

Systematic Review and Meta-analysis of the Effectiveness of Topical Aloe vera on Diaper Dermatitis with Parameters Degree of Diaper Dermatitis with Scale

Rinda Gita Atikasari¹, Diah Adriani Malik¹, Retno Indar Widayati¹, Puguh Riyanto¹, Asih Budiastuti¹, Muslimin¹ and Hardian²

¹Department of Dermatovenereology, Faculty of Medicine, Diponegoro University/Dr.Kariadi Hospital Medicine Center, Jl Dr. Sutomo No.16,50244, Semarang, Indonesia.

²Department of Physiology, Faculty of Medicine, Diponegoro University, Jl Prof Soedarto, Tembalang,50275, Semarang, Indonesia.

*Correspondence:

Jl. Prof. Soedarto, Tembalang, Tembalang Sub-district, Kota Semarang District, Central Java 50275, Indonesia, E-mail: rindakulkel@gmail.com

Received: 25 September 2021; Accepted: 13 October 2021

Citation: Atikasari RG, Malik DA, Widayati RI, et al. Systematic Review and Meta-analysis of the Effectiveness of Topical *Aloe vera* on Diaper Dermatitis with Parameters Degree of Diaper Dermatitis with Scale. *Dermatol Res.* 2021; 3(2): 1-11.

ABSTRACT

Background: For toddlers younger than 36 months, most of them still use diapers, so diaper rashes frequently appear in the diaper area. To improve the skin barrier, a moisturizer is needed to repair the skin barrier. Besides, the ceramide gold standard of moisturizer for diaper dermatitis, topical ingredients with natural ingredients can be used, for example, topical Aloe vera.

Objective: To prove the effectiveness of topical Aloe vera moisturizer compared to other topical ingredients against diaper dermatitis.

Methods: The results of the electronic database search Medline Pubmed, Scopus, EBSCOhost, ProQuest, Cochrane library, ClinicalTrials.gov, found 5 articles were included in the qualitative review (n = 289 subjects) and 4 articles (n = 214 subjects) were included in the meta-analysis.

Results: Meta-analysis showed that after the administration of topical Aloe vera, there was a mean difference in the score of the degree of diaper dermatitis before and after therapy, the result showed negative value in the studies which were included the treatment group with Aloe vera. This indicates a decrease in the degree of diaper dermatitis after treatment with Aloe vera. The control group also showed that the mean score difference in the degree of diaper dermatitis after administration of control therapy was all negative. This shows that after the administration of therapy in the control group there was also a decrease in the score of the degree of dermatitis. The biggest decrease in the degree of diaper dermatitis was in the study conducted by Murni 2020, which was -2.10 ± 1.39 . The lowest decrease in the degree of diaper dermatitis was found in the study conducted by Badelbuu 2019 B which received Chamomile, which was -0.93 ± 1.08 . Meanwhile, in the Panahi's study, the heterogeneity test results showed the value of $Q=5,324$ $df=43$; $p=0,256$, $I^2=24,866$. This shows that the data is homogeneous, it is in line with the results of the statistical Q test and heterogeneity, the results of the I^2 test obtained $p < 0.001$ which also indicates the data is homogeneous. The analysis was carried out using a fixed effect model because the data were homogeneous. The results of the meta-analysis showed that the statistical Q value was z value = -0.969 ($p = 0.047$). It has quite meaningful results.

Conclusion: The meta-analysis showed that statistically there were only slight differences, but there were also studies that provided significant results. Topical application of Aloe vera appears to be more effective. The results of qualitative analysis on other skin barrier function parameters indicate that topical Aloe vera can improve skin barrier function in diaper dermatitis patients. In addition, it provides the same results as standard therapy and several other topical therapies that had been studied which had a good effect on repairing the skin barrier.

Keywords

Topical *Aloe vera*, Diaper dermatitis, Diaper rash.

Introduction

Dermatitis is a skin inflammation that is acute, sub-acute, or chronic in response to the influence of exogenous and endogenous factors that cause clinical abnormalities in the form of polymorphic fluorescence and itching [1]. The prevalence of dermatitis in Indonesia is 6.8% of all skin diseases. There are various kinds of dermatitis, one of which is irritant contact dermatitis. The prevalence is increasing every year, with the risk of dry skin [1,2]. One of the irritant contact dermatitis issues, namely diaper dermatitis, is a skin disorder (skin rash) that arises due to inflammation in the diaper-covered area, which usually appears in the genitals, around the anus, buttocks, groin, and lower abdomen [3,4].

This disease often occurs in infants and toddlers who wear diapers, usually at the age of less than 3 years, mostly at the age of 9 to 12 months [5]. Based on data released by the World Health Organization (WHO) in 2012, the prevalence of diaper dermatitis in infants is quite high, namely 25% of 6,840,507,000 babies born in the world [6]. The incidence of diaper dermatitis in Indonesia reaches 7-35% which affects male and female infants under three years of age [6,7].

Interference in the structure of the fat layer and the damage of stratum corneum integrity can cause irritation, which is easily penetrated by microorganisms and activate the Langerhans cells of the epidermis. Lipase and protease enzymes in feces can disrupt the integrity of the stratum corneum and degrade proteins, so that they can penetrate the skin barrier. Penetrants or irritants that interact with keratinocytes stimulate the release of cytokines which then affect the dermal blood vessels and cause inflammation. These irritants can also promote proliferation, metabolism, and differentiation, resulting in the epidermis rearranging the stratum corneum and resulting in damaged structures, abnormal water regulation, and inadequate desquamation [7].

Diaper dermatitis is caused by the alterations of skin lipids and hydration accompanied by a rough stratum corneum, which is different from normal skin conditions. Hence, irritants more easily penetrate the damaged skin barrier and the area of skin changes due to diaper wear can affect the structure, function, and response of the skin barrier. This is due to the reduction in ceramides which causes impaired skin barrier function which results in an increase of fluid loss through the skin, so that the skin becomes drier and more sensitive to various physical and chemical influences. In a state of increased skin hydration, the risk of maceration in diaper dermatitis patients increases [8].

Skin irritation and the risk of maceration in diaper dermatitis cause a decrease in skin function. The parameters of the skin barrier assessment can be assessed by non-invasive methods; for diaper dermatitis, it can be assessed clinically with the degree of dermatitis

from mild to severe, on a 5-point scale [9–12]. Therapy for diaper dermatitis can use zinc oxide for the prevention or treatment of moderate type of diaper dermatitis; For more severe diaper dermatitis, antifungal agents and low potency corticosteroids such as hydrocortisone are required. Lesions that have not improved can use a mixture of nystatin ointment and 1% hydrocortisone ointment in the same ratio. Low potency topical corticosteroids are generally a safe use medicine for children and are recommended for moderate to severe diaper dermatitis. Combination therapy of antifungals and corticosteroids of medium-high potency is not recommended because it can cause skin atrophy and is more easily penetrated in occlusive diaper conditions [7,12].

One of the therapeutic options to improve the function of the skin barrier is a moisturizer. The epidermal barrier repair by moisturizing prevent the penetration of irritants and allergens which are the triggers of eczematous lesions, such as the antigenic toxin produced by *Staphylococcus aureus*. In addition, moisturizers are also useful in prevention and maintenance therapy [13,14]. *Aloe vera* is one of plant species having the natural ingredients which has function as a skin moisturizer, wound healer, antioxidant, antifungal, anti-inflammatory, antiaging, and antiseptic. Thus, the use of *Aloe vera* moisturizer in providing therapy for diaper dermatitis is currently growing rapidly. *Aloe vera* gel contains water, polysaccharides (glucomannan and acemannan), carboxypeptidase, magnesium, zinc, calcium, glucose, cholesterol, salicylic acid, gamma linolenic acid (GLA), vitamins A, C, E, lignin, saponins, sterols. and amino acids [15]. Mucopolysaccharide content in *Aloe vera* can help increase skin moisture, stimulate fibroblasts that produce collagen and elastin so that the skin is more elastic [16-18].

Currently, the studies related to *Aloe vera* (*Aloe vera*) are developing very rapidly. The existing studies showed that topical *Aloe vera* can reduce trans epidermal water loss scores and increase water content in the stratum corneum, reduce inflammation and antimicrobial activity, which makes it possible to apply *Aloe vera* in dermatology as an additional topical ingredient for diaper dermatitis therapy [13]. Therefore, the researcher of this study interested in knowing the effectiveness of administering *Aloe vera* gel as an additional topical ingredient on the skin of diaper dermatitis patients. The purpose of this systematic review and meta-analysis was to analyze the effectiveness of topical *Aloe vera* as a therapy against diaper dermatitis.

Materials and methods

Data collection was conducted online at Pubmed-MEDLINE, Scopus, EBSCO, Cambridge Core, Elsevier Clinical Key, ProQuest, Springer Link, Cochrane library, ClinicalTrials.gov, Web of Knowledge, Web of Science, and the World Health Organization international clinical trials registry, as well as hand searching from the library with a time span of 2012 to 2021. The types of this study are observational meta-analysis, systematic review and meta-analysis. The population of this study is the result of clinical trials on the use of *Aloe vera* moisturizer against diaper dermatitis.

The sample of this study is a research report on the use of *Aloe vera* moisturizer on diaper dermatitis skin that meets the following criteria: Research on the effectiveness of topical *Aloe vera* against diaper dermatitis both caused by candida infections and irritants starting from 2012-2020; Studies using topical *Aloe vera* on diaper dermatitis skin; In the form of clinical trials with/without randomization; Age range 0 – 3 years; Do not suffer from systemic disease; Research outcomes in the form of degrees of dermatitis: Articles written in English or Indonesian. The sample size was all research reports regarding the use of topical *Aloe vera* on diaper dermatitis skin which matched the research criteria.

Research Procedures

Information sources and electronic database search strategies include Medline Pubmed database, EBSCO, ProQuest, Elsevier Clinical Key, Cochrane library, ClinicalTrials.gov, Web of Knowledge, Web of Science, and the World Health Organization international clinical trials registry. Other sources are reference lists, conference proceedings, researchers in the field, and journals. The search for information sources is carried out until the data analysis was conducted. The following Medical Subject Headings (MeSH) terms are used to create two subgroups of citations (1) *Aloe vera*; (2) topical agents; (3) diaper rash. The three subgroups are combined using the Boolean term 'and' to combine subgroup (1) with other subgroups, then the term 'OR' is used to combine subgroups (2) and (3) so as to obtain a subset of citations relevant to the research question. The literature search was performed based on the 2009 PRISMA flowchart. Three researchers conducted an independent literature search and the reference lists of all primary articles and the most recent literature reviews were checked to identify articles that were not found. Any disagreements in paper selection and data extraction were resolved by consensus.

Using the prepared data extraction forms, data were extracted independently by three researchers. This form is based on the data extraction form from the modified cochrane library. The data recorded were the treatment with *Aloe vera*, other moisturizers or without intervention as well as the TEWL score, the degree of dermatitis. The risk of bias was assessed using the Cochrane Risk of Bias Tool for Randomized Controlled Trials.

Data analysis

Prior to data analysis, the collected data will be checked for completeness and correctness of the data. The data were input into a computer. Research characteristics data such as research title and year was recorded in the data extraction form. Data in the form of treatment with *Aloe vera*, other topical ingredients or without intervention as well as the degree of dermatitis were extracted from the research report and input them into the data extraction form.

The systematic review and meta-analysis of weighted mean differences between the treatment and control groups was analyzed using the Cochrane systematic review software (Review Manager (RevMan) [Computer program] Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014).

Results and discussion

Electronic data searches were conducted online at Pubmed-MEDLINE, Scopus, EBSCO, Cambridge Core, Elsevier Clinical Key, ProQuest, Springer Link, Cochrane library, ClinicalTrials.gov, Web of Knowledge, Web of Science, and the World Health Organization international clinical trials registry, as well as hand searching from libraries with a time span of 2012 to 2012 obtained 115 relevant articles. From 115 initial screening, 16 of them were duplicated so that only 99 articles were relevant. After checking the title and removing duplication, there were 28 research articles. The abstracts of these articles were then reviewed so that 18 articles were excluded, consisting of 9 literature review articles, 1 article with no result and 9 primary research articles out of the topic of this meta-analysis. 28 full-text articles were assessed for eligibility, and 1 of them was excluded because they have the same content and researchers, only the year of article publication that is different. From 18 articles that were assessed for exclusion, the remaining 9 studies were used in qualitative and quantitative studies to assess the effectiveness of topical *Aloe vera* against diaper dermatitis and against other topical ingredients. The process of searching the study literature shown in Figure 1.

The total sample of 9 studies was 333 people with a mean age of 0-36 months. All studies included the diagnosis of diaper dermatitis as an inclusion criterion in sampling. In this study, patients who had mild to severe grades of diaper dermatitis were selected. As well as several studies using additional moisturizers/topical ingredients such as *Aloe vera*, calendula oil or chamomille oil, henna, virgin coconut oil compared to standard therapy for diaper dermatitis.

Several studies show that the application of *Aloe vera* is more than other topical ingredients. According to the study of Badelbuu et al., topical *Aloe vera* can be used as the main treatment.

Research Characteristics

Base on the result, research sites were carried out in Iran (n=5), followed by Indonesia (n=3), India (n=1). All studies were clinical trials with or without randomization (n=9). The total sample of 9 studies was 333 people, 91 people in the study use *Aloe vera* treatment and 93 people in the study use other topical ingredients. The average age included in the study with the use of *Aloe vera* was the majority aged of 6-24 months and the average age in studies with the use of other topical ingredients was 0-36 months. All studies included a diagnosis of diaper dermatitis of all degrees as inclusion criteria in sampling. There were 4 studies selecting patients with diaper dermatitis who were treated with topical *Aloe vera*, and there were also 5 studies using other topical ingredients treatment instead of standard therapy for diaper dermatitis.

The studies which concern to diaper dermatitis were all assessed by the degree of dermatitis and onset of recovery. For the studies related to topical *Aloe vera*, for instance, the study by Badelbuu et al in 2019 [10], in which the study used topical *Aloe vera* in the form of 95% ointment. In this study, the sample was 90 patients

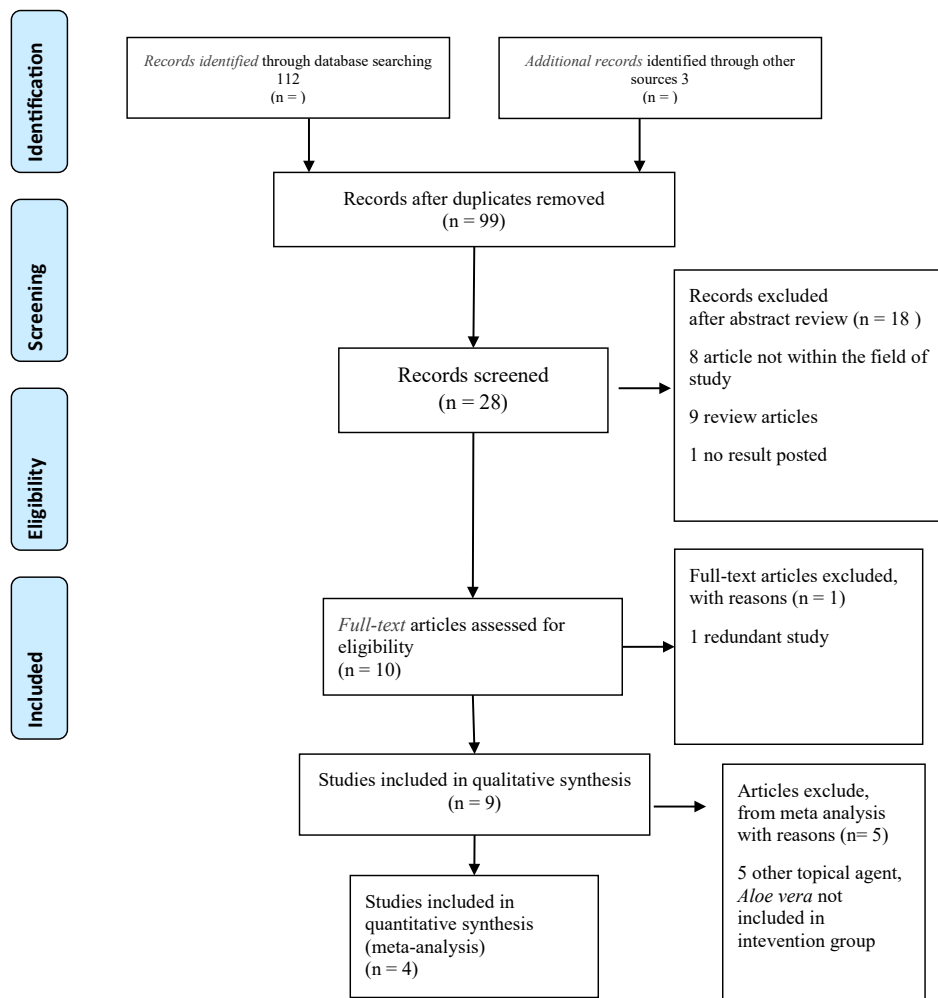


Figure 1: Flowchart of identification and selection of research literature in systematic review and meta-analysis.

with an average age of 4-6 months, Badelbuu study concern to the use of *Aloe vera* and other topical ingredients, namely chamomile which was compared to the control group who received zinc oxide, clotrimazole and hydrocortisone which were the standard therapy for diaper dermatitis. The treatment group was given topical *Aloe vera* and topical chamomile.

Result of Qualitative Data Analysis (Systematic Review)

Five literatures were analyzed qualitatively [26-30]. Result was presented as follows:

1. Heri 2018 [26]

This research was conducted in Indonesia using 18 samples with age criteria of 0-12 months. The research method used was a quasi-experimental design with pre and post-test, and had a higher risk of bias. This study used a comparison between olive oil. This study assessed the degree of dermatitis with 3 scales which were observed for 3 days with the treatment given to the group with olive oil and the control group using aquabides smeared twice a day. In this study, the degree of dermatitis in the group before the first-degree treatment was 5 respondents (55.6%). The assessment was carried out on the first day and third day with the results on the first day getting an average of 1.3 ± 0.6749 , while on the third day

the average was 1.056 ± 0.779 . Assessment with the percentage, there are 5 respondents (55.6%) experienced a change in the degree of dermatitis on a scale of 0 with the use of olive oil, while for the control group there was no change. The alteration of diaper rash degree is due to the use of olive oil in the treatment of diaper dermatitis in moisturizing and providing improvement to the skin barrier. Theoretically, olive oil has several benefits for softening the skin, maintaining moisture and skin elasticity and facilitating the skin regeneration process.

2. Meliyana 2017 [27]

This study was conducted to determine the effect of giving coconut oil on the incidence of diaper rash in infants aged of 3-24 months. This study used a quasi-experimental method with one group pre-test post-test design pre-experimental design. The total sample was 16 respondents. The research was conducted on the treatment group and the control group. The study used 3 degrees of dermatitis scale, the scale was assessed before and after the treatment given. Treatment of giving coconut oil twice a day in the morning and evening, was carried out for 4 days. Prior to the treatment, the scale of dermatitis 1 was 8 correspondents (50%), while the second degree was 8 correspondents (50%) with a mean of 1.50. After being given the intervention of coconut oil for 4

days, the average degree of diaper rash in babies decreased, there were 7 babies who experienced degree 0 (no rash), 7 babies who experienced degree 1 (redness) and 2 babies who still experienced degree 1 with a mean of 0.69. Among of them, there were 6 babies who experienced diaper dermatitis grade 2 to grade 1, 6 babies who experienced dermatitis of grade 1 to dermatitis of grade 0, 1 baby from grade 2 dermatitis to grade 0, and 2 babies who did not experience a change in dermatitis of grade 1. Hence, about 95% of coconut oil treatment shows the effectiveness of coconut oil to babies who have diaper dermatitis. Coconut oil contains natural moisturizers and contains medium chain saturated fatty acids that easily penetrate the skin layers and maintain skin elasticity. It also contains lauric acid, which is converted into monoglyceride in the body, which is a monoglyceride compound that has antiviral, antibacterial, antibacterial and antiprotozoal properties.

3. Keshavarz, et al. 2016 [28]

This study was to determine the effectiveness of the topical ingredients use of traditional henna and hydrocortisone treatment for the treatment of diaper dermatitis. This study used a triple blind randomized clinical trial method. Using 88 respondents, which were divided into 2 groups, namely the treatment group using 25% of henna oil and the control group using hydrocortisone cream. The assessment in this study used the degree of dermatitis, the treatment given three times a day and observed for 5 days. As well as being assessed on the first, third and fifth day. In this study the treatment was divided into two groups, 41 correspondents using henna oil and 41 correspondents using hydrocortisone cream. The results obtained were on the first and third day of examination, there were no significant results for both groups. The mean score on the fifth day, the mean score of patients with grade 0 of treatment group with henna was 37 (90.2), while the mean score of grade 0 patients with hydrocortisone was 25 [28]. However, on the fifth day, there were significant results in patients receiving henna oil compared to the use of hydrocortisone cream. In this study, there is a slight risk of bias and has good research quality.

Henna is a natural plant that can provide anti-inflammatory, antipyretic and analgesic effects. In addition, it is mentioned that it can be as an antioxidant, immunomodulator and can reduce the effects of corticosteroids. In the treatment of diaper dermatitis, a good barrier repair with appropriate cream selection and frequency of diaper changes, is very helpful for treating diaper dermatitis.

4. Mahmoudi, et al 2013 [29]

This study compared the effect of bentonite and calendula in providing a therapeutic effect on diaper dermatitis. This study was conducted in India in 2015, the research method used was a double blind randomized controlled trial. This study used 100 samples taken from 1 to 24 months of age, with a mean age of 6.45 ± 5.53 months for the calendula group, and 7.35 ± 6.28 months for the bentonite group. The materials used are bentonite 50% cr and calendula 1.5% cr. Before being applied, this topical material was also tested for allergies on the patient's arm and waited for 20 minutes to see if the patient had a history of the topical material. This study assessed the healing time produced by these two topical

ingredients. Observations were conducted for 3 days, and were assessed on the first and third days. The treatment was given by giving cream to the calendula and bentonite groups three times a day for three days. In this study, in the first 6 hours the results showed that bentonite cream was 44%, while calendula was 27%. And the results obtained in this study for the onset of recovery during treatment until it improved for approximately 3 days from bentonite at 44.14 ± 23.95 hours, while for calendula it was 86.43 ± 24.13 hours. Therefore, from the results obtained, the use of bentonite cream heals faster than calendula cream. This study also has a fairly low risk of bias. Bentonite is included in the type of mineral in the form of aluminium phyllosilicate. This ingredient can be as a moisturizer, protect the skin and increase absorption. In another study, it was also stated that bentonite was very effective for hand dermatitis.

5. Nourbakhsh, et al 2016 [30]

This study was conducted to determine the effectiveness of topical ingredients containing 2% magnesium in the treatment of diaper dermatitis. This study used a double-blind clinical trial study method. In this study, correspondents aged less than 2 years were included. Using 64 samples of patients with diaper dermatitis. The results of the study obtained onset of recovery (healing time). The mean age was 1.9 ± 0.8 years and the mean age in the control group was 1.9 ± 0.6 years. The first treatment group used ingredients containing calendula and magnesium, while the second treatment group only used calendula. The treatment given three times a day in groups 1 and 2 was observed for 5 days. The results obtained in this study mean the duration of the day in the treatment group using a cream containing calendula and magnesium 2% 1.5 ± 0.5 days and in the control-group using calendula cream 3.25 ± 0.67 days.

The mean days of the treatment group showed significant results compared to the control group. According to James et al, the effectiveness of magnesium use for dermatitis had been studied and showed good results in restoring skin condition and protecting skin against allergens, as well as being able to moisturize and replace fat on the skin, thus, it can reduce symptoms of dermatitis.

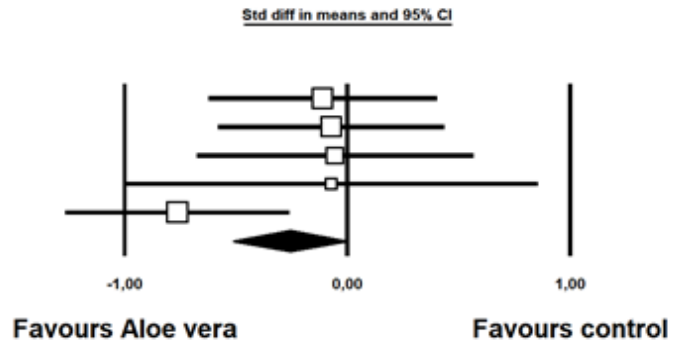
Quantitative Data Result (Meta-Analysis)

The mean score difference of the degree of dermatitis before and after treatment in the treatment group who received *Aloe vera* and the control group is shown in Table 1.

Table 1: The difference in the mean score of the degree of diaper dermatitis before and after treatment in the treatment group that received *Aloe vera* and the control group.

No	Name of the Researchers	Control Type	Treatment		Control	
			Average \pm SD	n	Average \pm SD	n
1	Badelbuu 2018 [9]	Plasebo	-1,04 \pm 0,88	30	-1,10 \pm 0,75	29
2	Badelbuu 2019 [10]	Chamomile	-1,04 \pm 0,88	30	-0,93 \pm 1,08	30
3	Shaharast 2018 [12]	Zinc oxide	-1,80 \pm 0,90	20	-1,75 \pm 0,90	20
4	Murni 2020 [25]	VCO	-2,10 \pm 1,39	9	-2,00 \pm 1,38	9
5	Panahi 2012 [11]	Calendula	-1,19 \pm 1,01	32	-1,91 \pm 0,89	34

Study name	Subgroup within study	Statistics for each study						
		Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Sima 2019 A	Plasebo	-0,112	0,261	0,068	-0,623	0,399	-0,429	0,668
Sima 2019 B	Chamomile	-0,073	0,258	0,067	-0,579	0,433	-0,283	0,777
Bayat 2018	Zinc oxide	-0,055	0,316	0,100	-0,675	0,565	-0,175	0,861
Murni 2020	VCO	-0,072	0,472	0,222	-0,997	0,852	-0,153	0,878
Yunes 2012	calendula	-0,764	0,255	0,065	-1,264	-0,264	-2,994	0,003
Overall		-0,258	0,130	0,017	-0,512	-0,004	-1,969	0,047



Fixed-effect model
Heterogeneity: Q value: 5.324, df=4, p=0,256, I²=24,866
Test for overall effect: Z value= -0.969; p=0,047

Table 2: The meta-analysis results of the effectiveness of *Aloe vera* therapy compared to control groups on the degree score of iaper dermatitis.

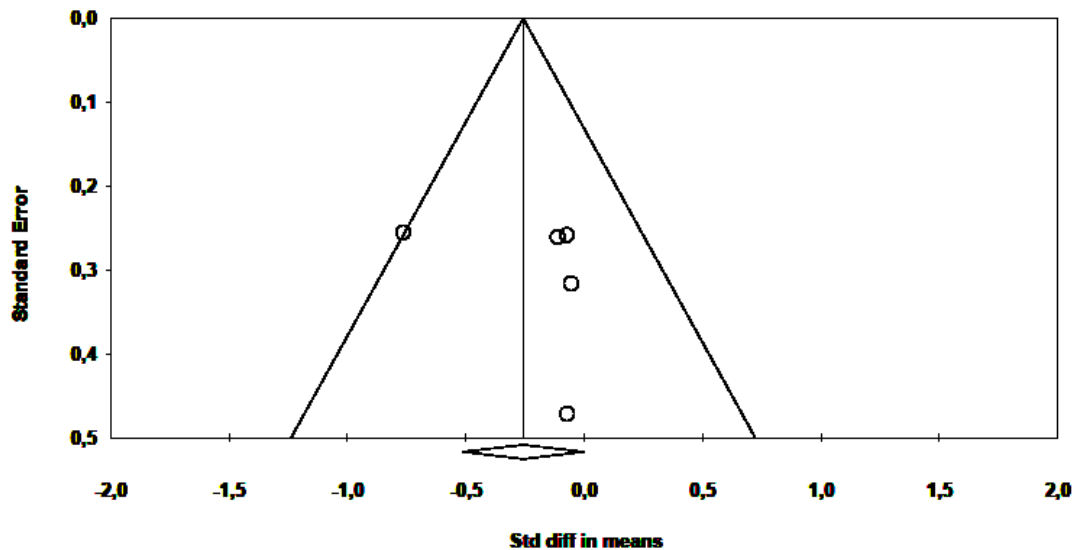


Figure 2: Funnel plot using 4 studies of therapeutic efficacy with topical *Aloe vera* on diaper dermatitis.

In table 2 the average difference in the degree of diaper dermatitis before and after therapy in studies belonging to the treatment group with *Aloe vera* is negative. This indicates a decrease in the degree of diaper dermatitis after treatment with *Aloe vera*. The control group also showed that the mean score difference in the degree of diaper dermatitis after administration of control therapy was all negative. This shows that after the administration of therapy in the control group there was also a decrease in the score of the degree of dermatitis. The biggest decrease in the degree of diaper dermatitis was in Murni 2020 study, which was -2.10 ± 1.39 [25]. The lowest decrease in the degree of diaper dermatitis was found in Badelbuu 2019 study which received Chamomile, which was -0.93 ± 1.08 [10].

The results of the meta-analysis of the effectiveness of *Aloe vera* therapy compared to controls for the treatment of diaper dermatitis are shown in Table 2.

Table 2 showed the results of a meta-analysis of the effectiveness of *Aloe vera* therapy compared to controls on the lower degree score of

diaper dermatitis. The results of the heterogeneity test showed the value of $Q=5,324$ $df=43$; $p=0,256$, $I^2=24,866$. This shows that the data is homogeneous, in line with the results of the statistical Q test and heterogeneity, the results of the I² test obtained $p < 0.001$ which also indicates the data is homogeneous. The analysis was carried out using a fixed effect model because the data were homogeneous. The results of the meta-analysis showed that the statistical Q value was z value = -0.969 ($p = 0.047$). This shows that the overall administration of *Aloe vera* can significantly reduce the score of the degree of diaper dermatitis.

Table 6 also shows the results of the meta-analysis of the mean difference in overall diaper dermatitis degree score -0.258 ± 0.13 (95% CI = -0.512 to -0.004). This shows that the score of the degree of diaper dermatitis after treatment with *Aloe vera* was lower than the control, but statistically the difference was significant ($p=0.047$).

Sensitivity analysis by excluding one of the studies included in the meta-analysis did not change the overall results. Overall

results still showed that the administration of *Aloe vera* still gave a significant decrease in diaper dermatitis score ($p = 0.047$).

An assessment of the existence of publication bias is shown in Figure 2.

Figure 2 showed that the funnel plot is symmetrical with the standardized difference in mean value on the right side of the zero line (Badelbuu 2018, Badelbuu 2019, Shahparast 2018 and Murni 2020 studies). The Panahi study is shown on the left. The results of the analysis with the Egger regression test gave non-significant results ($p=0.664$). This shows statistically no publication bias [12].

Risk of Bias from the included studies

The research articles included in the meta-analysis were 4 studies (namely Badelbuu et al, 2019; Panahi et al, 2012; Shahparast et al, 2018; and Murni, 2020 with the data of pre and post treatment. Four studies that conduct a meta-analysis report data with the outcomes of dermatitis degree with 5 scales. Those four studies report the dermatitis degree of pre- and post-treatment.

The risks of bias from studies included in the analysis, both qualitative and quantitative, were assessed using The Cochrane Collecting data-form for RCTs only [20] and The Cochrane Collaboration's tool for assessing risk of bias in randomized trials [21], including randomization, allocation concealment, blinding of study subjects, blinding outcomes, incomplete outcome data, selection of reported outcomes, and other biases. The risk assessment of bias from each of these aspects is then converted according to Agency for Healthcare Research and Quality (AHRQ) standards. The risk assessment for bias is shown in Table 3. Risk of bias in the studies are included.

	Random sequence generation	Allocation concealment	Blinding (participants and personnel)	Blinding (outcome assessment)	Selective reporting	Other sources of bias	Incomplete outcome data	Other bias	Overall
Badelbuu 2019 (10)	+	+	+	+	+	+	+	+	+
Shahparast 2018 [12]	-	-	?			?	+		
Murni 2020 [25]	-	-	-	-	?	?	?	?	-
Panahi 2012 [11]	?	?	?	?	+	?	+	+	?

Table 3: Risk of bias in the included studies.

Risk of bias in studies used for systematic reviews and meta-analyses. Circle symbol of ● with a positive sign indicating a low

risk of bias, circle symbol of ● with a question mark the risk of bias cannot be assessed, circle symbol of ● with a negative sign indicates a high risk of bias.

Table 3 showed that the study of Badelbuu 2019 has a low risk of bias. Shahparast 2018 study belongs to non-assessable bias risk. Badelbuu 2018 study is stated as a double blind RCT using the 6-block method but the subject selection mechanism used a convenience sampling mechanism. The allocation mechanism is not clearly defined so the risk of bias is high. Badelbuu's study also mentioned that blinding was carried out on staff and patients, but the mechanism for blinding was not explained. All subjects can be followed-up. Other risks of bias were also not described. Based on this issue, the risk of bias in Shahparast 2018 research is included in the non-assessable category. Murni 2020 study is a clinical trial study that includes a quasi-experimental randomized trial but the method of randomization is not explained. Blinding is not explained whether it is conducted or not. Other sources of bias could not be assessed. Incomplete also cannot be assessed. Based on this statement, Murni 2020 study is included in the category of high risk of bias. Panahi 2012 study which is in the method mentioned that randomization was carried out but the randomization method was not explained, the method of blinding and concealment was also not explained. The risk of bias is not explained but there is a possibility of observer bias. All cases were followed-up for completion and no other source of bias was reported. Overall, Panahi' study is in the category of unclear risk of bias.

Therefore, 4 studies that were included in meta-analysis, only 1 study had a low risk of bias (25.0%). Heri 2018 study did not include methods of randomization, allocation concealment, blinding of research subjects or blinding of outcomes. Meanwhile, Panahi's study on Blinding of Participants and Personnel and Blinding of Outcome Assessment got unclear results, causing the risk of bias to be of fair quality. However, this research is categorized as a fairly good quality of evidence. Maliyana's study, 2017 has a high risk of bias for Blinding of Participants and Personnel and Random sequence generation, as well as selective reporting. While Shahparast, et al 2018 also have a high risk of bias towards Blinding of Participants and Personnel. Therefore, Heri's study in 2017 is categorized as low quality of evidence.

Discussion

Diaper dermatitis, also known as diaper rash, is an inflammation of the skin in areas covered by diapers, namely the thighs, buttocks, and anal area. This disease is one of the most common skin diseases in infants and children whose diapers are always wet and rarely changed, it can also occur in incontinent patients who require diapers to collect urine or feces. increased skin hydration, moist skin is more easily injured due to friction of the diaper when the child moves and is more easily irritated. Wet skin also allows the growth of bacteria and fungi that can increase local skin pH, increasing fecal lipase and protease activity. Diaper dermatitis can also be caused by *Candida albicans* which is a secondary parasite. The use of antibiotics also increases the colonization of *Candida albicans* [7,23].

Other factors include contact with skin irritants (urine, feces, bile salts), mechanical friction (skin to skin, diapers to skin), skin pH, nutritional or dietary status (feces composition), diarrhea, and certain medical conditions. The appearance of irritation in diaper dermatitis basically occurs due to irritation (stimulation), especially from urine and feces that are in contact for too long with the skin, making the skin wet and easily irritated. Urine and feces are major contaminants of the diaper area, both of which contribute to irritant diaper dermatitis. Urine has an acidic pH of 4.6-8, feces has a basic pH of 6.5-7.5, and the pH of the skin in the diaper area, especially the buttocks is around 5.5 [24,25]. The mixture of feces and urine changes the pH of the skin to a more alkaline >6. Proteases and lipases in feces become more active at high pH, whereas proteins and fats in the skin tend to be degraded and cause irritation or dermatitis, while fecal microbiota can cause irritant diaper dermatitis. Urine also contains various organisms, including bacteria ammoniagenes which can convert urea into ammonia. Infants with diaper dermatitis also usually occur because of atopic history, Th2 dominance in atopic dermatitis patients causes maturation of B cells and converts IgM into IgE. The filaggrin gene (FLG) on chromosome 1q21 that encodes a key protein in epidermal differentiation also plays a role in the appearance of clinical symptoms in atopic dermatitis, namely dry and scaly skin.

Aloe vera barbadense Miller contains 72 substances needed by the body. Among the 72 substances, there are 18 kinds of amino acids, carbohydrates, fats, water, vitamins, minerals, enzymes, hormones and drug class substances such as antibiotics, antiseptics, antibacterial, anti-cancer, anti-viral, anti-fungal, anti-infective, anti-bacterial, anti-inflammation, anti-swelling, anti-parkinsonian, anti-atherosclerosis, and anti-drug resistant to antibiotics. Bio-molecularly, it is also mentioned that *Aloe vera* which can be called as phytochemicals, such as vitamins, enzymes, minerals, sugars, salicylic acid, lignin, saponins, amino acids and anthraquinones which is contained in the leaves of the plant extract can act like strong siderophores, which chelate iron from the medium and degrade the bacterial biofilms. Indeed, *A. vera* leaves are reported containing as many as 75 nutritional fruits and 200 active compounds from the main components of anthraquinones (aloin, anthranol and aloetic acid) with vitamins.

Therefore, based on the research that was carried out in a meta-analysis (quantitative) and a systematic review (quantitative) on topical *Aloe vera* and other topical ingredients to find out whether it can be statistically proven the effectiveness of topical *Aloe vera* in improving the degree of diaper dermatitis, in this case improving the skin barrier.

In this study, quantitative data based on four studies on diaper dermatitis were treated, one of them with topical *Aloe vera* and some compared with standard therapy as a control or using other topical ingredients as a comparison. Shows different results. Of the 4 studies, correspondents who received topical *Aloe vera* therapy experienced a decrease in dermatitis grade scores. There

is one study that gives good results statistically, namely the study according to Panahi. Existing research has assessed the efficacy of topical *Aloe vera* and calendula in treating diaper dermatitis. In a study conducted by Panahi et al said that this study used 2 groups which were the treatment group (aloe n=32) and the control group (calendula n=34). For the results of *Aloe vera* having an improvement after being treated with *Aloe vera* it can reduce patients with a higher grade of dermatitis score to a lower one. For *Aloe vera* cream, it is said to also have a significant effect in reducing the score of the degree of diaper dermatitis.¹⁰ The results of the meta-analysis of the effectiveness of *Aloe vera* therapy compared to controls on the score of the degree of diaper dermatitis. The results of the heterogeneity test showed the value of $Q=5,324$ $df=43$; $p=0,256$, $I^2=24,866$. This shows that the data is homogeneous, in line with the results of the statistical Q test and heterogeneity, the results of the I2 test obtained $p < 0.001$ which also indicates the data is homogeneous. The analysis was carried out using a fixed effect model because the data were homogeneous. The results of the meta-analysis showed that the statistical Q value was z value = -0.969 ($p = 0.047$). This shows that the overall administration of *Aloe vera* can significantly reduce the score of the degree of diaper dermatitis. Meanwhile, of the 4 *Aloe vera* studies that can be done in a meta-analysis, the correspondent obtained is the most correspondent with mild-moderate degrees.

The mean score difference in the degree of diaper dermatitis before and after therapy in studies included in the treatment group with *Aloe vera* was negative. This shows a decrease in the degree of diaper dermatitis after treatment with *Aloe vera*. While in the control group there was also a decrease in the degree of diaper dermatitis, the largest was in the Murni 2020 study, which was -2.10 ± 1.39 using Virgin coconut oil as a control. The lowest decrease in the degree of diaper dermatitis was found in the Badelbuu 2019 study which received Chamomile, which was -0.93 ± 1.08 .

Based on research by Badelbuu 2019 it was concluded that there was no significant difference between the administration of *Aloe vera* compared to routine therapy, namely a mixture of zinc oxide, hydrocortisone and clotrimazole or other topical ingredients such as chamomile. With a mean result of -1.04 ± 0.88 in the treatment group with placebo comparison and the average treatment group with chamomile comparison -1.04 ± 0.88 for the placebo control group that used routine therapy had a mean of -1.10 ± 0.75 chamomile was -0.93 ± 1.08 , based on these results, there was also no significant difference with the administration of *Aloe vera* compared to chamomile and placebo containing routine therapy. So, giving *Aloe vera* can be used as an alternative to diaper dermatitis. Compared with routine and topical chamomile therapy, according to Badelbuu, there is no difference in the healing process using *Aloe vera* or routine therapy or chamomile. In Badelbuu's study it was also said that, patients with oral lichen planus used *Aloe vera* ointment therapy compared to triamcinolone after 8 weeks based on statistical data, giving *Aloe vera* ointment more recommended than triamcinolone [10].

Research according to Shahparast et al 2015 also said that the administration of topical *Aloe vera* to 40 children who compared topical *Aloe vera* and zinc oxide therapy, was the same in terms of reducing the degree of diaper dermatitis. According to Shahparast, there was no significant difference between the administration of zinc oxide and *Aloe vera* in diaper dermatitis patients. The results of the meta-analysis for the treatment group mean -1.80 ± 0.90 and the control group using zinc oxide has a mean of -1.75 ± 0.90 . So that the results are also less significant and prove statistically that *Aloe vera* therapy has the same effectiveness as zinc oxide. In this journal it is also said that therapy for diaper dermatitis can be divided into two, namely herbal or chemical. Some examples of chemical plants such as zinc oxide, corticosteroids, lanolin and vitamins A-D, these ingredients can also have the effect of allergic dermatitis which can also inhibit the healing process. Usually for zinc oxide can be used as well as prevention and therapy, especially if the patient has been using long-term corticosteroids. Herbal plants such as *Aloe vera* also have antibacterial, anti-inflammatory, antifungal properties and can help heal wounds. However, the magnesium lactate content in *Aloe vera* can also cause allergies or irritation so that it can inhibit the healing process in dermatitis. However, in this study it was said that the potential of *Aloe vera* gel is a natural ingredient that can replace chemical therapy such as zinc oxide, because there is no significant difference between the administration of *Aloe vera* and zinc oxide in reducing the score of the degree of dermatitis.

Aloe vera registration have reported to accelerate the healing of diaper dermatitis. There was no significant difference between topical *Aloe vera* and virgin coconut oil (VCO). The average results in the treatment group obtained an average of -2.10 ± 1.39 , while in the control group -2.00 ± 1.38 . For the results of the average, it does not show significant results for topical *Aloe vera* compared to virgin coconut oil so that the administration of *Aloe vera* or VCO can give good results in improving the degree of diaper dermatitis. In this case, topical *Aloe vera* given to infants with diaper dermatitis showed a decrease in the degree of diaper dermatitis. For the use of VCO for babies who have diaper dermatitis, there is also a decrease in the degree of diaper dermatitis score. In this study it was also said that topical *Aloe vera* can be used as a prevention and treatment of diaper dermatitis because it can prevent irritation and maintain skin moisture, so as to prevent the occurrence of diaper dermatitis. This is in accordance with Indivara's theory, 2010 VCO (Virgin Coconut Oil) can cure diaper rash. One of the contents of VCO is lauric acid. Lauric acid is also found in breast milk (ASI). This lauric acid when consumed by the body will be converted into monolaurin. Monolaurin in the blood is what functions as an immune agent, it can also function to repair damaged body tissues. VCO uses not too high heating so as to maintain vitamin E and enzymes contained in coconut flesh. Meanwhile, the results between topical *Aloe vera* and VCO did not have a significant difference, so *Aloe vera* can also be used for accelerated healing therapy for diaper dermatitis [25].

The results of the meta-analysis of the difference in the mean score of overall diaper dermatitis were -0.258 ± 0.13 (95% CI

$= -0.51$ to -0.004). This shows that the score of the degree of diaper dermatitis after treatment with *Aloe vera* was lower than the control, but statistically the difference was significant ($p=0.047$). Sensitivity analysis by excluding one of the studies included in the meta-analysis did not change the overall results. Overall results still showed that the administration of *Aloe vera* still gave a significant decrease in diaper dermatitis score ($p = 0.047$).

The qualitative data study was based on five studies that used other topical materials, namely using bentonite compared to calendula. With the effectiveness of bentonite much faster to improve diaper dermatitis compared to calendula. Because bentonite has an effect as a moisturizer, skin protector and as a water absorbent. It is a type of aluminum phyllosilicate mineral. And Bentonite is also in the form of jelly so it is very good to use as a moisturizer. The advantages of bentonite are no side effects and cheap. In a study conducted by Mahmoudi et al, it was stated that in the first 6 hours an improvement in the degree of diaper dermatitis was visible compared to calendula. In another study, it was also stated that bentonite applied to injured rats can also help heal rat wounds. Bentonite applied to diaper dermatitis for the first 6 hours gave an improvement in the degree of dermatitis 88% ($n=44$), and only 54% ($n=27$) was given calendula cream in the first 6 hours. So, for calendula cream can also be used as a therapy in diaper dermatitis if it does not have a severe degree.

For further research, using olive oil by Heri 2018. Olive oil can also be effective in improving the condition of diaper dermatitis, as evidenced by the results of improving the degree of diaper dermatitis in treated infants compared to controls. Olive Oil contains ingredients that are useful for maintaining damaged skin and is rich in vitamin A, where vitamin A can function to repair the epidermis and dermis layer system down to the DNA level. In addition, olive oil also contains vitamin B2, vitamin C, vitamin D and vitamin E. For vitamin B2 it is useful for repairing tissues, Vitamins C, E and D can increase immunity, and vitamin E can function as an antioxidant. While the comparison is only cleaned using aquabides which is less effective because aquabides does not help improve skin moisture [26].

For further research, using coconut oil by Meliyana 2017 also proves that coconut oil is effective in repairing the skin barrier so that it can reduce the degree of diaper dermatitis in infants. This study proves that from 8 babies who have grade 1 diaper dermatitis and 8 babies who have grade 2 diaper dermatitis, there are 6 babies who experience diaper dermatitis grade 2 to grade 1, 6 babies who have grade 1 diaper dermatitis to grade 0, 1 baby from grade 2 to grade 1, but there was 1 baby who had no change in the degree of dermatitis. From the study, it was also said that the provision of coconut oil must also be in a clean condition and the patient's parents should change diapers more often. According to the study, coconut oil can serve to help treat diaper dermatitis from mild to severe degrees. Because the function of coconut oil itself is also as a natural moisturizer that contains medium chain saturated fatty acids that easily enter the skin tissue. The lauric acid and

capric acid contained in coconut oil can kill viruses. Lauric acid is converted by the body into monocarpine which is a monoglyceride compound that acts as an antiviral, anti-bacterial, antibiotic and antiprotozoa. The benefits of coconut oil are comparable to mineral oil, and can prevent dryness and peeling of the skin [27].

Another study for diaper dermatitis can use other topical ingredients, namely using 2% magnesium cr. In Administration of magnesium cream was more effective compared to calendula [30]. In this study assessed the healing time of diaper dermatitis. So far, magnesium and calendula are known as therapies that can cure diaper dermatitis. So, this study wanted to compare between magnesium and calendula. The results obtained in this study were faster healing when using magnesium cream than calendula. The results obtained that the average patient receiving calendula therapy with 2% magnesium cream experienced an accelerated healing of 1.5 ± 0.5 days, while the average of the control group with calendula cream alone experienced an improvement in diaper dermatitis on an average of 3.25 ± 0.67 days.

So that the mean of the treatment group compared to the control group was significant with p-value <0.001 . However, it is also said that calendula is also effective in treating mild diaper dermatitis. In this case, magnesium can be useful as an anti-inflammatory, repair wounds and can reduce inflammation in atopic dermatitis. For calendula itself it is also said that it is better used in the therapy of atopic dermatitis. However, frequent diaper changes should also be considered in therapy for diaper dermatitis. In another study, it was also stated that Pastropid et al conducted a study that patients after abdominal and perineal incisions were given zinc chloride spray and Magnesium hydroxide showed a decrease in wound size and experienced a fairly good healing process.

Keshavarz et al. 2016 conducted a study in Iran using henna oil as a traditional topical ingredient in treating diaper dermatitis compared to standard therapy with hydrocortisone cream. The content of henna consists of *Lawsonia inermis* L leaves which contain lawsone. The function of lawsone is as an antifungal, antibacterial. And the content of tannins in henna extract is astringent and can reduce sweat production. This study was divided into 2 groups consisting of 41 infants in each group, the henna group and the 1% hydrocortisone group. In this study, it was stated that on the administration and assessment on the first to third day there was no significant change compared to hydrocortisone ($P > 0.05$). However, on the fifth day the application of henna gave significant results ($P < 0.001$) compared to 1% hydrocortisone cream ($P = 0.042$). This is evidenced by the healing to degree 0 on the fifth day with henna having a higher amount than the administration of hydrocortisone [28].

In this study, it was stated that natural ingredients such as henna which contains lawsone can fight bacterial strains such as antibiotics such as tetracycline, ampicillin, gentamicin and ciprofloxacin. While there is also mentioned in other studies that the effectiveness of natural henna extract with 1% hydrocortisone cream can help cure dermatitis due to radiation rays in breast

cancer patients. The advantage of this henna is that it is a natural ingredient that is inexpensive but has anti-inflammatory, antipyretic and analgesic and antioxidant effects. So that it can help repair the skin barrier damaged by urine and feces, and prevent damage to the skin barrier.

From 5 studies on diaper dermatitis using other topical ingredients besides *Aloe vera*, it can also be proven that topical ingredients other than standard therapy can help to cure diaper dermatitis even though standard therapy for diaper dermatitis is not given. The selected topical ingredients including *Aloe vera* are also ingredients that are easily available and have a fairly affordable price. In one study it was also said that the use of natural ingredients as substitutes in diaper dermatitis therapy has been used for many years.

The use of some topical ingredients such as bentonite plus calendula has a very fast healing. Coconut oil and henna are also very good in improving the degree of diaper dermatitis in babies. In one study, it was also recommended that doctors know more about the advantages and disadvantages of the products used for therapy.

Conclusion

Several studies were obtained, namely research on diaper dermatitis using other topical materials apart from conventional therapy. One of the topical ingredients that are quite good and easy to obtain is *Aloe vera*. Where *Aloe vera* has quite a lot of functions so that it can improve the skin barrier. *Aloe vera* compared to conventional therapy also has the same results in improving the degree of dermatitis. In 4 studies, a meta-analysis of *Aloe vera* compared to other topical ingredients gave the same results as routine therapy and other topical ingredients that improve skin barrier properties. There is one study that shows the effectiveness of topical *Aloe vera* compared to calendula in improving the degree of diaper dermatitis. However, from several studies, there are a lot of topical ingredients from nature that can be used as replacement therapy for the treatment of diaper dermatitis. *Aloe vera* can also be used as herbal replacement therapy, especially if patients with diaper dermatitis have been using steroids or chemical therapy for too long. Because according to statistical data there is no significant change between herbal therapy and chemical therapy. Apart from *Aloe vera*, there are also other herbal therapies which are natural ingredients. Some natural ingredients such as henna, magnesium, olive oil, coconut oil and bentonite plus calendula can function as anti-inflammatory, antioxidant, antifungal, antibiotic and some can be anti-viral. So that it can help in maintaining skin moisture and can repair damaged skin barriers. Therapy using natural ingredients can improve the degree of diaper dermatitis and still pay attention to hygiene when changing diapers and the frequency of diaper changes to get maximum results, and avoid the risk of infection due to hygiene.

References

1. Nanto SS, Kedokteran F, Lampung U. Kejadian Timbulnya Dermatitis Kontak Pada Petugas Kebersihan Contact DermatitisEventsDue toWorkOnHygiene Personnel. 2015; 4: 147-152.

2. Satriana Nengsih S, Alim A, Gafur A. GAMBARAN KEJADIAN DERMATITIS (Studi Deskriptif Dermatitis di Puskesmas Layang Kelurahan Layang Kecamatan Bontoala Kota Makassar Provinsi Sulawesi Selatan). *J Heal Community Empower*. 2019; 2: 103-114.
3. Herwanto N, Hutomo M. Studi Retrospektif : Penatalaksanaan Dermatitis Atopik (Retrospective Study : Management of Atopic Dermatitis). *Penatalaksanaan Dermat Atopik*. 2016; 28: 8-17.
4. Prabowo PY, Adioka IGM, Mahendra AN, et al. Karakteristik Dan Manajemen Dermatitis Kontak Alergi Pasien Rawat Jalan Di Rumah Sakit Indera Denpasar Periode Januari-Juli 2014. 2017; 6: 1-6.
5. Merrill L. Prevention, Treatment and Parent Education for Diaper Dermatitis. *J Chem Inf Model*. 2019; 19: 326-344.
6. Bahruddin AD. Hubungan Penggunaan Popok Instan Terhadap Kejadian Ruam Popok Pada Bayi Di Posyandu Wilayah Kerja Desa Panca Tunggal Kabupaten Lampung Selatan 2018. *J Kebidanan Malahayati*. 2019; 5: 122-127.
7. Irfanti RT, Betaubun AI, Arrochman F, et al. Diaper dermatitis. *CDK Ed Khusus C*. 2020; 47: 50-55.
8. Mustifah EF, Dewi SR, Hastuti R, et al. Perbandingan Fungsi Barrier Kulit Pasien Dermatitis Atopik antara Krim Aloe vera dan Krim Seramid : Penelitian Awal. 2018; 45: 571-575.
9. Badelbuu SG, Javadzadeh Y, Jabraeili M. Evaluation of the Effect of Aloe vera Ointment with Chamomile Ointment on Severity of Children's Diaper Dermatitis : A Randomized, Double-Blind Clinical Trial. *World Family Medicine Journal/ Middle East Journal of Family Medicine*. 2018; 16: 47-51.
10. Badelbuu SG, Javadzadeh Y, Jabraeili M, et al. Effect of Aloe vera Gel versus Chamomile Ointment on Extent of children with Diaper Rash: A Double-Blind Randomized Controlled Trial. *Int J Pediatr*. 2018; 7: 9461-9469.
11. Panahi Y, Sharif MR, Sharif A, et al. A randomized comparative trial on the therapeutic efficacy of topical Aloe vera and calendula officinalis on diaper dermatitis in children. *Sci World J*. 2012; 2012: 810234.
12. Shahparast B, Montaseri S, Soltanian M, et al. Comparison of the effects of Aloe vera gel & zinc oxide ointment on Dipper rash in children aged 6 to 18 months referred to healthcare centers in Firouzabad 2015-2016. *Ann Trop Med Public Heal*. 2018; 13.
13. Wan Mohd Azizi WS, Azad AK, Ahmad NA, et al. Clinical efficacy of Aloe vera based products available in the market as skin moisturiser measured by tewl value and skin hydration level by using dermalab technology. *Pharmacologyonline*. 2016; 2016: 42-49.
14. Fishbein AB, Mueller K, Lor J, et al. Systematic review and meta-analysis comparing topical corticosteroids with vehicle/ moisturizer in childhood atopic dermatitis. *J Pediatr Nurs*. 2019; 47: 36-43.
15. Malik I Z. Aloe vera: a Review of Its Clinical Effectiveness. *Int Res J Pharm*. 2013; 4: 75-79.
16. Khoirini F. Peran gel lidah buaya dalam mengurangi xerosis. *J media Kesehat*. 2007; 9: 72-77.
17. Lee D, Kim HS, Shin E, et al. Polysaccharide isolated from Aloe vera gel suppresses ovalbumin-induced food allergy through inhibition of Th2 immunity in mice. *Biomed Pharmacother*. 2018; 201-210.
18. Kumar R, Singh AK, Gupta A, et al. Therapeutic potential of Aloe vera-A miracle gift of nature. *Phytomedicine*. 2019; 60: 152996.
19. Moher D, Liberati A, Tetzlaff J, et al. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *J Clin Epidemiol*. 2009; 62: 1006-1012.
20. Jaya DB, Syamsul A. Formulasi Sediaan Gel Sari Lidah Buaya (Aloe vera L.) sebagai Obat Luka. *J Dunia Farm [Internet]*. 2016; 1: 1-6.
21. Higgins JPT, Thomas J. Collecting data-form for RCTs only. In: Higgins JPT, Thomas J, editors. *Cochrane Handbook for Systematic Reviews of Interventions Version 5.10*. The Cochrane Collaboration. 2011.
22. Higgins JPT, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ*. 2011; 343: d5928-d5928.
23. Firmansyah, Asnaniar, Waodesri, et al. Pengaruh pemberian virgin coconut oil (VCO) terhadap ruam Popok pada Bayi. 2019; 1: 40-48.
24. Klunk, Christopher, Domingues, et al. An update on diaper dermatitis. *Clin Dermatol*. 2014; 32: 477-487.
25. Pandaleke TA, Pandaleke HEJ. Etiopatogenesis Dermatitis Atopi. *J Biomedik*. 2014; 6.
26. Murni S. Pengaruh pemberian Aloe vera terhadap percepatan penyembuhan ruam popok (Diaper rash) pada bayi usia 0-2 tahun (Studi Di BPM Siti Hotijah S.ST.M.Mkes Kab. Bangkalan). Undergraduate thesis, STIKes Ngudia Husada Madura. 2020.
27. Heri. Perawatan perianal dengan minyak zaitun terhadap ruam popok bayi. *Kesehat suara forikes [Internet]*. 2018; 9.
28. Meliyana E. Pengaruh Pemberian Coconut Oil Terhadap Kejadian Ruam Popok Pada Bayi. *Citra Delima J Ilm STIKES Citra Delima Bangka Belitung*. 2018; 2: 71-80.
29. Keshavarz A, Zeinaloo AA, Mahram M, et al. Efficacy of traditional medicine product henna and hydrocortisone on diaper dermatitis in infants. *Iran Red Crescent Med J*. 2016; 18.
30. Mahmoudi M, Adib-Hajbaghery M, Mashaieki M. Comparing the effects of bentonite & calendula on the improvement of infantile diaper dermatitis: A randomized controlled trial. *Indian J Med Res*. 2015; 142: 742-746.
31. Nourbakhsh SM, Rouhi-Boroujeni H, Kheiri M, et al. Effect of Topical Application of the Cream Containing Magnesium 2% on Treatment of Diaper Dermatitis and Diaper Rash in Children a Clinical Trial Study. *J Clin Diagn Res*. 2016; 10: WC04-6.