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Comparative study of 5% permethrin, 10% neem leaf extract, and 10% brotowali stem extract for scabies treatment

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Background: Scabies, a contagious skin infestation caused by *Sarcoptes scabiei* var. *hominis*, remains a significant public health issue, particularly in developing countries. Permethrin is the standard treatment; however, emerging limitations such as potential mite resistance highlight the need for effective alternatives.

Objective: This study compared the efficacy, safety, and quality-of-life impact of 5% permethrin lotion with 10% neem (*Azadirachta indica*) leaf extract lotion and 10% brotowali (*Tinospora crispa*) stem extract lotion among students in Islamic boarding schools, a population highly susceptible to recurrent scabies.

Methods: A true experimental pre- and post-test controlled design was conducted involving 61 male students diagnosed with scabies. Participants were randomized into three treatment groups: 5% permethrin, 10% neem leaf extract, or 10% brotowali stem extract. The study was carried out from April to May 2021. Clinical improvement was assessed using lesion counts based on the Physician Global Assessment (PGA), while quality of life was evaluated using the Dermatology Life Quality Index (DLQI). Adverse effects were documented, and bivariate analyses were performed.

Results: All three treatments significantly reduced lesion counts ($p < 0.05$), with no significant difference in median PGA scores between groups ($p > 0.05$). DLQI scores improved significantly in all groups, with earlier improvements observed by day 7 in the neem and brotowali groups. No adverse effects were reported.

Limitations: Treatment adherence and exact application duration could not be fully controlled, and the possibility of reinfestation could not be excluded.

Conclusion: Neem leaf extract and brotowali stem extract lotions are as effective and safe as permethrin in treating scabies and improving patient quality of life. Both offer promising, affordable alternatives for scabies management in resource-limited settings.

KEYWORDS

Azadirachta indica, *Tinospora crispa*, permethrin, scabies, quality of life

1 Introduction

Scabies is a contagious skin disease caused by the infestation of the mite *Sarcoptes scabiei* var. *hominis*, which remains a public health issue worldwide, particularly in developing countries (1). This disease can affect individuals of all ages and genders, but it is most common among children and young adults (1–3). Scabies can cause significant morbidity, both directly

through itchy skin lesions and indirectly through psychosocial impacts and the risk of secondary infections (4–6).

The prevalence of scabies in Indonesia remains high, particularly in densely populated areas such as Islamic boarding schools (*pesantren*). This is attributed to several factors, including low hygiene levels, poor sanitation, and a lack of awareness about the disease (7–9). Untreated scabies can lead to complications from secondary infections (4, 5). Additionally, scabies can significantly reduce the quality of life of those affected due to intense itching and the social stigma associated with the disease (10, 11).

The treatment of scabies currently relies on the use of topical medications such as permethrin and benzyl benzoate (12–14). However, widespread and repeated use of these medications can increase the risk of resistance in *S. scabiei* var. *hominis* mites (12, 15). If this resistance becomes widespread in the future and no alternative treatments are available, it will pose a serious problem (12). Additionally, permethrin, the primary drug used in scabies therapy, has drawbacks such as being relatively expensive (2). Considering that the majority of scabies patients come from lower socioeconomic backgrounds and have limited health education, there is a need for an alternative treatment that is economical, safe, and effective.

One potential alternative therapy is using natural ingredients such as neem leaf extract (*Azadirachta indica*). Neem has long been used traditionally to treat various skin diseases, including scabies (16). Existing literature suggests that neem leaves contain active compounds such as azadirachtin that have antiparasitic and anti-inflammatory effects (17–19). Previous research compared the effectiveness of 5% neem oil cream and 5% permethrin cream on rabbits and found an increase in the number of mites that died in each neem cream treatment (20).

Another alternative therapy that can be used is brotowali stem extract (*Tinospora cordifolia*). From several studies on brotowali, there is actually an anti-inflammatory effect in *T. cordifolia*, which contains quaternary alkaloids such as berberine, palmatine, jatrorrhizine, and magnoflorine. Berberine and its salts have antibacterial effects, antifungal and antipyretic properties. Berberine has cytotoxic and neoplasm-inhibiting effects (21). One of the studies that discussed this therapy was the study from Castillo et al. (22), with the result that 50% *T. cordifolia* lotion showed a significant decrease in all parameters. The treatment resulted in a significant reduction in infestation levels and predilection sites, accompanied by clear clinical improvement during the assessment.

However, further research is needed to confirm the effectiveness and safety of neem (*Azadirachta indica*) leaf extract and brotowali (*Tinospora crispa*) stem extract as alternative scabies therapies in humans, especially in specific populations such as children and adolescents, who are more frequently affected by scabies. This study aims to investigate the effectiveness of 10% neem (*Azadirachta indica*) leaf extract lotion and 10% brotowali (*Tinospora crispa*) stem extract lotion in terms of clinical improvement, quality of life, and adverse effects, compared with the standard 5% permethrin lotion among students in Islamic boarding schools.

2 Materials and methods

2.1 Study design

This study adopts a true experimental design with pre- and post-controlled groups. The diagnosis of scabies was made by a

dermatologist based on anamnesis, physical examination of dermatological status, and skin scraping. The diagnostic criteria for scabies followed the guidelines of The International Alliance for the Control of Scabies (IACS) 2018. A 5% permethrin lotion (PT Surya Dermato Medica Laboratories, Surabaya, Indonesia), a 10% neem leaf extract lotion or a 10% brotowali stem extract lotion was administered to male students diagnosed with scabies at an Islamic boarding school in Malang, Indonesia. After obtaining ethical approval, the study period was from April to May 2021.

2.2 Sample size calculation

The sample size was determined using the formula:

$$n = \frac{(Z_{\alpha} [P_o (1 - P_o)] + Z_{\beta} [P_a (1 - P_a)])^2}{P_a - P_o^2}$$

Here, n represents the minimum sample size, Z_{α} is the value from the standard normal distribution at a given α level, Z_{β} is the value from the standard normal distribution at a given β level, P_o is the proportion in the population, P_a is the estimated proportion in the population, and $P_a - P_o$ is the estimated difference between the proportion studied and the proportion in the population.

The calculation for the minimum sample size (n) is as follows:

$$n = \frac{(2.576 \sqrt{[0.06(1 - 0.06)]} + 2326 \sqrt{[0.5(1 - 0.05)]})^2}{(0.5 - 0.06)^2}$$

$$n = 17.5 \approx 18$$

Thus, the minimum sample size required in this study was 18 per group, resulting in a combined total of 54 cases and controls. To ensure representativeness, the minimum sample size was increased by 10% to account for potential drop-outs. Consequently, the minimum total sample size was 60 participants.

2.3 Patients' criteria

Inclusion criteria included: (1) Male patients aged 8–20 years; (2) subjects diagnosed with scabies according to IACS 2018 criteria; (3) have not received topical or oral antiparasitic, steroid, or antihistamine therapy in the previous 4 weeks; (4) willing to participate in the study, understand the study procedures and possible adverse effects by signing informed consent.

Meanwhile, the exclusion criteria included: (1) Crusted scabies or impetiginized scabies; (2) History of allergy or irritation to 5% permethrin; (3) history of allergy or irritation to 10% neem (*Azadirachta indica*) leaf extract; (4) history allergy or irritation to 10% brotowali stem extract; (5) the presence of other inflammatory skin diseases based on history taking and physical examination.

Drop-out criteria include: (1) Patients who did not follow the treatment as directed; (2) patients who did not complete the treatment of scabies; (3) patients who withdrew as research subjects; (4) patients

who went to other treatment centers during the study or used other scabicial drugs without the permission of the researcher; (5) on the day of evaluation, the subject was not available or could not be contacted; (6) patients who suffered severe adverse effects during treatment so that they could not continue the study.

2.4 Preparation of neem (*Azadirachta indica*) leaf extract and lotion making

Neem leaf extraction was carried out using the maceration method. Fresh neem leaves obtained from the garden of UPT Materia Medica Batu, Malang, were cleaned, dried, and pulverized into powder. A total of 100 grams of neem leaf powder was then soaked in 500 mL of 96% ethanol solvent in a tightly closed container. The maceration process lasted for 72 h at room temperature, with periodic stirring every 12 h to ensure the solvent penetrated evenly and optimally into the leaf powder. After the maceration period was complete, the mixture was filtered using a filter cloth and filter paper to separate the filtrate from the leaf residue. The filtrate obtained was then evaporated using a rotary evaporator at 40 °C until all the solvent evaporated, leaving a thick extract of neem leaves. The resulting extract was stored in a tightly closed container and placed in a refrigerator to prevent degradation until used in the 10% neem leaf extract lotion formulation.

2.5 Procedure for using topical medications

Subjects in the first group were given 5% permethrin lotion, while subjects in the second group were given 10% neem leaf extract lotion subjects in the third group were given 10% brotowali stem extract lotion. Subjects in the first group were given 5% permethrin lotion, subjects in the second group were given 10% neem (*Azadirachta indica*) leaf extract lotion, and subjects in the third group were given 10% brotowali (*Tinospora crispa*) stem extract lotion. Approximately 10–15 mL of lotion was applied to the entire body surface from the neck down, at night at around 7:30 p.m., left on for 8–12 h, and then rinsed off the next morning. The application was performed once a week and repeated in the second week, resulting in a total of two applications.

2.6 Evaluation

Treatment evaluation by three dermatologists was conducted on day 0 (before therapy) and days 7 and 14 (after therapy). Drug effectiveness was measured by clinical improvement consisting of the appearance of skin lesions using Physician Global Assessment (PGA) scoring on a scale of 1 to 7 where score one was assessed as clearance of all lesions and score seven if there were additional new lesions after treatment.

The patient's quality of life was assessed by the Dermatology Life Quality Index (DLQI) questionnaire consisting of the answers "not at all or irrelevant," "a little," "a lot" or "very much" with corresponding scores of 0, 1, 2, and 3, respectively. The assessment was calculated by summing the individual question scores, which resulted in a

maximum value of 30 and a minimum value of 0. The total sum of the numbers was assigned a grade 1 (0–1) means no effect on the patient's life, grade 2 (2–5) means a small effect, grade 3 (6–10) means a moderate effect, grade 4 (11–20) means a large effect, and grade 5 (21–30) means a very large effect. Each section of the DLQI questionnaire is scored across six domains: domain 1 (symptoms and feelings), domain 2 (daily activities), domain 3 (pleasure), domain 4 (work and school), domain 5 (personal relationships), and domain 6 (treatment).

Evaluation of adverse effects assessed were erythema, edema, burning, irritation, or others during the use of therapy. Subjects and boarding school supervisors were instructed to discontinue treatment and report to the investigator if any of the adverse effects occurred. Persistent itching or post-scabies hyper/hypopigmented skin lesions were not considered adverse effects of therapy, as these sequelae result from hypersensitivity reactions to mite allergens and products that persist for several weeks despite successful therapy (23).

2.7 Statistical analysis

Friedman's test was used to analyze differences in PGA and DLQI values on days 0, 7, and 14. If the results were significant, the Wilcoxon test was continued. To highlight the differences in PGA and DLQI values among the 5% permethrin, 10% brotowali (*Tinospora crispa*) stem extract, and 10% neem (*Azadirachta indica*) leaf extract groups, we used the Mann–Whitney test. Differences were declared significant if the p-value was less than 0.05. All tests were performed using the Statistical Package for Social Sciences (SPSS) version 20 program (IBM, Chicago, IL, USA).

3 Results

3.1 Patient characteristics

A total of 65 subjects were initially enrolled and randomly allocated into three groups. However, four participants were lost to follow-up during the first-week evaluation, resulting in 61 subjects included in the final analysis (21 in the 5% permethrin group, 21 in the 10% neem (*Azadirachta indica*) leaf extract group, and 19 in the 10% brotowali (*Tinospora crispa*) stem extract group). Two participants from the neem group and two from the permethrin group did not return for evaluation.

The mean ages of patients in the permethrin and neem groups were approximately 13.7 years, while the brotowali group had a mean age of approximately 13.8 years. Before treatment, the average duration of scabies was 18.2 weeks in the permethrin group, 20.5 weeks in the neem group, and 22.1 weeks in the brotowali group. The baseline clinical characteristics of the three groups are presented in Table 1.

3.2 Effectiveness of treatment

The results of the Wilcoxon test in the 5% permethrin, 10% neem (*Azadirachta indica*) leaf extract, and 10% brotowali (*Tinospora crispa*) stem extract groups demonstrated a significant difference ($p < 0.05$)

TABLE 1 Clinical characteristics.

Category	Intervention		
	5% permethrin (<i>n</i> = 21)	10% neem leaf extract (<i>n</i> = 21)	10% brotowali stem extract (<i>n</i> = 19)
Age, (mean ± SD)	13.71 ± 1.06	13.76 ± 0.83	13.84 ± 0.76
Duration of scabies, (mean ± SD)	18.19 ± 10.78	20.48 ± 14.64	22.06 ± 18.98
Grade, <i>n</i> (%)			
7	4 (9.5%)	4 (9.5%)	3 (4.92%)
8	16 (38.09%)	16 (38.09%)	14 (22.95%)
9	1 (2.3%)	1 (2.3%)	2 (3.28%)
Scabies history, <i>n</i> (%)			
Yes	11 (26.19%)	11 (26.19%)	12 (19.67%)
No	10 (23.81%)	10 (23.81%)	7 (11.48%)

in the median number of lesions between days 0, 7, and 14. This finding indicates that all three treatments effectively reduced the number of skin lesions in scabies patients (Table 2).

The Mann–Whitney U test showed no statistically significant changes in median PGA scores among the three groups at any time point ($p > 0.05$) (Table 3).

3.3 Quality of life

On day 0, disruptions to work and school activities were the most pronounced, with scores of 52.38% in the permethrin group, 41.67% in the neem group, and 40.21% in the brotowali group, while personal relationships were the least affected. By day 7, these disruptions had decreased to 42.86% for permethrin, 36.67% for neem, and 35.21% for brotowali, with further improvement in personal relationships. By day 14, all domains showed significant improvement, especially work and school, which dropped to 10.32% for permethrin, 26.67% for neem and 25.21% for brotowali. Third treatments effectively improved patients' quality of life, as evidenced by decreased DLQI scores across all domains (Figure 1).

In the 5% permethrin group, the Wilcoxon test results showed that the median DLQI on day 7 compared to day 0 was not significantly different, but day 14 was significantly different from day 0. These results indicate that 5% permethrin is able to reduce DLQI in patients with scabies and improve the quality of life of patients. Furthermore, in the 10% neem leaf extract group, the Wilcoxon test results showed significantly different medians on days 0, 7, and 14. While, in the 10% brotowali stem extract group, the Wilcoxon test results showed significantly different medians on days 0, 7, and 14. This finding indicates that 10% neem leaf extract and 10% brotowali stem extract can improve patients' quality of life since day 7 (Table 4).

Based on the Mann–Whitney test results, the median DLQI in the 5% permethrin, 10% neem leaf extract groups, and 10% brotowali stem extract group was not significantly different (Table 5).

TABLE 2 Number of skin lesions in patients before and after treatment with 5% permethrin, 10% neem leaf extract, and 10% brotowali stem extract.

Intervention	Day	Median ± IQR	<i>p</i>
5% permethrin	0	31.00 ± 33.50	0.000*
	7	29.00 ± 32.00 ^a	
	14	25.00 ± 30.00 ^{ab}	
10% neem leaf extract	0	46.00 ± 52.00	0.001*
	7	33.00 ± 52.50 ^a	
	14	30.00 ± 38.00 ^{ab}	
10% brotowali stem extract	0	56.00 ± 60.00	0.001*
	7	37.00 ± 62.50 ^a	
	14	35.00 ± 43.00 ^{ab}	

* $p < 0.05$: Significant difference by Friedman test. ^aMedian number of lesions significantly different ($p < 0.05$) compared to day 0. ^bMedian number of lesions significantly different ($p < 0.05$) compared to day 7.

TABLE 3 Clinical improvement of skin lesions in the 5% permethrin, 10% neem leaf extract, and 10% brotowali stem extract.

Day	Intervention	Median ± IQR	<i>p</i>
7	5% permethrin	4.67 ± 1.16	0.349
	10% neem leaf extract	4.95 ± 1.43	
	10% brotowali stem extract	6.00 ± 2.00	
14	5% permethrin	4.38 ± 1.32	0.289
	10% neem leaf extract	4.67 ± 1.28	
	10% brotowali stem extract	5.00 ± 2.00	

Tested using Mann–Whitney.

3.4 Adverse effects

All treatments were well tolerated, with no reported adverse effects such as irritation, redness, burning, or allergic reactions in any of the three groups.

4 Discussion

This study compares the effectiveness of 5% permethrin lotion, 10% neem. This study compares the effectiveness of 5% permethrin lotion, 10% neem (*Azadirachta indica*) leaf extract lotion, and 10% brotowali (*Tinospora crispa*) stem extract lotion. The mean age in permethrin groups and neem groups was the same, at about 13.7 years, while in brotowali groups about 13.8 years. The prevalence of scabies found in children is the highest, and several risk factors that cause children to become a high-risk group for scabies infestation are bad hygiene, and the age- related socialization of children to adolescents tends to be closer, which increases the possibility of transmitting each other (24–26). Students who were living in an Islamic boarding school were likely to socialize and have a close friendship, which made them tend to sleep together and exchange their clothes. This condition would allow the faster spread of scabies and increase the possibility of scabies reinfestation among them. A previous study in an Islamic

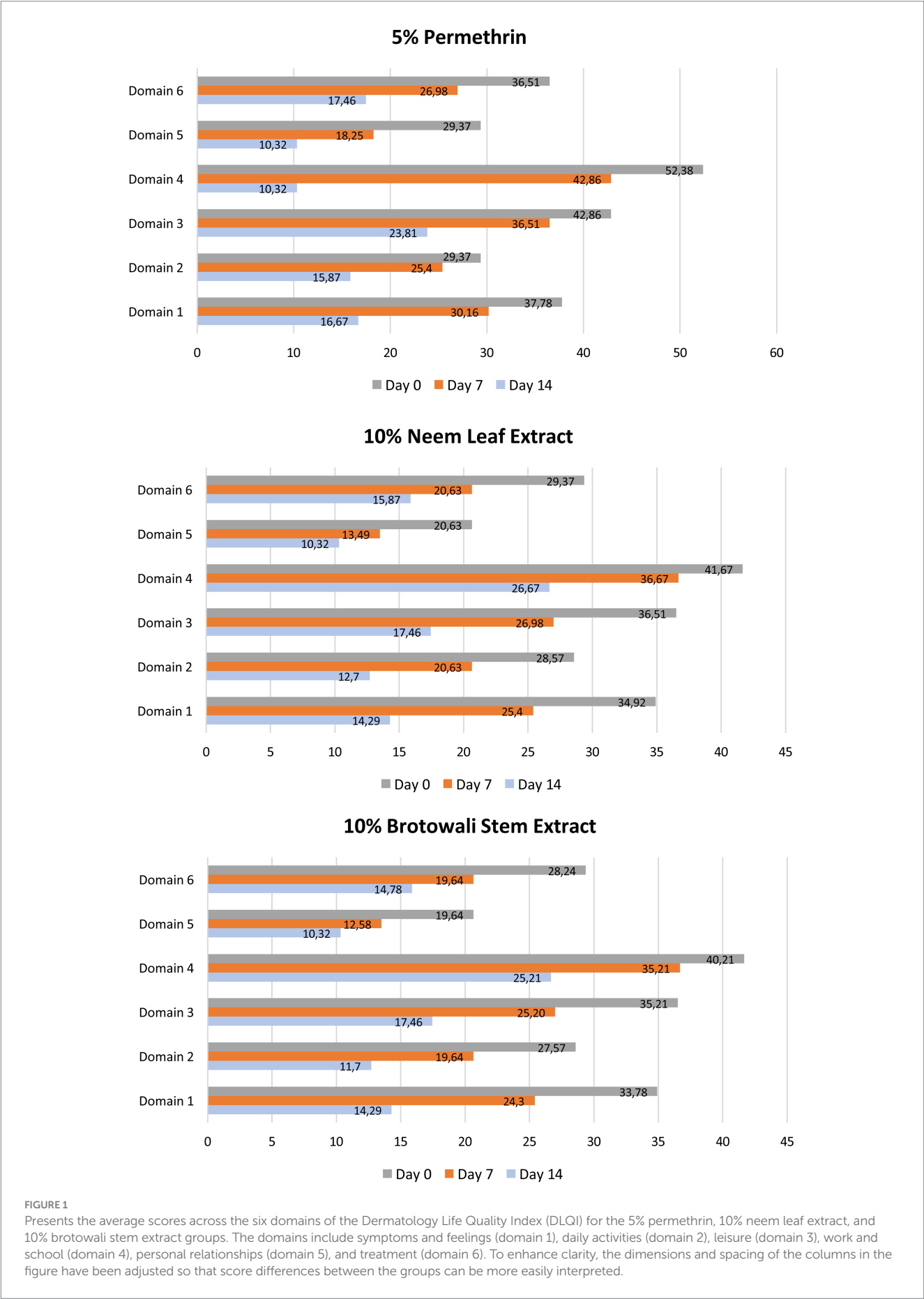


TABLE 4 Patients' quality of life before and after treatment with 5% permethrin, 10% neem leaf extract, and 10% brotowali stem extract.

Intervention	Day	Median $\pm$ IQR	<i>p</i>
5% permethrin	0	3.33 $\pm$ 1.50	0.003*
	7	3.00 $\pm$ 2.00	
	14	2.67 $\pm$ 1.00 ^{ab}	
10% neem leaf extract	0	3.33 $\pm$ 1.00	0.000*
	7	3.00 $\pm$ 1.00	
	14	2.67 $\pm$ 1.00 ^a	
10% brotowali stem extract	0	3.33 $\pm$ 1.00	0.000*
	7	3.00 $\pm$ 1.00	
	14	2.67 $\pm$ 1.00 ^a	

**p* < 0.05: Significant difference based on the Friedman test. ^aSignificantly different (*p* < 0.05) compared to day 0. ^bSignificantly different (*p* < 0.05) compared to day 7.

TABLE 5 Differences in Dermatology Life Quality Index (DLQI) in the 5% permethrin, 10% neem leaf extract, and 10% brotowali stem extract groups.

Day	Intervention	Median $\pm$ IQR	<i>p</i>
0	5% permethrin	3.33 $\pm$ 1.50	1.000
	10% neem leaf extract	3.33 $\pm$ 1.00	
	10% brotowali stem extract	3.33 $\pm$ 1.00	
7	5% permethrin	3.00 $\pm$ 2.00	0.980
	10% neem leaf extract	3.00 $\pm$ 1.00	
	10% brotowali stem extract	3.00 $\pm$ 1.00	
14	5% permethrin	2.67 $\pm$ 1.00	0.792
	10% neem leaf extract	2.67 $\pm$ 1.00	
	10% brotowali stem extract	2.67 $\pm$ 1.00	

Tested using Mann–Whitney.

boarding school reported that at least 10–15 students were in a bedroom (26). These students' density may also contribute to the spread of scabies infestation.

This study found that all three lotions 5% permethrin, 10% neem (*Azadirachta indica*) leaf extract, and 10% brotowali (*Tinospora crispa*) stem extract tended to have similar efficacy in reducing the number of lesions among subjects with scabies. This outcome is in line with the studies conducted by Wardani et al. (27) and Zainal et al. (28), which reported that 10% neem leaf extract cream and 10% brotowali stem extract cream demonstrated comparable efficacy to 5% permethrin cream during the 2-week observation period.

The vehicle for topical drugs should be cosmetically acceptable and easy to use in order to improve patient compliance. Thus, the choice of vehicle also influences adherence to therapy (29). In this study, a lotion formulation was selected because it is easy to apply, spreads well over large body areas, and provides a cooling sensation that minimizes irritation and enhances comfort. The lotions used in this study were prepared using an oil-in-water (O/W) emulsion base consisting of an oil phase (liquid paraffin, cetyl alcohol, stearic acid, and glycerol monostearate), an aqueous phase (purified water and

glycerin), preservatives (methylparaben and propylparaben), and the respective active ingredients 5% permethrin, 10% neem (*Azadirachta indica*) leaf extract, or 10% brotowali (*Tinospora crispa*) stem extract. These characteristics make lotion an appropriate vehicle, particularly for children and adolescents, who generally prefer formulations that feel light and comfortable on the skin (30).

Most subjects in this study reported that work and school were the most disrupted aspects of life due to scabies infestation, followed by symptoms and feelings, particularly itching. Scabies affects the quality of life in both adults and children (31). Several studies have shown that students with scabies tend to experience a decline in quality of life and academic performance (32, 33). After therapy, this study found a decrease in DLQI scores across all domains by the end of the evaluation, indicating improved quality of life with treatment. Notably, unlike the 5% permethrin lotion, the 10% neem leaf extract lotion and the 10% brotowali stem extract lotion showed improvements in the patients' quality of life as early as day 7.

Neem leaves are also known to reduce itching in patients with scabies. Although the exact mechanism responsible for this antipruritic effect has not been fully elucidated, it is believed to be related to the plant's anti-inflammatory activity (2). Several bioactive compounds in neem leaves such as limonoids and epoxy-azadiradione are reported to possess anti-inflammatory properties (34, 35). This further emphasizes the importance of characterizing the extract used in this study, as identifying the presence of these compounds may help explain its therapeutic effect. The antipruritic benefit is plausible given that the pathophysiology of itching is closely associated with the inflammatory response (2).

The clinical trial conducted by Castillo et al. (22) also demonstrated favorable outcomes in scabies patients, showing that brotowali (*Tinospora crispa*) lotion produced results comparable to 5% permethrin after a 2-week observation period, with significant reductions in lesion count, lesion distribution, and pruritus. Several studies suggest that the therapeutic benefits of brotowali are related to its anti-inflammatory constituents, particularly quaternary alkaloids such as berberine, palmatine, jatrorrhizine, and magnoflorine. This again highlights the importance of characterizing the extract used in this study, as confirming the presence of these compounds may help explain the observed clinical improvement. Berberine and its salts possess antibacterial, antifungal, and antipyretic properties, which can contribute to reduced inflammation and exudation in scabetic lesions, along with overall improvement of the disease. In addition, brotowali extract has been reported to exhibit immunostimulatory activity, which may further support its therapeutic role.

In addition to assessing the effectiveness and quality of life of patients with scabies, this study also evaluated the presence of adverse effects that may occur during treatment. Overall, the administration of therapy in this study was well tolerated, and during therapy, there were no reported or found complaints of adverse effects such as irritation, redness, burning, or allergic reactions from all three groups. In line with previous studies that did not show any significant adverse effects in the administration of either 10% neem leaf extract cream, 10% brotowali stem extract cream, or 5% permethrin cream, the results of this study are consistent (27, 28).

However, this study has several limitations, including patient compliance with treatment and the difficulty of accurately evaluating the duration of application, making it challenging to ensure that the medication was used correctly as instructed. Reinfestation due to

re-contact with undiagnosed scabies cases was also possible. For future research, stricter supervision can be implemented by collaborating with Islamic boarding school administrators, increasing the concentration of both neem (*Azadirachta indica*) leaf extract and brotowali (*Tinospora crispa*) stem extract to further assess their potential effectiveness, and administering treatment simultaneously to the entire study population to minimize reinfestation.

In conclusion, scabies remains a recurrent issue in Islamic boarding schools. All three 5% permethrin lotion, 10% neem leaf extract lotion and 10% brotowali stem extract lotion effectively reduce the number of lesions and improve the quality of life for scabies patients, with no adverse effects reported in all three treatment group. This suggests that 10% neem leaf extract lotion and 10% brotowali stem extract lotion could be a viable alternative to 5% permethrin lotion.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by University of Brawijaya Malang. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin.

Author contributions

DW: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. AY: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software,

Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. VL: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

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