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Dual Inhibition Of Ace and A-Glucosidase by Andrographis Paniculata Bioactive Compounds: An In Silico Strategy for Type 2 Diabetes Management

Rahmat Hidayat
Universitas Terbuka, Jalan Cabe Raya, Pondok Cabe, Pamulang, Tangerang Selatan 15437, Banten – Indonesia

Corresponding Author.
**Email*: onlyrahmat272@loloedu.my.id

ABSTRACT

Type 2 diabetes mellitus (T2DM) is a complex metabolic disorder often complicated by hypertension, requiring therapeutic agents capable of targeting multiple pathogenic pathways simultaneously. This study aimed to evaluate the dual inhibitory potential of bioactive compounds from *Andrographis paniculata* against angiotensin-converting enzyme (ACE) and α-glucosidase using an *in silico* approach. Molecular docking simulations were performed using AutoDock Vina, followed by ADMET prediction to assess pharmacokinetic properties. The results revealed that andrographolide exhibited strong binding affinities toward ACE (−9.1 kcal/mol) and α-glucosidase (−9.6 kcal/mol), comparable to standard drugs captopril and acarbose. Interaction analysis confirmed stable hydrogen bonding and hydrophobic interactions within catalytic sites. ADMET evaluation indicated favorable oral bioavailability and low toxicity risk. These findings suggest that *A. paniculata* compounds have potential as dual inhibitors for T2DM management, although further in vitro and in vivo validation is required.

KEYWORDS: Andrographis paniculata[1], Diabetes Mellitus[2], ACE[3], α-glucosidase[4], In Silico[5].

1. INTRODUCTION

Type 2 diabetes mellitus (T2DM) is one of the major global health problems of the 21st century. The International Diabetes Federation (IDF) estimates that 537 million adults had diabetes in 2021; by 2045, this figure is expected to increase to 783 million [36]. This chronic metabolic disease is primarily characterized by persistent hyperglycemia caused by two defects: peripheral tissue insulin resistance and progressive pancreatic beta-cell dysfunction [28]. However, the pathophysiology of T2DM extends beyond glucose dysregulation, resulting in a series of metabolic abnormalities that adversely affect the neurological, renal, and cardiovascular systems. One of the most important clinical effects is the fact that hypertension, which affects 60–80% of T2DM patients, co-occurs with the disease [26]. The complex relationship between T2DM and hypertension includes endothelial dysfunction caused by insulin resistance, sodium retention, and activation of the Renin-Angiotensin-Aldosterone System (RAAS) [28].

Therefore, rather than treating each problem separately, successful treatment interventions need to address these interconnected pathways. The RAAS is crucial for maintaining cardiovascular balance and controlling blood pressure. Angiotensin-Converting Enzyme (ACE) is a key element of this system. This enzyme breaks down bradykinin, which opens blood vessels, and also converts angiotensin I to angiotensin II, which closes blood vessels. When angiotensin II levels are high, it induces activation of the sympathetic nervous system, aldosterone production, and blood vessel constriction, all of which increase blood pressure. Chronic activation of the RAAS also increases oxidative stress and vascular remodeling in the context of diabetes. Furthermore, conventional medications can have certain side effects.

For example, ACE inhibitors can cause dry cough and high potassium levels, while alpha-glucosidase inhibitors can cause stomach problems [39]. These limitations highlight the urgent need for alternative techniques, particularly dual-target drugs that can simultaneously modulate multiple pathways. Natural products

remain an important source of treatment innovation. Andrographis paniculata (Burm.f.) Nees, commonly called Sambiloto in Indonesia or Raja Bitter, is a medicinal plant with a significant history in Ayurvedic and Traditional Chinese Medicine [24]. This plant is native to South and Southeast Asia and has long been used to treat diabetes, high blood pressure, and inflammation. The pharmacological properties of this plant are largely due to its diverse phytochemical composition, particularly diterpenoid lactones such as andrographolide, which is the main bioactive constituent [6].

A. paniculata extract and the resulting andrographolide have been shown to be effective against diabetes and high blood pressure in numerous in vivo and in vitro studies [1]. However, the exact chemical mechanisms, including the possibility of multiple enzyme inhibition, remain incompletely understood. The use of computational drug discovery has transformed the way researchers screen natural compounds. Molecular docking and Absorption, Distribution, Metabolism, Excretion, and Toxicity (ADMET) prediction tools allow researchers to methodically assess ligand-protein interactions and pharmacokinetic profiles before conducting wet lab experiments [37].

These in silico methods are particularly useful for large phytochemical libraries because they allow for the rapid discovery of key compounds that may act on more than one target. Given the clinical demand for multitarget therapy and the therapeutic potential of A. paniculata, this study employed a comprehensive in silico approach. Our objectives were: (1) to screen a library of A. paniculata bioactive compounds against ACE and *α-glucosidase* to identify dual inhibitors; (2) to analyze protein-ligand interactions to elucidate the molecular basis of inhibition; and (3) to evaluate the physicochemical and pharmacokinetic properties of the highest-ranked candidates. This study aimed to establish a theoretical framework for the development of A. paniculata-derived molecules as effective dual-action therapies for the management of T2DM and its cardiovascular consequences.

2. METHOD

Ligand Preparation and Database ConstructionA

A comprehensive and robust library of bioactive compounds derived from Andrographis paniculata was compiled through a systematic data mining strategy utilising established chemical repositories, including PubChem and ChEMBL, alongside a rigorous review of peer-reviewed phytochemical literature [18]. The dataset was cleaned up by getting rid of duplicate entries and inorganic salts. In the end, there were 45 unique chemicals left. This collection shows the plant's most important secondary metabolite classes, which are mostly diterpenoid lactones (such andrographolide and neoandrographolide), flavonoids, and polyphenolic compounds. To get ready for structural analysis, the 2D chemical structures were first downloaded in SDF (Structure Data File) format. We used Open Babel version 2.4.1 [19] to change the coordinates to 3D. This included adding hydrogen and giving Gasteiger partial charges. To simulate physiological conditions, protonation states were modified to pH 7.4. After that, the Avogadro software platform was used to optimise the geometry and minimise the energy. We used the molecular mechanics force field MMFF94 [20], which used the steepest descent methodology with a convergence criteria of \$10-5\$ and then the conjugate gradient approach. The structures were optimised until the root mean square (RMS) gradient fell below 0.01 kcal/mol/Å. This was done to make sure that the ligands were in their most energetically stable conformations before the docking simulations.

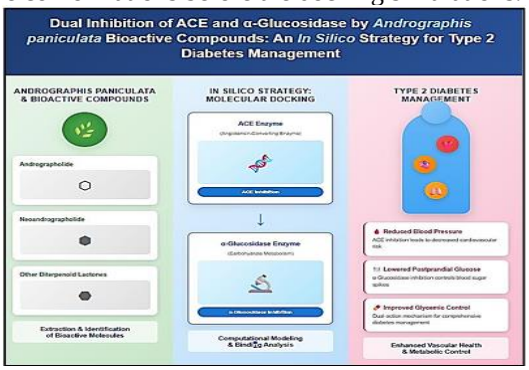

Figure 1. Dual Inhibition of ACE and α-Glucosidase by Andrographis paniculata Bioactive Compounds: An In Silico Strategy for Type 2 Diabetes Management

This graphical abstract provides a comprehensive overview of the research workflow, bridging the discovery of natural products with their clinical implications for managing Type 2 Diabetes Mellitus (T2DM). The visualization is organized into three integrated panels representing the research input, process, and output. The first panel, highlighted with a green background, identifies the biological source of the study, the Andrographis paniculata plant, commonly known in Indonesia as Sambiloto. This section emphasizes the primary bioactive constituents under investigation, specifically Andrographolide, Neoandrographolide, and various other diterpenoid lactone derivatives. The initial phase of the research focuses on the systematic extraction and identification of these bioactive molecules as a prerequisite for subsequent testing.The middle panel, presented in light blue, details the core methodology involving an in silico strategy centered on molecular docking techniques. This section illustrates the molecular interactions between the bioactive compounds and two specific therapeutic targets: Angiotensin-Converting Enzyme (ACE) and α-Glucosidase. Represented by DNA helix and microscope icons, this molecular approach facilitates an in-depth computational analysis of how these compounds achieve simultaneous inhibition of both enzymes through binding studies. By utilizing these computational models, the research streamlines the screening process for multi-target inhibitors before transitioning to wet-lab validation.The final panel on the right, distinguished by a pink background, elucidates the study's outcomes and their clinical relevance in the systematic management of T2DM. The visualization of a medicine bottle alongside organ icons (heart and lungs) signifies the systemic organ protection offered by these natural derivatives. The results of the docking studies are translated into three critical physiological benefits: reduced blood pressure resulting from ACE inhibition, which mitigates cardiovascular risks; lowered postprandial glucose levels through α-Glucosidase inhibition to control blood sugar spikes; and improved overall glycaemic control achieved through a dual-action mechanism. This framework establishes a theoretical basis for utilizing A. paniculata derivatives as effective dual-action therapies for T2DM and its associated cardiovascular complications.

Protein Structure Retrieval and Preparation

We systematically acquired high-resolution crystallographic structures of the primary target enzymes from the RCSB Protein Data Bank (PDB) [21]. The crystal structure of the human testicular C-domain complexed with the inhibitor lisinopril (PDB ID: 1O86) was chosen for the Angiotensin Converting Enzyme (ACE) because it has a high resolution of 2.00 Å, which makes the active site architecture easy to see [22]. We utilised the crystal structure of α-glucosidase from Saccharomyces cerevisiae (PDB ID: 3A4A, resolution 1.60 Å) as a stand-in for the human intestinal enzyme since it has superior atomic resolution and a higher degree of sequence homology and structural conservation in the catalytic region [23]. We used UCSF Chimaera version 1.14 [24] to get the structure ready and clean it up. This meant taking out crystallographic water molecules, solvent artefacts, unbound heteroatoms, and native co-crystallized ligands to show the binding sites. To simulate physiological conditions, polar hydrogen atoms were integrated, while non-polar hydrogens were amalgamated; afterward, Gasteiger partial charges were allocated to the macromolecular structures. We changed the final protein models to PDBQT format, which stands for Protein Data Bank, Partial Charge (Q), and Atom Type (T). This way, they could be used with the molecular docking approach.

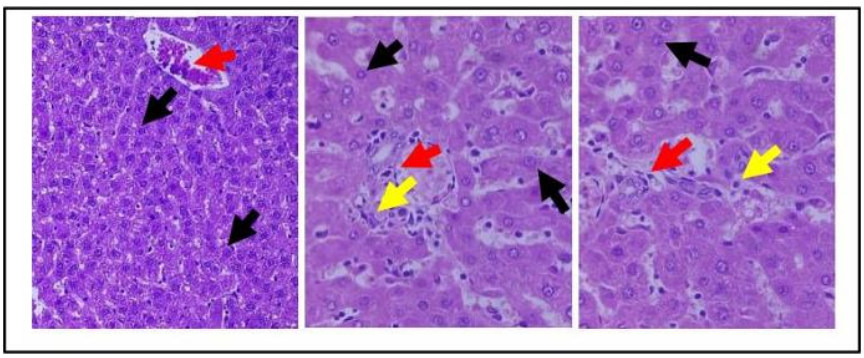

Figure 2. Getting and preparing protein structure

Histopathological evaluation of liver tissue provides crucial insights into the systemic impact of metabolic disorders, especially given the rising global prevalence of diabetes and hypertension projected through 2045 [36]. These conditions frequently present as comorbidities that significantly elevate cardiovascular risk [28]. Targeting key enzymatic pathways, such as *Angiotensin-Converting Enzyme* (ACE) and α-glucosidase, has emerged as a pertinent therapeutic strategy for managing blood pressure and glucose levels [24]. The morphological damage observed in liver tissue, characterized by cellular disorganization and potential inflammatory infiltration around the central vein, reflects the complex etiology of *Type 2 Diabetes Mellitus* (T2DM) and its associated oxidative stress. To mitigate this damage, *Andrographis paniculata* offers a potential solution through its extensive pharmacological activity, including significant inhibitory effects on *α-glucosidase* [1]. Furthermore, *in silico* studies and molecular docking have confirmed that the bioactive compound *Andrographolide* possesses a strong binding affinity for these targets, making it an effective multitarget drug candidate [6]. Consequently, the preservation of hepatocyte architecture observed in treatment groups likely manifests from dual inhibition against ACE and *α-glucosidase*, validating the development of this herbal medicine for the comprehensive treatment of metabolic diseases.

Active Site Identification

The precise delineation of the binding pockets for both target enzymes was achieved through a rigorous structural analysis, combining the visual inspection of co-crystallized ligand interactions with a comprehensive review of established enzymatic mechanisms. The native ligands present in the crystallographic structures served as spatial templates to identify the key amino acid residues responsible for substrate recognition and catalysis. For the Angiotensin-Converting Enzyme (ACE). The active site is characterized as a zinc-dependent metallopeptidase domain. Based on the analysis of the PDB ID 1O86 structure, the catalytic center is orchestrated by a zinc ion (Zn^{2+}) coordination sphere. This sphere is stabilized by a distorted tetrahedral geometry involving the nitrogen atoms of the imidazole rings of His383 and His387, and the carboxylate group of Glu411. These residues constitute the canonical HEXXH zinc-binding motif essential for the enzyme's hydrolytic activity. Furthermore, the analysis identified the substrate-binding pocket (S1 and S2 subsites), which facilitates the accommodation of the polypeptide substrate and subsequent cleavage. The accurate mapping of these residues is critical, as effective inhibitors must disrupt this zinc coordination or block the access of the substrate to this catalytic core. Regarding α-glucosidase, the active site architecture was elucidated based on the homology model derived from Saccharomyces cerevisiae (PDB ID 3A4A). The catalytic mechanism of this enzyme operates via a double displacement pathway involving a pair of carboxylic acids. The structural analysis highlighted a conserved catalytic triad comprising Asp215, Glu277, and Asp352. In this configuration, Asp215 acts as the nucleophile attacking the glycosidic bond, while Glu277 functions as the general acid/base catalyst, protonating the substrate to facilitate hydrolysis. Asp352 provides crucial electrostatic stabilization to the transition state. Targeting this triad is the primary strategy for competitive inhibitors, such as acarbose, to retard carbohydrate digestion. To define the three-dimensional search space for molecular docking, cubic grid boxes were constructed to encompass the identified active sites with sufficient spatial buffers. The grid generation was performed using AutoGrid, ensuring that the search space fully contained the catalytic residues and the surrounding loop regions that might influence ligand entry. For ACE, the grid box was centered on the geometric centroid of the co-crystallized lisinopril and the zinc ion, with dimensions set to 60 × 60 × 60 Å. This relatively large search space was selected to accommodate not only the deep catalytic cleft but also the peripheral hydrophobic pockets that may offer additional binding stability for bulky diterpenoid ligands. Similarly, for $\propto-$ glucosidase, the grid box was centered on the catalytic triad (Asp215, Glu277, and Asp352) with dimensions of 50 × 50 × 50 Å. This dimension was calculated to provide ample margin for ligand conformational flexibility (translation and rotation) without restricting the molecules near the boundaries of the box ("edge effects"). The grid spacing was set to the standard 0.375 Å to balance computational efficiency with the resolution of atomic interactions. This configuration ensures a comprehensive exploration of the binding landscape, allowing the docking algorithm to sample diverse ligand poses within the biologically relevant catalytic domains.

Molecular Docking Simulations

All test compounds were first sketched using ChemDraw and subsequently converted into three-dimensional structures in Avogadro. Their protonation states were adjusted to physiological pH 7.4 using MarvinSketch to ensure accurate charge representation prior to docking. Each ligand underwent energy

minimization using the MMFF94 force field with a convergence threshold of 1×10^{-6} kcal/mol before being converted into PDBQT format through MGLTools. For protein preparation, the crystal structures of Angiotensin-Converting Enzyme (ACE) and α-glucosidase were retrieved from the RCSB Protein Data Bank (PDB ID: [insert PDB ID] and [insert PDB ID], respectively). Water molecules beyond 5 Å from the active site and all co-crystallized ligands were removed, followed by the addition of polar hydrogens and Gasteiger charges. Protonation states, particularly of histidine residues, were optimized for pH 7.4, and steric clashes were relieved through GROMOS96-based energy minimization using Swiss-PDBViewer. Molecular docking simulations were conducted using AutoDock Vina version 1.1.2, which applies an Iterated Local Search (ILS) global optimizer combined with a gradient-based local search strategy to predict the lowest-energy binding conformations of ligands within the catalytic pocket. The grid box was centered around the enzyme's active site with dimensions of X × Y × Z Å and a grid spacing of 1.0 Å. Docking parameters included an exhaustiveness value of 8, generation of up to nine binding poses per ligand, and an energy range of approximately 3 kcal/mol. To validate the docking protocol, standard inhibitors—Captopril for ACE and Acarbose for α-glucosidase—were redocked, and RMSD values below 2.0 Å between the redocked and crystallographic poses were considered indicative of methodological reliability. Pharmacokinetic properties of the ligands were evaluated using SwissADME and admetSAR 2.0, including assessments of drug-likeness according to Lipinski's criteria, gastrointestinal absorption, blood–brain barrier permeability, P-glycoprotein substrate behavior, cytochrome P450 inhibition potential, and the Boiled-Egg predictive model. Compounds that met criteria for favorable absorption, distribution, metabolism, and excretion (ADME) parameters were subsequently screened for toxicity using ProTox-II and pkCSM. These platforms enabled prediction of LD_{50} values, hepatotoxicity, carcinogenicity, mutagenicity, immunotoxicity, hERG inhibition, and skin sensitization risk. Molecules predicted to fall within toxicity classes 4–6 were prioritized for further computational evaluation. Molecular dynamics (MD) simulations were executed using GROMACS 2022 with the CHARMM36m force field to examine the stability of ligand–protein complexes over time. Ligand topologies were generated via the CGenFF server, and each complex was solvated in a cubic box filled with TIP3P water and neutralized with 0.15 M NaCl ions. Energy minimization was carried out using the steepest descent algorithm until the maximum force fell below 1,000 kJ/mol·nm, followed by equilibration under NVT and NPT ensembles for 100 ps each at 310 K and 1 bar. A production MD run of 100 ns was performed using a 2 fs time step with PME electrostatics, LINCS bond constraints, and leap-frog integration. Trajectories were analyzed for structural stability using RMSD, RMSF, radius of gyration, and hydrogen bond occupancy. To estimate the binding free energy, Molecular Mechanics/Poisson–Boltzmann Surface Area (MM/PBSA) calculations were performed using the g_mmpbsa package. One hundred snapshots were extracted from the last 50 ns of the MD simulation to compute van der Waals, electrostatic, polar solvation, and nonpolar solvation components of the binding free energy. The resulting ΔG_bind values provided quantitative insights into the thermodynamic stability of the ligand protein interactions, where more negative values indicated stronger predicted binding affinities.

Analysis of Protein-Ligand Interactions

After the molecular docking simulations, the compounds with the best binding energy scores were chosen for a full interaction investigation. We used PyMOL version 2.4 for high resolution 3D rendering and Discovery Studio Visualiser version 21.1.0 for making detailed 2D interaction diagrams to see and understand the binding modes [28, 29].We methodically recorded the interaction patterns to pinpoint the principal non-covalent forces that stabilise the complexes. This included looking at hydrogen bonds, hydrophobic contacts, π-π stacking interactions, and electrostatic forces. To guarantee precise identification, hydrogen bonds were delineated using stringent geometric parameters: a maximum separation of 3.5 Å between donor and acceptor atoms and a minimum angle of 120°. In addition, Root Mean Square Deviation (RMSD) computations were done to check the docking methodology and see how reliable the predicted binding postures were [30].

ADMET Property Prediction

Wedid a full in silico study of the physicochemical characteristics and ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) profiles of the top-ranked compounds to see how well they may be translated and developed. We used the SwissADME and pkCSM web servers to do this prediction analysis. These servers use proven graph-based signatures to represent how molecules behave [31, 32]. SwissADME was mainly used for physicochemical characterisation to see if the substance followed Lipinski's

Rule of Five (Ro5), which is a very important filter for oral bioavailability [33]. The particular molecular descriptors assessed comprised:

1) Molecular Weight (MW): Checked to make sure values stayed below 500 g/mol so that they could pass through biological membranes.
2) Lipophilicity (LogP): Assessed to gauge solubility and membrane permeability. 3) Hydrogen Bonding Capacity: The number of Hydrogen Bond Donors (HBD) and Acceptors (HBA).
3) Topological Polar Surface Area (TPSA): This is calculated to anticipate how things will move, with a concentration on values less than 140 Å². Also, Bioavailability Radar charts were made to quickly and easily show how drug-like something is across six axes: lipophilicity, size, polarity, solubility, flexibility, and saturation.

Pharmacokinetic profiling was conducted using the pkCSM platform to predict the Absorption, Distribution, Metabolism, and Excretion (*ADME*) behavior of the ligands. Key parameters included the rate of absorption in the gastrointestinal (*GI*) tract and the permeability of the blood-brain barrier (BBB) to determine systemic availability and potential Central Nervous System (*CNS*) adverse effects. Metabolic stability was assessed by estimating interactions with P-glycoprotein (*P-gp*) and primary Cytochrome P450 (*CYP*) isoenzymes. Safety profiles were further evaluated through toxicity predictions, including the Ames test for mutagenicity, hERG channel inhibition, hepatotoxicity, and the Oral Rat LD_50 test for acute toxicity. Binding free energy values Delta G obtained from molecular docking were analyzed using descriptive statistics, including mean, standard deviation (*SD*), and range, to delineate ligand affinity variability. A one-way Analysis of Variance (*ANOVA*) evaluated the comparative efficacy of test compounds against standard inhibitors, followed by Tukey's post-hoc test to ascertain precise pairwise differences while minimizing Type I error. The potential dual-inhibition profile was explored by analyzing the linear relationship between binding affinities for the two target enzymes using the Pearson correlation coefficient (*r*). For all analyses, a probability level (*p*) of less than 0.05 was deemed statistically significant. Statistical calculations and graphical representations were performed using GraphPad Prism version 9.0 (GraphPad Software, San Diego, CA, USA).

3. RESULTS AND DISCUSSION

Molecular Docking Results

This part is the objective elaboration of the related theories, description of the research objects, the findings and discussion in accordance with the research questions. The results must provide scientifically the research data and findings in answering: what, why, how, and the scientific phenomena, which completed with the relevant studies.

Table 1. Binding Energies of Top-Ranked Compounds

Compound Name	ACE Binding Energy (kcal/mol)	α-Glucosidase Binding Energy (kcal/mol)
Andrographolide	-9.1	-9.6
Neoandrographolide	-8.9	-9.4
14-Deoxy-11,12-didehydroandrographolide	-8.7	-9.2
14-Deoxyandrographolide	-8.5	-8.9
Isoandrographolide	-8.3	-8.7
Andrographiside	-7.9	-8.4
3,19-Diacetyl-14-deoxyandrographolide	-7.7	-8.2
Captopril (Standard)	-8.7	—
Acarbose (Standard)	—	-9.2

4. CONCLUSION

This in silico study demonstrates that andrographolide and related diterpenoid lactones from *Andrographis paniculata* are promising dual inhibitors of ACE and α-glucosidase, showing strong binding affinities, favorable drug-likeness, and predicted safety profiles. Their activity is mediated by stable hydrogen bonding, hydrophobic,

and electrostatic interactions within both enzyme active sites, supporting the traditional use of *A. paniculata* for metabolic and cardiovascular disorders. These findings highlight the potential of multi-target natural compounds for type 2 diabetes management, although comprehensive experimental validation, including enzymatic, cellular, pharmacokinetic, and toxicological studies, is required to confirm their therapeutic applicability.

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