Trop J Phytochem Pharm Sci, September 2025; 4(9): 413 - 420 **ISSN 2955-1226 (Print)**
ISSN 2955-123(Electronic)

Tropical Journal of Phytochemistry & Pharmaceutical Sciences

Available online at https://www.tjpps.org

Original Research Article

In silico evaluation of antidiabetic potential of selected *Uvaria chamae* phytochemicals as adenosine monophosphate (AMP)-activated protein kinase modulators

Abdul-Basith Umar[1,2], Reward Agbamuche[1,2], Chibuike P. Okechukwu[1,2], Rufina O. Itamah[1,2], Oluwafemi Egbeyinka[2,3], Faith O. Airiohuodion[1,2], Chinoye C. Okpimah[4], Israel E. Ebhohimen[1,2]*

[1]*Department of Biochemistry, Ambrose Alli University, Ekpoma, Nigeria*
[2]*Bio-Sci Research Group, Department of Biochemistry, Ambrose Alli University, Ekpoma, Nigeria*
[3]*Glorious Vision University, Ogwa, Nigeria*
[4]*Independent Researcher, MSc in Drug Discovery and Development, University of Sunderland, United Kingdom*

ABSTRACT

Type 2 diabetes mellitus (T2DM) remains a major global health challenge characterised by impaired glucose and lipid metabolism. Activation of AMP-activated protein kinase (AMPK), a central regulator of cellular energy homeostasis, offers a promising therapeutic strategy for improving insulin sensitivity and metabolic balance. This study employed an *in silico* approach to evaluate selected phytochemicals from *Uvaria chamae*, including chamanetin, dichamanetin, uvaretin, isouvaretin, isochamanetin, pinocembrin, and linalool, for their potential as AMPK modulators. The compounds were assessed for physicochemical properties, drug-likeness, pharmacokinetics, and toxicity using SwissADME and ProTox-II, while molecular docking against the AMPK catalytic domain (PDB ID: 4CFF) was done using AutoDock Vina. All phytochemicals adhered to drug-likeness criteria and exhibited good oral bioavailability, with no structural alerts. Docking results revealed strong predicted binding affinities, ranging from -5.2 to -9.5 kcal/mol, compared with metformin (-4.5 kcal/mol). Chamanetin and dichamanetin showed the most favourable interactions with key residues within the AMPK ATP-binding pocket, suggesting potential as lead scaffolds for direct AMPK modulation. These findings provide molecular insight supporting the traditional use of *Uvaria chamae* in diabetes management and justify further biochemical and pharmacological validation of its active constituents.

Keywords: *Uvaria chamae*, Adenosine Monophosphate-Activated Protein Kinase, Molecular Docking, Diabetes Mellitus, Drug-Likeness

Received 30 October 2025
Revised 15 November 2025
Accepted 30 November 2025
Published online 01 December 2025

Introduction

Diabetes mellitus is a chronic metabolic disorder that affects millions of people worldwide, with increasing prevalence in both developed and developing countries.[1,2] It is characterised by persistent hyperglycaemia resulting from insufficient insulin secretion, insulin resistance, or a combination of both mechanisms.[1,3] The morbidity and mortality associated with diabetes arise primarily from its long-term complications, including cardiovascular diseases, nephropathy, retinopathy, and neuropathy.[3] Among the various forms, type 2 diabetes mellitus (T2DM) is the most prevalent, particularly affecting middle-aged and older adults. Despite its high incidence, the precise genetic determinants of T2DM remain poorly understood. Patients with this condition face markedly increased risks of stroke, heart failure, renal dysfunction, blindness, and limb amputation. Conventional management involves lifestyle modifications, dietary control, and pharmacological interventions such as oral hypoglycaemic agents or insulin therapy.[4]

*Corresponding author. Email: ebhohimen@aauekpoma.edu.ng
Tel: +2348078141995

Citation: Umar A-B., Agbamuche R., Okechukwu C.P., Itamah R.O., Egbeyinka O., Iroquoian F., Okpimah C.C., Ebhohimen I.E. *In silico* evaluation of antidiabetic potential of selected *Uvaria chamae* phytochemicals as adenosine monophosphate (AMP)-activated protein kinase modulators. Trop J Phytochem Pharm Sci, 2025; 4(9): 413 – 420 http://www.doi.org/10.26538/tjpps/v4i9.7

Official Journal of Natural Product Research Group, Faculty of Pharmacy, University of Benin, Benin City, Nigeria.

Advances in drug design have facilitated the development of several synthetic antidiabetic agents through *in silico* modelling, enabling the identification of biomolecules that interact specifically with molecular targets in human metabolic pathways.[5] Currently, therapeutic regimens for diabetes employ pharmacological agents including the biguanides, dipeptidyl peptidase-4 (DPP-4) inhibitors, sodium-glucose cotransporter-2 (SGLT2) inhibitors, sulfonylureas, and thiazolidinediones.[6] Among these, metformin, a biguanide derivative, remains the first-line drug for T2DM management and has been used clinically since the 1960s. It improves insulin sensitivity and lowers blood glucose levels without promoting weight gain or severe hypoglycaemia. Metformin exerts its antihyperglycemic action by activating adenosine monophosphate-activated protein kinase (AMPK), a primary regulator of cellular energy homeostasis.[7,8] Adenosine monophosphate-activated protein kinase activation enhances glucose uptake, promotes fatty acid oxidation, and suppresses hepatic gluconeogenesis.[4] Consequently, AMPK has become a validated molecular target for the development of novel antidiabetic compounds that mimic or potentiate metformin's mechanism of action.[9] Despite the therapeutic effectiveness of existing medications, prolonged use is often associated with high cost, limited accessibility, and adverse effects, creating a need for safer and more affordable alternatives.[6,10] Plants remain a valuable source of bioactive compounds with antihyperglycemic, antioxidant, and anti-inflammatory properties that may complement or substitute conventional therapies.[11,12]

Uvaria chamae is a medicinal plant widely used in Nigerian traditional medicine, like other plants, for managing diabetes, inflammation, and related metabolic disorders.[13,14] Phytochemical analyses of *U. chamae* have revealed a rich profile of bioactive constituents, including flavonoids such as chamanetin, isochamanetin, dichamanetin, and

pinocembrin, and benzophenone derivatives such as uvaretin and isouvaretin.[15] These compounds have established biological activities. For instance, uvaretin and isouvaretin exhibit cytotoxic effects against P-388 leukaemia and KB carcinoma cell lines, while alkaloids including armepavine, nornantenine, and corydine display cytotoxicity in L929 fibroblast-derived assays, with armepavine and nornantenine being the most potent.[16–18] Extracts from the roots and leaves of *U. chamae*, particularly polyphenol-rich fractions, have shown significant antioxidant activity through DPPH and ABTS radical scavenging, as well as activation of the Nrf2 signalling pathway.[19] Moreover, hydroethanolic root extracts have demonstrated *in vivo* antidiabetic effects, likely mediated through inhibition of digestive enzymes and improved glucose metabolism in alloxan-induced diabetic rats.[16] The roots of *U. chamae* are particularly abundant in uvaretin, a dihydrochalcone-type polyketide, and isouvaretin, a C-benzylated flavonoid, both of which contribute to the diverse pharmacological properties of the plant. Chamanetin, another prominent constituent, shares structural similarity with these compounds and is often categorised as a flavonoid due to its polyphenolic framework. The co-occurrence of chalcones and dihydrochalcones in the root of the plant provides a strong biochemical basis for its traditional ethnomedicinal applications.[15]

Although these phytochemicals show promise, there is no comprehensive molecular-level evidence that describes the interactions with validated antidiabetic targets such as AMPK. Understanding these interactions can provide mechanistic insights into how *U. chamae* exerts its reported antidiabetic effects. Therefore, this study employs *in silico* molecular docking to evaluate the binding affinities and interaction profiles of selected bioactive compounds from *U. chamae* roots against the AMPK catalytic domain (PDB ID: 4CFF), using metformin as a standard reference ligand.[20] The findings aim to elucidate the molecular basis for the antidiabetic activity of *U. chamae* and identify promising lead scaffolds for further drug development.

Materials and Methods

Computational Resources

All computational analyses were conducted on an HP EliteBook 9480M laptop powered by an Intel® Core™ i5-4310U CPU (2.00-2.60 GHz), 8 GB RAM, and a 64-bit Windows 10 Pro operating system. The software tools employed included BIOVIA Discovery Studio Visualizer (v25.1.0.24284), UCSF Chimera, AutoDock Vina (v1.2.7) and AutoDockTools (v1.5.7). Additional analyses were conducted using the web-based SwissADME platform (http://www.swissadme.ch). Protein structures were retrieved from the RCSB Protein Data Bank (PDB), and phytochemical structures were obtained from PubChem (https://pubchem.ncbi.nlm.nih.gov/).

Phytochemical Selection

Bioactive constituents of *Uvaria chamae* were identified through a review of relevant literature.[12,21,22] Seven phytochemicals with reported antidiabetic or metabolic regulatory potential were selected: chamanetin, dichamanetin, uvaretin, isouvaretin, isochamanetin, pinocembrin, and linalool. Metformin, an established AMPK activator, was the reference ligand (Table 1).

Table 1: 'Selected Bioactive Compounds from *Uvaria chamae* Extract and Reference Drug (Metformin) with PubChem Identifiers'

Compound	PubChem ID
Uvaretin	73447
Isouvaretin	509270
Chamanetin	21721821
Isochamanetin	5318528
Dichamanetin	181193
Pinocembrin	68071
Linalool	6549
Metformin	4091

ADME and Toxicity Predictions

Canonical SMILES strings for each compound were retrieved from the PubChem database, and the physicochemical properties, lipophilicity, solubility, pharmacokinetics, and drug-likeness were predicted using SwissADME.[23–26] Toxicological assessment was done using ProTox-II web server.[27] These data were used to select compounds with optimal oral bioavailability and no toxicity concerns for docking analysis.

Protein Retrieval and Preparation

The crystal structure of human AMPK (PDB ID: 4CFF) was retrieved from the RCSB Protein Data Bank. The downloaded protein structure corresponded to Biological Assembly 1 (BA1), containing chains C, D, and F. Pre-processing of the structure was performed using BIOVIA Discovery Studio Visualizer (v25.1.0.24284). The cleaned protein was saved in PDBQT format for docking

Active Site Definition

The AMPK active site was identified from the co-crystallised inhibitor staurosporine.[28] Staurosporine binds within the α-subunit of the ATP-binding pocket, comprising thirty residues in chain C: Thr21, Leu22, Gly23, Val24, Gly25, Gly28, Lys29, Val30, Lys31, Ile32, Ala43, Val44, Lys45, Ile77, Met93, Glu94, Tyr95, Val96, Gly99, Glu100, Glu143, Asn144, Val145, Leu146, Leu147, Lys154, Ile155, Ala156, Asp157, and Phe158. This region spans the glycine-rich loop, hinge, and activation loop of the kinase domain. The docking grid coordinates and grid box were: x,y,z = -59.593, -29.596, 146.716 Å and 40 × 52 × 40 Å, respectively.

Ligand Preparation

The three-dimensional (3D) conformers of selected phytochemicals were retrieved from PubChem in SDF format and converted to PDB format using UCFS Chimera. Each ligand was subsequently prepared in AutoDock Tools by adding polar hydrogens, assigning Gasteiger charges, and defining torsional flexibility. The ligands were then saved in PDBQT format for molecular docking.[29]

Molecular Docking Protocol

Docking was performed using AutoDock Vina to predict ligand-receptor binding affinities between *Uvaria chamae* phytochemicals and the AMPK. Binding free energy (ΔG) values were recorded in kcal/mol, with lower values indicating stronger predicted interactions.[30] Metformin was docked under identical conditions and used as a reference ligand. Post-docking, the lowest energy conformations were analysed for hydrogen bonding, hydrophobic interactions, and π–π stacking using BIOVIA Discovery Studio Visualizer.

Data Analysis

Docking results were analysed comparatively against metformin. Compounds exhibiting binding free energies ≤ -8.0 kcal/mol were classified as having strong affinity toward AMPK.[31,32] The physicochemical, pharmacokinetic, medicinal chemistry, and toxicity data from SwissADME and ProTox-II were integrated with docking outcomes to select compounds with binding affinity, favourable pharmacological and safety profiles.[33]

Results and Discussion

Physicochemical Profiling, Lipophilicity and Water Solubility

The key physicochemical parameters of *Uvaria chamae* metabolites compared with metformin are presented in Table 2. The seven ligands had molecular weights below 500 Da and satisfied Lipinski's rule of five.[25] Their topological polar surface area (TPSA) values (66-107 Å²) and limited numbers of rotatable bonds align with Veber's rule.[26]

The predicted lipophilicity of the metabolites is presented in Table 3. The Log P values were between 2.26 and 4.44, within the optimal range for oral drugs and consistent with high membrane permeability and bioavailability. In contrast, metformin, the reference compound, had a low Log P (-0.75), indicating high polarity but limited passive diffusion across lipid membranes. Overall, the *U. chamae* metabolites possess balanced polarity and lipophilicity conducive to efficient absorption and

cellular uptake, implying better membrane permeability and potential AMPK modulation compared to metformin.

The predicted solubility profiles (Table 4) revealed that the *U. chamae* metabolites exhibited moderate to low water solubility (Log S = -2.4 to -6.6), while metformin was highly soluble (Log S ≈ 0.2). Among the metabolites, linalool and pinocembrin were categorised as soluble, whereas dichamanetin had the lowest solubility. Although less soluble than metformin, the water solubility of the metabolites was within acceptable ranges for oral drugs and complied with Lipinski's rule of five and Veber's criteria.

Table 2: Physicochemical properties of *U. chamae* phytochemicals and Metformin

Compound	Molecular Weight (Da)~500	LogP	H-Bond Donors	H-Bond Acceptors	TPSA (Å²)	Rotatable Bonds
Uvaretin	378.42	3.88	3	5	86.99	7
Isouvaretin	378.42	4.43	2	5	79.9	2
Chamanetin	362.38	3.3	3	5	86.99	3
Isochamanetin	362.38	3.4	3	5	86.99	3
Dichamanetin	468.5	4.44	4	6	107.22	5
Pinocembrin	256.25	2.26	2	4	66.76	1
Linalool	154.25	2.66	1	1	20.23	4
Metformin	129.16	-0.75	4	2	88.99	3

Table 3: Lipophilicity properties of *U. chamae* phytochemicals and Metformin

Compound	iLOGP	XLOGP3	WLOGP	MLOGP	Silicos-IT LogP	Consensus LogP
Uvaretin	2.82	4.87	4.22	2.72	4.75	3.88
Isouvaretin	3.92	5.65	4.94	2.52	5.1	4.43
Chamanetin	2.3	4.31	3.78	2.11	3.99	3.3
Isochamanetin	2.67	4.44	3.78	2.11	3.99	3.4
Dichamanetin	3.01	5.88	5.07	2.79	5.46	4.44
Pinocembrin	2.11	2.88	2.48	1.27	2.55	2.26
Linalool	2.7	2.97	2.67	2.59	2.35	2.66
Metformin	0.77	-1.06	-1.03	-0.56	-1.85	-0.75

Table 4: Water solubility properties of *U. chamae* phytochemicals and Metformin

Phytochemicals	ESOL LogS	ESOL Solubility (mg/mL)	ESOL Solubility (mol/mL)	ESOL Class	Ali LogS	Ali Solubility (mg/mL)	Ali Solubility (mol/mL)	Ali Class	Silicos- IT LogSw	Silicos-IT Solubility	Silicos-IT Solubility (mol/L)	Silicos-IT class
Uvaretin	-5.27	2.04E-03	5.40E-06	Moderately soluble	-6.43	1.40E-04	3.70E-07	Poorly soluble	-6.94	4.37E-05	1.16E-07	Poorly soluble
Isouvaretin	-5.98	3.93E-04	1.04E-06	Moderately soluble	-7.09	3.06E-05	8.09E-08	Poorly soluble	-6.21	2.33E-04	6.15E-07	Poorly soluble
Chamanetin	-5.1	2.90E-03	7.99E-06	Moderately soluble	-5.85	5.11E-04	1.41E-06	Moderately soluble	-6.29	1.85E-04	5.11E-07	Poorly soluble
Isochamanetin	-5.18	2.40E-03	6.62E-06	Moderately soluble	-5.99	3.75E-04	1.03E-06	Moderately soluble	-6.29	1.85E-04	5.11E-07	Poorly soluble
Dichamanetin	-6.63	1.11E-04	2.36E-07	Poorly soluble	-7.9	5.84E-06	1.25E-08	Poorly soluble	-8.54	1.34E-06	2.86E-09	Poorly soluble
Pinocembrin	-3.64	5.81E-02	2.27E-04	Soluble	-3.94	2.93E-02	1.14E-04	Soluble	-4	2.58E-02	1.01E-04	Soluble
Linalool	-2.4	6.09E-01	3.95E-03	Soluble	-3.06	1.35E-01	8.75E-04	Soluble	-1.84	2.20E+00	1.43E-02	Soluble
Metformin	0.22	2.17E+02	1.68E+00	Highly soluble	-0.32	6.18E+01	4.79E-01	Very soluble	0.17	1.90E+02	1.47E+00	Soluble

Pharmacokinetic Properties

Pharmacokinetic predictions presented in Table 5 indicate that all *U. chamae* metabolites and metformin displayed high gastrointestinal (GI) absorption, suggesting good oral bioavailability. Most metabolites were predicted to be non-permeant across the blood-brain barrier (BBB), except linalool and pinocembrin, which showed potential for BBB penetration. Several compounds, notably uvaretin and chamanetin, were predicted to inhibit cytochrome P450 (CYP) isoenzymes. Metformin, in contrast, exhibited no CYP inhibition and very low skin permeability (log Kop = -7.84) relative to the *U. chamae* metabolites (-4.6 to -5.8). Overall, the phytochemicals demonstrated favourable pharmacokinetic properties supporting their potential as orally active AMPK modulators.

Drug-Likeness and Medicinal Chemistry

All *Uvaria chamae* metabolites met major drug-likeness criteria, showing zero or minimal violations across Lipinski, Ghose, Veber, Egan, and Muegge filters (Table 6). Each metabolite achieved a

 ISSN 2955-1226 (Print)
ISSN 2955-123(Electronic)

bioavailability score of 0.55, comparable to metformin. However, metformin recorded more Ghose and Muegge violations due to its small molecular size and high polarity. These results indicate that the *U. chamae* compounds have physicochemical and pharmacokinetic properties favourable for oral drug candidates for AMPK modulation.

Table 5: Pharmacokinetic properties of *U. chamae* phytochemicals and Metformin

Phytochemicals	GI Absorption	BBB permeant	Pgp substrate	CYP1A2 inhibitor	CYP2C19 inhibitor	CYP2C9 inhibitor	CYP2D6 Inhibitor	CYP3A4 inhibitor	log Kp (cm/s)
Uvaretin	High	No	No	Yes	Yes	Yes	Yes	Yes	-5.15
Isouvaretin	High	No	No	No	Yes	Yes	No	No	-4.6
Chamanetin	High	No	Yes	No	Yes	Yes	Yes	Yes	-5.45
Isochamanetin	High	No	No	No	Yes	Yes	Yes	Yes	-5.36
Dichamanetin	High	No	No	No	Yes	Yes	No	No	-4.98
Pinocembrin	High	Yes	No	Yes	Yes	No	No	No	-5.82
Linalool	High	Yes	No	No	No	No	No	No	-5.13
Metformin	High	No	No	No	No	No	No	No	-7.84

Table 6: Drug-likeness and bioavailability score of *U. chamae* phytochemicals and Metformin

Phytochemicals	Lipinski #violations	Ghose #violations	Veber #violations	Egan #violations	Muegge #violations	Bioavailability Score
Uvaretin	0	0	0	0	0	0.55
Isouvaretin	0	0	0	0	1	0.55
Chamanetin	0	0	0	0	0	0.55
Isochamanetin	0	0	0	0	0	0.55
Dichamanetin	0	1	0	0	1	0.55
Pinocembrin	0	0	0	0	0	0.55
Linalool	0	1	0	0	2	0.55
Metformin	0	3	0	0	2	0.55

Structural & Medicinal Chemistry Analysis

Structural alerts and synthetic feasibility parameters are presented in Table 7. All *U. chamae* metabolites exhibited no PAINS (Pan-Assay INterference compound) alerts, suggesting the absence of reactive or promiscuous substructures likely to cause false-positive biological activity. Most compounds showed one or two lead-likeness violations, primarily attributed to molecular size, yet remained within acceptable optimisation thresholds. Their synthetic accessibility scores (2.7-4.2) indicate moderate ease of synthesis, comparable to metformin (3.11). Isouvaretin and dichamanetin exhibited slightly higher values, reflecting more complex structural frameworks. Overall, the *U. chamae* metabolites display favourable medicinal chemistry characteristics, with low toxicity risk and promising potential as lead scaffolds for AMPK-targeted antidiabetic drug development.

Binding Affinity from Molecular Docking

Molecular docking revealed that all *Uvaria chamae* phytochemicals bound more strongly to the AMPK catalytic domain than metformin, which exhibited a binding free energy of -4.5 kcal/mol (Table 8). The binding affinities of the metabolites ranged between -5.2 and -9.5 kcal/mol, indicating stable interactions with the AMPK active site. Among these, chamanetin and dichamanetin had the lowest binding energies and formed multiple hydrogen bonds and hydrophobic contacts with key ATP-binding residues. These findings suggest that chamanetin and dichamanetin may act as potent AMPK modulators, with comparable or superior binding potential to metformin if the ligand-target interaction is worked out. The observed affinity and interaction pattern support the herbal medicinal use of *U. chamae* extract in diabetes management.

Table 7: Medicinal Chemistry properties of *U. chamae* phytochemicals and Metformin

Phytochemicals	PAINS #alerts	Brenk #alerts	Leadlikeness #violations	Synthetic Accessibility
Uvaretin	0	0	2	2.89
Isouvaretin	0	2	2	4.08
Chamanetin	0	0	2	3.63
Isochamanetin	0	0	2	3.61
Dichamanetin	0	0	2	4.15
Pinocembrin	0	0	0	2.96
Linalool	0	1	1	2.74
Metformin	0	2	1	3.11

Table 8: Binding energy from molecular docking of *U. chamae* phytochemicals and Metformin

Ligand	Binding Energy (kcal/mol)
Uvaretin	-8.3
Chamanetin	-9.5
Isochamanetin	-8.7
Dichamanetin	-9.3
Isouvaretin	-8.0
Linalool	-5.2
Pinocembrin	-8.4
Metformin	-4.5

ISSN 2955-1226 (Print)
ISSN 2955-123(Electronic)

Ligand Interaction Analysis

The lowest binding free energy conformations, between the ligands and AMPK are presented in Figures 1-8. Notably, chamanetin and dichamanetin formed multiple hydrogen bonds and hydrophobic interactions with key residues within the ATP-binding cleft. In contrast, metformin interacted primarily through polar contacts near the hinge region, consistent with its small size and high polarity. These interaction profiles suggest that the larger, moderately lipophilic *U. chamae* metabolites may achieve stronger and more extensive binding to AMPK, thereby enhancing their potential as natural modulators of the activity of the enzyme.

Adenosine monophosphate-activated protein kinase is a central cellular energy sensor that plays a crucial role in regulating glucose and lipid homeostasis.[34] Activation of AMPK promotes glucose uptake, enhances fatty acid oxidation, and suppresses hepatic gluconeogenesis. These processes collectively contribute to improved metabolic balance and glycaemic control in Type 2 diabetes mellitus. Metformin, a widely used first-line antidiabetic drug, exerts its therapeutic effect primarily through AMPK activation via both lysosomal and mitochondrial signalling mechanisms.[35,36]

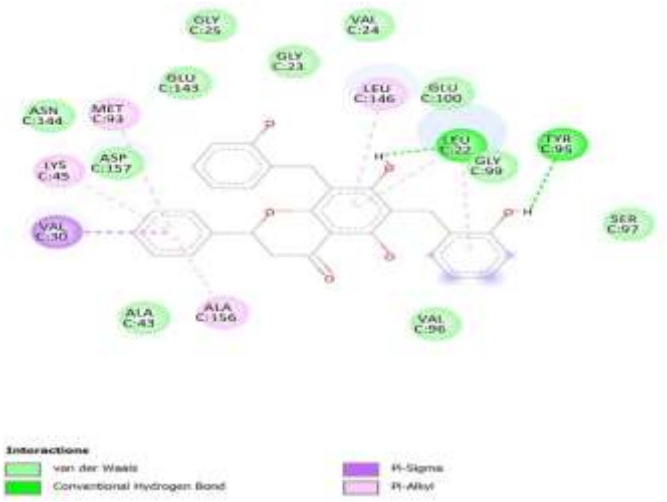

Figure 3: Dichamanetin-AMPK complex

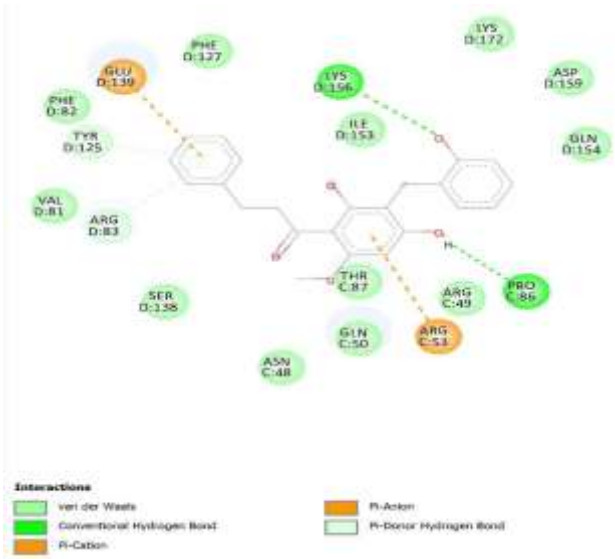

Figure 1: Uvaretin-AMPK complex

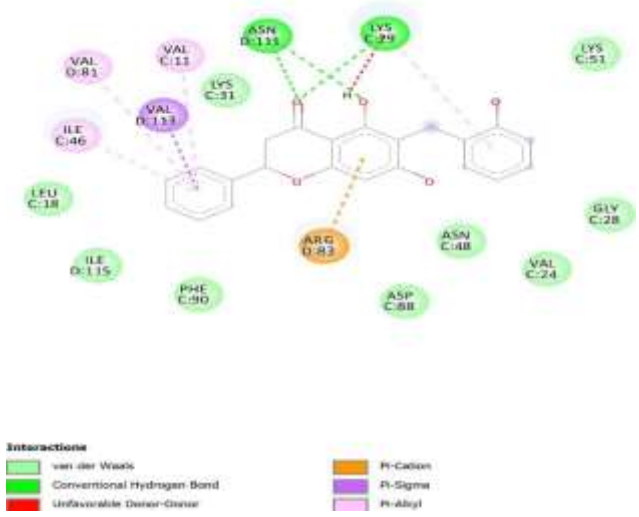

Figure 4: Isochamanetin-AMPK complex

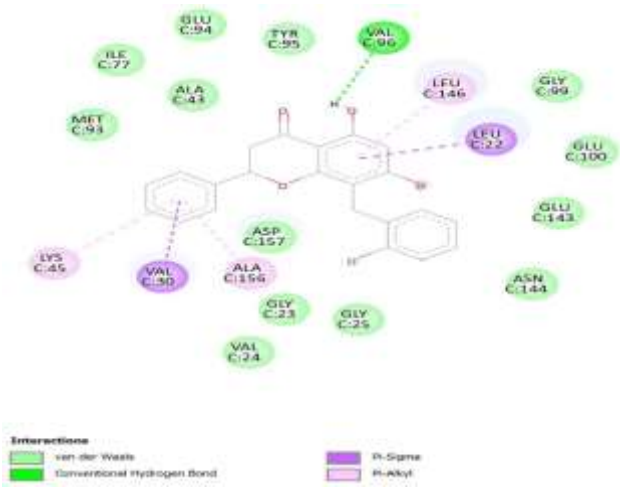

Figure 2: Chamanetin-AMPK complex

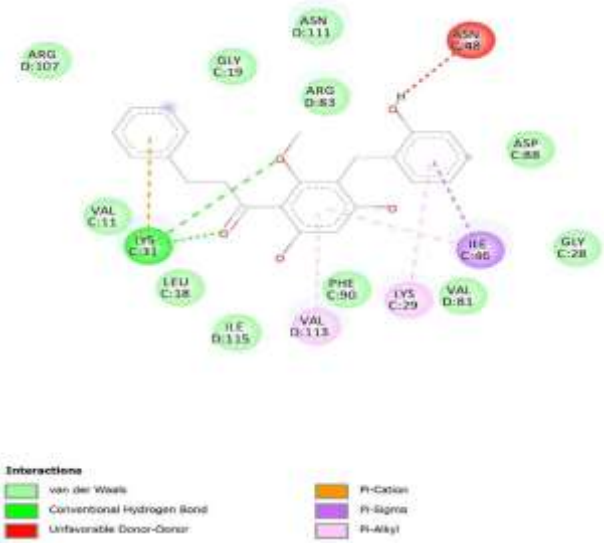

Figure 5: Isouvaretin-AMPK complex

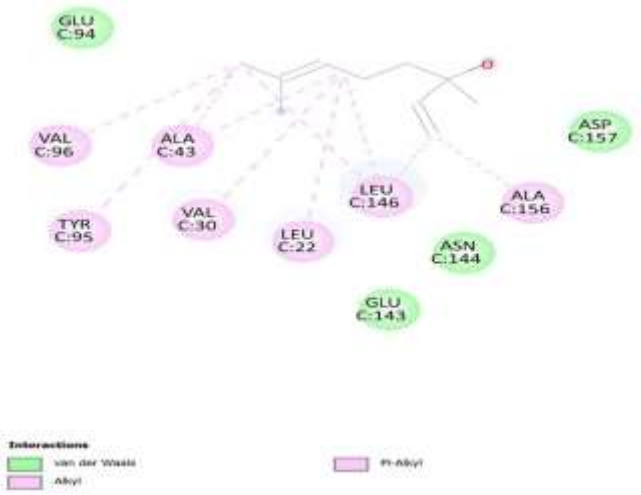

Figure 6: Linalool-AMPK complex

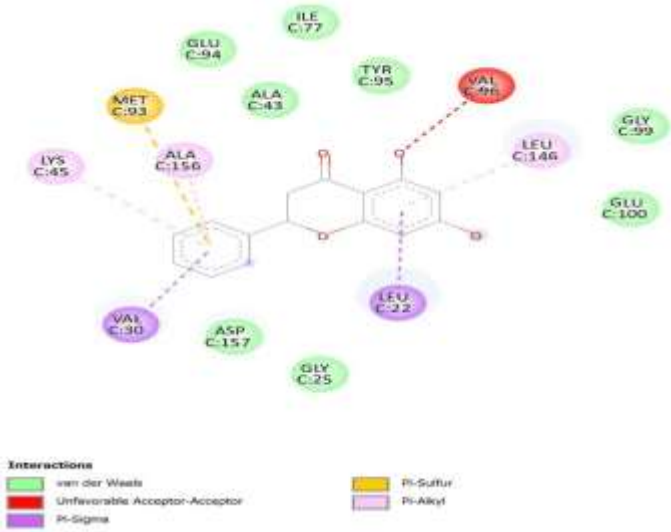

Figure 7: Pinocembrin-AMPK complex

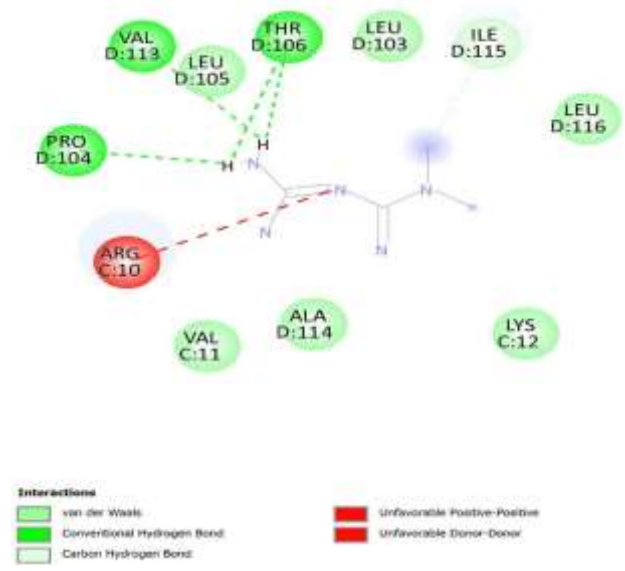

Figure 8: Metformin-AMPK complex

The docking results demonstrated that the constituents of *U. chamae* exhibited stronger binding affinities for the AMPK catalytic domain compared with metformin (Table 8). The more favourable binding affinities for the phytochemicals may be attributed to their polyphenolic structures, characterised by multiple hydroxyl groups and conjugated aromatic rings that facilitate hydrogen bonding and π-π stacking interactions within the AMPK ATP-binding pocket.

The strong binding affinities observed for the *U. chamae* flavonoids are consistent with growing evidence that naturally occurring polyphenols and flavonoids can directly or indirectly modulate AMPK activity. For instance, Ren *et al*. reported that berberine activates AMPK through lysosomal pathways independent of canonical upstream kinases, highlighting the capacity of plant-derived metabolites to influence AMPK signalling. Similarly, several polyphenolic compounds have been shown to enhance AMPK phosphorylation, improve insulin sensitivity, and contribute to glycaemic regulation.[37]

Previous pharmacological studies on *U. chamae* extracts have demonstrated potent antihyperglycemic, anti-inflammatory, and antioxidant activities in experimental diabetic models.[38] However, the precise molecular mechanisms underlying these effects were not clear. The present *in silico* findings suggest that AMPK modulation may be one of the principal pathways through which *U. chamae* extract exerts its therapeutic effects. The strong affinity supports their potential as lead scaffolds for novel antidiabetic drug design.

However, it is important to interpret these results within the context of the complex pharmacology of metformin. The mechanism of drug action is not solely dependent on direct AMPK binding; rather, it involves mitochondrial respiratory inhibition and PEN2-AXIN-mediated signalling cascades that indirectly activate AMPK.[36]

Conclusion

This study provides computational evidence supporting the potential of *Uvaria chamae* phytochemicals as modulators of AMP-activated protein kinase, a validated target for type 2 diabetes mellitus therapy. All the evaluated metabolites demonstrated favourable physicochemical and pharmacokinetic properties that align with drug-likeness criteria, as well as strong predicted binding affinities for the AMPK catalytic site. Notably, chamanetin and dichamanetin exhibited the most stable interactions, surpassing metformin in binding affinity and drug-likeness parameters. These findings underscore the ethnomedicinal use of *U. chamae* extract in diabetes management and identify its constituents as promising scaffolds for antidiabetic drug development. Although molecular docking offers valuable predictive insights, further molecular dynamics simulations, *in vitro* enzyme assays, and *in vivo* validation are required to confirm the biological relevance of these interactions. The integration of computational modelling with experimental pharmacology will be essential to translate these *in silico* observations into clinically useful AMPK-targeted therapeutics derived from *Uvaria chamae*.

Conflict of interest

The authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

Acknowledgements

We wish to acknowledge the Bio-Sci Research Group, Department of Biochemistry, Ambrose Alli University, Ekpoma, Edo State, Nigeria, for the technical support and guidance during this research work.

References

1. Hossain MJ, Al-Mamun M, Islam MR. Diabetes mellitus, the fastest growing global public health

concern: Early detection should be focused. Health Sci Rep. 2024;7:1–5.
2. Antar SA, Ashour NA, Sharaky M, Khattab M, Ashour NA, Zaid RT, Roh EJ, Elkamhawy A, Al-Karmalawy AA. Diabetes mellitus: Classification, mediators, and complications; A gate to identify potential targets for the development of new effective treatments. Biomed and Pharmacother. 2023;168:1–25.
3. Abu OD, Umar A-B, Ekperusi SE, Ohikhuare F. Assessment of cardiac oxidative status of diabetic Wistar rats exposed to methanol fraction of ethanol extract of *Dialium guineense* stem bark. *Biomed J Sci Tech Res.* 2024;57: 49002–49009.
4. Lamoia, TE, Shulman GI. Cellular and molecular mechanisms of metformin action. Endocr Rev. 2021;42:77–96
5. Ibrahim SO, Lukman HY, Ebhohimen IE, Babamale HF, Abdulkadir FR, Zubair MF, Atolani O. Chemoinformatic-aided antidiabetic analysis of the therapeutic potential of phytoconstituents in *Eremomastax speciosa* extracts. Borneo J Pharm. 2024;7:172–186
6. Grant PJ, Cosentino F. The 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. Eur Heart J. 2019;40:3215–3217.
7. Goel S, Singh R, Singh V, Singh H, Kumari P, Chopra H, Sharma R, Nepovimova E, Valis M, Kuca K, Emran TB. Metformin: Activation of 5′ AMP-activated protein kinase and its emerging potential beyond anti-hyperglycemic action. Front Genet. 2022;13:1-15. https://doi.org/10.3389/fgene.2022.1022739
8. González-Casanova JE, Navarro-Marquez M, Saez-Tamayo T, Angarita L, Durán-Agüero S, Fuentes-Barría H, Bermúdez V, Rojas-Gómez DM. New Perspectives on the Molecular Action of Metformin in the Context of Cellular Transduction and Adipogenesis. Int J Mol Sci. 2025;26:3690. https://doi.org/10.3390/ijms26083690
9. Entezari M, Hashemi D, Taheriazam A, Zabolian A, Mohammadi S, Fakhri F, Hashemi M, Hushmandi K, Ashrafizadeh M, Zarrabi A, Ertas YN, Mirzaei S, Samarghandian S. AMPK signaling in diabetes mellitus, insulin resistance and diabetic complications: A pre-clinical and clinical investigation. Biomed & Pharmacother. 2022;146:1–17.
10. Ebhohimen IE, Izevbigie ON. Nephroprotective Activities of Medicinal Plants and Natural Drugs. in *Biopharmacological Activities of Medicinal Plants and Bioactive Compounds.* Eds. Singh, A. & Bithel, N. Nova Science Publishers, New York, 2021;231–244.
11. Ebhohimen IE, Idiakheua OD, Itamah RO, Orowo EO. Antioxidant capacity of *Azadirachta indica, Persea americana,* and *Mangifera indica* leaves polyherbal extract. Trop J Nat Prod Res. 2025;9:896–902.
12. Daï EH, Hermann HJS, Idohou R, Ouédraogo A, Kakaï RG, Hotes S, Assogbadjo AE. Modeling current and future distribution patterns of *Uvaria chamae* in Benin (West Africa): Challenges and opportunities for its sustainable management. Heliyon 2023;9:1–11.
13. Mutiu AA, Miracle MA, Nabilat TY, Emmanuel OA. *In vitro* anti-inflammatory and anti-ulcerogenic potential of ethanol extract of *Carica papaya* leaves: Phytochemical and molecular docking studies. TJPPS. 2025;4:341–354.
14. Tupas GD, Otero MCB, Ebhohimen EI, Egbuna C, Aslam M. Anti-diabetic lead compounds and targets for drug development. in *Phytochemistry: An in-silico and in-vitro Update*. Eds. Kumar, S. & Egbuna, C. Springer Nature, 2019;1–23.
15. Agbebi EA, Omotuyi OI, Oyinloye BE, Okeke UB, Apanisile IO, Okor B, Adefabijo D. Ethnomedicine, phytochemistry, and pharmacological activities of *Uvaria chamae* P. Beauv.: A comprehensive review. Naunyn Schmiedebergs Arch Pharmacol. 2024;397:5421–5436.
16. Emordi JE, Agbaje EO, Oreagba IA, Iribhogbe OI. Antidiabetic effects of the ethanolic root extract of *Uvaria chamae* P. Beauv (Annonaceae) in alloxan-induced diabetic rats: A potential alternative treatment for diabetes mellitus. Adv Pharmacol Sci. 2018;2018:1314941
17. Sinha R, Kumar P, Sikdar A. A comprehensive review on chalcone analogues-versatile scaffold with medicinal and biological potential. J Appl Pharm Sci Res. 2023;6:10–15.
18. Salehi B, Quispe C, Chamkhi I, El Omari N, Balahbib A, Sharifi-Rad J, Bouyahya A, Akram M, Iqbal M, Docea AO, Caruntu C, Leyva-Gómez G, Dey A, Martorell M, Calina D, López V, Les F. Pharmacological properties of chalcones: A review of preclinical including molecular mechanisms and clinical evidence. Front Pharmacol. 2021;11:1-21. https://doi.org/10.3389/fphar.2020.592654
19. Popoola TD, Guetchueng ST, Ritchie KJ, Awodele O, Dempster NM, Akinloye O, Sarker SD, Fatokun AA. Potent Nrf2-inducing, antioxidant, and anti-inflammatory effects and identification of constituents validate the anti-cancer use of *Uvaria chamae* and *Olax subscorpioidea*. BMC Complement Med Ther. 2021;21:234.
20. Adewusi JA, Adams AA, Ibidotun TO, Ezekiel TA. Phytochemical profiling, antioxidant, and antidiabetic activities of defatted ethanol aerial extract of *Heliotropium indicum*: Insights from GC-MS and *in vitro* studies. TJPPS. 2025;4:320–328
21. Fall D, Duval RA, Gleye C, Laurens A, Hocquemiller R. Chamuvarinin, an acetogenin bearing a tetrahydropyran ring from the roots of *Uvaria chamae*. J Nat Prod. 2004;67:1041–1043.
22. Mariita RM, Ogol CKPO, Oguge NO, Okemo PO. Methanol extract of three medicinal plants from Samburu in Northern Kenya show significant antimycobacterial, antibacterial and antifungal properties. RJMP. 2011;5:54–64.
23. Huang T, Sun J, Zhou S, Gao J, Liu Y. Identification of direct activator of adenosine monophosphate-activated protein kinase (AMPK) by structure-based virtual screening and molecular docking approach. Int J Mol Sci. 2017;18: 1408.
24. Daina A, Michielin O, Zoete V. SwissADME: A free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules. Sci Rep. 2017;7:42717.
25. Lipinski CA, Lombardo F, Dominy BW, Feeney PJ. Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. Adv Drug Deliv Rev. 2001;46:3–26.
26. Veber DF, Johnson SR, Cheng HY, Smith BR, Ward KW, Kopple KD. Molecular properties that influence the oral bioavailability of drug candidates. J Med Chem. 2022;45:2615–2623.
27. Banerjee P, Kemmler E, Dunkel M, Preissner R. ProTox 3.0: A webserver for the prediction of toxicity of chemicals. Nucleic Acids Res. 2024;52:W513–W520.
28. Al-Nema M, Gaurav A, Lee VS. Docking based screening and molecular dynamics simulations to identify potential selective PDE4B inhibitor. Heliyon 2020; 6:1-12.

29. Morris GM, Huey R, Lindstrom W, Sanner MF, Belew RK, Goodsell DS, Olso AJ. Software news and updates AutoDock4 and AutoDockTools4: Automated docking with selective receptor flexibility. J Comput Chem. 2009;30:2785–2791.
30. Ebhohimen IE, Onyijen OH, Arora V, Arora V, Adeleke VT, Okpeku M. Mutation Pattern in the Receptor Binding Motif of SARS-CoV-2 Variants and the Effect on Molecular Interactions in Docked Ligand Complexes. Trop J Nat Prod Res. 2022;6:1262–1267.
31. Terefe EM, Ghosh A. Molecular docking, validation, dynamics simulations, and pharmacokinetic prediction of phytochemicals isolated from *Croton dichogamus* against the HIV-1 reverse transcriptase. Bioinform Biol Insights. 2022;16: 1-20.
32. Wong F, Krishnan A, Zheng EJ, Stärk H, Manson AL, Earl AM, Jaakkola T, Collins JJ. Benchmarking AlphaFold -enabled molecular docking predictions for antibiotic discovery. Mol Syst Biol. 2022;18:1-20.
33. Ebhohimen IE, Okolie NP, Okpeku M, Unweator M, Adeleke VT, Edemhanria L. Evaluation of the antioxidant properties of carvacrol as a prospective replacement for crude essential oils and synthetic antioxidants in food storage. Mol. 2023;28:1315.
34. Jîtcă G. The role of AMPK activation in metabolic regulation, energy homeostasis and aging: A comprehensive overview. ITPS. 8, 1–15 (2024).
35. Steinberg GR, Hardie DG. New insights into activation and function of the AMPK. Nat Rev Mol Cell Biol 2023;24:1–18.
36. Sugawara K, Ogawa W. New mechanism of metformin action mediated by lysosomal presenilin enhancer 2. J Diabetes Investig. 2023;14:12–14 https://doi.org/10.1111/jdi.13925.
37. Clemente-Suárez VJ, Martín-Rodríguez A, Beltrán-Velasco AI, Rubio-Zarapuz A, Martínez-Guardado I, Valcárcel-Martín R, Tornero-Aguilera JF. Functional and therapeutic roles of plant-derived antioxidants in Type 2 Diabetes Mellitus: Mechanisms, challenges, and considerations for special populations. Antioxidants. 2025;14:725. https://doi.org/10.3390/antiox14060725
38. Sanvee SCJ, Kombate B, Kantati YT, Kpoyizoun PK, Badjabaissi E, Assih M, Diallo A, Bakoma B. Phytochemistry, antihyperglycemic, antioxidant and anti-inflammatory Properties of *Uvaria Chamae* and *Sida linifolia* extracts: Potential implication in diabetic disease. Phcog J. 2024;16:582–590.