BIOLOGY, MEDICINE, & NATURAL PRODUCT CHEMISTRY ISSN 2089-6514 (paper)
Volume 15, Number 1, April 2026 | Pages: 357-364 | DOI: 10.14421/biomedich.2026.151.357-364 ISSN 2540-9328 (online)

Unveiling the Synergistic Multi-Target Antidiabetic Mechanism of Indonesian Scientific Jamu Formulation: A Computational Study

Andri Prasetiyo*, Teguh Sugiarto, Esti Mulatsari, Esti Mumpuni, Vandrico Junky, Fadhiil Muhammad Dzaki Adipura, Claudya Fransiska Pratamauli Nainggolan
Faculty of Pharmacy, Universitas Pancasila, Jl. Srengseng Sawah, Jagakarsa, DKI Jakarta 12640, Tel./Fax. : +6221 7270086, Indonesia.

Corresponding author*
andriprasetiyo@univpancasila.ac.id

Manuscript received: 25 December 2025. Revision accepted: 13 April 2026, Published: 24 April 2026.

Abstract

This study aimed to evaluate the multi-target antidiabetic potential of bioactive compounds within the Indonesian Scientific Jamu formulation (consisting of *Andrographis paniculata*, *Curcuma xanthorrhiza*, *Cinnamomum burmannii*, and *Syzygium polyanthum*) via an *in silico* approach targeting PPAR-γ, DPP-4, AKR1C3, and SGLT2. Molecular docking simulations were performed to screen 238 bioactive compounds using Molegro Virtual Docker to predict binding affinities, while ADMET properties were analyzed using pkCSM. The simulation revealed that Cinnamoside, Procyanidin B2, Bisandrographolide B, and Gemin D exhibited the lowest energy on their respective targets. Significantly, 2,6-Di-O-galloyl-β-D-glucose emerged as a superior multi-target compound, consistently outperforming standard drugs (Pioglitazone, Teneligliptin, Glimepiride, and Empagliflozin) against all four receptors. It was concluded that the formulation contained potent compounds acting through a synergistic multi-target mechanism, specifically 2,6-Di-O-galloyl-β-D-glucose, providing a molecular rationale for the formulation's clinical efficacy.

Keywords: Antidiabetic; In silico; Indonesian Scientific Jamu; Molecular docking; Multi-target.

Abbreviations: PPAR-γ: Peroxisome Proliferator-Activated Receptor gamma; DPP-4: Dipeptidyl Peptidase-4; AKR1C3: Aldo-Keto Reductase 1C3; SGLT2: Sodium-Glucose Cotransporter-2; ADMET: Absorption, Distribution, Metabolism, Excretion, and Toxicity; RMSD: Root Mean Square Deviation; PDB: Protein Data Bank.

INTRODUCTION

Diabetes mellitus (DM) is a chronic metabolic disorder characterized by hyperglycemia caused by defects in insulin secretion, insulin action, or both. The prevalence of DM continues to rise globally, posing a significant burden on public health systems. According to the International Diabetes Federation (IDF) Diabetes Atlas 10th Edition, the number of people with diabetes in Indonesia was estimated to reach 19.5 million in 2021, placing the country among the top five with the highest number of diabetes cases in the world (IDF, 2021). Furthermore, the 2023 Indonesian Health Survey (SKI) reported that the prevalence of diabetes mellitus based on doctor diagnosis in the population of all ages was 1.7%, with a notable increase in undiagnosed cases (Kementerian Kesehatan RI, 2023).

To address this challenge, the Indonesian government promotes the Scientific Jamu (*Jamu Saintifik*) program to provide evidence-based traditional medicines. One of the standardized formulations developed is the Antidiabetic Scientific Jamu (*Ramuan Jamu Kencing Manis*), which consists of four medicinal plants: *Syzygium polyanthum* (Salam), *Andrographis paniculata* (Sambiloto), *Cinnamomum burmannii* (Kayu Manis), and *Curcuma xanthorrhiza* (Temulawak) (Kementerian Kesehatan RI, 2019). Clinically, this formulation works by inhibiting hepatic glucose production, delaying intestinal glucose absorption, and enhancing insulin secretion. However, diabetes is a multifactorial disease, and effective management often requires modulating multiple pathological pathways simultaneously.

Therefore, understanding the molecular interaction between bioactive compounds and specific therapeutic targets is crucial. In this study, four key proteins were selected based on their pivotal roles in glucose homeostasis. Peroxisome Proliferator-Activated Receptor gamma (PPAR-γ) is a nuclear receptor essential for regulating glucose metabolism and insulin sensitivity. Dipeptidyl Peptidase-4 (DPP-4) is an enzyme that degrades incretin hormones; its inhibition prolongs the half-life of GLP-1, thereby stimulating insulin secretion. Aldo-Keto Reductase 1C3 (AKR1C3) is involved in steroid metabolism and its overexpression is linked to oxidative stress and insulin resistance in adipose tissue (Liu et al. 2021). Lastly, Sodium-Glucose Cotransporter-

2 (SGLT2) facilitates glucose reabsorption in the kidneys, and its inhibition promotes glucosuria to lower blood glucose levels (Vallon and Verma, 2021).

Despite the clinical evidence supporting the jamu formulation, the specific molecular mechanisms of its bioactive compounds against these multiple diabetic protein targets remain to be fully elucidated. In the field of drug discovery, *in silico* approaches, particularly molecular docking, have become essential for screening bioactive compounds from natural products efficiently. A recent study demonstrated the validity of this approach using Molegro Virtual Docker to evaluate antidiabetic activity against key targets such as PPAR-γ, DPP-4, and SGLT2 (Rhahmadini et al. 2025).

Building upon this validated methodology, this study aims to systematically evaluate the multi-target mechanism of 238 bioactive compounds contained in the Indonesian Scientific Jamu formulation via a virtual screening approach. Unlike previous studies that often focus on single targets or limited compounds, this research simultaneously investigates interactions with the four aforementioned protein targets. Through this comprehensive screening, this study seeks to identify potential synergistic compounds, specifically examining if top-ranked candidates can act as potent multi-target agents, thereby providing a molecular rationale for the formulation's clinical efficacy.

MATERIALS AND METHODS

Materials

The materials used in this study were digital data of protein structures and chemical compounds. The target proteins were Peroxisome Proliferator-Activated Receptor gamma (PPAR-γ) (PDB ID: 3K8S), Dipeptidyl Peptidase-4 (DPP-4) (PDB ID: 3VJK), Aldo-Keto Reductase 1C3 (AKR1C3) (PDB ID: 4YVX), and Sodium-Glucose Cotransporter-2 (SGLT2) (PDB ID: 7VSI), obtained from the RCSB Protein Data Bank. The ligand library consisted of 238 bioactive compounds identified from the Indonesian Scientific Jamu formulation, comprising *Andrographis paniculata* (Burm.f.) Nees, *Curcuma xanthorrhiza* Roxb., *Cinnamomum burmannii* (Nees & T.Nees) Blume, and *Syzygium polyanthum* (Wight) Walp., with 3D structures retrieved from PubChem. Pioglitazone, Teneligliptin, Glimepiride, and Empagliflozin were used as standard drugs.

Instruments

The research was conducted using a personal computer equipped with an Intel® Core™ i3-1115G4 Processor and 8 GB RAM. The software packages utilized included ChemDraw Professional and Chem3D Ultra 22.2.0 for structure preparation, Molegro Virtual Docker (MVD) version 6.0 for molecular docking simulations, and Biovia Discovery Studio Visualizer v25.1.0 for interaction analysis. Pharmacokinetic predictions were performed using pkCSM and SwissADME web servers.

Preparation of Ligands and Receptors

The crystal structures of PPAR-γ (3K8S), DPP-4 (3VJK), AKR1C3 (4YVX), and SGLT2 (7VSI) were prepared using the Molegro Virtual Docker (MVD) preparation module to stabilize the structures by removing water molecules and assigning partial charges (Mulatsari et al. 2020). A library of 238 bioactive compounds was converted into 3D structures and subjected to energy minimization using the MMFF94 force field to achieve thermodynamically stable conformations prior to simulation (Prasetiyo et al. 2024).

Docking Protocol Validation

The docking algorithm was validated by redocking the native ligand into the active site of each receptor. The protocol was considered valid if the Root Mean Square Deviation (RMSD) between the redocked pose and the crystallographic ligand was ≤ 2.0 Å, ensuring the reproducibility and accuracy of the method (Rhahmadini et al. 2025).

Molecular Docking

Molecular docking was performed using the MolDock scoring function in MVD. The search space was defined within a specific radius centered on the active sites: PPAR-γ (X=37.16, Y=3.19, Z=41.25), DPP-4 (X=51.94, Y=64.95, Z=34.65), AKR1C3 (X=6.63, Y=11.94, Z=17.42), and SGLT2 (X=38.46, Y=50.43, Z=46.16). The best ligand conformations were selected based on the lowest Rerank Score, indicating the strongest binding affinity (Sari et al. 2020).

ADMET and Drug-Likeness Analysis

Physicochemical properties were evaluated based on Lipinski's Rule of Five using the SwissADME web server to predict oral bioavailability. Additionally, pharmacokinetic profiles, including Absorption, Distribution, Metabolism, Excretion, and Toxicity (ADMET), were predicted using pkCSM to assess the safety and efficacy of the top-ranked compounds (Abdullah et al. 2021).

RESULTS AND DISCUSSION

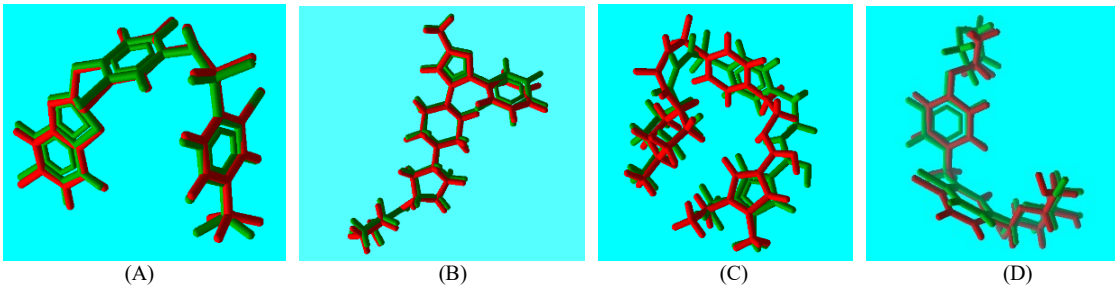
Validation of Docking Method

The molecular docking protocol was validated by redocking the native ligand into the active site of each target protein: PPAR-γ (3K8S), DPP-4 (3VJK), AKR1C3 (4YVX), and SGLT2 (7VSI). The analysis confirmed that all receptors met the validation criteria with Root Mean Square Deviation (RMSD) values ≤ 2.0 Å. The DPP-4 receptor exhibited the lowest RMSD (0.365 Å), followed by PPAR-γ (0.392 Å), SGLT2 (0.648 Å), and AKR1C3 (1.322 Å). These results indicate that the

docking parameters and defined search space are reliable for predicting ligand interactions (Rhahmadini et al. 2025). The validation data and visualization are presented in Table 1 and Figure 1.

Table 1. Validation results of molecular docking protocol on four diabetes-related protein targets.

Receptor	PDB ID	Score Function	Algorithm	RMSD (Å)	Status
PPAR-γ	3K8S	Plants Score [GRID]	MolDock SE	0.39191	Valid
DPP-4	3VJK	MolDock Score [GRID]	MolDock Optimizer	0.36461	Valid
AKR1C3	4YVX	MolDock Score	Iterated Simplex	1.32165	Valid
SGLT2	7VSI	MolDock Score [GRID]	MolDock Optimizer	0.64804	Valid



(A) (B) (C) (D)

Figure 1. Visualization of docking protocol validation showing the superimposition of native ligands (red) and redocked ligands (green) in the active sites of (A) PPAR-γ; (B) DPP-4; (C) AKR1C3; and (D) SGLT2.

Interaction with PPAR-γ Receptor

Cinnamoside exhibited the strongest affinity for PPAR-γ (-276.108 kcal/mol), significantly outperforming Pioglitazone (-103.732 kcal/mol) (Table 2). Visual analysis confirmed a dense hydrogen bond network with key residues SER 289, ARG 288, GLU 343, and LYS 367, contributing to superior thermodynamic stability compared to the standard drug (Sari et al. 2020), as depicted in Figure 2.

Table 2. Top-ranked bioactive compounds docking results against PPAR-γ (3K8S) compared to Pioglitazone.

No	Ligand Name	Rerank Score (kcal/mol)
1	cc_Cinnamoside	-276.108
2	ep_2,6-Di-O-galloyl-ß-D-glucose	-133.558
3	ap_5,4_-Dihidroxy-7,8,2_,3_-tetramethoxy flavone 5-glucoside	-125.185
4	ep_Squalene	-124.013
5	cx_1,5-Dihydroxy-1,7- bis(4-hydroxy-3- methoxyphenyl)-4,6- heptadien-3-one	-123.63
6	cc_Icariside DC	-121.164
7	cc_Cinnacasside E	-120.241
8	ep_Darendoside A	-119.863
9	ap_3-O-beta-D-Glucopyranosylandrographolide	-118.164
10	cc_Kelampayoside A	-118.125
11	ep_gamma-tocopherol	-117.867
12	cx_dihydrocurcumin	-116.751
13	ep_a-tocopherol	-114.777
14	cc_Cinnacasside A	-113.269
15	cx_Curcumin	-113.097
16	cc_8-C-Glucopyranosylepicatechin	-111.506
17	cx_1,7-Bis(4-hydroxy-3-methoxyphenyl)-3,5-heptanediol	-111.39
18	ap_5-Hydroxy-7,8,2_,3_-tetramethoxyflavone 5-glucoside	-110.456
19	cx_Demethoxycurcumin	-109.509
20	ap_5,2_,3_-Trihydroxy-7,8-dimethoxyflavone 3_-glucoside	-109.502
21	cx_Demethoxycurcumin	-108.275
22	ap_Andrographiside	-107.583
23	cc_6-C-Glucopyranosylepicatechin	-107.226
24	cc_Epicatechin 3-O-beta-D-glucopyranoside	-103.792
25	Pioglitazone (*Standard Drug*)	-103.732

Note: *cc = Cinnamomum burmannii Cortex; ep = Eugenia polyantha (Syzygium polyanthum); ap = Andrographis paniculata; cx = Curcuma xanthorrhiza.*

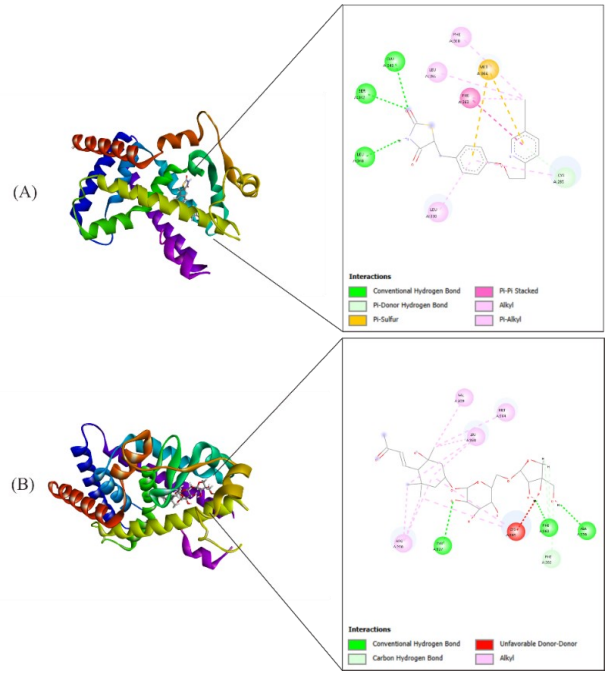


Figure 2. 2D visualization of amino acid interactions in the PPAR-γ (3K8S) binding pocket with (A) Standard drug Pioglitazone; and (B) Top-ranked compound Cinnamoside.

Interaction with DPP-4 Receptor

Procyanidin B2 showed potent inhibition of DPP-4 (-119.716 kcal/mol) compared to Teneligliptin (-93.501 kcal/mol) (Table 3). It anchored to the active site via GLU 205 (shared with Teneligliptin) and established additional stabilizing hydrogen bonds with ARG 358 and VAL 207, effectively blocking the catalytic site (Sari et al. 2020) (Figure 3).

Table 3. Top-ranked bioactive compounds docking results against DPP-4 (3VJK) compared to Teneligliptin.

No	Ligand Name	Rerank Score (kcal/mol)
1	cc_Procyanidin B2	-119.716
2	ep_Gemin D	-117.92
3	ap_Bisandrographolide C	-114.047
4	cx_Demethoxycurcumin	-112.767
5	cc_Icariside DC	-112.234
6	cc_Cinnacasside C	-112.089
7	cc_Procyanidin B7	-110.98
8	cc_Cinnacasside A	-110.583
9	ep_Mulberrofuran C	-108.939
10	cx_letestuianin A	-108.264
11	cx_bisdemethoxycurcumin	-107.844
12	cc_Procyanidin B1	-107.213
13	ep_Darendoside A	-106.182
14	cc_8-C-Glucopyranosylprocyanidin B2	-105.868
15	ap_Neoandrographolide	-105.066
16	ap_Skullcapflavone I 2_-O-glucoside	-104.648
17	ep_2,6-Di-O-galloyl-ß-D-glucose	-103.986
18	ap_Bisandrographolide B	-103.198
19	cc_Procyanidin B5	-101.892
20	cc_Cinnamoside	-100.472
21	ap_3-O-Caffeoylquinic acid	-100.102
22	cc_6-C-Glucopyranosylepicatechin	-99.602
23	cc_6-C-Glucopyranosylprocyanidin B2	-98.500
24	ap_5-Hydroxy-7,8,2_,3_-tetramethoxyflavone 5-glucoside	-97.709
25	ap_3-O-beta-D-Glucopyranosylandrographolide	-97.570
26	cc_Procyanidin C1	-96.739
27	ap_Andrographiside	-96.497
28	ep_ß-sitosterol	-96.395
29	ep_2,3-(S)-Hexahydroxydiphenoyl-D-glucose	-95.937
30	cx_1,5-Dihydroxy-1,7- bis(4-hydroxy-3-methoxyphenyl)-4,6- heptadien-3-one	-95.666
31	ap_5-Hydroxy-7,8,2_-trimethoxyflavone 5-glucoside	-95.396
32	ep_malvidin	-95.085
33	ap_Andropanoside	-94.89
34	ep_Thannilignan	-94.626
35	ap_5,2_,3_-Trihydroxy-7,8-dimethoxyflavone 3_-glucoside	-96.194
36	ap_14-Deoxy-17-hydroxyandrographolide	-93.968
37	Teneligliptin (*Standard Drug*)	-93.501

Note: *cc = Cinnamomum burmannii Cortex; ep = Eugenia polyantha (Syzygium polyanthum); ap = Andrographis paniculata; cx = Curcuma xanthorrhiza.*

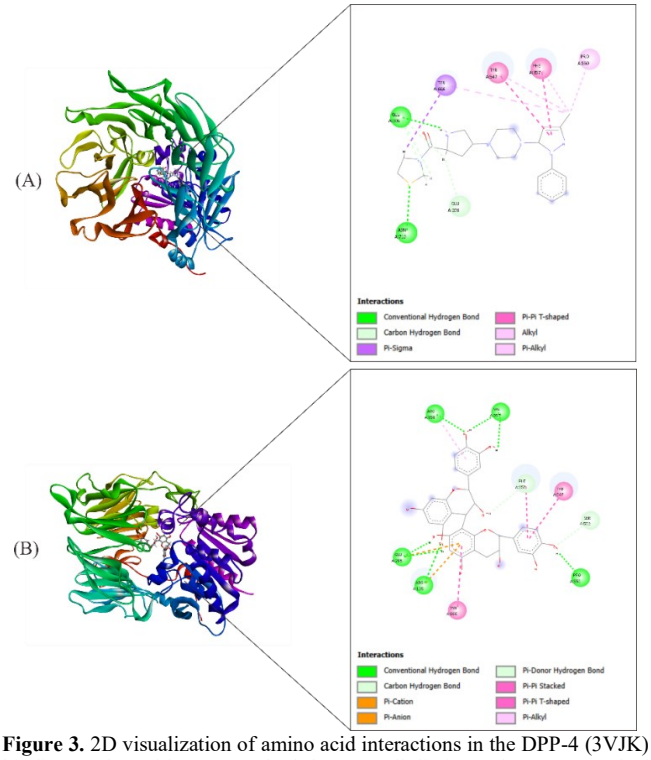


Figure 3. 2D visualization of amino acid interactions in the DPP-4 (3VJK) binding pocket with (A) Standard drug Teneligliptin; and (B) Top-ranked compound Procyanidin B2.

Interaction with AKR1C3 Receptor

Bisandrographolide B demonstrated the highest affinity for AKR1C3 (-150.050 kcal/mol) relative to Glimepiride (-120.088 kcal/mol) (Table 4). The ligand formed specific hydrogen bonds with ASN 167, LEU 128, and

TRP 227 (Figure 4). The interaction with TRP 227 facilitates a highly stable and specific binding distinct from the standard drug interaction (Prasetiyo et al. 2024).

Table 4. Top-ranked bioactive compounds docking results against AKR1C3 (4YVX) compared to Glimepiride.

No	Ligand Name	Rerank Score (kcal/mol)
1	ap_Bisandrographolide B	-150.05
2	cc_8-C-Glucopyranosylepicatechin	-128.256
3	cc_Randilongin	-127.084
4	cc_8-C-Glucopyranosylprocyanidin B2	-125.798
5	cc_Cinnacassiol	-125.082
6	ep_Gemin D	-122.575
7	ep_2,6-Di-O-galloyl-ß-D-glucose	-122.462
8	cc_Cinnacasside A	-121.607
9	Glimepiride (*Standard Drug*)	-120.088

Note: *cc = Cinnamomum burmannii Cortex; ep = Eugenia polyantha (Syzygium polyanthum); ap = Andrographis paniculata; cx = Curcuma xanthorrhiza*

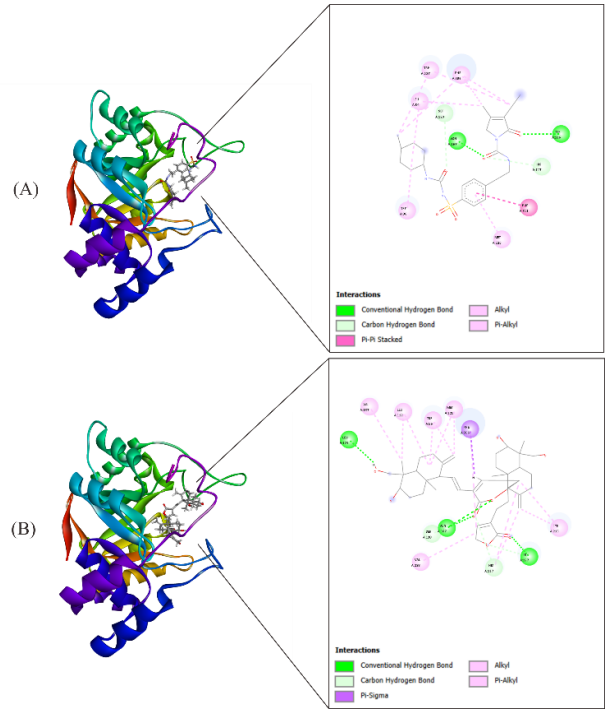


Figure 4. 2D visualization of amino acid interactions in the AKR1C3 (4YVX) binding pocket with (A) Standard drug Glimepiride; and (B) Top-ranked compound Bisandrographolide B.

Interaction with SGLT2 Receptor

Gemin D emerged as the top SGLT2 inhibitor (-162.131 kcal/mol), surpassing Empagliflozin (-130.043 kcal/mol) (Table 5). It maintained critical interactions with ASN 75 and ASP 454 while forming unique hydrogen bonds with GLN 457 and ASP 158 (Figure 5), which compensated for steric constraints and stabilized the complex (Sari et al. 2020).

Table 5. Top-ranked bioactive compounds docking results against SGLT2 (7VSI) compared to Empagliflozin.

No	Ligand Name	Rerank Score (kcal/mol)
1	ep_Gemin D	-162.131
2	cc_Cinnacasside E	-149.876
3	ap_Skullcapflavone I 2_-O-glucoside	-149.51
4	cc_Cinnacasside C	-144.513
5	ep_2,6-Di-O-galloyl-ß-D-glucose	-136.597
6	cx_1,5-Dihydroxy-1,7- bis(4-hydroxy-3-methoxyphenyl)-4,6- heptadien-3-one	-136.224
7	ap_5,4_-Dihidroxy-7,8,2_,3_-tetramethoxy flavone 5-glucoside	-132.208
8	cc_Kelampayoside A	-132.045
9	Empagliflozin (*Standard Drug*)	-130.043

Note: *cc = Cinnamomum burmannii Cortex; ep = Eugenia polyantha (Syzygium polyanthum); ap = Andrographis paniculata; cx = Curcuma xanthorrhiza.*

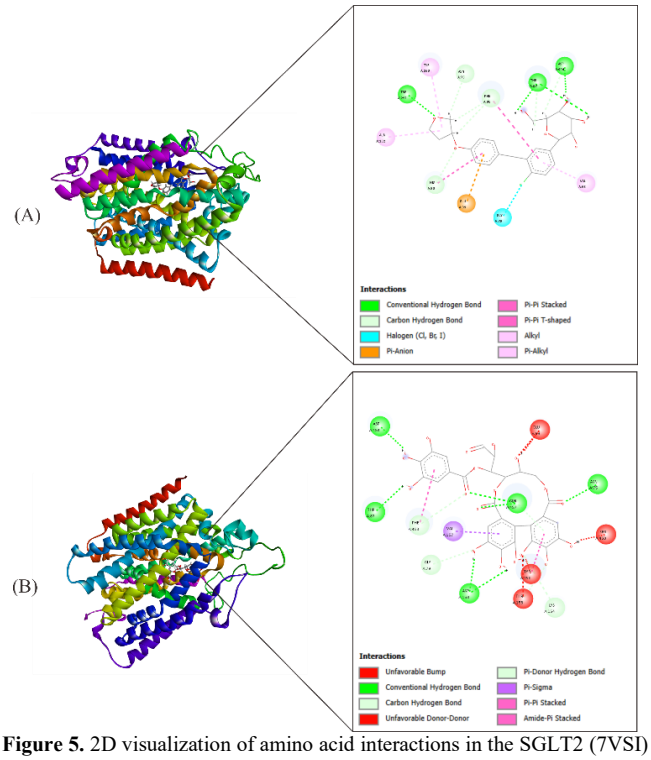


Figure 5. 2D visualization of amino acid interactions in the SGLT2 (7VSI) binding pocket with (A) Standard drug Empagliflozin; and (B) Top-ranked compound Gemin D.

Potential of 2,6-Di-O-galloyl-β-D-glucose as a Multi-Target Antidiabetic Agent

Given the complexity of diabetes, multi-target therapies are often more effective than single-target approaches. This study identified 2,6-Di-O-galloyl-β-D-glucose, a hydrolysable tannin from *Syzygium polyanthum* (Hidayati et al. 2021), as a superior multi-target candidate. It consistently exhibited stronger binding affinities than standard drugs across all targets: PPAR-γ (-133.558 kcal/mol), DPP-4 (-103.986 kcal/mol), AKR1C3 (-122.462 kcal/mol), and SGLT2 (-136.597 kcal/mol) (Table 6).

Structurally, the presence of multiple galloyl groups allows this compound to adapt flexibly to diverse binding

pockets (Figure 6). Mechanism analysis revealed that it anchors to ARG 288 in PPAR-γ, blocks the catalytic residue GLU 206 in DPP-4 (Sari et al. 2020), targets HIS 117 in AKR1C3 (Liu et al. 2021), and interacts with ASP 454 and GLN 457 in SGLT2 (Vallon and Verma 2021). These multi-pathway interactions provide a strong molecular rationale for the synergistic efficacy of the Indonesian Scientific Jamu formulation.

Table 6. Multi-target binding profile of 2,6-Di-O-galloyl-β-D-glucose compared to standard drugs across four diabetic protein targets.

Target Receptor	PDB ID	Ep_2,6-Di-O-galloyl-β-D-glucose (kcal/mol)	Standard Drug	Rerank Score (kcal/mol)
PPAR-γ Agonist	3K8S	-133.558	Pioglitazone	-103.732
DPP-4 Inhibitor	3VJK	-103.986	Teneligliptin	-93.501
AKR1C3 Inhibitor	4YVK	-122.462	Glimepiride	-120.088
SGLT2 Inhibitor	7VSI	-136.597	Empagliflozin	-130.043

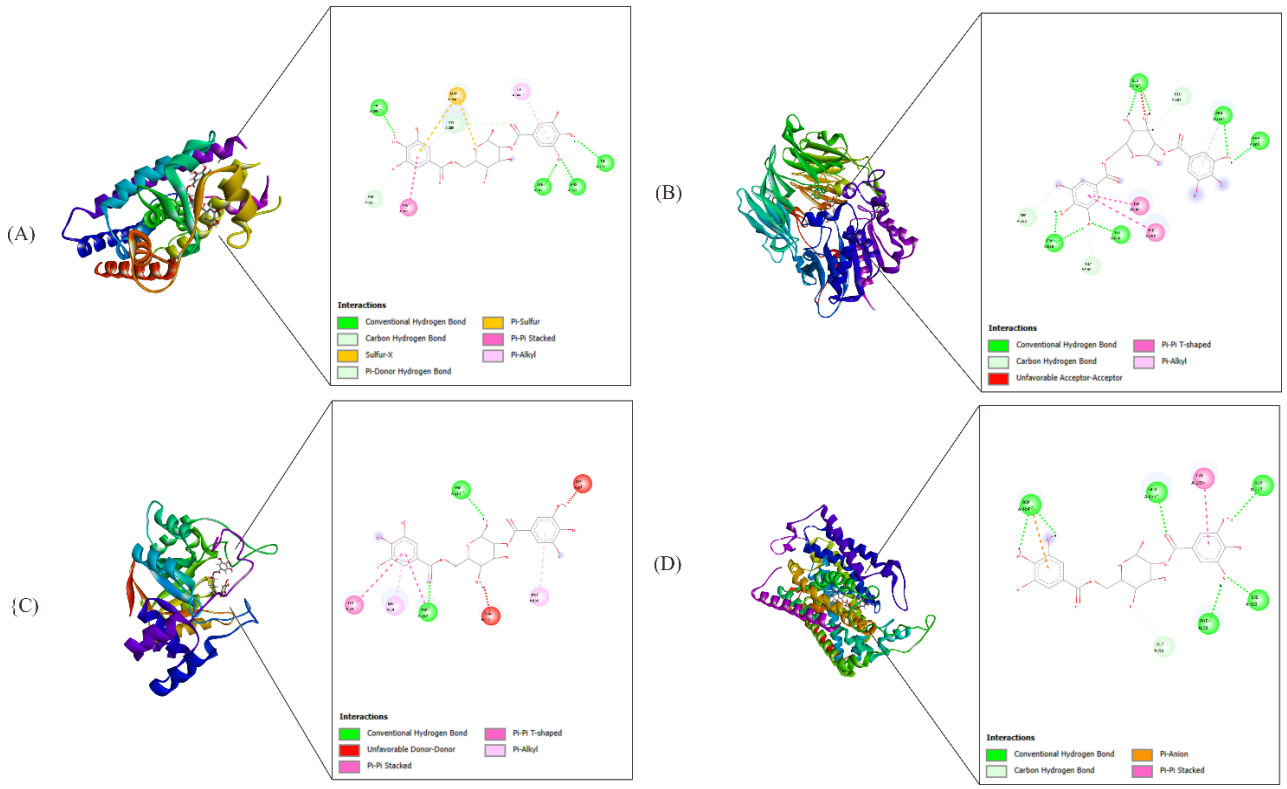


Figure 6. 2D visualization of amino acid interactions of the multi-target compound 2,6-Di-O-galloyl-β-D-glucose with (A) PPAR-γ (3K8S); (B) DPP-4 (3VJK); (C) AKR1C3 (4YVX); and (D) SGLT2 (7VSI).

Drug-Likeness Analysis (Lipinski's Rule of Five)

To evaluate oral bioavailability potential, the physicochemical properties of the top-ranked compounds were assessed based on Lipinski's Rule of Five (RO5). The analysis revealed that all top candidates, including the multi-target agent Ep_2,6-Di-O-galloyl-β-D-glucose, failed to meet the strict criteria of RO5 (Table 7). These violations were primarily due to high molecular weight (>500 Da) and an excess number of hydrogen bond donors and acceptors.

While these violations theoretically suggest poor membrane permeability, it is important to note that Lipinski's rule is derived from synthetic small molecules and is often not applicable to natural products. Many effective herbal compounds, such as tannins and glycosides (e.g., Cinnamoside and Gemin D), exhibit therapeutic efficacy despite violating these rules. Their high polarity and multiple hydroxyl groups, while reducing passive diffusion, are precisely the structural features that allow them to form extensive hydrogen bond networks with protein targets (Rhahmadini et al. 2025).

Table 7. Drug-likeness prediction of top-ranked compounds based on Lipinski's Rule of Five.

Compound Name	Parameter				Eligibility
	Molecular Weight (<500 Da)	Log P (<5)	H-Bond Acceptor (<10)	H-Bond Donor (<5)	
Cinnamoside	518.556	-2.1221	12	7	No
Procyanidin B2	578.526	2.995	12	10	No
Bisandrographolide B	664.88	5.512	8	4	No
Gemin D	634.455	-0.4539	18	11	No
2,6-Di-O-galloyl-β-D-glucose	484.366	-1.2584	14	9	No

Pharmacokinetic (ADMET) Profile Prediction

To further assess druggability, pharmacokinetic parameters including Absorption, Distribution, Metabolism, Excretion, and Toxicity (ADMET) were predicted. As presented in Table 8, AP_Bisandrographolide B demonstrated excellent intestinal absorption (84.9%), suggesting high oral bioavailability. In contrast, the glycosidic and tannin-based compounds, including Ep_2,6-Di-O-galloyl-β-D-glucose (31.7%), showed lower absorption rates consistent with their high molecular weights.

Regarding metabolism, none of the compounds were predicted to inhibit the CYP2D6 enzyme, and only Bisandrographolide B showed potential inhibition of CYP3A4, suggesting a low risk of adverse drug-drug interactions. Crucially, the toxicity assessment revealed that none of the top candidates exhibited hepatotoxicity. Their predicted LD50 values ranged from 1.366 to 2.211 g/kg, classifying them within the safe to slightly toxic category (GHS Category 4/5). This supports the safety profile of the traditional jamu formulation for long-term consumption (Abdullah et al. 2021).

Table 8. ADMET profile prediction of top-ranked bioactive compounds.

Compund Name	Absorbtion		Distribution		Metabolism				Excretion	Toxicity	
	Intestinal absorption (%)	VDss (log L/kg)	Fraction unbound (human)	BBB permeability (log BB)	CYP2D6 substrate	CYP2D6 inhibitor	CYP3A4 substrate	CYP3A4 inhibitor	Total Clearance (log ml/min/kg)	LD50 (g/kg)	Hepato toxicity
Cinnamoside	33.382	-0.895	0.651	-1.698	No	No	Yes	No	1.016	1.504	No
Procyanidin B2	55.566	-1.385	0.16	-1.722	No	No	Yes	No	0.139	2.211	No
Bisandrographolide B	84.901	0.137	0.035	-1.113	No	No	Yes	Yes	0.2	2.118	No
Gemin D	23.546	-1.779	0.334	-2.81	No	No	Yes	No	0.513	1.452	No
2,6-Di-O-galloyl-β-D-glucose	31.724	-1.663	0.47	-2.177	No	No	Yes	No	0.495	1.366	No

General Discussion

The integration of molecular docking and ADMET prediction provides robust *in silico* evidence supporting the empirical efficacy of the Indonesian Scientific Jamu formulation. The study identified specific bioactive compounds that not only exhibit strong affinity towards key diabetic targets (PPAR-γ, DPP-4, AKR1C3, and SGLT2) but also possess favorable safety profiles. In particular, the discovery of 2,6-Di-O-galloyl-β-D-glucose as a multi-target agent offers a compelling molecular explanation for the synergistic effects observed in the herbal mixture. These findings suggest that the formulation acts through a "network pharmacology" mechanism, where multiple compounds modulate various pathological pathways simultaneously, thereby reinforcing its potential as a standardized herbal medicine for diabetes management.

CONCLUSIONS

This study demonstrates that the Indonesian Scientific Jamu formulation contains bioactive compounds that modulate multiple diabetic pathways, validating its empirical use. Specifically, Cinnamoside, Procyanidin B2, Bisandrographolide B, and Gemin D were identified as the strongest ligands for PPAR-γ, DPP-4, AKR1C3, and SGLT2, respectively. A novel finding of this research is the identification of Ep_2,6-Di-O-galloyl-β-D-glucose as a superior multi-target agent that consistently outperformed standard drugs across all tested mechanisms. Although the top-ranked compounds exhibit a favorable safety profile with no predicted hepatotoxicity, their violation of Lipinski's rules suggests potential challenges in oral bioavailability. Therefore, further studies involving *in vitro* and *in vivo* assays are

recommended to validate their biological activity, alongside the development of advanced formulation strategies to enhance their absorption.

Acknowledgment: The authors would like to express their gratitude to the Faculty of Pharmacy, Universitas Pancasila, for providing the necessary facilities and software to conduct this research. We also extend our appreciation to the Medicinal Plant and Traditional Medicine Research and Development Centre (B2P2TOOT), Ministry of Health of the Republic of Indonesia, for providing the scientific data on the jamu formulation.

Authors' Contributions: Andri Prasetiyo, Esti Mulatsari & Esti Mumpuni designed the study. Teguh Sugiarto, Vandrico Junky, Fadhil M.D Adipura & Claudya F.P Nainggolan carried out the computational work and simulations. Teguh Sugiarto & Andri Prasetiyo analyzed the data. Teguh Sugiarto, Vandrico Junky, Fadhil M.D Adipura, Claudya F.P Nainggolan & Andri Prasetiyo wrote the manuscript. All authors read and approved the final version of the manuscript.

Competing Interests: The authors declare that there are no competing interests.

Funding: The authors declare no external funding.

REFERENCES

Abdullah, S. S., Putra, P. P., Antasionasti, I., Rundengan, G., Suoth, E. J., Abdullah, R. P. I., & Abdullah, F. (2021). Analisis sifat fisikokimia, farmakokinetik dan toksikologi pada Pericarpium Pala (*Myristica fragransa*) secara artificial intelligence. *Chem. Prog*, *14*(2), 81–88.

Artasensi, A., Pedretti, A., Vistoli, G., & Fessi, L. (2020). Type 2 diabetes mellitus: A review of multi-target drugs. *Molecules*, *25*(8), 1987.

Ayuningtyas, D. P., & Nurkhasanah, N. (2023). In silico study of curcuminoid compounds in *Curcuma xanthorrhiza* against Dipeptidyl Peptidase-4 (DPP-4) receptor as antidiabetic. *Pharmaciana*, *13*(1), 1–10.

Chaudhury, A., Duvoor, C., Reddy Dendi, V. S., Kraleti, S., Chada, A., Ravilla, R., ... & Mirza, W. (2017). Clinical review of antidiabetic drugs: Implications for type 2 diabetes mellitus management. *Front. Endocrinol.*, *8*, 6.

Daina, A., Michielin, O., & Zoete, V. (2017). SwissADME: A free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules. *Sci. Rep.*, *7*, 42717.

Hidayati, M. D., Ersam, T., & Shimizu, K. (2021). Antidiabetic potential of *Syzygium polyanthum* (Wight) Walp. leaves extract and its isolated compounds. *J. Appl. Pharm. Sci.*, *11*(2), 102–109.

International Diabetes Federation. (2021). *IDF Diabetes Atlas* (10th ed.). International Diabetes Federation.

Kementerian Kesehatan RI. (2019). *Sebelas Ramuan Jamu Saintifik: Pemanfaatan Mandiri oleh Masyarakat*. Balai Besar Penelitian dan Pengembangan Tanaman Obat dan Obat Tradisional (B2P2TOOT).

Kementerian Kesehatan RI. (2023). *Laporan Survei Kesehatan Indonesia (SKI) 2023: Dalam Angka*. Badan Kebijakan Pembangunan Kesehatan.

Lipinski, C. A., Lombardo, F., Dominy, B. W., & Feeney, P. J. (2001). Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. *Adv. Drug Deliv. Rev.*, *46*(1-3), 3–26.

Liu, C., Zhang, Y., & Li, X. (2021). Aldo-keto reductase 1C3 (AKR1C3): A potential therapeutic target for metabolic disorders and insulin resistance. *Front. Endocrinol.*, *12*, 654–662.

Mulatsari, E., Martati, T., Mumpuni, E., & Dewi, N. L. (2020). In silico analysis of antiviral activity of analog curcumin compounds. *J. Jamu Indones.*, *5*(3), 114–121.

Pires, D. E., Blundell, T. L., & Ascher, D. B. (2015). pkCSM: Predicting small-molecule pharmacokinetic and toxicity properties using graph-based signatures. *J. Med. Chem.*, *58*(9), 4066–4072.

Prasetiyo, A., Martati, T., & Saputra, P. W. (2024). In silico study of bioactive compounds in Herba Sambiloto (*Andrographis paniculata* Burm. F. Nees) as HIV-1 reverse transcriptase inhibitor. *J. Jamu Indones.*, *9*(2), 55–63.

Rhahmadini, Y. T., Taqwa, I. A., Dhani, M., Mawijaya, A., Susanti, E., Simanjuntak, J. D., Mulatsari, E., Mumpuni, E., & Prasetiyo, A. (2025). Molecular docking study of bioactive compounds in Senggugu (*Clerodendrum serratum* (L.) Moon) as antidiabetics. *J. Kim. Ris.*, *10*(1), 60–73.

Sari, I. W., Junaidin, J., & Pratiwi, D. (2020). Studi molecular docking senyawa flavonoid Herba Kumis Kucing (*Orthosiphon stamineus* B.) pada reseptor α-glukosidase sebagai antidiabetes tipe 2. *J. Farmagazine*, *7*(2), 54–60.

Thomsen, R., & Christensen, M. H. (2006). MolDock: A new technique for high-accuracy molecular docking. *J. Med. Chem.*, *49*(11), 3315–3321.

Vallon, V., & Verma, S. (2021). Effects of SGLT2 inhibitors on kidney and cardiovascular function. *Annu. Rev. Physiol.*, *83*, 503–528.

Wulandari, L., Retnaningtyas, Y., & Noverda, A. (2022). Molecular docking analysis of cinnamaldehyde from *Cinnamomum burmannii* against PPAR-gamma receptor. *J. Pharm. Sci.Community*, *19*(1), 25–30.

Yuliana, N. D., Budijanto, S., & Verawati, B. (2023). Metabolite profiling and antidiabetic potential of *Andrographis paniculata* extract via in silico and in vitro approaches. *Hayati J.Biosci.*, *30*(2), 289–299