

## Peer Review File

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### Reviewer A

The review is well-written and covered the mechanisms by which borneol may increase as well as decrease the BBB permeability

1. The manuscript needs to be free of grammatical mistakes.

**Reply1:** We gratefully thank the reviewer for the critical comment. We have checked the full text and corrected any possible grammatical mistakes.

2. Line No. 179-185- describe the combination therapy of edaravone and borneol in the treatment of ischaemic stroke. Can authors throw more light on role of borneol in improving brain delivery of edaravone. Borneol tends to reduce the permeability of BBB in case of stroke. So, how can it increase delivery of drug across the BBB?

**Reply2:** We gratefully thank the reviewer for the critical comment. **Regarding your first question "Can authors throw more light on role of borneol in improving brain delivery of edaravone."** We conducted a review of relevant literature to add this aspect of the argument. And in this article, we may not have mentioned that borneol improve brain delivery of edaravone. However, we added more evidence for synergistic treatment with borneol and edaravone in the hope of providing stronger evidence for our conclusions (see Page 7, line 205-211). **And regarding your second question " So, how can it increase delivery of drug across the BBB?".** Borneol increase the permeability of the physiological BBB and decrease the permeability of the pathological BBB. The mechanism is complex, involving P-gp proteins (1), Ca<sup>2+</sup>-eNOS-NO pathway(2), NO content(3), etc. For instance, borneol can inhibit the P-gp and enhance the transcytosis pathway, thereby reducing the permeability of the blood-brain barrier and promoting the passage of drugs through this barrier into the brain, effectively exerting their therapeutic actions. And this review focuses on the role of borneol in two diseases: ischemic stroke and cerebral gliomas. We analyzed how borneol open the BBB in cerebral gliomas in this review.

(1) Yu B, Ruan M, Dong X, et al. The mechanism of the opening of the blood-brain barrier by borneol: a pharmacodynamics and pharmacokinetics combination study. *J Ethnopharmacol* 2013;150(3):1096.

(2) Altmann JB, Yan G, Meeks JF, et al. G protein-coupled estrogen receptor-mediated effects on cytosolic calcium and nanomechanics in brain microvascular endothelial cells. *J Neurochem* 2015;133(5):629.

(3) Wu Jj, Wang HJ, Yang S, et al. [Borneol promotes catalpol and puerarin crossing through blood-brain barrier in focal cerebral ischemic rats]. *Zhongguo Zhong Yao Za Zhi* 2016; 41(21):3988-3995

3. Borneol alone and in combination with anticancer agents has shown to enhance ROS generation that leads to the destruction of tumor cells. Authors could add this mechanism of borneol's action in treatment of glioma. The suggested reference is

Rajput A., Kasar A., Thorat S., Kulkarni M. Borneol: A plant-sourced terpene with variety of

promising pharmacological effects. Nat. Prod. J. 2023 13(11):13-28.  
10.2174/2210315512666211221115143

**Reply3:** We gratefully thank the reviewer for the critical comment. In response to the critical comment, we added some data in review (see Page 12, line 388-391).

### **Reviewer B**

The authors presented a progress report on the research related to the regulation and mechanism of borneol on the blood-brain barrier in pathological states: a narrative review focused on ischemic stroke and cerebral glioma. The topic seems to be of utmost importance in the field of natural products domain and is interesting, and I think it is fully within the aims and scopes of the Journal. I find that this review advances our understanding of the field. The paper provides considerable impact. Figures are appropriate and easy for readers. The mechanistic aspect of borneol and its stereoisomers have been discussed effectively.

Sections relatively inflammatory signalling, oxidative stress, and cellular signalling are much generalized. A review should be more than a compilation of the results reported in the literature. It should, in fact, be a critical assessment of the present knowledge with some clear conclusions. I would definitely suggest to improve the sections in terms of mechanistic approaches considering some graphical figures for easy understanding of the process. Information throughout the manuscript needs improvement in drawing important inferences from the available information. Please add a proper structured abstract for the review article.

**Reply1:** We gratefully thank the reviewer for the critical comment. In response to the critical comment, we added more detailed conclusions in review (see Page 10, line 322-331).

Conclusions are too short. Therefore, it can be elaborated. Conclusion is not clear and there is a need to draw a few recommendations from this review exercise.

Major apprehension of this paper is lacking discussion and information synthesis from documented information.

What about a general comment on these results? What about a real discussion on these results? Potential future perspectives and their major strength need to be highlighted.

Thereafter the article can be accepted for publication.

**Reply2:** We gratefully thank the reviewer for the critical comment. In response to the critical comment, we added more detailed conclusions, analyses, and prospects for the future in review (see Page 14-15, line 443-491).