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OPEN PEER REVIEW

Sb(V) Kaempferol and Quercetin Derivative Complexes: Synthesis, Characterization and Antileishmanial Activities

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About this report

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

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1 Original submission

0 comments

No public comments in this round.

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.

Dear Editor

Regards for valuable comments, they were addressed accordingly and highlighted in the text. In addition, one of the compounds, kaempferol diacetate (KDA, 4), was removed from the study due to the ambiguity in its structure.

Q1: Please do NOT write the authors' full names in the reply to the reviewers' file, and submitted files because we want to make our review process as blind as possible. We suggest writing only the first letter of your first name and last name. Example: In the acknowledgment part, instead of Sara Hamilton, you can write S.H.

Response: The author name was removed from response to reviewers file

Q2: Figure(s) of the supplementary file is not mentioned in the text correctly. Please, mention the supplementary file in the text consecutively.

Response: I have corrected all the figure captions in the supplementary file consecutively as Fig. 1s to Fig.28s. The following phrase was also added to the main manuscript text in result section as follows:

“NMR, IR, and mass spectra are available in the supplementary file (Fig. 1s-Fig.28s).”

Associate Editor 1:

Dear Author

This is with reference to an article entitled: Sb (V) Kaempferol and Quercetin derivative complexes: synthesis, characterization and antileishmanial activities which has been submitted for possible publication in Iran J Pharm Res.

The submission ID is: 128379. Please refer to this number in any future correspondence. During the review process, you can keep track of the status of your manuscript by accessing the journal's website. Please note that submitting a revision of your manuscript does not guarantee eventual acceptance and that your revision should be subject to review by the referees. Please include a point-by-point response to the editor and highlight the changes made during revision by giving the text a yellow background and resubmit again with the submission ID 128379.

Q1- Minor English editing is required in your manuscript.

Response: The English and grammar were revised accordingly.

Q2- The structured abstract is necessary for the research Article in Iran J Pharm Res. Correct this part according to “Instruction for author”

Response: the abstract structure was corrected according to the IJPR Instruction for the authors.

Q3- The abstract is too long and needs to summarize.

Response: The abstract was summarized and written concisely accordingly.

Q4- The ‘Introduction part” should be extended especially about the importance and the beginning study about Sb (V) Kaempferol and Quercetin complexes

Response: The introduction part was extended by the explanation of flavonol in antileishmanial drug discovery, accordingly.

Q5- Supply the supplementary file, including analysis data (NMR, Mass, UV, IR)

Response: supplementary file including analysis data (NMR, Mass, UV, IR) was implemented.

2 Revision 1

2 comments · 20 Jun 2022 – 25 Jun 2022

Referee 1 Reviewer

MAJOR REVISION 20 Jun 2022

In this study, some derivatives of quercetin and kaempferol in complex with Sb were synthesized and evaluated against Leishmania major. The rationale behind the design of these compounds seems very well planned as the authors implement two different toxic agents against this parasite. Also, the discussion section was well written. However, there are lots of grammatical errors and typos which need serious attention. Thus, this manuscript needs major revision and could be published after these errors are fixed. I strongly recommend having your manuscript checked and corrected by a native English-language editing service and providing the certificate.

My comments are as follows:

1. line 9: “acetic anhydride acid” should be changed to “acetic anhydride”
2. line 11: “substitution” should be deleted
3. line 14: “mass” should be changed to ESI-MS. Please apply this change to all occurrences of the word “mass”.
4. line 21: “more” should be changed to “the highest”
5. line 24: rewrite the sentence as follows: All flavonol Sb (V) complexes showed higher activity compared with meglumine antimonate in anti-amastigote effect.
6. line 27: “compared to” should be changed to compared with
7. keywords should be written in alphabetical order
8. In the introduction section: each topic should be discussed in a separate paragraph rather than in consecutive sentences. I also suggest illustrating the structures of the mentioned compounds, their mechanisms of anti-leishmanial activity, or the general structures of the novel compounds in a figure.
9. line 53: “through their complex study” should be changed to “through studying their complex formation”
10. all numbers of atoms in formulas should be written as subscripts
11. Please write the full forms of abbreviations when they are mentioned for the first time in the text.
12. line 77: 60.54%
13. In Figure 1: Please add the yields of each step to the general scheme.
14. Please use more up-to-date references published after 2019.

Referee 2 Reviewer

MINOR REVISION 25 Jun 2022

In this article, the authors have tried to introduce a group of new derivatives resulting from the incorporation of tin cations and powerful antioxidant molecules such as quercetin and Kaempferol. The authors have corrected some of the specific flaws in their article based on the comments of the Honorable First Reviewer. It seems that this article can be published in the journal after a brief review.

1. Please provide a detailed list of all abbreviations in the text, along with their full forms in parentheses at first mention. Whenever an abbreviation appears for the first time in the text, its full form should be written as well.

2. It is suggested that the authors refer to some studies on other biological properties of flavonoids at the beginning of their manuscript; for instance, the following three references are strongly suggested:

A) Tasdemir D, Kaiser M, Brun R, Yardley V, Schmidt TJ, Tosun F, Rüedi P. Antitrypanosomal and antileishmanial activities of flavonoids and their analogues: in vitro, in vivo, structure-activity relationship,

and quantitative structure-activity relationship studies. Antimicrob Agents Chemother. 2006 Apr;50(4):1352-64.

B) Noori S, Rezaei Tavirani M, Deravi N, Mahboobi Rabbani MI, Zarghi A. Naringenin Enhances the Anti-Cancer Effect of Cyclophosphamide against MDA-MB-231 Breast Cancer Cells Via Targeting the STAT3 Signaling Pathway. Iran J Pharm Res. 2020 Summer;19(3):122-133.

C) Mahboubi Rabbani, S. M. I.; Zarghi, A., Selective COX-2 inhibitors as anticancer agents: a patent review (2014-2018). Expert Opinion on Therapeutic Patents 2019, 29 (6), 407-427.

3. Stronger evidence appears to be needed to hypothesize that quercetin and camphorol may facilitate the reduction of antimony ions to a lower oxidation form, thereby helping to improve the effectiveness of antimony against Leishmania parasites. Do the authors have reliable spectroscopic data to support their hypothesis? Alternatively, could a similar technique be suggested to confirm the conclusion?

3

Revision 2

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.

Dear Editor

Regards for valuable comments, the article was corrected, and responses to the comments were given point by point as follows. In addition, the grammar and English of the text were checked and corrected precisely.

Reviewer 1:

In this study, some derivatives of quercetin and kaempferol in complex with Sb were synthesized and evaluated against Leishmania major. The rationale behind the design of these compounds seems very well planned as the authors implement two different toxic agents against this parasite. Also, discussion section was well written. However, there are lots of grammatical errors and typos which need serious attention. Thus, this manuscript needs major revision and could be published after fixing these errors. I strongly recommend to have your manuscript checked and corrected by a native English edit service and to provide the certificate.

Response: The English and grammar of the manuscript were checked and corrected by one of the expert authors in English, and also it was checked by Grammarly software. The comments were also corrected point by point and highlighted in text as follows:

My comments are as follows

1. line 9: “acetic anhydride acid” should change to “acetic anhydride”

Response: It was corrected.

2. line 11: “substitution” should be deleted

Response: It was corrected.

3. line 14: “mass” should change to ESI-MS. Please apply this change to all mass words.

Response: It was corrected in the whole text.

4. line 21: “more” should change to “the highest”

Response: It was corrected.

5. line 24: rewrite the sentence as follows: All flavonol Sb (V) complexes showed higher activity compared with meglumine antimonate in anti-amastigote effect.

Response: It was rewritten, accordingly.

6. line 27: “compared to” should change to compared with

Response: It was corrected.

7. keywords should be written in alphabetical order

Response: Keywords were rewritten in alphabetic order, accordingly.

8.1 In introduction section: each topic should be discussed in different paragraphs not in following sentences.

Response: Different paragraphs were separated, accordingly.

8.2. And I also suggest to illustrate the structures of mentioned compounds or their mechanism of anti-leishmanial activity or the general structures of the novel compounds in a figure.

Response: In the introductuin section, we have added a new figure to illustrate the structures of mentioned flavonoids entitled “Flavonoids with leishmanicidal activity by the order of activities. a) flavon-3-Ols, b) flavones (13).”

Figure 1. Flavonoids with leishmanicidal activity by the order of activities. a) flavon-3-ols, b) flavones (13).

9. line 53: “through their complex study” should change to “through studying their complex formation”

Response: It was corrected.

10. all numbers of atom in formula should be written subscript

Response: All of the numbers of atoms in the formula were written subscript, accordingly.

11. Please write the full version of abbreviations when mentioned for the first time in the text.

Response: Full versions of abbreviations were added to text whenever they appeared for the first time.

12. line 77: 60.54%

Response: It was corrected.

13. In Figure 1: Please add yields of each step to the general scheme.

Response: yields of each step were added as follows. In the case of steps c, and d they were following each other. Therefore, the yield of step d was implemented. In step e, because of the fact that it is complexation and two isomers cis and trans were obtained, we omitted the yield percentage.

Figure 2. Reagents and conditions for the synthesis of Sb (V) 7-O-paramethylbenzyl quercetin complex: (a) Anhydride acetic (Ac2O), N-Methyl-2-pyrrolidone (NMP), 140 °C, 8 h, Yield: 81.7 % (b) Thiophenol, imidazole, NMP, −10°C, 1 h, Yield: 41.1 % (c) 4-methylbenzyl chloride, Na2CO3, acetone, room tempreture, 3 h. (d) NH3/MeOH (2M), 0 °C, 5 min, Yield: 35.2 % (e) SbCl5, glacial acetic acid, MeOH, 30 min.

14. Please use more updated references after 2019.

Response: The following references were added, accordingly.

14. Noori S, Rezaei Tavirani M, Deravi N, Mahboobi Rabbani MI, Zarghi A. Naringenin Enhances the Anti-Cancer Effect of Cyclophosphamide against MDA-MB-231 Breast Cancer Cells Via Targeting the STAT3 Signaling Pathway. Iran. J. Pharm. Res. 2020;19(3):122-33

15. Ortiz S, Vásquez-Ocmín PG, Cojean S, Bouzidi C, Michel S, Figadere B, Grougnet R, Boutefnouchet S, Maciuk A. Correlation study on methoxylation pattern of flavonoids and their heme-targeted antiplasmodial activity. Bioorg. Chem. 2020; 104:104243.

20. Barbosa VT, de Menezes JB, Santos JCC, de Assis Bastos ML, de Araújo-Júnior JX, do Nascimento TG, et al. Characterization and stability of the antimony-quercetin complex. 2019;9(3):432-8.

Reviewer 2:

In this article, the authors have tried to introduce a group of new derivatives resulting from the incorporation of tin cations and powerful antioxidant molecules such as quercetin and Kaempferol. The authors have corrected some of the specific flaws of their article based on the note of the Honorable First Judge. It seems that this article can be published in the journal after a brief review.

1. Please provide a detailed list of all abbreviations in the text along with the full form in parentheses in for the first time. Whenever the abbreviation appears for the first time in the text, its full form should be written as well.

Response: The abbreviation list was added, accordingly after the abstract as follows:

Abbreviations: Ac2O: Acetic anhydride; DMSO-d6: Deuterated dimethyl sulfoxide; DFT: Density Functional Theory; FBS: Fetal Bovine Serum; FTIR: Fourier Transform Infrared; KDA: Kaempferol-3, 4′-diacetate; K-Sb: Sb (V) Kaempferol complex; KTA: Kaempferol-3,7, 4′-triacetate; NMP: N-Methyl-2-Pyrrolidone; NMR: Nuclear Magnetic Resonance; ESI mass: Electrospray Ionization mass; Nrf2/HO-1: Nuclear factor erythroid 2-related factor 2/Heme Oxygenase 1; PBS: Phosphate-buffered saline; PM3: Parametric Method 3; QPA: Quercetin-3,5,7, 34′,′-pentacetate; QPMB: 7-O-paramethylbenzyl quercetin; QPNB: 7-O-paranitro benzyl quercetin; QPMB-Sb: Sb (V) 7-O-Paramethylbenzyl quercetin complex; QPNB-Sb: Sb (V) 7-O-Paranitrobenzyl quercetin complex; Q-Sb: Sb (V) Quercetin complex; QTA: Quercetin 3,5,3′4,′-tetraacetate; RM: Reaction Mixture; ROS: Reactive Oxygen Species; Sb (V): Antimony pentavalent; TLC: Thin-Layer Chromatography;

2. It is suggested that the authors refer to some studies performed regarding other biological properties of flavonoids at the beginning of their manuscript; for instance, three following references are strongly suggested:

A) Tasdemir D, Kaiser M, Brun R, Yardley V, Schmidt TJ, Tosun F, Rüedi P. Antitrypanosomal and antileishmanial activities of flavonoids and their analogues: in vitro, in vivo, structure-activity relationship, and quantitative structure-activity relationship studies. Antimicrob Agents Chemother. 2006 Apr;50(4):1352-64.

B) Noori S, Rezaei Tavirani M, Deravi N, Mahboobi Rabbani MI, Zarghi A. Naringenin Enhances the Anti-Cancer Effect of Cyclophosphamide against MDA-MB-231 Breast Cancer Cells Via Targeting the STAT3 Signaling Pathway. Iran J Pharm Res. 2020 Summer;19(3):122-133.

C) Mahboubi Rabbani, S. M. I.; Zarghi, A., Selective COX-2 inhibitors as anticancer agents: a patent review (2014-2018). Expert Opinion on Therapeutic Patents 2019, 29 (6), 407-427.

Response: We have added the following text in the introduction, accordingly.

In a study by Tasdemir on 105 phenolic compounds, Most of the flavones and flavon-3-ols showed remarkable antileishmanial activity. In flavon-3-oLs, 3,7,3’,4’-flavone (fisetin), 3-hydroxyflavone, and quercetin, and in flavones luteolin showed potent activities respectively with IC50 values of 0.6-1.0 µg/ml (13). Less activities of flavanes with saturated (Δ2,3) derivatives like naringenin, implied the significance of the C-2 and C-3 double bond (13). Although this change may lead to the enhancement of other effects of naringenin (14). Flavanoids showed also other biological activities like antioxidant, immunomodulatory, cytotoxic or synergic effects against other protozoa or different cancer cells (13-16).

13. Tasdemir D, Kaiser M, Brun R, Yardley V, Schmidt TJ, Tosun F, Rüedi P. Antitrypanosomal and antileishmanial activities of flavonoids and their analogues: in vitro, in vivo, structure-activity relationship, and quantitative structure-activity relationship studies. Antimicrob. Agents Chemother. 2006; 50(4):1352-64.

14. Noori S, Rezaei Tavirani M, Deravi N, Mahboobi Rabbani MI, Zarghi A. Naringenin Enhances the Anti-Cancer Effect of Cyclophosphamide against MDA-MB-231 Breast Cancer Cells Via Targeting the STAT3 Signaling Pathway. Iran. J. Pharm. Res. 2020;19(3):122-33

15. Ortiz S, Vásquez-Ocmín PG, Cojean S, Bouzidi C, Michel S, Figadere B, Grougnet R, Boutefnouchet S, Maciuk A. Correlation study on methoxylation pattern of flavonoids and their heme-targeted antiplasmodial activity. Bioorg. Chem. 2020; 104:104243.

16. Yang B, Liu H, Yang J, Gupta VK, Jiang Y. New insights on bioactivities and biosynthesis of flavonoid glycosides. Trends Food Sci. Tech. 2018;79:116-24.

3. Stronger evidence appears to be needed to hypothesize that quercetin and camphorol may facilitate the reduction of antimony ions to a lower oxidation form, thereby helping to improve the effectiveness of antimony against Leishmania parasites. Do the authors have reliable spectroscopic data to support their hypothesis? Or else, may one similar technique been suggested to confirm the conclusion?

Response: We agree with the respected reviewer. This part needs more evidence to hypothesize that quercetin and Kaempferol may facilitate the reduction of antimony ions to a lower oxidation form. Therefore, we omitted this part of the conclusion from the text. Instead, we added a new paragraph “Probably, inside the host macrophages, by breaking down the complex into antimony and quercetin or kaempferol analogs, the observed antiparasitic effects can be related to both Sb(V)/Sb(III) conversion and flavonoid antileishmanial activities. However, new approaches need to be done on the antiparasitic effects of flavonol antimony (V) complexes to elucidate their exact mechanism of action.”

3 Revision 2

0 comments

No public comments in this round.

4

Revision 3

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.

Dear Editor

Regards for the useful comments. We have revised the manuscript according to the reviewer's points. The changes are highlighted in the text.

Reviewer 1:
My comments on this manuscript were fully addressed by the authors and the English has been improved.
This paper is accepted for publication.
Reviewer 2:
1. It is suggested that respected authors replace some of their old references with newer references that have been written since 2017.

Response: Nine of the references were updated. However, two of the old references are still required to be cited.

2. Argue a little more about the importance of leishmania treatment considering that the prevalence of this disease has become much less than in the past. Why should we seek to design new drugs for leishmaniasis today?

Response: This part was added in the introduction part accordingly as follows:

"Leishmaniasis is caused by an intracellular parasite of the genus Leishmania which is found in two manifestations, visceral and cutaneous. It is the third most important arthropod-borne disease that has been widely reported in more than 89 countries and more than 350 million people are at risk. The estimated number of infected people is 12 to 15 million with approximately 2 million new cases annually, of which approximately 0.5 million have visceral leishmaniasis and 1.5 million have cutaneous leishmaniasis. In terms of country distribution, more than two-thirds of new leishmaniasis cases have been reported in six countries, including Brazil, Colombia, Afghanistan, and Iran (1, 2).

In the past years, effective drugs were discovered against Leishmania, but, it is currently a neglected parasitic disease, which its drug toxicity, the need for Injectable administration, high failure rate, and the emergence of drug resistance have faced serious problems with its current treatments. Therefore, a sustained effort to discover new drugs that do not have high toxicity or failure in treatment is necessary to effectively control the disease."

Associate Editor's Comments:

Associate Editor 1:
Dear Author
This is with reference to an article entitled: Sb (V) Kaempferol and Quercetin derivative complexes: synthesis, characterization and antileishmanial activities which has been submitted for possible publication in Iran J Pharm Res
The submission ID is: 128379
Reviewer 2 has two comments to improve the manuscript. This paper is accepted for publication after this correction.
1. It is suggested that respected authors replace some of their old references with newer references that have been written since 2017.
2. Argue a little more about the importance of leishmania treatment in the "introduction section" considering that the prevalence of this disease has become much less than in the past. Why should we seek to design new drugs for leishmaniasis today?
Please include a point-by-point response to the reviewers and highlight the changes made during revision by giving the text a yellow background.
Thank you for submitting your manuscript to Iran J Pharm Res.
Sincerely,
Iran J Pharm Res Editorial Office

4 Revision 3

0 comments

No public comments in this round.