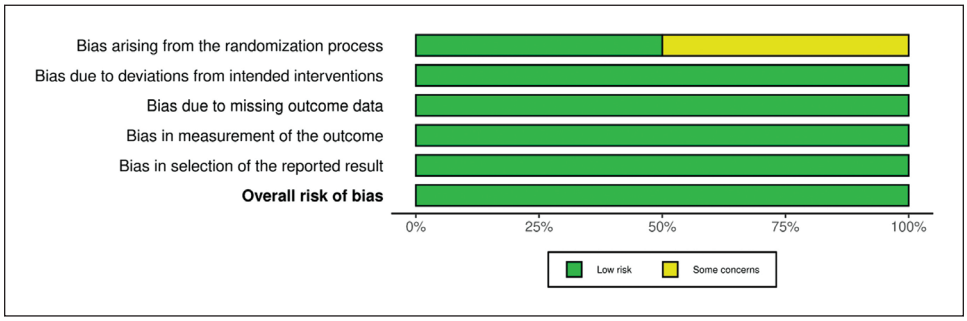

Figure 3. Risk of bias summary plot for studies reporting 'reduction in pruritus scores' (n=2).

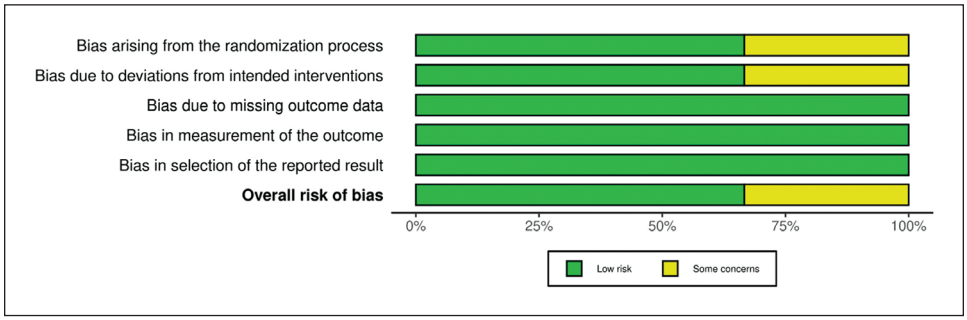

Figure 4. Risk of bias summary plot for studies reporting 'adverse events' (n=3).

Senna alata versus 10% crotamiton

Based on one RCT (N=64), evidence suggests that *S. alata* 50% lotion, when compared against 10% crotamiton, may lead to fewer instances of complete clearance of lesions (RR 0.07 [0.01, 0.53]; low certainty of evidence) (Appendix C.4), and it may slightly reduce adverse events (RR 0.55 [0.21, 1.45]; low certainty of evidence).[41] The evidence for both outcomes was downgraded by two levels for imprecision.

Tinospora rumphii versus placebo

We are uncertain if *T. rumphii* lotion differs in clearance of lesions when compared to placebo (RR 5.28 [0.76, 36.43], 2 RCTs, N=71; very low certainty of evidence) (Figure 7) (Appendix C.5). Evidence was downgraded by two levels for imprecision and one level due to high risk of bias in one study. There was no significant heterogeneity between the two studies (I^2=0), probably reflective of the similarity in dosage forms used.

Yoro 2005 also suggests that *T. rumphii* lotion reduces pruritus scores in patients with scabies when compared to placebo (MD 2.67 [2.40, 2.94], N=40; high quality of evidence).

Tinospora rumphii versus 5% permethrin

One study[31] suggests that *T. rumphii* lotion slightly improves clearance of lesions when compared to 5% permethrin lotion (RR 1.40 [0.91, 2.15], N=60; high certainty of evidence) (Figure 8). However, there is little or no difference in the reduction of pruritus scores between the two groups (MD 0.10 [0.03, 0.17], N=60; high certainty of evidence) (Figure 9) (Appendix C.6). Similarly, there may be little or no difference in the occurrence of adverse events between the two (RR 1.04 [0.82, 1.32], N=60; low certainty of evidence).

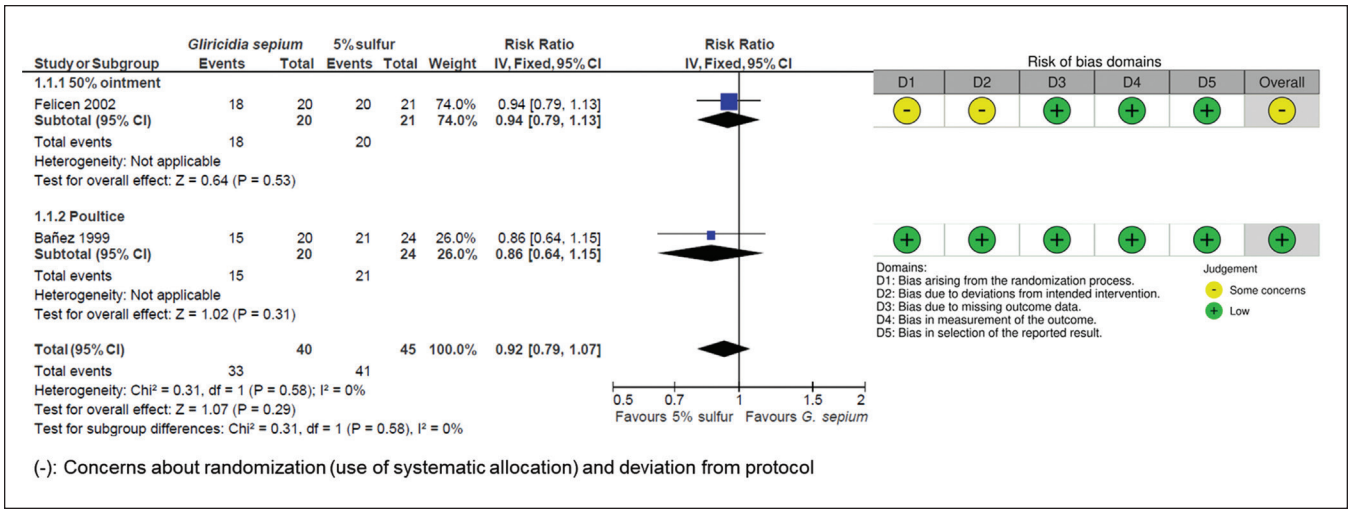

Figure 5. Forest plot for complete clearance for *Gliricidia sepium* vs 5% sulfur comparison.

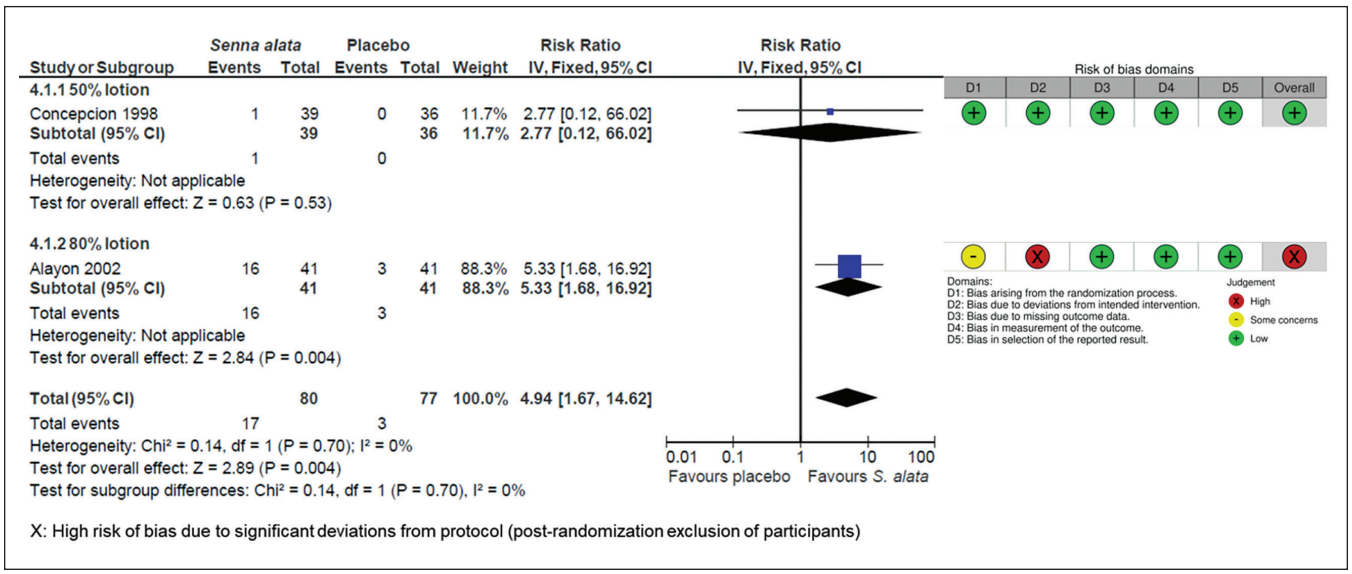

Figure 6. Forest plot for complete clearance for *Senna alata* vs placebo comparison.

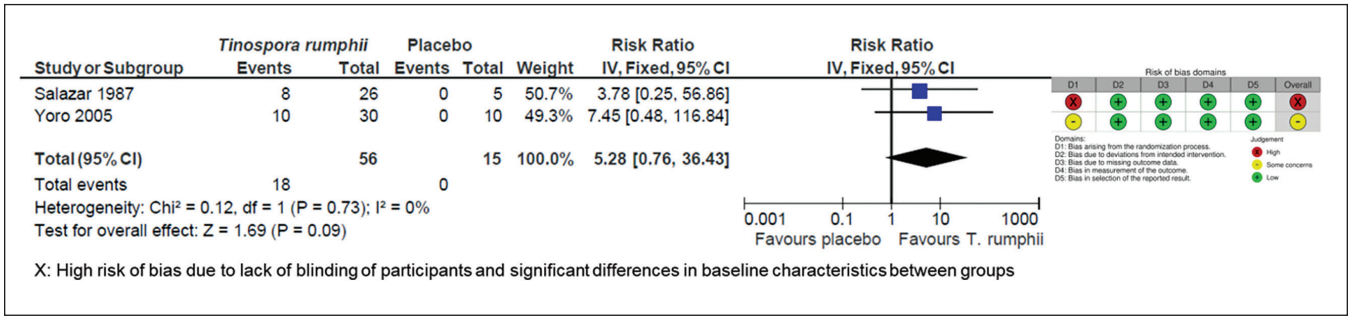

Figure 7. Forest plot for complete clearance for *Tinospora rumphii* vs placebo.

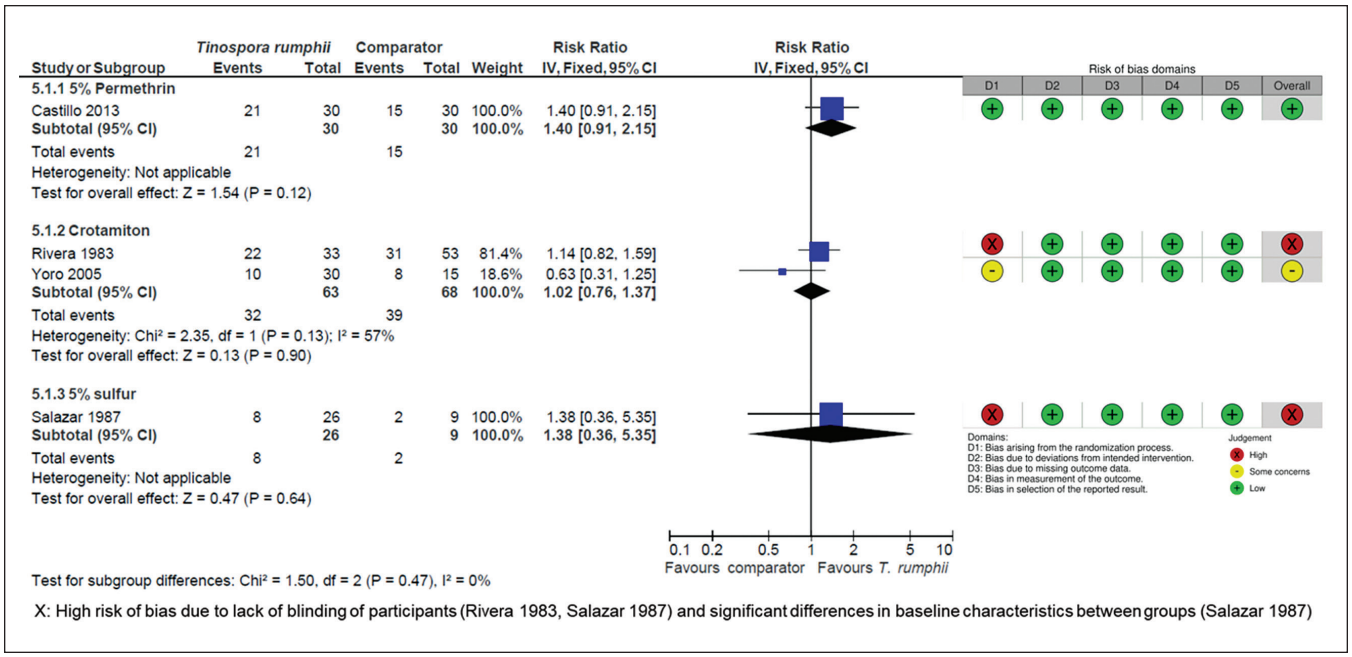

Figure 8. Forest plot for complete clearance for *Tinospora rumphii* vs 5% permethrin, crotamiton, or sulfur comparison.

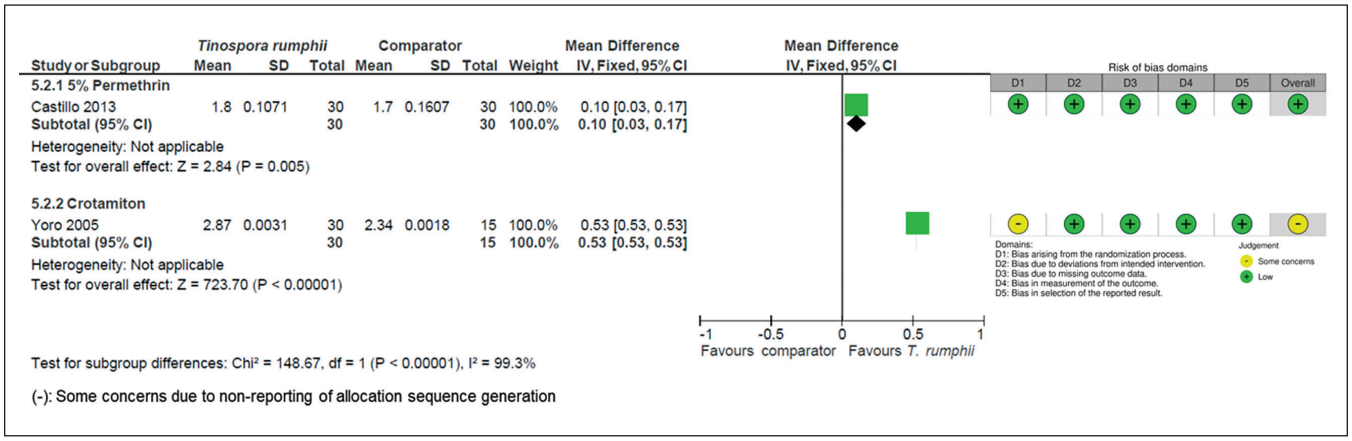

Figure 9. Forest plot for reduction of pruritus scores for *Tinospora rumphii* vs 5% permethrin or crotamiton comparison (not pooled).

Tinospora rumphii versus crotamiton

We are uncertain if *T. rumphii* lotion or aqueous extract leads to complete clearance of lesions when compared to crotamiton (RR 1.02 [0.76, 1.37], 2 RCTs, N=131, very low certainty of evidence) (Figure 8) (Appendix C.7). The evidence was downgraded by one level each due to risk of bias and inconsistency and two levels for imprecision.

The results of Yoro 2005 suggest that *T. rumphii* lotion reduced pruritus scores versus crotamiton (MD 0.53 [0.53, 0.53], N=45, high certainty of evidence) (Figure 9).

Tinospora rumphii versus 5% sulfur

We are uncertain if *T. rumphii* lotion differs in clearance of lesions when compared to 5% sulfur (RR 1.38 [0.36, 5.35], N=35; very low certainty of evidence) (Figure 8) (Appendix C.8). Evidence was downgraded by two levels for imprecision and one level due to high risk of bias.

Serious Adverse Events

We intended to include serious adverse events (e.g., death, hospitalization, disability, etc.) as the primary outcome in evaluating the safety of our plants of interest. However, no such events were reported in all of the studies that reported adverse events.

Subgroup and Sensitivity Analyses

Subgroup analyses according to variables such as age, sex, and severity of infestation could not be performed due to few studies per pooled analyses. Sensitivity analysis comparing fixed-effects versus random-effects models as well as worst-

case and best-case scenario analyses based on dropouts did not change the conclusions for the pooled comparisons (Appendix D). We were unable to do sensitivity analysis excluding high risk of bias studies due to few pooled studies.

DISCUSSION

Summary of Main Findings

Pooled analysis for complete clearance of lesions suggests that there is probably little or no difference between *G. sepium* and 5% sulfur.[26,40] On the other hand, we are uncertain about the efficacy of *S. alata* versus placebo, *T. rumphii* versus crotamiton, and *T. rumphii* versus placebo.[26,28,29,41,42] *T. rumphii* lotion reduced itch significantly compared to 5% permethrin, 10% crotamiton, or placebo. There were no serious adverse events in both pooled or individual studies.

Our review shows that *Gliricidia sepium,* locally known as 'kakawati' or 'madre de cacao,' is probably comparable to 5% sulfur in the clearance of scabies lesions. Phytochemical and preclinical studies of *G. sepium* highlight its rich array of bioactive compounds, including flavonoids, saponins, tannins, alkaloids, and polyphenols. Several flavonoids have been shown to have insecticidal properties, however, none of these compounds have been isolated and tested on their possible acaricidal activity.[24,43] Data from one of the included studies also point towards its better physical qualities versus 5% sulfur in terms of odor and stickiness, suggesting *G. sepium* poultice may be an effective and acceptable alternative.[21]

On the other hand, we are uncertain whether *S. alata* lotion improves clearance of lesions versus placebo in the pooled analysis of two RCTs, with the study using a higher concentration (80%) showing more benefit. This may suggest using *S. alata* in more concentrated formulations. Of the three plants included in this review, *S. alata* is the only one included in the DOH's list of scientifically validated medicinal plants for its potent antifungal activity.[18] The dermatophytic activities displayed by *S. alata* are linked to bioactive compounds, such as anthranols, anthrones, flavonoids, phenols, tannins, and anthracene derivatives.[23,30] However, their individual or collective mode of action has not yet been elucidated.

We are likewise uncertain regarding the effect of *T. rumphii* versus crotamiton. The two studies pooled for this comparison differed in the dosage form in which *T. rumphii* was prepared, with one using the aqueous extract and a lotion in the other. Clearance of lesions appeared similar in the treatment arms of both studies, leading to no statistically significant difference between them. There is also uncertainty regarding the difference of *T. rumphii* lotion and placebo in clearance of lesions. While the individual studies and the pooled analysis reported appreciable benefit for *T. rumphii* lotion over placebo, we could not draw conclusions from this comparison because of the very low certainty of evidence. Extensive phytochemical investigations led to the identification of 167 phytoconstituents belonging to diverse chemical classes, including clerodane-type furanoditerpenoids, alkaloids, flavonoids, and steroidal compounds.[30] While numerous *in vitro* investigations have verified its antiparasitic properties, no such studies have been conducted on the human scabies mite.

Data for the other primary outcomes – reduction in pruritus scores and adverse events – could not be pooled due to limited studies for each of the three medicinal plants. Pruritus is an important clinical manifestation of scabies as nocturnal itch is a common complaint among patients, and its resolution is among the goals of scabies management. The two studies that measured pruritus scores were on *T. rumphii* lotion but used different comparators.[27,29] With high certainty of evidence, *T. rumphii* lotion reduces itch significantly when compared to placebo, 5% permethrin, or 10% crotamiton. The results of these individual studies may suggest that *T. rumphii* lotion may be comparable or even better than permethrin or crotamiton at relieving scabietic pruritus.

Only three out of seven studies that measured adverse events reported the following: pruritus, rashes, burning sensation, and erythema.[26,27,31] No serious adverse events were reported across all studies. All adverse events were minor, transient, and did not require any discontinuation of the interventions. There may be little or no difference between *G. sepium* ointment and 5% sulfur or between *T. rumphii* lotion and 5% permethrin in this regard. On the other hand, *S. alata* lotion may even slightly reduce adverse events compared to crotamiton. These results suggest that both herbal and traditional scabicides are generally safe and well tolerated.

Our findings are similar to that of a previous network meta-analysis by Thadanipon et al. that showed moderate efficacy and safety of herbal medicines (neem, aloe vera, mixture of *P. corylifolia, C. anthelminticum, C. tora,* and *Tinospora cordifolia*), ranking midway among 9 to 12 antiscabetic agents across the outcomes of cure, persistent itching, and adverse events.[44] There was no statistically significant difference in terms of efficacy against other interventions. When comparing their safety, however, herbal medicines were found to have fewer adverse events than sulfur (RR 5.30 [2.24, 12.52]). However, only one herbal medicine among four were our herbs of interest, that is, *T. rumphii* or *cordifolia.*[27]

Overall Completeness and Applicability of Evidence

The setting of most included studies is reflective of the distribution and transmissibility of scabies: five RCTs were conducted in residential institutions where there may be crowding, such as youth detention centers, correctional facilities, and orphanages. Furthermore, whereas the entire population included patients of all ages, the majority of the enrolled participants were of the pediatric age, which mirrors the predilection of scabies towards children, as well as the elderly and immunocompromised individuals.[1,2]

This review included all different dosage forms in which the plant materials were prepared (e.g., ointment,

lotion, soap, poultice, aqueous extract), which could have affected the results due to the non-standardization of the methods of preparation. Although all of them contain the purported active ingredients from the plants, the dosage form determines their stability, liberation, and rate and extent of absorption into the systemic circulation. Clearance of lesions and adverse events were likely measured and reported similarly across studies. However, pruritus scores were rated differently in the studies that included them, as some used the visual analog scale, another employed the Global Evaluation Scoring system,[3] while another did not even report the scale used.[29,31,41]

Quality of the Evidence

Individually, each of the studies reported promising results of the selected medicinal plants in the treatment of scabies. However, the evidence drawn from these studies may, for the most part, be insufficient to confirm their safety and efficacy due to the following issues:

1. Though all of the studies claimed to have randomly allocated participants to treatment groups, four of the nine RCTs did not report their method of randomization, for which we could not rule out the possibility of bias.
2. There were unclear descriptions of participant flow in most of the studies, where there were either no or ambiguous statements on dropouts, deviations from randomization, and exclusions from analysis.
3. There was great variation in terms of the methods of preparation, dosage form, dosage, and duration of interventions and follow-up, which limited our ability to pool data for our quantitative analyses.

Limitations of Included Studies

For the three pooled synthesis we did, there were only two studies per comparison, *G. sepium* vs sulfur (N = 85), *T. rumphii* vs placebo (N = 71), and *S. alata* vs placebo (N =157). The small sample sizes may have contributed to the wide confidence intervals. There were also differences in the preparations for *S. alata* (varying concentrations, 50% and 80%) and *G. sepium* (varying preparations, poultice vs ointment). Although there was no statistical heterogeneity, we cannot speculate on which concentration or preparation was more effective since they were not compared head-to-head.

Limitations of Review Process

We could not retrieve the full-text reports of three RCTs (N for two studies = 66; no information for 3rd study) which may affect our findings. This review only included complete clearance of lesions (complete cure) in our analysis, although several studies reported partial cure rates as well. Sensitivity analysis that included partial cure showed a change in direction of benefit for *T. rumphii* vs placebo. This may suggest that cure definitions need to be more standardized and involve inputs from patient advocates. Publication bias is possible since we only hand searched for unpublished studies from thesis/dissertations within the University of the Philippines Manila. Funnel plots could have helped us determine bias but there were only few studies per comparison.

CONCLUSIONS

Implications for Practice

Gliricidia sepium (kakawati) probably has no difference in efficacy with 5% sulfur, thus, it may be given as a safe, effective, and acceptable alternative in the management of scabies. It is uncertain, however, whether *Senna alata* (akapulko) or *Tinospora rumphii* (makabuhay) are as effective as existing topical treatment in achieving complete clearance of lesions.

There may be merit for the future inclusion of formulations of our plants of interest, particularly *G. sepium*, in our armamentarium against scabies. Primary care physicians, especially those practicing in remote areas where accessibility to drugs is a problem but where traditional medicine is embraced, may educate their patients regarding the preparation of kakawati as an alternative scabicide.[15]

Implications for Policy

We recommend that relevant government bodies (Department of Health, Department of Science and Technology, the Philippine Institute of Traditional and Alternative Health Care, etc.) invest funds into further establishing the efficacy and safety of herbal preparations, specifically *Gliricidia sepium,* studying its integration into our local treatment protocols as an alternative for scabies, and the development of a suitable and inexpensive dosage form. Standardized instructions on preparation, storage, and dosing regimen must be followed.

In the pursuit of equitable access to health services, there is a need to standardize community health practices and develop practice guidelines for practitioners in resource-limited settings, such as geographically isolated and disadvantaged areas.[45]

Implications for Research

While our review reports uncertainty regarding the comparative efficacy of *S. alata* and *T. rumphii* with topical scabicides, individually, the studies suggest either non-inferiority against standard care or benefit over placebo. There is thus a clear need for more randomized controlled trials of adequate sample size, sufficient duration, and robust methodologic quality to draw conclusive evidence on the comparative efficacy and safety of these plants. To reduce the risk of bias, these trials should ensure random sequence generation, allocation concealment, and blinding to interventions. In studying the absolute effect of herbal medicine, investigators may encounter difficulties in blinding participants especially when preparations with these actives contain a distinct odor or texture. The use of odor-masking

agents in both treatment arms or developing a placebo that has the same physical characteristics as the intervention may be recommended to overcome this.

Evaluation of safety must also consider the presence of serious adverse events. Our review detected none due to their rarity and the small sample sizes of the included studies. Hence, future systematic reviews may expand their eligibility criteria to include non-RCTs, such as pharmacovigilance databases and case reports. Patient-reported outcomes such as quality of life, cost-effectiveness, treatment adherence, and acceptability should also be considered as these are essential in formulating recommendations for future practice.

Aside from establishing their efficacy and safety in the treatment of scabies, future research on these plants must also focus on isolating and identifying relevant phytoconstituents, elucidating their mode/s of scabicidal action, optimizing their dosage form and methods of preparation, and developing a suitable dosing regimen.

Availability of Data, Code, and Other Materials

Template data collection forms; data extracted from included studies; data used for all analyses, may be requested from the author.

Statement of Authorship

All authors certified fulfillment of ICMJE authorship criteria.

Author Disclosure

All authors declared no conflicts of interest.

Funding Source

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REFERENCES

1. WHO. Scabies [Internet]. Scabies [cited 2024 Aug 19]. Available from: https://www.who.int/news-room/fact-sheets/detail/scabies
2. CDC. About Scabies [Internet]. Scabies. 2024 [cited 2024 Aug 19]. Available from: https://www.cdc.gov/scabies/about/index.html
3. Murray RL, Crane JS. Scabies. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 [cited 2024 Aug 19]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK544306/
4. Karimkhani C, Colombara DV, Drucker AM, Norton SA, Hay R, Engelman D, et al. The global burden of scabies: a cross-sectional analysis from the Global Burden of Disease Study 2015. Lancet Infect Dis. 2017 Dec;17(12):1247–54. doi: 10.1016/S1473-3099(17)30483-8. PMID: 28941561. PMCID: PMC5700804.
5. Micali G, Lacarrubba F, Verzì AE, Chosidow O, Schwartz RA. Scabies: Advances in Noninvasive Diagnosis. PLoS Negl Trop Dis. 2016 Jun 16;10(6):e0004691. doi: 10.1371/journal.pntd.0004691. PMID: 27311065. PMCID: PMC4911127.
6. Neglected tropical diseases [Internet]. [cited 2024 Aug 19]. Available from: https://www.who.int/news-room/questions-and-answers/item/neglected-tropical-diseases
7. Genuino R, Villanueva III E, Batac MCF, Eusebio MER, Ortiz YR, Ang VR, et al. A systematic review of epidemiologic studies on scabies in the Philippines. Acta Med Philipp. 2024;58(22):92-105. doi: 10.47895/amp.vi0.8719.
8. Salavastru CM, Chosidow O, Boffa MJ, Janier M, Tiplica GS. European guideline for the management of scabies. J Eur Acad Dermatol Venereol JEADV. 2017 Aug;31(8):1248–53. doi: 10.1111/jdv.14351. PMID: 28639722.
9. Sunderkötter C, Aebischer A, Neufeld M, Löser C, Kreuter A, Bialek R, et al. Increase of scabies in Germany and development of resistant mites? Evidence and consequences. J Dtsch Dermatol Ges J Ger Soc Dermatol JDDG. 2019 Jan;17(1):15–23. doi: 10.1111/ddg.13706. PMID: 30480868.
10. Mounsey KE, Holt D, McCarthy J, Currie BJ, Walton SF. Scabies: Molecular perspectives and therapeutic implications in the face of emerging drug resistance. Future Microbiol. 2008;3(1):57–66. doi: 10.2217/17460913.3.1.57. PMID: 18230034.
11. Mbuagbaw L, Sadeghirad B, Morgan RL, Mertz D, Motaghi S, Ghadimi M, et al. Failure of scabies treatment: a systematic review and meta-analysis. Br J Dermatol. 2024 Jan 23;190(2):163–73. doi: 10.1093/bjd/ljad308. PMID: 37625798.
12. Humphreys EH, Janssen S, Heil A, Hiatt P, Solomon G, Miller MD. Outcomes of the California ban on pharmaceutical lindane: clinical and ecologic impacts. Environ Health Perspect. 2008 Mar;116(3):297–302. doi: 10.1289/ehp.10668. PMID: 18335094. PMCID: PMC2265033.
13. DOH Administrative Order No. 172, S. 2004 - GUIDELINES ON THE REGISTRATION OF HERBAL MEDICINES - Supreme Court E-Library [Internet]. [cited 2024 Aug 19]. Available from: https://elibrary.judiciary.gov.ph/thebookshelf/showdocs/11/42163
14. Gopinath H, Aishwarya M, Karthikeyan K. Tackling scabies: novel agents for a neglected disease. Int J Dermatol. 2018 Nov;57(11):1293–8. doi: 10.1111/ijd.13999. PMID: 29663338.
15. Integrating traditional and complementary medicine into health systems: social, economic and health considerations [Internet]. [cited 2024 Aug 19]. Available from: https://www.who.int/publications/m/item/integrating-traditional-and-complementary-medicine-into-health-systems--social--economic-and-health-considerations
16. Department Circular 168-A s. 1995: Listing of Philippine herbal medicinal plants. [Internet]. [cited 2024 Aug 19]. Available from: https://www.herdin.ph/index.php/component/herdin/?view=research&cid=59879
17. Maramba-Lazarte CC. Benefits of mainstreaming herbal medicine in the Philippine healthcare system. Acta Med Philipp. 2020 Feb 5;54(1):3-4. doi: 10.47895/amp.v54i1.1078.
18. Maramba C. Guidebook on the proper use of medicinal plants. 2017. Manila: National Integrated Research Program on Medicinal Plants.
19. Abdelhameed M, Wafaey A, El Hawary S, Kirollos F. An overview on *Gliricidia sepium* in the pharmaceutical aspect: a review article. Egypt J Chem. 2022 Apr 11.
20. Krishnappa K, Dhanasekaran S, Elumalai K. Larvicidal, ovicidal and pupicidal activities of *Gliricidia sepium* (Jacq.) (Leguminosae) against the malarial vector, *Anopheles stephensi* Liston (Culicidae: Diptera). Asian Pac J Trop Med. 2012 Aug;5(8):598–604. doi: 10.1016/S1995-7645(12)60124-2. PMID: 22840446.
21. Banes J, Nazareno R, Medel R. Clinical trial on the effectiveness of *Gliricidia sepium* (Kakawati) in treating patients with scabies in the Antipolo CBHP. Philipp J Microbiol Infect Dis. 1999 Sep 30;28(4).
22. Legaspi CLB, Maramba-Lazarte CC. The phytochemical content and the in vitro antifungal properties of *Senna alata* (Linn.) Roxb.: A Review. Acta Med Philipp. 2020 Feb 5;54(1):86-93. doi: 10.47895/amp.v54i1.1111. A
23. Oladeji OS, Adelowo FE, Oluyori AP, Bankole DT. Ethnobotanical description and biological activities of *Senna alata*. Evid-Based Complement Altern Med ECAM. 2020 Feb 21;2020:1–12. doi: 10.1155/2020/2580259. PMID: 32148534. PMCID: PMC7054808.
24. Chatterjee S, Chatterjee S, Dutta S. An overview on the ethnophytopathological studies of *Cassia alata* – an important medicinal plant and the effect of VAM on its growth and productivity. International Journal of Research in Botany. 2012; 2(4):13-9.
25. Neamsuvan O, Kama A, Salaemae A, Leesen S, Waedueramae N. A survey of herbal formulas for skin diseases from Thailand's three

southern border provinces. J Herb Med. 2015 Oct 1;5. doi: 10.1016/j.hermed.2015.09.004
26. Alayon J, Alcantara R. Efficacy and acceptability of 80% akapulco (*Cassia alata*) lotion in the treatment of scabies. Filip Fam Physician. 2002 Jun 1;40(3).
27. Rivera E, Millan-Sison E. A comparative study of the efficacy of crotamiton and *Tinosphora rumphii* in the treatment of scabies in children. J Philipp Med Assoc. 1983 Jan 1;20(1).
28. Salazar N, Moragas TR, Tarrayo MG, Montalban CS, Sabordo NT, Bustos DG, et al. *Tinospora rumphii Boerl.* (makabuhay) in the treatment of scabies. Rec Achiev Tech Coop Proj. 1987 Nov 30.
29. Yoro MS, Llamasares-De Franci J. A comparative study of the efficacy of formulated *Tinospora rumphii Boerl.* lotion and crotamiton in the treatment of scabies in children. Philipp J Pediatr. 2005;54(4). A
30. Haque E, Bari MS, Khandokar L, Anjum J, Jantan I, Seidel V, et al. An updated and comprehensive review on the ethnomedicinal uses, phytochemistry, pharmacological activity and toxicological profile of *Tinospora crispa* (L.) Hook. f. & Thomson. Phytochem Rev Proc Phytochem Soc Eur. 2023;22(1):211–73. doi: 10.1007/s11101-022-09843-y. PMID: 36345416. PMCID: PMC9630822.
31. Castillo AL, Osi MO, Ramos JDA, De Francia JL, Dujunco MU, Quilala PF. Efficacy and safety of *Tinospora cordifolia* lotion in *Sarcoptes scabiei var hominis*-infected pediatric patients: A single blind, randomized controlled trial. J Pharmacol Pharmacother. 2013 Jan;4(1):39–46.
32. RevMan [Internet]. [cited 2024 Aug 19]. Available from: https://training.cochrane.org/online-learning/core-software/revman
33. Pacific WHORO for the W. Working Group on Herbal Medicines, Manila, Philippines, 8-12 December 1997 : report [Internet]. 1997 [cited 2024 Aug 19]. Available from: https://iris.who.int/handle/10665/207932
34. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan—a web and mobile app for systematic reviews. Syst Rev. 2016 Dec 5;5. 10.1186/s13643-016-0384-4
35. RoB 2: A revised Cochrane risk-of-bias tool for randomized trials | Cochrane Bias [Internet]. [cited 2024 Aug 19]. Available from: https://methods.cochrane.org/bias/resources/rob-2-revised-cochrane-risk-bias-tool-randomized-trials
36. McGuinness LA, Higgins JPT. Risk-of-bias VISualization (robvis): An R package and Shiny web app for visualizing risk-of-bias assessments. Res Synth Methods. 2021 Jan;12(1):55–61.
37. Zeng L, Brignardello-Petersen R, Hultcrantz M, Mustafa RA, Murad MH, Iorio A, et al. GRADE Guidance 34: update on rating imprecision using a minimally contextualized approach. J Clin Epidemiol. 2022 Oct;150:216–24. doi: 10.1016/j.jclinepi.2022.07.014. PMID: 35934265
38. GRADEpro [Internet]. [cited 2024 Aug 19]. Available from: https://www.gradepro.org/
39. Ancheta BM, Asuncion MFV, Asuncion LR, Arquiza JL, Arcilla FR, Aragoncillo HH, et al. A preliminary experimental study on the efficacy of kakawati (*Gliricidia sepium*) soap together with the kakawati ointment preparation as compared to the use of the kakawati ointment alone in the treatment of scabies. Univ East Ramon Magsaysay Meml Med Cent J Health Sci. 2003 Dec 31;7(1).
40. Felicen GB, Fermo JV, Fermo TA, Felix AC, Paredes GT, Flores HB, et al. A comparative study on the cost-effectiveness of 50 percent *gliricidia sepium* (kakawati) ointment and 5 percent sulfur ointment in treating patients with scabies in Area III, Payatas, Quezon City. Univ East Ramon Magsaysay Meml Med Cent J Health Sci. 2002;6(1).
41. Concepcion MC, de Jesus L, Santos-Acuin C. A study on the efficacy and safety of 50% akapulco lotion in the treatment of scabies. Filip Fam Physician. 1998 Dec 31;37(1).
42. Hertel Pereira AC, Auer AC, Biedel L, de Almeida CM, Romão W, Endringer DC. Analysis of *Gliricidia sepium* leaves by MALDI Mass Spectrometry Imaging. J Am Soc Mass Spectrom. 2022 Mar 2;33(3):573–83. doi: 10.1021/jasms.1c00367. PMID: 35157449.
43. Aulanni'am A, Ora KM, Ariandini NA, Wuragil DK, Permata FS, Riawan W, et al. Wound healing properties of *Gliricidia sepium* leaves from Indonesia and the Philippines in rats (Rattus norvegicus). Vet World. 2021 Mar;14(3):820–4.
44. Thadanipon K, Anothaisintawee T, Rattanasiri S, Thakkinstian A, Attia J. Efficacy and safety of antiscabietic agents: a systematic review and network meta-analysis of randomized controlled trials. J Am Acad Dermatol. 2019 May;80(5):1435–44.
45. Capulong JA, Carandang A, Cariño RV, Castro M. An open trial on the efficacy and safety of kakawati (*Gliciridia sepium*) ointment in treating cases of scabies from selected orphanages in Metro Manila. Univ East Ramon Magsaysay Meml Med Cent J Health Sci. 2002;6(1).

APPENDICES

Appendix A. Search strategies

Table A1. PubMed search strategy (03 March 2024)

Search Number	Concept Terms	Study Hits
#1	Scabies OR "Sarcoptes scabiei" OR "Anti-scabies" OR Scabicid*	5713
#2	"Gliricidia sepium"	121
#3	"Senna alata"	63
#4	"Cassia alata"	98
#5	Akapulko	1
#6	Akapulco	2
#7	Acapulco	468
#8	"Tinospora rumphii"	5
#9	"Tinospora crispa"	89
#10	"Tinospora cordifolia"	575
#11	Makabuhay	1
#12	"Randomized controlled trial" OR "Controlled clinical trial" OR "Randomized" OR "Placebo" OR "Drug therapy" OR "Randomly" OR "Trial"	4243406
#13	#11 OR #10 OR #9 OR #8 OR #7 OR #6 OR #5 OR #4 OR #3 OR #2 OR "herbal medicine"[MeSH Terms] OR Herb* OR Plant* OR Botanical OR "Traditional herbal medicine" OR "Traditional chinese medicine" OR "Chinese herbal medicine" OR "plant extracts"[MeSH Terms]	1551896
#14	#1 AND #13	341
#15	#12 and #14	68

Table A2. CENTRAL search strategy (03 March 2024)

Search Number	Concept Terms	Study Hits
#1	Scabies OR "Sarcoptes scabiei" OR "Anti-scabies" OR Scabicid*	324
#2	"Gliricidia sepium"	6
#3	"Senna alata"	6
#4	"Cassia alata"	6
#5	Akapulko	1
#6	Akapulco	0
#7	Acapulco	29
#8	"Tinospora rumphii"	1
#9	"Tinospora crispa"	2
#10	"Tinospora cordifolia"	112
#11	Makabuhay	1
#12	#11 OR #10 OR #9 OR #8 OR #7 OR #6 OR #5 OR #4 OR #3 OR #2 OR "herbal medicine"[MeSH Terms] OR Herb* OR Plant* OR Botanical OR "Traditional herbal medicine" OR "Traditional chinese medicine" OR "Chinese herbal medicine"	57477
#13	MeSH descriptor: [Plant Extracts] explode all trees	10981
#14	MeSH descriptor: [Plants, Medicinal] explode all trees	1149
#15	MeSH descriptor: [Herbal Medicine] explode all trees	100
#16	#12 OR #13 OR #14 OR #15	58201
#17	#1 AND #16	22

Table A3. COPUS search strategy (03 March 2024)

Search Number	Concept Terms	Study Hits
#1	Scabies OR "Sarcoptes scabiei" OR "Anti-scabies" OR Scabicid*	17968
#2	(scabies OR "sarcoptes scabiei" OR "anti-scabies" OR scabicid*) AND ("gliricidia sepium" OR "senna alata" OR "cassia alata" OR akapulko OR akapulco OR acapulco OR "tinospora rumphii" OR "tinospora crispa" OR "tinospora cordifolia" OR makabuhay OR "herbal medicine" OR herb* OR plant* OR "plant extracts" OR botanical OR "traditional herbal medicine" OR "traditional chinese medicine" OR "chinese herbal medicine")	5223
#3	(TITLE-ABS-KEY (scabies OR "sarcoptes scabiei" OR "anti-scabies" OR scabicid*) AND TITLE-ABS-KEY ("gliricidia sepium" OR "senna alata" OR "cassia alata" OR akapulko OR akapulco OR acapulco OR "tinospora rumphii" OR "tinospora crispa" OR "tinospora cordifolia" OR makabuhay OR "herbal medicine" OR herb* OR plant* OR "plant extracts" OR botanical OR "traditional herbal medicine" OR "traditional chinese medicine" OR "chinese herbal medicine") AND TITLE-ABS-KEY ("randomized controlled trial" OR "controlled clinical trial" OR "randomized" OR "placebo" OR "drug therapy" OR "randomly" OR "trial"))	102

Table A4. EBSCO search strategy (04 March 2024)

Search Number	Concept Terms	Study Hits
#1	Scabies OR "Sarcoptes scabiei" OR "Anti-scabies" OR Scabicid*	3907
#2	(scabies OR "sarcoptes scabiei" OR "anti-scabies" OR scabicid*) AND ("gliricidia sepium" OR "senna alata" OR "cassia alata" OR akapulko OR akapulco OR acapulco OR "tinospora rumphii" OR "tinospora crispa" OR "tinospora cordifolia" OR makabuhay OR "herbal medicine"[MeSH Terms] OR herb* OR plant* OR "plant extracts"[MeSH Terms] OR botanical OR "traditional herbal medicine" OR "traditional chinese medicine" OR "chinese herbal medicine")	410
#3	(scabies OR "sarcoptes scabiei" OR "anti-scabies" OR scabicid*) AND ("gliricidia sepium" OR "senna alata" OR "cassia alata" OR akapulko OR akapulco OR acapulco OR "tinospora rumphii" OR "tinospora crispa" OR "tinospora cordifolia" OR makabuhay OR "herbal medicine"[MeSH Terms] OR herb* OR plant* OR "plant extracts"[MeSH Terms] OR botanical OR "traditional herbal medicine" OR "traditional chinese medicine" OR "chinese herbal medicine") AND ("randomized controlled trial" OR "controlled clinical trial" OR "randomized" OR "placebo" OR "drug therapy" OR "randomly" OR "trial")	32

Trial Registers
Search term for trial registers: "scabies'
PHRR = 2
HERDIN = 64
WHO = 14 (filter: Philippines)
CTG = 38 (filter: Philippines)

Appendix B. List of excluded studies

Study ID	Reason for exclusion
Capulong 2002 [43]	Wrong study design (not an RCT)
Rodriguez 2002 [44]	Wrong study design (quasi-experimental trial with no comparator group)

Appendix C. Summary of Findings Tables

Table C.1. *Gliricidia sepium* compared to placebo for patients with scabies

Patient or population: patients with scabies
Setting: Philippines
Intervention: *Gliricidia sepium*
Comparison: placebo

Outcomes	Nº of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with *Gliricidia sepium*
Complete clearance of lesions (Clearance) assessed with: Physician assessment follow-up: 7 days	49 (1 RCT)	⨁◯◯◯ Very low[a,b]	**RR 0.86** (0.63 to 1.18)	82 per 100	**11 fewer per 100** (30 fewer to 15 more)

*__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] *Downgraded two levels for high risk of bias in outcome measurement*
[b] *Downgraded one level for imprecision due to the lower limit of the CI crossing important benefit for placebo*

Table C.2. *Gliricidia sepium* compared to 5% sulfur for patients with scabies

Patient or population: patients with scabies
Setting: Philippines
Intervention: *Gliricidia sepium*
Comparison: 5% sulfur

Outcomes	Nº of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with 5% sulfur	Risk difference with *Gliricidia sepium*
Complete clearance of lesions (Clearance) assessed with: Physician assessment follow-up: mean 5 days	85 (2 RCTs)	⨁⨁⨁◯ Moderate[a]	**RR 0.92** (0.79 to 1.07)	91 per 100	**7 fewer per 100** (19 fewer to 6 more)

*__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.

Explanation
[a] Downgraded one level for imprecision due to confidence interval including benefit favoring both intervention and comparator

Table C.3. *Senna alata* compared to placebo for patients with scabies

Patient or population: patients with scabies
Setting: Philippines
Intervention: *Senna alata*
Comparison: placebo

Outcomes	Nº of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with *Senna alata*
Complete clearance of lesions (Clearance) assessed with: Physician assessment follow-up: mean 3 days	157 (2 RCTs)	⨁◯◯◯ Very low[a,b]	**RR 4.94** (1.67 to 14.62)	4 per 100	**15 more per 100** (3 more to 53 more)

*__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] Downgraded one level for risk of bias in one study due to deviations from intended intervention
[b] Downgraded two levels due to imprecision since the ratio of upper to lower limit of the CI is greater than 3

Table C.4. *Senna alata* compared to 10% crotamiton for patients with scabies

Patient or population: patients with scabies
Setting: Philippines
Intervention: *Senna alata*
Comparison: 10% crotamiton

Outcomes	Nº of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with 10% crotamiton	Risk difference with *Senna alata*
Complete clearance of lesions (Clearance) assessed with: Physician assessment follow-up: 3 days	64 (1 RCT)	⨁⨁◯◯ Low[a]	**RR 0.07** (0.01 to 0.53)	36 per 100	**33 fewer per 100** (36 fewer to 17 fewer)

*__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.

Explanation
[a] *Downgraded two levels for imprecision since the ratio of upper to lower limit of the CI is greater than 3*

Table C.5. *Tinospora rumphii* compared to placebo for patients with scabies

Patient or population: patients with scabies
Setting: Philippines
Intervention: *Tinospora rumphii*
Comparison: placebo

Outcomes	Nº of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with *Tinospora rumphii*
Complete clearance of lesions (Clearance) assessed with: Physician assessment follow-up: range 14 days to 33 days	71 (2 RCTs)	⨁◯◯◯ Very low[a,b]	**RR 5.28** (0.76 to 36.43)	3 per 100[c]	**14 more per 100** (1 fewer to 118 more)
Reduction in pruritus scores (Pruritus) follow-up: range 14 days	40 (1 RCT)	⨁⨁⨁⨁ High	–	The mean reduction in pruritus scores was **0**	MD **2.67 higher** (2.4 higher to 2.94 higher)

*__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; **MD:** mean difference; **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] *Downgraded one level for high risk of bias arising from randomization process*
[b] *Downgraded two levels due to imprecision since the ratio of upper to lower limit of the CI is greater than 3*
[c] *Continuity correction of 0.5 was applied due to zero events observed in placebo group (45)*

Table C.6. *Tinospora rumphii* compared to 5% permethrin for patients with scabies

Patient or population: patients with scabies
Setting: Philippines
Intervention: *Senna alata*
Comparison: 10% crotamiton

Outcomes	Nº of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with 5% permethrin	Risk difference with *Tinospora rumphii*
Complete clearance of lesions (Clearance) assessed with: Physician assessment follow-up: 14 days	60 (1 RCT)	⨁⨁⨁⨁ High[a]	**RR 1.40** (0.91 to 2.15)	50 per 100	**20 more per 100** (4 fewer to 57 more)
Reduction in pruritus scores (Pruritus) assessed with: Global Evaluation Scores Scale from: 0 to 3 follow-up: 14 days	60 (1 RCT)	⨁⨁⨁⨁ High	–	The mean reduction in pruritus scores was **0**	MD **0.1 higher** (0.03 higher to 0.17 higher)

*__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; **MD:** mean difference; **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.

Explanation
[a] *We did not downgrade for imprecision since the lower limit did not cross line of important benefit favoring 5% permethrin*

Table C.7. *Tinospora rumphii* compared to crotamiton for patients with scabies

Patient or population: patients with scabies
Setting: Philippines
Intervention: *Tinospora rumphii*
Comparison: crotamiton

Outcomes	Nº of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with crotamiton	Risk difference with *Tinospora rumphii*
Complete clearance of lesions (Clearance) assessed with: Physician assessment follow-up: range 3 days to 14 days	131 (2 RCTs)	⨁◯◯◯ Very low[a,b,c]	**RR 1.02** (0.76 to 1.37)	57 per 100	**1 more per 100** (14 fewer to 21 more)

*__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] *Downgraded one level for high risk of bias arising from randomization process*
[b] *Downgraded one level due to visual inconsistency and significant heterogeneity (I^2=57%)*
[c] *Downgraded two levels for imprecision due to confidence interval including important benefit favoring both intervention and comparator*

Table C.8. *Tinospora rumphii* compared to 5% sulfur for patients with scabies

Patient or population: patients with scabies
Setting: Philippines
Intervention: *Tinospora rumphii*
Comparison: 5% sulfur

Outcomes	Nº of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with 5% sulfur	Risk difference with *Tinospora rumphii*
Complete clearance of lesions (Clearance) assessed with: Physician assessment follow-up: range 26 days to 33 days	35 (1 RCT)	⨁◯◯◯ Very low[a,b]	**RR 1.38** (0.36 to 5.35)	22 per 100	**8 more per 100** (14 fewer to 97 more)

*__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] *Downgraded one level for high risk of bias arising from randomization process*
[b] *Downgraded two levels for imprecision due to confidence interval including important benefit favoring both intervention and comparator*

Appendix D. Sensitivity analyses

Comparison	No. of RCTs (N)	Main analysis	Sensitivity analysis	Impact on direction of benefit
***G. sepium* vs 5% sulfur**				
Fixed-effect vs random effects	2 (85)	0.92 [0.79, 1.07]	0.92 [0.79, 1.07]	No change
Worst case scenario	2 (90)		0.88 [0.72, 1.06	No change
Best case scenario	2 (90)		0.91 [0.78, 1.07]	No change
***S. alata* vs placebo**				
Fixed-effect vs random effects	2 (157)	4.94 [1.67, 14.62]	4.94 [1.67, 14.62]	No change
Complete cure only vs complete + partial cure		4.94 [1.67, 14.62]	2.77 [1.60, 4.79]	No change
***T. rumphii* vs placebo**				
Fixed-effect vs random effects	2 (131)	5.28 [0.76, 36.43]	5.28 [0.76, 36.43]	No change
***T. rumphii* vs crotamiton**				
Fixed-effect vs random effects	2 (71)	1.02 [0.76, 1.37]	0.91 [0.52, 1.61]	No change
Complete cure only vs complete + partial cure		1.02 [0.76, 1.37]	1.02 [0.92, 1.13]	No change