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Novel O-linked β-N-acetylglucosamine Transferase (OGT) Inhibitors from *Tinospora Cordifolia*: An *In-Silico* Approach

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Abstract: Diabetes mellitus (DM) characterized by excess blood sugar, is a multifactorial metabolic disease that has reached epidemic proportions worldwide. The International Diabetes Foundation (IDF) estimates that approximately 537 million adults will be living with DM in 2021. The total number of people living with DM is projected to rise to 783 million by 2045. According to the absolute or relative lack of insulin signaling, DM is classified into two major forms: Type 1 diabetes mellitus (T1DM) and Type 2 diabetes mellitus (T2DM). One of the proteins that play a major role in DM is O-linked β-N-acetylglucosamine Transferase (OGT) a glucose-dependent human enzyme that catalyzes the addition of UDP-GlcNAc on the serine and threonine residues of nuclear and cytoplasmic proteins. While this protein plays a vital role in cell cycle regulation and glucose metabolism, an aberration of it could be lethal, and up until now, there have been no reports of small molecule and potent plant-based inhibitors of OGT. In this study, we put molecular docking, ADME/Tox analysis, and MM/GBSA studies to use in identifying novel potent inhibitors of OGT from compounds of *Tinospora cordifolia*, and we compare our results with that of an established OGT inhibitor, OSMI-1. Based on docking scores and ligand-protein interactions, we predict four (4) top compounds; Apigenin, Bergenin, Diosmetin, and Syringin. In conclusion, the results from the ADME/Tox analysis have led to the prediction that a *T. cordifolia* compound (Bergenin) has better drug-like characteristics than the standard compound, OSMI-1.

Keywords: Diabetes mellitus; *Tinospora cordifolia;* O-linked β-N-acetylglucosamine Transferase (OGT); OSMI-1; molecular docking; ADME/Tox; MM/GBSA.

1. Introduction

Diabetes mellitus characterized by excess blood sugar is a multifactorial metabolic disease that has reached epidemic proportions worldwide. The International Diabetes Foundation (IDF) estimates that approximately 537 million adults will be living with DM in 2021. The total number of people living with DM is projected to rise to 783 million by 2045 [1]. O-GlcNAcylation of proteins is a reversible post-translational modification characterized by the cycling of O-GlcNAc moiety on the serine and threonine residues of thousands of nuclear and cytoplasmic proteins. This attachment and removal are catalyzed by O-linked β-

N-acetylglucosamine Transferase (OGT) and O-linked N-acetlyglucosaminase (OGA), respectively [2,3]. OGT is essential as deletion of this gene is lethal in mice embryos [4], it is believed to modulate cellular processes such as protein stability, signal transduction, and stress response [5,6], and the understanding of this modulation continues to grow. Aberration of this protein is implicated in many human pathologies, including diabetes mellitus, the onset, and progression of neurodegenerative diseases like Alzheimer's, heart failure, and cancer [7-10]. A study confirms that the overexpression of OGT protein in mice has been reported to result in a diabetic phenotype, directly establishing a link between diabetes and OGT [11]. Just like in other glycosyltransferases, UDP-GlcNAc, a product of the Hexosamine Biosynthesis Pathway, serves as a substrate for OGT, which is reportedly one of the major regulators of this protein as it is greatly affected by nutrient availability across the cell [12].

Several OGT inhibitors have been reported in recent years, some inhibitors have high molecular weight, cellular impermeability, an off-target effect resulting in cellular toxicity [9], and the ability to generate reactive oxygen species (ROS), and this renders them unfit for use in *in vivo* experiments [12,13]. This makes the discovery of potent, small molecule OGT inhibitors imperative as it will provide a means to understand the biological roles of O-GlcNAcylation further and also provide a solution to the problems caused by alterations in OGT activity.

Plant compounds are now extensively studied to discover potential drug compounds, and many novel drugs are plant-based as they compose enormous therapeutic activity with reduced side effects compared to synthetic drugs [14-16]. Conversely, there has been no report of natural compound OGT inhibitor. *T. cordifolia* is a plant that has been used in ancient Chinese and ayurvedic medicine. It is believed to lessen the impact of diabetic neuropathy in patients with diabetes. It has been so for several years [17], and it has been reported that when taken orally, the root extracts can regulate blood glucose levels, suppress oxidative stress markers, and improve insulin secretion [18,19].

In this study, we utilized the molecular docking approach. The top four ranking compounds (Apigenin, Bergenin, Diosmetin, and Syringin) and OSMI-1 were subjected to ADME/Tox analysis to determine and compare the pharmacological properties; we also put MM/GBSA to use to determine the free binding energies of the docked complexes. Bergenin showed better drug-likeness than the established OGT inhibitor (OSMI-1) [13], indicating that this *T. cordifolia* compound could be used to develop potent OGT inhibitors.

2. Materials and Methods

2.1. Receptor retrieval and preparation.

The 3D crystal structure of human OGT in a complex with a co-crystallized inhibitor, UDP-5SGlcNAc (PDB ID: 4GZ6) [20], was retrieved from the RCSB Protein Data Bank [21]. Preparation of this protein which includes preprocessing, optimization, and minimization, was done using the Protein Preparation Wizard module of Schrodinger-Maestro v11.1 [22]. Using a pH of ±7, structural water molecules were retained to maintain protein stability while redundant water molecules were deleted to accommodate novel ligands into the active site. Hydrogens were also added to fill in for the missing atoms and mediate hydrogen bridges and electrostatic forces [23].

2.2. Ligands mining and preparation.

The 2D format of *T. cordifolia* compounds was mined from the PubChem online database [24]. Using the LigPrep module of Maestro v.11.1 [25], the 200 compounds were prepared and converted to their 3D geometries preceding molecular docking. The stereoisomers were set to generate at most 32 per ligand, which eventually yielded 728 compounds at the end of the ligand preparation process; this was done to ensure docking to get the best fit within the protein active site.

2.3. Receptor grid generation.

Receptor grid generation is carried out before molecular docking to restrict the docking of the ligands within 4Å of the protein active site [26]. The grid was generated using an OPLS3 forcefield in the Glide module of Schrodinger-Maestro v11.1 [27]. The box measured at -133, 26.44, and 34.82Å (x, y, and z) for molecular docking.

2.4. Molecular docking.

Molecular docking is a computer-based structural method used in drug discovery and design [28]. It is an invaluable tool in identifying novel compounds with therapeutic properties and predicting interactions that occur between molecules and biological targets (ligand-protein interactions) at the molecular level [29]. The roles and applications of molecular docking in drug design and development have been extensively discussed [30,31].

We used the glide module of Schrodinger Maestro for this step [32]. The prepared ligands were docked at the protein active site within the pre-calculated receptor grid to prevent the docking of compounds beyond the active site. To rule out the occurrence of false negative results, this current study uses Extra precision (XP) ligand docking to compare the docking score of the four top-ranking compounds (Apigenin, Bergenin, Diosmetin, and Syringin) against OSMI-1 and also examine the molecular interactions made between the residues within 4Å at the OGT active site with OSMI-1 and the *T. cordifolia* compounds. The molecular docking was performed on a 950 GB RAM Ubuntu workstation using Schrödinger Maestro v11.1.

2.5. ADMET/Tox screening.

We used the Pro-Tox II (https://tox-new.charite.de/protox_II/index.php?site=home) and SwissADME (http://www.swissadme.ch/index.php) online servers to run the ADME/Tox analysis for the top compounds and OSMI-1, this was done to determine the pharmacokinetic profile, toxicity, and drug-likeness of the compounds [33].

2.6. MM/GBSA prediction.

The Molecular Mechanics/Generalized Born Surface Area (MM/GBSA) free binding energy calculations for the 5 protein-ligand complexes were carried out using the Prime module of the Schrödinger suite [34]. The Prime rotamer search algorithms using the OPLS3 force field and VSGB solvent model settings were used to look through the calculations [35].

3. Results and Discussion

3.1. Molecular docking analysis.

Here, we report the computational approach employed in discovering the top-ranking *T. cordifolia* compounds that could be potent, small molecule OGT inhibitors. The 2D structural representation of the *T. cordifolia* compounds and OSMI-1 are shown in Figure 1. The results from the extra precision (XP) glide docking is presented in Table 1. To further investigate their binding mechanism (residue interaction and bond communication), we study the 2D ligand interaction with the key active site residues of OGT (Figure 2). The 3D XP-glide docking poses of each protein-ligand complex are shown in their respective zoomed-in conformations in Figure 3 (A-E). OGT has molecular ultrastructure responsible for the catalytic addition of O-GlcNAc moiety on the serine and threonine residues of nuclear and cytoplasmic proteins [36,37]. Molecular inhibition of this protein has been a field of interest to many scientists as it will not only help understand the mechanism of this protein but also contribute to the discovery and development of potent drug candidates that will potentially curb the metabolic diseases associated with its alteration [38,39].

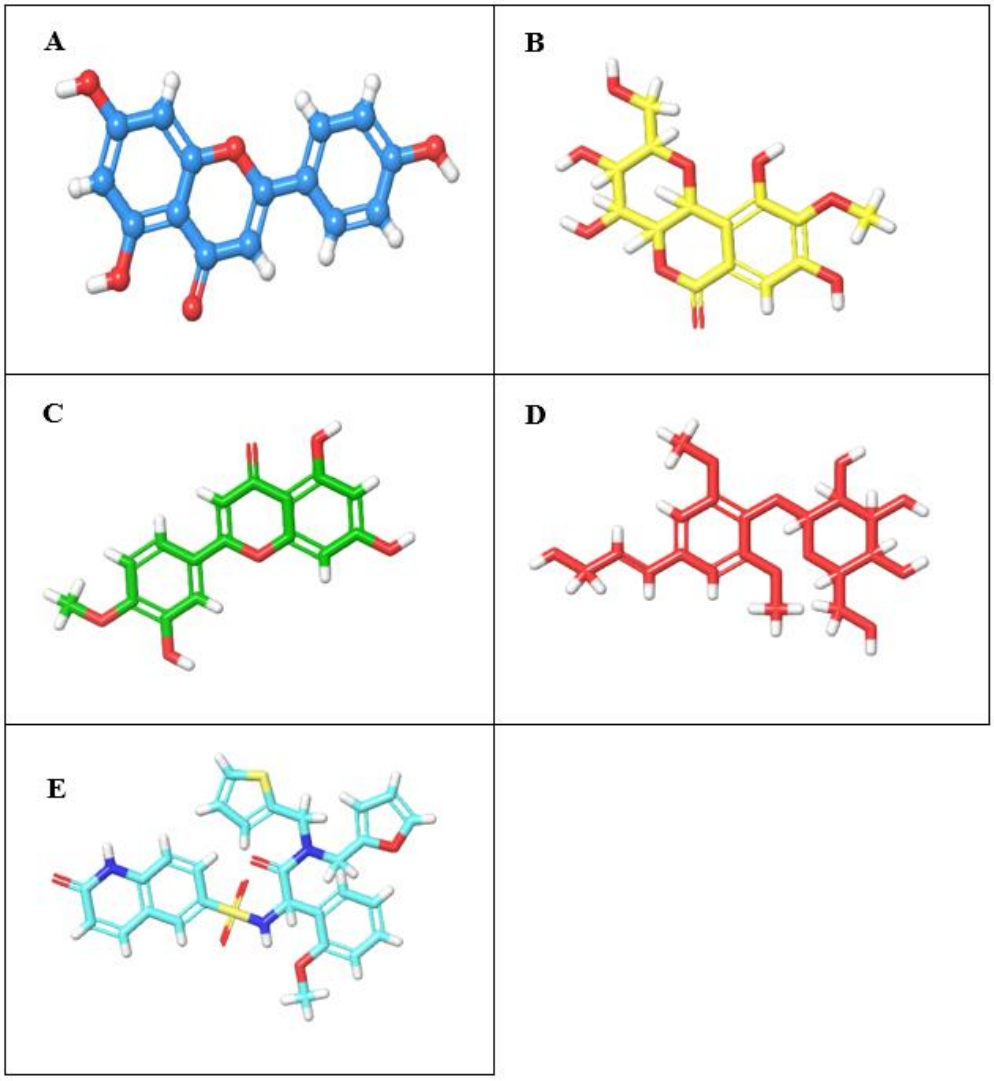

Figure 1. 2D structures of Apigenin (A), Bergenin (B), Diosmetin (C), Syringin (D), and OSMI-1 (E).

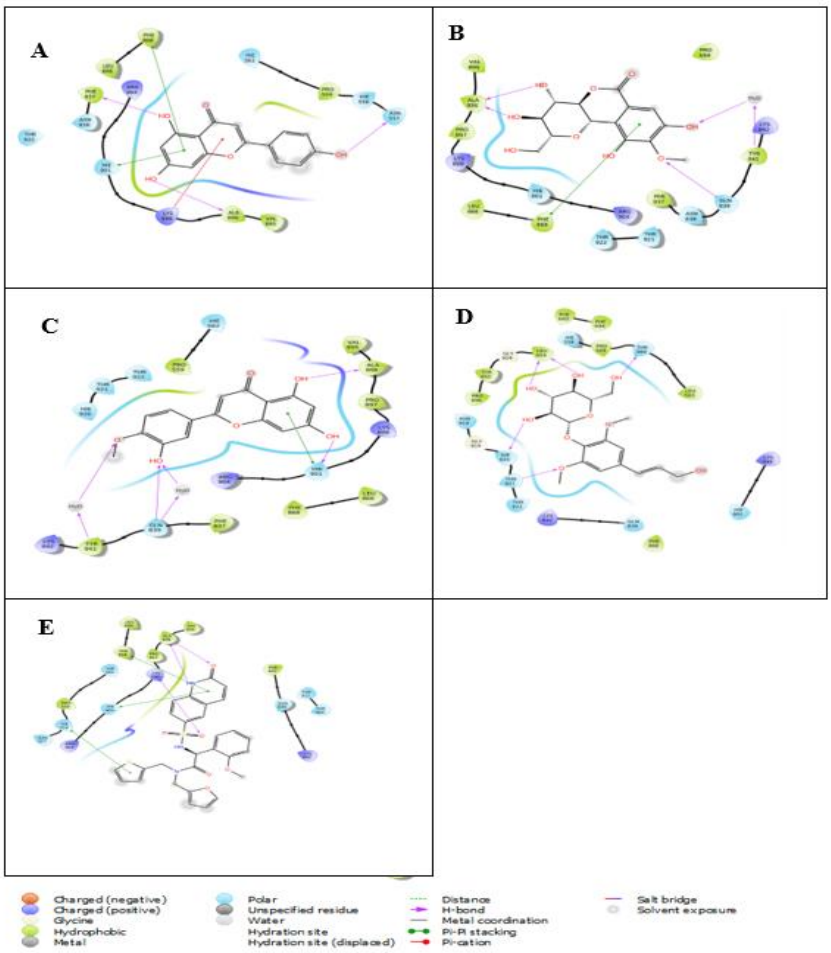

Figure 2. Ligand interaction diagrams of the protein-ligand complexes; Apigenin (A), Bergenin (B), Diosmetin (C), Syringin (D), and OSMI-1 (E).

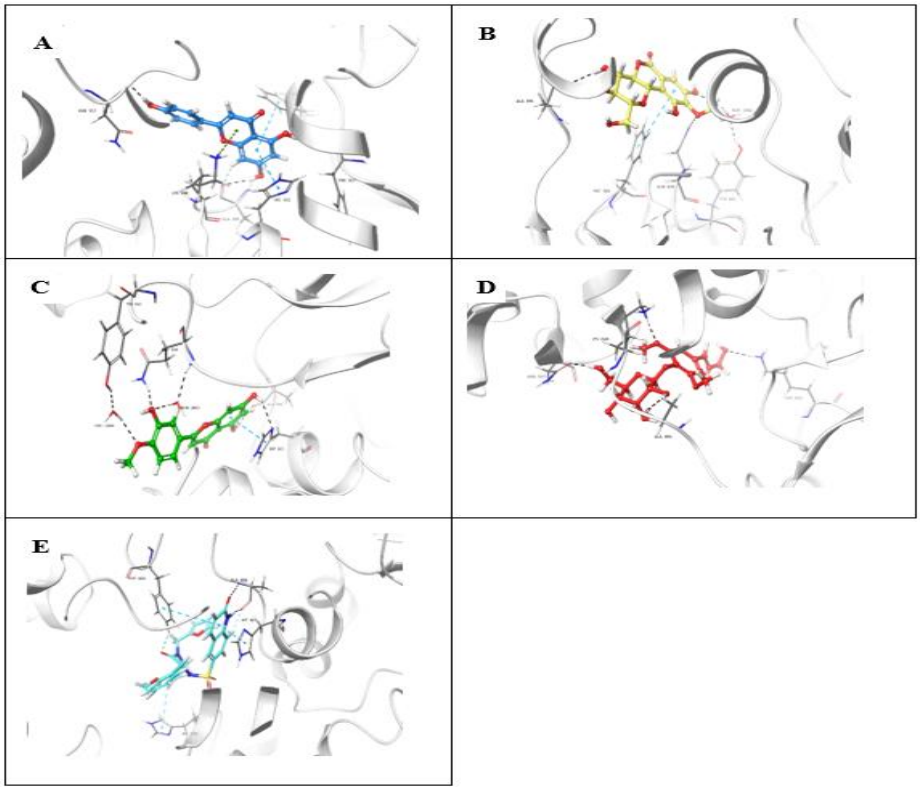

Figure 3. Apigenin (A), Bergenin (B), Diosmetin (C), Syringin (D), and OSMI-1 (E) in their 3D zoomed-in views.

Table 1. Docking scores and MM/GBSA dG binding scores of compounds

COMPOUND	DOCKING SCORE (kcal/mol)	MM/GBSA dG SCORE
Apigenin	-5.130	-47.161
Bergenin	-8.218	-35.152
Diosmetin	-7.507	-53.605
Syringin	-7.416	-43.907
OSMI-1	-6.320	-46.537

The compounds, Apigenin, Bergenin, Diosmetin, Syringin, and OSMI-1, showed docking scores of -5.130, -8.218, -7.507, -7.416, and -6.320, respectively, in Kcal/mol (Table 1). The presence of the hydrogen bond interactions determines the specificity of the protein-ligand binding [39]. Apigenin made three hydrogen bond interactions with PHE837, ASN557, and ALA896, one salt bridge with LYS898, and three Pi-stacking with HIS901 and PHE868 (Figure 2A). Salt bridges are the sturdiest non-covalent interactions at the molecular level [40]. Bergenin made three hydrogen bond interactions with TYR841, GLN839, and ALA896; one Pi-stacking was formed with PHE868 (Figure 2B). Diosmetin made three hydrogen bond connections with GLN839, TYR841, and ALA896, with a Pi-stacking with HIS901 (Fig. 2C). Syringin made four hydrogen bonds with the residues THR560, LEU653, HIS920, THR921 (Fig. 2D). OSMI-1 made hydrogen bond communications with LYS898, ALA896 and three Pi-stacking interactions with HIS901, HIS558, and PHE868 (Fig. 2E). In Figure 3 (A-E), the 3D interactions of the top compounds (Apigenin, Bergenin, Diosmetin, and Syringin) and OSMI-1 are shown in their zoomed-in conformations at the OGT active site [41]. All four compounds are deeply buried within the active site of OGT, and good interactions were made with most of the key residues within 4Å at the active site, such as LEU653, GLN839, TYR841, LYS842, HIS920, and THR921. Supporting evidence from previous studies on the inhibition of OGT show that interactions should be made with these residues as they aid ligand binding and inhibition of the protein [5,9,12,20,42]. These data corroborate evidence supporting our study that the interactions made by the *T. cordifolia* compounds are necessary for inhibiting OGT.

This study shows that the hit compounds interacted with the residues previously reported in other published protein-ligand complexes [19,37], signifying the potential of these *T. cordifolia* compounds as specific OGT inhibitors.

3.2. ADME/Tox analysis.

Computer-aided ADME/Tox prediction is essential in discovering and developing new drugs; it is economical and helps predict drug response [43,44]. ADMET prediction techniques were developed in 1863 and were solely concerned with how drug solubility affects toxicity [45]. In recent years, the focus has included *in vitro* testing. We predict the ADME/Tox properties of the top compounds and OSMI-1 using two online tools; SwissADME and ProTox II.

From the results in Table 2, Diosmetin is predicted to have the highest rate of gastrointestinal absorption among the top compounds; this is indicative of its high lipophilicity value, while the other two compounds showed very low lipophilicity profiles. Water solubility aids the distribution of molecules to cells. In addition to lipophilicity, a drug candidate must possess a good water solubility level to enable it to move in systemic circulation [46]. The estimated solubility (ESOL) class prediction showed that OSMI-1, which had the highest level of lipophilicity, exhibited the lowest water solubility. This implies that this compound could be poorly mobilized within systemic circulation compared to the other compounds, while the

other compounds with the lower lipophilicity values are shown to range from soluble to very soluble.

Table 2. Predicted physicochemical values of compounds using SwissADME.

Compound	Mol MW (g/mol)	Consensus Log P	ESOL Log S	ESOL Class	Bioavailability score	Rule of Five
Bergenin	328.27	-0.80	-1.33	Very Soluble	0.55	0
Syringin	372.37	-0.48	-1.03	Very Soluble	0.55	0
Diosmetin	300.26	2.19	-4.06	Moderately soluble	0.55	0
Apigenin	270.24	2.11	-3.94	Soluble	0.55	0
OSMI-1	563.64	3.52	-5.18	Moderately soluble	0.55	1

Table 3. Predicted pharmacokinetic values of compounds using SwissADME.

Compound	GI absorption	BBB Permeant	Pgp substrate	CYP1A2 inhibitor	CYP2C19 inhibitor	CYP2C9 inhibitor	CYP2D6 inhibitor	CYP3A4 inhibitor
Bergenin	Low	No	No	No	No	No	No	No
Syringin	Low	No	No	No	No	No	No	No
Diosmetin	High	No	No	Yes	No	Yes	Yes	Yes
Apigenin	High	No	No	Yes	No	No	Yes	Yes
OSMI-1	Low	No	No	Yes	Yes	No	No	Yes

Based on the Lipinski rule (Table 2), the bioavailability score and drug-likeness of the compounds showed that all hit compounds and OSMI-1 had a positive bioavailability score (0.55). A bioavailability score of 0.55 shows that the compound passes (not completely) the Lipinski rule-based filter of drug-likeness and is considered drug-like. Lipinski's five (Pfizer's rule of five) is used to evaluate the drug-likeness of a compound that would ensure human oral activity [47]. However, according to this rule, OSMI-1 has a penalty score of 1 due to the high molecular weight of 563.64g/mol.

The swissADME pharmacokinetic predictions in Table 3 also showed that none of the compounds could permeate the Blood-Brain barrier. Furthermore, none of the lead compounds is predicted to be a substrate of P-glycoprotein. P-glycoprotein is a member of ATP binding cassette (ABC) proteins which actively participate in the efflux of molecules from the cell [48]. This implies that none of the compounds would be prevented from bioaccumulating and eliciting their response within the cells. Further analyses showed that OSMI-1 and two of the compounds could inhibit the selected CYP isoforms and, therefore, would induce a drug-drug interaction. Bergenin and Syringin stand out by not inhibiting any of the selected CYP isoforms; therefore, they cannot induce a drug-drug interaction [49,50]. Cytochrome P450 (CYP) is a family of enzymes that catalyze phase 1 metabolism of xenobiotics at large.

Table 4 shows the toxicity predictions guided by Pro-tox II online server, and none of the test compounds were predicted to be carcinogenic or hepatotoxic. The predicted LD50 values also prove that Bergenin is the least toxic of all the compounds (10000mg/kg), while OSMI-1 is the most toxic (1700mg/kg).

Table 4. Predicted toxicity profile using ProTox II server.

Compound	Predicted LD50 (mg/kg)	Predicted Toxicity class	Carcinogenicity	Hepatotoxicity
Bergenin	10,000	6	-	-
Syringin	4,000	5	-	-
Diosmetin	3,919	5	-	-
Apigenin	2,500	5	-	-
OSMI-1	1700	4	-	-

3.3. MM/GBSA analysis.

Molecular docking was additionally assessed with MMGBSA free restricting energy which is identified with the post-scoring approach for OGT (PDB ID: 4GZ6) target. The accuracy of docking is confirmed by examining the lowest energy poses predicted by the scoring function. The Glide score and MM-GBSA free energy values are obtained when the ligands are docked to the active site. The MM-GBSA free energy scores for the *T. cordifolia* compounds and OSMI-1 are shown alongside the docking scores in Table 1.

4. Conclusions

Our study subjected compounds from *T. cordifolia* plant to *in silico* study and predicted four compounds; Bergenin, Apigenin, Syringin, and Diosmetin bind robustly to OGT compared to OSMI-1. Further subjection of these hit compounds to ADME/Tox screening shows that the hit compounds are partially drug-like, leaving Bergenin as the most drug-like compound compared to OSMI-1.

Our findings suggest that these compounds might be better drug-like molecules, and *T. cordifolia* leaf could be a good plant source for a drug-like compound that may treat neuropathy in diabetes by inhibiting the target enzyme OGT.

Albeit these findings are predictions by different tools, lead compound optimization and further *in vitro* and *in vivo* analysis are recommended to validate this prediction study.

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Conflicts of Interest

The authors declare no conflict of interest.

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