RESEARCH ARTICLE

Phenol Glucosides as Potential Inhibitors of SGLT1 for Enhanced Diabetes Mellitus Treatment in Patients with Declining Renal Function

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ABSTRACT

Diabetes mellitus poses a significant global health challenge, necessitating the continual search for innovative therapeutic strategies. While sodium-glucose cotransporter 2 (SGLT2) inhibitors have shown promise in diabetes management, their efficacy diminishes in patients with declining renal function.

This study aims to evaluate the potential of phenol glucosides as inhibitors for the sodium-glucose transport protein 1 (SGLT1), a key player in glucose uptake. We identified phlorizin as a representative phenol glucoside for experimental validation. The SGLT1 protein structure (PDB ID 7wmv) was analyzed through Ramachandran plot, ERRAT score, and ProSAweb Z-score, confirming its high-quality 3D conformation. A ligand-based virtual screening approach yielded 400 compounds that matched well with our pharmacophore models, including 10 compounds from virtual libraries. Notably, two compounds stood out for their high matching scores. Molecular docking simulations revealed strong binding affinities with SGLT1, especially for the compound CHEMBL2303983 with a binding energy of -11.2 kcal/mol.

ADMET analysis was conducted to evaluate the drug-likeness & safety profile of such high-affinity compounds. The compounds exhibited variable water solubility and moderate lipophilicity but were generally compliant with most drug-likeness rules. However, certain challenges such as low GI absorption and inability to cross the blood-brain barrier were identified. No PAINS or Brenk alerts were raised, suggesting a low likelihood of assay interference or toxicity.

In conclusion, our *in-silico* approach has identified promising candidates among phenol glucosides for inhibition of SGLT1, albeit with challenges in solubility and pharmacokinetics that require further optimization. The study opens new avenues for the synthesis and experimental verification of novel SGLT1 inhibitors.

Keywords: Phenol glucosides, SGLT1 inhibitors, Diabetes mellitus, Renal function, Molecular docking, Pharmacophore modeling, Diabetes treatment.

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INTRODUCTION

The chronic metabolic condition of diabetes mellitus, characterized by persistently high blood glucose levels, is a major and growing threat to global health. Controlling blood glucose levels is a crucial component of an overall complex strategy for managing diabetes and reducing the risk of complications. Sodium-glucose cotransporter 2 (SGLT2) inhibitors have shown great promise as a new class of diabetes medications due to their ability to increase glucose excretion through the kidneys. However, their usefulness may be lessened in people whose renal function is deteriorating because SGLT2 expression decreases in late-stage renal impairment.[1,2]

Because of this restriction, studies have focused on identifying additional therapeutic approaches that can meet the requirements of diabetes patients with impaired kidney function. Sodium-glucose cotransporter 1 (SGLT1) is highly expressed in the small intestine and is essential for glucose absorption from the intestinal lumen; our study investigates the possibility of phenol glucosides as inhibitors of SGLT1.

The pharmacological effects of phenol glucosides, a class of naturally occurring chemicals present in many plants, range from antioxidant to anti-inflammatory to diabetes-fighting. Potentially useful in patients with diminishing renal function who may not reap the full benefits of SGLT2 inhibition, their capacity to inhibit SGLT1 may provide a new strategy for managing diabetes.[3]

With the help of *in-silico* molecular docking and pharmacophore modeling, this paper seeks to learn whether or not phenol glucosides can be used as SGLT1 inhibitors. It is our hope that by better understanding the binding interactions and drug-like features of phenol glucosides, we can shed light on their potential as therapeutic agents for improving diabetes management, particularly for those with renal problems. By doing so, we aid in the search for better ways to meet the varying requirements of people with diabetes.

Diabetes patients with deteriorating renal function may benefit from inhibiting SGLT1 as a new treatment option. Improved post-meal glycemic control can be achieved with the help of SGLT1 inhibitors because of their ability to delay and diminish glucose absorption in the small intestine. This strategy is very useful for people who don't respond well to SGLT2 inhibition, the standard treatment method. While studies of other SGLT1 inhibitors continue, sotagliflozin is the first oral medicine to inhibit SGLT1 and SGLT2. Hopefully, this novel dual inhibition technique would be a useful adjunct to insulin therapy for adults with T1DM. Clinical trials have shown that people with type 2 diabetes who take sotagliflozin in addition to optimized insulin therapy have better outcomes after one year of treatment, including lower hemoglobin A1c levels, lower body weight, and a lower incidence of severe hypoglycemia compared to those on a placebo. According to secondary data, systolic blood pressure and the need for daily bolus insulin have also been shown to decrease. It should be noted, however, that SGLT2 inhibition did increase the incidence of diabetic ketoacidosis in certain patients. Alternative SGLT1 inhibitors, such as phenol glucosides, are being investigated as promising therapeutic options in diabetes control, particularly for patients with diminishing renal function while they wait for sotagliflozin's FDA approval.[4,5]

METHODS

Selection of Phenol Glucosides

We conducted an extensive literature review and database search to identify potential phenol glycosides for our study. Phenol glycosides with known pharmacological activities and accessibility for experimental validation were prioritized. The selection process also considered the diversity of phenol glycosides to ensure a comprehensive evaluation.

Protein Structure Preparation and Quality Assessment

Three dimensional structure of the human SGLT1 protein (PDB ID: 7wmv) was obtained from a reliable protein database, such as the Protein Data Bank (PDB). Prior to molecular docking simulations, the protein structure underwent rigorous preparation. This involved the removal of water molecules, the addition of hydrogen atoms, and energy minimization to optimize the protein's conformation. The quality of protein structure prepared and assessed by using https://saves.mbi.ucla.edu/ & https://prosa.services.came.sbg.ac.at/prosa.php server.[6,7]

Ligand Preparation

The selected phenol glucosides were obtained from chemical databases and prepared for molecular docking studies. Ligand structures were cleaned to remove structural anomalies, followed by energy minimization to achieve stable conformations. Partial charges were assigned to the ligands using appropriate force fields consistent with the protein preparation, and topology files were generated.[8]

Ligand-Based Virtual Screening

SwissSimilarity, a web-based tool available at http://www.swisssimilarity.ch, was used to carry out ligand-based virtual screening. This method is ideal for quickly sifting through tiny chemical libraries of varying sizes. The query made use of a specific SMILES-formatted molecule of phenol glucosides. Approved medications, bioactive chemicals, commercial molecules, and an extra 205 million virtual compounds that can be quickly synthesised with readily available reagents all made up the screening database.

The bioactive chemical category was the study's primary emphasis. For this purpose, we screened against the entirety of ChEMBL (version 29). The screening methods used to efficiently identify possible hits comprised traditional 3-point pharmacophore approaches and 2D molecular fingerprints.[9,10]

Molecular Docking

To learn more about how phenol glucosides attach to the SGLT1 protein, molecular docking simulations were run using CB-Dock, a cavity-detection guided blind docking (CB-Dock: An accurate protein-ligand blind docking programme (labshare.cn). The workflow involved several key steps:

Cavity detection

The first stage involved identifying potential binding sites within the protein structure. This is crucial for understanding where the ligands may interact with the protein most effectively.

Docking center and box size determination

For each phenol glucoside molecule, the center of the docking box and its dimensions were determined. This step ensures that the search space is appropriately defined for docking simulations.

Molecular docking simulations

Molecular docking simulations were executed once the search space was set. These simulations explore the potential binding interactions between the phenol glucosides and the identified protein cavities.

Evaluation of binding poses

Finally, the binding poses generated by the docking simulations were evaluated. This was based on docking scores, which provide a measure of the binding affinity. The most energetically favorable binding conformation for each phenol glucoside was then selected for further analysis.

Through these steps, the study aims to uncover how phenol glucosides interact with the SGLT1 protein, thereby providing insights that could be vital for drug discovery or therapeutic applications.[11]

ADMET Analysis

The phenol glucosides' ADMET properties were evaluated with the help of computer programmes and tools (like Swiss ADME). These tests shed light on how drug-like the compounds were, how well the body absorbed them, and whether or not they posed any health risks.[12,13]

RESULTS

Selection of Phenol Glucosides

We identified phlorizin, a phenol glucosides shown in Figure 1, with known pharmacological activities and accessibility for experimental validation. This selection encompassed a range of compounds, ensuring a comprehensive evaluation of their potential as SGLT1 inhibitors.

Assessment of Protein Structure Quality

The human SGLT1 protein structure, with PDB ID 7wmv, was subjected to a rigorous quality assessment using multiple online analytical tools to validate its suitability for subsequent computational studies. Below are the key findings from the quality evaluation:

Ramachandran plot analysis (Figure 2a)

Utilizing the PROCHECK server, a Ramachandran plot was generated that shows 90.6% of the amino acid residues in the PDB file 7wmv.pdb occupy energetically favorable regions. This high percentage suggests that the vast majority of amino acid residues are in energetically optimal conformations, affirming the structural soundness of the protein.

ERRAT score (Figure 2b)

The ERRAT tool gave an overall quality factor of 88.799% for the 7wmv.pdb structure. This impressive score attests to the structural quality and robustness of the protein's 3D conformation.

ProSAweb Z-score (Figure 2c)

The Z-Score assigned by ProSAweb was -7.5, indicating the structural attributes of 7wmv.pdb fall within the expected range for high-quality protein structures. This negative Z-score further corroborates the structural integrity of the protein.

Overall, the quality metricscomprising a favorable Ramachandran plot, a high ERRAT score, a negative ProSAweb Z-score, and stable energy profiles collectively confirm that the 3D structure of 7wmv.pdb is of exceptional quality and reliability, making it a strong candidate for further *in-silico* investigations.

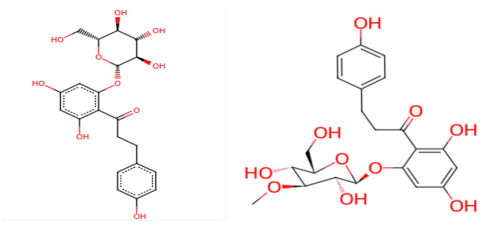


Figure 1: Selcted standard phlorizin

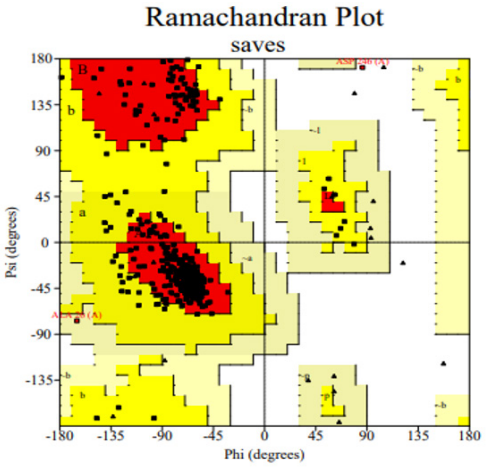


Figure 2a: Ramachandran plot analysis

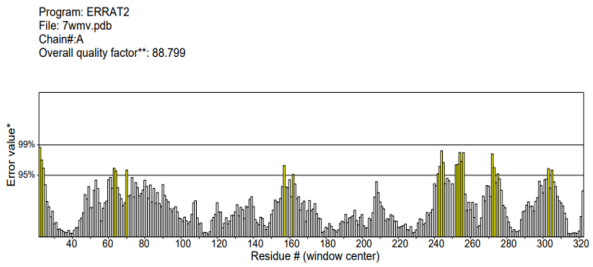
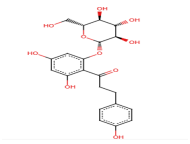
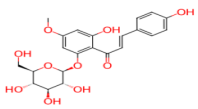
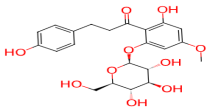
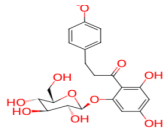
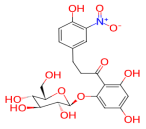
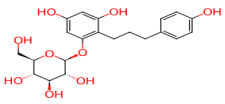
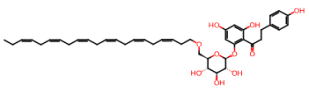
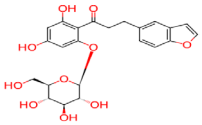
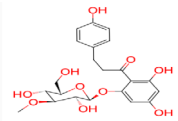
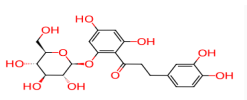
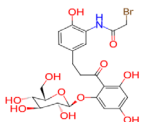


Figure 2 b: ERRAT score

Table 1: Result of ligand-based virtual screening

Sr. No.	CHEMBL ID and SMILES	Structure	Score
1	CHEMBL4303464 OC[C@H]1O[C@@H](Oc2cc(O)cc(O)c2C(=O)CCc2ccc(O)cc2)[C@H](O)[C@@H](O)[C@@H]1O		-9.6
2	CHEMBL495848 COc1cc(O)c(C(=O)/C=C/c2ccc(O)cc2)c(O[C@@H]2O[C@H](CO)[C@@H](O)[C@H](O)[C@H]2O)c1		-8.1
3	CHEMBL490513 COc1cc(O)c(C(=O)CCc2ccc(O)cc2)c(O[C@@H]2O[C@H](CO)[C@@H](O)[C@H](O)[C@H]2O)c1		-9.1
4	CHEMBL2303988 COc1ccc(CCC(=O)c2c(O)cc(O)cc2O[C@@H]2O[C@@H](CO)[C@@H](O)[C@H](O)[C@@H]2O)cc1		-9.5
5	CHEMBL2303990 O=C(CCc1ccc(O)c([N+](=O)[O-])c1)c1c(O)cc(O)cc1O[C@@H]1O[C@@H](CO)[C@@H](O)[C@H](O)[C@@H]1O		-9.6
6	CHEMBL516247 OC[C@H]1O[C@@H](Oc2cc(O)cc(O)c2CCCc2ccc(O)cc2)[C@H](O)[C@@H](O)[C@@H]1O		-8.8
7	CHEMBL2316184 CC/C=C\C/C=C\C/C=C\C/C=C\C/C=C\C/C=C\CCOC[C@H]1O[C@@H](Oc2cc(O)cc(O)c2C(=O)CCc2ccc(O)cc2)[C@H](O)[C@@H](O)[C@@H]1O		
8	CHEMBL1159635 O=C(CCc1ccc2occc2c1)c1c(O)cc(O)cc1O[C@@H]1O[C@H](CO)[C@@H](O)[C@H](O)[C@H]1O		-9.3
9	CHEMBL2303983 CO[C@@H]1[C@H](O)[C@H](Oc2cc(O)cc(O)c2C(=O)CCc2ccc(O)cc2)O[C@@H](CO)[C@H]1O		-11.2
10	CHEMBL4209400 O=C(CCc1ccc(O)c(O)c1)c1c(O)cc(O)cc1O[C@@H]1O[C@H](CO)[C@@H](O)[C@H](O)[C@H]1O		-9.6
11	CHEMBL2303985 O=C(CBr)Nc1cc(CCC(=O)c2c(O)cc(O)cc2O[C@@H]2O[C@@H](CO)[C@@H](O)[C@H](O)[C@@H]2O)ccc1O		-10.1

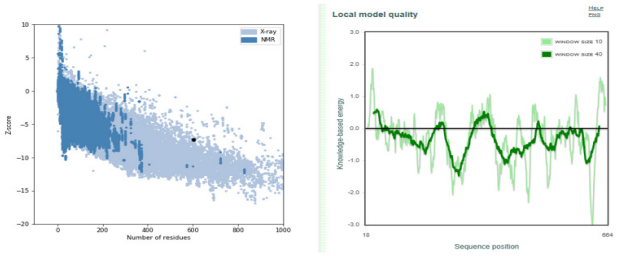


Figure 2c: Pro SA web Z score

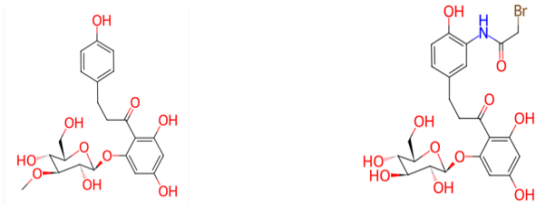


Figure 3: Most active phenol glycosides

Ligand-based Virtual Screening

Pharmacophore matching and hit identification

The screening process yielded a total of 400 hits that showed promising interactions based on our pharmacophore models and 2D fingerprints.

Virtual compounds

Interestingly, 10 of the hits were from the virtual compounds library shown in Table 1, suggesting new avenues for synthesis and further experimental verification.

High-potential candidates

compounds were singled out for their exceptionally high matching scores and are recommended for additional IVIVC (Figure 3).

Molecular docking

Molecular docking simulations revealed the binding interactions between the selected phenol glucosides and the SGLT1 protein. Several phenol glucosides exhibited strong binding affinities, with binding energies ranging from -6.4 to -11.2 kcal/mol (Table 2). Notably, CHEMBL2303983 phenol glucosides displayed the highest binding affinities, indicating robust interactions with the SGLT1 binding site (Figure 4).

ADMET Analysis

Table 3 displays the results of an ADMET study performed on a subset of the phenol glucosides.

The compound of interest has a variety of properties that provide insight into its suitability for drug development:

- **General Properties:** The molecular weight & number of heavy atoms are substantial, with a molar refractivity of 110.87 and a TPSA of 166.14 Å². These features may affect its pharmacokinetic properties.
- **Lipophilicity:** The compound shows varied log *p-values* depending on the estimation method, but generally leans towards being moderately lipophilic. The consensus Log Po/w is 0.68.

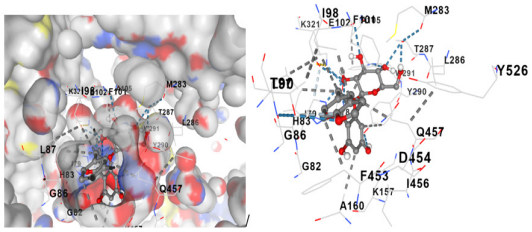


Figure 4: Docking results

Table 2: Molecular Docking

Vina score	*Cavity size*	*Center*			*Size*		
		X	*y*	*z*	*x*	*y*	*z*
-11.2	5465	96	105	110	35	30	21
-7.6	318	133	123	114	21	21	21
-7.3	568	96	98	98	21	21	21
-7.3	430	132	103	125	21	21	21
-6.4	303	107	121	124	21	21	21

Table 3: Results of ADMET Analysis

Category	*Property*	*Value/Description*
General Properties	Formula	C22H26O10
	Molecular weight	450.44 g/mol
	Num. heavy atoms	32
	Num. arom. heavy atoms	12
	Fraction Csp3	0.41
	Num. rotatable bonds	8
	Num. H-bond acceptors	10
	Num. H-bond donors	6
	Molar Refractivity	110.87
	TPSA	166.14 Å²
Lipophilicity	Log Po/w (iLOGP)	2.10
	Log Po/w (XLOGP3)	1.36
	Log Po/w (WLOGP)	0.45
	Log Po/w (MLOGP)	-1.20
	Log Po/w (SILICOS-IT)	0.68
	Consensus Log Po/w	0.68
Water Solubility	Log S (ESOL)	-3.24
	Solubility	2.60e-01 mg/mL; 5.77e-04 mol/l
	Class	Soluble
	Log S (Ali)	-4.45
	Solubility	1.59e-02 mg/mL; 3.54e-05 mol/l
	Class	Moderately soluble
	Log S (SILICOS-IT)	-2.35
	Solubility	2.03e+00 mg/mL; 4.50e-03 mol/l
	Class	Soluble
Pharma cokinetics	GI absorption	Low
	BBB permeant	No
	P-gp substrate	Yes
	CYP1A2 inhibitor	No
	CYP2C19 inhibitor	No

	CYP2C9 inhibitor	No
	CYP2D6 inhibitor	No
	CYP3A4 inhibitor	No
	Log Kp (skin permeation)	-8.08 cm/s
Drug likeness	Lipinski	Yes; 1 violation: NHorOH>5
	Ghose	Yes
	Veber	No;1violation:TPSA>140
	Egan	No; 1 violation:TPSA>131.6
	Muegge	No; 2 violations: TPSA>150, H-don>5
Medicinal Chemistry	PAINS	0 alert
	Brenk	0 alert
	Leadlikeness	No; 2 violations: MW>350, Rotors>7
	Synthetic accessibility	5.03
Bioavailability Score	Bioavailability Score	0.55

- **Water Solubility:** The compound has variable solubility based on different methods, ranging from moderately soluble to soluble.
- **Pharmacokinetics:** The compound is not expected to cross BBB & has low gastrointestinal (GI) absorption. It is a P-gp substrate but is not an inhibitor for various Cytochrome P450 enzymes.
- **Drug likeness:** The compound fulfills some drug-like criteria according to Lipinski and Ghose filters but violates Veber, Egan, and Muegge rules, primarily due to its TPSA and H-don values.
- **Medicinal Chemistry:** No PAINS or Brenk alerts suggest a lower likelihood of assay interference or toxicity. However, it falls short of lead likeness criteria due to its molecular weight and the number of rotatable bonds. It has a moderate synthetic accessibility score of 5.03.
- **Bioavailability:** The bioavailability score is moderate (0.55), indicating that while not ideal, it may still be a viable candidate for further optimization.

The compound has several attributes that could make it a candidate for drug development, but challenges exist. These include its solubility, pharmacokinetics, and certain drug-like properties. Further studies and optimizations are likely needed to ascertain the compound's suitability for medicinal applications.

CONCLUSION

The comprehensive *in-silico* analysis of phenol glucosides, particularly phlorizin, for their potential as SGLT1 inhibitors, has yielded several key insights. The human SGLT1 protein structure has been validated through multiple quality checks, such as Ramachandran plot analysis, ERRAT score, and ProSAweb Z-score, to be of high structural integrity. This makes it a suitable target for *in-silico* studies. The ligand-based virtual screening identified 400 hits, with 10 high-potential candidates. Molecular docking further narrowed down these candidates based on their binding affinity, revealing CHEMBL2303983 as a potential lead.

Most of the compounds followed Lipinski's rule of five, which indicates that they are drug-like and safe. However, problems with intestinal uptake and crossing the blood-brain barrier were identified. The compound showed no pains or Brenk alerts, suggesting a lower risk of toxicity or assay interference. However, it failed to meet the criteria for lead-likeness and showed moderate synthetic accessibility. While the compound's general properties such as molecular weight and lipophilicity, are within acceptable ranges, pharmacokinetic parameters such as solubility and GI absorption, present challenges that need to be addressed.

Bioavailability

The moderate bioavailability score suggests room for optimization.

In summary, the compound phlorizin, and especially CHEMBL2303983, shows promising attributes that could make it a viable candidate for drug development as an SGLT1 inhibitor. However, certain limitations related to solubility, pharmacokinetics, and drug-like properties warrant further investigation and optimization. Overall, the study provides a strong foundation for future experimental validations and sets the stage for the next steps in the drug discovery process.

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