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OPEN PEER REVIEW

The Effectiveness of a Topical Turmeric-Based Formulation on Contact Dermatitis: A Randomized, Double-Blind, Controlled Trial

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About this report

This open peer review (OPR) report shows the public comments made on this article during peer review, by the reviewers, the associate editor and the editor-in-chief, for every revision round, together with the authors' replies. Comments appear only with the consent of the people who wrote them. Reviewers who chose to sign their report are named; the others are shown as "Referee". Comments are edited for language only, and confidential remarks to the editors are not included.

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1 Original submission

3 comments · 5 Jun 2026 – 29 Jun 2026

Referee 1 Reviewer

MAJOR REVISION 5 Jun 2026

This is a clinical trial reporting the effect of a multi-ingredient herbal cream on contact dermatitis.
The study is generally interesting and is within the scope of the journal. The manuscript is well written with respect to English. Please recheck the text for minor typographical errors.
Scientifically, an acceptable set of evaluations has been performed, including both formulation and clinical assessments. However, the following points should be considered to improve the manuscript:
Title:
Please correct to “turmeric-based”.
Please correct to “A Randomized, Double-Blind, Controlled Trial”.
Keywords:
Some of the keywords seem irrelevant, e.g., End-Stage Liver disease, psychological, characteristics, memory, depression, anxiety, Methanol Extract, Rosmarinus, Antibacterial Activity, Anti-quorum Sensing. Please recheck and remove these terms.
Abstract:
Please correct “epidermal water loss” to “transepidermal water loss”.
Regarding “melanin and hemoglobin content”, the authors have claimed in the main text that, due to the color of the cream, these two parameters were not evaluated in the patients. Please remove them from the abstract.
Line 13: Please capitalize Covid-19.
Line 23: Please provide a brief introduction to and explanation of Persian medicine, since the audience may not be familiar with this traditional medical system.
Line 32-36: Grammatical correction is needed: the first sentence is in the simple present tense; the second sentence is in the simple past tense. Please revise.
Line 66: Were the total phenols and total flavonoids measurements performed on the cream or on the extracts? If they were performed on the cream, the compounds must have been extracted from the cream base; please explain this step as well. Also, please mention the wavelength used for the total phenols test.
Line 72: Total flavonoid content must have been expressed per gram of the cream, not per milliliter of the extract. Please correct. Also, please recheck the wavelength at which the total flavonoids measurement was performed (the usual wavelength in this method is 412 nm, not 425 nm).
Line 78: “spread ability”: please remove the space.
Line 80-87: Measurement of aristolochic acid is a phytochemical assay and is not related to pharmaceutical properties. Please move this part to the phytochemical assays section (after total flavonoid measurement).
Line 90: This part is too brief. Please provide more details on the investigated microbial strains and the microbiological techniques used for the assay.
Line 138: Please correct SPPS to SPSS.
Line 149: Please remove the calibration curve equation.
Line 150: The reported total phenol values seem to be wrong: first, the values must remain stable or decrease throughout the stability study, whereas your values increased! Second, the standard deviations for all reported means are very large (sometimes larger than the mean), which shows that either the measurements were performed with incorrect precision or the calculations are wrong (or there might be a problem with copying and pasting the numbers from an Excel file). Please recheck all your total phenol data. Additionally, there is no mention of a stability test in the methods section, so why did you measure the total phenol at 0, 1, 3, and 6 months? If a stability test was performed, you should—in addition to adding the test conditions to the

methods section—report all measurements at these four time points, not just total phenol. However, since this is a clinical trial, not a formulation study, I suggest that you remove the data for 1, 3, and 6 months and report only the initial total phenol value (which should be recalculated in any case).
Where is the result of the total flavonoids test?
Line 152: 27.36 ppm per what unit of weight? Please report the value correctly.
Line 154-157: You have only explained the goal here. Where are the results? What was the microbial count for each of the measurements? Were they within acceptable limits or not?
Line 188: What do you mean by the term “hydration(corneo)”?
Line 233: Please correct the spelling of “Lawson”.

Referee 2 Reviewer

MAJOR REVISION 24 Jun 2026

1- The study prespecified six biophysical skin parameters as primary outcomes. The authors should clarify which endpoint was used for sample-size estimation and discuss whether any multiplicity strategy was prespecified for the analysis of multiple co-primary outcomes.
Multiple outcomes were evaluated without adjustment for multiplicity, increasing the risk of type I error.
2- The CONSORT diagram suggests that all randomized participants were included in the final analysis. However, the manuscript should explicitly specify whether analyses were conducted according to the intention-to-treat, modified intention-to-treat, or per-protocol principle and describe the handling of missing data.
3- The manuscript states that melanin and hemoglobin measurements may have been affected by formulation dyes. If these measurements were potentially unreliable, their inclusion as outcomes should be reconsidered.
4- Primary efficacy conclusions are overstated.
The manuscript concludes that CLA cream significantly improves inflammatory symptoms and quality of life. However, most statistically significant findings are based on within-group analyses, whereas evidence of efficacy in randomized controlled trials should primarily rely on between-group comparisons.
For DLQI, the reported between-group p-value is 0.053, which does not meet the conventional significance threshold ($p<0.05$). Therefore, statements claiming significant superiority should be revised.

Editor-in-Chief

MAJOR REVISION 29 Jun 2026

Major Revision

2

Revision 1

AUTHORS' RESPONSE TO REVIEWERS

Authors' reply to reviewers

The next pages contain the authors' point-by-point reply to the comments of this revision round, as submitted with the revised manuscript. It is published as the authors wrote it.

Manuscript Title: The Effectiveness of a Topical Turmeric-Based Formulation on Contact Dermatitis: A Randomized, Double-Blind, Controlled Trial

Manuscript ID: [172121]

Dear Editor-in-Chief and Respected Reviewers,

We would like to express our sincere gratitude to the editorial team and the reviewers for their valuable time, expertise, and constructive comments on our manuscript. The insightful feedback provided has significantly contributed to improving the scientific quality and clarity of our work. We have carefully addressed all comments point-by-point and have revised the manuscript accordingly. All modifications have been highlighted within the revised manuscript to facilitate the review process.

We hope that the revised version now meets the standards required for publication in your esteemed journal.

Responses to Reviewer #1

Comment 1-1:

The study prespecified six biophysical skin parameters as primary outcomes. The authors should clarify which endpoint was used for sample-size estimation and discuss whether any multiplicity strategy was prespecified for the analysis of multiple co-primary outcomes. Multiple outcomes were evaluated without adjustment for multiplicity, increasing the risk of type I error.

Response:

We thank the reviewer for this valuable comment. We based our sample size calculation on the most relevant and reliable published study available at the time of our study design. Specifically, we used the data from Niazi et al. (2020) as a reference, which reported a proportion of 0.3 in the intervention group and 0.05 in the control group for the primary outcome. Using this difference in proportions, along with a two-sided alpha of 0.05 and 80% power, we estimated that a sample size of 32 participants per group would be sufficient to detect a clinically meaningful difference.

We acknowledge that the scarcity of comparable studies is a limitation of our work, and we have now explicitly discussed this in the Discussion section of the revised manuscript. We have also noted that further large-scale, well-designed studies are warranted to confirm our findings and to provide more robust data for future meta-analyses and sample size calculations.

We thank the reviewer for raising this critical methodological concern. We fully acknowledge that no multiplicity adjustment was prespecified in the original protocol. To address this limitation transparently, we applied the Bonferroni correction as a post-hoc sensitivity analysis. Accordingly, the adjusted significance level of $\alpha = 0.05/6 = 0.0083$. Under this adjusted

framework, only outcomes with p-values below 0.008 are considered statistically significant in the confirmatory sense.

Changes made in the manuscript: The Methods and Results sections have been revised accordingly.

Comment 1-2:

The CONSORT diagram suggests that all randomized participants were included in the final analysis. However, the manuscript should explicitly specify whether analyses were conducted according to the intention-to-treat, modified intention-to-treat, or per-protocol principle and describe the handling of missing data.

Response:

We thank the reviewer for this important methodological point. We confirm that the analyses were conducted according to the intention-to-treat (ITT) principle, and all randomized participants were included in their originally assigned groups, regardless of whether they completed the study or adhered to the intervention.

Two participants were excluded from the final analysis for the following reasons (one due to pregnancy and one due to side effects) and we had no real missing data.

Changes made in the manuscript: The Statistical Analysis subsection has been expanded to include this information.

Comment 1-3:

The manuscript states that melanin and hemoglobin measurements may have been affected by formulation dyes. If these measurements were potentially unreliable, their inclusion as outcomes should be reconsidered.

Response: We completely agree with the reviewer's valid concern. Given that the cream's color (derived from turmeric and Henna) could interfere with spectrophotometric measurements of melanin and hemoglobin, **these two parameters have been removed from the list of primary and secondary outcomes**. This limitation is explicitly acknowledged in the **Methods section**, and all related data have been removed from the **Results** section.
The **Abstract** and **Conclusion** have also been revised accordingly.

Changes made in the manuscript: Melanin and hemoglobin parameters have been removed from the Abstract, Methods, Results, and Conclusion sections.

Comment 1-4:

Primary efficacy conclusions are overstated. The manuscript concludes that CLA cream significantly improves inflammatory symptoms and quality of life. However, most statistically significant findings are based on within-group analyses, whereas evidence of efficacy in randomized controlled trials should primarily rely on between-group comparisons. For DLQI, the reported between-group p-value is 0.053, which does not meet the conventional significance threshold (p<0.05). Therefore, statements claiming significant superiority should be revised.

Response: We sincerely thank the reviewer for this critical and valuable comment. We completely agree that in randomized controlled trials and the primary evidence of efficacy should be based on between-group comparisons. Therefore, in the Results section, we have reported the mean differences between the two groups and the corresponding P-values derived from independent t-tests or Mann–Whitney U tests (for non-normally distributed data).

variable	Group				P-value
	a		b		
	Mean	SD	Mean	SD	
TIS	**3.10**	**1.60**	**2.03**	**1.46**	**0.003**
VAS	4.00	2.50	3.06	2.55	0.150
DLQI	5.06	5.50	2.71	4.29	0.053
TEWL	**7.64**	**13.08**	**-3.54**	**14.90**	**0.004**
SC Hydration	-11.60	14.13	-9.42	11.99	0.515
ph	0.57	1.48	0.27	1.41	0.107
Sebum	-12.90	21.04	-6.84	56.23	0.109

Revision of DLQI claims: Given that the between-group p-value for DLQI was 0.053, **any claim of statistically significant superiority has been removed**.

Changes made in the manuscript: The Discussion, Conclusion, and Abstract have been substantially revised to reflect a more cautious and conservative interpretation based on between-group comparisons.

Responses to Reviewer #3

Comment 3-1:

Title: Please correct to "turmeric-based". Please correct to "A Randomized, Double-Blind, Controlled Trial".

Response: We thank the reviewer for this suggestion. The title has been revised accordingly:
" The Effectiveness of a Topical Turmeric-Based Formulation on Contact Dermatitis: A Randomized, Double-Blind, Controlled Trial "

Changes made in the manuscript: The title has been corrected on the title page.

Comment 3-2:

Some of the keywords seem irrelevant, e.g., End-Stage Liver Disease, Psychological, Characteristics, Memory, Depression, Anxiety, Methanol Extract, Rosmarinus, Antibacterial Activity, Anti-quorum Sensing. Please recheck and remove these terms.

Response: We appreciate the reviewer's careful attention to the keywords. These terms were mistakenly chosen from word suggestion bar. The keywords have been **thoroughly revised** and are now fully relevant to the study:
New Keywords: Contact Dermatitis, Persian Medicine, curcuma longa, Lawsonia inermis, Aristolochia rotunda

Changes made in the manuscript: The keywords in the Abstract section have been corrected.

Comment 3-3:

Abstract: Please correct "epidermal water loss" to "transepidermal water loss". "Melanin and hemoglobin content" - authors have claimed in the main text that due to the color of the cream, these two parameters were not evaluated in the patients. Please remove them from the abstract. Line 13: Please capitalize Covid-19. Line 23: Please provide a brief introduction and explanation of Persian medicine since the audience may not be familiar with this traditional medical system.

Response: We thank the reviewer for these detailed editorial suggestions. All requested changes have been applied to the Abstract:

1. "Transepidermal water loss" has been substituted.
2. Melanin and hemoglobin parameters have been removed from the Abstract.
3. "Covid-19" has been capitalized.
4. A brief explanation of Persian Medicine has been added
5. **Changes made in the manuscript:** The Abstract has been fully revised.

Comment 3-4:

Lines 32-36: Grammatical correction is needed: the first sentence is in simple present tense; the second sentence is in simple past tense. Please revise.

Response: We appreciate the reviewer's attention to grammatical consistency. The tense has been harmonized, and both sentences are now written in the simple past tense to reflect general scientific statements.

Changes made in the manuscript: The Objectives section has been revised.

Methods and Materials Section

Comment 3-5:

Line 66: Was the total phenols and total flavonoids measurements performed on the cream or on the extracts? If it was performed on the cream, the compounds must have been extracted from the cream base; so, please explain this step, as well. Also, please mention the wavelength for total phenols test.

Response: We thank the reviewer for this technical question. The total phenols and total flavonoids measurements were determined in the cream samples. For extraction, 20 mL of boiling water was added to 2 g of cream. The mixture was then stirred using a magnetic stirrer for 30 minutes, followed by filtration. The resulting filtrate was used for the determination of total phenolic contents. The absorbance for the total phenols assay was measured at 765 nm.

- Since the total flavonoid content in the cream sample was below the detectable limit and could not be reliably quantified, the corresponding results were not reported. Therefore, the method for the determination of total flavonoid content has been removed from the Materials and Methods section of the revised manuscript.

Changes made in the manuscript: The Methods section has been revised and completed.

Comment 3-6:

Line 72: Total flavonoid content must have been expressed per gram of the cream, not milliliter of the extract. Please correct. Also, please recheck the wavelength in which total flavonoids measurement was done (usual wavelength in this method is 412 nm, not 425 nm).

Response: We appreciate this technical correction. Total Phenol and flavonoid content were expressed as milligram per gram of the cream. It was corrected in the text.

The total flavonoid content was analyzed according to the method described by Vafi et al.

The absorbance of the solution measured in 425 nm. The maximal absorption is in the range of 410–440 nm according to this article: **https://doi.org/10.1016/j.ab.2025.115794**

- Since the total flavonoid content in the cream sample was below the detectable limit and could not be reliably quantified, the corresponding results were not reported. Therefore, the method for the determination of total flavonoid content has been removed from the Materials and Methods section of the revised manuscript.

Changes made in the manuscript: The Results section for total flavonoids has been corrected.

Comment 3-7:

Line 78: "spread ability" please remove the space.

Response: Corrected to **"spreadability"**.

Changes made in the manuscript: The term has been corrected.

Comment 3-8:

Lines 80-87: Measurement of aristolochic acid is a phytochemical assay, not related to pharmaceutical properties. Please move this part to the phytochemical assays section (after total flavonoid measurement).

Response: We agree with the reviewer's suggestion. This section has been moved to the **Phytochemical Assays** section, appropriately placed after the total flavonoid measurement.

Changes made in the manuscript: The structure of the Methods section has been rearranged.

Comment 3-9:

Line 90: This part is too brief. Please provide more details on the investigated microbial strains and the microbiological techniques used for the assay.

Response: We have expanded this section with the following details:

- A cream sample was tested for total aerobic microbial count, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and total yeast and mold.
- Microbiological techniques**:** The **Pour Plate Method** was employed, and colony counts were performed after specified incubation periods.

Changes made in the manuscript: This part was added in the text.

Comment 3-10:

Line 138: Please correct SPPS to SPSS.

Response: Corrected to **SPSS**.

Changes made in the manuscript: The spelling has been corrected.

Results Section

Comment 3-11:

Line 149: Please remove the calibration curve equation.

Response: The calibration curve equation has been removed from the text.

Changes made in the manuscript: The Results section has been revised.

Comment 3-12:

Line 150: The reported total phenol values seem to be wrong: firstly, the values must be stable or decrease throughout the stability study; while your values are increased! Secondly, the standard deviations for all reported means are very large (sometimes larger than the mean) which shows either the measurements are performed with wrong precision, or the calculations are wrong (or there might be problem in copy-paste of the numbers from an Excel file). Please recheck all your total phenol data. Additionally, there is no mentioning of stability test in the methods section, so, why did you measure the total phenol at 0, 1, 3, and 6 months? If a stability test is done, you should- in addition of adding the test condition in methods section- report all measurements at these four timepoints, not just total phenol. But since this is a clinical trial not a formulation study, I suggest you to remove the 1, 3, and 6 months data and only report the primary total phenol value (which should be anyhow recalculated).

Response: -The correct phenol content value was 2.15 ± 1.58 mg of gallic acid equivalent per gram of cream. It was corrected in the text.

-To determine the shelf life of the formulation during the study period, a cream sample was stored under accelerated stability conditions (40°C and 75% relative humidity) for six months. The total phenolic content was measured every three months. Based on the results, the change in total phenolic content was less than 10%, indicating that the formulation remained stable throughout the study period. However, in accordance with the reviewer's valuable suggestion, and considering that this is a clinical study, this section has been removed from the manuscript. Only the total phenolic content of the cream at the time of production is now reported in the revised manuscript.

Changes made in the manuscript: The total phenol results table has been revised to include only baseline data. The Methods section has also been corrected.

Comment 3-13:

Where is the result of total flavonoids test?

Response: Since the total flavonoid content in the cream sample was below the detectable limit and could not be reliably quantified, the corresponding results were not reported. Therefore, the

method for the determination of total flavonoid content has been removed from the Materials and Methods section of the revised manuscript

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Comment 3-14:

Line 152: 27.36 ppm per what unit of weight? Please report the value correctly.

Response:

- The concentration of *aristolochic acid* was measured in the *A. rotunda* aqueous extract sample. Therefore, the result was reported as 27.36 ppm(µg/g) of extract.

Changes made in the manuscript: The unit has been corrected.

Comment 3-15:

Lines 154-157: You have only explained the goal here. Where are the results? What was the microbial count for each of the measurements? Were they within the acceptable level or not?

Response: We thank the reviewer for this important observation. Microbiological evaluation demonstrated the absence of *Staphylococcus aureus* and *Pseudomonas aeruginosa* in the cream formulation. The total aerobic microbial count and the total yeast and mold count were both less than 10 CFU/g, which were within the acceptable limits specified by British Pharmacopoeia (10^4 and 10^2 CFU/g, respectively). These findings indicate that the cream complied with the required microbiological quality standards.

Changes made in the manuscript: This part was modified in the text.

Comment 3-16:

Line 188: what do you mean by the term "hydration(corneo)"?

Response: This term refers to **Stratum Corneum Hydration**. The term has now been fully written out.

Changes made in the manuscript: The term has been corrected. (Line 130)

Comment 3-17:

Line 233: please correct the spelling of "Lawson".

Response: Corrected to **"lawsone"**.

Changes made in the manuscript: The spelling has been corrected. (Line 241)

Comment 3-18:

Minor typographical errors: Please recheck the text for minor typo errors.

Response: The entire manuscript has been carefully reviewed and all typographical errors have been corrected.

Changes made in the manuscript: A full editorial review has been conducted.

Response to Associate Editor's Comment

Editor Comment:

Major Revision. In addition to addressing the reviewers comments, please note that based on the corresponding clinical trial registry record, it appears that Dr. Laila Shirbeigi, who was listed as a principal investigator/contributor, has been omitted from the manuscript author list. Our review indicates that she is deceased; however, since she made a substantial scientific contribution to the study and met the applicable authorship criteria, her contribution must be appropriately recognized through authorship in accordance with accepted publication ethics.

Response: We sincerely thank the Editor for bringing this critical matter to our attention. We fully agree with this ethical requirement and, in accordance with the ICMJE authorship criteria and publication ethics guidelines, we confirm that **Dr. Laila Shirbeigi** made a substantial scientific contribution to the study design, data collection, and interpretation of results. Therefore, her name has been respectfully **added to the author list**, and her valuable contribution has been acknowledged in the **Acknowledgment** section. The authorship information has also been updated in the journal's submission system.

Changes made in the manuscript: Dr. Laila Shirbeigi's name has been added to the author list, and the Acknowledgment section has been completed.

Summary of Revisions

All comments raised by the reviewers and the Associate Editor have been carefully addressed. All modifications in the revised manuscript are clearly highlited for easy identification. The following files are submitted for re-evaluation:

1. **Revised Manuscript** (with all changes highlighted)
2. **Response to Reviewers** (this document)
3. **Revised Figures**

We are deeply grateful for the time and expertise that the reviewers and editors have devoted to improving our manuscript. We hope that the revised version now meets the journal's standards for publication.

Yours sincerely,

Alireza Abbassian
Associated Professor, Tehran University of Medical Sciences
2026.7.27

Declaration: All authors have reviewed and approved the revised manuscript and the responses to the reviewers' comments. No conflicts of interest are declared.

2 Revision 1

4 comments · 31 Jul 2026 – 15 Aug 2026

Referee 1 Reviewer

ACCEPT 31 Jul 2026

All comments have been sufficiently addressed. I recommend that the authors improve their Introduction and discussion by adding the following papers:
Vafi F, Bahramsoltani R, Abdollahi M, Manayi A, Hossein Abdolghaffari A, Samadi N, Amin G, Hassanzadeh G, Jamalifar H, Baeeri M, Heidari M. Burn wound healing activity of Lythrum salicaria L. and Hypericum scabrum L. Wounds: a Compendium of Clinical Research and Practice. 2016 Sep 29:WNDS20160929-2.

Mansouri P, Khademi A, Pahlevan D, Memariani Z, Aliasl J, Shirbeigii L. Review of medicinal remedies on hand eczema based on Iranian traditional medicine: A narrative review article. Iranian Journal of Public Health. 2016 Aug;45(8):986.

Parvizi MM, Saki N, Amiri-Ardekani E, Ahmadfard P, Pasalar M. The Prevalence of Using Traditional, Complementary, and Integrative Medicine by Patients With Epidermolysis Bullosa. Traditional and Integrative Medicine. 2024 Dec 28:357-63.

Rezghi M, Farahani AM, Asadi F, Mitra S, Dash R, Mozaffarpour SA, Memariani Z. Application of natural products in radiotherapy-induced dermatitis: a comprehensive review. Traditional and Integrative Medicine. 2021 Oct 3.

Mahdiye Abiyarghamsari Reviewer

ACCEPT 11 Aug 2026

No comments

Associate Editor

ACCEPT 14 Aug 2026

Accept

Editor-in-Chief

ACCEPT 15 Aug 2026

Accept