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INVESTIGATING THE EFFECT OF 1% CURCUMIN GEL AND PLACEBO ON PATIENTS WITH PLAQUE PSORIASIS

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ABSTRACT

Psoriasis is a common, chronic, and immunogenetic disease resulting from proliferation of keratinocytes that exists in five forms of plaque, guttate, inverse, pustular, and erythrodermic. Itchy skin is one of the most common symptoms of the disease and influences life quality. This study aimed to compare the effect of 1% curcumin gel made by the Center for Pharmaceutical Technologies Development of Jundishapur University in mild to moderate plaque psoriasis in a randomized and double-blind study as an inexpensive biologically active drug with placebo. The methods of data analysis used in this study - include descriptive statistics, mean, standard deviation, minimum and maximum pasi-score, dermatology life quality index (DLQI), and itchy skin index (QOL-Itchy) as well as inferential statistics including paired t-test, chi-square, and Mann-Whithney test. The analysis was performed by statistics consultant. In the intervention group, the average pasi-score before the treatment was 3.1; two weeks after the treatment it was 1.91 and the pasi-score decrease was significant. Also the average pasi-score reduction in this group was 30.46%; 19% of the patients showed weak therapeutic response, 56% showed average therapeutic response, 13% showed good therapeutic response, and 12% showed excellent therapeutic response. In the control group, the average pasi-score before the treatment was 3.17; after the treatment it was 2.75 where no significant difference was observed. The average pasi-score reduction in this group was 20.4% in which 84% of the patients showed weak response, 8% showed average response, and 8% showed excellent response. A comparison was performed between pasi-scores in intervention and control groups before and after the treatment by employing statistical tests. Though no significant difference was observed, the efficiency size showed that prescription of medicine has a modest effect on patients. In the intervention group, the second week after the end of treatment, the average pasi-score was 1.19; its effect was significant compared with the score before the treatment. The average pasi-score in the control group was 2.75; no significant difference was observed compared with the average score before the treatment. These results showed the continuous effect of medicine after the discontinuation of treatment and no recurrence during this period was observed. The results of this study and previous studies show that curcumin can have an important role in the treatment of psoriasis. It is important because curcumin is an inexpensive drug with less side effects than the existing drugs.

KEYWORDS: *plaque psoriasis, placebo, biologic medicine*

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INTRODUCTION

Psoriasis is a common, chronic, and immunogenetic disease resulting from the proliferation of keratinocytes that exists in 5 forms of plaque, guttate, inverse, pustular, and erythrodermic. This disease exists in 2% of the world population and in 75% of the cases, it occurs in people under 40 and the possibility of its complete recovery during 5 years is 15%. Also, 80-90% of psoriasis cases are plaque psoriasis where 80% are mild to moderate which means only less than 5% of the body is involved and the palms of hands, feet, facial and genitalia are not involved. In this form of disease, erythematous and scourer plaques can be seen in different parts of the body. The determination of disease intensity by measuring the pasi-score includes the extent of involvement, severity of erythema, thickness, and flaking.[1] Itchy skin is the most common symptom of the disease and influences quality of life. Dermatology Life Quality Index (DLQI) was used to investigate the effect of the disease on life quality and Qol-Itchy questionnaire was used[1] to determine the effect of itchy skin on life quality. Psoriasis is caused by the interaction of immune cells such as the gamma-delta T-cells in dermis and the keratinocytes of the skin. This interaction occurs through cytokines such as TNFα and interleukins 1, 6, 12, 17, 22, 23 and finally leads to the proliferation of keratinocytes.[1,3] The existing therapeutic methods of psoriasis are divided into systematic and topical categories and from mild to moderate plaque forms. The first line of treatment includes topical medicines such as corticosteroids, vitamin D3, and retinoids. This topical medicines should be taken in a limited time and cannot be taken in any site of body; moreover, this medicine has systemic and local side effects. solong-term use of this medicines makes complications.-[1] Moreover, due to the nature of the chronic disease, its management in a long-term period requires cost, time, and energy and the existing medicines could not satisfy the patients.[1] During recent years, systematic biologic medicines as severe forms of psoriasis that have not responded to other treatments are taken into consideration. These medicines function as TNFa inhibition and interleukin 12-23 inhibition and can control psoriasis in the long run. These medicines are more effective in the cases mentioned in this study than the existing cytotoxic drugs and therefore will have a key role in the treatment of psoriasis in the future. These drugs are only available as injection form at a very expensive cost (20000$ for a year)[1]. Therefore, production of low-cost biologic medicines in non-injection forms and potential for production in many countries seem necessary. In recent studies, it has been shown that 51% of psoriasis patients use supplemental hematology to treat their dermal disease and there are numerous reports about the effectiveness of turmeric in the treatment of psoriasis[1]. Curcumin has antioxidant, anti-inflammatory, anti-microbial, and anti-carcinogenic effects and in skin lesions it causes decreased itchy skin and improves life quality. Molecular and cellular pharmacological studies have shown that curcumin has an inhibitory effect on pre-inflammatory cytokines such as TNFa and interleukins 8, 12, 1, 2, 6 and indirectly inhibits interleukins 17-23 and reduces proliferation of keratinocytes; therefore, it can be concluded that curcuminhasthe potential to treat diseases resulted from these cytokines and proliferation of keratinocytes such as skin tumors and psoriasis[2]. The complications that existed about topical use of curcumin were due to low bioavailability resulted from Low solubility in water and instability of the drug which affected the functioning of curcuminin target cells. In recent years, the application of nanotechnology in curcumin formulation is tested by most researchers due to its potential in increasing the efficiency of curcumin. Placing curcumin in nano-emulsions leads to a significant increase in bioavailability, kinetic stability, and protection of active components of the drug in different conditions[2]. In the previous studies, oral curcumin C3 complex was found to be ineffective in the treatment of mild to moderate plaque psoriasis in human that was due to low bioavailability of its oral form, but administering 0.5% turmeric gel (curcuma langa) to mild to moderate plaque psoriasis significantly increased their average Pasi-Score as well as life quality[1]. Indeed, curcumin is the extract obtained from turmeric. Also, 1% curcumin gel in laboratory cases has indicated a similar effect as clobetasol 0.02% in improving psoriasis inflammation resulted from imiquimod[3]. In a study by Saraffian et al.[3] on 34 patients with mild to modest plaque psoriasis, the effect of 5% turmeric topical gel (curcuma langa) was investigated and the average Pasi-Score significantly increased in the lesions treated with turmeric compared with placebo (P>0.005). Also, the DLQI of patients significantly increased. In this study, side effects like dry skin (6%) were manifested and the stimulatory effect of the drug was 3% but none of them led to the discontinuation of the treatment. In a study by Rachmawit et al.[5] on the skin taken from snake, it was shown that the placement of curcumin on fat nano-emulsion in

water and formulation of a topical gel increases stability of the drug and its permeability as well as f protected the active components of the drug against chemical decomposition. In a systematic review by Baharat and colleagues[3] on the inhibitory effect of oral curcumin on TNFa and other inflammatory biomarkers, it was concluded that curcumin can be used as a low-risk and inexpensive oral medicine that shows its effects through inhibiting the production and function of TNFa. The effect of this medicine is proved in in vitro experiments and human and animal models. Also, curcumin in visible light creates sensitivity and is used in phototherapy method in psoriasis. In a review study by Shahrzad et al.,[4] it was stated that curcumin can have a role in the treatment of inflammatory diseases and may be used as a preventive drug in the future for these diseases. This study aimed to compare the effect of 1% curcumin gel made by the Center for Pharmaceutical Technologies Development of Jundishapur University in treating mild to moderate plaque psoriasis in a randomized and double-blind study as an inexpensive biologically active drug with placebo.

MATERIALS AND METHODS

Materials

Curcumin is employed in this study. It is a poly phenol which is derived from turmeric. In this study curcumin is used as a 1% topical gel.

Methods

This study is a clinical trial study. This study is a randomized and double-blind study including intervention and control groups during 2015-2017 in Imam Khomeini Hospital of Ahvaz under the supervision of Jundishapur University. The ethical committee approval No. for this case of study is IR.AJUMS.REC.1395.753 which is Available in WWW.IRCT.ir The population of this study consisted of patients with mild to modest plaque psoriasis based on clinical and pathological results whose measurement of disease involvement is less than 5% of the body surface (1% surface of the body equals a palm without fingers). It should be noted that written consent was taken from all participants in the study with explanations about the drug and possible complications. In this study, 20 patients were selected considering inclusion and exclusion criteria based on randomized method and prescription of drugs or placebo and were divided into intervention (16 patients) and control (13 patients) groups. It should be noted that 4 patients were excluded from the study due to lack of cooperation. Questionnaires were completed at three turns before, second week, and two weeks after the treatment and the therapeutic response at the second week and two weeks after the treatment was measured. Also, patients were referred for follow-ups two weeks after the treatment. Coded Drug and placebo were received in tubes from a pharmacist colleague with similar weight and packages, coding was “A” and “B”. In intervention group, 1% curcumin gel and placebo was used for treatment and patients were asked to use the drug on psoriasis plaques twice a day after every 12 hours as a thin layer and evaluations were performed for two weeks and after two weeks. Questionnaires related to QOL-Itchy and DLQI were completed by the patients three times (before the treatment, second week of the treatment, and two weeks after treatment). Moreover, demographic information and pasi-score were registered before the beginning of the treatment and in the next visits, the pasi-score and possible complications (dry skin, itchy skin, swelling, erythema, and other complications reported by the patient) were registered by another doctor who was not aware of the prescribed drug. Therapeutic responses at the second week and two weeks after the treatment were monitored according to the decreased pasi-score. Accordingly, patients were divided into five groups of mild (24%), average (25-49%), good (50-74%), excellent (75-99%), and improved (100%) therapeutic responses. After the study, final analysis of data was performed by the statistics consultants using SPSS 12. Therefore, the patient, the evaluator and the analyst were not aware of the substance used and due to the lack of access to the information about the effect of this mixture on score changes, first, in a pilot study on 20 patients, mean and standard deviation of scores were estimated and by α-0.05 and β-0.1, final sample size was estimated using the following formula:

$$n = \frac{\left(z_{1-\alpha/2} + z_{1-\beta}\right)^2 \times \left(s_1^2 + s_2^2\right)}{\left(\bar{x}_1 - \bar{x}_2\right)^2}$$

$$z_{1-\alpha/2} = 1.96$$

$$z_{1-\beta} = 1.28$$

Table 1
Research variables

Characteristics of the variable	Independent	Dependent	Quantitative		Qualitative		Practical definition	
			Continuous	Discrete	Nominal	Ranking		
Age	*		*				According to the insurance	Year
Life quality before treatment	*			*			According to the patient's statement	
Life quality at the end of the treatment		*		*			According to the patient's statement	
Complications		*			*		According to the clinical finding	
Gender	*				*		According to the patient's appearance	
Plaque location	*				*		According to the clinical finding	
Pasi-score before treatment	*		*				According to the clinical finding	
Pasi-score of periodic visits		*	*				According to the clinical finding	
Itchy skin index before treatment	*			*			According to the patient's statement	
Itchy skin index after treatment		*		*				
Therapeutic response		*				*	According to the estimations by the doctor	

Data collection was performed by a checklist containing demographic information, information related to the components, pasi-score, final pasi-score, complications (dry skin, itchy skin, swelling, erythema, and other complications reported by the patient), and questionnaires related to DLQI and QOL-Itchy. Information registration was performed before the treatment, the second week of the treatment, and two weeks after the treatment and the resulted data were analyzed in a computer using SPSS 12. The methods for data analysis included descriptive statistics, mean, standard deviation, minimum and maximum pasi-scores, FLQI, and QOL-Itchy as well as inferential statistics including t-test, paired t-test, chi-square, and Mann-Whithney. This analysis was performed by statistics consultant. In Table (1), research variables are presented. Given the nature of the disease and medicine, no moral problem existed in performing the analysis. The patients were assured that their information will remain confidential and a written consent was obtained from them.

RESULTS

Initially 20 patients participated in this study but4 patients were excluded from it due to lack of cooperation. Finally 16 patients continued the study for whom thetreatment (16 lesions in control group) and placebo (13 lesions in control group) were administered simultaneously and randomly on lesions on the left and right sides of their bodiesfor g two weeks and twice a day and the results are as follow: average age of patients in intervention group was 36.56 and in control group was 36.46 with almost no significant difference. In both the groups involved in the study, the minimum age was 6 andthe maximum age was 96., There were 5 females and 11 males in the intervention group and 4 females and 9 males In the control group Regarding the location of psoriasis plaques, in the intervention group, there were 13 lesions at the lower extremity, 1 lesion at the palm of the hand, and 1 lesion at the sole of the feet. In the control group, there were 9 lesions at the lower extremity, 1 lesion at the trunk, 1 lesion at the palm of the hand, and 1 lesion at the sole of the feet.

QOL-Itchy

In this study, QOL-Itchy was assessed by a questionnaire including 26 questions before the beginning of the treatment, during the second week of the treatment, and two weeks after the treatment. As the questionnaire was designed for people above 18, 2 patients who were under 18 were excluded from statistical estimations;likewise a patient who didn't have itchy skin was also exempted. Therefore, the data of 13 patients was used for statistical computations related to QOL-Itchy. Initial mean of QOL-Itchy was 67, the mean of the same index after two weeks was 83 and two weeks after the treatment was 83 and after the test of normality, paired sample statistics, paired samples correlation, paired sample test (Table 4-1) and obtaining Sig (2-tails) =000, it was concluded that QOL-Itchy difference was significant and the medicine was effective in the treatment of itchy skin.

Table 2
Tests of Normality

	Kolmogorov-Smirnova			Shapiro-Wilk		
	Statistic	**df**	**Sig.**	**Statistic**	**df**	**Sig.**
pruritus b.	.169	13	.200*	.925	13	.295
pruritus.a	.176	13	.200*	.878	13	.066

. This is a lower bound of the true significance.
a. Lilliefors Significance Correction

Table 3
Paired Samples Statistics

		Mean	N	Std. Deviation	Std. Error Mean
Pair 1	pruritus.b	67.0000	13	17.12698	4.75017
	pruritus.a	83.0769	13	26.36115	7.31127

Table 4
Paired Samples Correlations

		N	Correlation	Sig.
Pair 1	pruritus.b & pruritus.a	13	.929	.000

Table 5
Paired sample test

		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference		t	df	Sig.
					Lower	Upper			
Pair 1	kharesh.b - kharesh.a	-16.07692	12.21653	3.38826	-23.45930	-8.69455	-4.745	12	.000

DLQI

In order to investigate this index, a questionnaire including 11 questions was used before the treatment, during the second week of the treatment, and two weeks after the treatment.Two patients who were under 16 were exempted from this investigation and therefore only 14 patients. were involved. The mean of primary DLQI at the beginning was 32.2, at the second week was 35.1 and two weeks after the treatment was 35.1. This was investigated by test of normalities, paired sample statistics, paired samples correlations, paired sample test (Table 6-9) and the results showed that the use of this medicine can improve life quality.

Table 6
Tests of Normality

	Kolmogorov-Smirnova			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
qol.b	.151	14	.200*	.939	14	.408
qol.a	.136	14	.200*	.962	14	.759

****. This is a lower bound of the true significance.***
a. Lilliefors Significance Correction

Table 7
Paired Samples Statistics

		Mean	N	Std. Deviation	Std. Error Mean
Pair 1	qol.b	33.4286	14	7.11136	1.90059
	qol.a	35.0000	14	5.73786	1.53351

Table 8
Paired Samples Correlations

		N	Correlation	Sig.
Pair 1	qol.b&qol.a	14	.977	.000

Table 9
Paired Samples Test

		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference				
					Lower	Upper			
Pair 1	qol.b - qol.a	-1.57143	1.94992	.52114	-2.69728	-.44558	-3.015	13	.010

Investigating the changes of pasi-score

Investigation of this index in the intervention group showed that the average pasi-score decreased from 3.1 to 1.91 during the second week and remained at 1.91after two weeks. In the control group, the mean decreased from 3.17 to 2.75 and two weeks after the treatment, it was 2.75. Comparison of pasi-score before and after intervention and two weeks after the treatment was performed in both the intervention and control groups and the results of statistical tests showed that the changes in the pasi-score before and after intervention are significant (Table 10-13).

Table 10
Tests of Normality

	Kolmogorov-Smirnova			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
pasi1	.183	16	.158	.940	16	.352
pasi2	.169	16	.200*	.958	16	.619

. This is a lower bound of the true significance.
a. Lilliefors Significance Correction

Table 11
Paired Samples Statistics

		Mean	N	Std. Deviation	Std. Error Mean
Pair 1	pasi1	3.088	16	1.0782	.2695
	pasi2	1.913	16	.7898	.1975

Table 12
Paired Samples Correlations

		N	Correlation	Sig.
Pair 1	pasi1 & pasi2	16	.814	.000

Table 13
Paired Samples Test

		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference				
					Lower	Upper			
Pair 1	pasi1 - pasi2	1.1750	.6319	.1580	.8383	1.5117	7.438	15	.000

The Pasi-score investigation in the control group showed that its mean changed from 3.17 to 2.75 and after two weeks of using placebo, it was 2.75. Sig (2-tailed) = 003 showed that these changes are not significant (Table 14-17).

Table 14
Tests of Normality a

	Kolmogorov-Smirnovb			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
pasi1	.175	13	.200*	.947	13	.555
pasi2	.151	13	.200*	.949	13	.582

. This is a lower bound of the true significance.
a. group = control
b. Lilliefors Significance Correction

Table 15
Paired Samples Statisticsa

		Mean	N	Std. Deviation	Std. Error Mean
Pair 1	pasi1	3.177	13	1.0199	.2829
	pasi2	2.746	13	1.1738	.3255

a. group = control

Table 16
Paired Samples Correlationsa

		N	Correlation	Sig.
Pair 1	pasi1 &pasi2	13	.938	.000

a. group = control

Table 17
Paired Samples Testa

		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference				
					Lower	Upper			
Pair 1	pasi1 - pasi2	.4308	.4151	.1151	.1799	.6816	3.742	12	.003

a. group = control

Comparison of the pasi-scores before and after the treatment was performed by t-test and levene test and the results showed that the paci-score changes were not significant.

Investigation and measurement of the effect size
Although changes of the pasi-scores in the intervention and control groups were not significant, the effect size and estimation of Cohen's criterion showed that this intervention had a moderate effect in clinical aspect (Table 18).

Table 18
Group Statistics

	group	N	Mean	Std. Deviation	Std. Error Mean
pasi2	case	13	2.046	.7838	0.2174
	control	13	2.746	1.1738	0.3255

Cohen's d = (2.046 - 2.746)/0.998035 = 0.701378.
Gates' *delta* = (2.046 - 2.746)/1.1738 = 0.596354.
Hedges' g = (2.046 - 2.746)/0.998035 = 0.701378.

Investigating the therapeutic response
Investigating the therapeutic response based on decreased pasi-score in the intervention and control groups showed that in the intervention group, 2 patients had weak response (>25%), 9 had average response (25-50%), 2 had good response (50-75%) and 2 s had excellent response (>75%) and the average pasi-score decrease was 30.46%.One patient did not respond to the treatment. In the control group, 2 patients did not respond to the treatment, 9 had weak response, 1 had average response, and 1 patient had excellent response and the average pasi-score decrease was 20.4% (Table 19).

Table 19
Investigating therapeutic response based on the pasi-score in the intervention and control groups

Decreased pasi-score	>Weak25%	Average25-50%	Good50-75%	Excellent75-99%	Complete improvement100%	Average pasi-score decrease
Intervention group	2	9	2	2	0	30.46
Control group	11	1	0	1	0	20.4

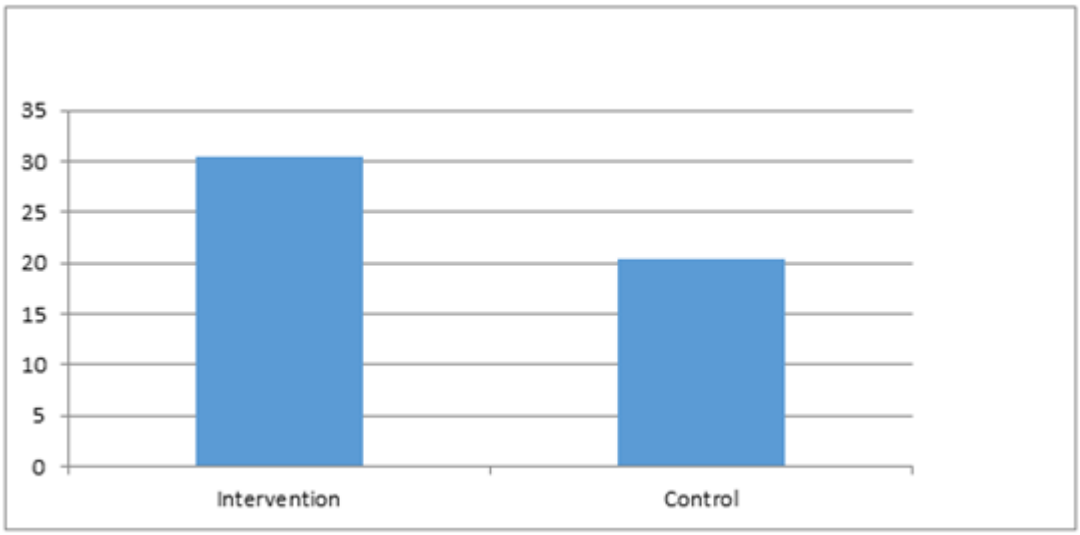

Figure 1
Decreased pasi-score in the intervention and control groups

DISCUSSION AND CONCLUSION

For this study, 16 patients who were suffering from plaque psoriasis with skin lesions at the left and the right sides of their bodies were exposed to treatment with medicine and placebo that were randomly used on them. Finally, 16 patients including 5 females and 11 males with an average age of 36.56 entered the intervention group and 13 patients including 4 females and 9 males with an average age of 36.46 entered the control group. The minimum age was 6 and the maximum age was 96 in both the groups. The results of the study showed that two weeks after the end of the treatment, the mean of DLQL was 35.1 which was a significant difference compared with the level before the treatment that was 33.2. Also, the mean of QOL-Itchy two weeks after the treatment was 83 which showed a significant difference with the mean at the beginning of the treatment that was 67., The pasi-score index was used to monitor the response to treatment. In the intervention group, the average pasi-score before the treatment was 3.1 and two weeks after the treatment was 1.91. A significant decrease in the pasi score was thus noted as shown in figure 1. This showed that the effects of medicine continued even after discontinuation of the treatment and no recurrence of the disease was observed. Also, in this group, the pasi-score decreased by 30.46% and 19% of patients showed weak response, 56% showed average response, 13% showed good response, and 12% showed excellent response. In the control group, the average pasi-score before treatment was 3.17 and after treatment was 2.75 and no significant difference was observed. In this group, the average pasi-score decrease was 20.4% and 84% of patients showed weak response, 8% showed average response, and 8% showed excellent response. Comparison of the pasi-scores between the intervention group and the control group before and after the treatment was performed by statistical tests and no significant difference was observed, but efficiency size estimation showed that the prescription of medicine had an average clinical effect. In this study, except one case (6.25%) of mild increase in itchy skin, no side effect was observed and the treatment was not stopped in the middle. Since the use of topical curcumin is a

modern method in plaque psoriasis treatment, only one similar study is found and other studies have supported the biochemical effects of curcumin that may be effective at the pathogenesis pathway of psoriasis. In a study by Sarafianet al.[2] on 34 patients with mild to modest plaque psoriasis, the effect of 5% turmeric topical gel (curcuma langa) was investigated where the average Pasi-Score was significantly high in the lesions treated with turmeric compared with placebo and this was consistent with the present study.[2]In a study by Sun et al.[4], the effects of 1% curcumin and 0.02% clobetasol on psoriasis dermatitis caused by immaculate were similar and this shows the effectiveness of curcumin.[4] The questionnaire used by y Desai et al.[7], in a study to determine the effect of itchy skin on life quality (QOL-Itchy) was used in this study too.[7] To sum up, the results of this study and previous studies show that topical curcumin, as an inexpensive drug with less side effects, can have an important role in the treatment of psoriasis; however, this requires more studies with larger sample size and longer follow-ups and the use of different doses in other formulations of these medicines can be helpful in finding the most effective dose of formulation.

AUTHOR CONTRIBUTION STATEMENT

Yaghoobi R conceived of the presented idea. Soghrati M and Pazyar N developed the theory with the aim of Yaghoobi R. Parvin N carried out the experiment, verified the analytical methods and wrote the manuscript with the aim of all other authors.

CONFLICT OF INTEREST

Conflict of interest declared none.

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