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Article

In Silico Study of Phytochemical Compound from Kluwih (*Artocarpus camansi*) Leaves as Potential Candidate for Antidiabetic Targeting Aldose Reductase

Dinah Umaimah Radani, Ignasia Anindya Pintagratia, Anindya Nursanti Syaiful, Fahri Renaldi, Fachrizal Dwi Kautsar, Dhania Novitasari*

Department of Pharmaceutical Analysis and Medicinal Chemistry, Faculty of Pharmacy, Padjadjaran University, West Java 45363, Indonesia
* Correspondence: dhania@unpad.ac.id

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Abstract

Diabetes Mellitus (DM) is a disease characterized by increased blood glucose levels. The most common type of diabetes is type 2 diabetes mellitus. Aldose Reductase is an enzyme that works in the polyol pathway. The polyol pathway is the pathway where glucose is metabolized by aldose reductase into sorbitol. The end result of this polyol pathway will accumulate in the tissue so that there is a disruption of the osmolarity of the basal membrane which can cause complications of diabetes mellitus. Therefore, the activity of the aldose reductase enzyme must be inhibited, one of which is using chemical compounds so that complications such as cataracts do not occur. Tests conducted in this study include Lipinski's RO5, ADMETox, pharmacophore screening, and molecular docking. From the test results, it was found that the most potential compound in treating Diabetes Mellitus is Cycloartenol Acetate.

Keywords: Aldose Reductase, *Artocarpus camansi*, Diabetes Mellitus.

1. INTRODUCTION

Diabetes mellitus (DM) is a condition in which the body cannot produce insulin hormone normally according to need. The body also cannot optimally utilize the insulin produced, causing blood sugar levels to spike above normal [1]. DM treatment can use drugs that inhibit the aldose reductase enzyme, which has the PDB code 2HV5. Aldose reductase is an enzyme that functions to regulate glucose metabolism in the polyol pathway, which is responsible for the formation of

fructose and glucose [2]. Diabetic patients can experience cataract complications due to increased aldose reductase activity in the polyol pathway, leading to increased sorbitol production and accumulation in the intracellular space. The drug used as a comparison in this study is Zopolrestat.

Plants have become the main source of alternative medicines in the health sector because synthetic chemical drugs cause several side effects [3]. Traditional medicine using natural ingredients is one of the alternative treatments for diabetes mellitus; one example is the kluwih leaf. Kluwih leaves (*Artocarpus camansi*) are one example of a medicinal plant that has been evaluated for its potential as a therapeutic agent for people with diabetes [4]. Kluwih leaves are a traditional medicinal plant that is efficacious as an antidiabetic drug. Kluwih leaves contain several bioactive compounds that have been successfully identified. The compounds contained in kluwih leaves include chalcone, flavone, flavonol, lupeol, luteolin, and others [5]. The purpose of this study was to examine the potential of kluwih leaves (*Artocarpus camansi*), which contain compounds that could serve as an alternative treatment for Diabetes Mellitus.

2. MATERIALS AND METHODS

2.1. Lipinski Rule of Five Prediction

The chemical structure of the test compound was obtained from the PubChem database and extracted as a SMILES string. Furthermore, the structural information was entered into the Property Calculator feature of the MCule website to obtain parameters such as molecular weight, logP value, number of hydrogen bond donors, and acceptors. This data was used to evaluate the suitability of the compound to the Lipinski's Rule of Five criteria, which reflects the potential suitability of the compound for oral administration, namely no more than one violation of the rules: MW $\leq$ 500 Da, logP $\leq$ 5, H-bond donor $\leq$ 5, and H-bond acceptor $\leq$ 10 [6].

2.2. ADMET Prediction

Evaluation of ADME parameters and toxicity was carried out using the Pre-ADMET web-based platform. The previously obtained molecular structure of the compound was converted to .mol format. through the ADME Prediction and Toxicity Prediction features. From the prediction, comprehensive information is obtained regarding the absorption, distribution, metabolism, excretion, and toxic potential of the analyzed test compound, including predictions of human intestinal absorption, blood-brain barrier penetration, P-gp substrate, CYP450 inhibition, and potential mutagenicity and carcinogenicity. The results are stored and analyzed to evaluate the compound's safety and potential as a drug [6]..

2.3. Geometry Optimization

The SMILES structure of the test compound was imported into Chem3D Pro 12.0 to generate a 3D model. The structure optimization process was carried out using the Minimize Energy feature, with the Root Mean Square (RMS) Gradient threshold set to 0.010. After the optimization was complete, the 3D structure of the compound was saved in several file formats: .mol, .sdf, and .pdb for use in the next docking stage.

2.4. Pharmacophore Modelling

Modeling was performed using LigandScout v4.4.5. The active and decoy compound databases were obtained from the DUDE website, then entered into Ligand-Based Perspective. All molecules in the database were set as "training", then saved as .ldb files. Furthermore, the test compound database was imported and set as "test" in the same format.

The modeling process began by creating clusters of active compounds, and one molecule was selected from each cluster as a representative. Pharmacophore models (1–10) were created and copied to the Screening Perspective for validation by comparing active and decoy compounds using ROC curves. The model with the best Area Under the Curve (AUC) value was used to screen test compounds and identify those with high activity potential (hit compounds) [7].

2.5. Molecular Docking

The target protein (ALDR, PDB ID: 2HV5) was downloaded from RCSB PDB and prepared in BIOVIA Discovery Studio 2020 to remove natural ligands and add polar hydrogens. The receptor was then optimized in AutoDock with

Kollman charges and saved as a .pdbqt file. Test compounds were also processed with hydrogen additions, Gasteiger charges, and torsion settings. Validation was performed by redocking the natural ligand using grid box settings: size (X = 40, Y = 40, Z = 36) and center coordinates (X = 2.757; Y = 24.31; Z = 16.335) with a distance between points of 0.375 Å. Molecular docking was performed in the Command Prompt using autogrid4.exe and autodock4.exe. The genetic algorithm parameters were set to 100 runs. The results, in the form of binding energies and inhibition constants, were further analyzed quantitatively and visualized in 2D and 3D using BIOVIA Discovery Studio to enhance the depiction of binding interactions [8].

3. RESULT

3.1. Lipinski's Rule of Five

Lipinski's Rule of Five (Ro5) has been a widely used guideline for nearly two decades to evaluate drug-like properties, particularly for predicting the oral bioavailability of compounds based on key physicochemical parameters. According to Ro5, a molecule is more likely to exhibit favorable absorption, distribution, metabolism, and excretion (ADME) if it adheres to the following criteria: molecular weight (MW) below 500 Da, a lipophilicity (LogP) value under 5, no more than 5 hydrogen bond donors (HBD), and fewer than 10 hydrogen bond acceptors (HBA) [9].

Table 1. Lipinski's RO5 Results

Compound Name	Molecular Weight (< 500 Da)	Log P (<5)	Hydrogen Bond		Explanation
			Donor (< 5)	Acceptor (< 10)	
Friedelinol	428.73 g/mol	10.08	1	1	Fullfil Requirement
Squalene	396.68 g/mol	10.21	0	0	Fullfil Requirement
B-sitosterol	414.71 g/mol	9.34	1	1	Fullfil Requirement
Stigmasterol	412.69 g/mol	8.56	1	1	Fullfil Requirement
Phytol	296.53 g/mol	8.19	1	1	Fullfil Requirement
chalcone	208.26 g/mol	3.08	0	1	Fullfil Requirement
Cycloartenol	426.72 g/mol	9.78	1	1	Fullfil Requirement
Cycloartenol Acetate	468.75 g/mol	10.35	0	2	Fullfil Requirement
Flavonol	238.24 g/mol	3.40	1	3	Fullfil Requirement
Flavanon	224.25 g/mol	3.14	0	2	Fullfil Requirement
Xanthone	196.20 g/mol	3.39	0	2	Fullfil Requirement
Luteolin	286.24 g/mol	2.53	4	6	Fullfil Requirement
Lupeol	426.72 g/mol	9.87	1	1	Fullfil Requirement
Triterpenoid	552.76 g/mol	5.88	3	7	Fullfil Requirement

Based on the data results of Ro5 in Table 1. Data has shown that fulfilling the requirement with a few small non-compliant results yields Ro5. Notably, most sterols and terpenoids, including Friedelinol, Squalene, and B-sitosterol, have LogP values that significantly exceed the limit (ranging from 8.19 to 10.35), suggesting poor aqueous solubility and a high likelihood of off-target tissue accumulation. Additionally, the Triterpenoid violates the MW threshold at 552.76 Da, potentially hindering its membrane permeability. While some compounds, such as Chalcone and Luteolin, fully comply with Ro5, others, like those that are within 5 HBDs, are borderline cases that may still face bioavailability challenges. These discrepancies highlight the importance of accurate Ro5 assessment, as mislabeling non-compliant compounds could lead to unrealistic expectations in early drug discovery, particularly for natural products that often deviate from traditional drug-like properties. For such molecules, alternative administration may need to be considered.

3.2 ADMET Prediction

Developing a new drug typically takes 10 years and costs $1.1 billion, with many candidates failing in clinical trials due to poor pharmacokinetics (PK) or toxicity. To reduce these risks, computational methods are now widely used to predict ADMET (absorption, distribution, metabolism, excretion, and toxicity) and other key physicochemical properties early in the discovery process. These tools help prioritize safer, more drug-like molecules before costly clinical testing begins [10].

Table 2. ADMET Prediction Results

Compound Name	Absorption		Distribution		Toxicity	
	HIA (%)	Caco-2 (nm/sec)	PPB (%)	BBB	Mutagen	Carcinogen
Friedelinol	100.000000	46.84	100.000000	22.32	Non-Mutagen	Carcino_Mouse: (-) Carcino_Rat: (+)
Squalene	100.000000	23.40	100.000000	27.46	Mutagen	Carcino_Mouse: (+) Carcino_Rat: (+)
B-sitosterol	100.000000	52.37	100.000000	19.88	Non-Mutagen	Carcino_Mouse: (+) Carcino_Rat: (-)
Stigmasterol	100.000000	52.33	100.000000	19.89	Non-Mutagen	Carcino_Mouse: (+) Carcino_Rat: (+)
Phytol	100.000000	37.62	100.000000	19.07	Non-Mutagen	Carcino_Mouse: (+) Carcino_Rat: (-)
Chalcone	100.000000	54.59	94.83	1.51	Mutagen	Carcino_Mouse: (-) Carcino_Rat: (-)
Cycloartenol	100.000000	50.02	100.000000	20.37	Non-Mutagen	Carcino_Mouse: (+) Carcino_Rat: (+)
Cycloartenol Acetate	100.000000	53.38	100.000000	19.36	Non-Mutagen	Carcino_Mouse: (+) Carcino_Rat: (+)
Flavonol	95.33	32.26	86.59	0.79	Mutagen	Carcino_Mouse: (-) Carcino_Rat: (+)
Flavanon	100.000000	55.82	92.34	2.24	Mutagen	Carcino_Mouse: (+) Carcino_Rat: (+)
Xanthone	100.000000	53.25	100.000000	2.37	Mutagen	Carcino_Mouse: (+) Carcino_Rat: (+)
Luteolin	79.42	4.539	99.71	0.36	Mutagen	Carcino_Mouse: (-) Carcino_Rat: (+)
Lupeol	100.000000	47.17	100.000000	22.71	Mutagen	Carcino_Mouse: (-) Carcino_Rat: (+)
Triterpenoid	95.34	8.627	90.46	0.02	Non-Mutagen	Carcino_Mouse: (+) Carcino_Rat: (+)

Absorption parameters shown in Table 2 demonstrate that most compounds have excellent human intestinal absorption (HIA > 95%), indicating strong potential for oral bioavailability. Notable exceptions include Luteolin (79.4% HIA), which may face absorption limitations due to its polarity. Caco-2 permeability data further support these trends, with compounds like Chalcone (54.6 nm/sec) and Flavanon (55.8 nm/sec) showing high permeability, while Luteolin (4.5 nm/sec) and Triterpenoid (8.6 nm/sec) exhibit lower permeability, likely due to their larger size or polar nature.

Plasma protein binding (PPB) is notably high (>90%) for sterols and terpenoids such as Friedelinol, Squalene, and Lupeol, suggesting these compounds may require higher doses to achieve therapeutic effects due to reduced free drug availability. Blood-brain barrier (BBB) penetration is significant for lipophilic compounds like Friedelinol (22.3) and Squalene (27.5), indicating potential CNS activity or neurotoxicity risks. Conversely, polar compounds such as Luteolin (0.37) are unlikely to cross the BBB, thereby minimizing CNS-related side effects.

Mutagenicity is a concern for several compounds, including Squalene, Chalcone, Flavonol, and Luteolin, which are flagged as mutagens. These findings suggest potential genotoxic risks warranting further investigation. Carcinogenicity data reveal mixed results, with some compounds like Squalene showing positive carcinogenic effects in both mice and rats. In contrast, others, such as Chalcone and Phytol, are negative in one or both species. These discrepancies highlight the importance of species-specific toxicity studies.

3.3. Pharmacophore Screening

The next stage involved pharmacophore modeling to analyze structural similarities between test compounds and reference ligands. Ten pharmacophore models were generated and validated using 100 active compounds and 400 decoys, with performance evaluated using ROC curve analysis and AUC.

From this screening, Model 6 emerged as the top performer, demonstrating superior discriminatory power with 432 hits. Outperforming other models, including Model 8 (429 hits) and Model 5 (429 hits). Two compounds showed particularly strong pharmacophore alignment: Cycloartenol Acetate (Fit Score: 36.61) and Xanthone (Fit Score: 36.55). The consistent hit rates across models (429-432 hits) confirm the reliability of the screening approach.

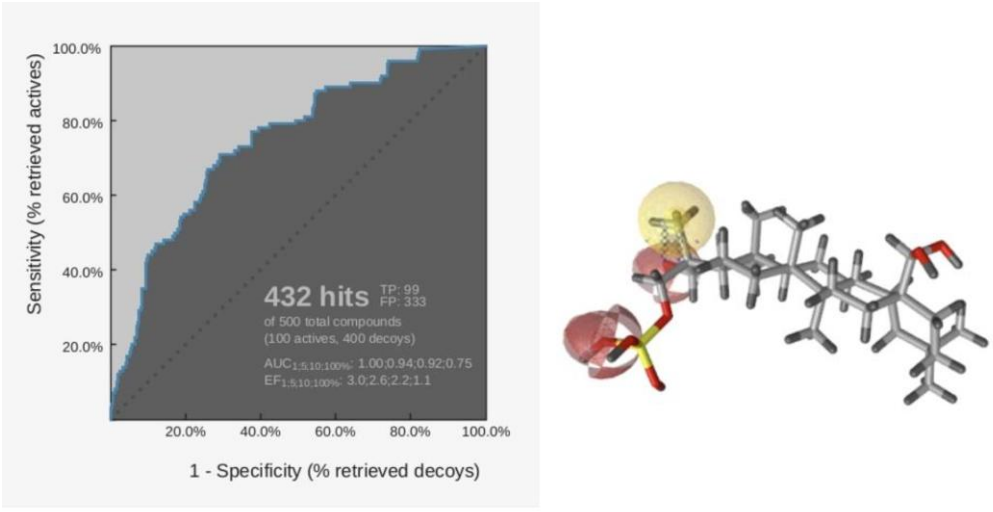

Figure 1. (A) Best Pharmacophore Modeling Results of Validation, (B) Pharmacophore Model Screening Results of Cycloartenol Acetate

3.4. Molecular Docking

The final stage of this in silico study involved molecular docking simulations to investigate interactions between bioactive compounds from kluwih leaves (*Artocarpus camansi*) and the aldose reductase (ALR2) enzyme target. Using a validated

grid box configuration with RMSD ≤2 Å, we maintained consistent docking parameters for all test compounds to ensure reliable comparison of binding interactions. The simulations revealed several Kluwih Leaves derivatives that demonstrated significant binding affinity for ALR2's active site, particularly by interacting with key catalytic residues, including CYS 298, TRP 111, and THR 113.

Notable compounds such as B-sitosterol exhibited exceptional binding energy (-12.43 kcal/mol) and remarkably low inhibition constant (Ki = 0.000774 μM), forming crucial hydrogen bonds with CYS 303 and extensive van der Waals interactions with surrounding residues. Other promising compounds included cycloartenol acetate (-10.81 kcal/mol, Ki = 0.01188 μM), which interacted with THR 113, and stigmasterol (-11.45 kcal/mol, Ki = 0.00407 μM), binding to VAL 47. These interactions were comparable to or better than the reference drug Zopolrestat.

The molecular visualizations, generated using BIOVIA Discovery Studio 2020, clearly demonstrated how these natural compounds occupy the enzyme's active site while maintaining favorable interactions with surrounding hydrophobic pockets. Particularly interesting was B-sitosterol's exceptional binding performance through both specific hydrogen bonding and extensive hydrophobic contacts, suggesting a potent and stable inhibition mechanism. These findings highlight Kluwih Leaves as a promising source of novel ALR2 inhibitors that could potentially be developed for managing diabetic complications.

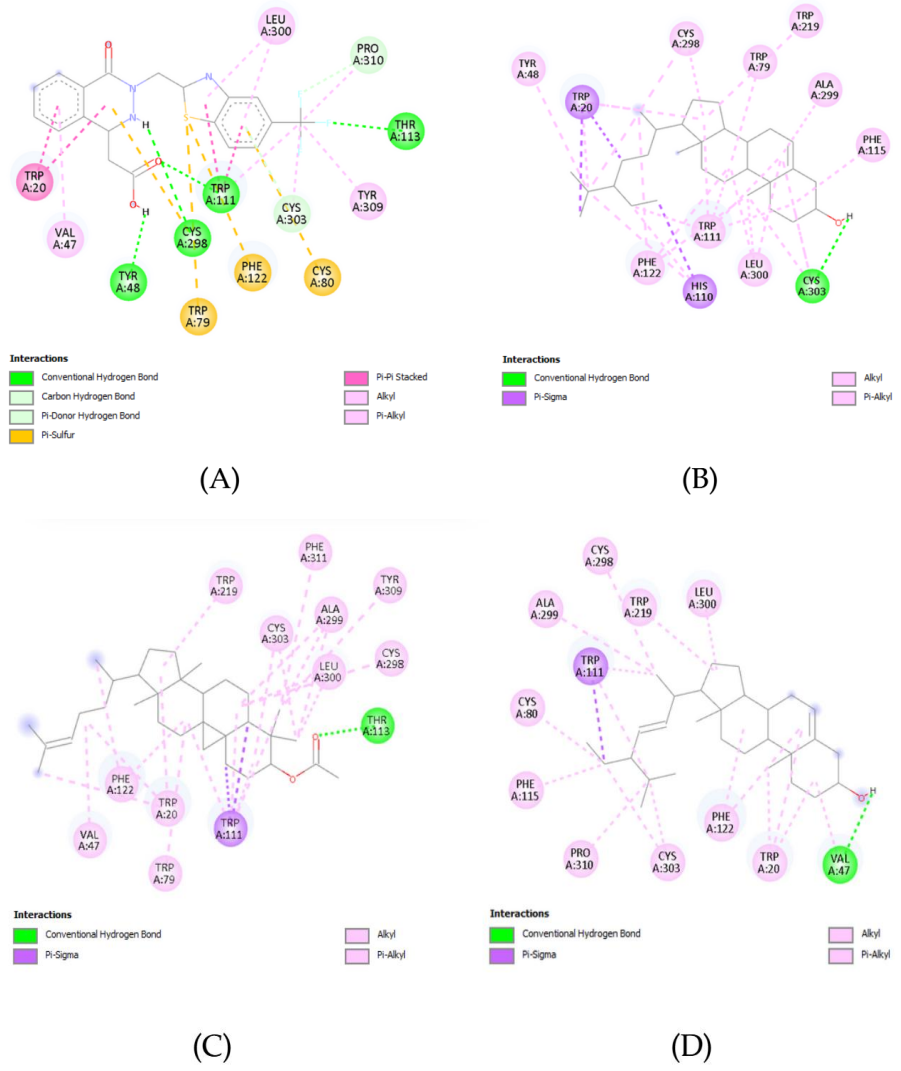

Figure 2. 2D Visualization of Zopolrestat (A), B-Sitosterol (B), Cycloartenol Acetate (C), and Stigmasterol (D)

Table 3. Molecular Docking Results

Compound Name	Binding Energy (kkal/mol)	Ki (μM)	Interaction with Amino Acids		
			Hydrogen Bond	Van der Waals	Ikatan Lainnya
Ligan Alami	-6.45	18.56	CYS 298, TRP 111, THR 113, CYS 303, PRO 310	-	HIS 110, LYS 77, CYS 80, TRP 79, PHE 122, TYR 48, VAL 47, LEU 300, TYR 309, TRP 20
Zopolrestat	-11.0	0.008	TRP111, CYS298, TYR48, THR113, CYS303, PRO310	-	TRP20, VAL47, TRP79, PHE122, CYS80, TYR309, LEU300
Flavonol	-8.55	0.53	THR 113, CYS 80, CYS 303	-	PHE 122, TRP 111, LEU 300, ALA 299, PRO 310
B-sitosterol	-12.43	0.0007	CYS 303	-	TYR 48, TRP 20, CYS 298, TRP 219, TRP 79, ALA 299, PHE 115, TRP 111, PHE 122, HIS 110, LEU 300
Chalcone	-8.16	1.04	CYS 303	-	TRP 111, CYS 298
Cycloartenol	-10.38	0.02	-	-	PHE 122, VAL 47, LEU 300, ALA 299, TYR 48, HIS 110, TRP 20, TRP 79, TRP 111, TRP 219, CYS 298, CYS 303, PHE 311, PRO 310, TYR 309
Cycloartenol acetate	-10.81	0,01	THR 113	-	PHE 311, TYR 309, TRP 219, ALA 299, CYS 303, LEU 300, CYS 298, TRP 111, TRP 20, PHE 122, TRP 79, VAL 47
Flavanone	-8.83	0.33	CYS 80, THR 113	-	TRP 111, PHE 122, LEU 300, ALA 299, CYS 303
Friedelinol	-8.36	0.74	PRO 310	-	TRP 111, VAL 47, LEU 300, ALA 299, TYR 48, TRP 20, TRP 79, TRP 111, TRP 219, CYS 298, CYS 303, PHE 122, PHE 311, TYR 309
Lupeol	-8.25	0.89	-	-	PRO 218, LEU 300, TRP 219, TRP 20, TRP 111, TRP 79, TYR 48, VAL 47
Luteolin	-8.22	0.94	LEU 300, CYS 303, CYS 80	-	ALA 299, TRP 111, PHE 122
Phytol	-9.11	0.21	LEU 300	-	CYS 303, TRP 219, CYS 298, TRP 111, PHE 122, VAL 47,

					TYR 48, TRP 20, HIS 110, TYR 209
Squelene	-10.69	0.01	-	-	TRP 111, VAL 47, LEU 300, ALA 299, TYR 48, TRP 20, TRP 219, CYS 298, CYS 303, PHE 122, TYR 309, PRO 310, PRO 112, TYR 209, HIS 110
Stigmasterol	-11.45	0.004	VAL 47	-	TRP 111, TRP 20, TRP 219, LEU 300, ALA 299, PHE 122, PRO 310, CYS 303, CYS 298, CYS 80, PHE 115
Triterpenoid	1.43	-	TRP 111	-	TRP 20, TRP 219, LEU 300, CYS 298, HIS 110, TYR 209, PHE 122, UNN 0
Xanthone	-8.24	0.91	-	-	TRP 111, CYS 303, LEU 300

4. DISCUSSION

This study employed rigorous molecular docking simulations to evaluate potential ALR2 inhibitors, using Zopolrestat as the reference drug. The docking protocol utilized an optimized grid box configuration centered at coordinates X=17.247, Y=-6.715, Z=13.582 with dimensions of 40×40×40 points and a fine spacing of 0.375 Å, generating 68,92 grid points to ensure comprehensive mapping of the enzyme's active site while maintaining computational efficiency. The molecular docking results demonstrate several natural compounds exhibit superior binding to aldose reductase (ALR2) compared to the native ligand (-6.45 kcal/mol, Ki=18.56 μM) and the reference drug Zopolrestat. B-sitosterol emerged as the most potent inhibitor, with a remarkable binding energy (-12.43 kcal/mol) and an exceptionally low Ki (0.0007 μM), forming a hydrogen bond with CYS 303 and extensive van der Waals interactions with multiple residues, including TRP 111 and LEU 300.

Other promising compounds include cycloartenol acetate (-10.81 kcal/mol, Ki=0.011μM), which binds THR 113, and stigmasterol (-11.45 kcal/mol, Ki=0.004 μM) interacting with VAL 47. Squalene also showed strong binding (-10.69 kcal/mol, Ki=0.01μM) through hydrophobic interactions. These results suggest these natural compounds may serve as effective ALR2 inhibitors, potentially offering improved therapeutic options for diabetic complications. The comprehensive interaction profiles reveal how each compound engages distinct residues within the ALR2 active site, with B-sitosterol exhibiting particularly extensive contacts that likely contribute to its exceptional binding affinity. These findings warrant further investigation into the potential of these compounds as novel antidiabetic agents targeting aldose reductase.

Based on research conducted on the aldose reductase receptor, hydrogen bonds involving residues CYS298 and HIS110 are key indicators of aldose reductase receptor inhibition [11]. In addition, the stability of the ligand bond is also increasingly strengthened by the presence of PHE112, TRP111, ALA299, and TYR209 residue bonds. In the molecular docking test that has been carried out, both zopolrestat and native ligands have hydrogen bonds with fairly similar residues, consisting of CYS298, TRP111, THR113, CYS303, and PRO310 [12]. These results indicate that these five residues are key residues in inhibiting the aldose reductase receptor. From the tests that have been conducted on 14 compounds in Kluwih Leaf plants, the cycloartenol acetate compound is the most potential compound in inhibiting aldose reductase when compared to zopolrestat and native ligands. The compound has one hydrogen bond to the same residue as the comparator, namely THR113. Then, the presence of PHE112, ALA229, TYR209, CYS289, and CYS303 also helps

stabilize and strengthen the bonds formed. In addition to the bond factor with the residues formed, the inhibition constant and free bond energy of the cycloartenol acetate compound are also quite close to those of zopolrestat and even exceed those of natural ligands. The cycloartenol acetate compound also has a fit score distinct from that of xanthone, indicating that its shape and chemical features are suitable for aldose reductase. In the Lipinski RO5 profile, cycloartenol acetate has 1 violation, namely the LogP (Lipophilicity) value, which exceeds 5, making the compound tend not to dissolve in the aqueous phase. This can be overcome by modifying the compound's chemical structure or by recommending a dosage form other than oral. In the ADMET profile. Several studies have demonstrated that 24-methylene cycloartenol acetate, a structurally related analogue, exhibits antidiabetic activity through inhibition of alpha-glucosidase [13-14], an intestinal enzyme whose inhibition delays the digestion of complex carbohydrates and attenuates postprandial hyperglycaemia, the same therapeutic mechanism exploited by the clinically approved drug acarbose. If cycloartenol acetate shares or retains this alpha-glucosidase inhibitory activity, the compound would possess a dual-target antidiabetic mechanism: reducing intracellular glucose-mediated damage in insulin-sensitive tissues via AR inhibition, while simultaneously limiting systemic glucose absorption via alpha-glucosidase inhibition [15]. Such dual-target activity would confer a therapeutically advantageous pharmacological profile, as it would address both the upstream glycaemic burden and the downstream cellular consequences of chronic hyperglycaemia [16,17].

Cycloartenol demonstrates a convergence of evidence across multiple evaluation criteria that collectively make a strong preliminary case. Its binding to a shared key residue (THR113), supplementary stabilization across five hydrophobic contacts, binding energy comparable to a clinical reference compound, a favourable fit score, and independent evidence of alpha-glucosidase inhibition from analogues together constitute a robust molecular rationale. The single RO5 violation (LogP) is the primary pharmacokinetic concern but is addressable through formulation science or lead optimisation [18]. The compound should now advance to in vitro enzymatic assays to confirm AR inhibitory activity in solution, followed by cell-based models of hyperglycaemia-induced polyol flux, and ultimately to in vivo diabetic animal models to assess both efficacy and safety [19]. Its natural origin from Kluwih leaves also opens the door to ethnopharmacological validation and lower regulatory risk relative to wholly synthetic scaffolds [20].

In sum, cycloartenol acetate is a lead compound, not yet a drug candidate, but its profile justifies prioritisation for further preclinical investigation within a diabetes drug discovery pipeline. Further development of cycloartenol acetate could proceed through two main strategies: (1) isolation and structural confirmation from *Artocarpus camansi* leaves, followed by in vitro enzyme inhibition assays; and (2) structural modification via molecular modeling to improve solubility or binding affinity. Long-term, this compound may serve as a scaffold for the development of anti-cataract drugs targeting aldose reductase. It is hoped that this research can be further developed through structural modification, plant isolation, or wet lab testing to develop alternative therapies for cataracts due to diabetes complications.

5. CONCLUSION

Cycloartenol acetate exhibits promising aldoreductase-inhibitory activity with the lowest binding energy among other bioactives in *A. camansi*. Further evaluation through in vitro studies is urged to confirm activity regarding the development of *A. camansi* for diabetes therapy and maintenance.

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