

Efficacy of Topical Rosemary Extract Lotion versus Topical 2% Ketoconazole Lotion in the Treatment of Seborrheic Dermatitis: A Double-Blind Randomized Controlled Clinical Trial

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ABSTRACT Introduction: Seborrheic dermatitis manifests as greasy itchy lesions commonly affecting sebum-rich areas like the scalp and face. Its prevalence is 11.6% in the general population, with various internal and environmental factors contributing to its development.

Objectives: This study aimed to compare the efficacy of rosemary extract lotion in the treatment of seborrheic dermatitis in comparison with topical 2% ketoconazole lotion.

Methods: This double-blind randomized controlled clinical trial included 42 patients with scalp seborrheic dermatitis, divided into rosemary lotion and ketoconazole lotion groups. Both lotions were applied twice daily for two months. The severity of scalp dandruff was assessed using the Adherent Scalp Flaking Score (ASFS). The itchiness of the scalp and quality of life were assessed using itchy quant and the Dermatology Life Quality Index (DLQI), respectively. Stata software version 14.2 was applied for statistical analysis.

Results: The reduction in ASFS score was statistically significant in patients in the ketoconazole group in comparison with the patients in the rosemary group ($P = 0.011$). However, the reduction in itching score was statistically significant more in the rosemary group at the end of the first and second months in comparison with the ketoconazole group ($P < 0.001$). The statistical analysis demonstrated no significant difference in the reduction of DLQI scores between the rosemary and ketoconazole groups at the end of one and two months after starting the treatment in both crude and adjustment with base-line score analysis.

Conclusion: Both rosemary and ketoconazole lotions were effective in treating scalp seborrheic dermatitis and in decreasing patients' DLQI score.

Introduction

Seborrheic dermatitis is a type of chronic inflammatory skin disorder characterized by the emergence of erythematous scaly lesions on the skin [1]. This condition can affect the scalp and other seborrheic areas of the body, including the face, eyebrows, behind the ears, upper chest regions, flexor areas of the body, and generally areas with higher sebum production [2].

The primary cause of seborrheic dermatitis is not fully understood [3]. A variety of internal and environmental factors can serve as potential triggers for this condition. It is thought that the growth and colonization of *Malassezia* species, which are drawn to the lipids found in sebum-producing areas, triggers an immune response and the appearance of symptoms related to this condition [4]. Compounds in the skin's lipid composition and individual sensitivity are also believed to be involved in this disease [5]. The simultaneous presence of these factors can contribute to the pathogenesis of the disease.

The treatment of seborrheic dermatitis focuses on alleviating symptoms, improving associated signs, and reducing the likelihood of disease recurrence. As mentioned earlier, the primary pathogen responsible for seborrheic dermatitis is *Malassezia*, so the most commonly used drugs are topical antifungal and anti-inflammatory agents [6]. Several drugs and treatments have been introduced to reduce skin lesions in seborrheic dermatitis. Topical ketoconazole, tacrolimus, and corticosteroids are among the most commonly used drugs, although some side effects have been reported [7]. Researchers are striving to find systemic or more localized treatments. In terms of treatment, three main categories—keratolytics, anti-inflammatories, and antifungals—are beneficial for managing this condition. Keratolytic drugs prevent the formation of scales and at the same time help the penetration of other topical drugs [8]. Topical steroids and calcineurin inhibitors have been found to effectively manage inflammation, whereas antifungal medicines exert their therapeutic effects by lowering the colonization of *Malassezia* [9].

Each of these drugs has its own specific side effects. Topical corticosteroids can lead to atrophy, telangiectasia, and acne [10], while calcineurin inhibitors may cause itching, burning, and erythema [11]. Additionally, some species of *Malassezia* show resistance to antifungal drugs.

A meta-analysis conducted by Jain and colleagues aimed to explore recent findings regarding the antifungal properties of plant oils against pathogens involved in dandruff. The study highlighted the global significance of herbal oils such as tea tree oil, lemon oil, and rosemary oil in dermatology. These oils have a lot of aromatic secondary metabolites, like terpenes and phenolic parts, which make them very good at killing microbes and stopping biofilm from forming. The study suggested that these oils have a high potential for development as anti-dandruff formulations, but further studies are needed to prove their efficacy in treating dandruff [12].

Aytollahi and colleagues conducted a review study that underscored the growing scientific focus on herbal extracts due to their enhanced efficacy and reduced adverse effects within the pharmaceutical and cosmetic sectors. The study mentioned various herbal shampoos with anti-dandruff properties that are effective and safe without the side effects of chemical agents. The researchers concluded that herbal extracts are gaining attention, and clinical evidence regarding their therapeutic effects in seborrheic dermatitis is prompting further studies [13].

Rosemary is among the plants that have gained attention in recent years. This plant is a therapeutic herb that originates in the Mediterranean region and is grown globally. Moreover, the use of this herbal remedy is common among the Iranian population, which could be related to the advice of the Persian medical sages in the treatment of some diseases, especially dermatologic conditions [14-17]. Because it has verbenone and other chemicals like camphor, cineole, β -myrcene, carnosic rosmarinic acid, volatile oil, phenolics, and α -pinene, rosemary oil can kill germs and viruses, reduce inflammation, protect nerves, and lower blood sugar. Moreover, evidence has revealed that rosemary can enhance blood circulation in the scalp. Therefore, many pharmaceutical

and cosmetic products have used rosemary in various ways [18-21].

Muyima and colleagues also demonstrated that the oil extracts of three plants, including rosemary, have antifungal effects on various fungal species. They suggested that with extraction of their essential oils, they could be used as an alternative to chemical compounds [22].

Objectives

To our knowledge, there were limited number of studies on the effects of rosemary on dandruff and the successful role of rosemary in treating some inflammatory skin conditions. Therefore, we aimed to assess the efficacy of a rosemary lotion in the treatment of dandruff in comparison with ketoconazole.

Methods

Study Design, Population, Sampling, and Sample Size Calculation

This study was a double-blind randomized controlled clinical trial on patients suffering from seborrheic dermatitis of the scalp between 2021 and 2022. In this regard, patients were included in the study based on the consecutive sampling method. The sample size was calculated based on similar previous studies and using Stata software version 14.2 with the “samps” module. With a type I error (alpha) of 0.05 and a study power of 80%, the minimum sample size was calculated to be 21 patients in each study group. The study protocol was registered on the Iranian Registry of Clinical Trials (IRCT) website with a trial registration number of IRCT20221001056063N1 (link: <https://irct.behdasht.gov.ir/trial/66140>; <https://irct.behdasht.gov.ir/trial/66140>).

Inclusion and Exclusion Criteria

Patients with seborrheic dermatitis who visited the Dermatology Clinic of Shahid Faghihi Hospital, Shiraz, Iran were included in the study. The diagnosis was based on the clinical presentation of the patients. Patients between 18 and 60 years old with clinically diagnosed scalp seborrheic dermatitis with an Adherent Scalp Flaking Score (ASFS) above 10 and a Dermatology Life Quality Index (DLQI) score above 2 were included in this study. Patients with seborrheic dermatitis in areas other than the scalp, those who had used antibiotics or immune-modulating drugs in the month before the study, those who had used any topical medication in the two weeks before entering the study or systemic medication in the month before entering the study that could affect seborrheic dermatitis, and individuals with scalp diseases such as lichen plano pilaris (LPP) were excluded. Patients were

prohibited from using soaps or shampoos effective for seborrheic dermatitis on the scalp during the study.

Randomization and Blinding

The patients were divided into two groups using Random Allocation Software version 1.0.0. In this regard, the patients were randomly divided into rosemary lotion and ketoconazole lotion groups using block randomization, with six blocks of four (group A and group B). In addition, dark envelopes were used to conceal the random allocation sequence.

Moreover, this study was designed as a double-blind clinical trial. In order to blind the patients, the clinical trial team, and the outcome assessor of the outcomes, the patients received the lotions of rosemary and ketoconazole in the same packaging, appearance, volume, and odor.

Intervention

In this study, we enrolled 21 patients in each group (Group A and Group B). In this regard, rosemary lotion 5% manufactured by Barij Essence Company, Kashan, Iran, was given to the patients in Group A, and ketoconazole lotion 2% to the patients in Group B. Furthermore, we advised the patients to apply the lotion twice a day to areas with lesions on their scalp for two months. Assessments and necessary evaluations were performed at the beginning of treatment and then one and two months later. A dermatologist who was unaware of the patients' medication regimens examined and evaluated patients during visits and follow-up.

Data Collection and Outcomes Measure

In the first visit, we obtained the patients' medical history and demographic information. We also performed a physical examination, photographed the skin lesions, and assessed the extent of the disease. Then, at each patient visit, the severity of scalp dandruff was assessed using the Adherent Scalp Flaking Score (ASFS) [4]. According to the ASFS scoring system, the scalp is divided into eight areas, and each area is scored from 0 to 10 based on the severity of scalp dandruff. It is important to note that flakes detached from the scalp and scattered in the hair are not included in the scoring (Figure 1).

Additionally, the level of itching was assessed using the Itchy Quant scale, a numerical rating scale ranging from 0 to 10 [5]. Moreover, the patients' quality of life was evaluated at each visit using the Persian version of the DLQI, which has been validated for reliability and validity [23]. Adverse drug reactions, such as skin dryness, itching, burning, contact dermatitis, peeling, redness, and so on, were also examined at each visit.

scalp division into 8 sections
for ASFS score grading scale



- 0- no scaling
- 2- slight scaling
- 4- some scaling
- 6- moderate scaling
- 8- heavy scaling
- 10- very heavy scaling

Figure 1. Adherent Scalp Flaking Score (ASFS) grading system.

Ethical Statements

The Research Ethics Committee of Shiraz University of Medical Sciences (Ethics Code: IR.SUMS.MED.REC.1401.090) approved the study's protocol. Furthermore, the researchers presented the aim of the study to the participants before enrolling them in the study. In addition, all of the patients signed a written informed consent form to participate in the study. The patients were free to withdraw from the study at any time during the study.

Statistical Analysis

We used Stata software version 14.2 for data analysis. Descriptive statistics, including mean and standard deviation for quantitative data and frequency and percentage for categorical data, were used. For comparisons between the demographic characteristics of the two groups, the independent t-test was employed for parametric variables, and the chi-square test was used for categorical variables. Moreover, we used the ANOVA/ANCOVA test to compare the outcomes of the study. In this regard, the crude analysis of one and two months after beginning the treatments as well as base-line adjusted analyses were applied. To estimate the effect size, the mean difference (MD) and standard mean difference (SMD), including Cohen's d, were calculated. A significance level (p-value) was considered equal to or less than 0.05.

Results

Demographic Data and Patient Information before Treatment in Both Groups:

The present study enrolled 42 patients, with 21 participants in each study group. At the end of the study, 39 patients, including 19 patients in the rosemary lotion group and 20 patients in the ketoconazole group, completed the study and were analyzed, as shown in the CONSORT diagram of the study (Figure 2). As shown in Table 1, the patients in both groups were approximately similar in the variables of age, sex, and marital status.

Outcomes Measures

ASFS Score

In both groups, the ASFS scores before intervention did not show a statistically significant difference. Both the ketoconazole and rosemary groups demonstrated a reduction in the ASFS score over time. However, the crude and base-line score adjustment analysis showed that the reduction in ASFS score was statistically significant in patients on ketoconazole in comparison with the patients in the rosemary group ($P = 0.011$), as shown in Table 2.

Itchy Quant Scores

The initial mean Itchy Quant scores in the rosemary and ketoconazole groups were 5.19 ± 1.69 and 5.23 ± 1.48 , respectively, showing no considerable difference between them. After treatment, there was a statistically significant reduction in Itchy Quant scores in both groups. The reduction was more statistically significant in the rosemary group at the end of the first and second months than the ketoconazole group in both crude and base-line score adjustment analyses, as shown in Table 2.

DLQI Scale

The average DLQI index in the rosemary and ketoconazole groups before treatment was 9.86 ± 4.03 and 9.38 ± 4.18 , respectively, showing no considerable difference. After receiving treatment, the DLQI scale in both groups significantly decreased. As shown in Table 3, the statistical analysis demonstrated no significant difference in the reduction of DLQI scores between the rosemary and ketoconazole groups at the end of one and two months after stating the treatment in both crude and adjustment with base-line score analysis.

Adverse Effects Evaluation

In the rosemary group, two patients withdrew from the study due to scalp burning and itching. Additionally, two individuals in this group expressed discomfort with the scent of the lotion, but they continued participating in the study, considering its effectiveness. In the ketoconazole group, one patient reported itching but continued to participate in the study.

Discussion

The present study aimed to investigate the efficacy of a rosemary extract lotion in the treatment of seborrheic dermatitis and compare it with 2% ketoconazole lotion in a double-blind randomized controlled trial. The results of our study revealed that both ketoconazole and rosemary topical

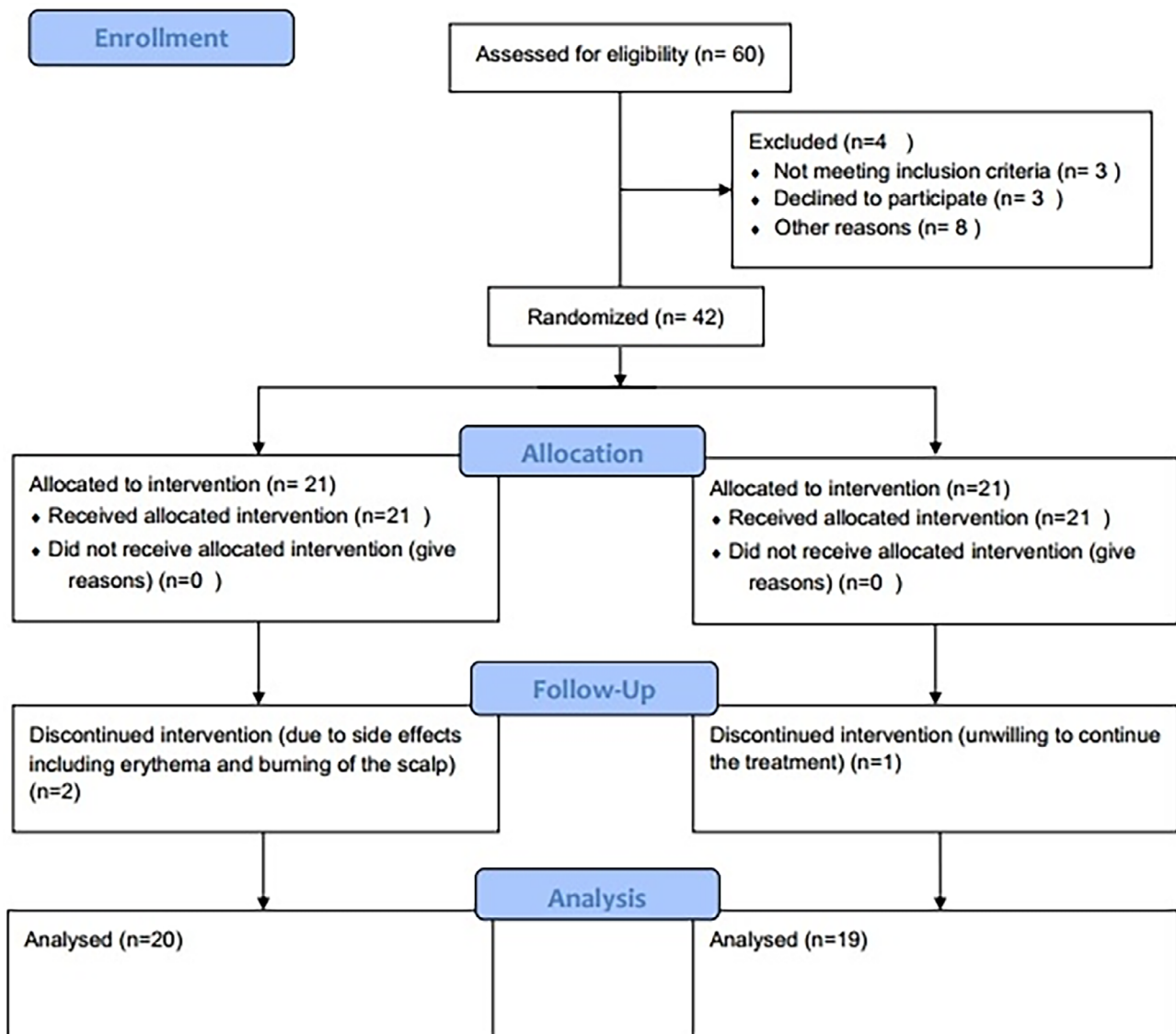


Figure 2. CONSORT Flow Diagram of the Study.

Table 1. Demographic Characteristics of the Patients who Participated in the Study.

Variables	Rosemary Lotion (N=21)	Ketoconazole Lotion (N=21)	p-value
Age mean± SD	34.67± 8.88	33.90± 6.60	0.754
Sex N(%)			0.346
Male	11 (52.38)	14 (66.67)	
Female	10 (47.62)	7 (33.33)	
Marital Status N(%)			0.513
Single	6 (28.57)	8 (38.10)	
Married	15 (71.43)	13 (61.90)	

lotion were effective in the treatment of scalp seborrheic dermatitis. However, the ketoconazole lotion was more effective in reducing the ASFS score, although rosemary lotion reduced the itching score more of the patients with seborrheic dermatitis. In addition, the DLQI score of the patients with

seborrheic dermatitis significantly decreased in both groups of the study, similarly.

Recently, the literature has demonstrated that a remarkable number of patients with chronic and acute conditions preferred to use complementary and alternative medicine,

Table 2. Efficacy of Rosemary Lotion vs Ketoconazole Lotion in the Treatment of Dandruff in Seborrheic Dermatitis: Evaluation of the ASFS and Itching Score Pre- and Post-Intervention according to Different Models.

Outcome	Model	Time point	Rosemary Lotion (N=19)	Ketoconazole Lotion (N=20)	Mean Difference (95% CI)	Cohen's d (95% CI)	Partial Eta2	p-value\$	Adjusted R2
ASFS	Crude	Pre	25.80 ± 7.50	23.43 ± 5.48	2.38 (-1.72 to 6.48)				
		1st month	5.05 ± 2.14	3.23 ± 2.09	1.81 (0.44 to 3.19)	0.85 (0.19 to 1.51)	0.16	0.011	0.136
		2nd month	2.63 ± 1.16	1.6 ± 1.72	1.03 (0.25 to 1.81)	0.85 (0.19 to 1.49)	0.16	0.011	0.140
	Adjusted	Pre	25.80 ± 7.50	23.43 ± 5.48	2.38 (-1.72 to 6.48)				
		1st month	4.85 ± 1.76	3.42 ± 1.72	1.42 (0.28 to 2.55)	0.82 (0.16 to 1.47)	0.09	0.016	0.427
		2nd month	2.57 ± 1.11	1.66 ± 1.11	0.91 (0.18 to 1.63)	0.10 (-0.54 to 0.72)	0.12	0.016	0.267
Itching score	Crude	Pre	5.19 ± 1.69	5.23 ± 1.48	-0.05 (-1.04 to 0.94)				
		1st month	0.90 ± 0.48	1.48 ± 0.47	-0.58 (-0.89 to -0.27)	-1.21 (-1.89 to -0.52)	0.27	<0.001	0.253
		2nd month	0.47 ± 0.51	0.9 ± 0.55	-0.42 (-0.77 to -0.08)	-0.79 (-1.45 to 0.14)	0.14	0.017	0.120
	Adjusted	Pre	5.19 ± 1.69	5.23 ± 1.48	-0.05 (-1.04 to 0.94)				
		1st month	0.92 ± 0.42	1.45 ± 0.41	-0.53 (-0.80 to -0.26)	-1.28 (-1.96 to -0.58)	0.23	<0.001	0.444
		2nd month	0.49 ± 0.50	0.88 ± 0.50	-0.38 (-0.76 to -0.06)	-0.77 (-1.41 to 0.19)	0.12	0.022	0.218

* Calculated based on one-way ANOVA/ANCOVA; ** Significant ($P \leq 0.05$); a. Adjusted for baseline pre-treatment score (calculated based on Oneway ANOVA / ANCOVA model).

Table 3. Efficacy of Rosemary Lotion vs Ketoconazole Lotion in the Treatment of Dandruff in Seborrheic Dermatitis: Evaluation of the Dermatology Life Quality Index Pre- and Post-Intervention according to Different Models.

outcome	Model	Time point	Rosemary Lotion (N=19)	Ketoconazole Lotion (N=20)	Mean Difference (95% CI)	Cohen's d (95% CI)	Partial Eta2	p-value\$	Adjusted R2
DLQI	Crude	Pre	9.86 ± 4.03	9.38 ± 4.18	0.47 (-2.09 to 3.04)				
		1st month	2 ± 1.01	2.14 ± 0.98	-0.14 (-0.79 to 0.50)	-0.14 (-0.77 to 0.49)	0.01	0.657	-0.021
		2nd month	1.15 ± 0.76	0.95 ± 0.76	0.21 (-0.29 to 0.70)	0.27 (-0.36 to 0.90)	0.02	0.400	-0.007
	Adjusted	Pre	9.86 ± 4.03	9.38 ± 4.18	0.47 (-2.09 to 3.04)				
		1st month	1.99 ± 0.62	2.15 ± 0.60	-0.16 (-0.56 to 0.24)	-0.26 (-0.89 to 0.37)	0.01	0.419	0.612
		2nd month	1.17 ± 0.63	0.94 ± 0.63	0.22 (-0.18 to 0.64)	0.36 (-0.28 to 0.99)	0.02	0.269	0.311

* Calculated based on one-way ANOVA/ANCOVA; ** Significant ($P \leq 0.05$); a. Adjusted for baseline pre-treatment score (calculated based on Oneway ANOVA / ANCOVA model).

particularly herbal remedies [24-26]. In this regard, some evidence supports the efficacy of herbal remedies in the treatment or improvement of several dermatological conditions [27-29].

Considering the concerns associated with the use of conventional drugs for seborrheic dermatitis, such as non-compliance with medication instructions, drug resistance, and side effects, various studies have been conducted on the use of medicinal plants. *Coronata serratula*, *Cirsium eriophorum*, *Myrtus communis*, *Apium graveolens*, *Quassia amara*, and *Ananas comosus* are some plants that have been shown to help reduce the itching and flaking that come with the disease and to stop the growth of *Malassezia* fungi in the lab. After four weeks of treatment with the prepared cream containing these ingredients, a significant reduction in the seborrheic dermatitis score was recorded [30]. These compounds of medicinal plants have led to a more diverse range of treatments for seborrheic dermatitis. For example, a shampoo based on *Rosa centifolia* petal extract was found to have anti-inflammatory, antioxidant, and sebum secretion prevention properties. Similar effects were reported for tea tree oil-based shampoos [31].

Recent studies have highlighted the anti-microbial, antioxidant, and anti-inflammatory properties of rosemary, making it suitable for various dermatological conditions. Panahi and colleagues conducted a study to investigate the clinical efficacy of rosemary oil in treating androgenetic alopecia and compared its effects with 2% minoxidil over a period of six months in 100 patients. Both groups experienced a significant increase in hair count at the 6-month endpoint compared to the baseline [32]. The study conducted by Lahraseb and colleagues also showed that the simultaneous use of rosemary topically can enhance the efficacy of minoxidil in the treatment of alopecia areata [33].

This finding of our study regarding the reduction in the ASAF score in patients with seborrheic dermatitis was consistent with a study by Mangion and colleagues, who reported that azoles could significantly reduce the ASFS score after treatment [34]. Another study, by Ashtiani and colleagues, showed a reduction in flaking and itching as well as a decrease in the ASFS score in the group using ketoconazole. Another group of patients used Cepigene® shampoo, which includes rosemary plant in the composition of this shampoo; the ASFS score in this group decreased after the use of this substance [35].

Another remarkable finding in our study was the reduction in the level of scalp itching in both groups receiving ketoconazole and rosemary, and this reduction was significantly more prominent in the patients in the rosemary group. A comprehensive review by Francisco and colleagues supports this result, indicating that patients using rosemary-containing compounds reported less itching after

treatment [36]. This result was in line with the findings of a study by Bidhendi and colleagues [37], who showed that participants who used a polyherbal extract lotion, including the extract of rosemary, experienced less scalp itching than those in the azole group. The study by Ashtiani and colleagues also showed that Cepigene® shampoo, compared to ketoconazole, had a greater ability to reduce the itch and scale of the disease [35].

Additionally, in this study, the DLQI score showed an increase in patient quality of life after each visit for both the rosemary and ketoconazole treatment groups. A review of the effects of herbal oils on seborrheic dermatitis found that rosemary-containing oils led to better treatment outcomes, decreased disease recurrence, and higher patient satisfaction [12], which supported the results of our study.

The scientific research suggests that rosemary extract's essential oils are rich in aromatic secondary metabolites, such as terpenes and phenolic components, which possess antimicrobial properties. Furthermore, empirical data have indicated that rosemary essential oil has the potential to be utilized in the development of anti-dandruff products [12 38-42]. Additionally, rosmarinic acid has been identified as the primary component of rosemary plant, according to multiple studies. This component has the potential to contribute to the reported antibacterial and anti-inflammatory activities [21 43 44].

There were some limitations in this study. First, the wide ranges of the confidence interval values of the effect sizes reported in Tables 2 and 3 indicated that the results of this study were inconclusive, which could be due to the low sample size of this study. Therefore, further studies with a larger sample size are strongly recommended. Moreover, the present study was only focused on the clinical aspect of treating seborrheic dermatitis with a lotion made from rosemary extract in comparison with ketoconazole lotion. Therefore, the phytochemical component analyses of this herbal remedy were not conducted in this study, and it is recommended to do so in future studies. Finally, in this case, we did not follow up with the patients for a longer time to evaluate the reoccurrence of the disease. Therefore, we recommend further studies to examine patients for the reoccurrence of seborrheic dermatitis and its symptoms over a longer period of time, especially after discontinuing the medication.

Conclusion

According to the results of our study, both 5% rosemary extract lotion and 2% ketoconazole lotion demonstrated efficacy in reducing the ASFS scale, with the role of rosemary being more pronounced. Both treatments reduced the itching scale (itchy quant) and improved the quality of life for patients. No significant difference was observed between the

two groups. Considering the results of this study, rosemary may be a suitable treatment option for patients with scalp seborrheic dermatitis, particularly in cases of non-response to azoles, side effects, or severe itching. However, further extensive studies are recommended to provide more reliable results for the treatment of these patients.

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