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Characterization of schweinfurthinol 9-O-β-D-pyranoglucoside as a potential anti-diabetic compound via in-silico studies

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Abstract. Schweinfurthinol 9-O-β-D-pyranoglucoside (SP) was isolated from *Euonymus laxiflorus* Champ. (ELC) and found as novel α-glucosidase and α-amylase inhibitors in our previous works via experimental studies. This work aims to further characterize SP as a potential inhibitor of α-glucosidase and α-amylase and develop an anti-diabetic drug via in-silico studies. Molecular docking indicated that SP interacted with targeting enzymes α-glucosidase (Q6P7A9) and α-amylase (1SMD) with acceptable RMSD values (≤2.0 Å) and showed an efficient binding energy with DS values of –10.4 and –12.0 kcal/mol, respectively. The binding energy of SP is comparable with that of acarbose, an anti-diabetic compound, with DS values of –11.2 to –12.7 kcal/mol for enzymes Q6P7A9 and 1SMD, respectively. The analysis indicated that SP satisfied all the requirements of Lipinski's Rules of Five while acarbose might conform to approximately 20% of Lipinski's rules criteria. Furthermore, SP showed satisfied ADMET properties in the required permitted limit. The result of this work suggested that SP might be a potential candidate with good drug-likeness properties and a high possibility of being an anti-diabetic drug.

Keywords: α-glucosidase inhibitors, α-amylase inhibitors, diabetes, schweinfurthinol 9-O-β-D-pyranoglucoside

1 Introduction

Type-2 diabetes (T2D), a chronic metabolic disorder, has been recognized as a global health problem and significantly reduces people's life quality worldwide [1]. Some therapies have been investigated for T2D treatment, and the use of α-amylase inhibitors (aAIs) and α-glucosidase inhibitors (aGIs) has been considered as an effective therapy for the management of T2D [2, 3]. To date, several enzyme inhibitors, such as acarbose, voglibose, and miglitol, have been available. However, the use of these commercial enzyme inhibitors may result in some side effects, including diarrhea, flatulence, and abdominal discomfort [4]. Thus, discovering new drugs from natural sources for T2D treatment still demonstrates a significant demand.

aAIs and aGIs may result from several sources such as chemical synthesis [5], microbes [6], and medicinal plant [7]. Among these sources, herbal extracts are available natural sources for obtaining enzyme inhibitors [4, 7]. Thus, discovering new aAIs and aGIs from medicinal plants has received much interest.

Aiming to provide aAIs and aGIs for natural and safe therapies of T2D, we collected and tested a number of indigenous herbals growing in the Central Highland of Vietnam for their potential anti-diabetic effects. The trunk bark extract of *Euonymus laxiflorus* Champ. was found potent of α-amylase and α-glucosidase inhibitory activities [8, 9]. Various aAIs [10] and aGIs [11] were isolated from this herbal extract and elucidated for their chemical structures. Of these, schweinfurthinol 9-O-β-D-pyranoglucoside (SP) was identified as a new compound and exhibited potent effects for both α-amylase and α-glucosidase inhibitory activities. In this study, we investigate the interaction and bond energy of SP towards targeting enzymes, as well as the drug likeness and the absorption, distribution, metabolism, excretion and toxicity (ADMET) properties of SP via an in-silico study.

2 Computational methods

2.1 Docking study protocol

Molecular docking was performed following some of the steps mentioned in previous reports [3, 12].

- *Preparation of enzyme structures*: The structures of α-glucosidase (Q6P7A9) and α-amylase (1SMD) were obtained from the Worldwide Protein Data Bank for preparation of their 3-D structures via using MOE-2015.10 software. The binding sites on enzymes were found via utilizing the site finder in MOE. A virtual pH of 7 was set to prepare Q6P7A9 and 1SMD structures.
- *Preparation* of *inhibitors (ligands) structures*: Schweinfurthinol 9-O-β-D-pyranoglucoside and acarbose (AB) structures were prepared and optimized by using ChemBioOffice 2018 software and MOE software, respectively.
- *Docking performing and the obtained out-put data*: The two ligands (SP and AB) were docked into the binding sites of protein Q6P7A9 and 1SMD by using the MOE software. Some major output data, including docking score (DS) values, the root mean square deviation (RMSD) values, linkage types, compositions of amino acids, and the bond distances were used for analysis.

2.2 Lipinski's Rules of Five and ADMET properties analysis

The drug-likeness was investigated via Lipinski's Rules of Five performance by using online software [13], and a web tool [14] was used for the prediction of some pharmacokinetic parameters of absorption, distribution, metabolism, excretion and toxicity.

3 Results and discussions

3.1 Potential enzymes inhibitory effect of SP and AC via docking and DFT analysis

In an in-silico study, an inhibitor compound may interact with enzyme at numerous binding sites (BSs), and only the most stable intermolecular structure (named binding site) was selected for further investigation and discussion [15]. The most BSs on α-glucosidase (Q6P7A9) and α-amylase (1SMD) were found by using the site finder function of MOE and illustrated in Fig. 1.

The BSs of Q6P7A9 contain 59 amino acids with some residues, including Phe362, Met363, Arg594, Pro595, Arg608, His714, His717, Val718, Phe859, Asp861, Ser865, Leu866, Gly867, Val868, Leu869, and Glu870. The BSs of 1SMD also contain 59 amino acids with several residues, including Arg267, Asn301, Gln302, Arg303, Gly304, His305, Gly309, Ala310, Ser311, Ile312, Thr314, Trp316, Asp317, Trp344, Arg346, Phe348, Gly351, Lys352, Asp353, and Asp356.

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In a docking study, the root mean square deviation (RMSD) and docking score (DS) were considered as important indicators for the determination of the significant interaction (RMSD ≤ 2.0Å) and effective inhibition (DS ≤ −3.20 kcal/mol) of an inhibitor ligand towards the targeting enzyme [16, 17].

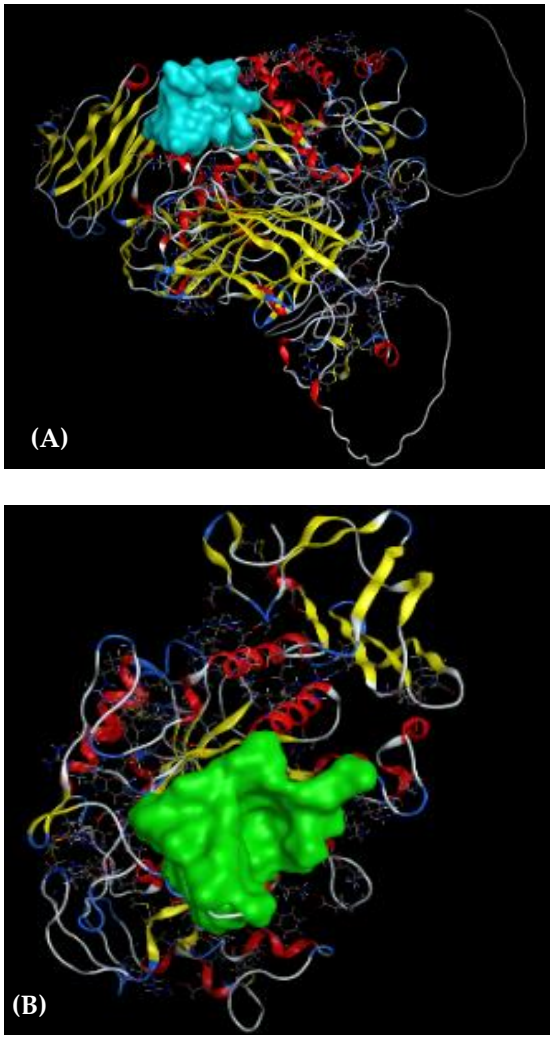

Fig. 1. 3D enzyme structures and binding sites of enzyme Q6P7A9 (A) and 1SMD (B)

As shown in Table 1, schweinfurthinol 9-O-β-D-pyranoglucoside interacts significantly with Q6P7A9 and 1SMD with low RMSD values of 1.59 and 0.98 Å, respectively. Acarbose, an anti-diabetic agent, was also subjected to docking and exhibited accepted RMSD values of 1.87 and 1.70 Å, respectively. Both SP and AB showed an efficient bond energy with very low DS values in the range of –10.4 to –11.2 kcal/mol and –12.0 to –12.7 kcal/mol for Q6P7A9 and 1SMD, respectively. These data indicate that SP is a potent inhibitor towards both enzymes α-glucosidase and α-amylase in the targeting anti-diabetic drug.

Table 1. Data of docking study of ligand SP and AB binding with enzyme Q6P7A9 and 1SM

Inhibitors	Enzyme	RMSD (Å)	DS (kcal/mol)
SP	Q6P7A9	1.59	–10.4
AB	Q6P7A9	1.87	–11.2
SP	1SMD	0.98	–12.0
AB	1SMD	1.70	–12.7

To entirely understand the behaviour of the inhibitors and enzymes, we examined their detailed interaction at the BSs (Fig. 2, 3, 4, and 5). SP effectively bound to α-glucosidase Q6P7A9 (Fig. 2) via interacting with two amino acids Glu876 and Gly867 to create two linkages of one H-donor and one H-acceptor with a distance/energy bond values of 3.01 Å/–1.0 kcal/mol, and 3.03 Å/–0.6 kcal/mol, respectively. Acarbose also interacts significantly with Q6P7A9 (Fig. 3) with several amino acids (Ser584, Glu870, Glu196, His717) at the binding sites and creates five bonds. Acarbose interacts with Glu870 via two H-donor bonds with the bond length and energy values in the range of 2.84–3.33 Å, and –1.2 to –3.7 kcal/mol. This ligand interacts with Ser584 and His717 via one H-donor bond and one H-pi bond. The detailed linkages, their bond distance and energy are also summarized in Table 2.

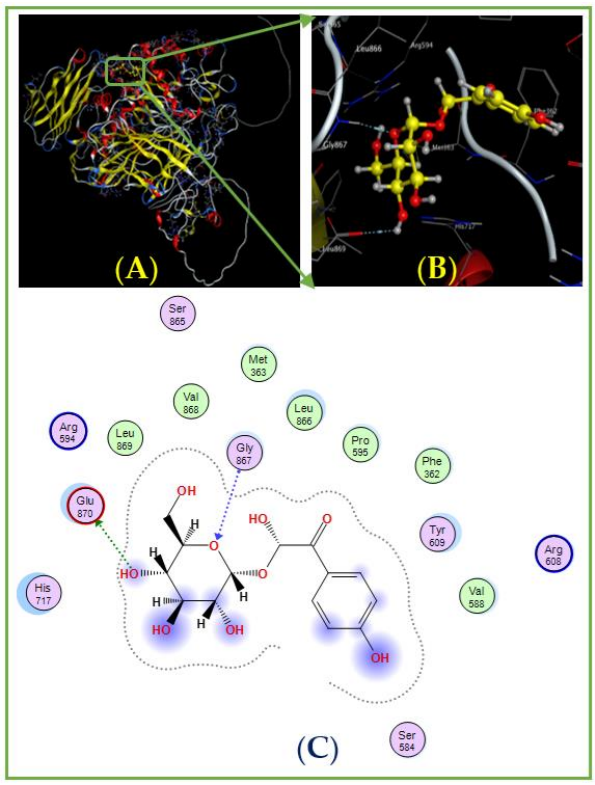

Fig. 2. SP-Q6P7A9 complex at binding site (A) and its detail 3D (B) and 2D structures (C)

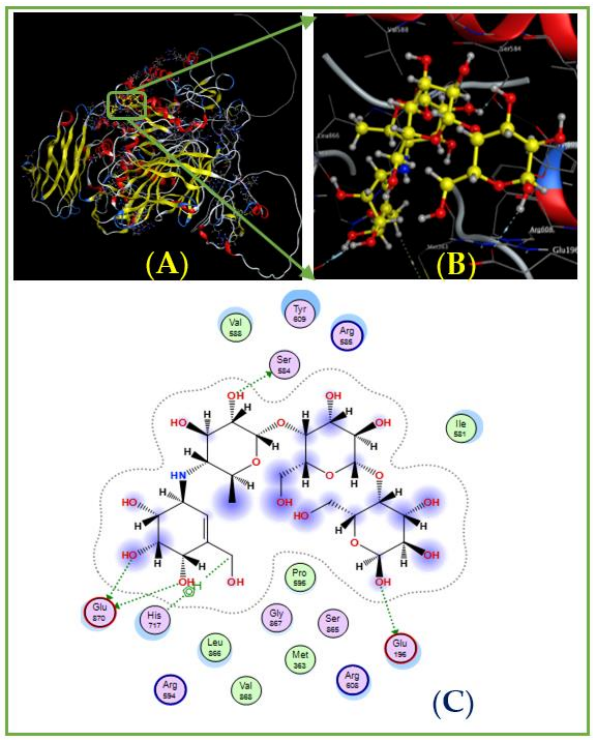

Fig. 3. AB-Q6P7A9 complex at binding sites (A) and its detailed 3D (B) and 2D structures (C)

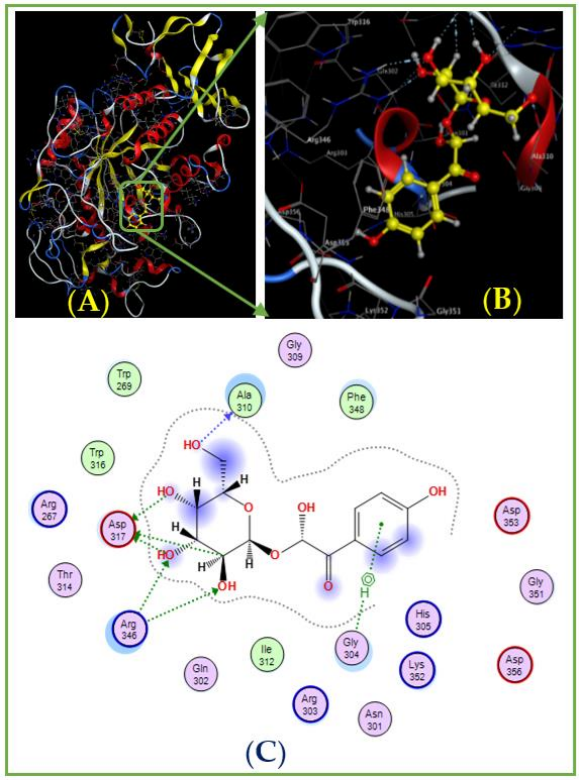

Fig. 4. SP-1SMD complex at binding sites (A) and its detailed 3D (B) and 2D structures (C)

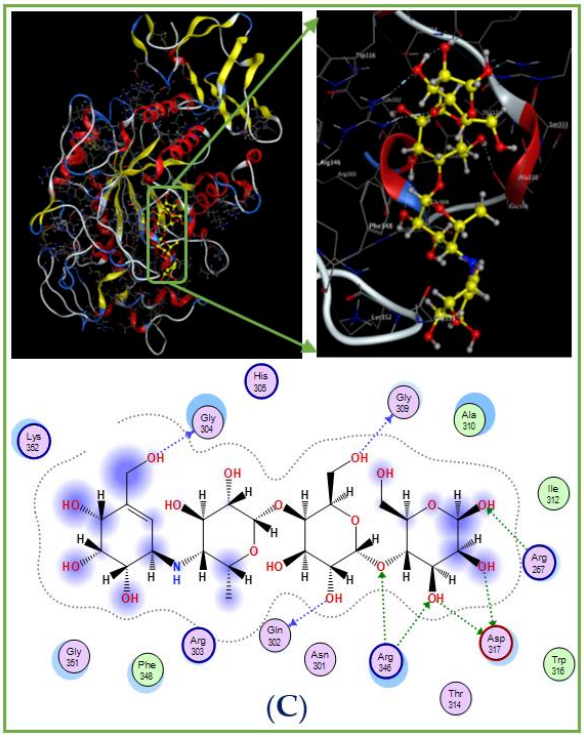

Fig. 5. AB-1SMD complex at binding site (A) and its detailed 3D (B) and 2D structures (C)

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Regarding the interaction with α-amylase 1SMD, both SP and AB also bind effectively to 1SMD by connecting with some amino acids and generating numerous interactions. As shown in Fig. 4, the ligand SP binds to 1SMD via creating eight linkages. Among them, there are three H-donor bonds and three H-acceptor bonds with Asp317 and Arg346, respectively. SP also creates one H-donor and one pi-H bond with Ala310, and Gly304, respectively. The detailed interaction of AB with 1SMD is shown in Fig. 5. Acarbose binds to 1SMD via eight bonds with some prominent amino acids and the detailed interaction of this complex AB-1SMD is presented in Table 2.

The frontier molecular orbitals of these ligands were further investigated. The data of the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO) of these ligands are presented in Figure 6. The structures of SP and AB possess their low E_{HOMO} values of –6.81 and –6.12 eV, respectively, indicating their electronic stability is significant (commonly accepted <–5 eV) [21]. Previous reports indicate that these molecular structures have an energy gap corresponding to semiconductors (3.2 eV < EG < 9 eV), demonstrating the effective capability of intermolecular binding towards protein structures [22]. In our work, the molecular structures of the two inhibitors SP and AB have their energy gap values of 4.92 and 5.09 eV, respectively. Therefore, they have potential intermolecular binding capability towards the targeting enzymes.

Table 2. Detailed linkages, their bond length and energy between inhibitors ligands and enzyme Q6P7A9 and 1SM

Complex	Bonds	Amino acids [Distance (Å)/E (kcal/mol)/bond type]
SP-Q6P7A9	2 H-donor bonds	Glu870(3.01/−1.0/H-donor) Gly867(3.03/−2.3/H-donor)
AB-Q6P7A9	5 bonds (4 H-donor, 1 H-pi)	Ser584(3.00/−0.8/H-donor) Glu870(2.84/−3.7/H-donor) Glu870(3.33/−1.3/H-donor) Glu196(3.19/−1.2/H-donor) His717(4.63/−0.6/H-pi)
SP-1SMD	8 bonds (4 H-donor, 3 H-acceptor, 1 pi-H)	Asp317(3.43/−0.8/H-donor) Asp317(3.02/−1.3/H-donor) Asp317(3.30/−1.0/H-donor) Ala310(2.99/−1.9/H-donor) Arg346(3.12/−0.8/H-acceptor) Arg346(3.43/−0.6/H-acceptor) Arg346(3.18/−2.1/H-acceptor) Gly304(3.80/−0.6/pi-H)
AB-1SMD	8 bonds (5 H-donor, 3 H-acceptor)	Gln302(3.17/−1.4/H-donor) Asp317(3.16/−0.9/H-donor) Gly309(2.64/−1.0/H-donor) Asp317(2.81/−3.4/H-donor) Gly304(2.92/−1.6/H-donor) Arg346(3.00/−3.6/H-acceptor) Arg346(3.04/−2.3/H-acceptor) Arg267(3.22/−0.6/H-acceptor)

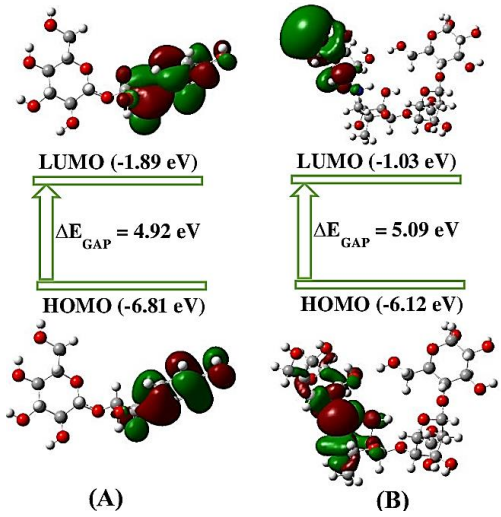

Fig. 6. HOMO and LUMO of compounds SP (A) and AB (B) analyzed by DFT at level of theory b3lyp/6-311++g(d,p)

3.2 Drug-likeness of SP and AB via Lipinski's Rules of Five

Lipinski's Rules of Five are commonly used to evaluate the drug-likeness of a compound [12, 18, 19]. The five rules include "molecular mass <500 Da; high lipophilicity with LogP value less than 5); the number of H-donors <5; the number of H-acceptors <10, and the molar refractivity in the range of 40–130". Based on these rules, a compound satisfying ≥2 criteria is suggested having properties of drug-likeness [18]. The data are indicated in Table 3.

Table 3. Lipinski's Rules of Five for schweinfurthinol 9-O-β-D-pyranoglucoside (SP) and acarbose (AB)

Rules	Compounds		Lipinski's rules
	SP	AB	
Mass (Da)	330	646	<500
H-donor	8	15	<5
H-acceptors	9	18	<10
LogP	–1.412	–9.591	<5
Molar Refractivity	73.30	136.52	40–130

As shown in Table 3, SP satisfies all the requirements of Lipinski's Rules of Five. These results indicate that SP has good drug-likeness properties and has a high possibility to be used as a drug [12, 18]. Acarbose satisfies approximately two requirements. Recently, various volatiles and phenolics identified from the trunk bark extract of the herbal *Euonymus laxiflorus* Champ. were also accessed for their drug-likeness with Lipinski's Rules of Five [19], and all the compounds satisfied at least 3–5 criteria. This study and our previous work [19] suggested that the *Euonymus laxiflorus* Champ. is a potential source for obtaining active constituents with high possibility of being a drug.

3.3 Analysis of ADMET properties of SP and AB

The ADMET properties of SP and AC were accessed (Table 4). Regarding the absorption property, SP exhibits moderate ability of absorption (intestinal absorption value of 25.796%), while AB displays poor absorption ability (4.172%).

In terms of drug distribution, the logVDss value of SP is 0.323 log L.kg^{-1}, indicating that this inhibitor shows a plasma-tissue balance (–0.15 < logVDss < 0.45). Both these inhibitors (SP and AB) may not cross the blood-brain barrier (BBB) since their BBB permeability values are low (logBB < −1). Concerning metabolism, SP and AB show no effects on the substrates and inhibitors of the cytochromes P450 family, indicating that these compounds may not be oxidized in the liver and may be stable in the living system [20]. Regarding the property of excretion, SP and AB may be carried out via the Organic Cation Transporter as they have a total clearance value of 0.583 and 0.428 log mL.min^{-1}.kg^{-1}, respectively [12]. Notably, both SP and AB demonstrate no AMES toxicity. Overall, SP show good ADMET properties in the required allotted limit.

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Table 4. ADMET properties of schweinfurthinol 9-O-β-D-pyranoglucoside (SP) and acarbose (AB)

Compound / Property	SP	AB	Unit
Absorption			
Water solubility	–0.594	–1.482	(1)
Caco2 permeability	–0.497	–0.481	(2)
Intestinal-absorption	25.796	4.172	(3)
Skin-permeability	–2.742	–2.735	(4)
P-glycoprotein substrate	No	Yes	(5)
P-glycoprotein I inhibitor	No	No	(5)
P-glycoprotein II inhibitor	No	No	(5)
Distribution			
VDss	0.323	–0.836	(6)
Fraction-unbound	0.619	0.505	(6)
BBB permeability	–1.338	–1.717	(7)
CNS permeability	–4.296	–6.438	(8)
Metabolism			
CYP2D6 substrate	No	No	(5)
CYP3A4 substrate	No	No	(5)
CYP1A2 inhibitor	No	No	(5)
CYP2C19 inhibitor	No	No	(5)
CYP2C9 inhibitor	No	No	(5)
CYP2D6 inhibitor	No	No	(5)
CYP3A4 inhibitor	No	No	(5)
Excretion			
Total Clearance	0.583	0.428	(9)
Renal OCT2 substrate	No	No	(5)
Toxicity			
AMES toxicity	No	No	(5)
Max. tolerated dose	0.353	0.435	(10)
hERG I inhibitor	No	No	(5)
hERG II inhibitor	No	Yes	(5)
Oral Rat Acute-toxicity (LD50)	2.573	2.449	(11)
Oral Rat Chronic Toxicity	5.004	5.319	(12)
Hepatotoxicity	No	No	(5)
Skin Sensitization	No	No	(5)
T.Pyriformis toxicity	0.285	0.285	(13)
Minnow-toxicity	3.775	16.823	(14)

Note: (1) log mol·L^{-1}; (2) log Papp (10^{-6} cm·s^{-1}); (3) %; (4) log Kp; (5) Yes/No; (6) log L·kg^{-1}; (7) log BB; (8) log PS; (9) log mL·min^{-1}·kg^{-1}; (10) log mg·kg–1·day^{-1}; (11) mol·kg^{-1}; (12) log mg·kg^{-1}_bw·day^{-1}; (13) log μg·L^{-1}; (14) log mM.

4 Conclusion

Schweinfurthinol 9-O-β-D-pyranoglucoside was evaluated as a potential antidiabetic drug via in-silico studies in this work. Schweinfurthinol 9-O-β-D-pyranoglucoside binds significantly to enzymes Q6P7A9 and α-1SMD with an acceptable RMSD value (≤2.0Å) and a good DS value of –10.4, and –12.0 kcal/mol, respectively, comparable with acarbose, an anti-diabetic compound with DS values of –11.2 to –12.7 kcal/mol. In general, schweinfurthinol 9-O-β-D-pyranoglucoside possesses drug properties and is non-toxic for human use. It satisfies all requirements of Lipinski's Rules of Five and ADMET properties. Schweinfurthinol 9-O-β-D-pyranoglucoside is, therefore, a potential candidate for T2D management.

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