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OPEN PEER REVIEW

Piperine and Lavender Oil Enriched Nanostructured Lipid Carriers to Inhibit *Staphylococcus aureus* Biofilm

Omolbanin Shahraki, Maryam Sadat Nabavinia, Abdolmotaleb Tiba, Sara Daneshmand

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1 Original submission

1 comment · 4 Nov 2024

Referee 1 Reviewer

MAJOR REVISION 4 Nov 2024

Dear Editor
Have a nice day.
The author investigated Piperine and Lavender Oil Enriched Nanostructured Lipid Carriers to Inhibit Staphylococcus aureus Biofilm.
I would suggest reconsidering the manuscript for publication only after the following major revision.
1. Typing and grammatical errors need to be corrected.
2. The clarity of figures is low.
3. Report the SD value for all quantitative data.
4. What are the reasons for combining piperine and lavender in the formulation?
5. What is the meaning of the following sentences?
"The encapsulation efficiency of piperine in nanocarriers was measured by the indirect method; thus centrifuge (Hettich, Germany) and filter (Amicon, cut off =14KD) were utilized."
6. It is necessary to mention the source of the materials used.
7. In the following sentences, which software has been used?
"whilst the predicted numbers for size, PDI and zeta potential by the software were recorded 179, 0.234 and -23.4".
8. It is necessary to superimpose the figures.
9. The encapsulation percentage part should be more complete.
10. It is necessary to rewrite the conclusion section more completely.
11. Please explain more about the novelty of your research.

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.

Response to Decision Letter and Reviewer Comments

Journal: ***Jundishapur Journal of Natural Pharmaceutical Products***

Manuscript ID: ***156837***

Title of Paper: **Piperine and Lavender Oil Enriched Nanostructured Lipid Carriers to Inhibit *Staphylococcus aureus* Biofilm**

Authors: O S, M S N, A T, S D

Dear Editor,

We appreciate the insightful feedback provided during the review process. We have revised the manuscript accordingly and have included a detailed point-by-point response to the reviewers' comments below. Thank you and the reviewers for your valuable time and helpful suggestions. We hope the revised manuscript meets your approval. We look forward to your response.

Thank you

Yours faithfully,

S. D

Reviewer 1:

I would like to thank the authors for their preparation of nanostructured lipid carriers with piperine and lavender oil, as well as for their study of the antibacterial effects against *Staphylococcus aureus* biofilm, please edit the following comments before publishing the article:

Due to numerous writing and literary issues, the article should undergo comprehensive editing, and it would be beneficial to obtain certification from a reputable institution.

The authors would like to thank the valuable comments from the reviewer. The entire manuscript was edited carefully, and grammatical and typographical errors were corrected.

The method for preparing nanocarrier systems (NLCs) is not clearly explained; for example, the name of the preparation method and the detailed procedure should be provided. Additionally, the referenced literature does not adequately describe the applied method. It is advisable to cite a research article for reference number 26.

The paragraph was edited as follows (the newly added sentences are highlighted in red):

To synthesize NLCs, a hot homogenization and ultrasound method was used. In this procedure, lipids were heated 5-10 °C above the melting point of the solid lipid. The lipophilic materials containing piperine, stearic acid, Span 80, and lavender oil were poured after weighing into a tube. The aqueous solution of poloxamer 188 was prepared in another tube. Then, the tubes were placed separately in a Bain-Marie (Memert, Germany) to heat and melt the containing materials. After isothermalization, the aqueous phase was added to the lipid phase, and the obtained pre-emulsion was homogenized via an Ultratorx homogenizer (Heidolph, Germany) at 11500 rpm for 3 min. Following the breaking of the emulsion particles, ultrasonic waves were employed for 3 min with 70% on and 30% off cycles. After sonication, the dispersion was left overnight at room temperature to cool down and yield the formation of NLCs. The blank nanoparticles were also prepared by the same method as defined above without adding piperine (S. Dolatabadi et al. 2021).

Reference:

Dolatabadi, S., Karimi, M., Nasirizadeh, S., Hatamipour, M., Golmohammadzadeh, S., & Jaafari, M. R. (2021). Preparation, characterization and in vivo pharmacokinetic evaluation of curcuminoids-loaded solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs). Journal of drug delivery science and technology, 62, 102352.

As the authors utilized a centrifuge at 6000 rpm for nanoparticle separation, please provide a reliable reference that supports this condition.

The correct form is “6000 × g”(Rodenak-Kladniew, Islan, de Bravo, Durán, & Castro 2017)

Reference:

Rodenak-Kladniew, B., Islan, G. A., de Bravo, M. G., Durán, N., & Castro, G. R. (2017). Design, characterization and in vitro evaluation of linalool-loaded solid lipid nanoparticles as potent tool in cancer therapy. *Colloids and Surfaces B: Biointerfaces*, *154*, 123-132.

Further clarification is needed regarding the application of ethanol as a solvent for piperine in the preparation of the positive control, especially considering that methanol is known to be an antibacterial agent.

Methanol, DMF, and DMSO are solvents commonly used in *in vitro* experiments, especially when investigating the effects of poorly soluble compounds on cellular systems. Piperine, for instance, has low water solubility (1 g/25 L) but high solubility in alcohol (1 g/15 mL).

In this study, a 10% methanol in water solution was used to prepare the stock solution of piperine. This stock solution was then serially diluted, ensuring that the final concentration of methanol in the culture medium was only 0.08%. This concentration is lower than the antimicrobial concentration of methanol, which is 1% for the most sensitive strains. Given that Staphylococcus aureus is a relatively resistant strain, the low concentration of methanol in the culture medium is unlikely to interfere with the experimental results (Dyrda, Boniewska-Bernacka, Man, Barchiewicz, & Słota 2019).

Reference:

Dyrda, G., Boniewska-Bernacka, E., Man, D., Barchiewicz, K., & Słota, R. (2019). The effect of organic solvents on selected microorganisms and model liposome membrane. *Molecular biology reports*, *46*, 3225-3232.

The statistical methods used in the methods section should be explained in a separate paragraph.

The authors would like to thank the precise comment from the respected reviewer.

Statistical analysis:

The results were statistically analyzed using one-way analysis of variance (ANOVA) with GraphPad Prism (version 6.00 for Windows, GraphPad Software, La Jolla California USA). Differences were considered significant when the p-value was less than 0.05. All tests were performed in triplicate (n = 3).

In accordance with experimental design methodology, the independent variable(s) and their respective ranges should be presented in distinct tables.

The central composite design—through Design-Expert software was employed to investigate the influence of different factors including lipid percentage, lipid ratio, surfactant percentage, feed ratio of surfactants,

and the percentage of piperine as the medicinal substance. The levels of these parameters are listed in Table 1.

Table 1: Amounts of variables in the response surface optimization.

Level	-1	0	+1
Lipid (w/w%)	3	4	5
Lipid ratio (stearic acid/lavender oil)	3	4	5
Surfactant (w/w%)	1	2	3
Feed ratio of surfactants	0.5	1.25	2
Drug (w/w%)	1	3	5

Moreover, various tables and graphs should include fitted models and relevant statistical indicators, including p-values, as well as demonstrate the effects of independent variables on dependent variables.

The authors would like to thank the reviewer for the precise comment. The indicators, units and error values were added to the data.

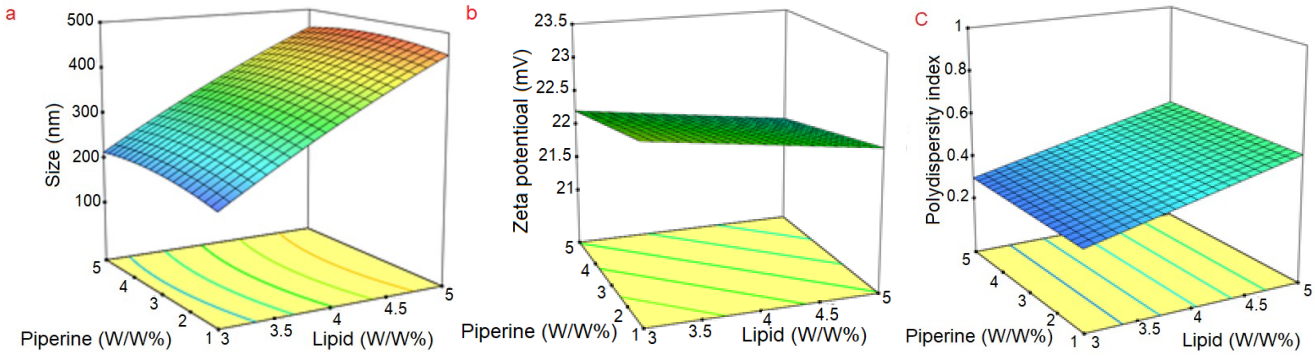


Figure1: The effect of piperine concentration and Lipid content on (A): particle size, (B): Zeta potential, (C): polydisperity index.

Figure 1a, Figure 1b, and Figure 1c indicate the response surface plots of particle size, zeta potential, and PDI with lipid and piperine content, respectively. It can be concluded that by increasing lipid and piperine content, PDI values increased, while a small change in zeta potential was observed. The most preferable formulation (No. 12), with a piperine concentration of 1%, a lipid concentration of 3%, a surfactant ratio of

2%, and a surfactant concentration of 3%, was selected and was repeated in triplicate to confirm the prediction results.

The empirical results for the formulation were 179.8, 0.416, and -23.8 for size, PDI, and zeta potential, respectively, while the corresponding predicted values were 181.2, 0.417, and -22.9. The two sets of data were compared, and the average relative error was calculated (Table 3). The obtained data showed that the optimization process of the formulation was effective.

If possible, please explain the release profile of piperine from the carrier system.

You raised an interesting point. We agree that evaluating the release profile of piperine from the carrier system provides valuable evidence on the application of our synthesized formulation. Since, the required materials are not available in our laboratory, performing this assay requires additional research budget and is very time-consuming.

The discussion section should include explanations for the obtained results and logical comparisons with findings from other studies.

In a research study, polysorbate-phospholipid micelles encapsulating piperine and azithromycin were synthesized to assess the oral absorption of piperine and its antibacterial effect. The results of optimization showed that 5.5% w/v of polysorbate yielded the highest solubilization of piperine. The results indicated that the highest and lowest zones of inhibition occurred at 100 mg/mL and 50 mg/mL, respectively (Kumari, Sharma, & Malviya 2020).

In another study, the authors reported piperine and gentamicin liposomes prepared by the dehydration-rehydration method. The antibacterial activity of the synthesized structures was assessed against methicillin-resistant Staphylococcus aureus bacteria. A decrease in the MIC and MBC values of gentamicin and piperine was observed upon the insertion of gentamicin into liposomes and liposomal combinations. Additionally, piperine liposomes exhibited efflux pump inhibition (Khameneh et al. 2015).

References:

Kumari, K., Sharma, P. K., & Malviya, R. (2020). Formulation-development and evaluation of polysorbate-phospholipid mixed micelles of piperine loaded with azithromycin. *Biointerface Res. Appl. Chem*, *10*, 6128-6138.

Khameneh, B., Iranshahy, M., Ghandadi, M., Ghoochi Atashbeyk, D., Fazly Bazzaz, B. S., & Iranshahi, M. (2015). Investigation of the antibacterial activity and efflux pump inhibitory effect of co-loaded piperine and gentamicin nanoliposomes in methicillin-resistant Staphylococcus aureus. *Drug development and industrial pharmacy, 41*(6), 989-994.

Finally, some references do not fully correspond with the content; therefore, a thorough revision and editing of the references are necessary.

We would like to thank the reviewers for their valuable comments and suggestions.

The references were updated.

Reviewer 2:

This manuscript presents a study on developing nanostructured lipid carriers (NLCs) containing piperine and lavender oil for inhibiting *Staphylococcus aureus* biofilm. The study seems attractive but it suffers from some major problems. Then, I recommend the authors to carefully check and correct the mentioned issues:

1. Page 2, Lines 41-43: The authors state that "NLCs owing to their incomplete crystal structure, have a higher loading capacity and can prevent the drug by virtue of the presence of liquid lipids and by avoiding lipid crystallization during the periods of production and maintenance." This statement must be supported by appropriate references and analysis of the formulation to prove that the NLCs have undergone lipid crystallization.

Solid Lipid Nanoparticles (SLNs) show some challenges. Their high water content ranging from 70% to 99.9%, can cause issues for their presence into final products. Additionally, their low drug loading capacity is a significant problem. This is due to the affinity of lipids to undergo recrystallization over time. During SLN production, lipids initially form in higher energy states (α or β’ modifications). However, upon storage, these particles can make the more stable form with lower energy of β form. Increasing organization reduces the available space for drug loading, as drug molecules often place in the defects or interstitial spaces within the lipid matrix. To overcome the limitations of SLNs, another class of lipid nanoparticles, called Nanostructured Lipid Carriers (NLCs), has been developed. NLCs are composed of a mixture of solid and liquid lipids, generally in a ratio of 70:30 to 99.9:0.1. The presence of liquid lipids decreases the overall melting point of the system, making several advantages, such as lower drug discharge during storage and higher drug loading capacity. The presence of liquid lipids in NLCs leads to a less organized lipid matrix,

cause more spaces for drug molecules to locate. However, lipophilicity and molecular structure are main factors for a drug to reside within an SLNs or NLCs system (Borges, de Freitas, Mateus, Fernandes, & Oliveira 2020).

Reference:

Borges, A., de Freitas, V., Mateus, N., Fernandes, I., & Oliveira, J. (2020). Solid lipid nanoparticles as carriers of natural phenolic compounds. *Antioxidants*, *9*(10), 998.

2. Page 3, Lines 84-86: The method for determining encapsulation efficiency is not clearly described. The authors should provide more details on the centrifugation process and how the supernatant was analyzed.

The encapsulation efficiency of piperine in nanocarriers was measured using an indirect method involving centrifugation (Hettich, Germany) and filtration (Amicon, cut-off = 14 kDa). Briefly, the filter device was filled with the NLCs nanosuspension and centrifuged at 6000 × g for 34 min. The encapsulated piperine remained in the filter device, while the free form passed through the filter. The ultra-filtrate solution was then analyzed to determine the amount of unloaded piperine.

Standard solutions of piperine were prepared at concentrations of 1, 2, 5, 10, and 20 µg/mL and their absorbance at 342 nm (the maximum wavelength of piperine) was measured using UV-Vis spectroscopy (J. E. N. Dolatabadi, Hamishehkar, Eskandani, & Valizadeh 2014).

Dolatabadi, J. E. N., Hamishehkar, H., Eskandani, M., & Valizadeh, H. (2014). Formulation, characterization and cytotoxicity studies of alendronate sodium-loaded solid lipid nanoparticles. *Colloids and Surfaces B: Biointerfaces*, *117*, 21-28.

3. Page 3, Lines 95-97: The FTIR spectroscopy method lacks detail. The authors should specify the range of wavenumbers scanned and the resolution used. Also, you need to present it as stacked spectra for easy comparison and analysis.

FTIR spectra were acquired using a KBr pellet method. A FTIR spectrophotometer (IR PRESTIGE SHIMADZU, Japan) was employed with a 16 cm^{-1} resolution, 10 scans, and a spectral range of 4000–500 cm^{-1} at ambient temperature.

The spectra are represented as the stack form.

4. Page 4, Lines 123-125, Comment: The preparation of bacterial suspension is not adequately described. The authors should provide information on how the 0.5 McFarland standard was prepared and verified.

2.6. Preparation of 0.5 McFarland standard

$BaSO_4$ standard (known as McFarland solution) was applied to standardize the concentration of bacterial inoculation and to conduct the microbial sensitivity test. To prepare the target $BaSO_4$ solution, 0.5 ml of barium chloride ($BaCl_2$) (0.048 M) was added to 99.5 ml of H_2SO_4 (0.18 M) and the acquired solution was mixed completely. The accurate density of standard turbidity was measured using a spectrophotometer (Perkinelmer, Germany) at 625 nm wavelength, and its absorption should be between 0.08 and 0.13, while the observed optical absorption was 0.09 λ.

Six mL of $BaSO_4$ was poured into tubes with lids of the same size as the bacterial suspension tubes. The tube lids were closed tightly and placed in the dark at room temperature. A 0.5 McFarland standard solution has a special turbidity (equal to 1.5×10^8 cfu/mL of the organism). Then, two or three colonies of bacteria are transfered to tubes containing 3 ml of sterile physiological serum (distilled water or NB liquid medium) after 48 h of bacteria culture. Finally, they are monitored by a spectrophotometer, expecting the absorption value between 0.08 and 1 at a wavelength of 625 nm.

5. Page 5, Table 1: The table lacks units for several parameters. The authors should include appropriate units for all measurements.

Thanks for your precise comment. The units were added.

6. Page 6, Lines 187-189: The authors claim that "NLC-Pip has a greater effect on the Staphylococcus aureus biofilm than free piperine and also, the nanoparticle without piperine." However, they do not provide statistical analysis to support this claim.

According to Figure 4, a significant relationship was observed between the encapsulation of drug molecules via NLCs formulation and decrease in the amount of ODr.

The data of spectrophotometric absorption related to biofilm production implied that in the NLC-Pip, the amount of biofilm formation had reached zero. As seen in Figure 4, in the NLC-Pip, the biofilm had almost disappeared. For gentamicin, the rate of biofilm formation was approximately zero, and there was no significant level of difference between NLC-Pip and gentamicin as a control drug. In contrast, free piperine

and piperine-free NLCs showed the maximum optical density ratio (ODr), displaying the highest biofilm formation (p-value < 0.001 and p-value < 0.01, respectively), as compared to the synthesized formulation. Specifically, NLC-Pip demonstrated an enhancement in the antimicrobial efficacy of piperine by approximately five-fold in comparison to its free form.(Langeveld, Veldhuizen, & Burt 2014). The most pronounced effect was detected in the NLCs-Pip formulation because the formulation can effectively bind to the bacterial surface and improve the release of piperine (Akbarzadeh et al. 2021).

Akbarzadeh, I., Shayan, M., Bourbour, M., Moghtaderi, M., Noorbazargan, H., Eshrati Yeganeh, F., Saffar, S., et al. (2021). Preparation, optimization and in-vitro evaluation of curcumin-loaded niosome@ calcium alginate nanocarrier as a new approach for breast cancer treatment. *Biology*, *10*(3), 173.

7. Page 9, References: Several references are outdated (pre-2015). The authors should include more recent literature to support their claims and demonstrate awareness of current research in the field.

Thanks for your precise comment. The references were updated.

8. Throughout the manuscript: The English language usage needs significant improvement. There are numerous grammatical errors and awkward phrasings that make the text difficult to follow in places.

The manuscript was entirely edited and the issues were corrected.

9.- Please check spelling carefully. Including: periods, commas, spaces, etc.

The authors would like to thank the valuable comments from the reviewer. The entire manuscript was edited carefully, and grammatical and typographical errors were corrected.

Reviewer 3:

Dear Editor

Have a nice day.

The author investigated Piperine and Lavender Oil Enriched Nanostructured Lipid Carriers to Inhibit *Staphylococcus aureus* Biofilm.

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

1. Typing and grammatical errors need to be corrected.

The authors would like to thank the valuable comments from the reviewer. The entire manuscript was edited carefully, and grammatical and typographical errors were corrected.

2. The clarity of figures is low.

The FTIR spectra are replaced with higher quality ones.

3. Report the SD value for all quantitative data.

The SD values were added to table 3.

4. what are the reasons for combining piperine and lavender in the formulation?

The below paragraph was added to the introduction section:

Various investigations have elucidated the presence of a moderate synergistic effect between essential oils and pharmaceutical agents, notably antibiotics, which is predominantly attributable to the membrane interactions of the constituents of essential oils; in this regard, essential oils present a compelling alternative for mitigating antibiotic utilization (Langeveld et al. 2014) .Considering that no piperine/lavender oil combination has been reported to date, the aim of this study was to examine in vitro interactions between lavender oil encapsulated within NLCs and piperine.

This sentence was added to section 3.7.

Specifically, NLC-Pip demonstrated an enhancement in the antimicrobial efficacy of piperine by approximately five-fold in comparison to its free form.(Langeveld et al. 2014).

Reference:

Langeveld, W. T., Veldhuizen, E. J., & Burt, S. A. (2014). Synergy between essential oil components and antibiotics: a review. *Critical reviews in microbiology*, *40*(1), 76-94.

5. What is the meaning of the following sentences?

"The encapsulation efficiency of piperine in nanocarriers was measured by the indirect method; thus centrifuge (Hettich, Germany) and filter (Amicon, cut off =14KD) were utilized.

The text was edited for clarity as follows:

The encapsulation efficiency of piperine in nanocarriers was measured using an indirect method involving centrifugation (Hettich, Germany) and filtration (Amicon, cut-off = 14 kDa). Briefly, the filter device was filled with the NLCs nanosuspension and centrifuged at 6000 × g for 34 min. The encapsulated piperine remained in the filter device, while the free form passed through the filter. The ultra-filtrate solution was then analyzed to determine the amount of unloaded piperine.

Standard solutions of piperine were prepared at concentrations of 1, 2, 5, 10, and 20 µg/mL and their absorbance at 342 nm (the maximum wavelength of piperine) was measured using UV-Vis spectroscopy (J. E. N. Dolatabadi et al. 2014).

Dolatabadi, J. E. N., Hamishehkar, H., Eskandani, M., & Valizadeh, H. (2014). Formulation, characterization and cytotoxicity studies of alendronate sodium-loaded solid lipid nanoparticles. *Colloids and Surfaces B: Biointerfaces*, *117*, 21-28.

6. It is necessary to mention the source of the materials used.

Lavender oil and piperine powder were purchased from Barijessence (Iran) and Gol Exir Pars (Iran), respectively. Stearic acid, Tween and Span 80 were obtained from Merck (Germany)**.** All culture media involving nutrient broth (NB), Mueller Hinton broth (MHb), blood agar (BA) and tryptic soy broth (TSB), $BaSO_4$ and H_2SO_4 were supplied by Merck (Germany). *Staphylococcus aureus* strain in the form of lyophilized vials was provided from Arian Mehr Center (Iran). DMSO was purchased from Dae jung (Korea). Gentamycin was provided by Zahravi Pharmaceutical Company (Iran).

7. In the following sentences, which software has been used?

"whilst the predicted numbers for size, PDI and zeta potential by the software were recorded 179, 0.234 and -23.4".

Design-Expert 10.0.3 software (Stat-Ease Inc., Minneapolis, MN, USA)

8. It is necessary to superimpose the figures.

The FTIR spectra were superimposed as figure 3a, 3b, 3c.

9. The encapsulation percentage part should be more complete.

The loading percentage was estimated at about 99% using the indirect method (SD = 4.15%, n = 3). To date, many different drugs and natural compounds have been formulated in lipid formulations such as NLCs and SLNs. One of the main characteristics in achieving high loading efficiency is the solubility of the drug in the lipid matrix. The preparation method is the other major factor. Another probable reason for high entrapment efficiency is the usage of lavender oil in the NLCs structure, which creates lattice imperfections where the molecules can be inserted (Borges et al. 2020). The regression equation for piperine was A = 0.083C + 0.084, and a linear correlation was observed in the range of 1-20 µg/mL (R^2 = 0.99).

10. It is necessary to rewrite the conclusion section more completely.

The anti-biofilm bioavailability of piperine was significantly improved by the formulation of piperine-NLCs. The formulation was prepared using Tween and Span as stabilizers, stearic acid as solid lipid, and lavender oil as liquid lipid, and a spherical nanosized formulation with a high level of entrapment

efficiency was obtained. According to the conducted studies and the obtained results concerning morphology, size, zeta potential, and IR spectroscopy, it is confirmed that the formulation of NLC-Pip with lavender oil is a suitable solution for targeted drug delivery that can improve the effectiveness of piperine and reduce its side effects. Moreover, the antimicrobial activity of NLC-Pip corroborates that these systems are potentially effective agents against bacterial biofilm, as the piperine-NLCs showed a five-fold higher anti-biofilm activity compared to free piperine. In accordance with the above-mentioned results, NLCs may deliver piperine with sustained release, while formulated with the essential oil of lavender, whose intrinsic therapeutic properties increase piperine's anti-biofilm efficiency.

11. Please explain more about the novelty of your research.

The below paragraph was added to the introduction section:

Various investigations have elucidated the presence of a moderate synergistic effect between essential oils and pharmaceutical agents, notably antibiotics, which is predominantly attributable to the membrane interactions of the constituents of essential oils; in this regard, essential oils present a compelling alternative for mitigating antibiotic utilization (Langeveld et al. 2014) .Considering that no piperine/lavender oil combination has been reported to date, the aim of this study was to examine in vitro interactions between lavender oil encapsulated within NLCs and piperine.

The below paragraph was added to section 3.7.

Numerous reports have examined the interplay between essential oils and antibacterial substances, including antibiotics. In the management of infections, there exist multiple scenarios where the co-administration of two or more antibiotics is imperative (Valcourt et al. 2016). Indeed, the implementation of combined antibiotic therapy has been employed to combat multi-resistant bacterial strains. Given their mechanisms of action, essential oils present a promising adjunctive option to be utilized alongside conventional antibiotics.

Reference:

Langeveld, W. T., Veldhuizen, E. J., & Burt, S. A. (2014). Synergy between essential oil components and antibiotics: a review. *Critical reviews in microbiology, 40*(1), 76-94. doi:https://doi.org/10.1016/j.colsurfb.2017.03.021

Valcourt, C., Saulnier, P., Umerska, A., Zanelli, M., Montagu, A., Rossines, E., & Joly-Guillou, M.-L. (2016). Synergistic interactions between doxycycline and terpenic components of essential oils encapsulated within lipid nanocapsules against gram negative bacteria. *International journal of pharmaceutics, 498*(1-2), 23-31.

2 Revision 1

1 comment · 5 Dec 2024

Referee 1 Reviewer

MAJOR REVISION 5 Dec 2024

Dear Editor
Have a nice day.
There are no attached files.