

## Peer Review File

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### Reviewer A

The manuscript entitled “Pharmacological activity of saffron and its component on dementia, a narrative review” summarizes the effect of saffron and SaiLuoTon on dementia prevention based on its effect on sleep disorder, depression, and AD patients.

Comment 1: The authors need to describe the outcomes of each clinical trials in more detail as well as the substance used.

Reply 1: As commented individual clinical trial was introduced more detail.

Comment 2: More detailed explanation of the pharmacological effects of saffron and crocin is required.

Reply 2: In the first sentence in section 8 the actual situation of dementia and AD in old age population and necessity of its prevention was explained, and pharmacological activities of crocin related to the prevent of dementia were indicated more detail using many recent references.

Comment 3: It would be better if authors suggest an action mechanism of saffron and crocin on AD or dementia prevention.

Reply 3: In conclusion the overview of mechanism related to crocin on dementia and AD was added.

Comment 4: The conclusion section may be concise and summarizing the findings instead of explaining the effect of crocin.

Reply 4: As the reviewer commented there are somewhat complicated because including individual results. Therefore, the author simplified the sentence only limited findings.

Comment 5: The author supposed that the revised sentence will be fit to the reviewer's suggestions. Overall, the oral administration of saffron is not confirmed enough to be effective for AD patients

Reply 5: All clinical evidences of saffron in this paper were done by oral administration and their activities for AD patients were clearly indicated.

Comment 6: There are many grammatical errors need to be improved

Reply 6: Authors read carefully and improved grammatical errors as the reviewer commented.

Comment 7: Line 60. There is not much summarized information of phytomedicines having anti-dementia activities

Reply 5: Since Table 3 shows several herbs and their active constituents, their references (23-33) were added to the original references, 7 and 8. The sentence of [via acetylcholine esterase inhibitor assays] was removed because there are several mechanisms included.

### **Reviewer B**

The manuscript reports on pharmacological and clinical activity of saffron and its component (crocin) on dementia.

Comment 1: First of all, the paper needs extensive language editing throughout. Some sentences are even incomprehensible.

Reply 1: Final English edition was done by a native checker of company.

Comment 2: The content needs to be ordered more stringently, e.g. pre-clinical vs. clinical data; data related to sleep, depression or dementia/cognition; data related to prevention or treatment. There are some redundancies regarding the relationship between dementia and sleep or depression, respectively. Part of the conclusion section would be better placed under the sections on active constituents and pre-clinical findings.

Reply 2: Since reviewer A suggested that conclusion section should be concise and summarizing the findings, the author simplified the sentence only limited findings.

Comment 3: Although the narrative review does not need a methodology section as stringent as a systematic review, a few more words about search strategy and selection of studies would be desirable.

Reply 3: As reviewer commented the several search terms were added in section 2. Methods such as Saffron, Crocus sativus, Crocin, Safety and toxicity of saffron, Quality control of saffron and Stability of crocin.

Comment 4: The section on saffron for dementia treatment, which should be the core section, is extremely short. Although, according to the title of the paper, effects of saffron on dementia are the main subject of the paper, not even the main results of the studies and the review mentioned in this section are reported. Both treatment with saffron or crocin alone and in combination with other TCM formulae deserve more elaborate (手の込んだ) presentation of results from clinical trials and reviews.

Reply 4: In the section 8 the actual situation of dementia and Alzheimer's patients in old age population and necessity of its prevention was explained, and then the pharmacological activities of crocin related to the prevent of dementia were added more detail using many recent references.

Comment 5: Some references (e.g. ref. #3 Ferri, C. P., Prince, M., Brayne et al. Global Prevalence of Dementia: a Delphi Consensus Study. *Lancet* 2005; 366: 2112–2117. doi:10.1016/S0140-6736(05)67889-0, #30 Zhou J, Zhou L, Hou D et al. Paeonol increases levels of cortical cytochrome oxidase and vascular actin and improves behavior in a rat model of Alzheimer's disease. *Brain Res* 2011; 1388: 141-147) do not provide the information/data referred to.

Reply 5: Ref. 3 and 30 are both informative for related evidences.

### **Editorial Office**

Comment 1: Reporting Checklist

Comment 1A: We suggest authors fill out and submit the "Narrative Review Checklist" (<https://cdn.amegroups.cn/static/public/18-narrative-review-Checklist.pdf>). The relevant page/line and section/paragraph number in the manuscript should be stated.

Reply 1A: As commented "We present the following article in accordance with the narrative review reporting checklist" was inserted at the end of the Introduction.

Comment 1B: The manuscript should also include a Reporting Checklist statement in the footnote: "The authors have completed the Narrative Review reporting checklist."

Reply 1B: Author inserted the statement of "The authors have completed the Narrative Review reporting checklist." in Footnote as requested.

Comment 2: Abstract

Comment 2A: Due to the recent editorial update on the regulations of manuscripts (<https://lcm.amegroups.com/pages/view/guidelines-for-authors#content-2-2>, 2.2.3 Narrative Review), please arrange the abstract as structured with "Background and Objective", "Methods", "Key Content and Findings", and "Conclusion".

Reply 2A: Abstract contained complete structure such as above mentioned. I prepared Abstract including "Background and Objective", "Methods", "Key Content and Findings" and "Conclusion" following to the new publication entitled "Effects of saffron and its active constituent crocin on cancer management: a narrative review" submitted by us in LCM.

Comment 2B: Line 24: "was systematically surveyed". We suggest the authors consider replacing "systematic" with "detailed" as this is not a scoping review.

Reply 2B: Systematically surveyed was removed.

Comment 2C: Conclusion (lines 28-36): To better focus on how the review may potentially impact future researches, clinical practice and policy making, could the authors refine the "Conclusions"?

Reply 2C: The author refined the conclusion as following.

Reported studies using saffron, crocin and the combination with other herbal medicines on dementia and AD have been surveyed, reviewed and analyzed. Clinical

trial data suggest that saffron and crocin have beneficial effects to improve memory in AD without serious side effect resulting that saffron and crocin can be supported as promising candidates for future clinical AD studies.

Comment 3: Introduction

Comment 3A: Figure 1-2: We suggest the authors delete the two tables and simply keep the description in the text (citing original references and specifying the data) due to the copyright issue and necessity.

Reply 3A: Tables 1 and 2 were removed and inserted sentences in the text.

Comment 3B: Lines 54-55: "It might be important issue to determine the reason why such difference occurred". The authors transitioned from dementia to diet as an influencing factor, which was important for getting attention to botanicals. However, the latter text does not seem to explain well the importance of saffron: what are the available dietary therapies? Why should we focus on botanicals? What are the available botanicals for dementia? Why focus only on saffron? There have been many similar reviews to this field (e.g., PMID: 30136324, 24848002, etc), please highlight the novelty of this review in the introduction: what does this review add to existing knowledge? How does this review differ from previous reviews?

Reply 3B: The safety of food is confirmed by its period of food experience. Such description cannot be found in the previous papers. So that a sentence "Saffron is seemed to be one of the most highly secure phytomedicine because saffron has the long food experience as spices" is added before GRAS by the FDA statement. This is an important highlight. Also the quality control of saffron is important in this article because the efficacy of saffron is depend on the concentration of crocin which is very changeable depending on several factors. Therefore this is also the necessary issue in this paper.

Comment 3C: Please use a structured introduction to increase readability: a) Background, b) Rationale and knowledge gap, c) Objective.

Reply 3C: Following to Comment 3-2), the structure of Introduction was arranged, so that the author supposed the revised Introduction may fit to the comment.

Comment 4: Methods

There is no Methods section provided. Detailed literature search information can help assess whether the search for xxx is comprehensive and up-to-date.

Considering the reviewers' comments and the LCM's Guidelines for Authors (<https://lcm.amegroups.com/pages/view/guidelines-for-authors> , content 2.2.3 Narrative Review ),

Comment 4A: We suggest that the authors add a separate paragraph about "Methods" after "Introduction" in the text, including date of search, timeframe, databases, search terms, inclusion and exclusion criteria, and selection process.

Reply 4A: Method was added after 1. Introduction.

Comment 4B: To further make the information more easy-going and self-explaining, please also include a completed table

(<https://lcm.amegroups.com/pages/view/guidelines-for-authors> , content 2.2.2

Narrative Review--Table X) in the Methods, which includes an independent supplement table to present detailed search strategy of one database as an example, or the authors could present search terms connected by the Boolean operators in the Table X. Here are two examples for your reference:

<https://atm.amegroups.com/article/view/91685/html> (See Table 1-2)

<https://atm.amegroups.com/article/view/91974/html> (See Table 1)

This part is essential as it reflects the sources of evidence (even though it is not a systematic review). This is to transparently report the process, not to judge it.

Reply 4B: Added.

Comment 5: Anti-dementia active constituents in phytomedicines

Comment 5A: Given that the topic of this review is "Pharmacological activity of saffron and its component on dementia", we suggest the authors could summarize the known components of saffron and the corresponding developed botanicals or compounds in a diagram or table.

Reply 5A: The title changed to "Pharmacological activity of saffron and crocin on dementia". Therefore, the author concentrated to the pharmacological activities of saffron and crocin.

Comment 5B: It would be great to summarize the specific effects of these drugs in different populations (e.g., Chinese, Japanese) in the context of the literature. Table 1 is missing, please provide it.

Reply 5B: "Table 1 Herb medicine, active constituent and their mechanism" was added.

Comment 6: Clinical use of saffron on sleep prevention and the relationship between sleep and dementia

Comment 6A: If possible, we suggest the authors could specify the saffron extract, such as whether it is an aqueous extract or an alcoholic extract (e.g., Line 87). With this and the information summarized in COMMENT 5(1), it would help the reader to have a clearer understanding of saffron.

Reply 6A: Alcoholic extractives of saffron were used for clinical study. Because the major active constituent, crocin is unstable against higher temperature, and also if water is used for extraction, inner  $\beta$ -glycosidase worked resulting in occurrence of cleavage on glycoside linkage which indicated the decrease of potency. These phenomena was indicated in the text.

Comment 7: Discussion

Comment 7A: We suggest the authors could discuss in depth and graphically summarize the action mechanisms of saffron and its components for dementia.

Reply 7A: Graphical summary was prepared and inserted as Fig.3.

Comment 7B: We suggest the authors could summarize: what are the main gaps in the existing research? What are the obstacles encountered? What are the directions for future research? What are the authors' suggestions for this?

Reply 7B: As previously pointed out the author stressed that saffron is the most safety herb medicine since it has a long food experience. However, since crocin, major pharmacologically active constituent in saffron is unstable against  $\beta$ -glycosidase attack, autooxidation and light, the concentration of crocin should be analyzed just before clinical experiment resulting that the quality control is necessary for its efficacy. However, the author can't find any comment for the concentration of crocin in saffron in publication related to clinical trials. The author supposed that this point is important for further clinical examination from now on,

Comment 7C: We suggest authors also consider discussing these included studies with an objective perspective. Specifically, which are more trustworthy while others are not? Have authors considered some (even the simplest/most obvious) limitations/quality of this evidence?

Reply 7C: It is not easy to evaluate the references individually.

Comment 7D: In addition, we recommend including a separate section on the STRENGTHS and LIMITATIONS of this review to promote a more intellectual interpretation.

Reply 7D: It seems to be very hard for authors.

Comment 8: Structural Formats

Given that there are several comments on structural formats (e.g. comments 2-4), authors may refer to the Structure template (<https://cdn.amegroups.cn/static/public/2.2.3-Structure%20of%20Narrative%20Reviews-template-V2022.11.4.docx>).

Reply 8: Running title "ANTI-DEMENCIA ACTIVE SAFFRON AND CROCIN" was added.