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IN SILICO MOLECULAR DOCKING STUDIES AND ADMET SCREENING OF THE PHYTOCONSTITUENTS URS-12-ENE AND NEOPHYTADIENE AS POTENTIAL ANTIDIABETIC AGENTS

M. Muthazhagi, P. Muthulakshmi, N. Nandhini, S. Narmatha, R. Naveen, R. Nirmala*

Department of Pharmaceutical Chemistry, Dhanalakshmi Srinivasan College of Pharmacy, Perambalur - 621212, Tamil Nadu, India.

***Corresponding Author: R. Nirmala**

Department of Pharmaceutical Chemistry, Dhanalakshmi Srinivasan College of Pharmacy, Perambalur - 621212, Tamil Nadu, India.

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ABSTRACT

Diabetes mellitus is a chronic metabolic disorder of global concern, with the number of affected individuals projected to rise from 590 million in 2025 to 853 million by 2050. Plant-derived phytoconstituents represent an attractive source of novel antidiabetic leads owing to their structural diversity and favourable safety profiles. In the present study, the binding interactions of two phytoconstituents, Urs-12-ene and Neophytadiene, were evaluated against two diabetes-associated targets, Glycogen Synthase Kinase-3 beta (GSK3-β; PDB ID: 7B6F) and Cholinesterase (PDB ID: 6QAB), using AutoDock Vina integrated within PyRx. Post-docking interaction analysis was carried out using BIOVIA Discovery Studio Visualizer, and drug-likeness and toxicity were predicted using SwissADME and pkCSM-based ADMET parameters. Urs-12-ene exhibited markedly stronger binding affinities than Neophytadiene against both targets, recording −8.1 kcal/mol against GSK3-β and −11.2 kcal/mol against cholinesterase, compared with −6.1 and −6.0 kcal/mol respectively for Neophytadiene. Both compounds satisfied most Lipinski drug-likeness criteria with a single lipophilicity violation and a bioavailability score of 0.55. Toxicity profiling revealed that Urs-12-ene was devoid of AMES mutagenicity, hepatotoxicity, hERG inhibition and skin sensitisation, whereas Neophytadiene showed predicted hERG II inhibition and skin sensitisation potential. These findings indicate that Urs-12-ene possesses favourable binding affinity, drug-likeness and safety characteristics, supporting its candidacy as a lead phytoconstituent for further antidiabetic drug development, pending experimental validation.

KEYWORDS: Molecular docking; ADMET; Urs-12-ene; Neophytadiene; GSK3-β; Cholinesterase; Diabetes mellitus; PyRx; AutoDock Vina.

1. INTRODUCTION

Computer-aided drug design (CADD) has become an indispensable tool in modern pharmaceutical research, reducing dependence on animal models while accelerating the identification of promising drug candidates.[1] Among the various in silico techniques, molecular docking is widely employed to predict the preferred orientation and binding affinity of a ligand within the active site of a target protein, thereby providing insight into the strength and nature of protein-ligand interactions.[2] PyRx, a virtual screening tool that integrates AutoDock Vina, enables efficient docking of multiple ligands against a target protein and ranks them according to binding energy.[3]

Docking studies find application across several domains of drug discovery, including virtual screening of compound libraries, lead optimisation, analysis of protein-protein interactions, toxicological risk assessment, and the investigation of bioactive natural products.[4,5] In particular, natural product research increasingly relies on docking to rationalise the

traditional use of medicinal plants and to identify novel bioactive constituents with therapeutic potential.[5] Docking models are generally interpreted within the framework of the lock-and-key model, the induced-fit theory, or the conformational ensemble model, each describing a different degree of conformational flexibility between ligand and receptor.[2]

Diabetes mellitus (DM) is a chronic metabolic disorder characterised by impaired insulin secretion, insulin resistance, or both, resulting in sustained hyperglycaemia.[6] Globally, the burden of DM has risen sharply, with the number of affected individuals increasing from 151 million in 2000 to an estimated 590 million in 2025, and projected to reach 853 million by 2050; currently 11.1% of adults aged 20-79 years live with the disease.[7] Persistent hyperglycaemia is associated with serious long-term complications, including diabetic nephropathy, neuropathy, retinopathy and cardiomyopathy.[6] Current pharmacotherapy includes biguanides, sulfonylureas, meglitinides, thiazolidinediones, alpha-glucosidase inhibitors, SGLT-2 inhibitors, DPP-4 inhibitors, GLP-1 receptor agonists, dopamine D2 agonists and amylin analogues, each acting through distinct molecular mechanisms to restore glycaemic control.[8,9]

Glycogen Synthase Kinase-3 beta (GSK3-β) is a serine/threonine kinase that negatively regulates insulin signalling; its inhibition enhances glycogen synthesis and improves insulin sensitivity, making it an attractive target for type-2 diabetes.[10] Cholinesterase enzymes, while traditionally associated with neurodegenerative disorders, have also been implicated in metabolic regulation and are increasingly explored as secondary targets in multi-target antidiabetic drug discovery.[10] Several phytochemical classes, including triterpenoids and diterpenes such as urs-12-en-24-oic acid derivatives and phytol-related compounds, have demonstrated promising binding affinities toward such diabetes-related targets in earlier in silico investigations.[11-20]

The present study was therefore undertaken to evaluate, through molecular docking and ADMET screening, the binding potential and pharmacokinetic suitability of two phytoconstituents, Urs-12-ene and Neophytadiene, against GSK3-β (PDB ID: 7B6F) and Cholinesterase (PDB ID: 6QAB), with a view to identifying potential lead molecules for further antidiabetic drug development.

2. MATERIALS AND METHODS

2.1 Selection of Target Proteins

The three-dimensional crystal structures of the target proteins GSK3-β (PDB ID: 7B6F) and Cholinesterase (PDB ID: 6QAB) were retrieved from the RCSB Protein Data Bank (http://www.rcsb.org). All co-crystallised water molecules, heteroatoms and bound ligands were removed prior to docking to prepare the receptor structures.

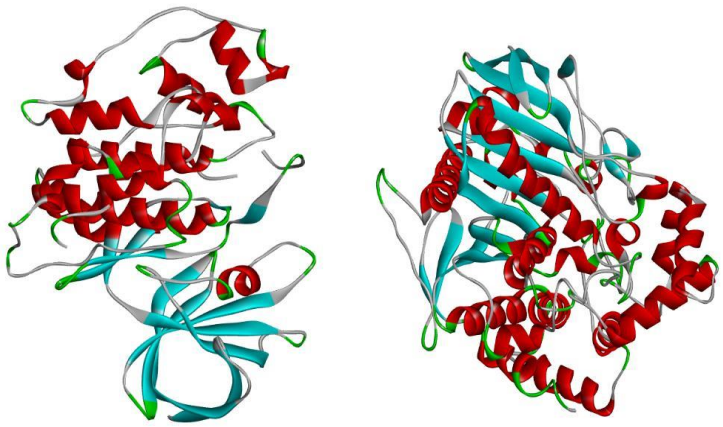

Fig. 1: Three-dimensional structures of (a) GSK3-β (PDB ID: 7B6F) and (b) Cholinesterase (PDB ID: 6QAB).

2.2 Selection and Preparation of Ligands

The three-dimensional structures of the phytoconstituents Urs-12-ene and Neophytadiene were obtained in structure data file (SDF) format from the PubChem compound database. Ligand structures were energy-minimised and converted to the required input format prior to docking.

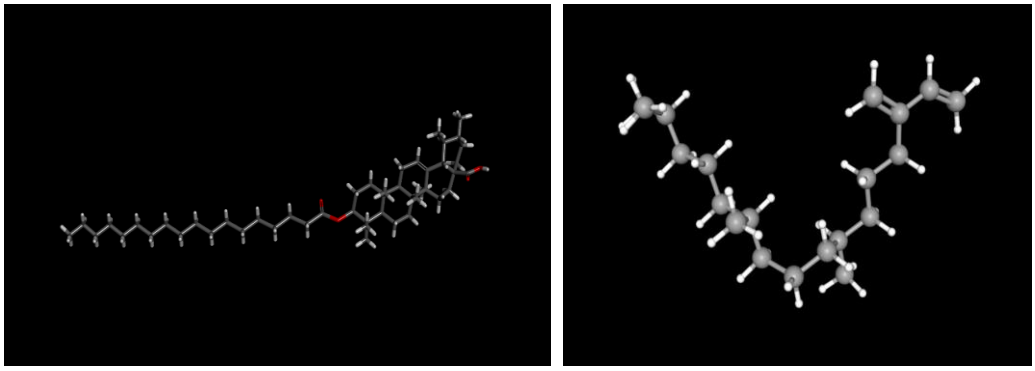

Fig. 2: Three-dimensional structures of (a) Urs-12-ene and (b) Neophytadiene (PubChem).

2.3 Molecular Docking Procedure Using PyRx

Molecular docking was performed using PyRx (version 0.8), which integrates AutoDock Vina as its docking engine. The protein and ligand molecules were imported into the PyRx workspace via the 'File → Load Molecule' option. Both receptor and ligand structures were subsequently converted to the AutoDock-compatible PDBQT format: the protein was processed using 'AutoDock → Make Macromolecule' and each ligand using 'AutoDock → Make Ligand'. A grid box was defined around the active/binding site of each target protein using the Vina Wizard, with grid parameters adjusted to enclose all relevant active-site residues. Docking was executed with an appropriate exhaustiveness setting, and AutoDock Vina generated multiple binding poses ranked by binding affinity (kcal/mol). The pose with the lowest (most negative) binding energy for each ligand-protein pair was selected for further analysis.

2.4 Post-Docking Interaction Analysis

The lowest-energy docked complexes obtained from PyRx were imported into BIOVIA Discovery Studio Visualizer for detailed interaction analysis. Both 3D and 2D interaction diagrams were generated to examine ligand orientation within the binding pocket. Amino acid residues located within 4-5 Å of the ligand were identified, and intermolecular interactions, including hydrogen bonds, hydrophobic (alkyl and π-alkyl) contacts and van der Waals forces, were catalogued along with the participating residues.

2.5 Drug-Likeness and ADMET Prediction

The drug-likeness of both phytoconstituents was evaluated according to Lipinski's Rule of Five, which considers molecular weight (≤500 Da), lipophilicity (Log P ≤5), hydrogen bond donors (≤5) and hydrogen bond acceptors (≤10) as predictors of oral bioavailability. ADMET (Absorption, Distribution, Metabolism, Excretion and Toxicity) properties, including AMES mutagenicity, hERG I/II inhibition, oral rat acute and chronic toxicity, hepatotoxicity, skin sensitisation, and aquatic toxicity (T. pyriformis and minnow), were predicted using established in silico ADMET prediction platforms.

3. RESULTS AND DISCUSSION

3.1 Binding Affinity of Phytoconstituents

The docking scores obtained for Urs-12-ene and Neophytadiene against GSK3-β (7B6F) and Cholinesterase (6QAB) are summarised in Table 1. Against GSK3-β, Urs-12-ene exhibited a binding affinity of −8.1 kcal/mol compared with −6.1 kcal/mol for Neophytadiene, indicating a substantially stronger and more stable interaction within the catalytic pocket. Since inhibition of GSK3-β enhances insulin signalling and glycogen synthesis, this finding suggests that Urs-12-ene may possess greater potential as a GSK3-β-targeted antidiabetic agent.

An even more pronounced difference was observed against Cholinesterase (6QAB), where Urs-12-ene recorded a binding affinity of −11.2 kcal/mol, indicative of a highly stable protein-ligand complex, whereas Neophytadiene showed a comparatively moderate affinity of −6.0 kcal/mol. The superior affinity of Urs-12-ene toward 6QAB is likely attributable to extensive hydrophobic and van der Waals contacts within the active-site pocket, consistent with the non-polar, multi-ring triterpenoid skeleton of the molecule. Notably, docking scores more negative than −7.0 kcal/mol are generally regarded in the literature as indicative of biologically relevant binding.[11-13]

For both ligand-protein complexes, the lowest-energy poses returned RMSD upper- and lower-bound values of 0.0 Å, confirming that the selected conformations represent stable, reproducible binding orientations rather than artefacts of pose variability.

Table 1: Molecular docking results of Urs-12-ene and Neophytadiene against GSK3-β (7B6F) and Cholinesterase (6QAB)

Ligand	Target Protein (PDB ID)	Binding Affinity (kcal/mol)	RMSD/ub (Å)	RMSD/lb (Å)
Urs-12-ene	GSK3-β (7B6F)	−8.1	0.0	0.0
Neophytadiene	GSK3-β (7B6F)	−6.1	0.0	0.0
Urs-12-ene	Cholinesterase (6QAB)	−11.2	0.0	0.0
Neophytadiene	Cholinesterase (6QAB)	−6.0	0.0	0.0

3.2 Protein-Ligand Interaction Profiling

Interaction analysis using Discovery Studio Visualizer revealed that the binding of Urs-12-ene within the GSK3-β active site was stabilised predominantly through van der Waals contacts and alkyl interactions involving residues PRO346, LYS349, ASP355, THR356, ALA358, LEU359, PHE360, ASN361, PRO357, HIS381 and ALA382. In the Cholinesterase (6QAB) complex, Urs-12-ene formed van der Waals, π-sigma, alkyl and π-alkyl interactions with residues including TRP82, ALA328, ASP70, TYR332, TRP430, MET437, HIS438 and TYR440, reflecting extensive hydrophobic burial of the triterpenoid scaffold within the binding cleft.

Neophytadiene, in contrast, displayed a more diffuse network of van der Waals and alkyl/π-alkyl interactions with a larger number of peripheral residues in both targets, but with fewer high-strength contacts, consistent with its weaker overall binding affinities. The dominance of hydrophobic interactions for both ligands is consistent with the non-polar character of the triterpenoid and diterpene scaffolds, which lack hydrogen bond donor or acceptor groups (Table 2).

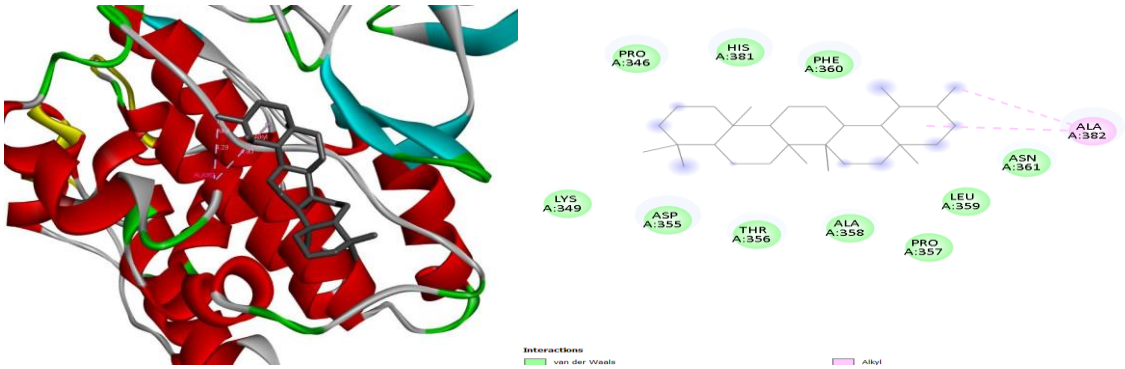

Fig. 3: Docking pose and 2D interaction diagram of Urs-12-ene with GSK3-β (7B6F).

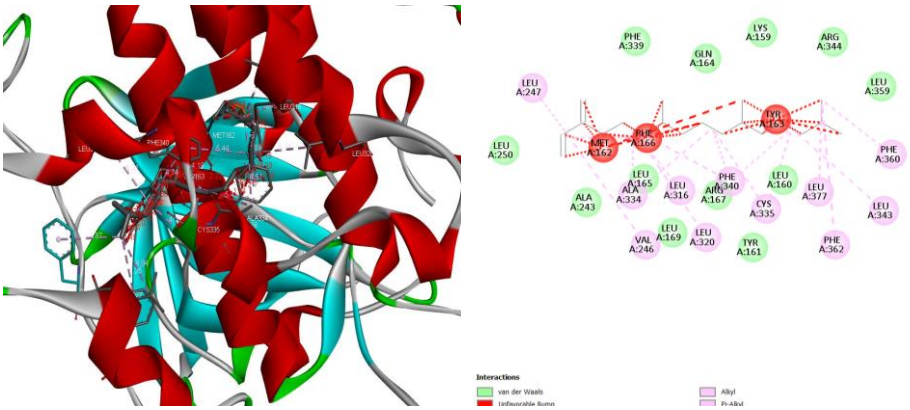

Fig. 4: Docking pose and 2D interaction diagram of Neophytadiene with GSK3-β (7B6F).

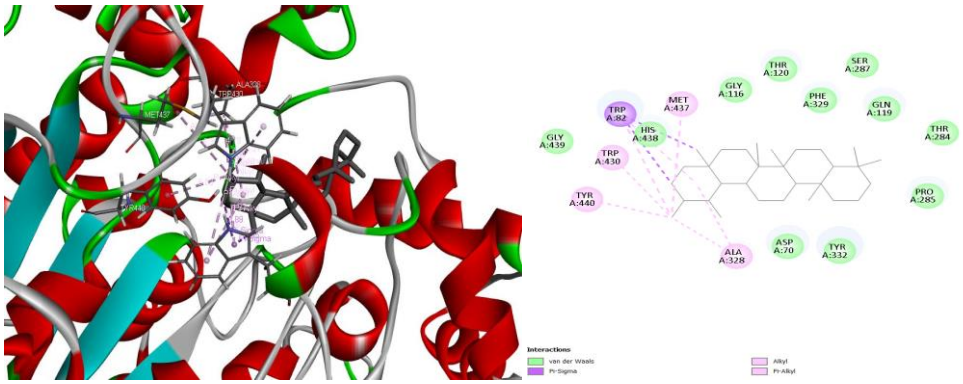

Fig. 5: Docking pose and 2D interaction diagram of Urs-12-ene with Cholinesterase (6QAB)

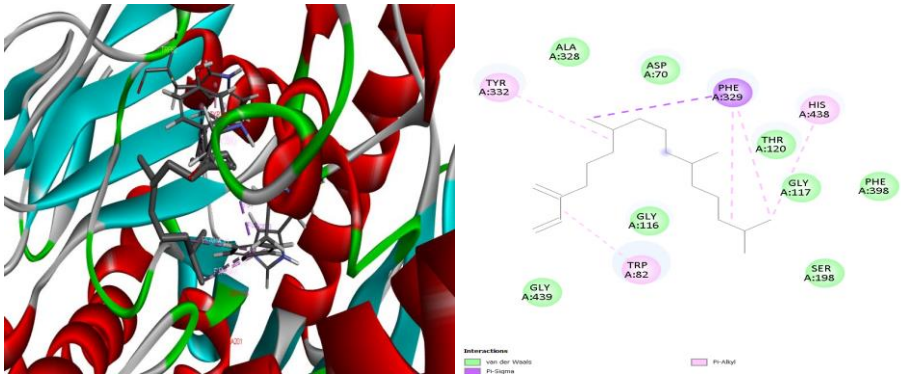

Fig. 6: Docking pose and 2D interaction diagram of Neophytadiene with Cholinesterase (6QAB).

3.3 Drug-Likeness Evaluation

Drug-likeness was assessed according to Lipinski's Rule of Five, the results of which are presented in Table 2. Urs-12-ene (molecular weight 410.72 Da) and Neophytadiene (molecular weight 278.52 Da) both satisfied the molecular weight criterion (≤500 Da) and showed zero hydrogen bond donors and acceptors. Both compounds, however, exceeded the recommended lipophilicity threshold (Log Po/w ≤5), recording values of 5.00 and 5.05 respectively, representing the sole Lipinski violation for each molecule. Neophytadiene additionally exceeded the rotatable bond limit (13 vs. ≤10). Both compounds returned an identical bioavailability score of 0.55, suggesting moderate oral absorption potential despite their lipophilic character.

Table 2: Drug-likeness (Lipinski) parameters of Urs-12-ene and Neophytadiene.

Parameter	Urs-12-ene	Neophytadiene	Reference Value
Molecular weight (Da)	410.72	278.52	≤ 500
Rotatable bonds	0	13	≤ 10
H-bond acceptors	0	0	≤ 10
H-bond donors	0	0	≤ 5
Lipophilicity (Log Po/w)	5.00	5.05	≤ 5
Water solubility (Log S, Ali)	−10.49	−9.53	–
Lipinski violations	1 (Log P)	1 (Log P)	0 preferred
Bioavailability score	0.55	0.55	–
Leadlikeness violations	No	No	–

3.4 Toxicity (ADMET) Profile

Predicted toxicity parameters for both compounds are summarised in Table 3. Urs-12-ene demonstrated a favourable safety profile, with negative predictions for AMES mutagenicity, hERG I and hERG II inhibition, hepatotoxicity and skin sensitisation. Its predicted oral rat acute toxicity (LD50) of 2.206 mol/kg and chronic toxicity (LOAEL) of 2.981 log mg/kg bw/day further support a relatively low acute and chronic toxicity risk. Neophytadiene, while also AMES-negative and non-

hepatotoxic, was predicted to inhibit the hERG II channel and to possess skin sensitisation potential, with lower LD50 (1.473 mol/kg) and LOAEL (1.158 log mg/kg bw/day) values, indicating comparatively higher toxicity risk. Both compounds showed measurable aquatic toxicity toward T. pyriformis and fathead minnow, with Neophytadiene displaying the higher predicted aquatic toxicity of the two.

Table 3: Predicted ADMET/toxicity parameters of Urs-12-ene and Neophytadiene.

Toxicity Endpoint	Urs-12-ene	Neophytadiene	Unit
AMES toxicity	No	No	Yes/No
Max. tolerated dose	0.302	0.272	log mg/kg/day
hERG I inhibitor	No	No	Yes/No
hERG II inhibitor	No	Yes	Yes/No
Oral rat acute toxicity (LD50)	2.206	1.473	mol/kg
Oral rat chronic toxicity (LOAEL)	2.981	1.158	log mg/kg_bw/day
Hepatotoxicity	No	No	Yes/No
Skin sensitisation	No	Yes	Yes/No
T. pyriformis toxicity	0.285	1.65	log µg/L
Minnow toxicity	−7.077	−2.039	log mM

3.5 Overall Interpretation

Taken together, the docking and ADMET data indicate that Urs-12-ene consistently outperformed Neophytadiene across both target proteins, exhibiting more negative binding energies (−8.1 and −11.2 kcal/mol versus −6.1 and −6.0 kcal/mol), a larger number of stabilising hydrophobic interactions with key active-site residues, and a more favourable predicted toxicity profile (absence of hERG II inhibition, skin sensitisation and lower aquatic toxicity). The particularly strong affinity of Urs-12-ene for Cholinesterase (−11.2 kcal/mol) suggests that, beyond its action on GSK3-β-mediated insulin signalling, this compound may also engage secondary targets relevant to metabolic regulation, supporting a potential multi-target mechanism of action. While both phytoconstituents share a single Lipinski violation related to high lipophilicity, this is a common feature of terpenoid natural products and does not preclude further pharmacological development. Collectively, these findings position Urs-12-ene as the more promising candidate of the two for progression toward in vitro enzyme inhibition assays and in vivo antidiabetic evaluation.

4. CONCLUSION

The present in silico study evaluated the molecular docking and ADMET properties of the phytoconstituents Urs-12-ene and Neophytadiene against the diabetes-associated target proteins GSK3-β (7B6F) and Cholinesterase (6QAB) using PyRx/AutoDock Vina and BIOVIA Discovery Studio. Urs-12-ene displayed superior binding affinities toward both targets (−8.1 kcal/mol and −11.2 kcal/mol, respectively), formed more extensive stabilising interactions with key active-site residues, and exhibited a more favourable drug-likeness and toxicity profile compared with Neophytadiene. These results suggest that Urs-12-ene may serve as a promising lead phytoconstituent for the development of novel antidiabetic agents acting through inhibition of GSK3-β and/or cholinesterase. Further molecular dynamics simulations together with in vitro enzyme inhibition assays and in vivo studies are warranted to validate the therapeutic potential of Urs-12-ene as identified in this study.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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