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Original Research Article

Maltase-Glucoamylase Inhibitory Activity of Isolated Compounds from *Swertia Chirata* (Wall) Clarke: An *In Silico* Molecular Docking and Pharmacokinetic Prediction Study

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Abstract

Diabetes is a metabolic disorder that has worldwide become a major health concern. Medications in current management of diabetes are efficient, although they are significantly associated with intense side effects. Nature has always been a primary source of safer medications historically. As synthetic procedures involves high amount of costs, *in silico* methods has become essential in drug development methods for screening large dataset of compounds against a target receptor with better rates of success. This study thus aims to explore novel compounds from *Swertia chirata* that can be effectively used in diabetes management through computational methods. The compounds of *S. chirata* were screened against human Maltase-glucoamylase (PDB ID: 2QMJ) using Maestro V10.1 of Schrodinger LLC by molecular docking method. In addition, pharmacokinetic and ADME/T properties were analyzed through SwissADME online server. Best docked poses were then visualized using Discovery Studio software. Molecular docking studies revealed that Sweroside had the best docking score (-6.039 kcal/mol) against 2QMJ and similar interactions with receptor's amino acid residues as like the standard drug. Also ADME/T properties of this compound were within the accepted range. In this research, the molecular docking, binding mode and ADME/T characteristics confirm that phytochemicals from this plant especially Sweroside can be a potential lead molecule as anti-diabetic medication.

Keywords: Sweroside, ADME/T, Molecular docking, *Swertia chirata*, Maltase glucoamylase.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a disease condition where the body does not use insulin properly. This may happen due to body's resistance to insulin. Although pancreas at first tries to cope up the situation by producing extra insulin, over the time it's ability decreases and blood glucose level constantly rises in the body [1, 2]. According WHO report of 2016, around 422 million individuals globally (roughly 8.5% of adults) are currently experiencing this disease and the number is rising continuously [3]. This chronic disease not only impacts the metabolism of carbohydrates, but also changes the metabolism of lipids and proteins in advanced phases, leading to more deadly microvascular and macrovascular complications [4, 5]. Regulation of blood glucose levels by inhibiting intestinal glucosidase production using R-glucosidase inhibitors is one of the therapeutic options for type 2 diabetes treatment [6-8].

Maltase-glucoamylase (MGAM) is an alpha-glucosidase digestive enzyme. It consists of two subunits with differing substrate specificity. Studies have shown that its N-terminal catalytic domain has highest activity against maltose, while the C-terminal domain has a broader substrate specificity and activity against glucose oligomers [9-11]. Thus N-terminal catalytic domain of maltase-glucoamylase (ntMGAM) is one of the potential intestinal glucosidase targets. At present, only few drugs are available as alpha-glucosidase inhibitors that constitute a category of anti-hyperglycemic drugs to regulate post-prandial glucose concentrations by reversibly inhibiting digestive alpha-glucosides, along with some major side effects [12-15].

Thus, developing diabetes medications with fewer side effects remains a large arena where the medical system faces enormous challenges. This leads to emerging demand for natural products with anti-diabetic activity as historically they have less side effects. *Swertia chirata* (Family: Gentianaceae) is one of the ethno-pharmacologically used anti-diabetic plants [16, 17]. This plant also showed other significant activities along with anti-diabetic properties like anti-oxidant [18], anti-inflammatory [19], hepato-protective [20], anti-carcinogenic activities [21].

Molecular docking is a basic tool for virtual screening of novel compounds that can potentially be used to treat complicated illnesses. Docking is a more comprehensive way to search for new therapeutically effective compounds by an accurate and faster prediction method. Docking method precisely and accurately visualizes complicated structural activity relationships, precise binding modes and ligand interactions with the protein molecule's amino acid residues to detect the pharmacological characteristics of drug molecules [22]. The current study implies *in silico* molecular docking approach to discover novel MGAM inhibitors with suitable ADME/T properties.

MATERIALS AND METHODS

Preparation of Receptor

Three dimensional crystal structure of MGAM protein (PDB ID: 2QMJ) was retrieved from the RCSB Protein Data Bank in pdb format with 1.9 Å resolution [11]. Protein structure was prepared and refined using the Protein Preparation Wizard of Schrödinger-Maestro v10.1. Charges and bond orders were assigned, hydrogens were added to the heavy atoms, zero order bonds were created to metals, disulfide bonds were created, selenomethionines were changed to methionines and all waters were eradicated that were beyond 5Å from het groups. Finally energy minimization was performed using OPLS_2005 force field with heavy atoms convergence to 0.30 Å RMSD (root-mean-square-deviation).

Preparation of Ligands

A thorough review of literatures on *S. chirata* was performed and 10 isolated compounds were retrieved. Compound structures of Mangiferin, Swertiamarin [23], Chiratenol, Episwertenol, Swertanone, Swertenol, Taraxerone [24], Amarogentin, Amaroswerin, Sweroside [25] were downloaded from Pubchem database in 2D sdf format. Ligprep3.3 wizard in Schrödinger Suite 2015-1 was used to prepare the ligands before performing molecular docking [26]. 3D geometries were created and proper bond orders were assigned for the individual ligands applying OPLS_2005 force field [27]. Ionization states of the ligands were generated by using Epik3.1 of Schrödinger Suite at pH7.0±2.0. A maximum of 32 possible stereoisomers per ligand were obtained and lowest energy ring conformation for each ligand was created using Epik3.1.

Ligand based ADME/T and molecular properties analysis

In selecting compounds as prospective drug applicants, their molecular characteristics play a vital part. Lipinski's rule of five (RO5) filter was applied to screen the ligands as drug candidates, which states that the compound has more permeability and passive absorption if it does not violate more than one of Lipinski, i.e. molecular weight <500; hydrogen bond acceptor count ≤10; hydrogen bond donor count ≤5; lipophilicity (log $P_{o/w}$ <5) and molar refractivity between 40 and 130 [28-30]. SwissADME online database was used to screen the molecular properties of the compounds [31].

Receptor Grid Generation

Receptor grid was created keeping the default parameters (Van der Waals scaling factor 1.00 and charge cutoff 0.25 and OPLS_2005 force field) around the active site of receptor which was defined by the co-crystallized ligand. The box was generated to each direction with a measurement of 14 Å × 14 Å × 14 Å for docking experiments [32, 33].

Glide Standard Precision (SP) Ligand Docking

Glide standard precision (SP) ligand docking protocol of Schrödinger Maestro v10.1 was performed for molecular docking of ligands against the target receptor. In this method the ligands are allowed to be flexible while receptor is fixed. Van der Waals scaling component and fractional charge cutoff was chosen to be 0.80 and 0.15, respectively for ligand atoms. Epik state penalties were added to docking scores and post docking minimization was performed. Final scoring was performed on energy minimized poses and showed as Glide score. Ligand poses having the least Glide score was considered as the best docked mode and recorded for each ligand. Finally the best docked poses were further analyzed for 3D binding interactions with amino acid residues using Biovia Accelrys Discovery Studio [34] software.

RESULTS

Molecular property and ADME/T analysis of the compounds revealed that all the compounds were suitable for docking except Amarogentin, Amaroswerin and Mangiferin (Table-1). The docking results were expressed as docking score and docking energy (Table-2). Among all the compounds, Sweroside showed the highest docking scores against MGAM receptor with a docking score of -6.039 kcal/mol. Other compounds showed docking scores from -5.855 to -2.203 kcal/mol. Sweroside showed hydrogen bond interaction with the ASP327, ARG526, ASP542 and HIS600 residues of MGAM receptor. Also it formed a hydrogen bond with a co-crystallized water molecule with a distance of 1.86 Å (Table-3).

Table-1: Molecular properties of the compounds of *S. chirata* by SwissADME

Molecule	PID	MW	HBA	HBD	MR	iLog P	BS
Amarogentin	115149	586.54*	13*	6*	142.07*	2.46	0.11
Amaroswerin	45359883	602.54*	14*	7*	143.27*	2.61	0.11
Chiratenol	14831162	426.72	1	1	134.88*	4.65	0.55
Episwertenol	101619548	426.72	1	1	134.88*	4.67	0.55
Mangiferin	5281647	422.34	11*	8*	100.70	0.71	0.17
Sweroside	161036	358.34	9*	4	80.92	1.77	0.56
Swertanone	102285187	424.7	1	0	133.92*	4.48	0.55
Swertenol	21726415	426.72	1	1	134.88*	4.67	0.55
Swertiamarin	442435	374.34	10	5	82.12	1.74	0.11
Taraxerone	92785	424.7	1	0	133.92*	4.55	0.55

PID= Pubchem ID; MW= Molecular weight; g/mol (acceptable range: <500); HBA= Hydrogen bond acceptor (acceptable range: ≤10); HBD= Hydrogen bond donor (acceptable range: ≤5); iLogP= High lipophilicity (expressed as LogP, acceptable range: <5); MR= Molar refractivity (acceptable range: 40-130); BS= Bioavailability Score; * denotes violation of acceptance criteria.

Table-2: Docking scores and receptor ligand complex energy parameters of ligands against 2QMJ

Receptor	Molecule	Docking score (kcal/mol)	Glide Energy (kcal/mol)	Glide Emodel (kcal/mol)	Glide Gscore (kcal/mol)
2QMJ	Miglitol	-7.4	-37.784	-60.485	-7.403
	Sweroside	-6.039	-48.476	-64.157	-6.039
	Swertiamarin	-5.855	-45.055	-55.917	-5.856
	Chiratenol	-2.68	-29.497	-34.537	-2.68
	Taraxerone	-2.615	-26.919	-31.3	-2.615
	Swertenol	-2.485	-26.757	-31.347	-2.485
	Episwertenol	-2.273	-24.264	-27.775	-2.273
	Swertanone	-2.203	-25.186	-28.34	-2.203

Table-3: Bonding interactions of standard drug and best docked ligand with the amino acid residues of 2QMJ

Interactions	Molecule			
Hydrogen bond	Miglitol		Sweroside	
	Residue	Distance (Å)	Residue	Distance (Å)
	ASP327	1.89	ASP327	1.68, 1.79
	ARG526	1.92	ARG526	2.09
	ASP542	1.95, 2.10	ASP542	1.82
			HIS600	2.13
Other interactions	TYR299	4.34	H_2O	1.86
	ASP327	4.5		
	H_2O	1.8		

DISCUSSION

Molecular docking is a computational strategy in which efficient and cost-effective researches can be conducted with specific ligands to find novel compounds against a target receptor. This is a comprehensive protocol where the binding modes and affinities can be predicted for a set of compounds against an X-ray crystallographic structure of protein [35]. A set of isolated compounds from *S. chirata* were screened against MGAM receptor in quest of novel anti-diabetic medication.

All the compounds showed suitable binding poses against MGAM receptor of which Sweroside showed the best interactions (Figure-1). The docking score of Sweroside (-6.039 kcal/mol) indicates that this compound has good affinity towards the MGAM receptor. Also the Glide energy and Glide Emodel scores of the compound are -48.476 and -64.157 respectively which indicated stable binding interactions with receptor. It is notable that this compound formed similar hydrogen bonds with the receptor like the standard drug Miglitol (Figure-2). Hydrogen bond interactions of Sweroside with residues ASP327 (1.68 Å, 1.79 Å), ARG526 (2.09 Å), ASP542 (1.82 Å) and HIS600 (2.13 Å) at small distances indicate the strong receptor binding affinity of this compound as the binding site residues for the standard drug are also similar (Table-3).

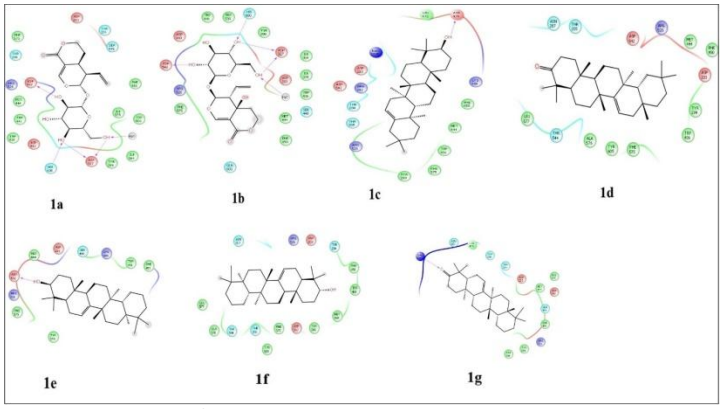

Fig-1: Interactions between the best pose ligand of Sweroside (1a), Swertiamarin (1b), Chiratenol (1c), Taraxerone (1d), Swertenol (1e), Episwertenol (1f) and Swertanone (1g) with amino acid residues of 2QMJ in 2D view

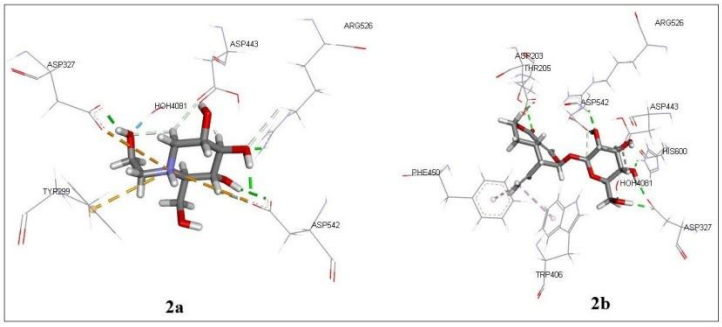

Fig-2: 3D interactions of Miglitol (2a) and Sweroside (2b) with the Maltase-glucoamylase enzyme

ADME/T properties of a drug candidate plays very crucial role as many molecules fail in clinical trial for not having suitable pharmacokinetic properties [36]. Sweroside has very suitable properties for oral delivery as this compound has lower molecular weight which increases the permeation of drugs [37], lower lipophilicity (log $P_{o/w}$) denoting better oral absorption and bioavailability [38], and fewer hydrogen-bonding interactions relating to higher permeability and absorption [29]. Therefore, as an anti-diabetic drug applicant, this compound is very potential.

CONCLUSION

In the drug development phase, finding new compounds with less side effects and optimum therapeutic activity is an imperative requirement. This research reflects the molecular docking of compounds from *S. chirata*, a traditionally used anti-diabetic medicinal plant against Maltase-glucoamylase (MGAM) receptor, involved in diabetes. Sweroside possesses the highest docking score and suitable binding interactions with amino acid residues of MGAM receptor making it an ideal lead molecule for developing anti-diabetic medication. Further comprehensive quantitative structure activity relationship study may confirm its effectiveness and safety within animal models.

Conflict of Interest

The authors declare that they have no conflict of interest.

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