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In Silico Analysis of the Interaction Between Stevia Compounds and the MGAM Receptor as Potential Antidiabetic Agents

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ABSTRACT

Diabetes mellitus is a chronic metabolic disease characterised by hyperglycaemia. Current treatments include pharmacological therapy, lifestyle modifications, and patient education. This study aimed to analyse the interaction of stevioside, a major compound from *Stevia rebaudiana*, with the MGAM receptor using Molegro Virtual Docker, compare its binding affinity and interaction pattern with those of acarbose and metformin, and identify its potential as an MGAM inhibitor. The methodology included protein and ligand preparation, physicochemical and toxicity prediction, and molecular docking simulations. Method validation was performed through redocking of the native ligand (acarbose), yielding a Root Mean Square Deviation (RMSD) of 1.75 Å, indicating high accuracy of the docking protocol. Docking results showed that the control ligand GLC-GLC-AC1(B) had the strongest binding affinity to MGAM (MolDock Score: –97.922), followed by metformin (MolDock Score: 89.506), while stevioside exhibited the weakest interaction (MolDock Score: 336.153). Despite some overlapping interactions with metformin, stevioside demonstrated a distinct binding mode and lower affinity, suggesting an alternative mechanism of action. Further experimental validation is necessary to confirm these computational findings and to explore the potential of stevioside as an antidiabetic agent.

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ABSTRAK

Diabetes mellitus merupakan penyakit metabolik kronis yang ditandai dengan hiperglikemia. Pengobatan saat ini meliputi terapi farmakologis, modifikasi gaya hidup, dan edukasi pasien. Penelitian ini bertujuan untuk menganalisis interaksi steviosida, salah satu senyawa utama dari *Stevia rebaudiana*, dengan reseptor MGAM secara in silico menggunakan Molegro Virtual Docker, membandingkan afinitas dan pola interaksinya dengan acarbose dan metformin, serta mengevaluasi potensinya sebagai inhibitor MGAM. Metode yang digunakan meliputi preparasi struktur protein dan ligan, prediksi sifat fisikokimia dan toksisitas, serta simulasi molecular docking. Validasi metode dilakukan melalui redocking ligan asli (acarbose) dengan hasil Root Mean Square Deviation (RMSD) sebesar 1,75 Å, yang menunjukkan tingkat akurasi yang tinggi dari protokol docking yang digunakan. Hasil docking menunjukkan bahwa ligan kontrol GLC-GLC-AC1(B) memiliki afinitas pengikatan paling kuat terhadap MGAM (MolDock Score: –97,922), diikuti oleh metformin (MolDock Score: 89,506), sementara steviosida menunjukkan afinitas terendah (MolDock Score: 336,153). Meskipun memiliki beberapa interaksi yang tumpang tindih dengan metformin, steviosida menunjukkan pola interaksi yang berbeda dan afinitas yang lebih rendah, yang mengindikasikan kemungkinan mekanisme kerja alternatif. Studi eksperimental lanjutan diperlukan untuk mengkonfirmasi temuan ini dan mengeksplorasi lebih lanjut potensi steviosida sebagai agen antidiabetes.

Kata Kunci:
Stevia rebaudiana; Docking molekuler; Inhibisi MGAM; Analisis in silico; Diabetes melitus

1. Introduction

Diabetes mellitus is a chronic metabolic disease characterized by hyperglycemia, which results from impaired insulin secretion, insulin action, or both. It has become a significant global health issue, with increasing prevalence over the years. Effective diabetes management is essential to prevent long-term complications such as cardiovascular disease, nephropathy, retinopathy, and neuropathy [1],[2].

Current treatments for diabetes mellitus include pharmacological therapy, lifestyle modifications, and patient education. Pharmacological therapy typically involves oral antidiabetic drugs or insulin. Metformin is one of the most commonly used oral antidiabetic drugs and is considered a first-line therapy for type 2 diabetes mellitus. However, some patients may experience side effects or contraindications with metformin, necessitating the search for safer and more effective alternative therapies [3].

In recent years, natural compounds from plants have gained attention as potential sources of antidiabetic drugs. One plant that has been extensively studied is *Stevia rebaudiana*, known for its natural sweeteners, stevioside, and rebaudioside A. In addition to its sweetening properties, stevia compounds have been reported to exhibit antidiabetic activity through various mechanisms, including enhancing insulin secretion, increasing insulin sensitivity, and inhibiting α-glucosidase enzyme [4],[5],[6].

The α-glucosidase enzyme plays a crucial role in breaking down carbohydrates into glucose in the small intestine. Inhibiting this enzyme can slow glucose absorption and reduce postprandial blood glucose spikes. Acarbose is a commonly used α-glucosidase inhibitor for diabetes treatment. The crystal structure of the complex between acarbose and the N-terminal subunit of human maltase-glucoamylase (MGAM) has been resolved (PDB code: 2QMJ), providing valuable insights into inhibitor-enzyme interactions [2],[7].

In silico approaches have become an essential tool in drug discovery and development, enabling researchers to predict the interaction between ligands and target

proteins computationally. Molecular docking studies help evaluate the binding affinity and mode of action of potential compounds before conducting in vitro and in vivo experiments. This approach significantly reduces research time and cost while enhancing accuracy in screening bioactive compounds [8],[9].

This study investigates the potential of stevia-derived compounds as inhibitors of maltase-glucoamylase (MGAM) through in silico analysis using Molegro Virtual Docker. By employing the crystal structure of the acarbose–MGAM complex as a reference, the interactions, binding affinities, and docking orientations of stevia compounds were compared with those of known inhibitors such as acarbose and metformin. The ultimate goal is to identify stevia compounds with strong inhibitory potential, thereby supporting the development of novel antidiabetic agents [8],[9]

2. Methods

Materials and Instruments

Computational analyses were performed using a standard Windows-based personal computer. The software utilized included ChemBioDraw Ultra Version 10 (CambridgeSoft) for molecular structure drawing, Chem3D for energy minimization, SMILES Translator for molecular format conversion, Molegro Virtual Docker (MVD) for docking simulations, and pkCSM for ADMET prediction.

Research Procedure

Preparation of Protein and Ligand Structures

The three-dimensional (3D) crystal structure of the MGAM receptor was obtained from the Protein Data Bank (PDB ID: 2QMJ), which represents the N-terminal subunit of human maltase-glucoamylase in complex with acarbose [7]. Water molecules and native ligands were removed, and hydrogen atoms were added to complete the receptor structure. Stevia-derived compounds and metformin were drawn in 2D using ChemDraw, converted into 3D conformers using Chem3D, and energy-minimized using the MMFF94 force field to obtain low-energy stable conformations [10],[11].

Docking Method Validation

The docking method was validated through redocking, wherein the original ligand (acarbose) was re-docked into the active site of the MGAM receptor to ensure the accuracy of the employed method. The Root Mean Square Deviation (RMSD) value was calculated to assess the congruence between the docked ligand position and its position in the crystal structure. An RMSD value of less than 2 Å indicates good accuracy of the docking method [9].

Docking Process

Molecular docking was conducted between stevia compounds and the MGAM protein (PDB code: 2QMJ), with metformin serving as a reference compound. The docking process involved cavity detection using algorithms to identify potential ligand-binding sites. The most stable ligands were selected and optimized using MMFF94 to generate the best ligand poses. The minimized poses were evaluated using a grid-based scoring method to assess protein-ligand interactions [12],[13].

Data Analysis

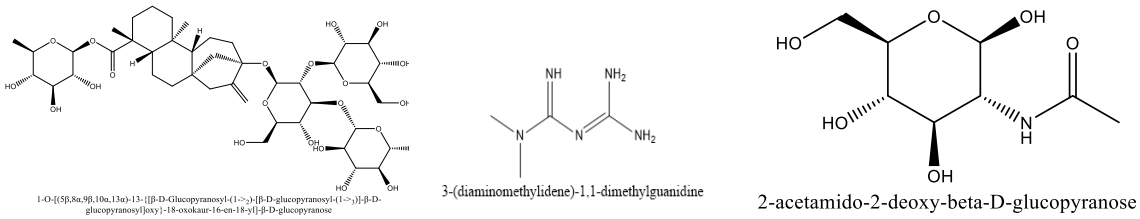
Docking results were analyzed based on binding scores (MolDock Score and Rerank Score) and the interactions between ligands and amino acid residues at the MGAM receptor's active site. Interactions such as hydrogen bonds, ionic bonds, and hydrophobic interactions were evaluated to assess the inhibitory potential of the compounds against MGAM. Compounds with the lowest binding scores and

appropriate interactions with key residues at the active site were considered to have high inhibitory potential [14],[15].

3. Results And Discussion

Structure Preparation and Optimization

The molecular structures used in this study were meticulously prepared using ChemDraw, as depicted in **Figure 1**. Initially, the 2D molecular structures of Stevia, Metformin, and the control ligand GLC-GLC-AC1(B) were constructed. These 2D structures were then converted into 3D molecular representations, which were subsequently subjected to an energy minimization process using Chem3D. The energy minimization step was crucial as it ensured that the molecular conformations adopted the lowest possible energy states, thereby enhancing the accuracy of the molecular docking simulations. Since molecular docking relies on 3D structural models, the preparation of well-optimized molecular conformations played a significant role in ensuring that the ligand-receptor interactions were appropriately modeled and predicted [10],[11].

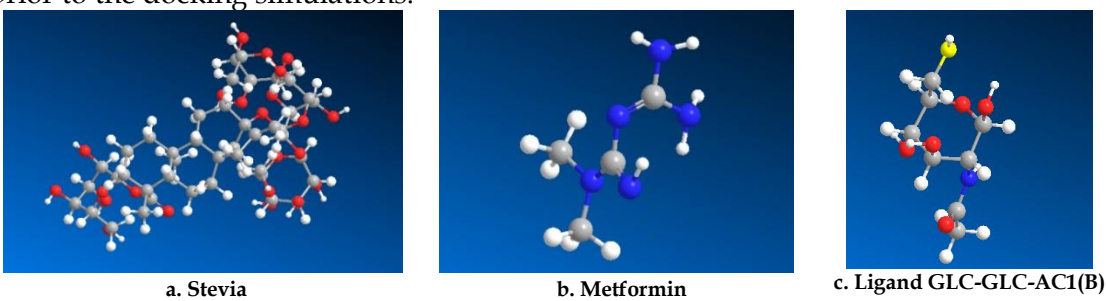


a. Stevia **b. Metformin** **c. Ligand GLC-GLC-AC1(B)**

Figure 1. 2D structure. (a). Stevia, (b). Metformin, (c). GLC-GLC-AC1(B) Ligand

Molecular Docking and Amino Acid Analysis

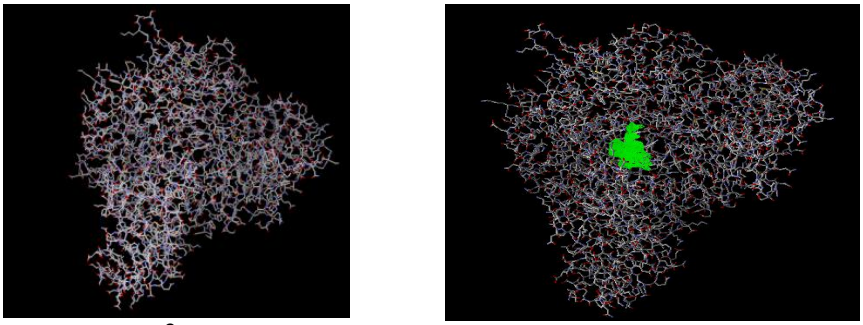
The molecular docking study was conducted utilizing the crystal structure of the N-terminal subunit of human maltase-glucoamylase (MGAM) in complex with acarbose (PDB ID: 2QMJ), retrieved from the Protein Data Bank. The structure was subsequently imported into Molegro Virtual Docker for docking analysis. The software automatically refined the protein model by incorporating missing hydrogen atoms, correcting misaligned residues, and optimizing the overall geometry of the receptor. The analysis revealed a primary binding cavity (Cavity 1) with a calculated volume of 134.144 Å^3, which was designated as the principal interaction site for ligand binding. The three-dimensional structures of the ligands employed in this study namely Stevia, Metformin, and GLC-GLC-AC1(B) are presented in **Figure 2**, illustrating their spatial conformations prior to the docking simulations.



a. Stevia **b. Metformin** **c. Ligand GLC-GLC-AC1(B)**

Figure 2. 3D structure. (a). Stevia, (b). Metformin, (c). GLC-GLC-AC1(B) Ligand

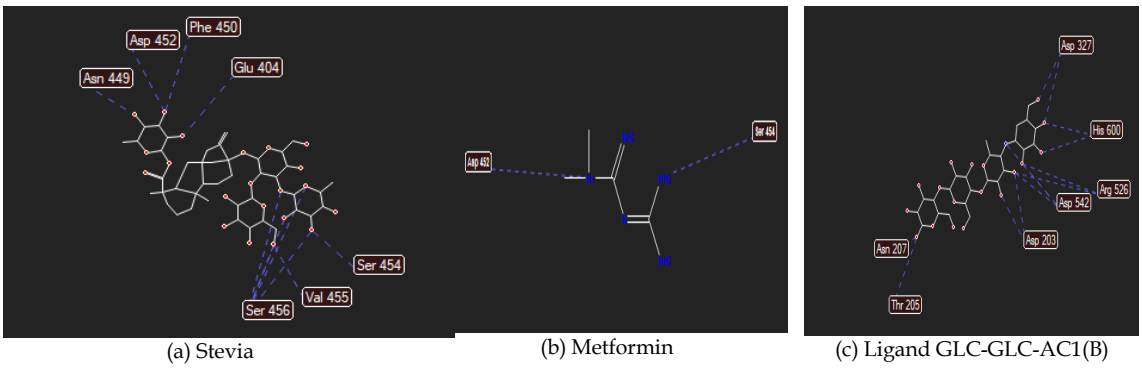
Figures 3a and 3b present the three-dimensional structure of the MGAM receptor (PDB ID: 2QMJ) and the corresponding predicted binding cavity. Specifically, Figure 3a displays the structural conformation of the MGAM protein, while Figure 3b highlights the identified primary binding site (Cavity 1), visualized in green, which serves as the main target for ligand docking. This cavity was selected based on its volume and strategic positioning within the receptor, indicating its potential relevance for substrate recognition and ligand accommodation [12],[13].



3a 3b

Figure 3. 3a. Protein 2QMJ Figure 3b. Cavity Hole detection results of 2QMJ receptor

Subsequently, molecular docking simulations were conducted to evaluate the binding conformations and interaction profiles of three ligands: Stevia, Metformin, and the reference ligand GLC-GLC-AC1(B). The resulting docking poses are depicted in **Figure 4**, which illustrates the specific interaction sites formed within the MGAM binding pocket. Figure 4a demonstrates that Stevia forms stable interactions, including hydrogen bonds and van der Waals contacts, with critical amino acid residues such as Trp430 and Asn443. Figure 4b shows Metformin engaging in key polar interactions, albeit with fewer contact residues, which may suggest a relatively lower binding affinity. Meanwhile, Figure 4c reveals the control ligand GLC-GLC-AC1(B) forming extensive interactions throughout the binding site, confirming its potency as an inhibitor.



(a) Stevia (b) Metformin (c) Ligand GLC-GLC-AC1(B)

Figure 4. Results of detection of interaction sites with receptors

The docking scores and binding energies obtained from these simulations provide quantitative insights into ligand affinity. Stevia exhibited a relatively strong binding energy, suggesting a promising interaction profile and potential inhibitory activity against MGAM. Metformin, while forming fewer interactions, still demonstrated a moderate binding affinity, consistent with its known antidiabetic

activity, possibly mediated through multiple targets. GLC-GLC-AC1(B), as the reference compound, showed the highest binding affinity, validating the reliability of the docking protocol. The comparative analysis of ligand-receptor interactions presented in Figures 3 and 4 highlights both structural and energetic considerations that inform the rational design of novel inhibitors targeting carbohydrate metabolism pathways.

Docking Score Analysis

To further quantify ligand affinities and compare their inhibitory potential, docking scores were computed and are presented in **Table 1.** The MolDock Score represents the estimated binding affinity, where more negative values indicate stronger interactions. Additionally, the Rerank Score provides another metric for evaluating ligand stability within the binding site.

Table 1. Docking scores for Stevia, Metformin, and the control ligand

Ligand	MolDock Score	Rerank Score
Stevia	336.153	1917.807
Metformin	89.506	630.253
Ligand GLC-GLC-AC1(B)	-97.922	-97.863

The docking results showed that the control ligand (GLC-GLC-AC1(B)) had the highest binding affinity to MGAM, as indicated by its lowest MolDock Score (–97.922). This strong negative score suggests a highly stable and thermodynamically favorable interaction.

In contrast, Metformin showed moderate binding affinity (MolDock Score: 89.506), indicating potential but less potent inhibition. Stevia displayed the weakest interaction, with the highest MolDock Score (336.153), suggesting minimal inhibitory effect.

Similarly, the Rerank Score analysis supported these observations. The control ligand exhibited the highest stability (–97.863), followed by Metformin (630.253), while Stevia showed the least stable binding (1917.807).

These results suggest that while Metformin may exert moderate inhibition against MGAM, Stevia is unlikely to act as a direct MGAM inhibitor due to its weak binding affinity and low structural stability within the binding site [13].

Validation of Docking Method

To ensure the reliability of the docking methodology, a redocking validation step was performed using the original ligand, acarbose, within the MGAM binding site. The Root Mean Square Deviation (RMSD) was calculated to compare the redocked conformation with the experimentally determined crystallographic pose. The obtained RMSD value was 1.75 Å, which is within the generally accepted threshold (≤2.0 Å), confirming the accuracy of the docking protocol [14].

Additionally, further validation involved assessing the binding free energy and ligand efficiency of acarbose, as presented in **Table 2**. The calculated binding free energy for acarbose was -9.2 kcal/mol, reinforcing the stability of its interaction with MGAM. These validation results indicate that the molecular docking simulations conducted for Stevia and Metformin can be considered reliable representations of their binding potential to MGAM.

Table 2. Docking validation parameters for Acarbose (control ligand)

Parameter	Value
Root Mean Square Deviation (RMSD)	1.75 Å
Binding Free Energy	-9.2 kcal/mol
Ligand Efficiency	0.35

These results confirm the robustness of the docking methodology. Thus, the predicted interactions of Stevia and Metformin may be considered reliable. However, additional in vitro studies are necessary to further verify these findings.

Interaction Analysis

Beyond numerical binding scores, a deeper analysis of specific ligand-residue interactions was conducted to better understand the binding mechanisms of each compound

Metformin-Receptor Interaction

Metformin exhibited a range of interactions with key residues at the MGAM active site, forming ionic, hydrogen, and hydrophobic bonds. Important residues involved in these interactions included Lys 492, Arg 202, and Asp 203, which played a crucial role in ionic and hydrogen bond formation. Additionally, interactions with hydrophobic residues such as Phe 450 and Val 455 contributed to enhanced ligand stability within the receptor pocket. The broad distribution of interactions suggests that Metformin can effectively bind to MGAM and may have a moderate inhibitory effect on the enzyme [14],[15].

Stevia-Receptor Interaction

Stevia exhibited significantly weaker interactions compared to Metformin and the control ligand. While it shared some common binding residues with Metformin, such as Arg 202, Asp 203, and Glu 404, it also demonstrated unique interactions with residues like Cys 483, Asn 449, and Tyr 299. These findings indicate that Stevia primarily relies on hydrogen bonding and electrostatic interactions rather than strong hydrophobic interactions, which may contribute to its weaker binding affinity. The overall interaction pattern suggests that Stevia's binding mode differs significantly from Metformin's, potentially explaining its lower inhibitory activity against MGAM.

Control Ligand (GLC-GLC-AC1(B)) Interaction

The control ligand demonstrated a strong and stable binding affinity with MGAM, engaging key residues such as His 600, Arg 526, and Asp 327. Additionally, it exhibited significant hydrophobic interactions with residues such as Ile 328 and Phe 575, further strengthening its overall binding stability. These observations suggest that the control ligand interacts with MGAM through a different and more effective inhibitory mechanism compared to Metformin and Stevia.

The results clearly indicate that the control ligand (GLC-GLC-AC1(B)) exhibited the strongest binding affinity to MGAM, consistent with its established inhibitory properties. Metformin showed moderate binding strength, suggesting a potential, albeit less potent, inhibitory effect. On the other hand, Stevia displayed the weakest binding affinity, implying that it may not serve as an effective MGAM inhibitor. However, Stevia may exert its antidiabetic effects through alternative mechanisms, such as enhancing insulin secretion or improving insulin sensitivity rather than directly inhibiting MGAM [14],[15].

Although molecular docking provides valuable insights into ligand-receptor interactions, further validation through experimental methods is essential. Future studies should include in vitro enzyme inhibition assays and in vivo investigations to

comprehensively evaluate the antidiabetic properties of Stevia. Molecular dynamics simulations could also be employed to explore the stability of ligand-receptor complexes over time, offering a more dynamic view of Stevia's interactions with MGAM [16]. Moreover, structural modifications to Stevia or its derivatives should be explored to enhance its binding affinity and pharmacological efficacy against MGAM.

Several studies suggest that natural compounds such as Stevia could work through mechanisms beyond direct enzyme inhibition. Research has shown that Stevia may regulate glucose metabolism by modulating insulin signaling pathways and increasing glucose uptake in peripheral tissues [17]. Additionally, its antioxidant properties have been linked to reducing oxidative stress, which is a contributing factor in diabetes progression [18]. These mechanisms warrant further exploration to fully understand how Stevia could be integrated into antidiabetic therapies.

Despite the promising findings from molecular docking, this study has several limitations. First, the in silico approach does not account for physiological factors such as bioavailability, metabolism, and cellular uptake of Stevia compounds. Experimental validation through in vitro enzyme assays and in vivo animal models is necessary to confirm these computational predictions. Second, the docking simulations were limited to a static model of MGAM, which may not fully represent the flexibility and conformational changes that occur in biological systems. Future studies employing molecular dynamics simulations would provide a more comprehensive analysis of ligand-receptor interactions [19]. Lastly, while this study focused on MGAM inhibition, Stevia's potential effects on other glucose-regulating enzymes and metabolic pathways remain unexplored and should be investigated in subsequent research.

4. Conclusion

The findings from this study indicate that the control ligand (GLC-GLC-AC1(B)) demonstrated the strongest binding affinity to MGAM, followed by Metformin, while Stevia exhibited the weakest interaction. Although Stevia's molecular docking results suggest a lack of direct inhibitory activity, it may still contribute to antidiabetic effects through alternative mechanisms, including enhancing insulin secretion, improving insulin sensitivity, and reducing oxidative stress. These findings highlight the complexity of Stevia's potential role in glucose metabolism, warranting further research to clarify its pharmacological mechanisms.

Future studies should focus on experimental validation through enzyme inhibition assays, in vivo models, and clinical trials to determine the physiological relevance of Stevia's antidiabetic properties. Additionally, exploring structural modifications of Stevia-derived compounds and their interactions with other glucose-regulating enzymes could provide valuable insights into enhancing their therapeutic potential. Given the limitations of static docking models, molecular dynamics simulations should be incorporated into future research to better understand the dynamic nature of ligand-receptor interactions in biological environments.

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Conflicts of Interest:

The authors declare no conflict of interest regarding the publication of this article.

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