OSHADA JOURNAL
Oshada; Jurnal Kesehatan
https://nawalaeducation.com/index.php/O/index
Volume 3 Nomor 1, February 2026
e-ISSN : 3047-017X
DOI : https://doi.org/10.62872/o.v3i1.511

Comparative Molecular Docking and ADMET Analysis of Bioactive Compounds from Curcuma xanthorrhiza and Momordica charantia as Potential DPP-4 Inhibitors

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Input	: January 09, 2026	Revised	: January 22, 2026
Accepted	: February 20, 2026	Published	:February 28, 2026

ABSTRACT

Background: Type 2 Diabetes Mellitus (T2DM) is characterized by impaired insulin secretion and insulin resistance. Dipeptidyl Peptidase-4 (DPP-4) regulates glucose homeostasis by degrading incretin hormones such as GLP-1, making it a key therapeutic target. Natural bioactive compounds from Curcuma xanthorrhiza and Momordica charantia have demonstrated antidiabetic potential, but comparative evaluation of their activity as DPP-4 inhibitors remains limited. **Methods:** Molecular docking was performed using CB-Dock2 integrated with AutoDock Vina against DPP-4 (PDB ID: 4A5S). Curcumin and xanthorrhizol from C. xanthorrhiza, and momordicin I and kuguacin J from M. charantia were evaluated. Sitagliptin was used as a positive control. Binding affinities and interactions with catalytic residues were analyzed. Pharmacokinetic and toxicity profiles were predicted using SwissADME and pkCSM. **Results:** All compounds demonstrated favorable binding affinities (< –7.0 kcal/mol). Kuguacin J exhibited the strongest binding (–8.7 kcal/mol), slightly exceeding sitagliptin (–8.5 kcal/mol), followed by momordicin I (–8.3 kcal/mol), curcumin (–8.2 kcal/mol), and xanthorrhizol (–7.3 kcal/mol). Key interactions involved Glu205, Glu206, Ser630, Tyr547, and Tyr662, indicating active-site occupation. ADMET analysis showed compliance with Lipinski's rule of five and high gastrointestinal absorption for all compounds. Kuguacin J demonstrated the most favorable safety profile with no predicted Ames toxicity or hepatotoxicity. **Conclusion:** Kuguacin J emerges as the most promising natural DPP-4 inhibitor candidate based on combined docking and ADMET evaluation. Further experimental validation is required to confirm its therapeutic potential in T2DM management.

Keywords: *DPP-4 inhibitor; molecular docking; ADMET; natural compounds; type 2 diabetes mellitus.*

INTRODUCTION

Type 2 Diabetes Mellitus (T2DM) constitutes a global health crisis characterized by a dramatically increasing prevalence. The World Health Organization projects a significant rise in T2DM cases, estimating 415 million patients between 2015 and 2018, with projections reaching up to 366 million by 2040, and Indonesia ranked sixth worldwide in T2DM prevalence in 2017 (Surya, 2023). The pathophysiology of T2DM is marked by complex dysfunction, including impaired insulin secretion from pancreatic beta cells and reduced tissue sensitivity to insulin, termed insulin resistance (Castro-Juárez, Ramírez-García, Villa-Ruano, & García-Cruz, 2018). This metabolic disorder represents a complex disease influenced by multifactorial interactions between genetic and environmental factors (Castro-Juárez, Ramírez-García, Villa-Ruano, & García-Cruz, 2018; Rahmawati & Hargono, 2018).

In response to this escalating disease burden, intensive efforts have been undertaken to identify novel therapeutic targets and develop more effective treatment strategies. A critical molecular target in T2DM management is the enzyme dipeptidyl peptidase-4 (Baziar et al., 2024; Deacon, 2019). DPP-4, a serine peptidase, inactivates incretin hormones such as glucagon-like peptide-1, which is essential for glucose homeostasis (Deacon, 2019; Mohd. Javed Naim, 2024; Самойлова et al., 2024). GLP-1 promotes glucose-dependent insulin secretion and suppresses glucagon release (Deacon, 2019; Fakih & Dewi, 2021; Самойлова et al., 2024). DPP-4 inhibition elevates circulating active GLP-1 levels, thereby enhancing insulin biosynthesis and secretion, which aids in managing hyperglycemia in T2DM patients (Fakih & Dewi, 2021; Mohd. Javed Naim, 2024; Самойлова et al., 2024).

Although synthetic DPP-4 inhibitors, known as gliptins, have proven effective in glycemic control, their clinical use is constrained by several limitations. Potential adverse effects include hypoglycemia, edema, weight gain, and gastrointestinal disturbances (Arba et al., 2018; Baziar et al., 2024). Additional concerns encompass short half-life, low oral bioavailability (Baziar et al., 2024), and risks of pancreatitis and pancreatic cancer, though further research is warranted (Saini, Sharma, & Khan, 2023). Non-selective DPP-4 inhibitors may also inhibit other DPP isozymes, impacting immune regulation, transplant biology, cancer cell proliferation, and metastasis (Farkhani, Sauriasari, & Yanuar, 2020). Consequently, there is an urgent need for novel antidiabetic agents with minimal side effects and superior safety profiles (Arba et al., 2018).

In the pursuit of innovative therapeutic agents, natural products have garnered substantial attention as viable alternatives. Curcuma xanthorrhiza and Momordica charantia, two plants long utilized traditionally for treating various ailments including diabetes, demonstrate promising antidiabetic activity (Kusuma & Maesaroh, 2020; Simamora et al., 2024; Wulandari, Salim, Santoso, & Putri, 2021). Curcuma xanthorrhiza contains bioactive compounds such as curcumin and xanthorrhizol, exhibiting anti-inflammatory, antioxidant, and antidiabetic properties (Kristianto et al., 2022; Simamora et al., 2024; Wulandari, Salim, Santoso, & Putri, 2021). Studies further indicate its capacity to mitigate oxidative stress in diabetic wound healing (Kristianto et al., 2022). Conversely, Momordica charantia is widely acknowledged as a traditional antidiabetic remedy (Ahmad, Hasan, Ahmad, Zishan, & Zohrameena, 2016; Kusuma & Maesaroh, 2020; Zen & Pramiastuti, 2019). Its fruit is enriched with antidiabetic constituents like charantin, polypeptide-p, vicine, glycosides, and karavilosides, exerting hypoglycemic effects via diverse mechanisms (Ahmad, Hasan, Ahmad, Zishan, & Zohrameena, 2016; Kusuma & Maesaroh, 2020; Zen & Pramiastuti, 2019). This study focuses on specific bioactive compounds—curcumin and xanthorrhizol from Curcuma xanthorrhiza, and momordicin I and kuguacin J from Momordica charantia—to explore their potential as DPP-4 inhibitors.

The application of computational methods, such as molecular docking and ADMET (absorption, distribution, metabolism, excretion, and toxicity) prediction, is pivotal in natural product-based drug discovery (Amin, Heryanto, Athaya, & Fitri, 2024, 2025). These in silico approaches provide substantial time and cost efficiencies over conventional experimental assays, obviating the need for physical samples or extensive laboratory infrastructure, they address common challenges with natural compounds, including chemical instability and suboptimal solubility, molecular docking predicts interactions and binding affinities between drug candidates and target proteins like DPP-4. ADMET prediction is essential for early pharmacokinetic profiling, candidate selection, and mitigating late-stage failures due to poor ADME properties or toxicity (Ancuceanu, Lascu, Drăgănescu, & Dinu, 2025).

Although the antidiabetic potential of Curcuma xanthorrhiza and Momordica charantia is well-documented, and molecular docking alongside ADMET prediction is widely employed, systematic comparative studies evaluating specific bioactives—curcumin, xanthorrhizol, momordicin I, and kuguacin J—as DPP-4 inhibitors via concurrent docking and ADMET analyses remain scarce in the literature. This research gap underscores the pressing need for comprehensive comparative analyses to pinpoint optimal natural DPP-4 inhibitors. Accordingly, this study conducts comparative molecular docking and ADMET predictions on curcumin and xanthorrhizol from Curcuma xanthorrhiza, and momordicin I and kuguacin J from Momordica charantia. The objectives are to identify and compare their DPP-4 inhibitory potential and ADMET profiles, thereby discovering safer, more effective antidiabetic candidates.

METHOD

Ligand and Protein Preparation

The three-dimensional structures of selected bioactive compounds from Curcuma xanthorrhiza and Momordica charantia were retrieved from the PubChem database, the crystal structure of Dipeptidyl Peptidase-4 (DPP-4) was obtained from the Protein Data Bank (PDB ID: 4A5S) (Wardani et al., 2025).

Molecular Docking

Blind docking simulations were conducted using the CB-Dock2, which integrates cavity detection with AutoDock Vina docking algorithms (Liu et al., 2022; Trott & Olson, 2010). The server automatically identified potential binding cavities (C1–C5) and calculated binding affinity values (kcal/mol). The best docking pose was selected based on the lowest binding energy. Sitagliptin was used as a positive control to validate docking performance. Protein–ligand interactions were analyzed to determine binding pocket location and interactions with key catalytic residues of DPP-4, including Ser630, Glu205, and Glu206.

ADMET Prediction

Pharmacokinetic and toxicity profiles were predicted using SwissADME (Daina et al., 2017) and pkCSM (Pires et al., 2015). Parameters evaluated included Lipinski's rule of five, gastrointestinal absorption, BBB (Blood–Brain Barrier) permeant, AMES toxicity, and hepatotoxicity. Compounds demonstrating favorable binding affinity and acceptable ADMET profiles were considered potential DPP-4 inhibitor candidates.

RESULTS

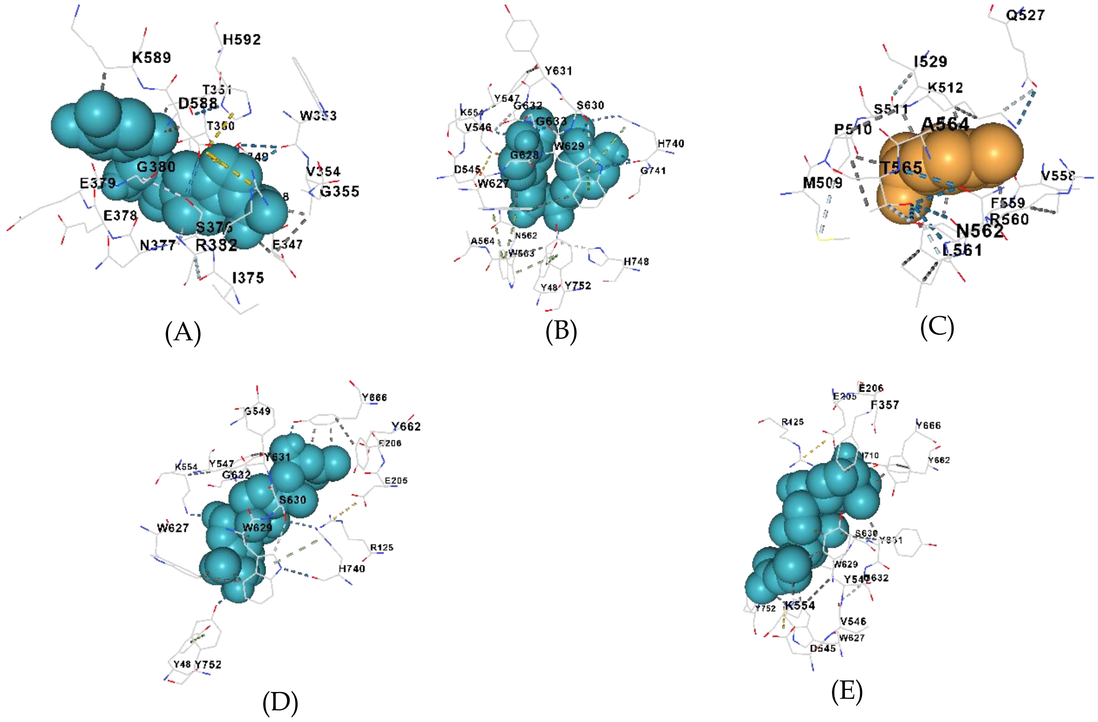
The binding interactions between selected bioactive compounds from Curcuma xanthorrhiza and Momordica charantia and the Dipeptidyl Peptidase-4 (DPP-4) enzyme were evaluated using CB-Dock2. The docking analysis predicted the binding affinity of each ligand, identified the most favorable binding cavities, and highlighted key interactions with catalytic residues.

The results are summarized in Table 1, which presents the binding energy values (kcal/mol) and the corresponding predicted cavities for each compound. The binding poses visualized in Figure 1 illustrate the orientation of the ligands within the DPP-4 active site.

Table 1. Comparative Molecular Docking Results of Selected Compounds Against DPP-4

Compound	Pocket ID	Binding Affinity (kcal/mol)	Cavity Volume (Å3)	Contac Residues
Sitagliptin	C1	-8.5	2631	GLU347, MET348, SER349, THR350, THR351, TRP353, VAL354, GLY355, ILE375, SER376, ASN377, GLU378, GLU379, GLY380, TYR381, ARG382, CYS394, PHE396, THR401, TRP402, GLU403, ASN420, GLU421, GLY424, MET425, PRO426, ASN520, GLU521, THR522, LYS523, TRP525, TYR585, GLN586, GLY587, ASP588, LYS589, ILE590, HIS592
Curcumin	C4	-8.2	1451	TYR48, ARG125, GLU205, MET425, GLN455, PRO475,

				PRO510, SER511, LYS512, LYS513, LEU514, GLN527, ILE529, ASP545, VAL546, TYR547, LYS554, ASP556, THR557, VAL558, PHE559, ARG560, LEU561, ASN562, TRP563, ALA564, THR565, TRP627, GLY628, TRP629, SER630, TYR631, GLY632, GLY633, TYR662, TYR666, ASN710, HIS740, GLY741, ILE742, ALA743, HIS748, TYR752
Xanthorrhizol	C2	-7.3	1455	GLU452, PRO475, GLY476, LEU477, LEU504, MET509, PRO510, SER511, LYS512, GLN527, ILE529, LEU530, VAL558, PHE559, ARG560, LEU561, ASN562, ALA564, THR565
Momordicin I	C4	-8.3	1451	TYR48, ARG125, GLU205, GLU206, PHE357, ASP545, VAL546, TYR547, GLY549, PRO550, CYS551, SER552, GLN553, LYS554, ASP556, ARG560, LEU561, ASN562, TRP563, ALA564, TYR585, TRP627, GLY628, TRP629, SER630, TYR631, GLY632, GLY633, TYR662, TYR666, ARG669, TYR670, HIS740, GLY741, ILE742, ALA743, HIS748, TYR752
Kuguacin	C4	-8.7	1451	TYR48, ASN51, ARG125, GLU205, GLU206, PHE357, ILE405, ARG429, TYR456, TYR457, ASP545, VAL546, TYR547, GLN553, LYS554, ASP556, VAL558, ARG560, LEU561, ASN562, TRP563, TYR585, TRP627, GLY628, TRP629, SER630, TYR631, GLY632, TYR662, TYR666, ASN710, HIS740, GLY741, ILE742, ALA743, HIS748, TYR752



(A) (B) (C)

(D) (E)

Figure 1: Molecular Docking Poses and Interaction Diagrams of Bioactive Compounds from *C. xanthorrhiza* and *M. charantia* with 4A5S Protein

(A). Sitagliptin; (B). Curcumin; (C). Xanthorrhizol; (D). Momordicin I; (E). Kuguacin J

To further assess the drug-likeness and pharmacokinetic suitability of the selected lead compounds, an in silico ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) evaluation was conducted. This analysis is essential to confirm that the bioactive constituents of Curcuma xanthorrhiza and Momordica charantia not only demonstrate strong binding affinity toward the DPP-4 enzyme but also exhibit favorable pharmacological characteristics for oral delivery. The predicted ADMET parameters, including compliance with Lipinski's rules and key safety indicators, are summarized in the following of table 2.

Table 2. In silico ADMET profiles of selected bioactive compounds from *Curcuma xanthorrhiza* and *Momordica charantia*

Compound	Lipinski Rule	GI Absorption	BBB Permeant	Ames Toxicity	Hepatotoxicity
Sitagliptin	0	High	Yes	No	Yes
Curcumin	0	High	No	No	No
Xanthorrhizol	0	High	Yes	No	No
Momordicin I	0	High	No	No	Yes

Kuguacin J	1	High	No	No	No

DISCUSSION

Molecular Docking Analysis

Dipeptidyl peptidase-4 (DPP-4) is an established drug target for type 2 diabetes mellitus (T2DM) because it breaks down incretin hormones like GLP-1 and GIP, which reduces insulin release (Drucker, 2007). Structurally, DPP-4 has a catalytic triad—Ser630, Asp708, and His740—and key binding residues that shape the S1 and S2 subsites, including Glu205, Glu206, Tyr547, Tyr662, and Trp629 (Kim et al., 2005). Potent inhibitors typically form strong electrostatic interactions with Glu205/Glu206 while occupying the S1 pocket's hydrophobic region (Nabeno et al., 2013).

All tested ligands showed binding affinities better than −7.0 kcal/mol, a commonly used cutoff for biologically relevant protein–ligand interactions in structure-based virtual screening (Kitchen, Decornez, Furr, & Bajorath, 2004). Kuguacin J achieved the best docking score at −8.7 kcal/mol, slightly outperforming the reference inhibitor sitagliptin, which scored −8.5 kcal/mol. Even small differences in predicted binding free energy can correspond to meaningful changes in binding equilibrium, indicating that Kuguacin J could have competitive inhibitory potential.

Residue interaction analysis showed that Kuguacin J, Momordicin I, and Curcumin contact Glu205, Glu206, Tyr547, Ser630, and Tyr662—residues repeatedly highlighted in crystallographic and computational studies as essential for DPP-4 inhibition (Kim et al., 2005; Nabeno et al., 2013). Interaction with Ser630 is especially important because this residue acts as the nucleophile in peptide bond hydrolysis; ligand occupancy near Ser630 likely disrupts substrate positioning and catalytic turnover. Aromatic residues like Tyr547 and Tyr662 further stabilize the ligand–enzyme complex through π–π stacking and hydrophobic interactions, key contributors to high-affinity inhibition (Nabeno et al., 2013).

Kuguacin J showed the strongest interaction network, likely because its extended triterpenoid scaffold makes more van der Waals contacts in the hydrophobic S1 pocket. Curcumin and Momordicin I also returned favorable binding energies (–8.2 and –8.3 kcal/mol), but their higher conformational flexibility could incur entropic costs on binding, potentially lowering overall complex stability despite forming favorable hydrogen bonds (Kitchen et al., 2004). Xanthorrhizol, with a docking score of –7.3 kcal/mol, made fewer stabilizing contacts in the catalytic cleft, which likely accounts for its weaker affinity. Overall, the docking order aligns with known structure–activity relationship (SAR) principles for DPP-4 inhibitors (Nabeno et al., 2013).

The docking score for sitagliptin matches values reported in previous computational studies (Meduru et al., 2016), supporting the reliability of the docking protocol used. Successfully reproducing the known binding behavior of a clinically approved inhibitor increases confidence in the comparative predictions made for the natural compounds in this study.

ADMET and Drug-Likeness Analysis

High binding affinity alone does not guarantee a viable drug; favorable pharmacokinetic and safety profiles are also essential. All tested compounds met Lipinski's Rule of Five, indicating they likely have acceptable oral bioavailability (Lipinski, Lombardo, Dominy, & Feeney, 2001). Additionally, predictions of strong gastrointestinal absorption reinforce their potential as orally administered agents.

Kuguacin J showed the most balanced pharmacological profile: it achieved the best docking score while showing no predicted Ames mutagenicity or hepatotoxicity. Its lack of blood–brain barrier (BBB) permeability could also lower the risk of central nervous system side effects—an advantage for antidiabetic drugs intended for long-term use. Taken together, these features make Kuguacin J an appealing lead compound.

Momordicin I, while showing strong binding affinity, was predicted in silico to be hepatotoxic—underscoring the value of early toxicity screening when prioritizing leads. Computational ADMET tools offer a useful preliminary risk assessment, but experimental validation is still essential. Reported differences between in silico predictions and clinical safety data highlight that computational toxicity models are supportive tools rather than definitive judgments (Drucker, 2007).

Modern drug discovery prioritizes multi-parameter optimization, weighing potency, selectivity, pharmacokinetics, and safety (Lipinski, Lombardo, Dominy, & Feeney, 2001). Combining docking results with ADMET predictions highlights Kuguacin J as the most promising compound from this set. However, its therapeutic potential still requires confirmation through molecular dynamics simulations, enzyme inhibition assays, and in vivo pharmacokinetic studies.

CONCLUSION

This study shows that bioactive compounds from Curcuma xanthorrhiza and Momordica charantia have strong potential as Dipeptidyl Peptidase-4 (DPP-4) inhibitors. Molecular docking results identified Kuguacin J as the top performer, with a binding affinity of -8.7 kcal/mol slightly more stable than the control drug Sitagliptin (-8.5 kcal/mol). The improved stability appears to stem from interactions in Pocket C4 with key residues including TYR48, HIS740, and HIS748.

ADMET analysis supports the promise of Kuguacin J and Curcumin as drug candidates. Both show high gastrointestinal absorption, no predicted blood–brain barrier permeation (BBB Permeant: No), and were not predicted to be mutagenic or hepatotoxic. Kuguacin J did show one Lipinski Rule of Five violation for lipophilicity (MLogP), but it still qualifies as a feasible oral candidate. By contrast, Momordicin I and Sitagliptin were predicted to have potential hepatotoxicity. Overall, Kuguacin J emerges as the leading natural compound for further development as a DPP-4 inhibitor for managing Type 2 Diabetes Mellitus.

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