

In Silico Analysis of *Momordica charantia* Triterpenoids as Adenosine Monophosphate-Activated Protein Kinase Ligands for Type 2 Diabetes Mellitus Therapy

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Abstract: Type 2 diabetes mellitus continues to rise and calls for safe therapeutic leads. This study assessed the potential of triterpenoids from bitter melon (*Momordica charantia*) as AMP-activated protein kinase (AMPK) ligands at the ATP-binding site through an in silico approach. AMPK (PDB ID: 4QFG) was prepared in YASARA; nine *M. charantia* triterpenoids and metformin were docked in PLANTS. Redocking of staurosporine validated the protocol (RMSD 0.2376 Å; ≤ 2.0 Å). Kuguacin J (-89.9934), Karavilagenin B (-86.4084), and Kuguacin R (-85.8514) yielded lower (more favorable) docking scores than metformin (-56.5325) and interacted with hinge residues (Val96 and Glu94/Glu100). As expected, the co-crystallized ligand (staurosporine) showed the most favorable docking score and served as an internal benchmark for pocket definition. Kuguacin J and Kuguacin R fulfilled Lipinski's Rule of Five, whereas Karavilagenin B showed one logP violation. All three compounds demonstrated high predicted intestinal absorption, were predicted as AMES-negative, non-inhibitors of CYP2D6, and potential CYP3A4 substrates. These findings identify the three triterpenoids as promising AMPK ligand candidates warranting further experimental validation.

Keywords: ADMET, AMPK, *Momordica charantia*, molecular docking, triterpenoid

Abstrak: Diabetes melitus tipe 2 (DMT2) terus meningkat dan menuntut kandidat terapi yang efektif serta aman. AMP-activated protein kinase (AMPK) berperan sebagai sensor energi sel dan target penting dalam pengendalian homeostasis glukosa dan lipid. Penelitian ini mengevaluasi potensi triterpenoid dari buah pare (*Momordica charantia*) sebagai ligan AMPK pada situs pengikatan ATP melalui pendekatan in silico. Struktur AMPK (PDB: 4QFG) dipreparasi menggunakan YASARA, sedangkan ligan uji terdiri atas sembilan triterpenoid *M. charantia* dan metformin sebagai pembanding. Protokol docking divalidasi melalui redocking ligan hasil kokristalisasi staurosporine menggunakan PLANTS dan menghasilkan RMSD 0,2376 Å ($\leq 2,0$ Å). Hasil docking mengidentifikasi Kuguacin J (-89,9934), Karavilagenin B (-86,4084), dan Kuguacin R (-85,8514) sebagai kandidat terbaik; ketiganya memiliki skor docking lebih rendah (lebih favorable) dibanding metformin (-56,5325) dan berinteraksi pada residu kunci hinge (Val96 dan Glu94/Glu100). Sesuai ekspektasi, staurosporine sebagai ligan hasil kokristalisasi menunjukkan skor docking paling favorable dan digunakan sebagai tolok ukur internal untuk definisi kantong pengikatan. Kuguacin J dan Kuguacin R memenuhi Aturan Lima Lipinski, sedangkan Karavilagenin B menunjukkan satu pelanggaran nilai logP. Ketiga senyawa tersebut menunjukkan prediksi penyerapan usus yang tinggi, diprediksi negatif terhadap uji AMES, bukan penghambat CYP2D6, dan berpotensi menjadi substrat CYP3A4. Temuan ini mengidentifikasi ketiga triterpenoid tersebut sebagai kandidat ligan AMPK yang menjanjikan dan layak untuk validasi eksperimental lebih lanjut.

Kata kunci: ADMET, AMPK, *Momordica charantia*, penambatan molekul, triterpenoid

INTRODUCTION

Diabetes mellitus (DM) is a chronic metabolic disease characterized by persistent hyperglycemia due to impaired insulin secretion, insulin resistance, or both (Kumar *et al.* 2020). The International

Diabetes Federation estimated that the global number of people living with diabetes reached 589 million and will continue to increase toward 2050, with a substantial burden in the Western Pacific region (IDF 2024). In Indonesia, the 2023 Indonesia Health

Survey reported a diabetes prevalence of 11.7%, increasing compared with Riskesdas 2018 (Kemenkes RI 2023). Type 2 diabetes mellitus (T2DM) accounts for the majority of cases and increases the risk of cardiovascular complications, neuropathy, and nephropathy, highlighting the need for effective and safe therapies (Suryasa *et al.* 2021).

AMP-activated protein kinase (AMPK) is a central cellular energy sensor that regulates glucose and lipid metabolism. AMPK activation promotes GLUT4 translocation to the plasma membrane, enhances glucose uptake, and suppresses hepatic gluconeogenesis (Shrestha *et al.* 2021). Metformin, the first-line drug for T2DM, modulates AMPK; however, long-term use may cause gastrointestinal adverse effects and is associated with vitamin B12 deficiency, which may aggravate neuropathy in some patients (Sayedali *et al.* 2023). Therefore, the search for new candidates-including natural products-with a balanced efficacy and safety profile remains important.

Bitter melon (*Momordica charantia*) is widely used as a traditional antidiabetic medicinal plant and has been reported to intervene in insulin signaling and GLUT4 pathways (Grace *et al.* 2019). Miura *et al.* (2009) reported that an aqueous extract of *M. charantia* (20 and 100 mg/kg body weight) increased AMPK phosphorylation in skeletal muscle of obese mice by 1.6-fold. Beyond extracts, momordicine-I, a major triterpenoid, was reported to modulate metabolism via AMPK activation in the context of metabolic reprogramming in cancer cells (Bandyopadhyay *et al.* 2024). Nevertheless, evidence for direct binding of individual bitter melon triterpenoids to the catalytic AMPK domain, particularly the ATP-binding pocket, remains limited. Iseli *et al.* (2013) showed that AMPK activation by bitter melon triterpenoids involves a CaMKK β -dependent mechanism, which does not necessarily reflect direct interactions within the catalytic pocket. Therefore, mapping ligand interactions at the ATP-binding site via molecular docking remains relevant as an early screening step to prioritize candidates for subsequent experimental validation. Importantly, docking at the ATP-binding pocket primarily maps predicted pocket occupancy and interaction patterns and does not, by itself, demonstrate AMPK activation. Because ATP-site binders can stabilize different functional states (including inhibitory binding modes), the functional consequence of binding should be confirmed in biochemical and/or cellular assays.

In silico approaches can integrate protein-ligand binding prediction with drug-likeness and ADMET profiling to reduce late-stage attrition due to insufficient efficacy or toxicity (Xiong *et al.* 2021; Sun *et al.* 2022). In line with studies using docking to explore potential AMPK modulators (Stanzione *et al.* 2021; Moon 2024), using the AMPK crystal structure PDB ID: 4QFG (selected because it contains the co-

crystallized ATP-site ligand staurosporine, enabling redocking-based protocol validation), this study aimed to identify *M. charantia* triterpenoids that can bind the AMPK ATP-binding site and to evaluate their drug-likeness and predicted ADMET properties.

MATERIALS AND METHODS

The AMP-activated protein kinase (AMPK) crystal structure (PDB ID: 4QFG) was downloaded from the Protein Data Bank (<https://www.rscb.org/>). The protein was prepared in YASARA by removing water molecules, separating the co-crystallized ligand, and adding hydrogen atoms. The prepared protein and the co-crystallized ligand were saved in MOL2 format. Although approximately 196 triterpenoids have been reported from *Momordica charantia* (Sun *et al.* 2021), the present study specifically focused on non-glycosylated (aglycone) triterpenoids. Glycosylated triterpenoids were excluded from the present study because this study was designed to evaluate the interaction of the triterpenoid aglycone scaffold with the ATP-binding site of AMPK. Accordingly, nine structurally characterized aglycone triterpenoids were selected from previous phytochemical studies, comprising eight compounds described by Karale *et al.* (2020) and Momordicine I reported by Villarreal-La Torre *et al.* (2020). The chemical structures of the selected triterpenoids are shown in Figure 1. Test ligands comprised metformin (reference drug) and the nine selected *M. charantia* triterpenoids obtained from PubChem (<https://pubchem.ncbi.nlm.nih.gov/>) and processed in MarvinSketch. All ligands were protonated at physiological pH (7.4), and 20 three-dimensional conformers were generated for docking (Purnomo 2020).

Docking Validation and Molecular Docking Simulation

The docking protocol was validated by redocking the co-crystallized ligand (staurosporine) into the AMPK catalytic pocket (ATP-binding site) using PLANTS. Method validity was evaluated using the root mean square deviation (RMSD) between the redocked pose and the crystallographic pose, with $\text{RMSD} \leq 2.0 \text{ \AA}$ as the acceptance criterion (Ruswanto *et al.* 2022). The binding site was defined based on the position of the co-crystallized ligand in AMPK (PDB ID: 4QFG), with the binding site center coordinates set at $x = 45.4844$, $y = -85.2318$, and $z = -24.4704$, and a binding site radius of 11.0415 $\text{\AA}$. After validation, the nine triterpenoids and metformin were docked using the same parameters. The docking search space was centered on the co-crystallized ligand position in 4QFG to focus screening on the ATP-binding pocket. Binding affinity was assessed using the docking score; lower scores indicate more stable predicted protein-ligand complexes (Puspitasari dkk. 2024).

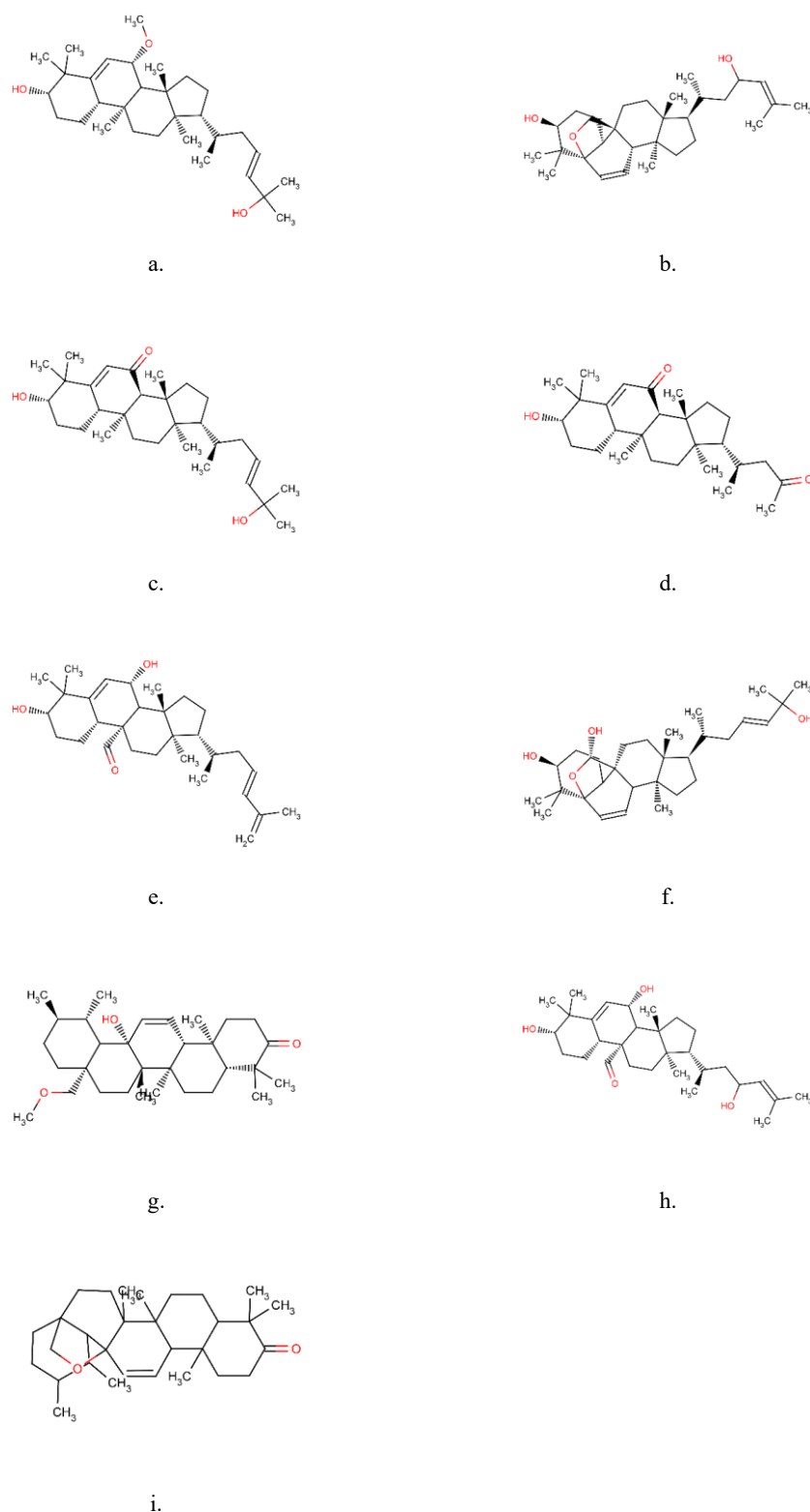


Figure 1. Chemical structures of the nine non-glycosylated (aglycone) triterpenoids from *Momordica charantia* selected for molecular docking against AMPK: (a) Karavilagenin B, (b) Karavilagenin E, (c) Kuguacin B, (d) Kuguacin C, (e) Kuguacin J, (f) Kuguacin R, (g) Momordicin, (h) Momordicine I, and (i) Momordicinin

Visualization and Interaction Analysis

Protein-ligand interactions were visualized using BIOVIA Discovery Studio Visualizer. The best-

scoring pose of each selected ligand was analyzed to identify key interactions (e.g., hydrogen bonds and

hydrophobic contacts) and residues contributing to complex stabilization.

Drug-Likeness and ADMET Prediction

Drug-likeness was evaluated using SwissADME (<http://swissadme.ch/>) to assess compliance with Lipinski's Rule of Five (Ro5) (Lipinski *et al.* 1997; Daina *et al.* 2017). ADMET (absorption, distribution, metabolism, excretion, and toxicity) properties were predicted using pkCSM (<https://biosig.lab.uq.edu.au/pkcsml/>), including Caco-2 permeability, human intestinal absorption (HIA), volume of distribution (VDss), blood-brain barrier permeability (logBB), CYP450 substrate/inhibitor status, total clearance, and AMES mutagenicity prediction (Pires *et al.* 2015). The predicted parameters were used to prioritize candidates with favorable oral pharmacokinetic properties and lower toxicity risk.

RESULTS AND DISCUSSION

Docking reliability depends on the validity of the docking protocol. Therefore, protocol validation was first performed by redocking the co-crystallized

ligand (staurosporine) into the AMPK catalytic pocket (ATP-binding site). The redocking produced an RMSD of 0.2376 Å, which is below the commonly accepted threshold (≤ 2.0 Å), indicating that the protocol can reproduce the experimental pose and is suitable for screening (Ruswanto *et al.* 2022). The overlay of staurosporine before and after redocking is shown in Figure 2.

Figure 3 presents the interaction pattern of staurosporine in the AMPK ATP-binding pocket. Staurosporine formed key interactions in the hinge region, particularly involving Val96 and Glu100. The hinge region is conserved among many protein kinases and often contributes to ligand recognition in the ATP pocket, supporting that the docking site definition was appropriate.

After protocol validation, docking was performed for nine bioactive triterpenoids from *M. charantia* and metformin as the reference. The docking scores and key interacting residues are summarized in Table 1. Using the same scoring function, all triterpenoids produced lower (more favorable) docking scores than metformin. Kuguacin J (-89.9934) had the



Figure 2. Staurosporine conformation before (yellow) and after (red) redocking in AMPK (PDB ID: 4QFG)

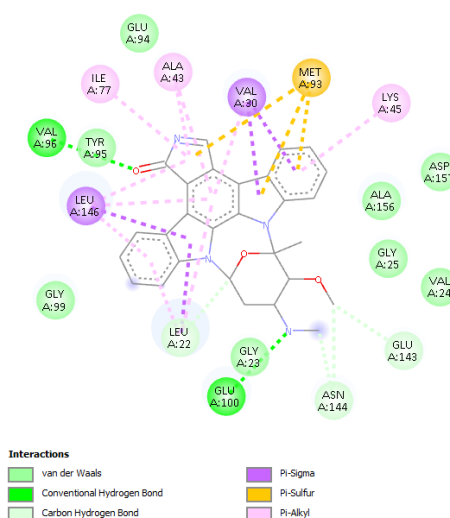


Figure 3. 2D interaction diagram of co-crystallized ligand (staurosporine) within the AMPK ATP-binding pocket (PDB ID: 4QFG), highlighting hinge-region contacts

Table 1. Results of compound docking against the AMPK enzyme

Bioactive compounds	Docking Score	Hydrogen Bond	Amino Acid Residues
Co-crystallized ligand (Staurosporine)	-121.5530	Val96, Glu100	Glu94, Ile77, Ala43, Tyr95, Leu146, Gly100, Val30, Met93, Lys45, Asp157, Ala156, Gly25, Val24, Glu143, Asn144, Gly23, Leu22
Metformin	-56.5325	Glu143, Asn144, Asp157	Leu146, Val30, Leu22, Met93, Ala156, Gly25
Karavilagenin B	-86.4084	Val96, Glu94	Tyr95, Val30, Ala156, Ala43, Met93, Leu146, Ile77, Asp157, Asn144, Gly25, Glu143, Leu22, Gly23, Glu100, Val24
Karavilagenin E	-76.9777	Asp157	Gly25, Asn144, Glu143, Gly23, Leu22, Glu100, Thr21, Ala156, Val30, Ile77, Leu146, Val96, Tyr95, Gly99, Ser97, Val32, Asp20
Kuguacin B	-75.9012	Glu94, Val96, Glu100	Tyr95, Ile77, Leu146, Ala156, Lys45, Ala43, Asp157, Glu143, Asn144, Met93, Val30, Leu22, Gly23, Gly25, Val24
Kuguacin C	-70.1696	Lys45, Glu100	Phe158, Ala43, Val30, Leu22, Gly23, Val24, Glu64, Asp157, Met93, Ala156, Leu146, Thr26, Ile77, Asn144, Glu143, Gly25
Kuguacin J	-89.9934	Glu100	Leu146, Met93, Ala43, Ala156, Val30, Leu22, Gly23, Glu94, Val96, Tyr95, Ile77, Asn144, Lys45, Glu143, Asp157, Gly25, Val24
Kuguacin R	-85.8514	Val96, Glu94, Asn144	Tyr95, Ile77, Leu146, Val30, Ala43, Leu22, Gly23, Glu100, Val24, Ala156, Met93, Asp157, Gly25, Glu143, Lys141
Momordicin	-67.0766	Leu22	Asp157, Asn144, Gly23, Glu100, Asp103, Ala156, Met93, Val30, Ile77, Leu146, Ala43, Val96, Gly99, Tyr95, Asp20, Gly98
Momordicine I	-82.7241	Glu100	Glu94, Leu22, Ile77, Leu146, Met93, Val30, Ala156, Gly23, Val24, Gly25, Glu143, Asn144, Asp157, Lys45, Ala43, Tyr95, Val96
Momordicinin	-69.9097	Val24	Tyr95, Val96, Leu146, Val30, Gly23, Asn144, Gly25, Asp157, Lys141, Glu143, Glu100, Leu22, Gly99

lowest score, followed by Karavilagenin B (-86.4084) and Kuguacin R (-85.8514), whereas metformin showed a higher score (-56.5325). These comparisons should be interpreted cautiously because docking scores are relative computational estimates generated by scoring functions and should not be considered as direct measurements of experimentally determined binding affinity (Pantsar & Poso 2018). Moreover, metformin primarily acts via cellular mechanisms that may not require strong binding to the ATP pocket, so a higher docking score does not diminish its clinical relevance.

Notably, the co-crystallized ligand (staurosporine) exhibited the most favorable docking score in Table 1, consistent with its role as the crystallographic reference bound to the AMPK ATP-binding pocket. While the screened triterpenoids did not surpass this co-crystallized benchmark, the top-ranked ligands reproduced key hinge-region contacts

(Val96/Glu94/Glu100), supporting a plausible binding mode within the ATP pocket and strengthening confidence in the pocket definition used for screening. Accordingly, these triterpenoids should be considered lead-like candidates for subsequent experimental validation rather than direct substitutes for the co-crystallized ligand.

Interaction analysis focused on the three best-scoring ligands (Kuguacin J, Karavilagenin B, and Kuguacin R) and metformin as a comparator. Two-dimensional interaction diagrams are shown in Figure 4. Kuguacin J formed a hydrogen bond with Glu100, while Karavilagenin B formed hydrogen bonds with Val96 and Glu94. Kuguacin R formed hydrogen bonds with Val96, Glu94, and Asn144. Overall, these patterns indicate a tendency to bind around the hinge region and near Val96, which may help orient ligands within the ATP-binding site. Metformin formed hydrogen bonds with Glu143, Asn144, and Asp157,

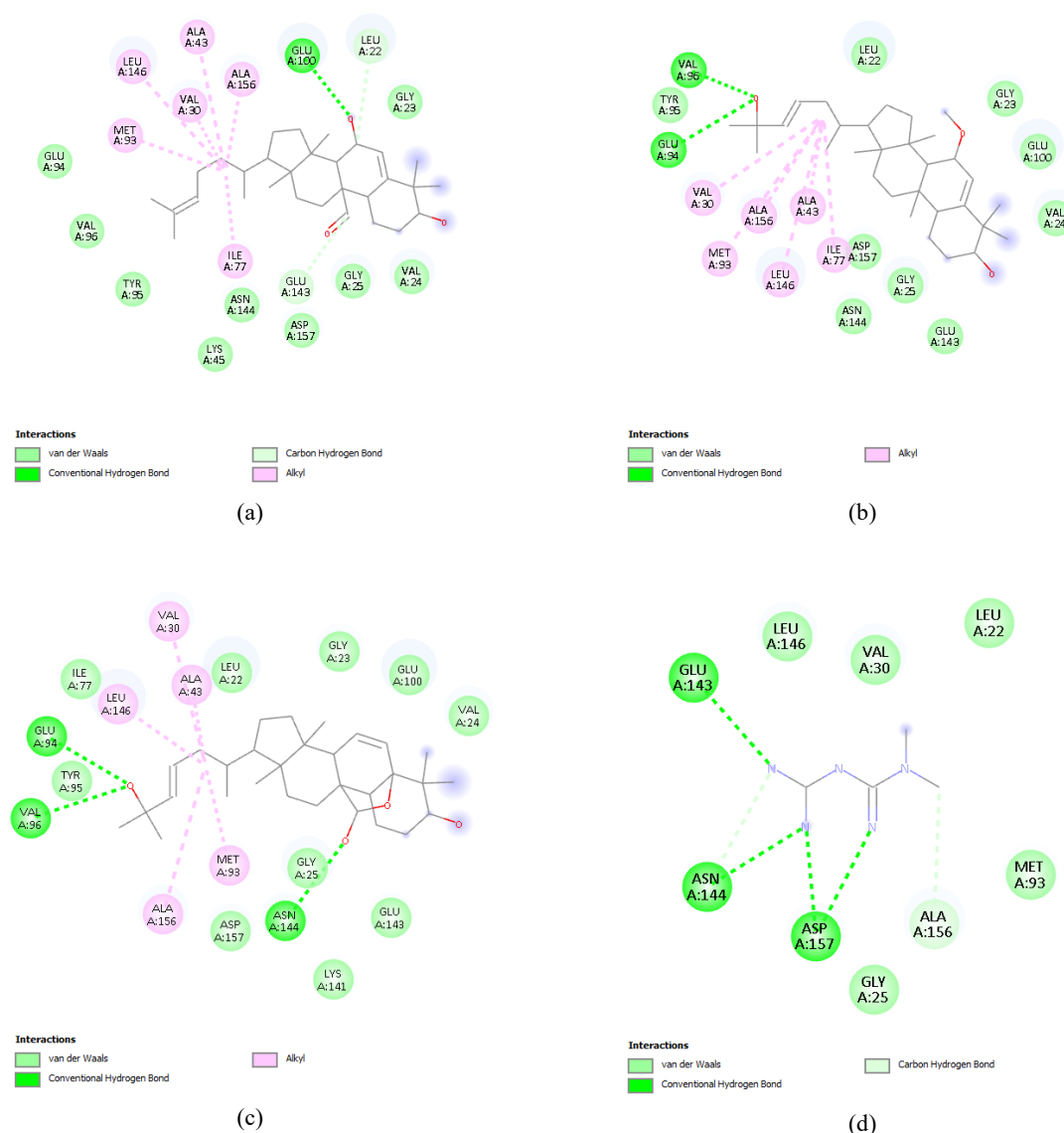


Figure 4. 2D interaction diagrams of the docked ligands at the AMPK ATP-binding site: (a) Kuguacin J, (b) Karavilagenin B, (c) Kuguacin R, (d) Metformin

but its higher docking score suggested a less stable predicted binding mode.

Drug-likeness was then assessed using Lipinski's Rule of Five (Ro5) as an early indicator of oral absorption and permeability, which involves four main criteria, such as molecular weight < 500 Da, $\log P < 5$, number of hydrogen donors < 5, and number of hydrogen acceptors < 10. Based on Table 2, Kuguacin J and Kuguacin R complied with Ro5, supporting their potential for oral bioavailability. Meanwhile, Karavilagenin B has one violation, namely a $\log P$ value of 5.20. A high $\log P$ value indicates increased lipophilicity, which can affect a compound's solubility (Lipinski *et al.* 1997; Daina *et al.* 2017). However, because it violates only one Ro5 parameter, Karavilagenin B still exhibits physicochemical characteristics that are relatively

supportive of its use as a candidate for an oral drug. In general, compounds that violate two or more Ro5 criteria tend to have issues with solubility, permeability, or oral bioavailability (Pirie *et al.* 2024).

Finally, pkCSM was used to predict pharmacokinetic and toxicological (ADMET) parameters (Pires *et al.* 2015). As summarized in Tables 3 and 4, Kuguacin J and Karavilagenin B exhibited good permeability values in Caco-2 cells ($>0.9 \times 10^{-6}$ cm/s), whereas Kuguacin R exhibited a lower permeability value. However, all three compounds had high Human Intestinal Absorption (HIA) values ($>90\%$), indicating good potential for intestinal absorption (Ahmed *et al.* 2020; Belal 2018). The steady-state volume of distribution (VDss) ranges from -0.172 to 0.107, indicating that

Table 2. Results of Lipinski's Ro5 test compounds

Bioactive compounds	Formula	Molecular Weight <500	Log P<5	Hydrogen Donor<5	Hydrogen Acceptor<10	Drug-likeness
Kuguacin J	C ₃₀ H ₄₆ O ₃	454.68	4.82	2	3	Yes
Karavilagenin B	C ₃₁ H ₅₂ O ₃	472.74	5.20	2	3	Yes
Kuguacin R	C ₃₀ H ₄₈ O ₄	472.7	4.57	3	4	Yes

Table 3. Predicted ADMET profile results for selected triterpenoid compounds using pkCSM - Part 1

Bioactive compounds	Absorption		Distribution		Metabolism	
	CaCo-2 Permeability	HIA	VDss (human)	BBB Permeability	CYP2D6 Substrate	CYP3A4 Substrate
Kuguacin J	1.161	96.061	-0.107	-0.495	No	Yes
Karavilagenin B	1.149	93.319	-0.140	-0.129	No	Yes
Kuguacin R	0.715	92.577	-0.172	-0.479	No	Yes

Table 4. Predicted ADMET profile results for selected triterpenoid compounds using pkCSM - Part 2

Bioactive compounds	Metabolism					Excretion	Toxicity
	CYP1A2 Inhibitor	CYP2C19 Inhibitor	CYP2C9 Inhibitor	CYP2D6 Inhibitor	CYP3A4 Inhibitor	Total Clearance	AMES Toxicity
Kuguacin J	No	No	No	No	No	0.491	No
Karavilagenin B	No	No	No	No	No	0.390	No
Kuguacin R	No	No	No	No	No	0.298	No

the compound tends to be distributed more in plasma than in tissues, resulting in potentially lower exposure to non-target tissues. Meanwhile, the logBB value ranges from 0.495 to -0.129, indicating that penetration of the blood-brain barrier (BBB) tends to be limited. These characteristics are advantageous because AMPK as a therapeutic target does not require penetration into the brain, thereby potentially minimizing neurological side effects (Belal 2018; Pires *et al.* 2015; Plisson & Piggott 2019). In terms of metabolism, none of the candidates are predicted to inhibit the major CYP isoforms (CYP1A2, CYP2C19, CYP2C9, CYP2D6, or CYP3A4); however, all candidates are predicted to be CYP3A4 substrates, which need to be further considered for potential drug interactions and metabolic stability in further studies (Zhao *et al.* 2021). This is in line with Belal's (2018) findings, which state that CYP3A4 substrates have the potential to interact with other drugs metabolized by this isoform. Negative AMES predictions for all candidates support a low risk of mutagenicity and carcinogenicity (Vijay *et al.* 2018). The AMES test is used to detect mutagenic potential, and negative results indicate that the compound does not have the potential to cause DNA damage and bacterial mutations that can lead to carcinogenicity. Overall, these results remain predictive and require further experimental validation to confirm the

accuracy of ADMET predictions and the clinical potential of the tested compounds.

CONCLUSION

This *in silico* study identified three bitter melon triterpenoids (Kuguacin J, Karavilagenin B, and Kuguacin R) as putative AMPK ATP-site ligands, showing more favorable docking scores than metformin. These compounds interacted with key residues within the AMPK catalytic pocket, supporting their potential interaction with the target protein. Kuguacin J and Kuguacin R complied with Lipinski's Rule of Five, whereas Karavilagenin B showed one violation related to logP while maintaining acceptable physicochemical characteristics. ADMET predictions indicated high intestinal absorption, AMES-negative toxicity, non-inhibition of CYP2D6, and potential CYP3A4 substrate activity. Although metabolic stability and potential drug-drug interactions require further investigation, these findings support prioritizing the three triterpenoids for subsequent *in vitro* and *in vivo* validation.

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REFERENCES

- Ahmed, I., Leach, D.N., Wohlmuth, H., De Voss, J.J. & Blanchfield, J.T. (2020). Caco-2 Cell permeability of flavonoids and saponins from *Gynostemma pentaphyllum*: The Immortal Herb. *ACS Omega*. **5**(34): 21561–21569.
- Bandyopadhyay, D., Tran, E.T., Patel, R.A., Luetzen, M.A., Cho, K., Shriver, L.P., Patti, G.J., Varvares, M.A., Ford, D.A., McCommis, K.S. & Ray, R.B. (2024). Momordicine-I suppresses head and neck cancer growth by modulating key metabolic pathways. *Cell Communication and Signaling*. **22**(1): 1–13.
- Belal, A. (2018). Drug likeness, targets, molecular docking and ADMET studies for some indolizine derivatives. *Pharmazie*. **73**(11): 635–642.
- Daina, A., Michielin, O. & Zoete, V. (2017). SwissADME: A free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules. *Scientific Reports*. **7**: 42717.
- Grace, S.R.S., Chandran, G. & Chauhan, J.B. (2019). Terpenoids: An activator of “fuel-sensing enzyme AMPK” with special emphasis on antidiabetic activity. In Öztürk, M. & Hakeem, K.R. (Eds). *Plant and Human Health, Volume 2: Phytochemistry and Molecular Aspects*. Pp. 227–244. Springer International Publishing. Cham, Switzerland.
- IDF. (2024). *Diabetes in Indonesia*. International Diabetes Federation.
- Iseli, T.J., Turner, N., Zeng, X.Y., Cooney, G.J., Kraegen, E.W., Yao, S., Ye, Y., James, D.E. & Ye, J.M. (2013). Activation of AMPK by bitter melon triterpenoids involves CaMKK β . *PLoS ONE*. **8**(4): e62309.
- Karale, P., Dhawale, S.C. & Karale, M.A. (2020). Antiobesity potential and complex phytochemistry of momordica charantia linn. with promising molecular targets. *Indian Journal of Pharmaceutical Sciences*. **82**(4): 548–561.
- Kemenkes RI. (2023). Prevalensi, dampak, serta upaya pengendalian hipertensi & diabetes di indonesia : visualisasi data ski 2023 (hasil survei kesehatan indonesia 2023). Kementerian Kesehatan Republik Indonesia.
- Kumar, R., Saha, P., Sahana, S. & Dubey, A. (2020). A review on diabetes mellitus: type1 & type2. *World Journal of Pharmacy and Pharmaceutical Sciences*. **9**(10): 838–850.
- Lipinski, C.A., Dominy, B.W. & Feeney, P.J. (1997). Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. *Advanced Drug Delivery Reviews*. **23**:3–25.
- Miura, T., Kawata, T., Takagi, S., Nanpei, M., Nakao, H., Ishihara, E. & Ishida, T. (2009). Effect of *Momordica charantia* on adenosine monophosphate-activated protein kinase in genetically type 2 diabetic mice muscle. *Journal of Health Science*. **55**(5): 805–808.
- Moon, D.O. (2024). Plant-derived flavonoids as AMPK activators: Unveiling their potential in type 2 diabetes management through mechanistic insights, docking studies, and pharmacokinetics. *Applied Sciences*. **14**(19): 8607.
- Pantsar, T. & Poso, A. (2018). Binding affinity via docking: Fact and fiction. *Molecules*. **23**(8): 1899.
- Pires, D.E.V., Blundell, T.L. & Ascher, D.B. (2015). pkCSM: Predicting small-molecule pharmacokinetic and toxicity properties using graph-based signatures. *Journal of Medicinal Chemistry*. **58**(9): 4066–4072.
- Pirie, R., Stanway-Gordon, H.A., Stewart, H.L., Wilson, K.L., Patton, S., Tyerman, J., Cole, D.J., Fowler, K. & Waring, M.J. (2024). An analysis of the physicochemical properties of oral drugs from 2000 to 2022. *RSC Medicinal Chemistry*. **15**(9): 3125–3132.
- Plisson, F. & Piggott, A.M. (2019). Predicting blood–brain barrier permeability of marine-derived kinase inhibitors using ensemble classifiers reveals potential hits for neurodegenerative disorders. *Marine Drugs*. **17**(2): 81.
- Purnomo, H. (2020). *Kimia komputasi untuk farmasi dan ilmu terkait-uji in silico senyawa anticovid-19*. Pustaka Pelajar. Yogyakarta.
- Puspitasari, A.D., Murti, N.K., Samsuri, A. & Shofiyah, J.L.N. (2024). Studi penambatan molekul senyawa metabolit sekunder batang kayu manis (*Cinnamomum burmanni*) sebagai kandidat obat antidiabetes mellitus tipe II. *Chimica et Natura Acta*. **12**(2): 114–120.
- Ruswanto, R., Nofianti, T., Mardianingrum, R., Kesuma, D. & Siswandono. (2022). Design, molecular docking, and molecular dynamics of thiourea-iron (III) metal complexes as NUDT5 inhibitors for breast cancer treatment. *Heliyon*. **8**(9): 1–10.
- Sayedali, E., Yalin, A.E. & Yalin, S. (2023). Association between metformin and vitamin B12 deficiency in patients with type 2 diabetes. *World Journal of Diabetes*. **14**(5): 585–593.
- Shrestha, M.M., Lim, C.Y., Bi, X., Robinson, R.C. & Han, W. (2021). Tmod3 Phosphorylation Mediates AMPK-Dependent GLUT4 Plasma Membrane Insertion in Myoblasts. *Frontiers in Endocrinology*. **12**: 1–7.
- Stanzione, F., Giangreco, I. & Cole, J.C. (2021). Use of molecular docking computational tools in drug discovery. In *Progress in Medicinal Chemistry*. Pp. 273–343. Elsevier. Amsterdam.

- Sun, L., Zhang, X., Dong, L., Zhang, C., Guo, P. & Wu, C. (2021). The triterpenoids of the bitter gourd (*Momordica charantia*) and their pharmacological activities: A review. *Journal of Food Composition and Analysis*. **96**: 103726.
- Sun, D., Gao, W., Hu, H. & Zhou, S. (2022). Why 90% of clinical drug development fails and how to improve it?. *Acta Pharmaceutica Sinica B*. **12(7)**: 3049–3062.
- Suryasa, I.W., Rodríguez-Gámez, M. & Koldoris, T. (2021). Health and treatment of diabetes mellitus. *International Journal of Health Sciences*. **5(1)**: I–V.
- Vijay, U., Gupta, S., Mathur, P., Suravajhala, P. & Bhatnagar, P. (2018). Microbial Mutagenicity Assay: Ames Test. *Bio-protocol*. **8(6)**: e2763.
- Villarreal-La Torre, V.E., Guarniz, W.S., Silva-Correa, C., Cruzado-Razco, L. & Siche, R. (2020). Antimicrobial activity and chemical composition of *Momordica charantia*: a review. *Pharmacognosy Journal*. **12(1)**: 1816–1841.
- Xiong, G., Wu, Z., Yi, J., Fu, L., Yang, Z., Hsieh, C., Yin, M., Zeng, X., Wu, C., Lu, A., Chen, X., Hou, T. & Cao, D. (2021). ADMETlab 2.0: An integrated online platform for accurate and comprehensive predictions of ADMET properties. *Nucleic Acids Research*. **49(W1)**: W5–W14.
- Zhao, M., Ma, J., Li, M., Zhang, Y., Jiang, B., Zhao, X., Huai, C., Shen, L., Zhang, N., He, L. & Qin, S. (2021). Cytochrome P450 enzymes and drug metabolism in humans. *International Journal of Molecular Sciences*. **22(23)**: 12808.
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