

Research Article

Molecular Docking and Interaction Profiles of p-Hydroxybenzoic Acid and Cyclohexane-1,2,3,4,5-pentol Previously Isolated from *Hyphaene coriacea* Gaertn. with Human Maltase-Glucoamylase and Pancreatic α -Amylase

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Inhibition of digestive enzymes involved in carbohydrate hydrolysis is a strategy for controlling postprandial hyperglycemia in type 2 diabetes. This study investigated, using molecular docking, the interactions of p-hydroxybenzoic acid and cyclohexane-1,2,3,4,5-pentol, isolated from *Hyphaene coriacea* Gaertn., with human pancreatic α -amylase and maltase-glucoamylase. Miglitol and acarbose were used as reference compounds. The three-dimensional structures of the ligands and target proteins (PDB IDs: 3L4W and 1B2Y) were retrieved from PubChem and the RCSB Protein Data Bank. Molecular docking was performed using PyRx 0.8, and the resulting interactions were analyzed with Discovery Studio Visualizer v2020. For α -amylase, the docking scores of the two phytochemicals were -5.4 and -5.5 kcal/mol, respectively, compared with -18.3 kcal/mol for acarbose. For maltase-glucoamylase, the respective scores were -5.9 kcal/mol for cyclohexane-1,2,3,4,5-pentol, -5.7 kcal/mol for p-hydroxybenzoic acid, and -5.5 kcal/mol for miglitol. Both phytochemicals occupied the catalytic pocket and interacted with several residues in the active sites of the enzymes studied. Although their overall binding profiles differed from those of the reference inhibitors, both compounds formed contacts with several catalytic residues also involved in the binding of the reference compounds.

However, the small differences in docking scores observed for maltase-glucoamylase and the unspecified stereochemical configuration of the cyclohexane-1,2,3,4,5-pentol isolated from the plant warrant cautious interpretation. These scores indicate potential structural binding patterns but do not establish higher binding affinity or actual enzyme inhibition. Further *in vitro* studies are therefore required to determine whether these compounds exhibit inhibitory activity, before proceeding to any subsequent *in vivo* evaluation.

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1. Introduction

Diabetes, characterized in part by chronic hyperglycemia, represents a major public health concern. In 2024, approximately 589 million adults aged 20-79 years were living with diabetes, and this figure is projected to reach 853 million by 2050^[1]. This growing burden has increased interest in approaches that may improve glycemic control, particularly in the postprandial period.

Postprandial hyperglycemia partly depends on the enzymatic hydrolysis of dietary carbohydrates. Pancreatic α -amylase initiates starch breakdown, whereas intestinal α -glucosidases, including maltase-glucoamylase, catalyze the terminal steps leading to the release of absorbable glucose^{[2][3]}. Inhibition of these enzymes slows carbohydrate digestion and underlies the mechanism of action of drugs such as acarbose and miglitol^{[4][5]}. Despite their therapeutic efficacy, these drugs may cause gastrointestinal adverse effects, sustaining interest in the search for bioactive compounds of plant origin^{[5][6]}.

Hyphaene coriacea Gaertn. is a tropical palm used in traditional medicine, and its fruit has attracted interest for its nutritional and phytochemical properties^{[7][8]}. Several classes of secondary metabolites have been identified in the fruit, including flavonoids, leucoanthocyanins, anthraquinones, tannins, polyphenols, and terpenoids^[9].

p-Hydroxybenzoic acid and cyclohexane-1,2,3,4,5-pentol were also isolated from the methanolic fruit extract, yielding 15 mg and 37 mg, respectively. Their structural assignments were proposed based on the available NMR data^[9]. These compounds were selected for the present study as molecules newly identified in this plant. As the stereochemistry of cyclohexane-1,2,3,4,5-pentol remains to be established, the structures investigated herein correspond to those proposed from the available data. The presence of

polar functional groups potentially capable of interacting with enzyme residues provides a rationale for their *in silico* investigation.

Previous studies have associated *p*-hydroxybenzoic acid with effects related to glycemic control in different experimental models^[10], whereas certain related cyclitols have demonstrated antidiabetic activity^[11]. Furthermore, the structures of human pancreatic α -amylase and maltase-glucoamylase have been characterized, providing a structural basis for the *in silico* investigation of ligand–enzyme interactions^{[12][13]}.

On this basis, we hypothesized that *p*-hydroxybenzoic acid and cyclohexane-1,2,3,4,5-pentol could interact with the catalytic sites of human pancreatic α -amylase and maltase-glucoamylase. The primary objective of this study was therefore to characterize their predicted binding modes and interaction profiles with these two enzymes using molecular docking and to estimate their predicted binding scores. Acarbose and miglitol were used as reference inhibitors to contextualize the predicted interactions. This study thus provides exploratory structural insights into the potential interactions of these two compounds with enzymes involved in postprandial hyperglycemia.

2. Materials and Methods

2.1. Ligand Selection and Preparation

Two compounds previously isolated from *H. coriacea* Gaertn., *p*-hydroxybenzoic acid and cyclohexane-1,2,3,4,5-pentol, were selected for this study. Miglitol and acarbose were used as reference inhibitors. Miglitol inhibits intestinal α -glucosidases involved in the terminal hydrolysis of oligo- and disaccharides, whereas acarbose inhibits pancreatic α -amylase and intestinal α -glucosidases^{[14][15]}.

Because the precise stereochemical configuration of the isolated cyclohexane-1,2,3,4,5-pentol has not yet been established, reference structures available in PubChem^[16] were used for this preliminary molecular docking study. The two compounds' 2D and 3D structures were downloaded in Structure Data File (SDF) format using their respective PubChem Compound Identifiers (CIDs). The structures provided by the database were retained without specific pH-dependent adjustments or exploration of alternative ionization states.

In contrast, the structures of acarbose and miglitol were extracted directly from the co-crystallized complexes corresponding to the Protein Data Bank (PDB) structures of the target receptors.

The three-dimensional ligand structures were subsequently converted to PDB format using Discovery Studio Visualizer v2020^[17]. The 2D structures and origins of the ligands are presented in Table 1.

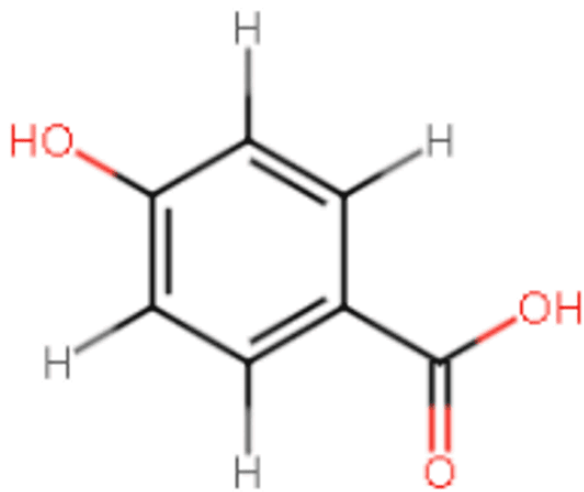
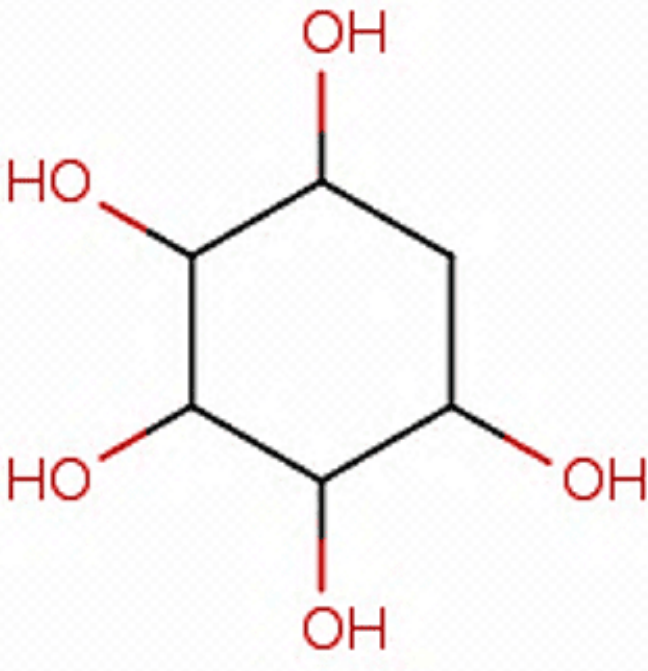
Ligand	Structure 2D	Source/identifier
<i>p</i> -Hydroxybenzoic acid		PubChem CID 135
Cyclohexane-1,2,3,4,5-pentol		PubChem CID 101715

Table 1. Structures and origins of the ligands used for molecular docking

2.2. Selection and Preparation of Target Proteins

The target proteins were selected based on their roles in carbohydrate hydrolysis and the regulation of postprandial blood glucose levels. Human pancreatic α -amylase and maltase-glucoamylase were therefore selected. Pancreatic α -amylase, an endoglycosidase, hydrolyzes internal $\alpha(1\rightarrow4)$ O-glycosidic bonds in starch and glycogen, whereas maltase-glucoamylase primarily cleaves terminal $\alpha(1\rightarrow4)$ linkages in oligosaccharides. These enzymes thus contribute to complementary stages of carbohydrate digestion.

The crystal structure of human pancreatic α -amylase in complex with acarbose was retrieved from the Protein Data Bank (PDB) under accession code 1B2Y^[12]. The structure of the N-terminal catalytic domain of human maltase-glucoamylase (ntMGAM) in complex with miglitol was retrieved under accession code 3L4W^[13].

Before molecular docking, both structures were prepared using BIOVIA Discovery Studio Visualizer v2020^[17]. The co-crystallized ligands, crystallographic water molecules, and heteroatoms not required for docking were removed. For pancreatic α -amylase (PDB ID: 1B2Y), Ca^{2+} and Cl^- ions were retained because of their structural roles in the enzyme^{[2][12]}. The prepared structures were then saved in PDB format for subsequent docking analyses.

2.3. Identification of Binding Sites

The binding sites were defined based on active-site residues reported in the literature for each target protein.

For human pancreatic α -amylase, the main residues considered were Trp58, Trp59, Tyr62, Gln63, His101, Leu162, Thr163, Leu165, Arg195, Asp197, Ala198, Glu233, His299, Asp300, and His305^{[2][12]}. Among these, Asp197, Glu233, and Asp300 are the principal catalytic residues of the enzyme^[2].

For human maltase-glucoamylase, the active-site region included Tyr299, Asp327, Ile328, Ile364, Trp406, Trp441, Asp443, Met444, Arg526, Trp539, Asp542, Phe575, and His600. Asp443 acts as the catalytic nucleophile, whereas Asp542 serves as the catalytic acid/base^[13].

2.4. Validation of the Molecular Docking Protocol

The docking protocol was validated by redocking the native co-crystallized ligands into the corresponding crystallographic structures of the target proteins. For each protein, the native ligand was

extracted and redocked into the active site under the same conditions used for the phytocompounds. The grid box was defined to encompass the active site and the corresponding binding pocket^[18].

The poses generated by PyRx 0.8 were subsequently imported into BIOVIA Discovery Studio Visualizer v2020 for molecular interaction analysis. Protocol accuracy was assessed by calculating the root-mean-square deviation (RMSD, Å) between the top-ranked predicted pose and the experimentally determined crystallographic conformation. The protocol was considered validated when the RMSD was ≤ 2.0 Å^[19]. The binding energies and interaction profiles of the redocked ligands were then used as reference points for interpreting the results obtained with the tested phytocompounds.

2.5. Molecular Docking of the Target Compounds

Molecular docking was performed using AutoDock Vina 1.1.2, as implemented in PyRx 0.8^{[20][21]}. For each target protein, polar hydrogens were added and Gasteiger partial charges were assigned using the AutoDock tools available in PyRx 0.8^[22]. The protonation states generated during this preparation step were retained, without specific pKa prediction or further adjustment of ionizable active-site residues according to pH. The proteins were then converted to PDBQT format.

The ligands were energy-minimized using the MMFF94 force field to reduce steric strain and optimize their three-dimensional geometries. They were subsequently converted to PDBQT format using Open Babel, as integrated into PyRx 0.8^[23].

For each target, a search box was centered on the active site to encompass the main catalytic residues. The box dimensions and center coordinates along the X, Y, and Z axes are reported in Table 2. Docking was therefore restricted to the catalytic cavity rather than performed using a blind-docking approach.

The exhaustiveness parameter was kept at its default value of 8. Up to nine poses were generated for each complex and ranked according to their docking scores. The top-ranked pose, corresponding to the most favorable score, was selected for analysis.

Protein-ligand interactions were examined using BIOVIA Discovery Studio Visualizer v2020, with particular attention to hydrogen bonds, hydrophobic and electrostatic interactions, and van der Waals contacts. No independent runs using different random seeds or convergence tests with higher exhaustiveness values were performed. Reproducibility across docking runs was therefore not assessed.

Target	Box dimensions (Å)			Center coordinates (Å)		
	X	Y	Z	X	Y	Z
α -amylase	23.8159	19.1433	22.5604	18.9005	5.7992	47.0057
Maltase-glucoamylase	20.7393	18.6852	21.8073	45.3819	92.3540	34.8180

Table 2. Search box parameters used for molecular docking

3. Results

3.1. Validation of the docking protocols

Redocking of the native co-crystallized ligands into their respective active sites reproduced their crystallographic conformations with satisfactory accuracy. The RMSD values between the best-scoring poses and the experimental conformations were 0.4001 Å for human pancreatic α -amylase and 1.8849 Å for human maltase-glucoamylase. Both values were below the 2.0 Å threshold used to validate the docking protocols.

The redocked reference ligands also retained the main hydrogen bonds and hydrophobic interactions with key residues in the active sites (Figure 1). These findings support the suitability of the docking protocols for analyzing the phytocompounds of *H. coriacea* Gaertn.

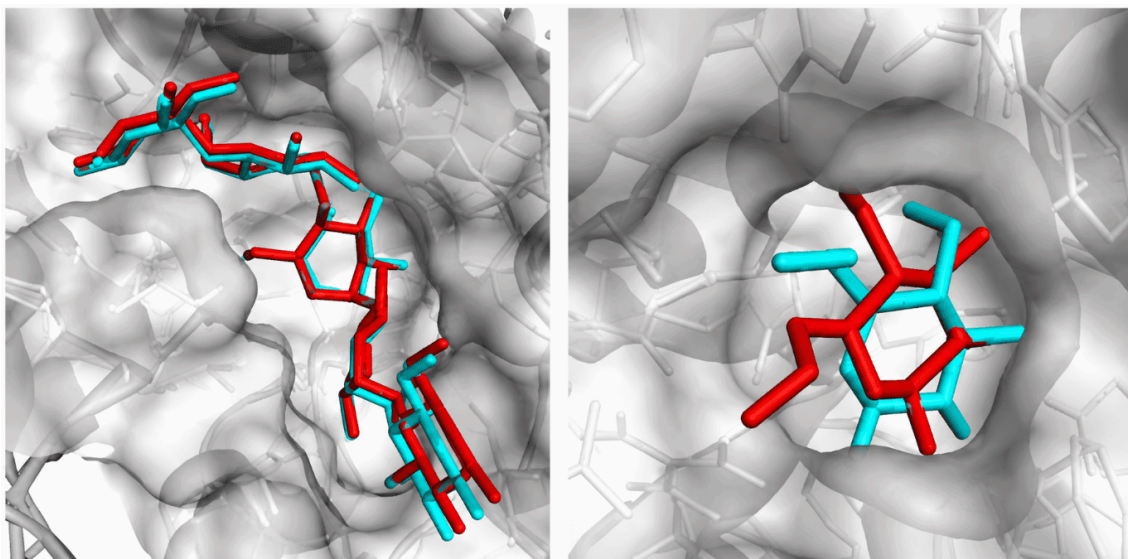


Figure 1. Superposition of the native co-crystallized ligand (cyan) and the redocked pose (red) within the active sites of the enzymes investigated. Left: acarbose bound to human pancreatic α -amylase (PDB ID: 1B2Y); right: miglitol bound to human maltase-glucoamylase (PDB ID: 3L4W). The receptor is represented as a ribbon, and the molecular surface surrounding the ligands represents the solvent-accessible surface. The main active-site residues are shown as sticks. The corresponding RMSD values were 0.4001 Å and 1.8849 Å, respectively.

3.2. Docking scores of the ligands against the target proteins

The analyses focused on the top-ranked poses (rank 1), selected according to the protocol described in Section 2.4. Interactions with active-site residues were subsequently examined *a posteriori* and did not influence the selection of the retained poses.

As shown in Table 3, both phytocompounds exhibited substantially less negative docking scores against human pancreatic α -amylase than acarbose (−18.3 kcal/mol). The particularly favorable score of this reference compound may reflect the extensive network of stabilizing interactions established by this relatively large oligosaccharide within the catalytic pocket. Against human maltase-glucoamylase, the two phytoligands yielded docking scores of −5.7 to −5.9 kcal/mol, close to that of miglitol (−5.5 kcal/mol), with differences of only 0.2–0.4 kcal/mol.

	<i>Human pancreatic α-amylase</i>		<i>Human maltase-glucoamylase</i>	
Ligand	Pose rank	Docking score (kcal/mol)	Pose rank	Docking score (kcal/mol)
Reference compound	1	-18.3 (acarbose)	1	-5.5 (miglitol)
<i>p</i> -Hydroxybenzoic acid	1	-5.5	1	-5.7
Cyclohexane-1,2,3,4,5-pentol	1	-5.4	1	-5.9

Table 3. Docking scores and ranks of the selected poses for the target proteins

The pose rank indicates the position of a pose among the conformations generated by AutoDock Vina and ranked according to predicted binding affinity. Rank 1 corresponds to the most favorable docking score.

3.3. Analysis of ligand interaction modes with α -amylase

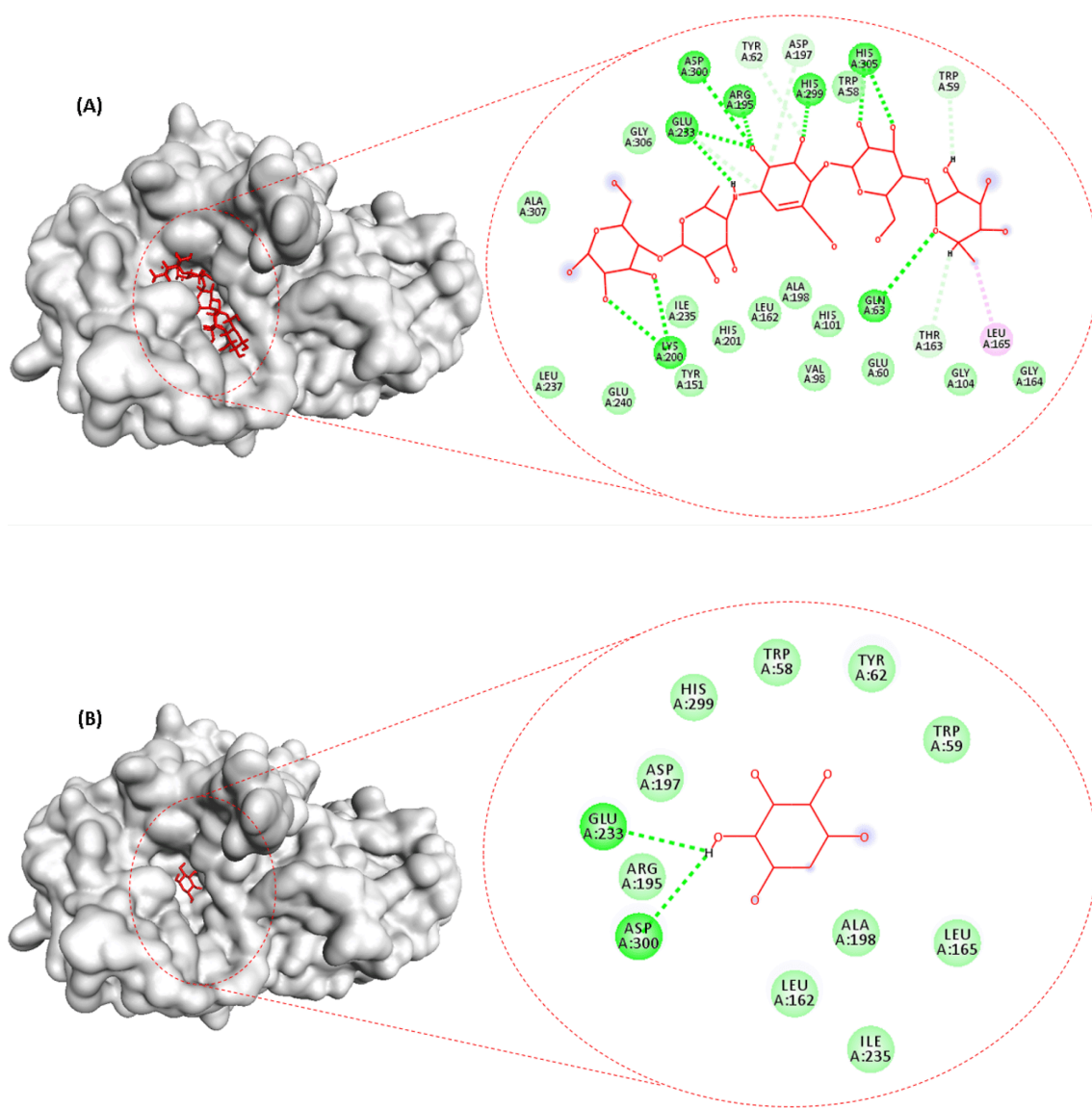
The selected poses occupy the active site of α -amylase and involve several residues within the catalytic pocket.

Acarbose forms multiple conventional hydrogen bonds with Arg195, Glu233, His299, His305, Gln63, Lys200, and Asp300. C–H–O-type interactions and other contacts are also observed with Tyr62, Trp59, Thr163, and Asp197. In addition, a π –alkyl interaction with Leu165 and several van der Waals contacts, particularly with Trp58, Leu162, Ala198, Val98, Ile235, and Gly306, are identified (Figure 2A). This dense interaction network is consistent with the particularly favorable docking score obtained for this reference compound.

Cyclohexane-1,2,3,4,5-pentol forms conventional hydrogen bonds between its hydroxyl groups and active-site residues, notably Glu233 and Asp300 (Figure 2B). Additional contacts involve Trp58, Trp59, Tyr62, Leu162, Leu165, Arg195, Asp197, Ala198, Ile235, and His299.

Finally, *p*-hydroxybenzoic acid adopts a distinct orientation within the catalytic pocket. Its carboxyl group forms conventional hydrogen bonds with Arg195 and His299 (Figure 2C). However, an unfavorable proximity to Asp300 is observed, which may contribute to reduced complex stabilization. Its aromatic

ring also establishes a π - π stacking interaction with Tyr62, complemented by van der Waals contacts with Trp58, Trp59, Leu165, Asp197, and Glu233.



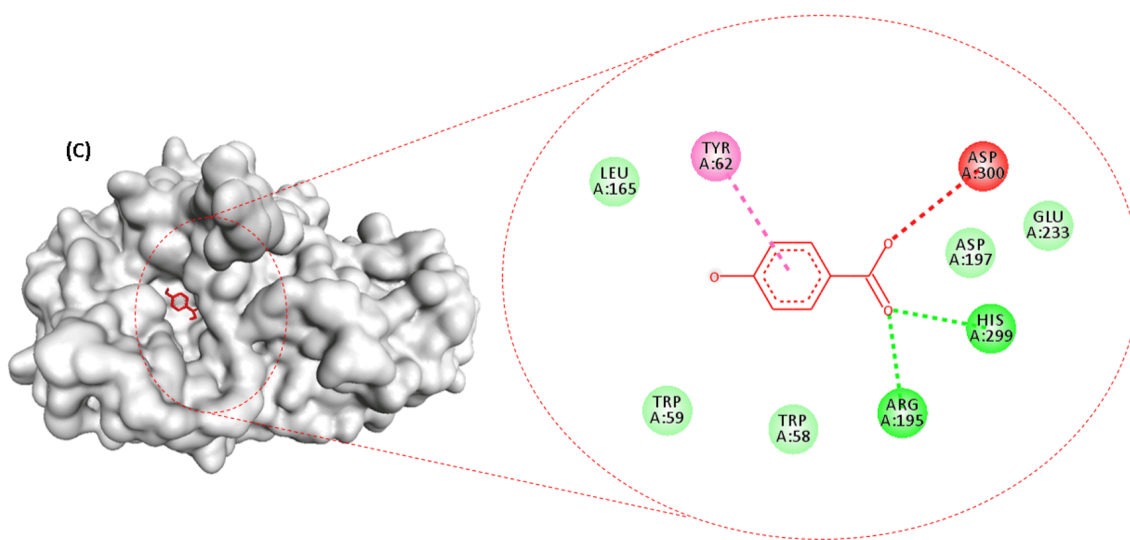


Figure 2. Three-dimensional (3D) and two-dimensional (2D) interaction profiles of the selected docking poses within the active site of human pancreatic α -amylase: (A) acarbose; (B) cyclohexane-1,2,3,4,5-pentol; and (C) *p*-hydroxybenzoic acid. In the 2D diagrams, hydrogen bonds are represented by green dashed lines, π -anion and π -alkyl interactions by beige and purple lines, respectively, unfavorable interactions by red lines, and van der Waals contacts by light green lines.

3.4. Analysis of Ligand Interaction Modes with Maltase-Glucoamylase

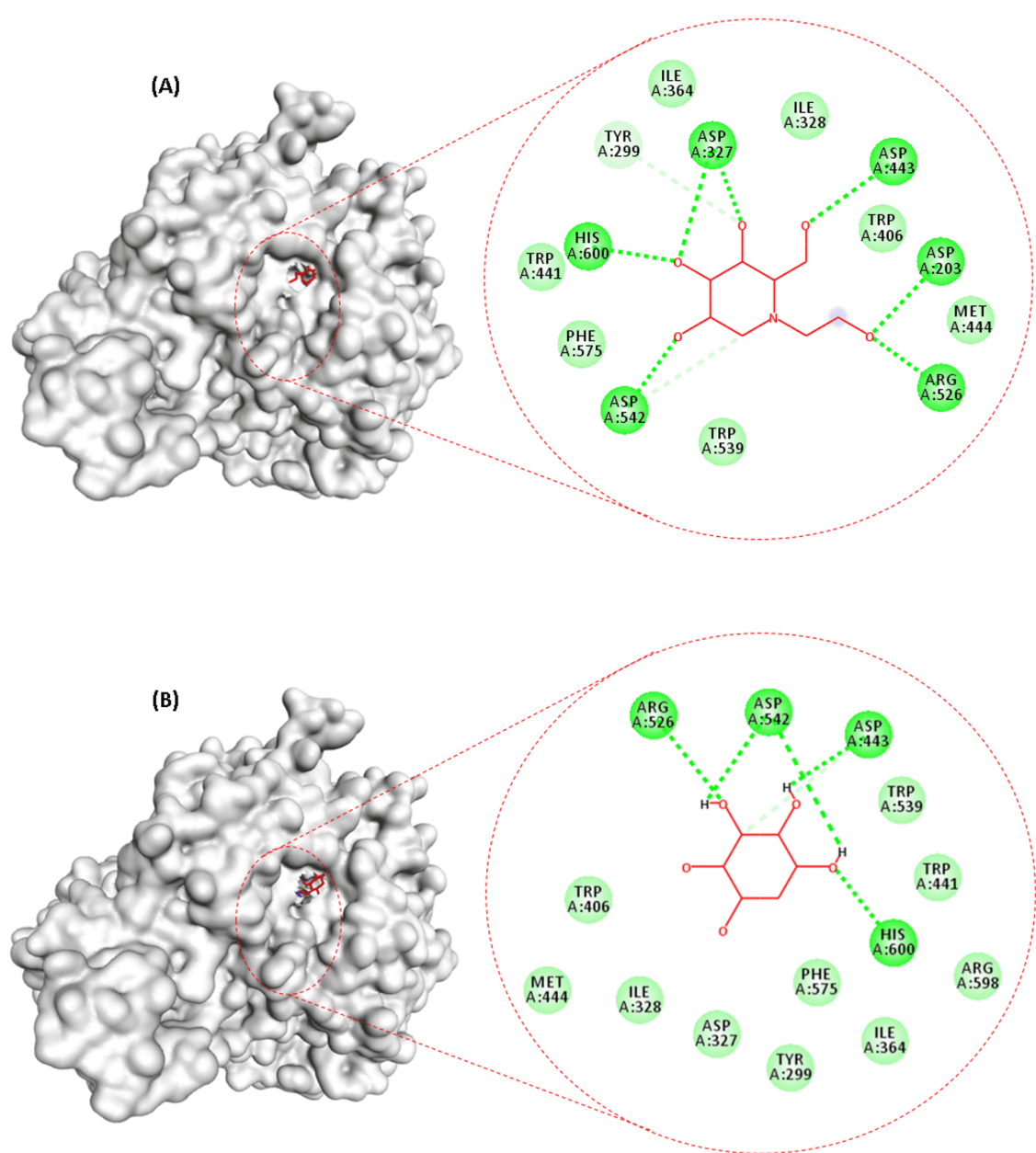
The selected poses occupy the active site of human maltase-glucoamylase and involve several residues within the catalytic pocket.

Miglitol forms seven hydrogen bonds involving, among others, Asp203, Asp327, Asp443, Asp542, Arg526, and His600. C–H–O interactions with Tyr299 and Asp542, together with van der Waals contacts involving Ile328, Ile364, Trp406, Trp441, Met444, Trp539, and Phe575, are also observed (Figure 3A). This interaction network contributes to its positioning within the catalytic pocket.

Cyclohexane-1,2,3,4,5-pentol forms hydrogen bonds with Asp443, Asp542, Arg526, and His600, as well as a C–H–O interaction with Asp443. These interactions are complemented by van der Waals contacts with Tyr299, Asp327, Ile328, Ile364, Trp406, Trp441, Met444, Trp539, Phe575, and Arg598 (Figure 3B). This interaction profile is consistent with the docking score obtained for this ligand.

Finally, *p*-hydroxybenzoic acid forms hydrogen bonds with Trp406 and Asp542, while its aromatic ring establishes a π -anion interaction with Asp443. Additional van der Waals contacts are observed with Tyr299, Asp327, Ile328, Trp441, Met444, Arg526, Trp539, Asp571, Phe575, and His600 (Figure 3C).

Both phytochemicals interact with Asp443 and Asp542, catalytic residues of maltase–glucoamylase, but exhibit interaction profiles distinct from that of miglitol, which forms a more extensive hydrogen-bonding network.



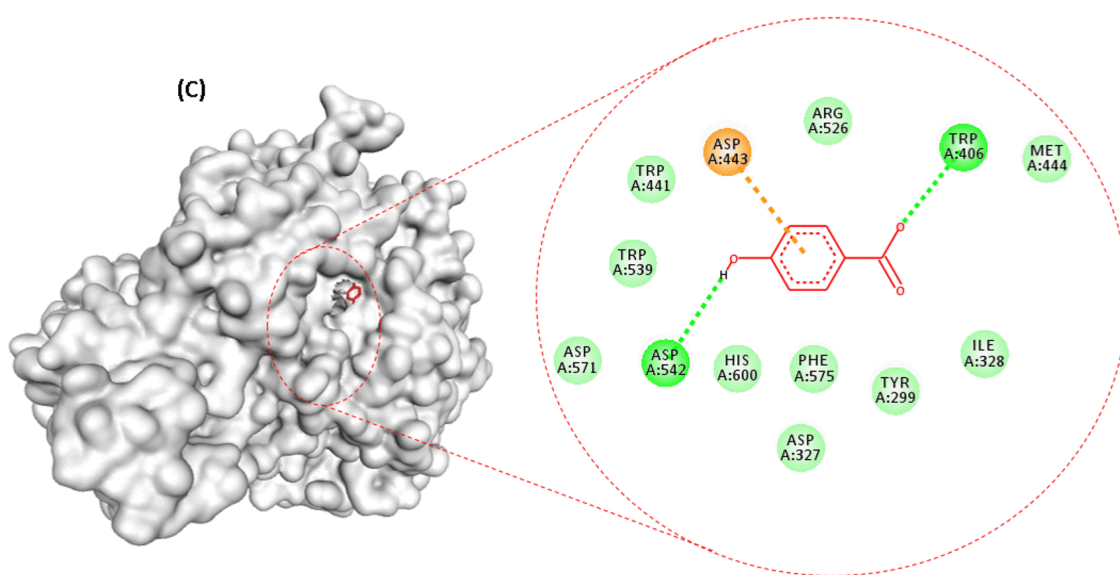


Figure 3. Three-dimensional (3D) and two-dimensional (2D) interaction profiles of the selected docking poses within the active site of human maltase-glucoamylase: (A) miglitol; (B) cyclohexane-1,2,3,4,5-pentol; and (C) *p*-hydroxybenzoic acid. For each ligand, the pose shown corresponds to the top-ranked pose (rank 1) obtained by docking and selected a priori for interaction analysis. In the 2D diagrams, hydrogen bonds are represented by green dashed lines, π -anion interactions by beige lines, unfavorable interactions by red lines, and van der Waals contacts by light green lines.

Superposition of the selected poses shows that the ligands occupy the same binding site (Figure 4).

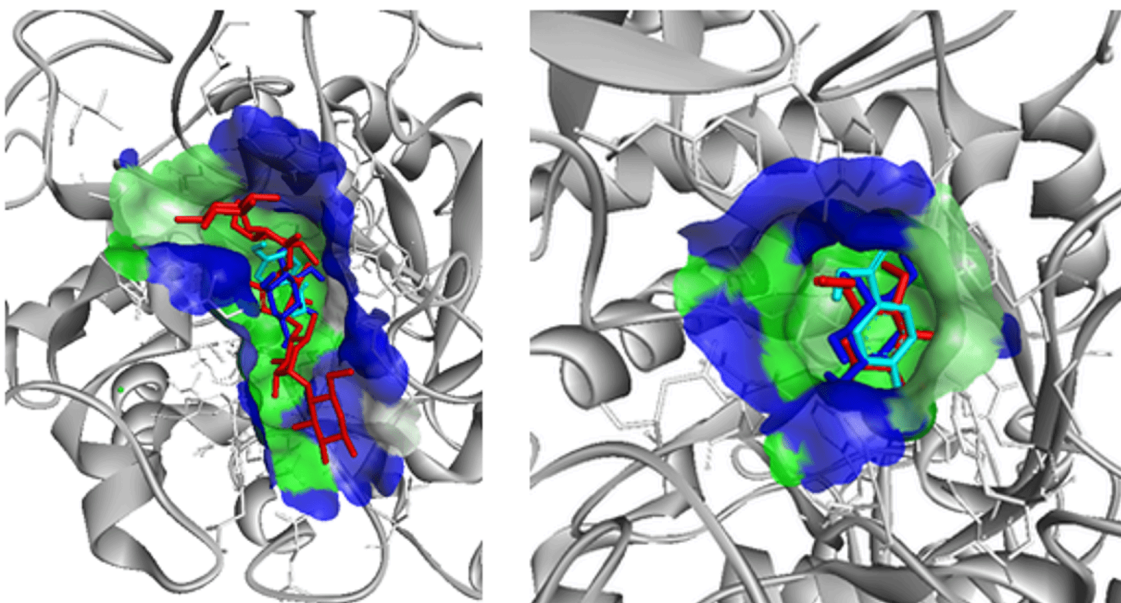


Figure 4. Superposition of the selected docking poses of the three ligands within the active sites of the enzymes investigated. Left: acarbose, cyclohexane-1,2,3,4,5-pentol, and *p*-hydroxybenzoic acid within the active site of human pancreatic α -amylase (PDB ID: 1B2Y). Right: miglitol, cyclohexane-1,2,3,4,5-pentol, and *p*-hydroxybenzoic acid within the active site of human maltase-glucoamylase (PDB ID: 3L4W). The reference ligands are shown in red, cyclohexane-1,2,3,4,5-pentol in blue, and *p*-hydroxybenzoic acid in green. The receptor is represented as a ribbon, and the molecular surface delineates the catalytic pocket. The superposition illustrates that the three ligands occupy the same binding pocket, albeit with distinct spatial orientations.

4. Discussion

This study evaluated *in silico* the interactions of *p*-hydroxybenzoic acid and cyclohexane-1,2,3,4,5-pentol, isolated from *H. coriacea* Gaertn., with human pancreatic α -amylase and maltase-glucoamylase. Acarbose and miglitol were used as reference inhibitors to compare docking scores and predicted binding modes.

For α -amylase, both phytochemicals yielded substantially less favorable docking scores than acarbose. This difference may partly reflect variations in ligand size and structure. The active site of α -amylase contains several carbohydrate-binding subsites, allowing oligosaccharide inhibitors such as acarbose to occupy a large portion of the catalytic cavity and establish numerous interactions^{[24][12]}. The size of acarbose therefore favors interactions across multiple subsites, consistent with its markedly more favorable docking score.

For *p*-hydroxybenzoic acid, the results are consistent with previous observations concerning natural phenolic compounds capable of interacting with enzymes involved in carbohydrate hydrolysis^{[25][26][27]}. However, these studies also highlight substantial variability in activity depending on both compound structure and the enzyme considered. The present findings therefore primarily suggest that *p*-hydroxybenzoic acid may interact with α -amylase, without establishing the extent of any inhibitory effect.

Evidence specifically concerning cyclohexane-1,2,3,4,5-pentol remains limited. Nevertheless, its polyhydroxylated structure allows a qualitative comparison with other bioactive cyclitols. *In vitro* inhibitory activity against α -amylase has been reported for D-pinitol^[28]. This comparison remains qualitative because of differences in substitution patterns and, particularly, the uncertainty surrounding the stereochemistry of the cyclohexane-1,2,3,4,5-pentol investigated in the present study.

For maltase-glucoamylase, the predicted docking scores for the two phytochemicals (−5.7 to −5.9 kcal/mol) were close to that of miglitol (−5.5 kcal/mol). Given the limitations of docking scoring functions, differences of 0.2–0.4 kcal/mol are too small to establish a robust ranking of these ligands^[20]. These values should therefore be interpreted as similar predicted scores under the conditions of the protocol used, rather than as quantitative differences in actual binding affinity.

Analysis of the binding modes provides additional structural information. Within maltase-glucoamylase, both phytochemicals interact with Asp443 and Asp542, which are catalytic residues of the enzyme. In α -amylase, the two phytochemicals, considered collectively, establish contacts with several active-site residues also involved in acarbose binding, notably Asp197, Glu233, and Asp300, although their interaction profiles differ.

These observations provide structural hypotheses consistent with a potential inhibitory effect. However, molecular docking does not experimentally measure binding affinity or enzymatic activity^[20]. The present results therefore do not establish actual inhibition of either α -amylase or maltase-glucoamylase. Rather, they support the need for experimental validation of both phytochemicals.

Another limitation concerns the stereochemical configuration of cyclohexane-1,2,3,4,5-pentol isolated from *H. coriacea* Gaertn., which has not been experimentally established. Consequently, the results obtained using the computational representation cannot be assigned to a specific naturally occurring stereoisomer. Protonation states were also not specifically evaluated. Furthermore, the use of a rigid receptor does not fully account for protein flexibility, solvent effects, or structural water molecules. The

absence of convergence tests at higher exhaustiveness levels and independent docking replicates further limits assessment of the robustness of the predicted poses. Finally, docking scoring functions remain approximations and cannot determine the actual binding free energy or the kinetics of inhibition in a biological system^[20].

These findings should therefore be complemented by stereochemical characterization of cyclohexane-1,2,3,4,5-pentol and, most importantly, *in vitro* enzymatic assays to determine the IC₅₀, the K_i where appropriate, and the mechanism of inhibition. Molecular dynamics simulations could subsequently provide further insight into complex stability and interaction dynamics. ADMET profiling would constitute a subsequent step if the biological activity of these compounds were confirmed.

5. Conclusions

In conclusion, this molecular docking study predicts that cyclohexane-1,2,3,4,5-pentol and *p*-hydroxybenzoic acid, isolated from *H. coriacea* Gaertn., can occupy the catalytic pockets of human α -amylase and maltase-glucoamylase. Their docking scores were markedly less favorable than that of acarbose for α -amylase but close to that of miglitol for maltase-glucoamylase.

These findings should nevertheless be interpreted with caution, given the limitations of molecular docking, particularly the use of a rigid receptor, the approximations inherent in scoring functions, and the uncertainty surrounding the stereochemical configuration of cyclohexane-1,2,3,4,5-pentol. In the absence of experimental validation, these predictions do not constitute evidence of actual enzyme inhibition.

In vitro enzymatic assays are therefore required to determine the IC₅₀, the K_i where appropriate, and the mechanism of inhibition. Molecular dynamics simulations, followed by *in vivo* studies if biological activity is confirmed, could further support this validation before any pharmacological implications are considered.

Statements and Declarations

Funding

No specific funding was received for this work.

Potential Competing Interests

No potential competing interests to declare.

Data Availability

The data underlying this study are available on Zenodo: NAZMOUL^[29], *Molecular docking data supporting the study of Hyphaene coriacea Gaertn. phytochemicals against human maltase-glucoamylase and pancreatic α -amylase*. Zenodo. DOI: 10.5281/zenodo.21989937. The dataset is made available under the Creative Commons Attribution 4.0 International (CC BY 4.0) license.

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