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Jundishapur Journal of Natural Pharmaceutical Products

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Peer Review Report for "Herbal Oral Gel Containing *Cassia fistula* and *Rosa x damascena*: A Natural Remedy with Anti-microbial Activity Against Recurrent Aphthous Stomatitis"

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Review Timeline:

Submit Date:	27 Apr 2025
Revised Date:	7 Jul 2025
Accepted Date:	11 Jul 2025

Revision (0)

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

REFEREE : Reviewer

13 May 2025

respectfully,

conclusion should be expanded.

limitation and bias and more suggestion for further studies should be considered.

RECURRENT APHTUS STOMATITIS SHOULD BE DIFFERENTIATED FROM SIMILAR APHTUS WITH OTHER ETIOLOGY IN INCLUSION CRITERIA AND OTHER APHTUS BE EXCLUDED.

Esmail Mohammadian : Reviewer

13 May 2025

Dear Editor

Have a nice day.

The author investigated Formulation and anti-microbial potential of an Oral Gel from Cassia fistula and Rosa damascena for the treatment of Recurrent Aphthous Stomatitis.

In my opinion, this manuscript cannot be considered for publication. The main reasons for this outcome are as follows:

1. The level of innovation in the topic of the article is low.
2. There is no accurate statistical analysis and strong scientific writing.

REFeree : Reviewer

15 May 2025

Dear Editor

The manuscript appears to be a well designed and valuable contribution to the field. After addressing the following revision, I believe it will be suitable for publication. You are presenting 1.7/0.7 as best without showing how it was determined to be optimal if the differences were statistically insignificant?

You list compounds from GC/MS but do not analyze which ones likely contribute to antimicrobial effect. highlight 3-5 key compounds in discussion are most likely responsible base on the literature.

If there are more clinical studies in this field, reference should be given to them.

You mention that antimicrobial activity dropped when EX/EO was combined with the gel, Explain why.

Fix your reference issue!

REFeree : Reviewer

18 May 2025

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REFeree : Reviewer

26 May 2025

I read the manuscript entitled "Formulation and anti-microbial potential of an Oral Gel from Cassia fistula and Rosa damascena for the treatment of Recurrent Aphthous Stomatitis" with interest. The followings are my questions and suggestions after first review:

Title:

1- Since Rosa damascena is a hybrid plant, it must be written as Rosa × damascena, all over the manuscript text.

Abstract:

- 1- Since Damask rose is a hybrid, it is not a species. Likewise, if you want to write the abbreviated form of its scientific name, it should be written as *R. × damascena*.
- 2- The names of microbial strains must be corrected: *Actinomyces viscosus*, *Candida albicans*. The bacterial name is wrong all over the manuscript.

Background:

- 1- Terpene carboxylic acids are not phenolic compounds.
- 2- You said that "various biological activities, such as anti-cancer (17), Anti-dysmenorrhea (18), anti-colitis (19) anti-inflammatory and Antioxidant (11, 20) anti-bacterial (21). Moreover, a double-blind study reported acceptable anti-aphthae activity of *R. damascena* EO (22). According to the data of some studies, compounds such as citronol, geraniol and nerol and phenylethyl alcohol are responsible for the anti-microbial potential of *R. damascena* EO, as provided by the phenolic acids in *C. fistula* Ex (23, 24)." Regarding the first sentence, and must be placed before last item which is antibacterial. Likewise, in the last sentence, that should be re-written as: such as citronol, geraniol, nerol and phenylethyl alcohol ...

Methods:

- 1- 3.1.1. Plant materials and identification: You had two different plant specimens which must have two distinct accession numbers after deposition in herbarium.
 - 2- 3.1.2. Extraction and preparation of Ex and EO: The volume of the solvent used for extraction, and the amount of damask rose used must be mentioned.
 - 3- 3.1.4. GC MS analysis: The column temperature was first set at 40 °C for 2 minutes and then was increased to 200 °C for 15 minutes at a speed of 10 mL/min (This must be 10°C/min).
 - 4- 3.2.3. Determination of minimum inhibitory concentration (MIC): You said that "The plant Ex or EO was prepared in the medium in a two-fold dilution. 100 µL of the serial dilution of the Ex or EO and 100 µL of the cell suspension (1.5×10^3 CFU/mL) were added to the wells containing 100 µl of broth medium." It seems that there is a mistake here; since EX/EO or the microbial suspensions are each prepared in broth medium, so you do not need to add broth medium to the wells. Besides, that the final volume is usually 200 µL.
 - 5- 3.2.3. Determination of minimum inhibitory concentration (MIC): It is not possible to determine MIC by "visual analysis". You must either use an indicator like TTC, or apply a microplate reader to achieve quantitative values.
 - 6- 3.2.5. Determination of Ex activity together with EO: This part can be deleted. It is not a different method. You can mention in the previous parts that you have tested the combinations too.
 - 7- : In the description of table 1, some corrections (highlighted) are needed; *C. fistula* Ex = *Cassia fistula* extract, *R. × damascena* EO = *Rosa × damascena* essential oil
- Results:

- 1- 4.1. Identification of compounds: what did you mean by "with a yield of 70% dry Ex."? Your extraction yield must be $147/500 = 29.4\%$
- 2- Regarding your GC/MS chromatogram, some peaks like those which are before minute 10, are not showed completely, as their tops are out of the figure. You must resize your chromatogram in a way that all tall peaks would be indicated completely.

3- Regarding Table 2, you must add a column for the reference retention indices for each compound. It is also needed to explain that how you have identified each compound, either it was based RI values or mass spectra or both. And in each case you should provide detailed information, e.g. your mass library, etc.

4- Regarding Table 3, it would be better if MIC and MBC results be showed in another separated table. In addition, the MBC for EO against *S. mutans* must be 3.125 rather than 3.25. Additionally, please provide more information about your positive controls.

5- In figure 2, if you had three replicate for each test, it is better to indicate the bars with mean $\pm$ SD.

Discussion:

1- "is infected with oral aphthous" could be incorrect, since aphthous is not an infectious disease necessarily. In addition, "is infected" refers to present time, and you should say has been infected, instead.

2- You said that "we observed relatively high anti-microbial activity from *C. fistula* Ex", while your MIC values are in the range of mg/ml, which generally are considered weak for antimicrobials.

3- The discussion part needs to be re-written, to resolve grammatical errors, etc.

4- You said "the inhibitory activity was reduced from 28, 17, and 358 10.66 mm to 23, 14.66, and 7.5 mm for *C. albicans*, *S. mutans* and *A. viscos* respectively" while the numbers are describing zone of inhibition values.

REFeree : Associate Editor

26 May 2025

Thank you for submitting your manuscript to JJNPP.

Please revise the manuscript and submit a point-by-point response to the reviewers' comments and concerns and highlight the changes in the text.

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, Jundishapur Journal of Natural Pharmaceutical Products

Thank you very much for your kind consideration of our manuscript entitled “Herbal oral gel containing *Cassia fistula* and *Rosa × damascene*: a natural remedy with anti-microbial activity against recurrent aphthous stomatitis” with Manuscript ID: 162211. We would like to express our sincere thanks to the reviewer for constructive and positive comments. We tried our best to answer all of them as completely as possible. The article text was completely revised and corrected base on reviewer comments and the changes in the final version of manuscript were highlighted by yellow color for reviewer 1, blue color for reviewer 2, gray color for reviewer 4 and green color for reviewer 5. Finally, we hope the corrected manuscript would be qualified for publication.

Regards,

Independent Review Report, Reviewer 1

Changes in the final version of manuscript were highlighted by yellow color

• The manuscript appears to be a well-designed and valuable contribution to the field. After addressing the following revision, I believe it will be suitable for publication. You are presenting 1.7/0.7 as best without showing how it was determined to be optimal if the differences were statistically insignificant?

Response: Thank you for your attention.

In fact, we found that there were clear zones of inhibition (size) against the bacteria and fungi tested in the 1.7/0.7. Therefore, we have stated that stronger inhibitory (not statistically) results were observed.

“The results of the combination showed that the most appropriate concentration of Ex in combination with EO against all three microorganisms was 1.7 and 0.7%, which led to stronger inhibitory results.”

- You list compounds from GC/MS but do not analyze which ones likely contribute to antimicrobial effect. Highlight 3-5 key compounds in discussion are most likely responsible base on the literature. If there are more clinical studies in this field, reference should be given to them.

Response: Thank you for highlighting this point. It was corrected in the title.

“Based on GC/MS data analysis, we identified various ingredients in *R. × damascene* EO such as citronol, geraniol, and nerol, whose anti-microbial potential was mentioned in previous researches (23, 24). In two studies by Tianyue et al. and Fajdek-Bieda et al., antioxidant, anti-inflammatory, and antimicrobial activities of citronol, geraniol, and nerol were observed against fungi and a wide range of Gram-negative and Gram-positive bacteria (32, 33).”

- You mention that antimicrobial activity dropped when EX/EO was combined with the gel, Explain why.

Response: The explanations were highlighted in the main text.

“This may be due to the interaction between the Ex/EO mixture and the gel structure, which leads to a slow release of the active ingredient, since increased contact time, slow release, and increased drug absorption are bold features of the gel.”

- Fix your reference issue!

Response: Thank you for pointing this out. The reference was checked and fixed by the EndNote program.

Independent Review Report, Reviewer 2

Changes in the final version of manuscript were highlighted by blue color

1- Since *Rosa damascena* is a hybrid plant, it must be written as *Rosa × damascena*, all over the manuscript text.

Response: Thanks for mentioning this point. It was corrected in main text.

“Herbal oral gel containing *Cassia fistula* and *Rosa × damascena*: a natural remedy with anti-microbial activity against recurrent aphthous stomatitis”

Abstract:

1- Since Damask rose is a hybrid, it is not a species. Likewise, if you want to write the abbreviated form of its scientific name, it should be written as *R. × damascena*.

Response: Thank you for highlighting this point. It was corrected in main text and highlighted by blue color.

2- The names of microbial strains must be corrected: *Actinomyces viscosus*, *Candida albicans*. The bacterial name is wrong all over the manuscript.

Response: Thank you for your attention. It was corrected in all over the main text and highlighted by blue color.

Background:

1- Terpene carboxylic acids are not phenolic compounds.

Response: Thanks for mentioning this point. It was corrected in main text.

“The extract (Ex) of different parts from *C. fistula* plant is used for medical purposes due to possessing a wide range of phenolic bioactive components such as glycoside derivatives, tannins, flavonoid derivatives and anthraquinones.”

2- You said that “various biological activities, such as anti-cancer (17), Anti-dysmenorrhea (18), anti-colitis (19) anti-inflammatory and Antioxidant (11, 20) anti-bacterial (21). Moreover, a double-blind study reported acceptable anti-aphthae activity of *R. × damascene* EO (22). According to the data of some studies, compounds such as citronol, geraniol and nerol and phenylethyl alcohol are responsible for the anti-microbial potential of *R. × damascene* EO, as provided by the phenolic acids in *C. fistula* Ex (23, 24).” Regarding the first sentence, and must be placed before last item which is antibacterial. Likewise, in the last sentence, that should be re-written as: such as citronol, geraniol, nerol and phenylethyl alcohol ...

Response: Thanks for attention. It was corrected in main text.

“various biological activities, such as anti-cancer (17), anti-dysmenorrhea (18), anti-colitis (19) anti-inflammatory, antioxidant (11, 20) and anti-bacterial (21). Moreover, a double-blind study reported acceptable anti-aphthae activity of *R. × damascene* EO (22). According to the data of some studies, compounds such as citronol, geraniol, nerol and phenylethyl alcohol”

Methods:

1- 3.1.1. Plant materials and identification: You had two different plant specimens which must have two distinct accession numbers after deposition in herbarium.

Response: Thanks for mentioning this point. It was corrected in main text.

“The plants were confirmed by Herbarium of the Faculty of Pharmacy, Department of Pharmacognosy, Jundishapur University, Ahvaz, Iran, and herbarium specimen numbers 1399.771 and A252450101FLP were assigned to *C. fistula* and *R. × damascene*, respectively.”

2- 3.1.2. Extraction and preparation of Ex and EO: The volume of the solvent used for extraction, and the amount of damask rose used must be mentioned.

Response: Thanks for your kind advice. It was corrected in main text.

“The crude Ex of *C. fistula* fruit was prepared by maceration method. Briefly, 500 gram of fresh and powdered *C. fistula* fruit was soaked in 70% ethanol (800 mL) for 72 hours.”

“Moreover, the EO of 300 gram fresh flowers of *R. × damascene* was separated by hydrodistillation technique by Clevenger pyrex apparatus for 3 hours.”

3- 3.1.4. GC MS analysis: The column temperature was first set at 40 °C for 2 minutes and then was increased to 200 °C for 15 minutes at a speed of 10 mL/min (This must be 10°C/min).

Response: Thank you for highlighting this point. It was corrected in main text.

“The column temperature was first set at 40 °C for 2 minutes and then was increased to 200 °C for 15 minutes at a speed of 10 °C/min.”

4- 3.2.3. Determination of minimum inhibitory concentration (MIC): You said that “The plant Ex or EO was prepared in the medium in a two-fold dilution. 100 µL of the serial dilution of the Ex or EO and 100 µL of the cell suspension (1.5×10^3 CFU/mL) were added to the wells containing 100 µl of broth medium.” It seems

that there is a mistake here; since EX/EO or the microbial suspensions are each prepared in broth medium, so you do not need to add broth medium to the wells. Besides, that the final volume is usually 200 μL .

Response: Thanks for your kind advice. It was corrected in main text.

“100 μL of the serial dilution of the Ex or EO and 100 μL of the cell suspension ($1.5 \times 10^3 \text{ CFU/mL}$) were added to each well with final volume 200 μL .”

5- 3.2.3. Determination of minimum inhibitory concentration (MIC): It is not possible to determine MIC by “visual analysis”. You must either use an indicator like TTC, or apply a microplate reader to achieve quantitative values.

Response: Thanks for attention. It was corrected in main text.

We determined the MIC visually from the turbidity produced by the growth of the microorganism (turbidimetry) using a loop. We cultured the first well with no growth, the previous one, and the next one on agar medium to ensure no growth.

“MIC values were determined by a loop and turbidimeter.”

6- 3.2.5. Determination of Ex activity together with EO: This part can be deleted. It is not a different method. You can mention in the previous parts that you have tested the combinations too.

Response: Thank you for your suggestion. It was corrected in main text.

“We have also tested mixing these two compounds according to the method described previously.”

7- : In the description of table 1, some corrections (highlighted) are needed; C.

fistula Ex = *Cassia fistula* extract, *R. × damascena* EO = *Rosa × damascena* essential oil

Response: Thanks for attention. It was corrected in main text.

“Abbreviations: CMC= Carboxymethyl cellulose, HPMC = Hydroxypropyl methylcellulose, *C. Fistula* Ex = *Cassia fistula* extraction, *R. × damascene* EO = *Rosa × damascene* essential oil, Q.S = Quantum satis, PEG 400 = Polyethylene glycol-400”

“Abbreviations: MIC, minimum inhibitory concentration; MBC, minimum bacterial concentration; *C. albicans*, *candida albicans*; *S. mutans*, *Streptococcus mutans*; *A.viscos*, *Actinomyces viscosus*; EO of *R. × damascene*, essential oil of *R. × damascene*; Ex of *C. fistula*, extract of *C. fistula*.”

Results:

1- 4.1. Identification of compounds: what did you mean by “with a yield of 70% dry Ex.”? Your extraction yield must be $147/500 = 29.4\%$

Response: Thanks for attention. It typing error was corrected in main text.

“147 gram of hydroalcoholic extract was obtained from 500 gram of *C. fistula* plant, with a yield of 29.4% dry Ex.”

2- Regarding your GC/MS chromatogram, some peaks like those which are before minute 10, are not showed completely, as their tops are out of the figure. You must resize your chromatogram in a way that all tall peaks would be indicated completely.

Response: Thanks for attention. The chromatogram was changed to the best possible resolution.

3- Regarding Table 2, you must add a column for the reference retention indices for each compound. It is also needed to explain that how you have identified each

compound, either it was based RI values or mass spectra or both. And in each case you should provide detailed information, e.g. your mass library, etc.

Response: Thanks for your suggestion. It was corrected in main text

“Essential oil compounds and their retention index (calculated based on the retention time of n-alkanes) were identified based on the Wiley library and published articles.”

4- Regarding Table 3, it would be better if MIC and MBC results be showed in another separated table. In addition, the MBC for EO against *S. mutans* must be 3.125 rather than 3.25. Additionally, please provide more information about your positive controls.

Response: Thanks for your kind advice. Table was corrected in main text.

Microbial Strains		MIC (mg/mL)				MBC (mg/mL)			
		EO of R. × damascene	Ex of C. fistula plant	Ex/EO	Gel formulation	EO of R. × damascene	Ex of C. fistula plant	Ex/EO	Gel formulation
<i>C. albicans</i> PTCC 5027		1.56	3.125	3.125	3.125	1.56	3.125	3.125	6.25
<i>S. mutans</i> ATCC 1683		3.125	6.25	6.25	12.5	3.125	6.25	6.25	12.5
<i>A. viscos</i> PTCC1202		6.25	12.5	6.25	12.5	6.25	12.5	12.5	12.5

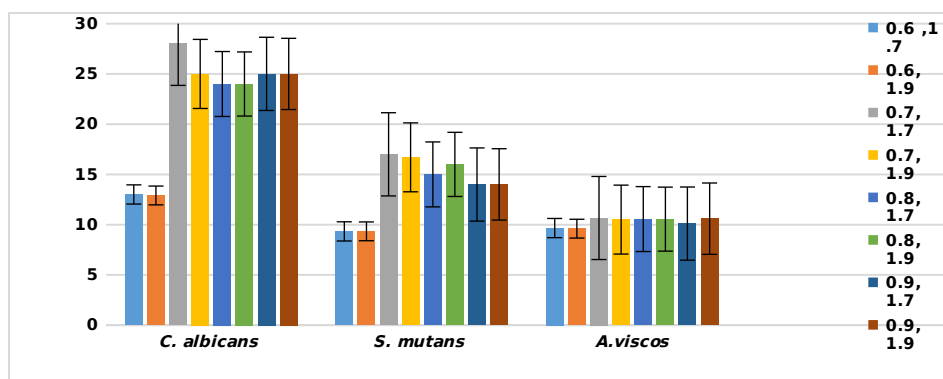
Abbreviations: *C. albicans*, candida albicans; *S. mutans*, Streptococcus mutans; *A. viscos*, Actinomyces viscosus; EO of Rosa × damascene, essential oil of Rosa × damascene; Ex of *C. fistula*, extract of *C. fistula*; NOF, Norfloxacin; FCZ, Fluconazole.

5- In figure 2, if you had three replicate for each test, it is better to indicate the bars with mean ± SD.

Response: Thanks for your kind advice. Figure 2 was corrected in main text.

Discussion:

1- “is infected with oral aphthous” could be incorrect, since aphthous is not an infectious disease necessarily. In addition, “is infected” refers to present time, and you should say has been infected, instead.



Response: Thank you for highlighting this point. It was corrected in main text.

“Up to 25% of the world population has been infected with oral aphthous more than once in their lifetime.”

2- You said that “we observed relatively high anti-microbial activity from *C. fistula* Ex”, while your MIC values are in the range of mg/ml, which generally are considered weak for antimicrobials.

Response: Thank you for your attention. We agree with you, but that was a typo that changed the meaning of the sentence. It was corrected in main text.

“Overall, a relatively higher antifungal role of *C. fistula* Ex was observed compared to antibacterial.”

3- The discussion part needs to be re-written, to resolve grammatical errors, etc.

Response: The discussion of the article was revised.

4- You said “the inhibitory activity was reduced from 28, 17, and 358 10.66 mm to 23, 14.66, and 7.5 mm for *C. albicans*, *S.mutans* and *A. viscos* respectively” while the numbers are describing zone of inhibition values.

Response: Thanks for your attention. It was corrected in main text

“Despite the observed additive anti-microbial effect of the Ex/EO mixture, when the mixture was combined with the gel, the zone of inhibition values decrease from 28, 17, and 10.66 mm to 23, 14.66, and 7.5 mm for *C. albicans*, *S.mutans* and *A. viscosus* respectively. However it was stronger compared to the EO or Ex individual.”

Independent Review Report, Reviewer 5

Changes in the final version of manuscript were highlighted by gray color

1. The level of innovation in the topic of the article is low.

Response: Thank you for your comment. In this study, we evaluated for the first time the antimicrobial activity of a herbal oral gel containing *C. fistula* Ex and *R. × damascene* EO for the treatment of RAS. In addition, the advantage of this study was the availability and procurement of both plants in Iran, which allows for more

appropriate investigations for future research. However we added and highlighted the reason for this study and innovation at the end of the background.

“In this study, for the first time, the antimicrobial activity of an herbal oral gel containing *C. fistula* Ex and *R. × damascene* EO for the successful treatment of RAS was evaluated. So that we can play a small role in alleviating the suffering of these patients.”

2. There is no accurate statistical analysis and strong scientific writing.

Response: We have made some changes to our analysis and writing based on the comments provided by the esteemed reviewers. We hope that these changes will be appropriate and approved.

Independent Review Report, Reviewer 5

Changes in the final version of manuscript were highlighted by green color

1) Conclusion should be expanded.

Response: Thanks for your kind advice. It was added in main text.

“The combination of Ex/EO showed relatively good antibacterial and antifungal activity against the tested bacterial and fungal strains, which requires further studies to isolate and highlight the main compounds more effective in antimicrobial activity. According to the present study, the gel formulation based on carbomer 940 with a completely uniform appearance, pH compatible with the oral cavity, suitable viscosity, acceptable dissolution and diffusion, maintaining stability and an expiration date of 65 days was the only ideal candidate with evident and acceptable anti-microbial performance in-vitro. However, focusing on the clinical use of this formulation due to genetic diversity and differences in pathogenic factors requires the design of a new in-vivo study in this field.”

2) Limitation and bias and more suggestion for further studies should be considered.

Response: Thanks for your suggestion. It was added in main text.

“This study has limitations. The study was conducted on standard strains, while microorganisms isolated from patients under clinical conditions may show different results, so it is recommended that this study be conducted as a comparative study between clinical isolates and standard strains

3) Should be differentiated from similar aphtus with other etiology in inclusion criteria and other aphtus be excluded

Thank you for your attention. In general, in this study, 3 standard microbial strains that could be the cause of the recurrent aphtus stomatitis were prepared and clinical cases were not included in this study. However, the word aphtus was replaced with recurrent aphtus stomatitis in all over the main text and highlighted by green color.

OPEN PEER REVIEW

Revision (1)