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Molecular docking of triterpene glycoside compounds (cucurbitane, charantin and momordicin) in bitter gourd (*Momordica charantia* L.) fruit extract as anti-diabetes mellitus type 2

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Abstract: Diabetes mellitus is a chronic metabolic disorder characterized by elevated blood glucose levels due to impaired insulin secretion, insulin resistance, or both. Type 2 diabetes mellitus (T2DM) accounts for approximately 90% of all diabetes cases and remains a significant global health challenge. Current pharmacological treatments often have limited efficacy and adverse side effects, necessitating the exploration of safer, more effective antidiabetic agents. *Momordica charantia* (bitter melon) is a medicinal plant known for its hypoglycemic properties, attributed to bioactive compounds such as cucurbitane-type triterpenoid glycosides, charantin, and momordicin. This study evaluated the potential of cucurbitane, charantin, and momordicin as antidiabetic agents for T2DM using molecular docking simulations. The crystal structure of aldose reductase (PDB ID 2HV5) was obtained from the Protein Data Bank, and AutoDock Tools 1.5.7 was used for docking studies. The binding affinities and interaction patterns of the test compounds were compared with zopolrestat, a standard ligand. Cucurbitane exhibited the lowest binding free energy (-11.70 kcal/mol), indicating the strongest interaction with the 2HV5 protein. All compounds demonstrated similarities in their interactions with key amino acid residues, suggesting comparable biological activity. These findings highlight cucurbitane's potential as a lead compound for developing more effective antidiabetic therapies for T2DM.

Keywords: diabetes mellitus, bitter gourd, cucurbitane, charantin, momordicin

Introduction

Diabetes mellitus is a chronic metabolic disorder characterized by elevated blood glucose levels resulting from abnormalities in insulin secretion, insulin action, or a combination of both [1]. It is broadly classified into two types: type I diabetes and type II diabetes. Type I diabetes is marked by the complete absence of insulin production, whereas type II diabetes arises from pancreatic β-cell dysfunction and insulin resistance [2]. Among these, type II diabetes mellitus accounts for approximately 90% of all diabetes cases, making its management a significant challenge in the medical field [3].

The pathophysiology of this disease involves multiple cellular pathways, including impaired the secretion and resistance of insulin and altered the metabolism of carbohydrate. Numerous proteins on human have been recognized as important regulators in the development and progression of diabetes. These include PPAR-γ, insulin receptor tyrosine kinase, (GFAT), glucokinase, 11 β-HSD, AMP-activated protein kinase, 11 β-HSD, dipeptidyl peptidase IV, insulin receptor substrates, interleukin-1β, dipeptidyl peptidase IV, GFAT and protein kinase B [4].

One therapeutic target in type II diabetes mellitus is aldose reductase, an enzyme implicated in glucose metabolism through the polyol pathway, which converts glucose into sorbitol and subsequently fructose. The protein structure of aldose reductase (PDB ID 2HV5), highlights its role in glucose metabolism. Elevated aldose reductase activity has been linked to hyperglycemia-induced complications, as it contributes to insulin insensitivity and elevated blood glucose levels [5,6].

While several pharmacological treatments are available for type II diabetes mellitus, including enzyme

inhibitors and hypoglycemic agents, these treatments often exhibit limited efficacy and are associated with adverse effects such as edema, gastrointestinal irritation, and other severe complications [7]. This underscores the urgent need for safer and more effective therapies for diabetes [8].

Momordica charantia L. belongs to the Cucurbitaceae family. This plant havebioactive compounds such as momordicin, cucurbitane-type triterpenoid glycosides and charantin. These compounds exhibit insulin-like structures and mechanisms of action. Notably, triterpenoid glycosides in bitter melon regulate blood glucose levels by enhancing AMP-activated protein kinase (AMPK) activity. This action promotes glucose uptake, fatty acid oxidation, and inhibition of hepatic glucose production and lipid synthesis [9].

This study aims to evaluate the interaction of triterpenoid glycoside compounds, specifically cucurbitane, charantin, and momordicin from bitter melon as potential antidiabetic agents for type II diabetes mellitus using molecular docking techniques.

Method

This study utilized triterpene glycoside compounds—cucurbitane, charantin, and momordicin—to evaluate their potential as antidiabetic agents through molecular docking simulations. The crystal structure of the target protein (PDB ID: 2HV5) was obtained from the Protein Data Bank (PDB) for use in the docking studies. Zopolrestat (ZST) was selected as a reference ligand to validate the docking protocol. Molecular docking simulations were conducted using AutoDock Tools version 1.5.7 (ADT 1.5.7).

The validation process commenced with the preparation of the protein and ligand structures. The 2HV5 protein structure was refined by removing the native ligand and solvent molecules, primarily water, to minimize interference during docking. Polar hydrogens were added to the protein to facilitate accurate intramolecular interactions with the ligand. To validate the docking method, the ZST ligand was docked to the 2HV5 protein. Grid box parameters were set with dimensions of 50 × 50 × 50 points along the X, Y, and Z axes, centered at coordinates (17.032, -6.715, 13.582), and a grid point spacing of 0.375 Å. The docking success was assessed by calculating the root mean square deviation (RMSD) value, with an acceptable threshold set at ≤ 2 Å. The docking results were visualized to analyze interaction types and locations, including hydrogen, carbon, sulfur, and alkyl bonds.

Following validation, docking simulations were performed for the test compounds—momordicin, cucurbitane, and charantin—with the 2HV5 protein. Binding energies were calculated for each compound and compared to that of the ZST ligand. Two-dimensional (2D) visualizations were generated to examine the interactions between the triterpene glycoside compounds and the amino acid residues of the 2HV5 protein. These interactions, including hydrogen bonds, alkyl bonds, and π-sigma bonds, were illustrated using colored dotted lines.

Additionally, the amino acid residues involved in binding for the test compounds were compared with those for the ZST ligand to evaluate the similarity of interaction patterns. This analysis provided insights into the potential biological activity of the triterpene glycosides.

The docking and visualization processes yielded detailed information regarding the stability and efficacy of the interactions between the triterpene glycoside compounds and the 2HV5 protein. This information is crucial for assessing the potential of these compounds as antidiabetic agents for the treatment of type 2 diabetes mellitus.

Results

Molecular docking

In this study, cucurbitane-2HV5 demonstrated a binding free energy higher than the momordicin-2HV5 and charantin-2HV5 complex (Table 1). The docking results for cucurbitane with the 2HV5 protein revealed a binding free energy of -11.70 kcal/mol, compared to -11.59 kcal/mol for zopolrestat. These results indicate that cucurbitane exhibits a lower binding energy, suggesting stronger interactions and potential antidiabetic activity.

Interaction analysis

Figure 1 illustrates the 2D visualization of the interactions between the amino acid residues of the 2HV5 protein and the compounds: zopolrestat, momordicin, cucurbitane, and charantin.

The 2D visualization of cucurbitane interactions revealed two π-sigma bonds with tryptophan (Trp) residues: Trp A:20 and Trp A:111, marked by purple dotted lines. Additionally, 10 alkyl bonds were observed

Table 1. Binding energy of test compounds to 2HV5

Compounds	Binding free energy (kcal/mol)	Amino acid residues
Zopolrestat/ZST (native ligand)	-11.59	Pro130, Tyr309, Leu300, Cys80, Phe122, Trp79, Trp111, Cys298, Lys77, His110, Val77, Trp20, Cys303
Momordicin	-9.21	Gln49, Val47, Trp20, Tyr48, His110, Trp219, Pro218
Cucurbitane	-11.70	Pro310, Tyr309, Cys303, Trp111, Leu300, Phe122, Trp219, Pro218, Trp79, Val47, Tyr48
Charantin	-8.50	Phe122, Val47, Trp219, Leu300, Leu124, Trp20, Cys298, Asn160, Ser159, Gln183

between cucurbitane and the following residues: proline (Pro) A:310, cysteine (Cys) A:303, tyrosine (Tyr) A:309, leucine (Leu) A:300, phenylalanine (Phe) A:122, tryptophan (Trp) A:219, proline (Pro) A:128, tyrosine (Tyr) A:48, valine (Val) A:47, and tryptophan (Trp) A:79.

Comparative analysis showed that the amino acid residues involved in cucurbitane interactions—Trp, Pro, Cys, Tyr, Leu, Phe, and Val—were also present in the zopolrestat interactions. This similarity in amino acid binding residues indicates that cucurbitane shares comparable interaction patterns with the native ligand, underscoring its potential as a competitive inhibitor and effective antidiabetic agent.

Discussion

Bitter melon extracts have long been recognized for their efficacy in lowering blood glucose levels. Several bioactive compounds with hypoglycemic potential, such as cucurbitane-type triterpenoid glycosides, charantin, and momordicin, have been extensively studied for their antidiabetic properties. Bitter melon contains various saponin-class compounds, including charantin, cucurbitacin, and momordicoside D, which exhibit promising antidiabetic activity [11]. Additionally, specific compounds such as 3β,7β,25-trihydroxy cucurbita-5,23 (E)-dien-19-al, charantal, charantoside XI, and 25ξ-isopropenylchole-5,6-ene-3-O-D-glucopyranoside have been analyzed using molecular docking techniques, further substantiating the potential of bitter melon as a source of antidiabetic agents [12].

Molecular docking studies utilize the root mean square deviation (RMSD) as a critical validation parameter to assess the accuracy of docking predictions. The RMSD value quantifies the difference between the experimentally determined conformation of the native ligand and the predicted conformation obtained through docking [13]. An RMSD value within the tolerance limit of ≤2 Å is considered indicative of reliable docking predictions [14]. The docking protocol employed in this study achieved an RMSD of 0.57, confirming its validity for further analyses.

The binding free energy is a key metric used to evaluate ligand-receptor interactions. A smaller binding free energy indicates a stronger interaction between the ligand and the target protein, reflecting a higher binding affinity [15]. For a compound to be considered biologically active and capable of stable interaction, its binding free energy must be ≤-7.00 kcal/mol [16].

Cucurbitane showed promising results in molecular docking analyses. Its binding free energy was lower than that of zopolrestat, suggesting a stronger interaction and greater affinity with the 2HV5 protein. Furthermore, the 2D visualization of amino acid interactions revealed significant overlap in residues between cucurbitane and ZST, including tryptophan (Trp), proline (Pro), cysteine (Cys), tyrosine (Tyr), leucine (Leu), phenylalanine (Phe), and valine (Val). This similarity in interaction patterns suggests that cucurbitane shares comparable biological activity with zopolrestat [17].

The results of this study demonstrate that cucurbitane has significant potential as an antidiabetic agent. Its strong binding affinity, stable interactions, and similar biological activity to the native ligand underscore its viability for further exploration in the development of treatments for type 2 diabetes mellitus.

Conclusion

Based on molecular docking results, cucurbitane demonstrated the strongest potential as an antidiabetic

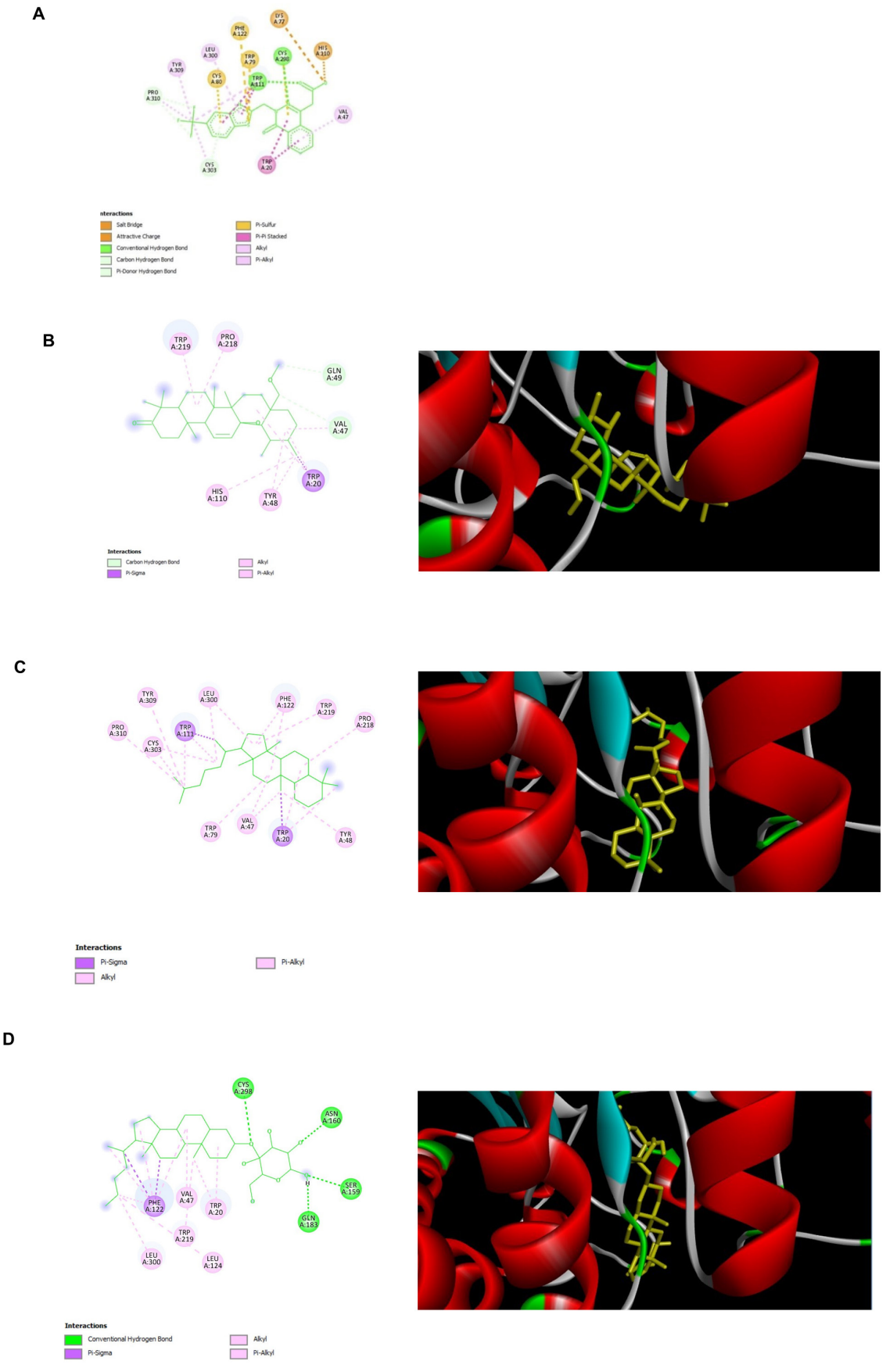

Figure 1. 2D visualization of amino acid residue and test compounds. (A) ZST ligand, (B) momordicin, (C) cucurbitane. (D) charantin

agent compared to momordicin and charantin. Despite differences in binding affinities, all three compounds exhibited similar interactions with key amino acid residues. These findings suggest that cucurbitane, along with momordicin and charantin, holds promise for further development as potential antidiabetic drug candidates for the treatment of type 2 diabetes mellitus.

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Declaration of interest

The authors declare no conflict of interest.

Author contributions

AHS, WNA conceptualized the research; DC, DMH, GMH, JTA, LGES, MP, NOC, AHS, WNA wrote the manuscript, interpreted and analyzed the data; All authors have read the final manuscript.

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