Author’s response to reviews

Title: Synthesis of crocetin derivatives and their potent inhibition in multiple tumor cells proliferation and inflammatory property of macrophage

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Author's response to reviews:

Dear Editor in Chief,

Thank you very much for providing us an opportunity to revise our manuscript entitled “Synthesis of crocetin derivatives and their potent inhibitory effects in multiple tumor cells proliferation and anti-inflammation in macrophage” (ID: BCAM-D-19-00111). We thank also the reviewers for their valuable time and efforts to read the manuscript and make the comments and suggestions. All the concerns and issues raised by the reviewers are addressed and listed below. All the revisions of the manuscript are highlighted with red color for the ease of review. We wish this revised version can be acceptable for publication in this journal.

On behalf of all the authors,

With kindest regards.

Li-Hua Peng, Ph.D, Associate Prof.
Editor

Comments:

As I received the comments from two reviewers, one reject and one major revise, BUT I read the draft carefully, I think the work is fine, so I hope you could revise your draft carefully and give me final chance to decide your work published or not.

Response: Thank you very much for your kind comment. We have revised our draft and checked the English writing carefully. All the revised contents were highlighted in blue for your kind reference.

Reviewer: 1

Comments:

The contents and methods of the study reported in this paper are very similar to that published by the author (Reference [10]), except that the synthesized crocetin derivatives are slightly different from that in the published article. So I think that this article is not suitable to BMC Complementary and Alternative Medicine.

Response: Thanks for your comments. Because the biological assays that have been used to indicate the anti-cancer and anti-inflammation activities of the compounds are similar to our previous paper, this manuscript looks similar to the previous one. However, these reported crocetin derivatives are compounds with totally different chemical structures.

1) The corcetin and the three derivatives reported in the previous paper are listed below.

GX (Corcetin): Chemical Formula: C20H24O4 Molecular Weight: 328.4022

GX-D: Chemical Formula: C30H42N2O2 Molecular Weight: 462.6667

GX-E: Chemical Formula: C28H42N2O2 Molecular Weight: 438.6453

GX-G: (2E,4E,6E,8E,10E,12E,14E)-N1, N16-dibenzyl-2,6,11,15-tetramethylhexadeca-2,4,6,8,10,12,14-heptaenenediamide

2) The compounds reported in the present manuscript are as follows:
GX-F: Chemical Formula: C24H34N2O2  Molecular Weight: 382.5390

GX-M: (2E,4E,6E,8E,10E,12E,14E)-N1, N16-bis(4-Fluorobenzyl)-2,6,11,15-tetramethylhexadeca-2,4,6,8,10,12,14-heptaenediamide

It can be seen that, for the compound of GX-F, it is quite different from the previous reported compounds. As the GX-M, it is a further modification of the GX-G with the fluorine element. Because fluorine’s electronegativity, size, omniphobicity/lipophilicity, and electrostatic interactions can dramatically influence the chemical reactivity of the compound. Two F atoms have been conjugated to GX-G to investigate the influence of this novel strategy in the solubility of crocetin.

Reviewer: 2

Comments:

&gt; Please include all comments for the authors in this box rather than uploading your report as an attachment. Please only upload as attachments annotated versions of manuscripts, graphs, supporting materials or other aspects of your report which cannot be included in a text format.

Response: Thanks for the suggestion. We have corrected it accordingly.

&gt; 1) Page 3, Line 19: The word potential to be changed to "effects".
Response: Sorry for the grammatical mistake, we have corrected it accordingly.

&gt; 2) Page 3, Line 21; "is compound" to be changed to "is a compound".
Response: We have rephrased the sentence as follows:

“Currently, it has been reported that the use of biomaterials such as poly (lactic-co-glycolic acid) and dendrimers can improve the bioavailability of the crocetin."
4) Page 3, line 46; 4-fluoro… and not 4-fluoro….
Response: Sorry for the typing error, we have corrected it accordingly.

5) Page 5, line 15; µg/ml and not µg/ml.
Response: We have corrected it accordingly.

6) Page 5, line 33; always place a space between numbers and SI unit.
Response: We have checked the draft carefully. All the corrected parts (numbers and SI unit) were highlighted in blue.

7) Page 6, line 25; "statistic" to be changed to "statistical".
Response: We have corrected it accordingly.

8) Page 6, line 27; "A value of .." should be changed to "A value at …".
Response: We have corrected it accordingly.

9) Page 6, line 34; In the experimental models there were not adequate controls.
Response: In our study, the adequate control is crocetin. Compared with crocetin, we could demonstrate that the synthesized derivatives with chemical modification have much higher solubility, anti-cancer effects and anti-inflammatory effect.

10) Page 10, line 45; delete "pharmacological".
Response: We have deleted it accordingly.

11) Page 11, lines 25-27; Rephrase the sentence.
Response: We have rephrased the sentence.
“Despite that various studies have reported the anti-oxidative effect of saffron, there are few study on the anti-inflammatory effects of crocetin to be reported [14].”

&amp;gt; 12) Page 13, line 43; Put the appropriate references for the sentence.
Response: We have put the appropriate references for the sentence.

“As the main pharmacological component of saffron, crocetin possesses various pharmacological activities such as anti-oxidation [4], hepatoprotection [6], neuroprotection [7], etc.”

&amp;gt; 13) Page 14, lines 4-6; Why the word broad-spectrum?
Response: In our study, the influence of these compounds in the viability of three kinds of cancer cell lines was investigated. And the results showed that with the increased solubility of the derivatives, the anti-tumor activity of the crocetin derivatives were obviously improved.

&amp;gt; 14) Page 14, line 17; "causes" should be changed to "cause".
Response: We have corrected it accordingly.

&amp;gt; 15) Page 15, line 9; "therapeutics" should be "therapeutic agent".
Response: We have corrected it accordingly.

&amp;gt; 16) Discussion should be reviewed, and grammar improved.
Response: We have checked the English writing and revised the grammatical mistakes carefully. Besides, we tried our best to conduct a line-by-line proofreading and editing to polish language of the whole manuscript.

&amp;gt; 17) Adequate control(s) should be added in the models.
Response: The reason has been listed at “Response &amp;gt; 9”).