

Peer Review File

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Reviewer A

The authors reported the findings of “Sinomenine: a potential antitumor agent”. The approach is quite good as the literature collection and summary in tables provide useful information to researchers in this field. Nonetheless, this requires significant revision. Below are my comments

We thank the reviewer for the good comment. We have carried out the corrections as suggested.

Comment 1: The discussion needs further improvements as well. Especially compare the results in this study with most recent related literature and do a critical evaluation on the trends/similarities/differences

Reply 1: We have modified our text as advised. (see Page12, line 324-336)

This review has the following improvement from the review by Gao LN published in 2019(56). First, nanocarriers and molecular modifications are considered to be effective methods for the development and utilization of sinomenine. Therefore, in addition to sinomenine, our review also described the anti-tumor effects of derivatives of sinomenine. And suggested that it is still necessary to improve the water solubility and bioavailability of sinomenine by using new technologies and new processes, such as drug synthesis, genetic modification or structural modification and optimization of natural active ingredients. Second, this review provides a more detailed explanation of the anti-tumor mechanism of sinomenine and its derivatives and describes the study of alleviating tumour complications. Third, this review enriches the literature on the antitumor mechanism of sinomenine and its derivatives and adds to the understanding of the antitumour potential of sinomenine and its derivatives. Finally, this review collects and summarizes the relevant literature in the form of tables to facilitate reference by researchers in the field.

[56]Gao LN, Zhong B, Wang Y. Mechanism Underlying Antitumor Effects of Sinomenine. Chin J Integr Med. 2019 Nov;25(11):873–8.

Comment 2: In its current state, the level of English throughout your manuscript does not meet the journal’s required standard. You may wish to ask a native speaker to check your manuscript for grammar, style and syntax, or use the professional language editing options

Please consider improving English editing and grammar according to the suggestions for shin work and readership acceptance.

Reply 2: We are sorry for the poor English of this manuscript. We have polished the language by the editing service to improve readability of the manuscript.

Comment 3: Overused Passive voice in the manuscript seems hard to read. Please carefully check the sections: introduction, results, discussion and conclusions. Please try to reword the phrases in the active voice.

Reply 3: We have polished the language by the editing service to improve readability of the manuscript.

Comment 4. Grammar and punctuation mistakes.

Reply 4: We have polished the language by the editing service to improve readability of the manuscript.

Comment 5. For consistency, please use the manuscript in just one English style (a non-variant British or British style).

Reply 5: We have use the manuscript in British style.

Comment 6. There are phrases with the verb in the wrong tense.Sentences with words misspelt.

Reply 6: We have polished the language by the editing service to improve readability of the manuscript.

Comment 7. Words overused or unnecessary

Reply 6: We have polished the language by the editing service to improve readability of the manuscript.

Comment 8. Nouns without determiner or unnecessary

Reply 8: We have polished the language by the editing service to improve readability of the manuscript.

Reviewer B

Comment The paper submitted for review is very well prepared. The analysis performed is thorough and demonstrates the potential use of Sinomenin in the treatment of chronic cancer.

The theme of the thesis concerning the search for new compounds with anticancer activity is an important research topic. However, the work should be complemented by the chemopreventive activity of the compound, as this is how it will be used. Unfortunately, there is nothing about this and there are publications available. In my opinion, what is described in the paper is precisely the chemopreventive properties of the compound. I think that after minor corrections the work can be accepted.

Reply:We thank the reviewer for the good comment. We have carried out the

corrections as suggested. The article has been complemented by the chemopreventive activity of sinomenine. (see Page 2, line 53-54; Page 7, line 170-171)

Reviewer C

Manuscript is interesting, but needs some revision, and part that should be improved are listed below:

Comment 1: Why in title of manuscript is chemical name of compound – alkaloid is Sinomenin, but correct name is Sinomenine, please check and correct

Reply1: We thank the reviewer for the good comment. Thanks for pointing out the typo in the title. We have carried out the corrections as suggested. (see Page 1, line 1)

Comment 2: Page 1, line 22: Name of plants should be in italic and start from capital letter. *Sinomenium acutum*.

Reply 2: We have carried out the corrections as suggested. (see Page 1, line 29; Page 2, line 47)

Comment 3: Authors mentioned that Page 1. line 28 “of sinomenine remains in the stage of basic experimental.” But they do not mentioned when this alkaloid was discovered and characterized and when its cytotoxic activities were confirmed.

Reply 3: We added some information about when this alkaloid was discovered and characterized and when its cytotoxic activities were confirmed. (see Page 2, line 47-54) *Sinomenium acutum* (Thunb) Rehd. et Wils was used to treat rheumatic diseases more than 1,000 years ago. In the early 20th century, Japanese scholars isolated its main active ingredient from plant ivy(3). Its molecular formula is C₁₉H₂₃NO₄. Since sinomenine was discovered, scholars across the world have confirmed the cytotoxic effect of sinomenine on a variety of cancer cells in vitro and in vivo. It has been found to have many functions, such as anti-inflammatory, analgesic, immunomodulation, anti-tumor and drug addiction effects(4). Researchers have suggested that sinomenine is an effective chemoprophylaxis agent for cancer.

[3]. Yamasaki H. Pharmacology of sinomenine, an anti-rheumatic alkaloid from *Sinomenium acutum*. *Acta Med Okayama*. 1976;30(1):1–20.

[4]. Li RZ, Guan XX, Wang XR, Bao WQ, Lian LR, Choi SW, et al. Sinomenine hydrochloride bidirectionally inhibits progression of tumor and autoimmune diseases by regulating AMPK pathway. *Phytomedicine*. 2023 Jun; 114:154751.

Comment 4: Why Authors mentioned suddenly “pictoine” in line 43 Page 2,? It is a mistake probably there should be written sinomenine.

Reply 4: Thanks for pointing out the typo in this paper. There should be written sinomenine. We have carried out the corrections as suggested. (see Page 2, line 54)

Comment 5: Page 11 line 253 ‘5.1 Sinomenin enhances chemosensitivity.’ and then on page 12 line 281 (the same number) 5.1 ‘Sinomenine enhances radiotherapy sensitivity.’

Reply 5: We have carried out the corrections. (see Page 11, line 292)

Comment 5: Page 13 Line 325 is picostigmine a derivative of sinomenine, it is unclear, if yes [please add: picostigmine, a derivative of sinomenine.

Reply 5: Thanks for pointing out the typo in this paper. It is a mistake and there should be written sinomenine. We have carried out the corrections as suggested. (see Page 12, line 341)

Comment 6: Maybe at the beginning Authors could mention the chemical names of some of the most popular sinomeline derivatives.

Reply 6: We have carried out the corrections as suggested. (see Page 2, line 56-58)