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Peer Review Report for "Quantification of Active Ingredients in Skin Lightening Creams Using HPLC Method in Iranian Market"

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Review Timeline:

Submit Date:	18 Feb 2025
Revised Date:	15 Jun 2025
Accepted Date:	23 Jun 2025

Revision (0)

Here, you can see the **Reviewers**, **Associate Editors** and **EICs'** comments from the beginning to the end of the revision process.

Hossein Malekzadeh : Reviewer

18 Feb 2025

This manuscript presents a study on the quantification of six active ingredients (hydroquinone, arbutin, kojic acid, ascorbic acid, propyl paraben, and butylated hydroxy anisole) in 58 skin-lightening creams available in the Iranian market. The authors developed and validated an HPLC method for simultaneous detection and quantification of these compounds. Given the potential toxicity of some of these ingredients at excessive concentrations, and the importance of accurate labeling of cosmetic products, this research is relevant and valuable.

Esmail Mohammadian : Reviewer

19 Feb 2025

Dear Editor

Have a nice day.

The author investigated quantification of active ingredients in skin lightening creams using HPLC method in Iranian market.

I would suggest reconsidering the manuscript for publication only after the following major revision.

1. Please perform full validation based on the following study in your research work:

U. Food and D. Administration, Guidance for Industry Bioanalytical Method Validation, US Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research, Rockville, MD, 2001.

2. Please report mean $\pm$ SD for all values.

3. Please compare the HPLC graphs of the standard samples and the real samples.

4. Please mention the solvents used for the extraction process in detail.

REFEREE : Reviewer

19 Feb 2025

Dear Editor,

The MS titled "Quantification of Active Ingredients in Skin Lightening Creams Using HPLC Method in the Iranian Market" addresses a critical issue in skin-lightening products. These products contain active ingredients such as hydroquinone, arbutin, and kojic acid which can have adverse effects if present in high concentrations. By employing high-performance liquid chromatography (HPLC), the author meticulously analyzes and quantifies these substances in 58 samples of skin-lightening creams. The main objective is to ensure these products meet acceptable safety standards. The study successfully identifies and quantifies six active ingredients within a 25-minute timeframe using the HPLC method. The findings reveal that hydroquinone and arbutin concentrations exceed permissible limits in some samples, raising concerns about their safety. In contrast, kojic acid, propylparaben, and butylated hydroxy anisole were found to be within acceptable levels. The research underscores the necessity for stricter regulation and monitoring of skin-lightening products to prevent potential toxicity and mislabeling.

I have some suggestions that could enhance the comprehensiveness of your study:

Questions:

1. What criteria were used to select the 58 samples? Was there any specific rationale behind this number or any limitations in sample collection?

2. In the results section, could you explain the correlation between different concentrations of active ingredients and the potential adverse effects observed? This would provide more context to the findings.

Suggestions:

1. Expand Statistical Analyses: Adding more statistical analysis to compare the results obtained from different samples can enhance the credibility of the findings (inter-day and intra-day RSD%, R% for samples).

2. Environmental Impact Assessment: Including an assessment of the environmental impact of the active ingredients in skin-lightening creams could add more value to the research.
3. Regulatory Recommendations: Based on your findings, it would be helpful to provide some regulatory recommendations to improve the monitoring and control of skin-lightening products in the Iranian market.
4. Lack of Method Comparison: The study solely relies on the HPLC method without comparing it to other analytical techniques that might also be effective in quantifying these ingredients. A comparison with alternative methods (e.g., GC-MS, LC-MS) could validate the accuracy and efficiency of the chosen approach.
5. Move information about how the samples were taken and the brand and location of their origin to a separate section.
6. Bring important information from the results section into a separate table.
7. Please use ($\mu\text{g/mL}$) instead of ppm.
8. Check the equations of the Calibration listed in Table 1.

OPEN PEER REVIEW

Revision (1)

Reply to Reviewers

Ideally, the reviewing process can significantly improve the submitted manuscripts by allowing the authors to take into account the advice of reviewers. Author(s) must reply to all reviewers' comments in a separate Word file, point by point. A "**Reply to Reviewers**" document is submitted along with revised manuscript during submission of revised files, summarizing the changes that the authors made in response to the reviewers' comments. The responses to reviewers' comments specifies how the authors addressed each comment the reviewers made.

You can read the authors' responses to the reviewers' comments in the next page.

Dear Editor in chief,

Thank you for giving me the opportunity to submit a revised draft of my manuscript titled **“Quantification of Active Ingredients in Skin Lightening Creams Using HPLC Method in Iranian Market”** to *Jundishapur Journal of Natural Pharmaceutical Products*. We appreciate the time and effort that you and the reviewers have dedicated to providing your valuable feedback on our manuscript. We are grateful to the reviewers for their insightful comments on our paper. We have been able to incorporate changes to reflect most of the suggestions provided by the reviewers. We have highlighted the changes within the manuscript.

Here is a point-by-point response to the reviewers' comments and concerns.

Reviewer 1:

Questions:

- 1) What criteria were used to select the 58 samples? Was there any specific rationale behind this number or any limitations in sample collection?

Answer: The available brands (25 different brands) in Tehran market were purchased. The different batches of these brands were also used for analysis in our study. In fact, we try to collect the samples from the available different brands in Tehran.

- 2) In the results section, could you explain the correlation between different concentrations of active ingredients and the potential adverse effects observed? This would provide more context to the findings.

Answer: The requested modifications are applied in the manuscript.

Suggestions:

- 1) Expand Statistical Analyses: Adding more statistical analysis to compare the results obtained from different samples can enhance the credibility of the findings (inter-day and intra-day RSD%, R% for samples).

Answer: The requested modifications are applied in Table.1 in the manuscript.

- 2) Environmental Impact Assessment: Including an assessment of the environmental impact of the active ingredients in skin-lightening creams could add more value to the research.

Answer: Thank you for pointing this out. We will absolutely carry out the recommended assessment in our future researches.

- 3) Regulatory Recommendations: Based on your findings, it would be helpful to provide some regulatory recommendations to improve the monitoring and control of skin-lightening products in the Iranian market.

Answer: Thank you for pointing this out. The requested modifications are done in conclusion section in the manuscript.

- 4) Lack of Method Comparison: The study solely relies on the HPLC method without comparing it to other analytical techniques that might also be effective in quantifying these ingredients. A comparison with alternative methods (e.g., GC-MS, LC-MS) could validate the accuracy and efficiency of the chosen approach.

Answer: The requested modifications are done in the background section in the manuscript.

- 5) Move information about how the samples were taken and the brand and location of their origin to a separate section.

Answer: The requested information about the samples is embedded in materials and methods section in standards and chemicals heading.

- 6) Bring important information from the results section into a separate table.

Answer: The information about validation parameters is presented in Table.1.

- 7) Please use ($\mu\text{g/mL}$) instead of ppm.

Answer: Thank you for pointing this out. The requested modifications are done.

- 8) Check the equations of the Calibration listed in Table 1.

Answer: The equations are checked.

Reviewer 2:

We appreciate the time and effort that you have dedicated to providing your valuable feedback on our manuscript.

Reviewer 3:

- 1) Please perform full validation based on the following study in your research work:

U. Food and D. Administration, Guidance for Industry Bioanalytical Method Validation, US Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research, Rockville, MD, 2001.

Answer: The full validation was carried out in our study. The validation parameters are showed in Table.1.

2) Please report mean $\pm$ SD for all values.

Answer: Average levels of all values were reported in the text of results and discussion section. Also RSDs were reported in Table.1.

3) Please compare the HPLC graphs of the standard samples and the real samples.

Answer: Thank you for pointing this out. The requested modifications are done.

4) Please mention the solvents used for the extraction process in detail.

Answer: The extraction solvent is mentioned in sample preparation section.

Associate Editor 1:

1) In abstract section, mention the regulatory limits for hydroquinone and arbutin that were used as the basis for determining non-compliance.

Answer: Thank you for pointing this out. The requested modifications are done.

2) In abstract section, specify how much the hydroquinone and arbutin levels exceeded the limits in the non-compliant samples (e.g., "the hydroquinone level in one sample was X% above the limit").

Answer: Thank you for pointing this out. The requested modifications are done.

3) In introduction section, provide more information on the regulatory landscape for cosmetic products in Iran, including the specific regulations regarding the use of hydroquinone, arbutin, kojic acid, and other ingredients in skin-lightening creams.

Answer: There are not any regulations regarding the use of hydroquinone, arbutin, kojic acid, and other ingredients in skin-lightening creams in Iran.

4) In introduction section, expand on the potential health risks associated with the use of hydroquinone, arbutin, and kojic acid, including the specific adverse effects and the levels at which these effects are likely to occur.

Answer: Thank you for pointing this out. The requested modifications are done.

5) In introduction section, explain why these six specific compounds were selected for analysis. Are these the most commonly used or most concerning ingredients in skin-lightening creams in Iran?

Answer: We selected these ingredients amongst others because they are amongst the most toxic and most used agents in lightening products, and they are often subject to international regulations. Since no standards have been established for these active ingredients in

whitening creams in Iran, one of the goals of this study is to highlight the importance of controlling and monitoring these ingredients in whitening creams and establishment of the standards.

- 6) Provide more details on the selection of the 58 skin-lightening creams. Were the creams selected randomly, or were they chosen based on specific criteria (e.g., popularity, brand, ingredients)?

Answer: The available brands (25 different brands) in Tehran market were purchased. The different batches of these brands were also used for analysis in our study. In fact, we try to collect the samples from the available different brands in Tehran.

- 7) Clarify why 20 mM NaH₂PO₄ buffer containing 10% methanol was chosen as the extraction solvent. Was this solvent optimized for the extraction of the target compounds from the cream matrix? Provide more detail about the sonication and centrifugation steps.

Answer: According to several articles, some extraction methods were tested and the best one was selected. The reference article was cited in the manuscript. The sonication and centrifugation steps are explained in detail in materials and methods section in sample preparation heading.

- 8) Proofread the manuscript carefully to correct any typos or grammatical errors.

Answer: All spelling and grammatical errors have been corrected.

- 9) Ensure consistency in the units used throughout the manuscript.

Answer: Thank you for pointing this out. The manuscript was checked to ensure about the units consistency.

We look forward to hearing from you in due to respond to any further questions and comments you may have.

Sincerely,

Mannan Hajimahmoodi

OPEN PEER REVIEW

Revision (1)

Esmaeil Mohammadian : Reviewer

13 May 2025

Dear Editor

Have a nice day.

The author studied the Quantification of Active Ingredients in Skin Lightening Creams Using HPLC Method in Iranian Market.

It is recommended to be accepted for publication after the following minor changes.

1. Please fully validate the newly developed method in your research work.

REFEREE : Reviewer

18 May 2025

Dear Editor,

I have evaluated the revised manuscript and the authors' responses to the reviewers' comments. While the revisions have significantly improved the manuscript, I recommend conditional acceptance pending the inclusion of spiked sample chromatograms to demonstrate method specificity and interference assessment.

Below is my detailed assessment:

The authors have thoroughly addressed methodological concerns, including:

Full validation data (Table 1) compliant with FDA guidelines.

Clarity in sample selection and extraction optimization.

Improved regulatory context (e.g., exceedance levels in Abstract).

The study provides valuable insights into unregulated skin-lightening products in Iran, aligning with global safety priorities.

To ensure the method's reliability for complex cosmetic matrices, the authors must: Include chromatograms of spiked samples (e.g., cream matrix + known concentrations of all six analytes) alongside the current standard and real-sample chromatograms (Figure 1)

Please convey this request to the authors. I am available to review the supplemental data promptly.

Best regards,
Mehdi

OPEN PEER REVIEW

Revision (2)

Reply to Reviewers

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You can read the authors' responses to the reviewers' comments in the next page.

Dear Editor in chief,

Thank you for giving me the opportunity to submit a revised draft of my manuscript titled **“Quantification of Active Ingredients in Skin Lightening Creams Using HPLC Method in Iranian Market”** to *Jundishapur Journal of Natural Pharmaceutical Products*. We appreciate the time and effort that you and the reviewers have dedicated to providing your valuable feedback on our manuscript. We are grateful to the reviewers for their insightful comments on our paper. We have highlighted the changes within the manuscript.

Here is a point-by-point response to the reviewers' comments and concerns.

Reviewer 1:

Question:

- Please fully validate the newly developed method in your research work.

Answer: The full validation was carried out based on “Validation of Analytical Procedures: Text & Method Q2 (R1). Guideline I. Switzerland: International Conference on Harmonization; 2005.” in our study. The validation parameters are showed in Table.1.

Reviewer 2:

- To ensure the method's reliability for complex cosmetic matrices, the authors must: Include chromatograms of spiked samples (e.g., cream matrix + known concentrations of all six analytes) alongside the current standard and real-sample chromatograms (Figure 1)

Answer: Thank you for pointing this out. The requested chromatogram is added to Figure1.

We look forward to hearing from you in due to respond to any further questions and comments you may have.

Sincerely,

Mannan Hajimahmoodi

OPEN PEER REVIEW

Revision (2)

Esmail Mohammadian : Reviewer

23 Jun 2025

Dear Editor

Have a nice day.

The addressed issues and concerns have been effectively resolved. Consequently, the reviewer concurs to proceed with the publication of this paper in its current state.