Peer-Review Report

# Peer Review of “Discovery of Novel Inhibitors of HMG-CoA Reductase Using Bioactive Compounds Isolated From Cochlospermum Species Through Computational Methods (Preprint)”

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**Related Article:**
Preprint (bioRxiv): https://www.biorxiv.org/content/10.1101/2025.01.19.633828v1

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**KEYWORDS**

statins; phytochemicals; Cochlospermum; hypercholesterolemia; molecular docking

*This is a peer-review report submitted for the preprint “Discovery of Novel Inhibitors of HMG-CoA Reductase Using Bioactive Compounds Isolated From Cochlospermum Species Through Computational Methods.”*

This review is the result of a virtual, collaborative live review discussion organized and hosted by PREreview and JMIR Publications on February 21, 2025. The discussion was joined by 13 people: 3 facilitators from the PREreview Team, 1 member of the JMIR Publications team, 1 author, and 8 live review participants. The authors of this review have dedicated additional asynchronous time over the course of 2 weeks to help compose this final report using the notes from the live review. We thank all participants who contributed to the discussion and made it possible for us to provide feedback on this preprint.

## Summary

Cholesterol is an essential component of cellular membranes and a precursor for the biosynthesis of steroid hormones, bile acids, and vitamin D. However, elevated low-density lipoprotein cholesterol is a major contributor to atherosclerosis and cardiovascular diseases, which are leading causes of morbidity and mortality worldwide. Inhibiting HMG-CoA (3-hydroxy-3-methylglutaryl-coenzyme A) reductase (HMGR) is a key therapeutic strategy for managing hypercholesterolemia, with statins serving as the most widely used competitive inhibitors; however, their prolonged use is associated with adverse effects. This study aims to identify novel, natural inhibitors of HMGR as potential alternatives to statins.

This study [1] used a molecular docking method to investigate the inhibitory potential of 84 phytochemicals from *Cochlospermum planchonii* and *Cochlospermum tinctorium* against human HMGR. Molecular docking is a purely computational technique used to predict how small molecules bind to proteins. Specifically, the author used a semirigid docking approach, meaning that the structure of the receptor was not allowed to change while the phytochemicals and statins were given some degree of flexibility at the binding pocket. The phytochemicals were screened for their drug-likeness and absorption, distribution, metabolism, excretion, and toxicity properties based on Lipinski’s rule of five, and 32 were docked against the enzyme’s HMG-binding site alongside its native ligand and 6 statins as controls. Docking results identified 10 promising inhibitors of HMGR. These compounds, including 3-O-methylellagic acid, all displayed strong binding affinities and interactions that were either comparable to or exceeding those of the statins used as control ligands.

These findings highlight the therapeutic potential of natural compounds in treating hypercholesterolemia. However, as indicated in the manuscript, further in vitro and in vivo experiments will be needed to establish their efficacy and safe therapeutic use.

## Concerns and Feedback

All reviewers found that the study was well written and comprehensive. There were no major concerns regarding the techniques or analyses. A few points were made during the discussion and are highlighted below:

- Reviewers appreciated the depth and thoroughness of the search through the literature of peer-review research. Some reviewers were surprised about the date (1991) of some studies related to the high-performance liquid chromatography–UV analysis of phytochemicals identified in the ethanolic and methanolic extract of *C tinctorium* and wondered whether there may be more recent studies to also consider.
- To increase the reproducibility of the study, some reviewers wondered if it would be possible to make the data and code used to analyze the data openly available.

- The figures and tables are comprehensive and clearly presented, with well-written descriptions. If feasible, reviewers would suggest ways to visually highlight key compounds listed in tables using colors, bold text, or labels. Furthermore, incorporating chemical structures directly within the relevant tables or as supplementary figures would further enhance the understanding of their molecular characteristics and potential interactions.
- While the author acknowledges the need for in vitro and in vivo validation studies, explicitly addressing potential computational limitations—such as docking inaccuracies, semirigid approach versus more flexible ones, or the absence of dynamic modeling—would further strengthen the discussion.
- Some reviewers suggested adapting the part of the study that identified the compounds through literature review into a systematic review.

## Concluding Remarks

We thank the author of the preprint for posting their work openly and for allowing the review of their work openly via live review. We also thank all participants of the live review call for their time and for engaging in the lively discussion that generated this review.

### Acknowledgments

PREreview and JMIR Publications thank the authors of the preprint for posting their work openly for feedback. We also thank all participants of the live review call for their time and for engaging in the lively discussion that generated this review.

### Conflicts of Interest

None declared.

### Reference

1. Olatoye TI. Discovery of novel inhibitors of HMG-CoA reductase using bioactive compounds isolated from Cochlospermum species through computational methods. BioRxiv. Preprint posted online on January 22, 2025. 2025. [doi: 10.1101/2025.01.19.633828]

### Abbreviations

**HMG-CoA:** 3-hydroxy-3-methylglutaryl-coenzyme A
**HMGR:** HMG-CoA reductase

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