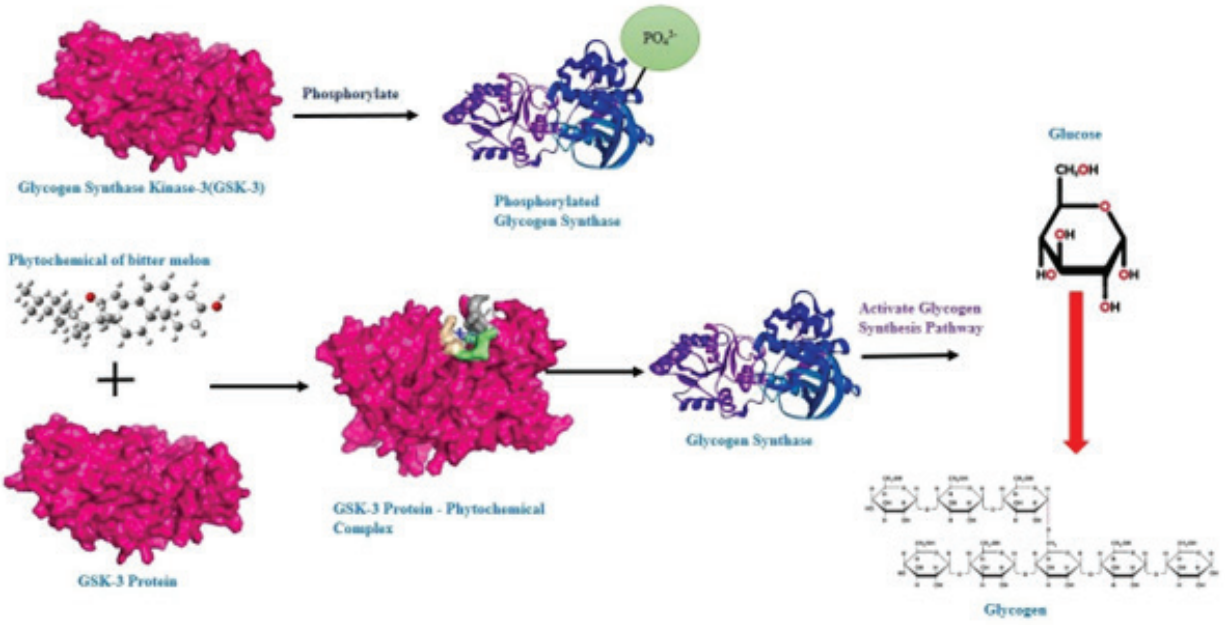
RESEARCH ARTICLE

Comparative Computational Analysis of the Antidiabetic Potential of Momordenol, Momordicilin, Charantin and Vicine from *Momordica charantia* (Bitter Melon)

F. N. Prasangika, S. B. Jayawardana, H. Rajapaksha and D. R. Pandithavidana*



Highlights

- Computational docking was used to evaluate the binding affinity, interaction modes, and stability of four major phytochemicals from *Momordica charantia* with GSK-3, an enzyme that inhibits glycogen synthase.
- Momordenol showed minimal violations of Lipinski's Rule of Five, indicating good potential as an oral drug candidate.
- The findings highlight momordenol's antidiabetic potential as a GSK-3 inhibitor and offer insights for developing new therapeutic agents.

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RESEARCH ARTICLE

Comparative Computational Analysis of the Antidiabetic Potential of Momordenol, Momordicilin, Charantin and Vicine from *Momordica charantia* (Bitter Melon)

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Abstract: *Momordica charantia*, a widely recognized medicinal plant in Eastern (Ayurvedic) medicine, is celebrated for its phytochemical constituents, which have demonstrated significant antidiabetic potential by effectively lowering blood glucose levels in diabetic patients. This study aimed to provide a comparative analysis of the antidiabetic potential of four bioactive compounds: momordenol, momordicilin, charantin, and vicine from *Momordica charantia*, relative to the reference compound, N-(4-methoxybenzyl)-N'-(5-nitro-1,3-thiazol-2-yl) urea (TUM). Molecular docking simulations revealed that momordenol exhibited the highest binding affinity as a potential natural antidiabetic agent, inhibiting the key enzyme glycogen synthase kinase-3 (GSK-3) with a docking score of -9.91 kcal/mol. Momordenol adhered to Lipinski's Rule of Five with minimal violations, suggesting its viability as an oral drug candidate. In silico ADMET analysis showed that both momordicilin and momordenol achieved superior intestinal absorption rates of 96.55% and 95.77%, respectively, compared to TUM's absorption rate of 84.38%, indicating enhanced oral bioavailability. Among the four compounds, momordicilin demonstrated the highest volume of distribution (VDss), indicating its broad systemic distribution, whereas momordenol and charantin were more localized in their distribution profiles. Toxicity assessment using ProTox 3.0 classified charantin in toxicity class 6, based on its LD_{50} value of 8000 mg/kg, suggesting its safety as a potential antidiabetic therapeutic. In contrast, momordenol and momordicilin exhibited moderate toxicity, yet they remain promising candidates for further pharmacological development.

Keywords: GSK-3; Charantin; Vicine; Momordenol; Momordicilin

INTRODUCTION

One of the top five global causes of death is diabetes mellitus (DM). The prevalence of DM is predicted to increase 783 million in 2045 (Richter et al., 2023). Diabetes contributed to an additional 460,000 deaths from kidney disease and elevated blood glucose accounts for 20% of fatalities from cardiovascular disease (Liu et al., 2021). In contrast, between 2000 and 2019, there was a 22% global decline in the likelihood of dying from any of the four major non-communicable diseases (cancer, chronic respiratory diseases, diabetes, or cardiovascular diseases) between the ages of 30 and 70 (Standl et al., 2019). Development of new therapies is crucial, as current treatments often fall short in terms of efficacy or are accompanied by significant side effects.

Herbs for the treatment of diabetes are not new, since ancient time, plants extracts have been used for threating diabetes. Bitter melon is a complex plant medicine that has remarkable long history of use both as a food and as a medicine (Gao et al., 2023). It is known as *Momordica charantia*, Bitter gourd, Kaila and Bitter squash. Triterpenes, steroids, alkaloids, lipids, and phenolic compounds are the principal phytochemicals available in bitter melon (Ullah et al., 2023). In Asia and other developing nations, a variety of traditional herbal treatments has been utilized to treat diabetes (Gao et al., 2023). One plant that has been intensively studied for the treatment of diabetes *is M. charantia.* Current scientific evidence demonstrates the advantageous role of *M. charantia*, so endowing it as one of the most promising plants for diabetes treatment (Suganthi, 2018). The eastern medicinal applications of *M. charantia* in India found that it is one of the most significant plants for reducing blood glucose levels in diabetic individuals (Terefe & Ghosh, 2022) A protein called glycogen synthase kinase-3 (GSK-3) has emerged as a significant target for the drug development due to its involvement in various metabolic and signalling pathways (Factor et al., 2013). The overall structure of the GSK-3 catalytic domain is similar to other protein kinases, containing an N-terminal lobe composed primarily of β-strands in a β barrel conformation, and a C-terminal lobe composed mostly of α-helices (Medina & Avila, 2011). Thus, in mammals, glycogen synthase kinase-3 exists in two isoforms: GSK-3α and GSK-3β as depicted in the 3D structures derived from the Protein Data Bank (PDB) entries in Figure 1. These isoforms encoded by separate genes are structurally similar but functionally distinct, with GSK-3α having a slightly higher molecular weight due to an additional 63 amino acid residues at the N-terminus (Hazarika et al., 2012).

One of the major reasons for choosing glycogen synthase kinase-3 (GSK-3) as a target for inhibitors (phytochemicals of bitter melon) in this investigation, is its distinct multifunctional serine/threonine kinase activity and phosphorylation induced inactivation (Ullah et al., 2023).

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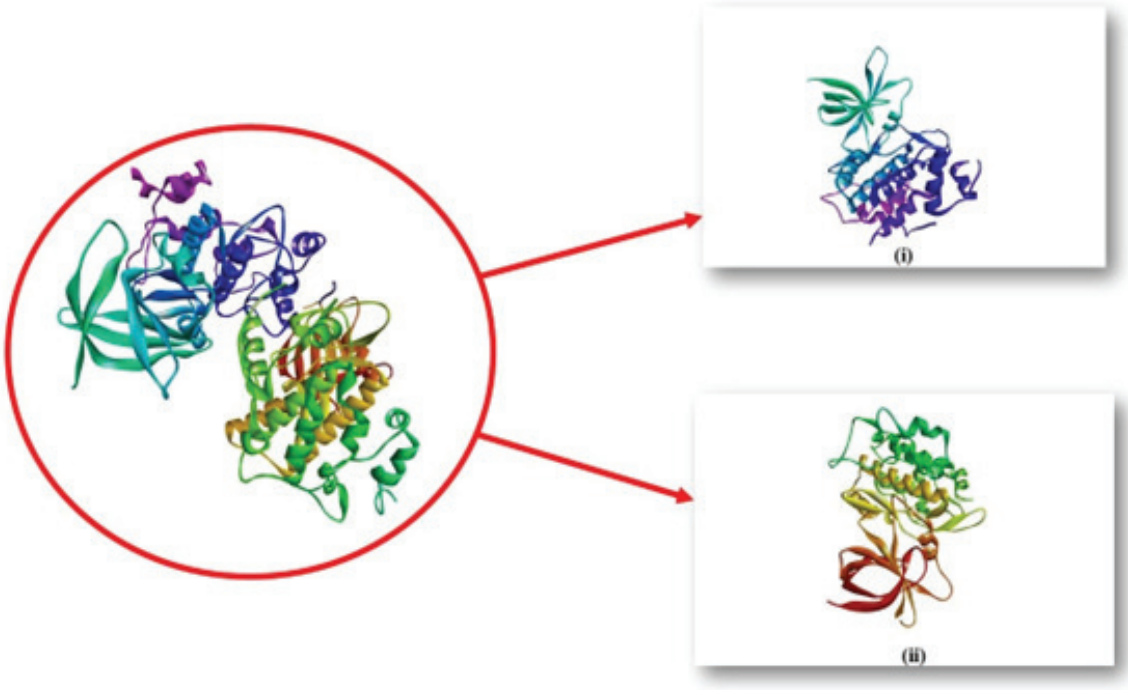


Figure 1: The 3D structures of glycogen synthase kinase-3 (GSK-3) protein and two isoforms: (i) GSK-3α and (ii) GSK-3β

PKB/AKT phosphorylates GSK-3 on serine 9 in response to insulin binding, prevents the enzyme from phosphorylating glycogen synthase (Factor et al., 2013). Glycogen can be synthesized by only unphosphorylated glycogen synthase, which is the active form of the enzyme. Consequently, it is essential for the transduction of proliferative and regulatory signals that emerge at the cell membrane in the insulin-signalling pathway, which may modify blood glucose levels (Gao et al., 2023). Patients with type 2 diabetes have higher GSK-3 activity and levels in their skeletal muscles, which suggests a favourable association between GSK-3 and insulin resistance (Suganthi, 2018). When antidiabetic phytochemicals, which are derived from bitter melon inhibit the GSK-3 protein (Liu et al., 2021), the phosphorylation of glycogen synthase (GS) is prevented and thus, the active form of GS can catalyse conversion of glucose to glycogen as lowering the level of blood sugar (This scenario has been illustrated in "highlights of the graphical abstract"). The major phytochemicals in bitter melon which are responsible for antidiabetic properties have been reported as vicine, momordicilin, momordenol, and charantin (Saeed et al., 2018). Among four of the major phytochemicals, charantin is a common cucurbitane-type triterpenoid (Desai & Tatke, 2015). Fresh bitter melon fruit contains momordenol as a natural sterol, and momordicilin as a triterpenoid (Hazarika et al., 2012). The main substance that has been identified from bitter melon seeds is vicine which is a glycol alkaloid. These four major phytochemicals available in bitter melon serve as both nutritional and bioactive compounds which possess insulin-like chemical structures (as shown in Figure 2) and properties (Joseph & Jini, 2013).

Although bench research studies were carried out (Xie et al., 2023) to investigate antidiabetic effect of these phytochemicals separately, a comparative study has been not conducted using a well-known standard drug. N-(4-methoxybenzyl)-N'-(5-nitro-1,3-thiazol-2-yl)urea (known as TUM) is a highly selective inhibitor of GSK-3 (Bhat et al., 2003) and it has been used widely in therapeutic applications as the reference compound and in research studies (Xie et al., 2023) . The binding affinities and inhibition potentials of major antidiabetic phytochemicals (momordenol, momordicilin, vicine, and charantin) available in bitter melon have been compared with those of TUM (reference inhibitor) in this research. According to the literature, no standard drug targeting the inhibition of phosphorylation of GSK-3 (deactivation) glycogen synthase enzyme has been approved by the US Food and Drug Administration. To fill this gap in the literature, we investigated the antidiabetic potential of these four major phytochemicals with the aim of supporting development of new medicinal products as potential treatment for diabetes.

At the very outset, geometry optimizations of those phytochemicals have been performed to minimize unrealistic geometries, bond lengths, and angles to obtain more stabilized docking starting points (Rajapaksha et al., 2021) and enhance the docking efficiency. This protein-ligand docking is a versatile tool to determine the best possible binding site of a ligand (phytochemical) to a target receptor (GSK). The binding affinities and types of interaction modes of the identified ligands (phytochemicals present in bitter melon) with GSK-3 protein were also investigated. Phytochemical binding pockets with GSK-3 protein have been visualized using Pymol and Biovia Discovery Studio (Banerjee et al., 2018). The ProTox-II server was used to acquire several toxicity metrics, including hepatotoxicity, carcinogenicity, mutagenicity, cytotoxicity, LD50 (mg/kg), and toxicity class of these phytochemicals (Yousaf et al., 2023). Moreover, pkCSM

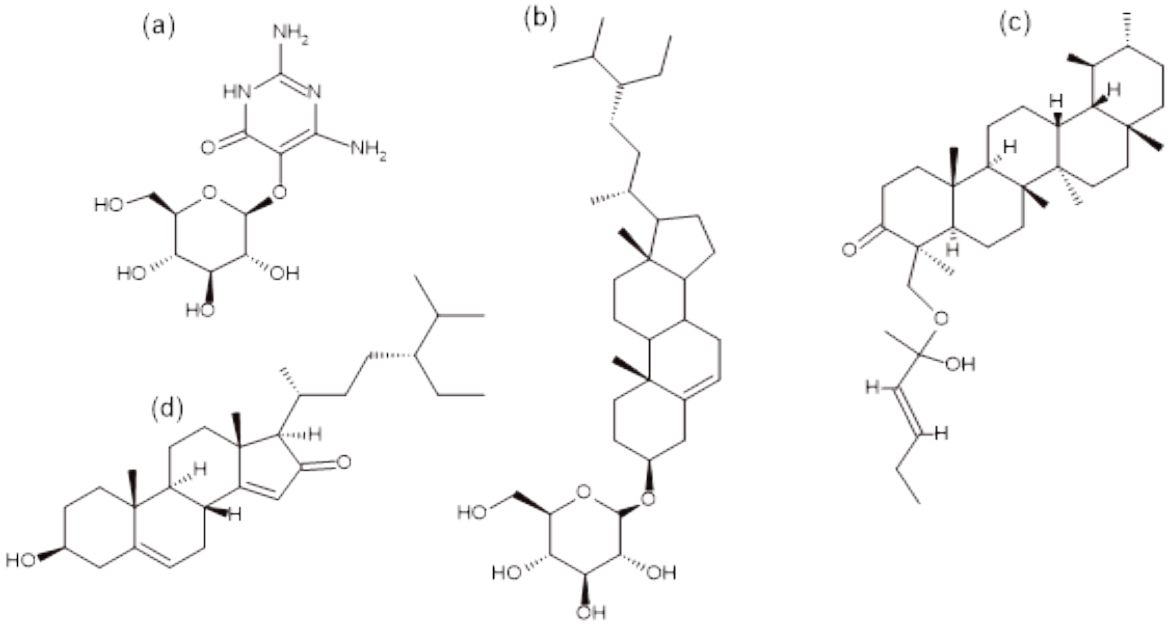


Figure 2: Antidiabetics phytochemicals found in bitter melon; (a) vicine, (b) charantin, (c) momordicilin and (d) momordenol

is an open database server that provides predictive models for assessing the pharmacokinetic properties of interested drug candidates. Absorption, distribution, metabolism, excretion, and toxicity (ADMET properties) of the selected phytochemicals were also studied as they play vital roles in determining the pharmacology of a medicinal agent (Pires et al., 2015).

METHOD AND MATERIALS

Computational calculations, optimizations, and molecular docking studies were done using a workstation with an Intel© Core i7 5820K CPU (3.3-3.6 GHz) and 32 GB RAM, and the Processor with Intel(R) Core (TM) i5-4570 CPU @ 3.20GHz and 4GB RAM.

Ligand preparation

The molecular structures of the ligands were retrieved from the PubChem database (NCBI) (https://pubchem.ncbi.nlm.nih.gov) in SDF format and then converted into PDB files using Open Babel. Then the ligand structures were geometrically optimized by using Gaussian 9 software & Gauss view 06. The structures were optimized using the density functional theory (DFT) method with B3LYP functional and 6-311G++ (d, p) basic set (Rappoport & Furche, 2010).

Protein preparation

The 3D structures of Protein molecules were downloaded from the Protein Data Bank (PDB) (https://www.rcsb.org) (PDB ID –1Q5K) according to the resolution and method (x-ray crystallography). Protein structures were cleaned by using Biovia Discovery Studio 2021. All water molecules, ligands, ions and heteroatoms were removed from the Protein molecule. (Arif et al., 2021) From the cleaned GSK-3 whole protein, two distinct protein chains were separated. GSK-3A and GSK-3B. The ligand was docked with each of these three proteins, GSK-3 whole protein, GSK-3A, and GSK-3B.

Molecular docking

Molecular docking studies were performed using Autodock Tool 1.5.6 AutoDock 4.2 by using the applied free energy function and the Lamarckian Genetic Algorithm (O'Boyle et al., 2011). Polar H atoms and Kollman united atom charges were added to the macromolecule and the Protein pdbqt file was prepared. The ligand pdbqt file was prepared by adding hydrogen atoms and Gasteiger charges. Protein and ligand pdbqt files were loaded into Autodock Tool 1.5.6 AutoDock 4.2 and grid parameter files (.gpf) and docking parameter files (.dpf) were generated. Grid parameter files and map files were generated by using Autogrid 4.2 (Terefe & Ghosh, 2022). The grid box with various dimensions was prepared to cover the three different proteins separately. In this study blind docking was performed. Molecular interactions between protein-ligand complexes, bond lengths, and amino acids in binding pockets were analyzed by using the protein-ligand interaction profiler (PLIP), an online web-based service (Ferreira et al., 2015) and the Discovery Studio. PyMOL was used to evaluate the AutoDock images and output in addition to the modelling studies (Yan et al., 2023).

Control inhibitor of the docking approach

Protein structures frequently contain inhibitors, which are stored in the RCSB protein data bank. Using the same level of theory, the structures of the inhibitors was optimized using data from the PubChem database. These optimized structures were used as ligands for docking analysis. The inhibitor was docked to GSK-3 protein using the same docking protocol, which was used for the docking of protein and phytochemicals in bitter melon. The binding energies of the docked conformation was analyzed using AutoDock Tools 1.5.6 (Terefe & Ghosh, 2022).

ADMET study

To predict the ADMET profiles of the selected phytochemicals, both the pkCSM web server and ProTox-II were employed. The pkCSM server offers detailed pharmacokinetic information, while ProTox-II provides an assessment of toxicity, including potential adverse effects and safety classifications. The ProTox-II server was used to acquire several toxicity metrics for phytochemicals, including hepatotoxicity, carcinogenicity, mutagenicity, cytotoxicity, LD50 (mg/kg), and toxicity class (Hua et al., 2023).

RESULTS AND DISCUSSION

After DFT calculations, energetically the most stable conformations of vicine, momordicilin, momordenol, and charantin were obtained (as shown in Figure 3) and their binding free energies with the enzyme, glycogen synthase kinase-3 were computationally investigated because this correlation provides valuable insight of potential efficacy of each phytochemical.

According to results in Table 1, momordenol demonstrated strongest binding affinity with the GSK-3 enzymatic protein as indicated by the most negative binding free energy of -9.91 kcal/mol compared to other three phytochemicals. The effectiveness of binding interactions can be also determined by comparing the magnitude of the inhibition constant (Ki value) which was obtained from the molecular docking of these phytochemicals with GSK-3 enzyme. This inhibitor constant, Ki can be also described as a "dissociation constant" of the docked protein-inhibitor complex (enzyme-phytochemical complex). The lower the potential of dissociation protein-inhibitor complex (having smaller Ki value) increases the potential of inhibition. The inhibition constant (dissociation constant) has been calculated using $Ki = e^{-\Delta G/(RT)}$, where ΔG is the free energy of binding, R is the gas constant (1.987 cal K^{-1} mol^{-1}), and T is the absolute temperature (298.15 K). Comparatively possessing the smallest inhibition constant (Ki =0.05 µM), momordenol has revealed its greatest inhibition potential on GSK-3 protein. In contrast, vicine showed the least negative binding free energy (-6.71 kcal/mol) to reflect the lowest binding affinity. It was further confirmed by its relatively higher value of the inhibition constant (Ki =11.99 µM). The binding free energies of the other two phytochemicals (charantin and momordicilin) demonstrated substantial binding potential with GSK-3.

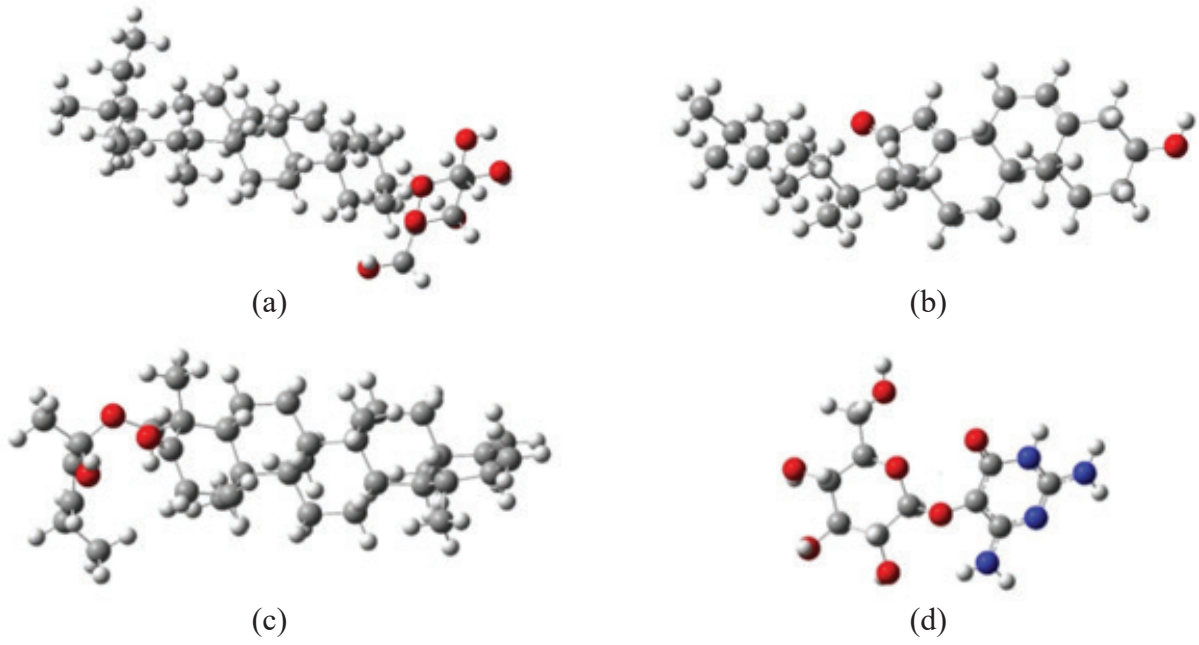


Figure 3: Optimized 3D structures of phytochemicals in bitter melon: (a) charantin, (b) momordenol, (c) momordicilin, and (d) vicine

Table 1: Binding free energies of optimized phytochemicals with glycogen synthase kinase-3

Name of the phytochemical	Lowest Binding energy (kcal/mol)	Mode of Action	Inhibition constant, (Ki) (µM)
Charantin	-8.49	Inhibitor	0.59
Momordicilin	-9.53	Inhibitor	0.10
Momordenol	-9.91	Inhibitor	0.05
Vicine	-6.71	Inhibitor	11.99
Reference (TUM)	-7.59	Inhibitor	2.74

The standard GSK-3 inhibitor, N-(4-methoxybenzyl)-N'-(5-nitro-1,3-thiazol-2-yl) urea possessed binding free energy of -7.59 kcal/mol and the inhibition constant of 2.74 μM. When compared to the standard inhibitor, it was evident that momordicilin, momordenol, and charantin exhibited significantly stronger binding affinity and higher inhibitory potential. Since glycogen synthase kinase-3 (GSK-3) exists as two homologs, GSK-3α and GSK-3β (encoded by independent genes), the binding free energies of those four phytochemicals with GSK-3 (whole protein structure), GSK-3α isoform, and GSK-3β isoform were separately computed further. According to the results of in silico investigation, momordenol exhibited the lower (more negative) binding free energies with GSK-3 protein structure as well as with both GSK-3α, and GSK-3β isoforms, indicating its higher binding affinities and stronger interactions as shown in Figure 4. Momordicilin also demonstrated the similar trend in binding interactions with GSK-3α and GSK-3β forms, compared with momordenol. Other two phytochemicals, charantin and vicine exhibited more selective binding with the GSK-3β form which is a key regulator of the glycogen metabolism.

These ligands (phytochemicals) have different chemical structures which cause them to interact with GSK-3 protein and its isoforms in different ways, depending on their unique functional groups and spatial arrangement, mode of interactions, including hydrogen bonding, π-π stacking, and electrostatic interactions. Computed results in Table 2 illustrates how momordenol, momordicilin, charantin and vicine interacted with key amino acid residues which have been located at binding sites of GSK-3 enzyme and its two isoforms (GSK-3α and GSK-3β).

Presence of favorable modes of secondary interactions between momordenol and GSK-3 further supported the evidence of its stronger binding affinity and higher inhibition potential.

A detailed view of the molecular interactions which stabilize this ligand-protein complex (the complex of momordenol and GSK-3) has been illustrated in Figure 5.

Aromatic residues in the binding site of GSK-3 are seen to engage in π-π interactions with the aromatic rings of momordenol to enhance binding specificity and stability. These interactions are crucial for a precise fit of momordenol within the GSK-3. It is evident that the combination of hydrogen bonding and electrostatic interactions available at the ligand-protein complex of these four phytochemicals significantly contributed to lowering the binding free energy of the complex. 2D illustrations of Figure 5 further reveal types of amino acid residues present in binding site of the GSK-3 protein contribute to form specific types of interactions (polar, non-polar, ionic interactions). The pi-sulfur bonds, amide pi-stacked bonds, and pi-stacking interactions were observed as prominent secondary interactions between N-(4-methoxybenzyl)-N'-(5-nitro-1,3-thiazol-2-yl) urea (TUM, the reference compound) and amnio acid residues of GSK-3 binding pocket. The pi-sulfur bond involved in interactions between sulfur and aromatic π-electron systems, while amide pi-stacked bond showed stacking between the amide groups and aromatic rings. Additionally, the pi-stacking interaction between aromatic rings further strengthens the complex of TUM-GSK-3.

Predicting human pharmacokinetic characteristics is crucial in drug discovery process as it helps to identify and improve the efficacy of candidate medicinal compounds. These characteristics are evaluated based on ADMET parameters, which encompass absorption, distribution, and metabolism, excretion, and toxicity profiles. *In silico*

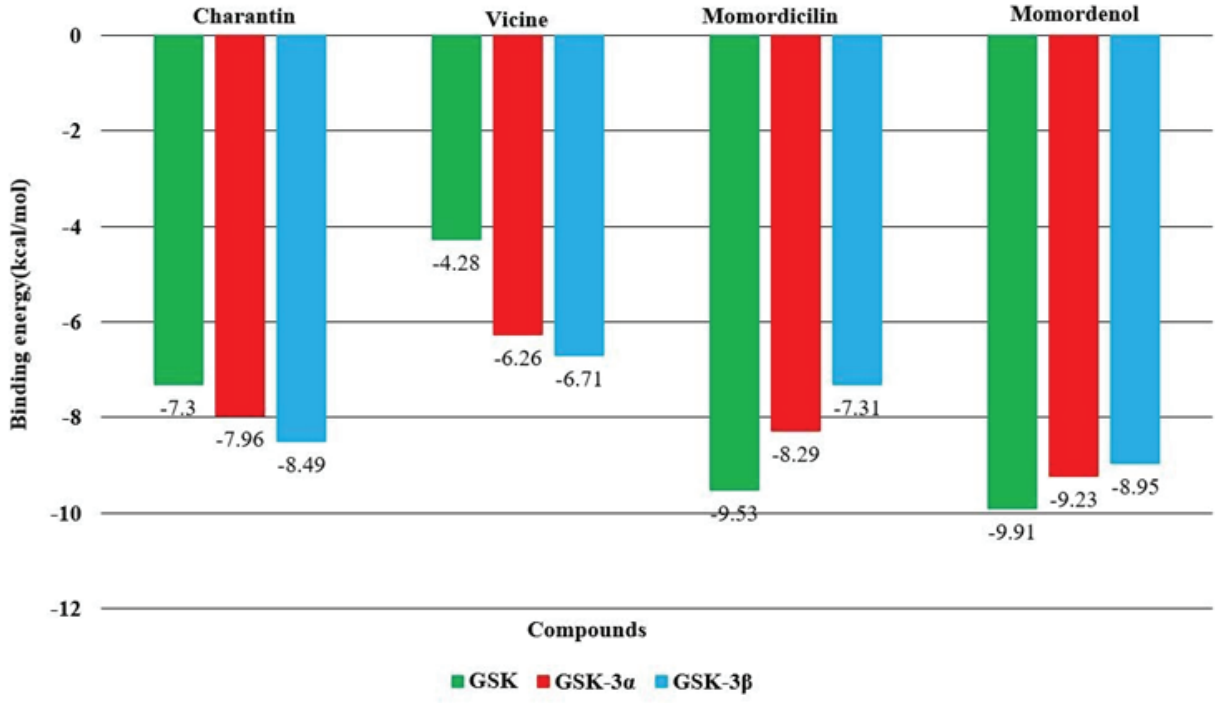


Figure 4: Binding free energies of four phytochemicals with GSK-3 (whole proteins), GSK-3α form and GSK-3β form

Table 2: Types of interactions investigated at ligand-protein binding pockets

Phytochemical	Protein	Mode of interaction	Key residuals of the binding pocket
Charantin	GSK-3		SER174, SER236, SER237, SER368, SER 369, GIY176, GLN365, THR330, THR326, HIS173
	GSK-3α		LEU273, ALA298, TYS297, GLU322, HIS299, PRO300, SER318, TRP301
	GSK-3β		THR152, LHR302, LYS303, LYS150, LEU252, VAL304, PHE305, ARG306, PRO307, GLN151
Momordenol	GSK-3		GLN296, GLN89, LYS271, LYS297, LYS91, ILE296, LEU88, GLU121, GLU125, VAL126, ASP90
	GSK-3α		GLY98,GLY202,SER66,SER203,LEU88,ASN 95, ARG96,GLU97,ALA204,PHE67,GLN89,ASP90
	GSK-3β		GLY253,SER147,SER219,TRY140,TYR221,GLN254, PRO255,PRO184,ARG220,TYR222,ARG144,LYS183, GLU249,GLN185
Momordicilin	GSK-3		GLY274,GLY68,THR275,PRO294,PHE67,SER66, LEU88,TYS271,TYS127,GLU125,TYR127,HLS299, VAL267,ALA298,ILE270
	GSK-3α		VAL135,ALA83,TYR134,TYR140,GLN185,ASN186, LYS183,SER66,PHE67,ASP200,GLY65,LYS85,VAL70, ARG144,LEU188
	GSK-3β		VAL304,LEU252,ILE256,GLN254,HIS299,GLU268, PRO258,PRO255,ASP264,GLY259,ASP260,TYR221
Vicine	GSK-3		HIS299,LEU252,PRO255,GLN254,PRO258,ILE256, VAL304,VAL272,PHE305,LYS303
	GSK-3α		HIS299,LEU252,PRO255,GLN254,PRO258,ILE256,VAL304, VAL272,PHE305,LYS303
	GSK-3β		LYS123,ASP124,LYS122,GLU125,GLU121,LEU88

: Unfavorable Acceptor – Acceptor : Carbon Hydrogen bond : Pi-Sigma
: Conventional Hydrogen : Pi-Pi T-Shaped : van der Waals
: Alkyl : Pi-Alkyl

analysis of ADMET properties of these four phytochemicals have been shown in Table 3.

As the drug absorption in the small intestine plays a vital role in determining a drug's bioavailability, both momordicilin and momordenol exhibited a higher percentage of intestinal absorption rates of 96.55% and 95.77% respectively compared with TUM's absorption rate of 84.38%, to offer superior oral bioavailability. In contrast, Vicine's absorption is markedly lower as 28.87%, indicating lowered bioavailability. The dipole moment, polar functional groups associated with water solubility of medicines and momordenol and momordicilin demonstrated relatively low solubilities compared to TUM which could affect their properties of dissolution and absorption. While vicine shows the highest water-solubility, it demonstrated lower absorption. This may be due to the poor permeability of the agent. Although water solubility of charantin is somewhat closer to TUM. VDss is a traditional pharmacokinetic parameter which represents an individual drug's propensity to either remain in the plasma or redistribute; a higher VDss indicates a greater amount of drug distributed into tissue. Among the four phytochemicals studied, momordicilin showed the highest VDss, suggesting extensive distribution throughout the body, whereas momordenol and charantin exhibit more localized distribution. These differences may affect the therapeutic efficacy and side effect profiles of these compounds. In terms of excretion, charantin has the highest total clearance value of 0.689, suggesting it is eliminated more rapidly than TUM which has the lowest clearance value of 0.052, and indicating slower elimination. The ADMET parameter of clearance of momordenol (0.565)

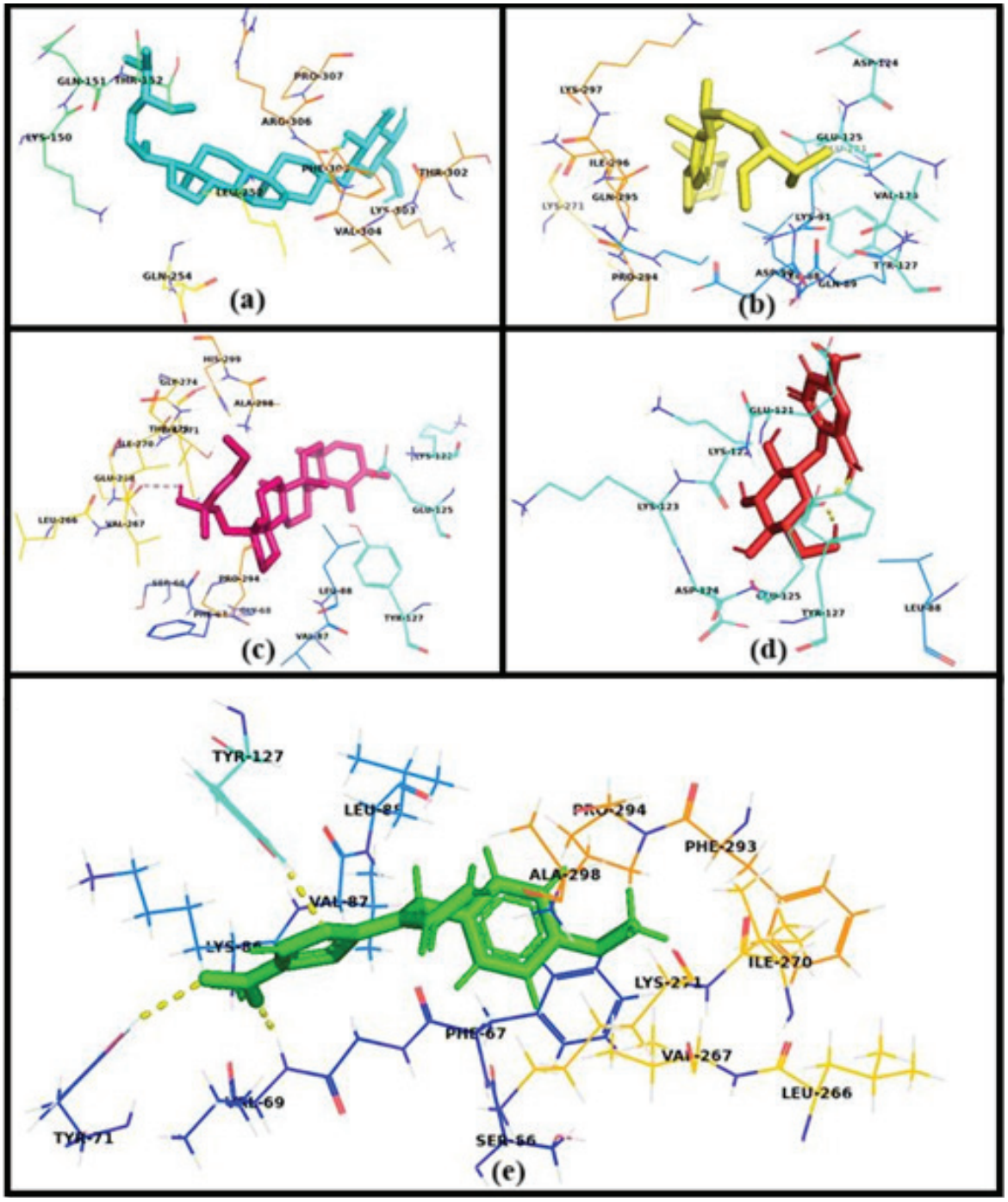


Figure 5: 2D representations of secondary interactions between GSK-3 protein with ligands; (a) charantin, (b) momordenol, (c) momordicilin, (d) vicine and (e) TUM (the reference compound)

Table 3: Comparative analysis of ADMET properties of four phytochemicals and the reference compound (TUM)

ADMET Parameter	Momordenol	Momordicilin	Charantin	Vicine	Reference (TUM)
Intestinal absorption (%)	95.77	96.55	79.677	28.87	84.38
Water solubility (log mol/L)	-6.346	-5.615	-4.741	-2.689	-4.263
VDss (human) (logL/kg)	0.008	-0.566	-1.163	0.988	-0.857
Total Clearance	0.565	0.135	0.689	0.252	0.052
LD50 (mg/kg)	1000	900	8000	1000	300
Toxicity class	4	4	6	4	3

is relatively higher than that of momordicilin (0.135), potentially affecting their duration of action. Toxicity assessments reveal that charantin possesses the highest value of LD_{50} (8000 mg/kg) and the lower toxicity class of 6 compared with TUM (300 mg/kg and toxicity class of 3). In summary, momordenol and momordicilin represent favourable profiles with high absorption and manageable toxicity, making them promising candidates for further development. This comparative analysis provides a comprehensive understanding of the potential clinical applications of these four antidiabetic phytochemicals relative to TUM.

CONCLUSIONS

In this study, a comparative computational analysis of four major phytochemicals from *Momordica charantia* revealed that they are potential antidiabetic agents by inhibiting the key enzyme, glycogen synthase kinase-3 and its two homologs of GSK-3α isoform and GSK-3β isoform. Momordenol exhibited the most negative binding free energy of -9.91 kcal/mol with the GSK-3 enzymatic protein compared with other three phytochemicals as it showed the highest binding affinity. This was further supported by its relatively lowest Ki value (0.05 μM) with the GSK-3 enzymatic protein. In silico analysis of secondary interactions revealed that momordenol exhibited the highest degree of bond strength, specificity, and proper orientation within the protein-binding pockets of all isoforms of GSK-3 enzyme. ADMET analysis indicated that both momordicilin and momordenol demonstrated higher intestinal absorption rates of 96.55% and 95.77%, respectively, compared with TUM's absorption rate of 84.38%, indicating superior oral bioavailability. Among the four phytochemicals, momordicilin showed the highest volume of distribution (VDss), suggesting its extensive distribution throughout the body, while momordenol and charantin exhibited more localized distribution. Toxicity analysis using ProTox 3.0 classified charantin as toxicity class 6 based on its LD_{50} value of 8000 mg/kg, suggesting its potential as a safe and effective antidiabetic drug. Meanwhile, momordenol and momordicilin displayed moderate toxicity, making them promising candidates for further development.

DECLARATION OF CONFLICT OF INTEREST

The authors declare no conflict of interest.

FUNDING INFORMATION

Funding was not requested.

AUTHOR CONTRIBUTION

Conceptualization, research supervision and manuscript editing: **D. R.P.;** Writing the first draft and computational simulations: **F. N. P.;** Molecular optimization: **S.B.J.**

Molecular optimization: **H.R.;** All authors have accepted responsibility for the content of the manuscript, reviewed all results, and approved the final version.

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