Research Article

In Silico Screening of Natural Compounds for Identification of GLP-1 Receptor Agonists for Type 2 Diabetes Mellitus

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Abstract

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder characterized by insulin resistance and impaired insulin secretion. Glucagon-like peptide-1 (GLP-1) receptor agonists represent an effective therapeutic strategy due to their ability to enhance glucose-dependent insulin secretion, suppress glucagon release, delay gastric emptying, and promote satiety. However, currently available GLP-1 agonists are largely peptide-based and require parenteral administration. In the present study, a structure-based computer-aided drug design (CADD) approach was employed to identify potential small-molecule GLP-1 receptor agonists from natural product libraries. The crystal structure of the GLP-1 receptor catalytic domain (PDB ID: 5TTG) was used as the target for virtual screening of 4000 natural compounds obtained from the AnalytiCon Discovery library. Molecular docking was performed using AutoDock Vina, and compounds with binding energies better than −11.0 kcal/mol were shortlisted. The top-ranking ligands were further evaluated for pharmacokinetic and drug-likeness properties using SwissADME. Several natural compounds demonstrated strong binding affinity, favorable ADMET profiles, and stable interactions with key GLP-1 receptor residues. These findings suggest that the identified compounds may serve as promising leads for the development of orally active GLP-1 receptor modulators, warranting further experimental validation.

Keywords: Type 2 diabetes mellitus, GLP-1 receptor, natural compounds, molecular docking, virtual screening, SwissADME

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Introduction

Type 2 diabetes mellitus (T2DM) is one of the most prevalent metabolic disorders worldwide, accounting for more than 90% of diabetes cases. It is characterized by chronic hyperglycemia resulting from insulin resistance and progressive pancreatic β-cell dysfunction. Long-term complications of T2DM include cardiovascular diseases, nephropathy, neuropathy, and retinopathy, posing a major global health burden.

Glucagon-like peptide-1 (GLP-1) is an incretin hormone that plays a critical role in glucose homeostasis. Activation of the GLP-1 receptor enhances insulin secretion in a glucose-dependent manner, suppresses glucagon release, delays gastric emptying, and reduces appetite. Although peptide-based GLP-1 receptor agonists such as liraglutide and semaglutide are clinically effective, their injectable nature, high cost, and stability issues limit widespread use. Therefore, the discovery of orally

bioavailable, non-peptidic GLP-1 receptor agonists is of significant interest.

Natural products represent a rich source of structurally diverse and biologically active molecules. Combined with computer-aided drug design (CADD) techniques, natural product screening offers a cost-effective and efficient strategy for early-stage drug discovery. In this study, we employed an integrated in silico workflow to identify potential natural GLP-1 receptor agonists using molecular docking and pharmacokinetic evaluation.

Materials and Methods

Protein Structure Preparation

The three-dimensional crystal structure of the GLP-1 receptor catalytic domain (PDB ID: 5TTG) was retrieved from the Protein Data Bank. The structure was selected based on its high resolution and suitability for structure-based screening. Receptor preparation was performed using AutoDock Tools by removing water molecules and heteroatoms, adding polar hydrogens, and assigning Kollman charges. The prepared protein was saved in PDBQT format for docking studies.

Ligand Dataset Preparation

A library of 4000 natural compounds was obtained from the AnalytiCon Discovery database. Ligands were converted from SDF format to three-dimensional structures using OpenBabel, followed by energy minimization. The optimized ligands were then converted into PDBQT format with appropriate torsional flexibility for docking.

Molecular Docking and Virtual Screening

Virtual screening was carried out using AutoDock Vina. A grid box encompassing the active binding pocket of the GLP-1 receptor was defined based on CASTp analysis. Docking simulations were performed batch-wise, and ligands were ranked according to their binding affinities. Compounds exhibiting binding energies better than −11.0 kcal/mol were shortlisted for further analysis.

ADMET and Drug-Likeness Analysis

The shortlisted compounds were evaluated using SwissADME to predict pharmacokinetic properties, including gastrointestinal absorption, lipophilicity, solubility, blood–brain barrier permeability, and compliance with Lipinski's Rule of Five. Compounds with favorable ADMET profiles and no PAINS alerts were considered potential drug candidates.

Interaction Analysis and Visualization

Docked ligand–receptor complexes were visualized using PyMOL and Discovery Studio. Key interactions such as hydrogen bonds, hydrophobic contacts, π–π stacking, and salt bridges were analyzed to understand binding stability and receptor compatibility.

Results and Discussion

Receptor Validation

Structural validation using PROCHECK, ERRAT, VERIFY3D, and WHATCHECK confirmed the reliability of the 5TTG structure. Approximately 85% of residues were located in favored regions of the Ramachandran plot, and ERRAT scores exceeded 90%, indicating good structural quality for docking studies.

Virtual Screening Outcomes

Docking of the 4000 natural compounds against the GLP-1 receptor identified several ligands with strong binding affinities (≤ −11.0 kcal/mol). These compounds demonstrated favorable steric complementarity within the receptor binding pocket, suggesting potential agonistic activity.

Pharmacokinetic Evaluation

SwissADME analysis revealed that many of the shortlisted compounds exhibited high predicted oral absorption, acceptable solubility, and compliance with Lipinski's rule. The absence of PAINS alerts further supported their suitability as drug-like molecules.

Ligand–Receptor Interaction Analysis

Visualization of docking poses revealed stable ligand–receptor interactions involving key residues of the GLP-1 receptor. Hydrogen bonding, hydrophobic interactions, and π–π stacking contributed to binding stability, supporting the predicted affinity of the shortlisted compounds.

Table 1. List of top-ranked natural compounds identified through virtual screening against the GLP-1 receptor along with their docking scores.

	A	B
1	Ligand	Affinity
2	ligand4041.pdbqt_log	-13.2
3	ligand3530.pdbqt_log	-13
4	ligand4098.pdbqt_log	-12.9
5	ligand3610.pdbqt_log	-12.8
6	ligand3486.pdbqt_log	-12.7
7	ligand3971.pdbqt_log	-12.7
8	ligand3508.pdbqt_log	-12.5
9	ligand4099.pdbqt_log	-12.5
10	ligand3998.pdbqt_log	-12.4

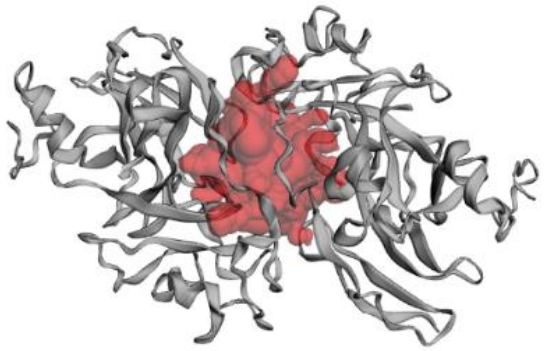

Figure 1. Three-dimensional structure of the GLP-1 receptor (PDB ID: 5TTG) used for docking studies.

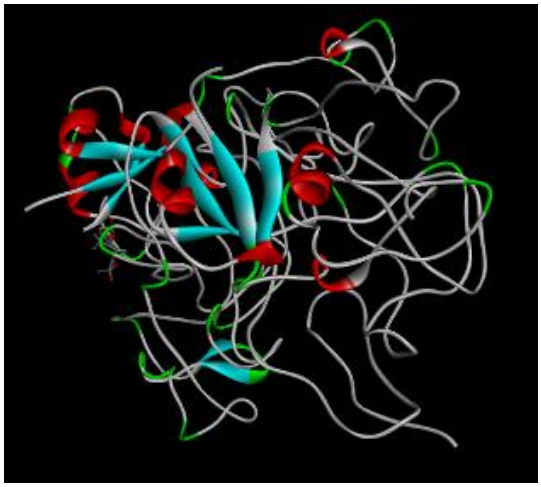

Figure 2. Representative docking pose of a top-ranked natural compound within the active site of the GLP-1 receptor showing key intermolecular interactions.

Conclusion

The present study demonstrates the effectiveness of an integrated CADD approach in identifying potential natural GLP-1 receptor agonists for the treatment of type 2 diabetes mellitus. Virtual screening and molecular docking identified several compounds with strong binding affinities and favorable pharmacokinetic properties. Acetoxy guaianolide emerged as a promising anti-diabetic herbal compound. An acetoxy guaianolide is a type of natural

sesquiterpene lactone (a complex organic molecule from plants) that features a guaianolide core structure with an acetoxy group (-OCOCH) attached at a specific position, often exhibiting biological activities like cytotoxicity (killing cancer cells) or anti-inflammatory effects, commonly found in plants of the Asteraceae family (like Chrysanthemum or Centaurea species).These natural compounds represent promising lead candidates for further in vitro and in vivo validation, with the potential to contribute to the development of orally active GLP-1 receptor modulators.

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References:

1. DeFronzo RA, Ferrannini E, Groop L, et al. Type 2 diabetes mellitus. *Nat Rev Dis Primers*. 2015;1:15019.
2. Cho NH, Shaw JE, Karuranga S, et al. IDF Diabetes Atlas: Global estimates of diabetes prevalence. *Diabetes Res Clin Pract*. 2018;138:271–281.
3. Drucker DJ. The biology of incretin hormones. *Cell Metab*. 2006;3(3):153–165.
4. Holst JJ. The physiology of glucagon-like peptide 1. *Physiol Rev*. 2007;87(4):1409–1439.
5. Nauck MA, Meier JJ. Incretin hormones: Their role in health and disease. *Diabetes Obes Metab*. 2018;20(S1):5–21.
6. Knudsen LB, Lau J. The discovery and development of liraglutide and semaglutide. *Front Endocrinol*. 2019;10:155.
7. Wootten D, Miller LJ. Structural biology of the GLP-1 receptor. *Trends Pharmacol Sci*. 2020;41(6):427–440.
8. Sliwoski G, Kothiwale S, Meiler J, Lowe EW. Computational methods in drug discovery. *Pharmacol Rev*. 2014;66(1):334–395.
9. Lionta E, Spyrou G, Vassilatis DK, Cournia Z. Structure-based virtual screening for drug discovery. *Curr Top Med Chem*. 2014;14(16):1923–1938.
10. Trott O, Olson AJ. AutoDock Vina: Improving docking speed and accuracy. *J Comput Chem*. 2010;31(2):455–461.
11. Morris GM, Huey R, Lindstrom W, et al. AutoDock4 and AutoDockTools4. *J Comput Chem*. 2009;30(16):2785–2791.
12. Daina A, Michielin O, Zoete V. SwissADME: A free web tool for ADME evaluation. *Sci Rep*. 2017;7:42717.
13. Lipinski CA. Lead- and drug-like compounds: The rule-of-five. *Drug Discov Today Technol*. 2004;1(4):337–341.
14. Baell JB, Holloway GA. New substructure filters for PAINS. *J Med Chem*. 2010;53(7):2719–2740.
15. Goodsell DS, Olson AJ. Automated docking of substrates to proteins. *Proteins*. 1990;8(3):195–202.
16. Newman DJ, Cragg GM. Natural products as sources of new drugs. *J Nat Prod*. 2020;83(3):770–803.
17. Harvey AL, Edrada-Ebel R, Quinn RJ. The re-emergence of natural products. *Nat Rev Drug Discov*. 2015;14(2):111–129.
18. Kirchmair J, Distinto S, Schuster D, et al. Predicting drug metabolism. *J Chem Inf Model*. 2015;55(2):246–263.