

Peer Review

Review of: "*In Silico* Evaluation of the Predicted Inhibitory Potential of p-Hydroxybenzoic Acid and Cyclohexane-1,2,3,4,5-pentol Isolated from *Hyphaene coriacea* Gaertn. Toward Human Maltase-Glucoamylase and Pancreatic α -Amylase"

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***InSilico* Evaluation of the Predicted Inhibitory Potential of p-Hydroxybenzoic Acid and Cyclohexane-1,2,3,4,5-pentol Isolated from *Hyphaenecoriacea* Gaertn. Toward Human Maltase-Glucoamylase and Pancreatic α -Amylase**

The inhibitory potential of p-hydroxybenzoic acid and cyclohexane-1,2,3,4,5-pentol isolated from *Hyphaene coriacea* on human maltase-glucoamylase and pancreatic α -amylase was investigated by molecular docking using AutoDock Vina with miglitol and acarbose as references, respectively. The results show that both compounds occupy the catalytic pockets and interact with several essential residues, notably Asp443 and Asp542 for maltase-glucoamylase, as well as Asp197, Glu233, and Asp300 for α -amylase. Cyclohexane-1,2,3,4,5-pentol notably exhibits a predicted affinity of -6.1 kcal/mol for maltase-glucoamylase, slightly more favourable than that of miglitol (-5.8 kcal/mol), while both phytocompounds remain significantly less favourable than acarbose towards α -amylase. The study is interesting due to the choice of physiologically relevant targets, the use of complexed crystallographic structures, and the detailed identification of ligand-residue interactions. Nevertheless, its conclusions remain preliminary: no validation of the protocol by redocking the co-crystallised ligands and calculating the RMSD is presented, the difference of 0.3 kcal/mol with miglitol is probably within the

margin of uncertainty of the scoring function, and the scores of ligands of very different sizes cannot be directly equated to their inhibitory potency. Furthermore, cyclohexane-1,2,3,4,5-pentol is studied without a defined stereochemical configuration, whereas this can profoundly alter its hydrogen bond network. The selection of poses ranked fourth for certain complexes, and unfavourable contacts with catalytic residues, the absence of molecular dynamics, free energy calculations, and enzymatic validation also limit the robustness of the interpretations. These results therefore allow for an interesting structural hypothesis to be formulated but do not demonstrate either effective inhibition, its competitive nature, or antidiabetic activity.

Questions

1. Did the authors validate their protocol by redocking miglitol and acarbose into their respective crystallographic structures, and what RMSD values were obtained compared to the experimental poses?
2. Why was cyclohexane-1,2,3,4,5-pentol docked without a defined stereochemical configuration, and how do the different stereoisomers influence the predicted affinities and interactions?
3. What quantitative criteria justified the selection of poses ranked fourth rather than poses with better scores, and does this selection introduce a bias in favour of interactions with catalytic residues?
4. Is the small difference between cyclohexane-1,2,3,4,5-pentol and miglitol toward maltase-glucoamylase (-6.1 vs. -5.8 kcal/mol) really significant considering the known uncertainty of AutoDock Vina scoring functions?
5. Can the authors experimentally confirm these predictions through enzymatic assays determining the IC_{50} or K_i values as well as the inhibition mechanism and then verify the stability of the complexes through molecular dynamics?
6. References to be added
 - a. <https://www.sciencedirect.com/org/science/article/abs/pii/S1573399825000654>
 - b. <https://www.sciencedirect.com/science/article/abs/pii/S0141813024069836>
 - c. <https://www.sciencedirect.com/science/article/abs/pii/S2405830023000903>
 - d. <https://www.sciencedirect.com/science/article/abs/pii/S0924224418309087>
 - e. <https://www.sciencedirect.com/science/article/pii/S1751731119003136>
 - f. <https://www.sciencedirect.com/science/article/abs/pii/S0010482525003208>

Declarations

Potential competing interests: No potential competing interests to declare.