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Research Article

Network Pharmacology and Molecular Docking Elucidate Key Targets and Multi-Pathway Modulation in the Antidiabetic Action of *Momordica charantia* L.

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ABSTRACT

Type 2 diabetes mellitus (T2DM) is characterised by hyperglycaemia resulting from insulin resistance, diminished tissue sensitivity to insulin, impaired β-cell function, or dysregulated glucagon secretion. It is a major public health concern in Malaysia, affecting nearly one in five adults. As there is currently no definitive cure, the disease management of T2DM relies on lifestyle management and pharmacological intervention. *Momordica charantia* L. (bitter gourd) is traditionally recognised for its antidiabetic properties, yet its key therapeutic targets and mechanisms of action remain incompletely understood. Therefore, this study employed an *in silico* approach to investigate the pharmacokinetic properties and antidiabetic activity of six key bioactive compounds in *M. charantia*, including stigmasterol glucoside (SG), β-sitosterol glucoside (BSG), diosgenin, oleanolic acid, stigmasterol, and β-sitosterol. The present results showed that all six compounds satisfied Lipinski's Rule of Five, indicating good oral bioavailability. In addition, SG, BSG, and diosgenin were found to be non-toxic with a predicted LD_{50} of 8000 mg/kg, while oleanolic acid, stigmasterol, and β-sitosterol showed moderate toxicity (LD_{50} between 890-2000 mg/kg). Network pharmacology analysis identified 97 potential compound targets associated with T2DM. KEGG and gene ontology enrichment analysis linked these targets to critical pathways including insulin signalling, insulin resistance, and endocrine resistance. In addition, molecular docking analysis further demonstrated strong binding affinities of the metabolites with key targets including α-amylase, MAPK8, CES1, PPARG, and GSK3B. Collectively, these findings indicated that *M. charantia* metabolites exert antidiabetic effects through multi-target and multi-pathway modulation. This work may provide a theoretical basis for the traditional use of *M. charantia* and supporting its potential as a source for novel T2DM therapeutics.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is primarily caused by diminished tissue sensitivity to insulin and defective insulin secretion by pancreatic β-cells (Galicia-Garcia et al., 2020). To date, there is no definitive cure for T2DM, and disease management relies primarily on continuous lifestyle modifications and medication such as metformin, sulfonylureas, dipeptidyl peptidase-4 (DPP-4) inhibitors, and thiazolidinediones (Shin et al., 2021). Nevertheless, the medications have been associated with side effects such as hepatotoxicity, congestive heart failure, cancer, hypoglycaemia, diarrhoea, and weight gain. This has driven increasing research into the antidiabetic potential of

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bioactive compounds from plants such as *Momordica charantia* L., a climber plant which is commonly known as bitter gourd or bitter melon.

M. charantia was reported to confer beneficial effects for T2DM in numerous studies, but its underlying mechanisms have not been fully established (Richter et al., 2023). Intensive research into the clinical efficacy of the bioactive compounds within *M. charantia* has yet to be undertaken as *M. charantia* is still widely considered a complementary or alternative medicine. Thus, the present study aims to conduct an *in silico* analysis, which combined network pharmacology and molecular docking analysis to investigate the pharmacokinetic properties and antidiabetic activity of bioactive compounds in *M. charantia*, including stigmasterol glucoside (SG), β-sitosterol glucoside (BSG), diosgenin, oleanolic acid, stigmasterol, and β-sitosterol. The present study provides new insight into the key targets and multi-pathway modulation in the antidiabetic action of *Momordica charantia* L., which may contribute towards the development of novel, multi-target phytotherapeutic agents for diabetes management.

MATERIALS AND METHOD

The structures of the six bioactive compounds from *M. charantia*: stigmasterol glucoside (SG), β-sitosterol glucoside (BSG), diosgenin, oleanolic acid, stigmasterol, and β-sitosterol were obtained through PubChem (https://pubchem.ncbi.nlm.nih.gov) in Structure Data File (.sdf) and canonical SMILES formats. Drug-likeness and toxicity profiles were evaluated using the Lipinski's Rule of Five, ProTox 3.0 toxicity prediction tools (https://tox.charite.de/protox3), and ADMETlab 3.0 (https://admetlab3.scbdd.com) to assess the pharmacokinetics and safety of these compounds for drug development. Next, compound-related targets were identified using PharmMapper (https://www.lilab-ecust.cn/pharmmapper/) and SwissTargetPrediction (http://www.swisstargetprediction.ch/) databases. In addition, the disease-related targets were identified using the DisGeNet (https://disgenet.com/) and GeneCards (https://www.genecards.org/) databases. Overlapping targets between the *M. charantia* bioactive compounds and the disease-associated genes were visualized using Venny 2.1.0. Core networks and key targets were further analysed using protein–protein interaction (PPI) network construction and KEGG pathway enrichment analysis to identify the underlying biological processes and signalling pathways. PPI network analysis was performed using STRING v12.0 (https://string-db.org/) and Cytoscape v3.10.3, while KEGG pathway analysis was performed using ShinyGO v0.82 (https://bioinformatics.sdstate.edu/go/). Finally, molecular docking analysis was performed using CB-Dock2 (https://cadd.labshare.cn/cb-dock2) and the results were visualised using Discovery Studio Visualizer v25.1.0.24284. Molecular docking analysis simulated the binding affinities and optimal conformations of *M. charantia* bioactive compounds with their target proteins to identify potential therapeutic interactions. The detailed database search parameters used in the present study are provided as supplementary material.

RESULTS AND DISCUSSION

Drug Likeness and Toxicity Evaluation

All six *M. charantia* bioactive compounds complied with Lipinski's Rule of Five, having no more than one violation (**Table 1,** refer to supplementary **Table S1** for details). SG and BSG have molecular weights of more than 500 g/mol, while diosgenin, oleanolic acid, stigmasterol, and β-stigmasterol have Moriguchi logarithm of the octanol-water partition coefficient (MlogP) over 4.15. The present results suggested good oral bioavailability for the compounds. In addition, SG, BSG, and diosgenin were found to be non-toxic, with an LD_{50} of 8000 mg/kg (**Table 2**). Conversely, oleanolic acid, stigmasterol, and β-sitosterol may have moderate toxicity, with LD_{50} between 890 – 2000 mg/kg. Based on these findings, SG, BSG, and diosgenin emerge as promising candidates for safe therapeutics, whereas oleanolic acid, stigmasterol, and β-sitosterol require further safety characterisation.

Table 1 Lipinski Rule of Five for the *M. charantia* compounds. SG: stigmasterol glucoside; BSG: β-sitosterol glucoside; Molecular weight (MW); Moriguchi logarithm of the octanol-water partition coefficient (MlogP)

Compound	Lipinski's rule of five (Accepted if < 2 violations)
SG	1 violation: MW>500
BSG	1 violation: MW>500
Diosgenin	1 violation: MlogP >4.15
Oleanolic Acid	1 violation: MlogP >4.15
Stigmasterol	1 violation: MlogP >4.15
β-sitosterol	1 violation: MlogP >4.15

Table 2 Toxicity profiles for the *M. charantia* compounds. SG: stigmasterol glucoside; BSG: β-sitosterol glucoside. Class 1-3: toxic, lethal if consumed; Class 4-5: moderate toxicity, harmful if consumed; Class 6: not toxic

Compounds	Predicted LD_{50} (mg/kg)	Predicted Toxicity Class
SG	8000	6
BSG	8000	6
Diosgenin	8000	6
Oleanolic Acid	2000	4
Stigmasterol	890	4
β-sitosterol	890	4

Target of Interest

Using PharmMapper, SwissTargetPrediction, GeneCards, and DisGeNET, we identified 67, 68, 50, 65, 55, and 54 T2DM-associated compound targets for SG, BSG, diosgenin, oleanolic acid, stigmasterol, and β-sitosterol respectively. The list of candidate targets is provided as supplementary material (supplementary **Table S2**). In total, we identified 97 unique predicted targets of the six *M. charantia* compounds relevant to T2DM (**Figure 1**).

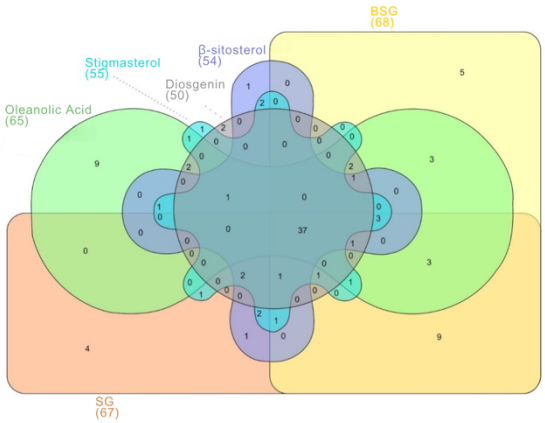

Figure 1 Venn diagram of the predicted compound targets for the six selected bioactive compounds from *M. charantia*.

Protein-protein Interaction (PPI) Network Analysis

Supplementary **Figure S1(a)** shows an overall PPI network diagram that was generated by STRING v12.0 using the 97 candidate targets with 97 nodes and 241 edges. The diagram was further analysed using Cytoscape v3.10.3 to produce five smaller network clusters. One network cluster was comprised of AMY1A, AMY1B, and AMY1C, which encode salivary α-amylase (Supplementary **Figure S1(b)**). This PPI network cluster has 3 nodes, 3 edges, and has AMY1C as the seed. The results highlighted the potential activity of *M. charantia* metabolites in interacting with α-amylase, a key enzyme in starch digestion and regulation of glucose homeostasis.

Kyoto Encyclopaedia of Genes and Genomes (KEGG) Pathway Analysis

ShinyGO 0.82 was used to analyse the gene ontology and perform KEGG pathway enrichment on the 97 candidate targets of *M. charantia*'s compounds against T2DM. According to the findings of the pathway enrichment network study in **Figure 2**, the identified targets are effective in regulating the metabolic pathways related to T2DM including insulin signalling, insulin resistance, and endocrine resistance pathways.

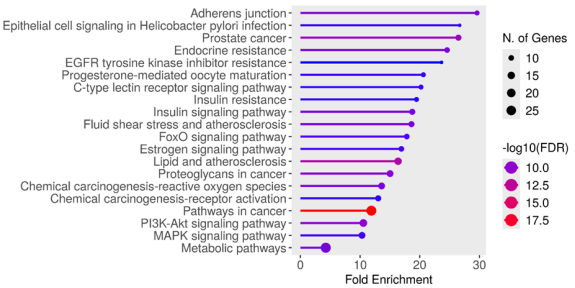

Figure 2 KEGG metabolic pathway analysis of the 97 candidate targets in *M. charantia* against T2DM.

From the KEGG pathway analysis, PTPRF, PTPN1, MAPK8, BRAF, MAPK1, GSK3B, PDE3B, CALM1, HK1, and PCK1 are the target proteins associated with T2DM in the insulin signalling pathway (Supplementary **Figure S2**). In addition, EGFR, IGF1R, SRC, ESR1, BRAF, MAPK1, MAPK14, MAPK8, MDM2 are the associated target proteins with T2DM in the endocrine resistance pathway (Supplementary **Figure S3**).

Next, supplementary **Figure S4** shows that PTPN11, MAPK8, GSK3B, PCK1, NR1H3, and NOS3 are the target proteins involved in the insulin resistance pathway which will contribute to T2DM. Notably, proteins such as MAPK8, GSK3B, and PCK1 are recurring genes that are involved in metabolic pathways related to T2DM, thus they are potential candidates for further molecular docking analysis.

Molecular Docking Analysis

The molecular docking analysis of α-amylase with acarbose as a control produced a Vina score (binding energy) of -7.8 kcal/mol. Diosgenin and stigmasterol were found to bind best to α-amylase with similar binding energies of -10.5 kcal/mol. These results suggested that diosgenin and stigmasterol can bind to the same site on α-amylase better than the known inhibitor acarbose, thus indicating the inhibitory effects of diosgenin and stigmasterol on α-amylase activity. The intermolecular interactions between α-amylase with acarbose, diosgenin, and stigmasterol are shown in **Figure 3**. The results are supported by a recent finding showing α-amylase inhibition activity (77.45%) of a traditional medicinal plant *Dioscorea deltoidea* Wall. ex Griseb which contains diosgenin (2.97% to 1.01% dry weight) (Nazir et al., 2025).

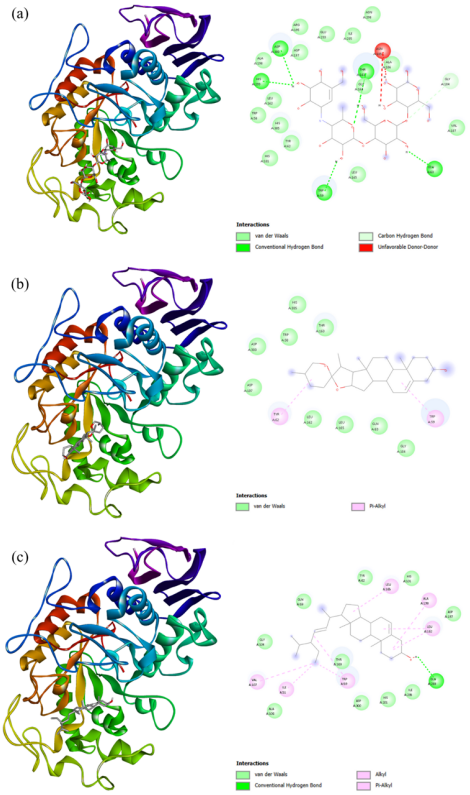

Figure 3 Intermolecular interactions of α-amylase with **(a)** acarbose; **(b)** diosgenin; **(c)** stigmasterol.

The inhibition of mitogen-activated protein kinase 8 (MAPK8), which encodes the Jun N-terminal kinase (JNK1) protein, is believed to play a role in mitigating insulin resistance in T2DM (Cao et al., 2024). In the present study, the molecular docking analysis of MAPK8 with SP600125 as a control produced a Vina score (binding energy) of -8.8 kcal/mol. Among the *M. charantia* compounds, stigmasterol was found to bind best to MAPK8 with a binding energy of -9.4 kcal/mol. Notably, SP600125 and stigmasterol were both

predicted to establish interaction with the same four residues in acarbose, including LEU168, ILE32, VAL40, and VAL158. These results show that stigmasterol can bind to the MAPK8 better than the known inhibitor SP600125, thus indicating the inhibitory effects of stigmasterol on MAPK8 activity. The intermolecular interactions of MAPK8 with SP600125 and stigmasterol are shown in **Figure 4**.

SP600125 is an orally active, reversible, and ATP-competitive JNK inhibitor that has been shown to help with T2DM by regulating progressive pancreatic β-cell dysfunction by suppressing autophagy and promoted apoptosis in RIN-m5f cells in rats (Wang et al., 2025). In addition, the present finding aligns with recent functional evidence that stigmasterol inhibits LPS-induced MAPK8 and MMP-1 overexpression in a rheumatoid arthritis model (Li et al., 2025), supporting the role of stigmasterol as a MAPK8 pathway inhibitor.

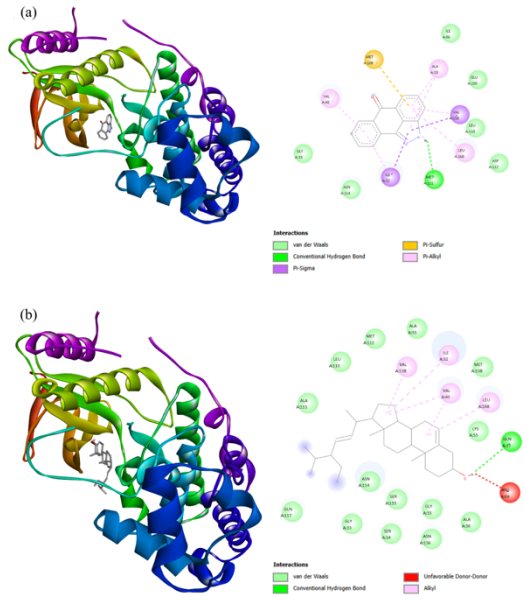

Figure 4 Intermolecular interactions of MAPK8 with **(a)** SP600125; **(b)** stigmasterol

Carboxylesterase 1 (CES1) is believed to be involved in the pathogenesis of T2DM. A study had concluded that the expression level of CES1 mRNA was linked with the risk factors for T2DM and also suggested that copy number variation of CES1 influences measures of glucose metabolism, which contributes to the genetic susceptibility to T2DM (Friedrichsen et al., 2013). CES1 activity has shown to be doubled in obese T2DM patients compared to lean individuals, and obese T2DM patients were noted to produce excessive fatty acids that were deposited in ectopic tissues (Dominguez et al., 2014).

Oleanolic acid has been previously reported as an inhibitor of CES1 (Wang et al., 2024). A study that tabulated herbal constituents as inhibitors of CES1 listed the Styrax plant with oleanolic acid as one of its natural constituents having an IC_{50} and K_i of 0.074 µM and 0.073 µM, respectively (Song et al., 2021). The low IC_{50} and K_i values indicate that oleanolic acid is an excellent inhibition of CES1. Therefore, oleanolic acid may have the potential to be developed as a novel drug molecule to combat obesity and T2DM as a CES1 inhibitor.

The molecular docking analysis of CES1 with WWL113 as a control produced a Vina score (binding energy) of -9.1 kcal/mol. Oleanolic acid was found to bind to CES1 with a better binding energy of -10.0 kcal/mol. These results show that oleanolic acid can bind to CES1 better than the known inhibitor WWL113, although the binding happens at different sites (**Figure 5**).

Peroxisome proliferator-activated receptor gamma (PPARG) gene plays a major role in T2DM development and recently, a study showed a significant association of individuals carrying the PPARG Ala12 variant with a reduced risk of T2DM (Sarhangi et al., 2020). T0070907 has been used as a PPARG inhibitor in a study involving a T2DM-induced Meibomian gland dysfunction rat model. The study concluded that T0070907 is an effective and selective PPARG antagonist, and that PPARG is the key to the pathogenesis of T2DM Meibomian gland dysfunction (Shi et al., 2024).

The molecular docking analysis of PPARG with T0070907 as a control produced a Vina score (binding energy) of -7.8 kcal/mol. Stigmasterol was found to bind best to PPARG with a binding energy of -11.3 kcal/mol. These results suggested that stigmasterol can bind to PPARG better than the known inhibitor T0070907, thus indicating the potential modulating effects of stigmasterol on PPARG activity (**Figure 6**).

Glycogen synthase kinase-3 (GSK-3) and its alpha and beta variants (GSK3A and GSK3B) have shown significant promise as a target for T2DM due to functional partitioning of the enzyme, tissue-selectivity and acute dosage-dependency of effects of inhibition (MacAulay & Woodgett, 2008). GSK-3 inhibitors have been shown to enhance insulin action in insulin-resistant skeletal muscle and improve glucose tolerance in T2DM rodent models. A 2003 study published by the American Diabetes Association showed that CHIR 98014 is a highly selective inhibitor of human GSK3B with a K_i value of 0.87 nmol/L. Additionally in the study, diabetic and insulin-resistant *db/db* mice treated with 30 mg/kg CHIR 98014 also exhibited a significant improvement in fasting hyperglycaemia within 4 hours of treatment (Ring et al., 2003).

Diosgenin has been established to operate downstream of the phosphatidylinositol-3-kinase (PI3K) pathway by inhibiting the reduction of GSK3B phosphorylation (Lee et al., 2007). On the other hand, GSK3 signalling pathway was found to be inhibited by diosgenin during an anticancer study (Fang et al., 2024). Given that inhibiting GSK-3 activity has been shown to improve insulin sensitivity and glucose metabolism in animal models of diabetes, T2DM management by GSK3B inhibition using diosgenin should be investigated (MacAulay & Woodgett, 2008).

The molecular docking analysis of GSK3B with CHIR 98014 as a control produced a Vina score of -9.9 kcal/mol. Diosgenin was found to bind best to GSK3B with a binding energy of -10.7 kcal/mol. These results show that diosgenin can bind to GSK3B better than the known inhibitor CHIR 98014, thus indicating the inhibitory effects of diosgenin on GSK3B activity. The intermolecular interactions of GSK3B with CHIR 98014 and diosgenin are shown in **Figure 7**.

Taken together, the selected *M. charantia* compounds were found to interact well with the selected T2DM targets, some showing a better binding energy compared to the known inhibitors. The results highlighted their potential to

be developed into therapeutic agents for T2DM. The molecular docking Vina scores/binding affinities for α-amylase, MAPK8, CES1, PPARG, and GSK3B are listed in **Table 3**.

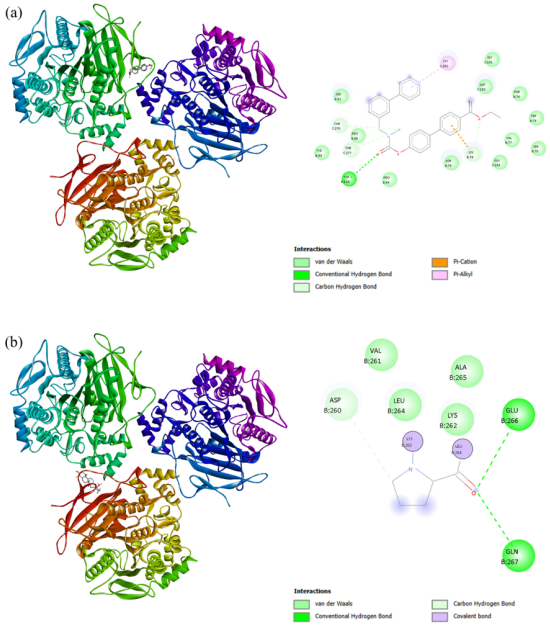

Figure 5 Intermolecular interactions of CES1 with **(a)** WWL113; **(b)** oleanolic acid

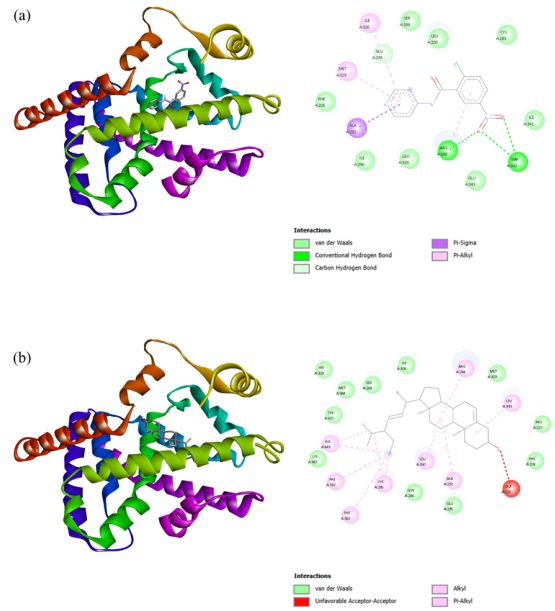

Figure 6 Intermolecular interactions of PPARG with **(a)** T0070907; **(b)** stigmasterol

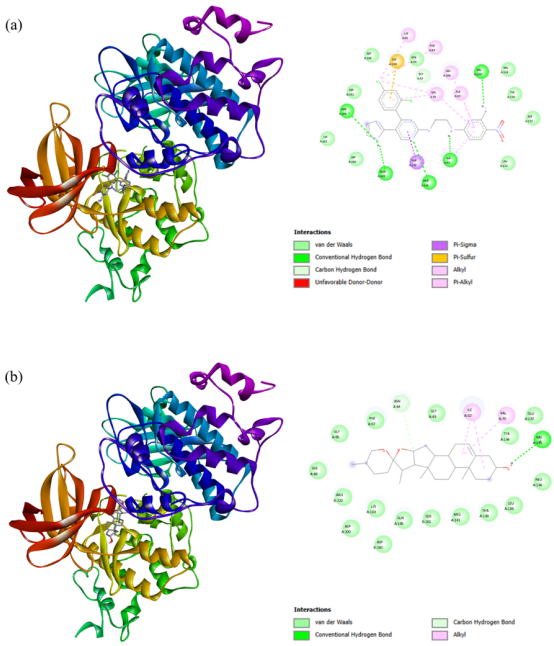

Figure 7 Intermolecular interactions of GSK3B with **(a)** CHIR 98014; **(b)** diosgenin

Table 3 Molecular docking Vina scores/binding energy (kcal/mol) of α-amylase, MAPK8, CES1, PPARG, and GSK3B with their respective controls and the six selected bioactive compounds of *M. charantia*

Compound	α-Amylase	MAPK8	CES1	PPARG	GSK3B
Control	Acarbose	SP600125	WWL113	T0070907	CHIR 98014
	-7.8	-8.8	-9.1	-7.8	-9.9
SG	-9.7	-9.0	-9.6	-9.8	-10.2
BSG	-10.4	-8.6	-9.4	-9.8	-9.9
Diosgenin	-10.5	-8.5	-9.1	-10.0	-10.7
Oleanolic acid	-9.7	-7.5	-10.0	-9.0	-9.3
Stigmasterol	-10.5	-9.4	-8.2	-11.3	-9.7
β-sitosterol	-9.1	-8.7	-8.0	-9.0	-9.9

CONCLUSION

This *in-silico* study provides a comprehensive evaluation of the antidiabetic potential of *Momordica charantia* L. (bitter gourd) through the integrated use of drug-likeness screening, network pharmacology, and molecular docking analyses. All six bioactive compounds including SG, BSG, diosgenin, oleanolic acid, stigmasterol, and β-sitosterol were found to satisfy Lipinski's Rule of Five, indicating good oral bioavailability, with SG, BSG, and diosgenin showing non-toxic profiles. Network pharmacology revealed 97 potential targets associated with type 2 diabetes mellitus (T2DM), mainly enriched in insulin signalling, insulin resistance, and endocrine resistance pathways. Protein–protein interaction and KEGG analyses identified several key hub targets, including PPARG, NOS3, BRAF, EGFR, and SRC, which play crucial roles in glucose regulation and insulin sensitivity. Molecular docking further highlighted α-amylase, MAPK8, CES1, PPARG, and GSK3B as the most

promising therapeutic targets, with diosgenin, β-sitosterol, and oleanolic acid demonstrating strong binding affinities superior to standard inhibitors. Nevertheless, it should be noted that although network prediction tools are highly useful in drug discovery, they have inherent limitations, as their outputs represent probabilistic predictions rather than definitive biological evidence. Network pharmacology primarily reveals associative relationships rather than causal mechanisms, while molecular docking relies on simplified scoring functions and rigid protein structures that may not accurately reflect physiological conditions. Furthermore, database-derived gene sets may be biased toward well-studied genes and pathways, potentially underrepresenting less-characterised targets. Collectively, the findings suggest that *M. charantia* may exert its antidiabetic effects via a multi-target, multi-pathway mechanism involving modulation of carbohydrate metabolism, insulin signalling, and lipid regulation. These results provide a theoretical basis for further *in vitro* and *in vivo* validation and underscore the potential of *M. charantia* phytochemicals as lead candidates in developing safer, plant-derived therapeutics for T2DM management.

Acknowledgement

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Conflicts of Interest

The author declares that there is no conflict of interest regarding the publication of this paper.

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