

OPEN PEER REVIEW

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Peer Review Report for "Design, Preparation, and ex vivo Skin Permeation of Naringenin Liposomal Formulation for Topical Delivery"

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Review Timeline:

Submit Date: 23 Nov 2025

Revised Date: 13 Dec 2025

Accepted Date: 21 Dec 2025

Revision (0)

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

Esmaeil Mohammadian : Reviewer

27 Nov 2025

Dear Editor

Have a nice day.

The author investigated "Design, Preparation, and Ex Vivo Skin Permeation of Naringenin Liposomal Formulation for Topical Delivery".

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

1. Has the Design of Experiment been reviewed?
2. Please revise the manuscript for lingual quality and typo mistakes.
3. Specify the p-value in all sections.

4. Duplicate phrases should be corrected.
5. All results are required to be reported with SD.
6. The main focus of the introduction should be on liposomes and naringenin.
7. Naringin is written in Materials and Methods?
8. Please provide a reference for the animal model. Has the skin been stored at – 20°C?
9. Explain the sonication speed and all parameters in the formulation.
10. The conclusion is overly general and repeats the introduction. No mention of study limitations.
11. Data such as EE=99% and particle size being the same before and after 3 months are questionable and unreliable.
12. There are weak scientific arguments in the discussion that lack accurate references.

REFeree : Reviewer

5 Dec 2025

- 1-Please check the punctuation and English grammar of the whole manuscript. Additionally, the English typographical error is present in the manuscript.
2. Please use the most recent references instead of Reference 28, because it is too old.
- 3-this section in the introduction is too long to have two references at the end of it. Please add more references for this section" The use of lecithin and cholesterol is fundamental in designing liposomes with optimal stability, permeability and therapeutic efficiency. Lecithin provides the amphiphilic bilayer structure, while cholesterol enhances its robustness and resistance to environmental and biological challenges. Together, they enable the development of reliable drug delivery systems that improve bioavailability, reduce side effects and allow targeted and controlled drug release. This synergy is a cornerstone in the advancement of liposome-based therapies. Also, liposomes are biocompatible and biodegradable and have low toxicity. They can encapsulate hydrophilic and lipophilic drugs and facilitate targeted drug delivery to tumor tissues. These advantages have led to the development of liposomes both as a research system and commercially as a drug delivery system(11, 12)."
- 4-Please add references for this section"Between nanoparticles liposomes offer several unique advantages for transdermal drug delivery, including enhanced drug solubility and stability, controlled release, improved biocompatibility, targeted delivery, and skin penetration enhancement. these advantages make liposomes a promising platform for the development new and improved transdermal drug delivery systems."
- 5-Please add references for this section:"Numerous studies have shown that naringenin can be used for a wide range of diseases due to its broad pharmacological effects both in vitro and in vivo."
- 6-Please mention the previous studies that were done on naringenin to enhance its solubility, and mention the novelty of the current work compared with previous ones.
- 7-Please add more detail or references for this "Minitab17 software was used to

evaluate the effect of independent variables on the studied parameters.” In the material and methods.

8. Please add the ethical code for using animals in the animal model section.

9-Please add a reference or more details about the method of assaying naringenin in the naringenin assaying section.

10, based on which knowledge authors use these two concentrations for cholesterol and lecithin and naringenin for constructing liposomes containing naringenin. If selecting these concentrations based on previous works, please add the references in the manuscript.

11-Please add a reference for this: “Entrapment efficiency Percent represents the ratio of the amount of drug loaded in the liposomes to the amount of drug used.”

12-Please add a reference for the entrapment efficiency formula.

13. Please add a reference for Franz diffusion cell methods.

14-Please remove this sentence” Minitab17 software was used to evaluate the effect of independent variables on the studied parameters.” from 2.1. Chemicals, and just mention it in the statistical analysis.

15-this sentence”Liposomes enhance drug permeation by increasing skin diffusion and distribution (20)”. is meaningless and not related to the previous sentence. Please revise it to more related to previous or next sentence in this section. It is better to mention it after reference 22.

16-please add these two article in discussion too.

1-“Preparation, Optimization , and Investigation of Naringenin -Loaded Microemulsion for Topical Application”

2-“Development of a novel polymer-based carrier for deformable liposomes for the controlled dermal delivery of naringenin”

18- 18- 18-the authors in discussion just mention the related work that was done on this topic. Please compare the current work with the previous study and mention whether the results of this research are compatible or incompatible with previous ones, and mention the advantages of this formulation compared with previous ones.

17- In conclusion, please mention the limitations of the current work, which formulation was found to be best, and future work should be done on this research.

REFeree : Reviewer

6 Dec 2025

• Subject

• 1) Is the article within the scope of the journal? yes

• 2) Does the article have novelty? yes

Title: Design, Preparation, and Ex Vivo Skin Permeation of Naringenin Liposomal Formulation for Topical Delivery

• 3) Does the title reflect the content appropriately? yes

• 4) Is there any abbreviation in the title? Yes

• Abstract

• 5) Is there a structured Abstract? The abstract is written twice in the first of manuscript. Remove one.

• 6) Are Keywords (3-10) selected from MESH? yes

- Introduction
- 7) Clarity of the objectives/hypotheses? (Are the objectives clearly stated?) yes
- 8) Does the Introduction include: "What we know," "What we don't know," and "Aims"? yes , the introduction are written good but the chemical structures of naringenin must be given in this part.
-
- Materials And Methods
- 9) Clearly describe the selection of participants (patients or laboratory animals, including controls). This research have not patients but have the laboratory animals.
- 10) Study Design Described Sufficiently? The study design is cosidered sufficient and appropriate.
- In line 87, what is the difference between Naringin and naringenin. Please correct it.
-
- 11) Adequacy of the sample studied? The sample is appropriate according to the procedure.
- 12) Subjects Representative of the Target Population? yes
- 13) Provided sample size calculation or justification? -
- 14) Control Subjects Appropriate?-
- 15) Power of study declared? Power of study is proper quality.
- 16) Reported actual P values for primary analyses?-
- 17) Blinding of Investigators (if applicable)?
- 18) Blinding of subjects (if applicable)?
- 19) Identify the methods apparatus (give the manufacturer's name and address in parentheses). The name of companies must be given for all materials and apparatus.
- 20) Identify procedures in sufficient detail to allow other workers to reproduce the results. In experimental part, the procedures are clearly written and can be use for reproducing the results.
- 21) Identify precisely all drugs and chemicals used, including generic name(s), dose(s), and route(s) of administration. It is explained in no.19.
- 22) Inclusion/Exclusion Criteria Explained? -
- 23) Appropriate Statistical Analysis? -
- Results
- 24) Appropriateness, clarity, and adequacy of the Tables and Figures? The Figures and tables are clearly prepared from the experimental part.
- 25) Present results in logical sequence in the text, tables, and illustrations, giving the main or most important findings. The results of all experiments are properly explained in text.
- 26) Duplicate data in graphs and tables? No
- 27) Use technical terms as non-technical in statistics, such as "random" (which implies a randomizing device), "normal," "significant," "correlations," and "sample."? -
- Discussion
- 28) Conclusion justified & substantiated?
- 29) Analysis supports the Conclusion? Conclusion is good written specially the results of reaserch article.

- References
- 30) Proper Writing of the References? yes
- 31) References for the last five years? yes

REFeree : Associate Editor

7 Dec 2025

1. Fundamental Compound Identity Error: The manuscript states "Naringin powder was purchased" (Materials, line 87) but consistently studies "naringenin" throughout. These are distinct compounds: naringin is a glycosylated flavanone with markedly different physicochemical properties (solubility, permeability, molecular weight) than the aglycone naringenin. This discrepancy undermines all reported data; the study's conclusions are invalid if the wrong compound was used.
2. Physiologically Impossible Permeability Data: The reported apparent diffusion coefficients (D_{app}) are scientifically implausible: values of 0.23–1.898 cm²/h (Table 4) exceed free diffusion in water (~0.5 cm²/h) by orders of magnitude. Correct skin D_{app} values are typically 10⁻⁶ to 10⁻⁸ cm²/h. Such errors indicate either catastrophic miscalculations or severe methodological artifacts, rendering all permeability parameters unreliable.
3. Severe Methodological Flaws Compromising Skin Barrier Integrity:
 - Receptor phase uses 67% methanol (2:1 methanol:buffer), which is known to extract skin lipids and artificially inflate drug flux
4. Invalid Characterization and Release Assessment:
 - No zeta potential, TEM imaging, or bilayer integrity confirmation to verify liposome formation and stability

REFeree : EIC

7 Dec 2025

The manuscript has been examined by expert reviewers who have concluded that the work is of potential interest to the readership of JJNPP. However, from their comments it is clear that major revision of this manuscript will be required before a decision can be made on its publication. I would be pleased to consider a revised manuscript that addresses the reviewers' concerns. Your revised manuscript will be returned to one or more of the original reviewers for further consideration.

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.

Reviewer / Editor	Comments / Questions	Author's Response	Location in Manuscript
Reviewer 0	1-Please check the punctuation and English grammar of the whole manuscript. Additionally, the English typographical error is present in the manuscript.	Response: We appreciate the reviewer's attention to detail. The entire manuscript has been carefully proofread. Punctuation marks, grammatical structures, and typographical errors (including the Naringin/Naringenin typo) have been corrected throughout the text.	Whole Manuscript
Reviewer 0	2. Please use the most recent references instead of Reference 28, because it is too old.	Response: Agreed. Reference 28 has been replaced with a recent review article describing the role of cholesterol in liposomal bilayers (<i>Kulkarni et al., 2021</i>).	Ref [11]
Reviewer 0	3-Please add more references for this section:” The use of <i>lecithin and cholesterol is fundamental...</i> ”	Response: Two additional recent references regarding the synergistic effect of lecithin and cholesterol on liposome stability have been added to this section.	Introduction, Ref [11, 12]
Reviewer 0	4-Please add references for this section:” Between <i>nanoparticles liposomes offer several unique advantages...</i> ”	Response: Proper citations supporting the advantages of liposomes in transdermal delivery have been added to this paragraph.	Introduction, Ref [18, 19]
Reviewer 0	5-Please add references for this section:” Numerous <i>studies have shown that naringenin can be used...</i> ”	Response: References covering the pharmacological effects of Naringenin (in vitro and in vivo) have been added to support this statement.	Introduction, Ref [20-22]
Reviewer 0	6-Please mention the previous studies that were done on naringenin to enhance its solubility, and mention the novelty of the current work	Response: A paragraph has been added summarizing previous attempts (e.g., elastic liposomes, nanoparticles). We highlighted that this study specifically optimizes a classic liposomal formulation using Factorial Design to balance encapsulation efficiency with permeation without using synthetic	Introduction (Last paragraph)

Reviewer / Editor	Comments / Questions	Author's Response	Location in Manuscript
	compared with previous ones.	surfactants.	
Reviewer 0	7-Please add more detail or references for this "Minitab17 software was used..." In the material and methods.	Response: This sentence was removed from the "Chemicals" section and moved to the "Statistical Analysis" section with more details regarding the factorial design method used.	Section 2.11
Reviewer 0	8. Please add the ethical code for using animals in the animal model section.	Response: The ethical approval code (IR.AJUMS.ABHC.REC.1400.025) has been added to the "Animal Model" section.	Section 2.2
Reviewer 0	9-Please add a reference or more details about the method of assaying naringenin in the naringenin assaying section.	Response: The assay method was based on a validated spectrophotometric method. A reference has been added, and the linearity range (5–50µg/ml) is now mentioned.	Section 2.3, Ref [2]
Reviewer 0	10, based on which knowledge authors use these two concentrations... If selecting these concentrations based on previous works, please add the references.	Response: The levels of lecithin and cholesterol were selected based on our preliminary screening studies and optimized ranges reported in previous literature for similar lipophilic drugs. Two references have been added to justify these ratios.	Section 2.4
Reviewer 0	11-Please add a reference for this: "Entrapment efficiency Percent represents the ratio..."	Response: A standard reference for liposome characterization definition has been added.	Section 2.7
Reviewer 0	12-Please add a reference for the entrapment efficiency	Response: The reference for the equation has been cited.	Section 2.7

Reviewer / Editor	Comments / Questions	Author's Response	Location in Manuscript
	formula.		
Reviewer 0	13. Please add a reference for Franz diffusion cell methods.	Response: The standard reference for the Franz diffusion cell method (<i>Franz T.J., 1975</i>) has been added.	Section 2.8, Ref [30, 31]
Reviewer 0	14-Please remove this sentence” <i>Minitab17 software was used...</i> ” from 2.1. Chemicals...	Response: Done. The sentence has been removed from Section 2.1 and consolidated in Section 2.11 (Statistical Analysis).	Section 2.1 & 2.11
Reviewer 0	15-this sentence” <i>Liposomes enhance drug permeation...</i> ” is meaningless... Please revise it.	Response: This sentence has been revised for clarity and moved to the Discussion section to ensure logical flow.	Discussion, Ref [20, 28]
Reviewer 0	16-please add these two articles in discussion too.	Response: Both suggested articles regarding Naringenin microemulsions and polymer-based carriers have been discussed and cited in the Discussion section.	Discussion, Ref [23, 24]
Reviewer 0	18- ...Please compare the current work with the previous study...	Response: A detailed comparison paragraph has been added to the Discussion. We compared our Flux (Jss) and Lag Time (Tlag) with findings from <i>Tsai et al.</i> and <i>Joshi et al.</i> , highlighting our formulation's advantages.	Discussion
Reviewer 0	17- In conclusion, please mention the limitations...	Response: The Conclusion has been rewritten. It now explicitly states the study's limitations (lack of in vivo human data) and suggests future studies.	Conclusion
Reviewer 2	5) Is there a structured Abstract? The abstract is written twice... Remove one.	Response: The duplicate abstract has been removed.	Abstract
Reviewer 2	8) ...chemical structures of naringenin must be	Response: The chemical structure of Naringenin has been added as Figure 1 in the	Introduction

Reviewer / Editor	Comments / Questions	Author's Response	Location in Manuscript
	given in this part.	Introduction section.	
Reviewer 2	10) ...In line 87, what is the difference between Naringin and naringenin. Please correct it.	Response: This was a regrettable typographical error in the "Materials" section. The substance used was indeed Naringenin (Aglycone, MW: 272.25), not Naringin. This has been corrected in the text.	Line 87 (Section 2.1)
Reviewer 2	19) Identify the methods apparatus... The name of companies must be given...	Response: The manufacturer names, cities, and countries for all apparatus (e.g., Rotary Evaporator, Sonicator, Franz Cells) have been added.	Materials & Methods
Reviewer 3	1. Has the Design of Experiment been reviewed?	Response: Yes, the Full Factorial Design (2^3) was reviewed. We clarified the independent and dependent variables in Section 2.4 and Table 1.	Section 2.4
Reviewer 3	3. Specify the p-value in all sections.	Response: Exact P-values (e.g., $P=0.03$ instead of $P<0.05$) have been included in the Results section where statistically significant differences were observed.	Results Section
Reviewer 3	5. All results are required to be reported with SD.	Response: All numerical results in the text and tables are reported as Mean $\pm$ SD ($n=3$).	Tables 2, 3, 4
Reviewer 3	7. Naringin is written in Materials and Methods?	Response: As mentioned, this was a typo. It has been corrected to "Naringenin".	Section 2.1
Reviewer 3	8. Please provide a reference for the animal model. Has the skin been stored at -20°C ?	Response: A reference for the rat skin preparation method has been added. The storage condition (-20°C) is standard for preserving skin barrier integrity for short periods, as supported by the added reference.	Section 2.2, Ref [29]
Reviewer 3	9. Explain the sonication speed and all parameters in the	Response: Sonication frequency (60 Hz) and power details have been added.	Section 2.4

Reviewer / Editor	Comments / Questions	Author's Response	Location in Manuscript
	formulation.		
Reviewer 3	10. The conclusion is overly general...	Response: The conclusion has been significantly revised to be specific to the findings, mentioning the optimal formulation (LIP-NG-8) and acknowledging limitations.	Conclusion
Reviewer 3	11. Data such as EE=99%... are questionable...	Response: Naringenin is a highly lipophilic compound (LogP ~2.5), leading to high entrapment efficiency in lipid bilayers, consistent with literature. Slight variations in particle size over 3 months were not statistically significant, indicating good stability.	Results Section
Associate Editor	1. Fundamental Compound Identity Error:	Response: We sincerely apologize for this confusion. The compound purchased and used was Naringenin (Sigma-Aldrich, Product No. N5893). The mention of "Naringin" in the Materials section was a typographical error. The molecular weight and properties discussed in the introduction correspond to Naringenin. We have corrected the text to "Naringenin".	Section 2.1
Associate Editor	2. Physiologically Impossible Permeability Data:	Response: We thank the editor for this crucial observation. Upon re-evaluating our raw data, we identified a unit conversion error in the calculation of Dapp. We have recalculated the parameters using the correct units. The corrected values (in the range of 10^{-4} to 10^{-5} cm ² /h) are now presented in Table 4.	Table 4
Associate Editor	3. Severe Methodological Flaws... (Methanol):	Response: We acknowledge that high concentrations of methanol can affect skin lipids. However, due to the extremely low water solubility of Naringenin, maintaining sink conditions was impossible with buffer	Limitations Section

Reviewer / Editor	Comments / Questions	Author's Response	Location in Manuscript
		alone. We have added a statement in the "Limitations" section acknowledging that this method might slightly overestimate intrinsic permeability but is valid for comparative ranking.	
Associate Editor	4. Invalid Characterization... (Zeta/TEM):	Response: This study focused on the screening of formulation variables (Lecithin/Cholesterol) on permeability. PDI values (<0.4) indicate acceptable homogeneity. We have added a note in "Future Work" that morphological analysis (TEM) and Zeta potential will be performed for the optimized formulation in the next phase.	Future Work

OPEN PEER REVIEW

Revision (1)

REFeree : Reviewer

20 Dec 2025

1-please use english punctuation in text. it is still has problem.

Esmail Mohammadian : Reviewer

20 Dec 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.

REFeree : Associate Editor

21 Dec 2025

The Ms is now suitable for publication in JJNPP

REFeree : EIC

21 Dec 2025

I am pleased to inform you that your manuscript has been accepted for publication in JJNPP.

Your work underwent a rigorous peer-review process, and the reviewers and editorial board were impressed by the originality, scientific rigor, and relevance of your findings. We believe your contribution will be of significant interest to our readership and will advance the field of natural pharmaceutical products.

Before publication, our production team will contact you regarding final formatting, proofs, and any necessary administrative steps. Please ensure that all authors have approved the final version of the manuscript and that any required ethical or copyright documentation is in order.

On behalf of the editorial board, I congratulate you and your co-authors on this excellent work and thank you for choosing to publish in JJNPP.