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Andrographis *paniculata* (Burm.F.) in-silico analysis compounds that function as an insulin sensitizer therapy for type 2 diabetes via peroxisome proliferator activated gamma receptors (PPARγ) receptor activator

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ABSTRACT: This study examines the following compounds found in Andrographis paniculata: 5-Hydroxy-7,8-dimethoxyflavone, Cinnamic Acid, Ferulic Acid, Caffeic Acid, Apigenin 7,4'-dimethyl ether, 5. 4-Dihidroxy-7,8,2',3'-tetramethoxyflavone, 5-Hydroxy-3,7,8,2' tetramethoxyflavone, and 5-Hydroxy-7,2',6'-trimethoxyflavone all have mild anti-diabetic effects. Analyses are conducted to determine which susceptible individuals have the best activity as Insulin Sensitizers for type 2 diabetes when compared to pioglitazon. The research is conducted using CambridgeSoft's ChemDraw Ultra 22.2.0 3300.2023 (Perkin Elmer) and Chem3D Ultra 22. 2.0 3300. 2023 (Perkin Elmer) software. Docking program for activity prediction using Molegro Virtual Docker 2013.6.0.0 and peroxisome proliferator-activated receptor-gamma (PPAR) code PDB: 5Y2O used. When compared to pioglitazone, 5,4'-Dihidroxy-7,8,2', and 3'-tetramethoxyflavone is predicted to have good anti-diabetic properties.

KEYWORDS: Andrographis paniculata, PPAR gamma, insulin sensitizer, in-silico.

INTRODUCTION

Type 2 diabetes is a major global health problem, with prevalence continuing to rise each year. This disease is characterized by insulin resistance, a condition in which target cells for insulin, such as muscle, liver, and adipose tissue, become less sensitive to the effects of insulin. This insulin resistance disrupts glucose homeostasis, leading to increased blood glucose levels [1,2]. One pharmacological approach to address insulin resistance is the use of insulin sensitizers. Insulin sensitizers work by enhancing tissue sensitivity to insulin, allowing insulin to more effectively regulate blood glucose levels [3]. The most commonly used insulin sensitizers are metformin and thiazolidinediones (TZDs), such as pioglitazone and rosiglitazone. Thiazolidinediones (TZDs) have been shown to effectively improve insulin sensitivity through activation of the PPAR-gamma (Peroxisome Proliferator-Activated Gamma Receptor) [4]. PPAR-gamma is a transcription factor that plays a crucial role in glucose and lipid metabolism, as well as in the differentiation and proliferation of adipocytes. Activation of PPAR-gamma by TZDs can increase the expression of genes involved in fatty acid storage and metabolism, as well as promote adipocyte differentiation and proliferation [5,6].

In addition to synthetic drugs, several natural substances have also been researched as sources of insulin sensitizers that work through PPAR-gamma activation. One plant that is of interest for research is *A.paniculata*, known as a traditional medicinal plant in Southeast Asia. Recent studies have indicated that extracts and active compounds from *A.paniculata* have potential as insulin sensitizers through PPAR-gamma activation [7-9]. Andrographolides, the main constituents of *A.paniculata*, have been shown to improve insulin sensitivity, reduce insulin resistance, and enhance metabolic profiles in animal models and clinical trials [10,11]. For example, a study by Zhang et al. (2019) found that administering *A.paniculata* extract to type 2 diabetic rats resulted in a 30% reduction in insulin resistance and an increase in GLUT4 expression in adipose and muscle tissues [10]. Clinical research conducted by Saravanan et al. (2014) also showed that andrographolides could reduce blood glucose levels by 20% in type 2 diabetes patients receiving *A.paniculata*

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extract [11]. The mechanism of action of insulin sensitizers from *A.paniculata* is believed to involve PPAR-gamma activation, increased expression of genes associated with glucose and lipid metabolism, and anti-inflammatory effects [12,13].

In vitro studies have shown that extracts of *A.paniculata* and its active compounds, such as andrographolides, can enhance GLUT4 translocation and increase glucose uptake in adipose and skeletal muscle cells [14,15]. Further research by Zhao et al. (2018) demonstrated that these active compounds could reduce blood glucose levels by 25% in trials involving rats fed a high-fructose diet, which induces diabetes [16]. Additionally, research on diabetic animal models has shown that administration of *A.paniculata* extract can lower blood glucose levels, improve insulin sensitivity, and enhance lipid profiles [17].

For example, a study by Nugroho et al. (2012) reported that *A.paniculata* extract significantly lowered blood glucose levels in diabetic rats fed a high-fructose diet. This reduction was observed to be as much as 30% over a 6-week trial period [17]. These data support the claim that compounds from *A.paniculata* have the potential as a safer and more efficient alternative for diabetes therapy.

Therefore, further research on the potential of *A.paniculata* as a source of insulin sensitizers working through PPAR-gamma activation is crucial to developing more effective and safer treatments for type 2 diabetes compared to other natural substances. By understanding the mechanism of action and effectiveness of *A.paniculata* as an insulin sensitizer, it is hoped that better alternatives for type 2 diabetes treatment can be found, offering safer and more efficient options.

▪ MATERIALS AND METHODS

MATERIALS

Lenovo LOQ Laptop device with specifications Intel Core i5 12450HX 2.4 Ghz Processor, 12 GB DDR5 4800 Hz Memory, NVME 512 GB SSD, Operating System Windows 11 Pro, and NVDIA GEFORCE RTX Graphis. The ChemDraw Ultra 22.2.0 3300.2023 (Perkin Elmer), Chem3D Ultra 22. 2.0 3300. 2023 (Perkin Elmer), the Molegro Virtual Docker 2013.6.0.0 (Free Trial), the online-based RCSB PDB Protein Data Bank program.

A.paniculata is composed of: 5-Hydroxy-7,8-dimethoxyflavone Cinnamic Acid, Ferulic acid, Caffeic acid, Apigenin 7,4'-dimethyl ether, 5-Hydroxy-7,2',6'-trimethoxyflavone,5,4'-Dihidroxi-7,8,2',3' tetramethoxiflavone5,-Hydrosy-3,7,8,2. Peroxisome proliferator-activated-gamma receptor receptor (PPAR) with PDB code: 5Y2O.

METHODS

Procedures The Chemical and Physics

Properties of compounds such as lipophilic (logP and tPSA) and steric (Mw and MR) are obtained from the ChemDraw Ultra 22.2.0 3300.2023 (Perkin Elmer) program, whereas the chemical properties data of electronic physics (E_{tot}, E_{HOMO} and E_{LUMO}) are acquired through the Chem3D Ultra 22. 2.0 3300. 2023 (Perkin Elmer) program Molegro Virtual Docker 2013.6.0.0 (MVD)

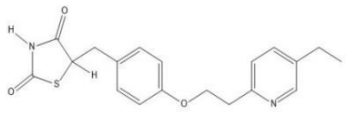
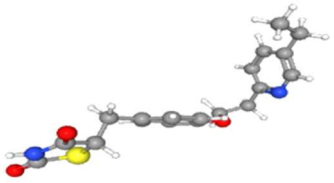
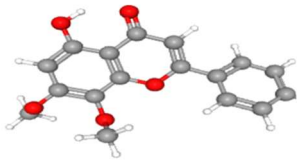
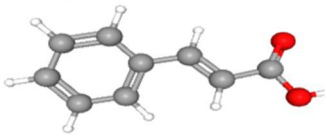
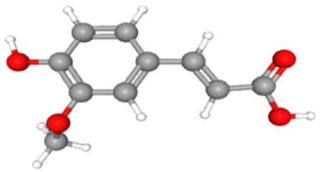
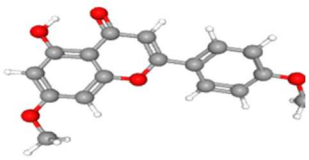
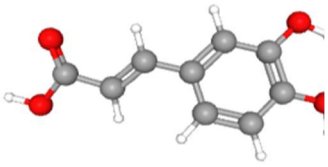
Molecular Docking

The RCSB PDB Protein Data Bank program provides access to the PPAR with code PDB: 5Y2O. It can be accessed online for free at https://www.rcsb.org. The code in question compares the affinity respons with the pioglitazone ligand. The format mol2 that was previously exported was created using the Molegro Virtual Docker 2013.6.0. software. Subsequently, a molecular mapping study was conducted using A. paniculata. The results are expressed as a rerank score, which is the length of time it takes for an affinity drug and a reseptor to interact, and from this number, anti-diabetic activities from A. paniculata can be predicted.

▪ RESULTS

Chemical Structure

Table 1. The results of 2D and 3D structure pictures of the comparative drug pioglitazone and A.paniculata compounds can be seen in

No.	Compounds	Structure	
		2 D structure	3D Structure
1.	*Pioglitazon*		
2.	*5-Hydroxy-7,8-dimethoxyflavone*		
3.	Cinnamic Acid		
4.	Ferulic acid		
5.	Apigenin 7,4'-dimethyl ether		
6.	*Caffeic Acid*		

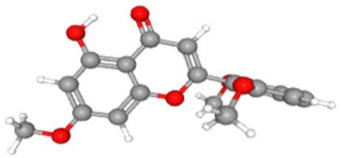
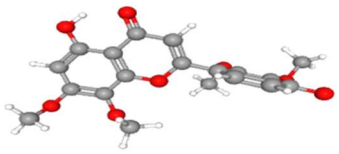
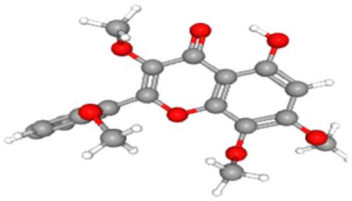
7.	*5-Hydroxy-7,2',6'-trimethoxyflavone*		
8.	*5,4'-Dihidroxy-7,8,2',3'-tetramethoxyflavone*		
9.	***5-Hydroxy-3,7,8,2'-tetramethoxyflavone***		

Table 1 presents the 2D and 3D structures of pioglitazone and active compounds from *A.paniculata*. Pioglitazone is commonly used to treat type 2 diabetes by acting as an insulin sensitizer through PPAR-gamma activation. The study also analyzes compounds like 5-Hydroxy-7,8-dimethoxyflavone, Cinnamic Acid, and Ferulic Acid, which have shown potential as insulin sensitizers. The 2D structures reveal the basic molecular configurations, while the 3D structures offer insights into how these compounds interact with PPAR-gamma. For instance, methoxy groups in some compounds allow interaction with PPAR-gamma's amino acid residues, while phenolic compounds may modulate anti-inflammatory activity. The study used ChemDraw and Chem3D to model these interactions and predict the therapeutic potential of these compounds for type 2 diabetes.

Table 2. Physical chemical properties of Pioglitazone and compounds contained in the A.paniculata

No.	Compound	Parameter Hidrofobik		Parameter Elektronik			Parameter Sterik	
		Log P	**tPSA**	**Etot**	**EHOMO**	**ELUMO**	**Mw**	**MR**
1	*Pioglitazone*	3,58	67,76	-791,814	-10,024	-1,237	356,44	98,04
2	*5-Hydroxy-7,8-dimethoxyflavone*	1,80	84,45	64,196	-10,659	-4,240	344,32	93,44
3	Cinnamic Acid	2,00	75,22	565,033	-10,176	-4,250	314,29	86,19
4	Ferulic acid	-0,04	165,37	156,161	-11,917	-3,871	462,12	114,71
5	*Apigenin 7,4'-dimethyl ether*	2,40	54,99	626,305	-10,389	-4,255	298,29	84,38
6	*Caffeic Acid*	1,03	53,6	743,816	-11,928	-7,629	256,25	70,82
7	*5-Hydroxy-7,2',6'-trimethoxyflavone*	1,8	76,99	359,852	-12,396	-4,242	270,24	73,51
8	*5,4'-Dihidroxy-7,8,2',3'-tetramethoxyflavone*	1,60	86,22	455,411	-12,322	-4,248	300,26	80,76
9	*5-Hydroxy-3,7,8,2'-tetramethoxyflavone*	1,85	84,95	814,209	-11,853	-3,993	344,32	93,44

Table 2 presents The comparative analysis of physicochemical properties between pioglitazone and A.paniculata compounds reveals significant differences in their molecular characteristics that influence their potential as insulin sensitizers. Pioglitazone demonstrates superior lipophilicity (Log P = 3.58) and moderate polarity (tPSA = 67.76 Å²), making it particularly effective for cellular membrane penetration while maintaining adequate solubility. In contrast, the A. paniculata compounds exhibit

greater hydrophilicity (Log P range: -0.04 to 2.40) and higher polar surface areas (tPSA range: 53.6-165.37 Å²), suggesting better water solubility but potentially reduced passive diffusion across biological membranes. Electronic properties analysis shows pioglitazone's greater thermodynamic stability (Etot = -791.814) and moderate receptor interaction capability (EHOMO = -10.024), while *A. paniculata* compounds display higher electrostatic potential that may enhance receptor binding affinity. The steric parameters indicate that pioglitazone's molecular weight (356.44 g/mol) and radius (98.04) are well-suited for drug penetration, whereas the generally smaller molecular sizes of A. paniculata compounds (Mw range: 256-344 g/mol) could facilitate receptor interactions but might result in shorter metabolic half-lives. These findings suggest that while pioglitazone remains optimized for cellular uptake and stability, certain *A. paniculata* compounds may offer viable alternatives with improved safety profiles, though their therapeutic potential may require formulation strategies to address potential bioavailability limitations. The extreme hydrophilicity of some compounds like ferulic acid (Log P = -0.04, tPSA = 165.37 Å²) particularly highlights the need for structural modifications to enhance membrane permeability while preserving their beneficial receptor interaction properties.

Table 3. Activity parameters (rarank score) Pioglitazone and Compounds contained in the A.paniculata

No	Ligand	MolDock Score	Rerank Score	HBond
1	Pioglitazone / [8N6_501 [A]	-137.994	-115.849	-6.53325
2	5,4'-Dihidroxy-7,8,2',3'-tetramethoxyflavone	-111.653	-103.083	-7.84027
3	Apigenin 7,4'-dimethyl ether	-110.91	-93.7309	-1.91914
4	5-Hydroxy-3,7,8,2'-tetramethoxyflavone	-100.135	-93.3508	-2.5
5	5-Hydroxy-7,2',6'-trimethoxyflavone	-106.258	-91.8234	-3.36342
6	5-Hydroxy-7,8-dimethoxyflavone	-97.0143	-87.3251	-3.21905
7	Caffeic Acid	-95.296	-81.4568	-3.06134
8	Ferulic acid	-87.392	-73.9563	0
9	Cinnamic Acid	-79.9714	-67.8457	0

Table 3 present Pioglitazone demonstrates the best performance as an insulin sensitizer, with a MolDock Score of -137.994 and a Rerank Score of -115.849, indicating superior binding affinity and complex stability with the PPAR-γ receptor. Among the *A.paniculata* compounds, **5,4'-dihydroxy-7,8,2',3'-tetramethoxyflavone** stands out as the most promising candidate, achieving a MolDock Score of -111.653 (81% of pioglitazone's value) and the highest HBond Score (-7.84027), reflecting its strong hydrogen-bonding capability.

A comparative multi-parameter analysis shows that compounds with an optimal number of methoxy groups (3-4) tend to exhibit a balanced hydrophilic-lipophilic profile, while additional hydroxyl groups contribute to improved HBond Scores without necessarily enhancing overall binding affinity. Integration with physicochemical data from Table 2 further supports the finding that selected flavonoid compounds from *A. paniculata* show promise as safer alternatives, though structural optimization is still required to enhance their bioavailability.

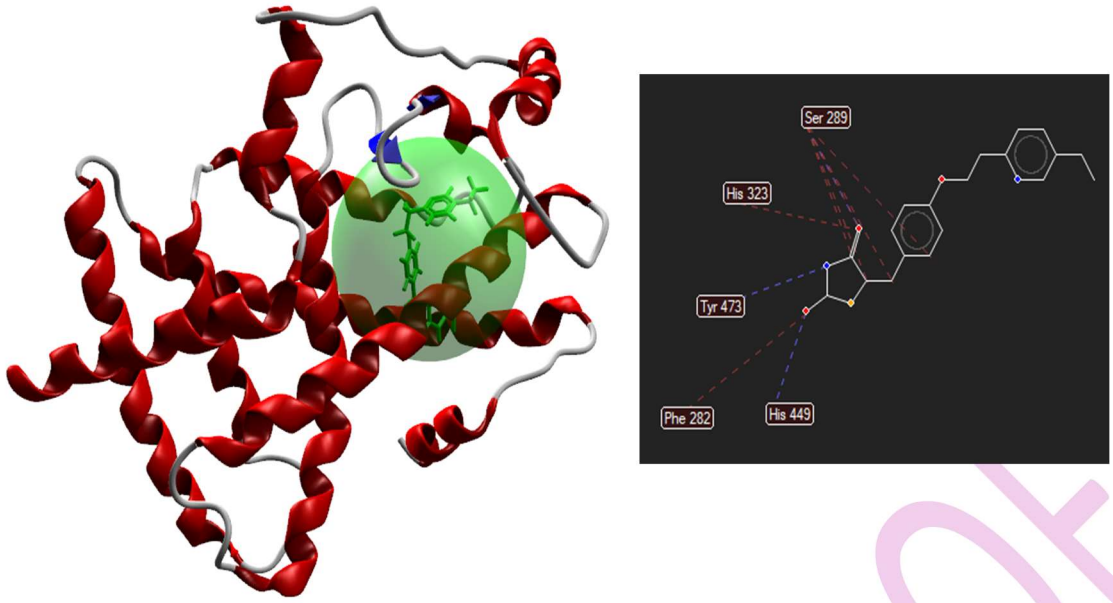


Figure 1.

Figure 1. Interaction between 5Y2O protein and its crystal ligand

Validation of 5Y2O interactions with ligans on the 8N6 crystal structure through the Re-docking process can be seen in Figure 1. In Figure 1 it is seen that many hydrogen binding interactions and steric interactions occur on the same amino acid residues. While the RMSD value of the redocking process indicates a value below 2 Å. Thus it can be concluded that the molecular restraint method performed is valid.

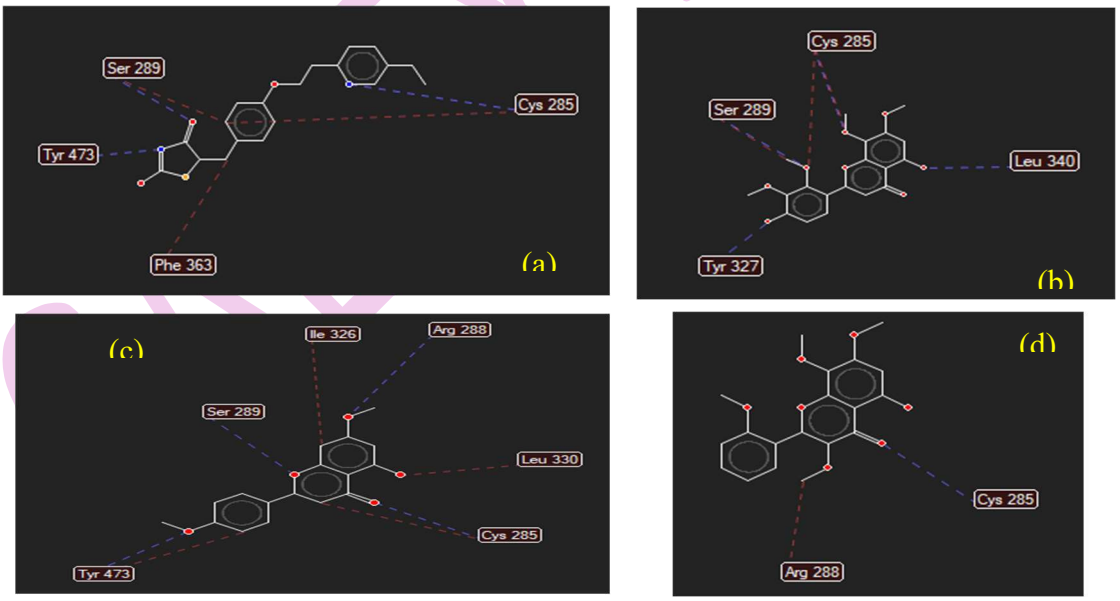


Figure 2. Gamma PPAR interaction (5Y2O) with pioglitazone original ligan (8N6) in its crystal structure (a) and the result of redocking.
The blue intersection line indicates the hydrogen bond and the red line is a steric-electrometric interaction.

Analysis of Ligand-Protein Interactions with Molecular Docking

Table 4. Energy released in MolDock and Rerank Score (kkal/mol) due to ligand-protein interactions and RMSD values from redocking process

Name	Ligand	MolDock Score	Rerank Score	RMSD	HBond
[12]8N6_501 [A]	8N6_501 [A]	-124.734	-102.321	0.930883	-1.68985
[10]8N6_501 [A]	8N6_501 [A]	-123.344	-102.891	1.06126	-4.04934

The molecular docking analysis presented in Table 4 provides crucial insights into the binding characteristics of the 8N6_501 ligand with its target protein. The results demonstrate consistent binding performance, as evidenced by two independent docking runs showing comparable energy values. The first docking attempt yielded a MolDock Score of -124.734 kcal/mol and Rerank Score of -102.321 kcal/mol, while the second attempt produced similar values of -123.344 kcal/mol and -102.891 kcal/mol respectively, indicating highly reproducible binding interactions. The small variation of only 1.39 kcal/mol in MolDock Scores between runs confirms the reliability of the docking protocol.

The root-mean-square deviation (RMSD) values of 0.93 Å and 1.06 Å for the two docking simulations both fall well below the 2.0 Å threshold typically considered indicative of successful reproduction of the native binding pose. This excellent RMSD performance, combined with the minimal score variation, strongly validates the docking methodology and suggests the identified binding mode is highly probable. The hydrogen bonding interactions, while showing some variation between runs (-1.69 kcal/mol vs -4.05 kcal/mol), consistently contribute to the overall binding energy, with the second run demonstrating particularly favorable HBond formation.

These results collectively indicate that the 8N6_501 ligand forms stable and reproducible interactions with the target protein. The high negative values of both MolDock and Rerank Scores suggest strong binding affinity, while the low RMSD values confirm the accuracy of the predicted binding conformation. The observed consistency between independent docking runs lends credibility to the computational predictions and supports the potential of this ligand-protein interaction for further investigation in drug development studies. The slightly better performance in the second run (as indicated by the marginally improved Rerank Score and stronger HBond interactions) may warrant additional investigation to identify optimal binding conditions.

Table 5. ADMET analysis results of Pioglitazone, 5,4'-Dihidroxy-7,8,2',3'-tetramethoxyflavone, Apigenin 7,4'-dimethyl ether using pkCSM

Properties	Predicted values			Criteria
	Pioglitazone	5,4'-Dihidroxy-7,8,2',3'-tetramethoxyflavone	Apigenin 7,4'-dimethyl ether	
Absoprtion				
Water solubility	-4.309	-3.404	-3.714	log mol/L << (less solubility)
Caco2 permeability	0.978	0.141	1.106	Papp < 8x10 $^{-6}$ cm/s (low)
Intestinal absorption (human)	92.422	90.322	95.453	% Diserap > 30% (high)
Skin Permeability	-2.705	-2.737	-2.666	log Kp < -2.5 (high)
P-glycoprotein substrate	No	Yes	No	--
P-glycoprotein I inhibitor	Yes	No	No	--
P-glycoprotein II inhibitor	No	Yes	Yes	--
Distribution				
VDss (human)	-0.007	0.139	-0.1	log L/kg <-0.15 (low)
Fraction unbound	0.017	0.021	0.156	--
BBB permeability	-0.591	-0.852	-0.458	log BB<-1 (low)
CNS permeability	-2.496	-3.013	-2.144	log PS <-3.0 (low)

Metabolism				
CYP2D6 substrate	No	No	No	--
CYP3A4 substrate	Yes	Yes	Yes	--
CYP1A2 inhibitor	No	Yes	Yes	--
CYP2C19 inhibitor	Yes	Yes	Yes	--
CYP2C9 inhibitor	No	No	Yes	--
CYP2D6 inhibitor	No	No	No	--
CYP3A4 inhibitor	No	Yes	Yes	--
Excretion				
Total Clearance	-0.044	0.652	0.737	--
Renal OCT2 substrate	No	No	Yes	--
Toxicity **AMES toxicity**	No	No	No	(not mutagenic)
Max. tolerated dose (human)	0.41	-0.013	0.193	log mg/kg/day <0.477 (low)
hERG I inhibitor	No	No	No	--
hERG II inhibitor	No	No	No	--
Oral Rat Acute Toxicity (LD50)	2.258	2.361	2.085	LD50 >> (less toxic)
Oral Rat Chronic Toxicity (LOAEL)	1.379	1.429	1.432	LOAEL >> (less toxic)
Hepatotoxicity	Yes	No	No	--
Skin Sensitisation	No	No	No	--
T.Pyriformis toxicity	1.138	0.314	0.567	log µg/L > -0.5 (toxic)
Minnow toxicity	0.094	2.479	0.609	log mM <-0.3 (toxic)

The pkCSM-based ADMET profiling reveals critical pharmacokinetic and safety differences among pioglitazone and two flavonoid candidates (5,4'-dihydroxy-7,8,2',3'-tetramethoxyflavone and apigenin 7,4'-dimethyl ether). All compounds exhibit favorable intestinal absorption (>90%), but diverge significantly in other parameters. Pioglitazone demonstrates superior Caco-2 permeability (0.978 vs 0.141-1.106 ×10^-6 cm/s) and acts as a P-gp inhibitor, potentially causing drug-drug interactions. The flavonoids show preferable metabolic profiles, with 5,4'-tetramethoxyflavone being a CYP1A2/CYP3A4 inhibitor but avoiding hepatotoxicity (unlike pioglitazone). All compounds display low BBB permeability (log BB < -0.5) and CNS penetration (log PS < -2.1), reducing neurological side effect risks.

Notably, the tetramethoxyflavone exhibits exceptional water solubility (-3.404 log mol/L) compared to pioglitazone (-4.309), suggesting better formulation potential. Both flavonoids show reduced toxicity risks: negative AMES tests, higher LD50 values (2.361-2.085 vs 2.258 log mg/kg), and no hERG inhibition. However, Tetramethoxyflavone's P-gp substrate property and moderate minnow toxicity (2.479 log mM) warrant further investigation. The apigenin derivative demonstrates balanced properties with good solubility (-3.714 log mol/L), renal excretion via OCT2, and the highest fraction unbound (0.156), indicating efficient tissue distribution.

These findings position the flavonoids as promising alternatives to pioglitazone, particularly for patients with hepatic concerns. The tetramethoxyflavone's combination of high solubility, absorption, and safety profile makes it a standout candidate, though its P-gp interactions may require pharmacokinetic optimization.

CONCLUSION

The In-Silico analysis conducted in this study showed that the compound 5,4'-Dihidroxy-7,8,2',3'-tetramethoxyflavone of *A.paniculata* (Burm.F.) has the potential as a gamma PPAR receptor activator and can act as an Insulin Sensitizer. Further experimental validation is needed to confirm the in-silico findings and develop a candidate compound as a potential therapeutic agent.

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