

In Silico Screening, Molecular Docking, and Pharmacokinetic Evaluation of Phenolic and Flavonoid Bioactive Compounds from *Cardiospermum halicacabum* Against Type 2 Diabetes...

Sushmitha. K¹, Umme Umaima S², Veeraraghavan. V^{*2}, Renuka Srihari.K³, and Kirankumar B⁴

¹Research Scholar, Department of Biochemistry, School of Allied Health Sciences, REVA University, Bangalore-64, Karnataka, India

²Department of Biochemistry, School of Allied Health Sciences, REVA University, Bangalore-64, Karnataka, India

³Department of Biochemistry, Maharani Lakshmi Ammanni College for Women, Bangalore-12, Karnataka, India

⁴Department of Biotechnology, Maharani Lakshmi Ammanni College for Women (mLAC), Bengaluru 560012, Karnataka, India.

Corresponding authors:

Dr.Veeraraghavan. V,

Professor, Department of Biochemistry, REVA University.

Email id:vveeraraghavan0617@gmail.com

ABSTRACT

Type 2 diabetes mellitus (T2DM) remains a major global health burden, driving continued interest in plant-derived bioactive compounds as safer, multi-targeted therapeutic alternatives to synthetic antidiabetic drugs. This study evaluated eight phenolic and flavonoid compounds isolated from *Cardiospermum halicacabum* apigenin, chrysoeriol, kaempferol, luteolin, p-coumaric acid, quercetin, gallic acid, and 4-hydroxybenzoic acid for their drug-likeness, pharmacokinetic behaviour, and inhibitory potential against Dipeptidyl Peptidase-IV (DPP-IV), a validated target enzyme in T2DM management, using in silico approaches. Lipinski's Rule of Five analysis confirmed that all eight compounds fully complied with the four criteria (molecular weight, logP, hydrogen bond donors, and acceptors), indicating favorable oral drug-likeness. ADMET prediction revealed superior intestinal absorption (74–93%) relative to metformin (59.4%), along with non-mutagenic, non-hepatotoxic, and non-cardiotoxic (hERG-negative) profiles, positioning these compounds as safer candidates than the standard reference drug on several toxicity parameters. Molecular docking against DPP-IV demonstrated that all eight compounds exhibited stronger binding affinities (-6.0 to -9.0 kcal/mol) than metformin (-5.4 kcal/mol), with luteolin showing the highest affinity (-9.0 kcal/mol), followed closely by apigenin, chrysoeriol, kaempferol, and quercetin (-8.7 kcal/mol each). Key interacting residues, including ARG560, THR565, and LYS512, were consistently engaged across the flavonoid compounds, suggesting a conserved and pharmacologically relevant binding pocket within DPP-IV. Collectively, these findings support the phenolic and flavonoid constituents of *C. halicacabum*, particularly luteolin, apigenin, and quercetin, as promising natural DPP-IV inhibitor candidates warranting further in vitro and in vivo validation for antidiabetic drug development...

Keywords: *Cardiospermum halicacabum*, Type 2 diabetes, Bioactive Compounds, Human dipeptidyl peptidase-IV...

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INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a complex metabolic disorder characterized by persistent hyperglycaemia resulting from a combination of insulin resistance, impaired pancreatic β -cell function, abnormal glucose metabolism, and disturbances in lipid metabolism (Fuentes-Barría et al. 2026; Albaghlany et al., 2026). Long-term uncontrolled hyperglycaemia is associated with serious complications affecting the cardiovascular system, kidneys, eyes, nerves, and other organs. Consequently, the identification of safe and effective molecules capable of regulating glucose metabolism remains an important objective in drug discovery (Młynarska et al., 2025; Wu et al., 2026).

Current antidiabetic therapy includes several pharmacological classes, such as biguanides, sulfonylureas, thiazolidinediones, sodium-glucose cotransporter-2 inhibitors, glucagon-like peptide-1 receptor agonists, and dipeptidyl peptidase-4 (DPP-4) inhibitors. Although these drugs are effective, limitations such as adverse effects, variable response, cost, and long-term therapeutic challenges have encouraged researchers to investigate structurally diverse natural products as potential sources of new antidiabetic agents (Baranowska et al., 2026; Nxumalo et al., 2026; Yu et al., 2026).

Medicinal plants contain diverse secondary metabolites, including flavonoids, phenolic acids, alkaloids, terpenoids, tannins, and glycosides. Among these, flavonoids have

*Author for Correspondence: Dr.Veeraraghavan. V,

received considerable attention because of their antioxidant, anti-inflammatory, enzyme-inhibitory, and metabolic regulatory properties. Flavonoids may potentially influence several processes associated with T2DM, including carbohydrate digestion, glucose absorption, insulin signalling, oxidative stress, and inflammatory pathways (Rodríguez-Negrete *et al.*, 2024; Ojong *et al.*, 2026)

Cardiospermum halicacabum L., commonly known as balloon vine, is a medicinal plant belonging to the family Sapindaceae. It has a history of use in traditional medicine and has been investigated for several pharmacological activities including antioxidant, anti-inflammatory, anti-arthritic and antidiabetic effects. A comprehensive review of the plant reported the presence of phenolic compounds, flavonoids, flavonoid glycosides and flavonoid glucuronides, while also highlighting the need to identify the individual compounds responsible for its biological activities (Elangovan *et al.*, 2022; Zhao *et al.*, 2026).

Phytochemical investigations have identified several flavonoids from *C. halicacabum*. These include quercetin, kaempferol, apigenin, luteolin, chrysoeriol, rutin and glycosylated/ glucuronidated flavonoids. One detailed phytochemical investigation isolated ten flavonoids, including quercetin-3-O-rhamnoside, kaempferol-3-O-rhamnoside, apigenin-7-O-glucuronide, chrysoeriol, apigenin, kaempferol, luteolin and quercetin. The antidiabetic potential of *C. halicacabum* has been investigated experimentally. In vitro studies have reported inhibitory activity of different extracts against the carbohydrate-digesting enzymes α -amylase and α -glucosidase, suggesting that constituents of the plant may help reduce carbohydrate breakdown and potentially attenuate postprandial glucose elevation (Cheng *et al.*, 2013; Linh *et al.*, 2023).

The aim of this study combining phytochemical screening, molecular docking and pharmacokinetic prediction can provide an integrated strategy for identifying *C. halicacabum* phenolic and flavonoids with promising characteristics against T2DM-associated molecular targets.

METHODOLOGY:

Phytochemical compilation and accession of phenolic and flavonoids compounds:

The phenolic and flavonoid compounds cross-checked and reported from *Cardiospermum halicacabum* against published phytochemical reports. Previous investigations have confirmed multiple flavonoids from the plant using chromatographic and spectroscopic methods (Cheng *et al.* 2013). The compounds apigenin, Chrysoeriol, kaempferol, luteolin, p-coumaric acid, quercetin, gallic acid, 4-hydroxybenzoic acid were obtained from the PubChem database (<https://pubchem.ncbi.nlm.nih.gov>) (Cheng *et al.*, 2013).

Preparation of Protein Structure: The RCSB Protein Data Bank (PDB) with the accession code 1X70 was used to retrieve the three-dimensional crystal structure of the HUMAN DIPEPTIDYL PEPTIDASE IV. The protein

structure was cleaned up for molecular docking analysis through standard procedures. Water molecules, heteroatoms, and co-crystallized ligands were deleted from the protein structure. Hydrogen atoms were introduced into the protein structure, and energy minimization was carried out to maximize the protein conformation. The active site of DPP-IV was located based on the co-crystallized ligand binding site and literature descriptions.

Molecular Docking: Molecular docking was performed to study the binding interactions between the active compounds from as a inhibitor of HUMAN DIPEPTIDYL PEPTIDASE IV (DPP-IV) as potential anti-diabetic target protein. flavonoids (4) and polyphenolic compounds (4) were used for molecular docking analysis with target proteins inhibitors using cavity detection-guided blind docking (CB-Dock-3). The docked complex results were visualized using PyMol Viewer software. Docking provides information about binding affinity and possible interactions that contribute to the inhibition and act as a potential anti-diabetic activity (Burranboina *et al.*, 2022; Yang Liu, *et al.* *et al.*, 2026).

ADMET analysis: ADMET analysis was carried out by using pkCSM (<https://biosig.lab.uq.edu.au/pkcsml/>) and ProTox 3.0 online tools for prediction of toxicities of small molecules (Pires *et al.* 2015).

RESULTS AND DISCUSSION:

All compound shown lipinski rule 5 thresholds. MW is well under 500 (ranging 138–302), LogP stays under 3 (mildly lipophilic, not excessively), HBA ≤ 10 , and HBD ≤ 5 . The "Lipinski" column value of 4 for every row indicates each compound satisfies all 4 criteria, Low molecular weight - all compounds are small molecules (under 310 Da), which favors good membrane permeability and absorption. Moderate, low LogP values (0.5–2.6) suggest these compounds are on the hydrophilic side rather than highly lipophilic consistent with polyphenols, which typically have multiple -OH groups. TPSA (Topological Polar Surface Area) is included as a supplementary drug-likeness and permeability indicator. Compounds with TPSA $< 90 \text{ \AA}^2$ (Apigenin at 90.9, borderline; gallic acid, p-coumaric acid, 4-hydroxybenzoic acid all 57–98) are more likely to have good oral absorption and even potential to cross the blood-brain barrier. Quercetin (131.36) and the flavonols with extra hydroxyl groups (kaempferol, luteolin, chrysoeriol > 100) have higher TPSA, largely due to their additional H-bond donor and acceptor -OH groups, which may modestly reduce passive membrane permeability despite still being drug-like compounds. The physicochemical and drug-likeness properties of eight phenolic and flavonoid constituents of *Cardiospermum halicacabum* are fully compliant with Lipinski's Rule of Five, indicating they possess favourable physicochemical properties for oral bioavailability and are promising candidates for further pharmacological/drug development studies.

Table 1: Lipinski rule 5 of *Cardiospermum halicacabum* Phenolic and flavonoids compounds

Sl. No	Compound name	Pub Chem Id	Molecular weight	logP	H-bond acceptors	H-bond donors	Lipinski	TPSA
1	Apigenin	5280443	270.24	2.68	5	3	4	90.9
2	Chrysoeriol	5280666	300.266	2.585	6	3	4	100.13
3	Kaempferol	5280863	286.239	2.282	6	4	4	111.13
4	Luteolin	5280445	286.239	2.282	6	4	4	111.13
5	p-Coumaric acid	637542	164.16	1.49	2	2	4	57.53
6	Quercetin	5280343	302.238	1.988	7	5	4	131.36
7	Gallic acid	370	170.12	0.501	4	4	4	97.99
8	4-Hydroxybenzoic acid	135	138.122	1.090	2	2	4	57.53

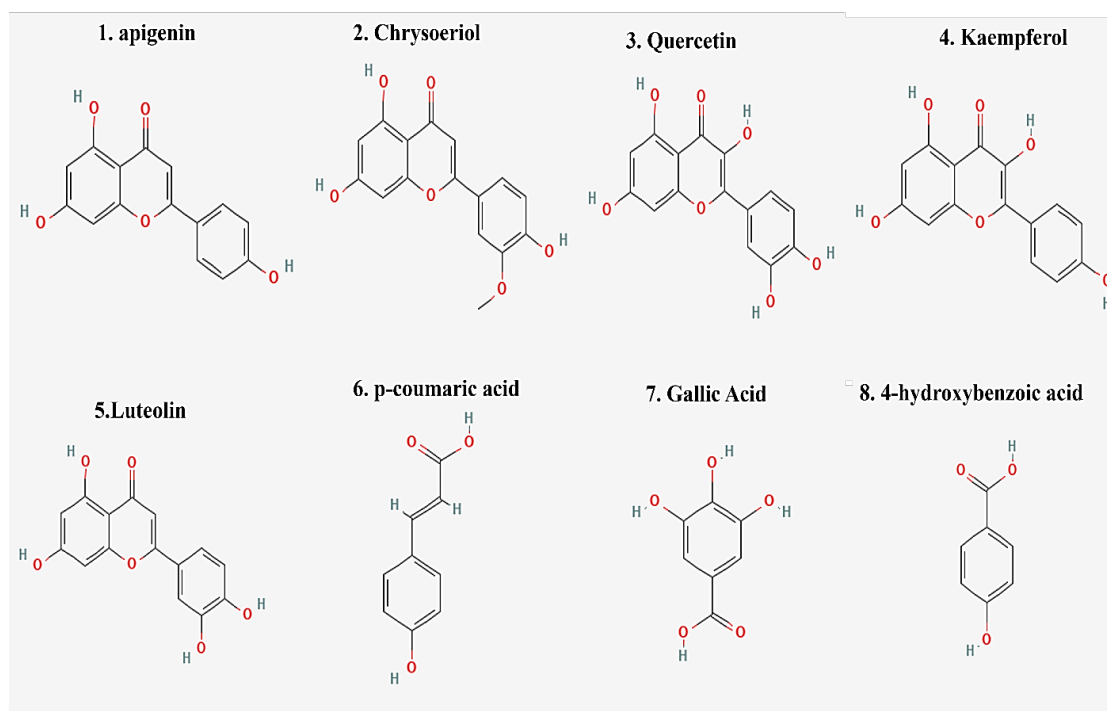


Figure 1: Chemical structures of Phenolic and flavonoids compounds

Molecular docking analysis:

Molecular docking was performed to investigate the interaction potential of phenolic and flavonoid constituents of *Cardiospermum halicacabum* with dipeptidyl peptidase-IV (DPP-IV), a therapeutically important target associated with glucose homeostasis. The docking results are summarized in Table 2. The investigated compounds exhibited predicted binding energies ranging from -6.0 to -9.0 kcal/mol, whereas the reference compound metformin showed a docking energy of -5.4 kcal/mol. Among the investigated phytoconstituents, luteolin exhibited the most favourable predicted binding energy (-9.0 kcal/mol) and formed three hydrogen-bond interactions with PRO451, ARG560 and PRO475. Apigenin, chrysoeriol, kaempferol and quercetin demonstrated similarly favourable docking energies of -8.7 kcal/mol, suggesting strong predicted

interactions with DPP-IV. Chrysoeriol formed four hydrogen bonds, whereas kaempferol exhibited the highest hydrogen-bond count among the flavonoids, forming five hydrogen bonds with ARG560, THR565, PRO510, ASN562 and LYS512. Quercetin and apigenin formed three hydrogen bonds each.

The docking results further demonstrated that hydrogen-bond number was not directly correlated with docking energy. For example, gallic acid formed five hydrogen bonds but showed a comparatively weaker docking score of -6.7 kcal/mol, whereas luteolin formed three hydrogen bonds but exhibited the most favourable docking score of -9.0 kcal/mol. This observation indicates that the predicted binding energy is determined by the combined contribution of different ligand-protein interactions rather than hydrogen bonding alone.

Among the non-flavonoid phenolic compounds, p-coumaric acid, gallic acid and 4-hydroxybenzoic acid exhibited docking energies of -6.5, -6.7 and -6.0 kcal/mol, respectively. Although these compounds showed weaker predicted binding than the major flavonoids, the interaction of 4-hydroxybenzoic acid with Arg125, Glu205 and Tyr662 is noteworthy because these residues are associated with recognized DPP-IV inhibitor-binding regions. Previous structural studies have established important roles for Arg125, Glu205/Glu206, Tyr547, Ser630 and Tyr662 in DPP-IV ligand recognition and inhibition. Collectively, the docking data suggest that luteolin is the most promising DPP-IV-binding candidate among the compounds evaluated, followed by apigenin, chrysoeriol, kaempferol

and quercetin. The strong predicted binding of these flavonoids may be associated with their aromatic scaffolds and multiple hydroxyl groups, which can facilitate hydrogen bonding and other stabilizing interactions within the protein binding site. Nevertheless, docking results should be interpreted as predictive rather than definitive evidence of enzyme inhibition. Structural validation, redocking of the native ligand, molecular dynamics simulation and in vitro DPP-IV inhibition assays would be required to confirm these findings. Contemporary DPP-IV docking studies similarly emphasize the importance of validating docking predictions through additional computational and experimental approaches.

Table 2: *Cardiospermum halicacabum* Phenolic and flavonoids compounds interaction with – DPP-IV.

Sl. No	Bioactive compounds	No. H-Bonds	Interactive amino acids	Energy values (kcal/mol)
1	Apigenin	3	ASP588,TRP3553,ARG382	-8.7
2	Chrysoeriol	4	THR 565, LYS512, ILE529	-8.7
3	Kaempferol	5	ARG560, THR5665, PRO510, ASN562LYS512	-8.7
4	Luteolin	3	PRO4510, ARG560, PRO475	-9
5	p-Coumaric acid	3	ASN562, THR565.LYS512,PHE559	-6.5
6	Quercetin	3	THR565, LYS512, ARG560	-8.7
7	Gallic acid	5	ARG560, GLN527, THR565	-6.7
8	4-Hydroxybenzoic acid	3	ARG125, GLU205, TYR662	-6
9	Metformin (4091)	3	MET348. ASP588,SER37666,THR351	-5.4

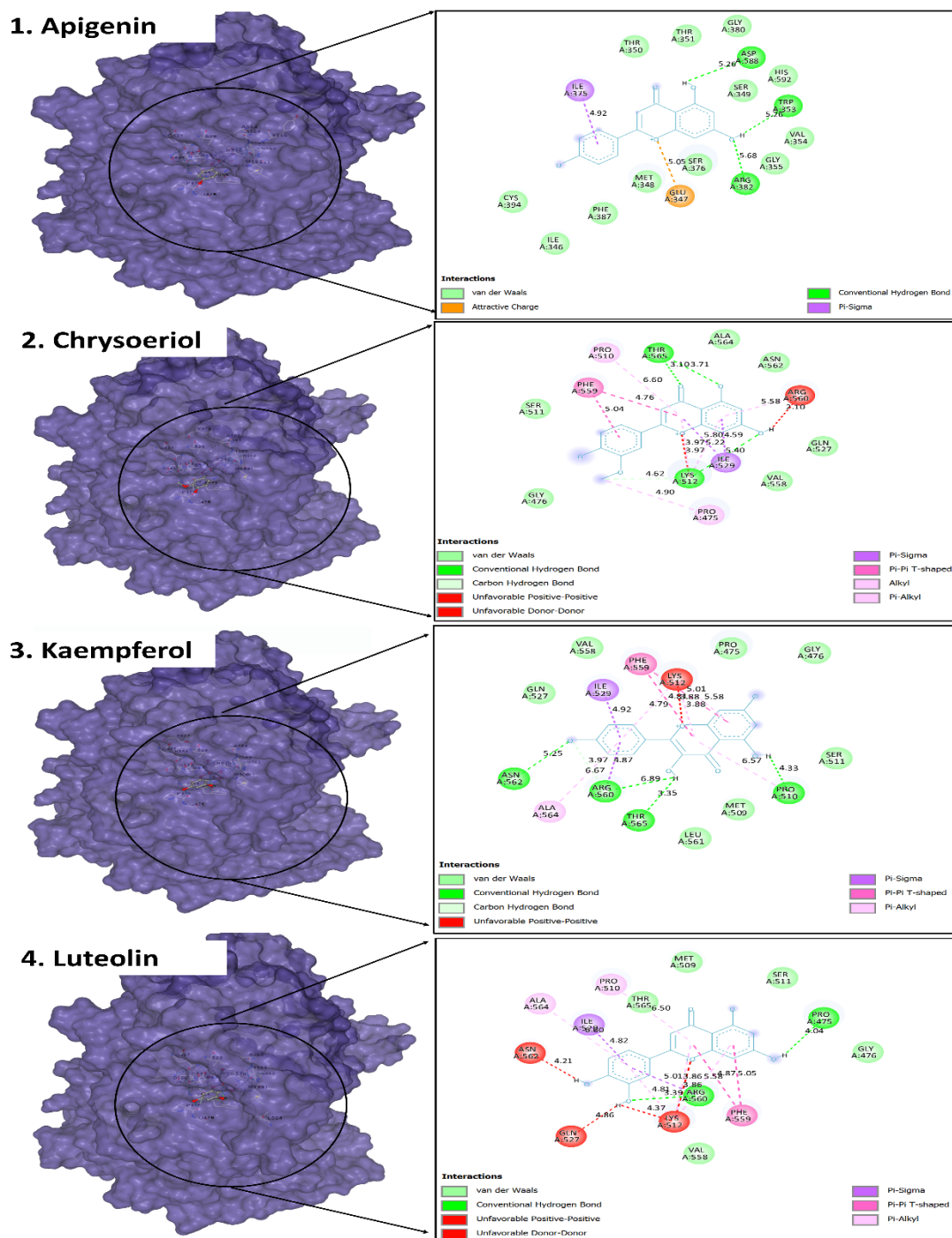


Figure 2: 2D and 3D Molecular interaction of Apigenin, Chrysoeriol, Kaempferol, Luteolin with DPP-IV.

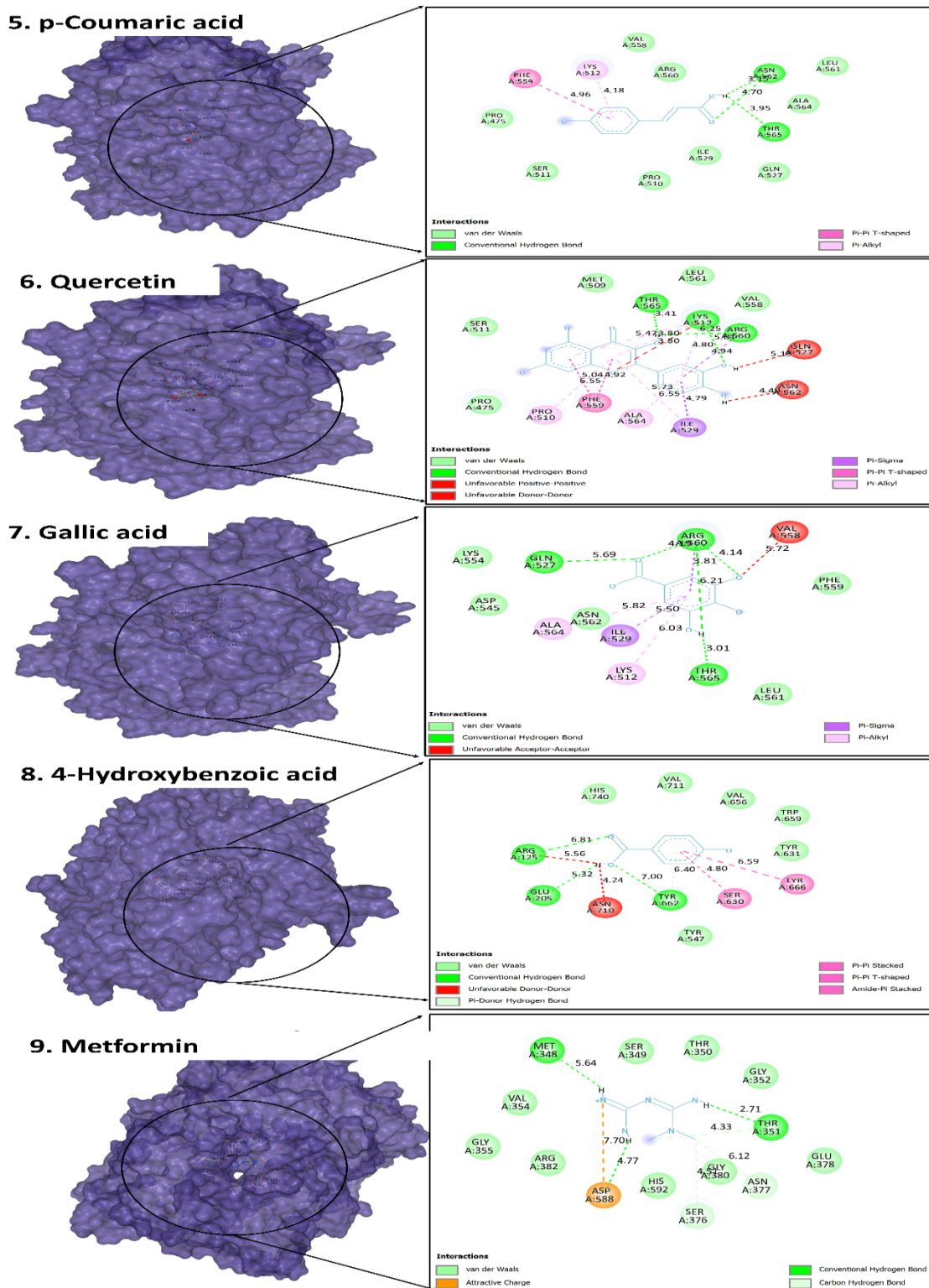


Figure 3: 2D and 3D Molecular interaction of p-Coumaric acid, Quercetin, Gallic acid, 4-Hydroxybenzoic acid, Metformin (PUB chem ID: 4091) with DPP-IV

ADMET Analysis:

Absorption: Water solubility (log mol/L) shown compounds range from -2.7 to -3.9, indicating moderate solubility, actually better (less negative) than Metformin's -2.707 in most cases except quercetin. Values above -4 generally indicate acceptable aqueous solubility for oral formulation. Caco2 permeability - Apigenin (1.007) and

Chrysoeriol (0.321) show positive values, suggesting good intestinal cell permeability. Kaempferol (0.032) is borderline; Luteolin and Quercetin are near zero negative, suggesting comparatively lower passive permeability consistent with their higher polarity (more -OH groups). Intestinal absorption (human) This is the standout metric. Apigenin (93.25%), Chrysoeriol (82.8%),

Kaempferol (74.3%), Luteolin (81.1%), and Quercetin (77.2%) all show higher predicted absorption than Metformin (59.4%) a drug known for famously poor and variable oral bioavailability (50-60%). This suggests these flavonoids may be well-absorbed orally, a very favorable finding. Skin permeability - All compounds (-2.735) are essentially identical to Metformin, indicating negligible/low skin penetration not relevant for oral route but relevant if topical formulations are considered. P-glycoprotein (P-gp) All compounds are predicted P-gp substrates (Yes), meaning they may be actively effluxed out of cells by this transporter, potentially limiting absorption and CNS penetration and creating drug-interaction risk. None are P-gp inhibitors (except Kaempferol shows Yes for P-gp I inhibitor) worth double-checking, as most other flavonoids are "No" for inhibition.

Distribution: VDss (Volume of distribution, log L/kg) Values (0.82–1.56) are all positive and higher than Metformin (-0.232), meaning these flavonoids are predicted to distribute more extensively into tissues rather than staying confined to plasma. Quercetin has the highest (1.559). Fraction unbound (Fu) Low values (0.07–0.21) indicate high plasma protein binding (i.e., only 7-21% of the drug circulates "free"/active) — common for polyphenolic compounds, which bind avidly to albumin. This is much lower than Metformin (0.811, i.e., ~81% unbound), meaning Metformin circulates largely free while these flavonoids are heavily protein-bound, which can reduce free drug availability but prolong action. BBB permeability All negative and more negative than Metformin (-0.946), particularly Quercetin (-1.098) — suggesting poor blood-brain barrier penetration. This is generally favorable if CNS side effects are undesired, but limiting if a CNS-targeted application is intended. CNS permeability (log PS) All strongly negative (-2 to -

4.2), reinforcing low CNS penetration consistent with BBB data. Quercetin shows the most negative (-3.065), i.e., least CNS-penetrant among the flavonoids.

Metabolism: Prediction CYP substrates (2D6, 3A4) All compounds are "No" not metabolized by these major CYP enzymes, suggesting metabolic stability via these pathways. CYP1A2 inhibitor All "Yes" potential to inhibit CYP1A2, raising a flag for drug-drug interactions with CYP1A2 substrates (e.g., caffeine, some antipsychotics). CYP2C19, CYP2C9, CYP2D6, CYP3A4 inhibitor Mixed pattern Apigenin and Chrysoeriol show "Yes" for CYP2C19 inhibition; most are "No" for CYP2C9, 2D6, and 3A4 inhibition. This selective inhibition profile (mainly CYP1A2, occasionally 2C19) suggests moderate interaction risk, primarily with CYP1A2 substrates.

Excretion: Clearance (log mL/min/kg) Values (0.41–0.60) are all higher than Metformin (0.1), suggesting faster systemic clearance meaning these compounds may have shorter half-lives and require more frequent dosing or sustained-release formulation for continuous therapeutic effect. Renal OCT2 substrate All "No" unlike Metformin (which is a classic OCT2 substrate), these flavonoids are not predicted to use the OCT2 renal transport pathway, reducing risk of interaction with OCT2-dependent renal drug elimination.

Toxicity: acute oral toxicity, the predicted LD50 values are relatively similar among the compounds. Chrysoeriol has the lowest predicted LD50 (2.337 log mol/kg), which indicates comparatively greater acute toxicity within this group because a lower LD50 corresponds to toxicity at a lower dose. For aquatic toxicity, chrysoeriol has the lowest minnow toxicity value (1.654 log mM), suggesting the greatest predicted aquatic toxicity among the flavonoids. Quercetin (3.721) has a substantially higher value and therefore a more favorable aquatic toxicity prediction.

Table 2: ADMET prediction of high energy interactive bioactive compounds of *Cardiospermum halicacabum*.

Model Name	Apigenin	Chrysoeriol	Kaempferol	Luteolin	Quercetin	Metformin	Unit
Absorption							
Water solubility	-3.329	-3.237	-3.04	-3.094	-2.925	-2.707	Numeric (log mol/L)
Caco2 permeability	1.007	0.321	0.032	0.096	-0.229	-0.339	Numeric (log Papp in 10 ⁻⁶ cm/s)
Intestinal absorption (human)	93.25	82.844	74.29	81.13	77.207	59.401	Numeric (%) Absorbed)
Skin Permeability	-2.735	-2.735	-2.735	-2.735	-2.735	-2.735	Numeric (log Kp)
P-glycoprotein substrate	Yes	Yes	Yes	Yes	Yes	Yes	Categorical (Yes/No)
P-glycoprotein I inhibitor	No	No	No	No	No	No	Categorical (Yes/No)
P-glycoprotein II inhibitor	No	No	No	No	No	No	Categorical (Yes/No)
Distribution							
VDss (human)	0.822	0.741	1.274	1.153	1.559	-0.232	Numeric (log L/kg)

Fraction unbound (human)	0.147	0.07	0.178	0.168	0.206	0.811	Numeric (Fu)
BBB permeability	-0.734	-0.943	-0.939	-0.907	-1.098	-0.946	Numeric (log BB)
CNS permeability	-2.061	-2.32	-2.228	-2.251	-3.065	-4.238	Numeric (log PS)
Metabolism							
CYP2D6 substrate	No	No	No	No	No	No	Categorical (Yes/No)
CYP3A4 substrate	No	No	No	No	No	No	Categorical (Yes/No)
CYP1A2 inhibitor	Yes	Yes	Yes	Yes	Yes	No	Categorical (Yes/No)
CYP2C19 inhibitor	Yes	Yes	No	No	No	No	Categorical (Yes/No)
CYP2C9 inhibitor	No	Yes	No	Yes	No	No	Categorical (Yes/No)
CYP2D6 inhibitor	No	No	No	No	No	No	Categorical (Yes/No)
CYP3A4 inhibitor	No	No	No	No	No	No	Categorical (Yes/No)
Excretion							
Total Clearance	0.566	0.597	0.477	0.495	0.407	0.1	Numeric (log ml/min/kg)
Renal OCT2 substrate	No	No	No	No	No	No	Categorical (Yes/No)
Toxicity							
AMES toxicity	No	No	No	No	No	Yes	Categorical (Yes/No)
Max. tolerated dose (human)	0.328	0.436	0.531	0.499	0.499	0.902	Numeric (log mg/kg/day)
hERG I inhibitor	No	No	No	No	No	No	Categorical (Yes/No)
hERG II inhibitor	No	No	No	No	No	No	Categorical (Yes/No)
Oral Rat Acute Toxicity (LD50)	2.45	2.337	2.449	2.455	2.471	2.453	Numeric (mol/kg)
Oral Rat Chronic Toxicity (LOAEL)	2.298	2.252	2.505	2.409	2.612	2.158	Numeric (log mg/kg bw/day)
Hepatotoxicity	No	No	No	No	No	No	Categorical (Yes/No)
Skin Sensitisation	No	No	No	No	No	Yes	Categorical (Yes/No)
T.Pyriformis toxicity	0.38	0.331	0.312	0.326	0.288	0.25	Numeric (log ug/L)
Minnow toxicity	2.432	1.654	2.885	3.169	3.721	3.972	Numeric (log mM)

CONCLUSION:

In conclusion the study evaluated eight phenolic and flavonoid compounds from *Cardiospermum halicacabum* as potential anti-diabetic agents targeting DPP-IV. All compounds fully complied with Lipinski's Rule of Five, exhibiting favorable molecular weight, lipophilicity, and hydrogen bonding parameters indicative of drug-likeness. ADMET predictions further supported their pharmacological suitability, revealing superior intestinal absorption relative to Metformin, along with non-

mutagenic, non-hepatotoxic, and non-cardiotoxic (hERG-negative) profiles, despite moderate CYP1A2 inhibition and P-glycoprotein substrate liability warranting further scrutiny. Molecular docking against DPP-IV demonstrated that every test compound bound more strongly than Metformin, with Luteolin showing the highest binding affinity (-9.0 kcal/mol), followed closely by Apigenin, Chrysoeriol, Kaempferol, and Quercetin (-8.7 kcal/mol each). Consistent interaction with key residues (ARG560, THR565, LYS512) across multiple flavonoids suggests a

conserved, druggable binding hotspot within the DPP-IV active site. Collectively, these findings identify Luteolin and related flavonoids as promising natural DPP-IV inhibitor candidates with favourable pharmacokinetic and safety profiles. Further *in vitro* enzymatic assays and *in vivo* validation are recommended to substantiate the therapeutic potential of these *C. halicacabum*-derived phytoconstituents in managing Type 2 Diabetes Mellitus.

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Authors' contributions : Sushmitha.

K worked and executed throughout the research work, Kirankumar B carried out the molecular docking and ADMET analysis, V. Veeraraghavan and Renuka Srihari edited and checked the manuscript.

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