

COMPUTATIONAL MOLECULAR DOCKING AND SIMULATION-BASED ASSESSMENT OF ANTI-INFLAMMATORY PROPERTIES OF *ASCLEPIAS SYRIACA* PHYTOCHEMICALS.

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Abstract

Inflammation is mediated by multiple signalling pathways involving cytokine regulators and lipid-metabolizing enzymes, making multi-target modulators a promising therapeutic strategy. This study employed an integrated molecular docking approach to evaluate the anti-inflammatory potential of 34 phytochemicals from *Asclepias syriaca* against four major inflammation-associated proteins: COX-1, JAK1, JAK2, and 5-LOX. Crystal structures of each target were prepared through systematic preprocessing, and ligand optimization was performed using PyRx with universal force-field energy minimization. AutoDock Vina-based docking revealed several high-affinity interactions, with daidzin (−10.6 kcal/mol), ellagic acid (−10.0 and −9.9 kcal/mol for JAK1 and JAK2), and genistin (−10.3 kcal/mol) emerging as the most potent binders across multiple targets. Multi-target analysis demonstrated that these three phytochemicals consistently exhibited strong affinities, whereas luteolin, catechin, and kaempferol showed moderate but broad-spectrum binding profiles.

Keywords: *Asclepias syriaca*; molecular docking; COX-1; JAK1; JAK2; 5-LOX; phytochemicals; anti-inflammatory agents; SwissADME; drug-likeness.

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1.Introduction

Inflammation is the defense mechanism which helps the body to protect itself against injury, and chemical stress (Liehn et al., 2015). When regulated properly this mechanism helps in the facilitation of tissue repair and enables normal biological processes (Eming et al., 2014). In contrast, sustained and unregulated inflammation is closely associated with several chronic disorders, including rheumatoid arthritis, inflammatory bowel disease, asthma, and various metabolic complications (Chen et al., 2017). Whereas commonly used anti-inflammatory drugs such as NSAIDs, corticosteroids, and selective enzyme inhibitors have proven effective in many cases, their long-term use is associated with several adverse effects such as gastrointestinal irritation, hormonal imbalance, reduced sensitivity to drugs, among others. (Bindu et al., 2020) These challenges indicate the need for new therapeutic agents that could regulate inflammation at a much safer and more selective manner (Uddin et al., 2012).

Medicinal plants have always been an important part of traditional healing systems (Rasool et al., 2012) (Mbuni et al., 2020). They contain many natural compounds that can reduce inflammation by acting as antioxidants, blocking certain enzymes, or controlling immune signals (Ravipati et al., 2012) (Arulselvan et al., 2016). *Asclepias syriaca* belongs to the family Apocynaceae and has been used in folk medicine to treat pain, swelling, and minor infections (Alonso et al., 2021). The plant is known to contain flavonoids, phenolic acids, and other useful molecules that show several biological effects (El-Hefny et al., 2023).

In this study, molecular docking was performed to understand how these phytochemicals from *A. syriaca* interact with major proteins linked to inflammation (Bibi et al., 2024). Docking helps to see how well each compound fits into the active site of a protein and to predict its binding strength and possible inhibitory role (Meng et al., 2011). This method is very helpful because it saves both time and cost in early drug discovery and gives clear ideas about the potential activity of plant compounds (Asiamah et al., 2023).

The research focused on four key proteins involved in inflammation JAK1, JAK2, COX-1, and 5-LOX (Shawky et al., 2022) (Agrawal et al., 2025). These proteins help in controlling immune signals and in forming prostaglandins and leukotrienes. The study aims to find which *A. syriaca* compounds bind well and interact effectively, showing its value as a plant with anti-inflammatory potential (Agrawal et al., 2025).

2. Materials and Methods

Ligand selection

The study included a group of 34 phytochemicals, which were chosen because they frequently appear in medicinal plants associated with anti-inflammatory activities (Gajić et al., 2025). Their chemical information such as structural data and identifiers was acquired directly from the PubChem database (Kim et al., 2021).

To ensure that the selected compounds were suitable for computational evaluation, their SMILES strings were examined using SwissADME (Daina et al., 2017). Basic physicochemical filters such as Lipinski's and Veber's guidelines were applied, to remove molecules with clearly unsuitable properties (Damilare et al., 2025). Only the compounds showing broadly acceptable characteristics were retained for docking (Sanchitra et al., 2025).

All compounds are handled in PyRx 0.9.8 by downloading the ligands in 3D SDF format for further preparation (Dallakyan et al., 2014). Then by using open Babel module within PyRx the structures were first cleaned and subjected to energy minimization which ensure a stable conformation for docking (Vikhar et al., 2024). each ligand was saved in PDBQT format, which is used for processing by Auto Dock Vina module within PyRx (Ayodele et al., 2023).

Table 1. Classification of selected phytochemicals identified in *Asclepias syriaca* with their PubChem CID and SMILES notation

S	CO	ID	SMILES
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COMPUTATIONAL MOLECULAR DOCKING AND SIMULATION-BASED ASSESSMENT OF ANTI-INFLAMMATORY PROPERTIES OF ASCLEPIAS SYRIACA PHYTOCHEMICALS.

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1	4-Hydr oxybenzoic acid	135	<chem>C1=CC(=CC=C1C(=O)O)O</chem>		16	Esculetin	5281416 <chem>C1=CC(=O)OC2=CC(=C(C=C21)O)O</chem>
2	7-Hydr oxyflavone	5281894	<chem>C1=CC=C(C=C1)C2=CC(=O)C3=C(O2)C=C(C=C3)O</chem>		17	Galliac acid	370 <chem>C1=C(C=C(C(=C1O)O)O)C(=O)O</chem>
3	Apigenin	5280443	<chem>C1=CC(=CC=C1C2=CC(=O)C3=C(C=C(C=C3O2)O)O)O</chem>		18	Genistin	5281377 <chem>C1=CC(=CC=C1C2=COC3=CC(=CC(=C3C2=O)O)O[C@H]4[C@@H]([C@H]([C@@H]([C@H](O4)CO)O)O)O)O</chem>
4	Benzoinic acid	243	<chem>C1=CC=C(C=C1)C(=O)O</chem>		19	Juglone	3806 <chem>C1=CC2=C(C(=O)C=CC2=O)C(=C1)O</chem>
5	Caffeic acid	689043	<chem>C1=CC(=C(C=C1/C=C/C(=O)O)O)O</chem>		20	Kaempferol	5280863 <chem>C1=CC(=CC=C1C2=C(C(=O)C3=C(C=C(C=C3O2)O)O)O)O</chem>
6	Catechin	9064	<chem>C1[C@@H]([C@H](OC2=CC(=CC(=C21)O)O)C3=CC(=C(C=C3)O)O)O</chem>		21	Luteolin	5280445 <chem>C1=CC(=C(C=C1C2=CC(=O)C3=C(C=C(C=C3O2)O)O)O)O</chem>
7	Catechol	289	<chem>C1=CC=C(C(=C1)O)O</chem>		22	Myricetin	5281672 <chem>C1=C(C=C(C(=C1O)O)O)C2=C(C(=O)C3=C(C=C(C=C3O2)O)O)O</chem>
8	Chlorogenic acid	1794427	<chem>C1[C@H]([C@H]([C@@H](C[C@@]1(C(=O)O)O)OC(=O)/C=C/C2=CC(=C(C=C2)O)O)O)O</chem>		23	Naringenin	439246 <chem>C1[C@H](OC2=CC(=CC(=C2C1=O)O)O)C3=CC=C(C=C3)O</chem>
9	Chrysoeriol	5280666	<chem>COC1=C(C=CC(=C1)C2=CC(=O)C3=C(C=C(C=C3O2)O)O)O</chem>		24	p-Coumaric acid	637542 <chem>C1=CC(=CC=C1/C=C/C(=O)O)O</chem>
10	Cyanidin	128861	<chem>C1=CC(=C(C=C1C2=[O+]C3=CC(=C(C=C3C=C2O)O)O)O)O</chem>		25	Protocatechuic acid	72 <chem>C1=CC(=C(C=C1C(=O)O)O)O</chem>
11	Daidzin	107971	<chem>C1=CC(=CC=C1C2=COC3=C(C2=O)C=CC(=C3)O[C@H]4[C@@H]([C@H]([C@@H]([C@H](O4)CO)O)O)O)O</chem>		26	Pyrogallol	1057 <chem>C1=CC(=C(C(=C1)O)O)O</chem>
12	Delpheidin	128853	<chem>C1=C(C=C(C(=C1O)O)O)C2=[O+]C3=CC(=CC(=C3C=C2O)O)O</chem>		27	Quercetin	5280343 <chem>C1=CC(=C(C=C1C2=C(C(=O)C3=C(C=C(C=C3O2)O)O)O)O)O</chem>
13	Ellagic acid	5281855	<chem>C1=C2C3=C(C(=C1O)O)OC(=O)C4=CC(=C(C(=C43)OC2=O)O)O</chem>		28	Resveratrol	445154 <chem>C1=CC(=CC=C1/C=C/C2=CC(=CC(=C2)O)O)O</chem>
14	Epicatechin	72276	<chem>C1[C@H]([C@H](OC2=CC(=CC(=C21)O)O)C3=CC(=C(C=C3)O)O)O</chem>		29	Salicylic acid	338 <chem>C1=CC=C(C(=C1)C(=O)O)O</chem>
15	Epigallocatechin	72277	<chem>C1[C@H]([C@H](OC2=CC(=CC(=C21)O)O)C3=CC(=C(C=C3)O)O)O</chem>		30	Sinapinic acid	1549 <chem>COC1=CC(=CC(=C1O)OC)/C=C/C(=O)O</chem>

		09 1	
3 1	Syrin gic acid	10 74 2	<chem>COC1=CC(=CC(=C1O)OC)C(=O)O</chem>
3 2	Taxif olin	43 95 33	<chem>C1=CC(=C(C=C1[C@@H]2[C@H](C(=O)C3=C(C=C(C=C3O2)O)O)O)O</chem>
3 3	trans - Cinn amic acid	44 45 39	<chem>C1=CC=C(C=C1)/C=C/C(=O)O</chem>
3 4	Vanil lic acid	84 68	<chem>C1=CC(=C(C(=C1)O)O)O</chem>

			synthesis and promotes inflammation (Gilbert et al., 2011)
4	1EQG	COX-1 (Cyclooxygenase- 1)	Maintains baseline prostaglandin production and gastric protection (Selinsky et al., 2001)

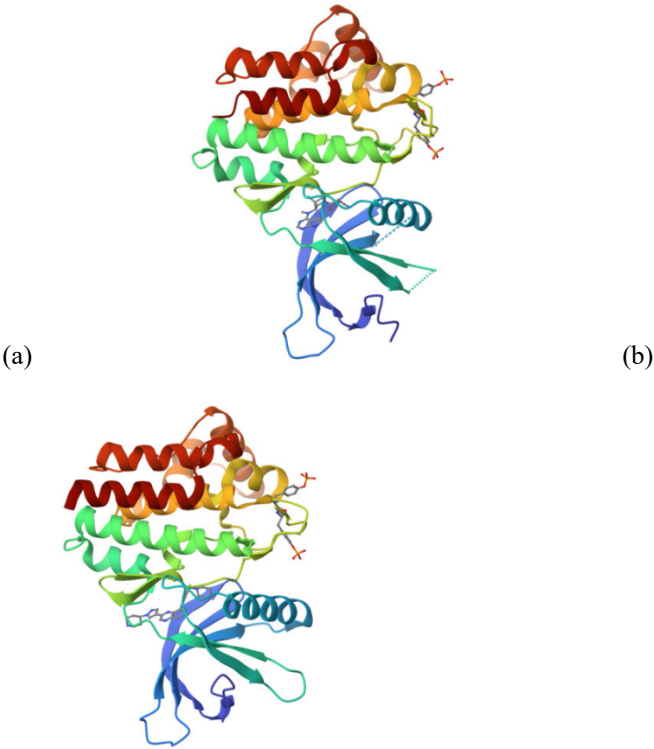
Target Protein Selection

The crystal structures of four inflammation-related human proteins were retrieved from the RCSB Protein Data Bank (Jacob et al., 2014; Shawky et al., 2022): Janus Kinase 1 (JAK1), Janus Kinase 2 (JAK2), cyclooxygenase-1 (COX-1), and 5-lipoxygenase (5-LOX). The selection of such targets could be attributed to their significance in cytokine signalling, in leukotriene formation, and in arachidonic acid driven inflammatory pathways. Thus, JAK1 and JAK2 are major regulators of the JAK–STAT cascade involved in immune responses (Sarapultsev et al., 2023), whereas COX-1 and 5-LOX function as key enzymes in the synthesis of prostaglandin and leukotriene (Rudrapal et al., 2023), respectively both significantly influencing inflammation related physiological and pathological mechanisms. Initial preprocessing was done in Molegro Molecular Viewer crystallographic water molecules, bound ligands, metal ions, and other non-essential heteroatoms were removed (Berisha et al., 2025). This cleanup step ensured the retention of only core structural elements necessary for docking studies, thus generating the receptor models ready for further analysis. The refined structures were then exported in PDB format (Jakšić et al., 2019).

Table 2. Inflammation-associated target proteins used for molecular docking

S.No	PDB ID	Target Protein	Biological Function
1	3EYG	JAK1 (Janus Kinase 1)	Mediates cytokine-driven signalling and immune responses (Williams et al., 2009)
2	3KRR	JAK2 (Janus Kinase 2)	Regulates cell growth, hematopoiesis, and proliferation (Baffert et al., 2010)
3	3O8Y	5-LOX (5-Lipoxygenase)	Initiates leukotriene

Figure 1. Three-dimensional structures of the selected Inflammation -associated target proteins, (a) JAK1, (b) JAK2, (c) 5-LOX, and (d) COX-1.



$$K_i = e^{(\Delta G/RT)}$$

In this equation, ΔG denotes the docking energy ($\text{kcal} \cdot \text{mol}^{-1}$), R is the universal gas constant ($1.987 \times 10^{-3} \text{ kcal} \cdot \text{mol}^{-1} \cdot \text{K}^{-1}$), and T represents the absolute temperature (298 K) (Parra et al., 2025). The resulting K_i values were first obtained in molar units (M) and then converted to micromolar (μM) for easier interpretation of binding potency (Gleeson et al., 2011).

Subsequently, the docked complexes were examined using Discovery Studio Visualizer 2025 to characterize the main stabilizing interactions within the active site, with hydrogen bonding emerging as the most consistent mode of interaction across the ligand protein models (Nyijime et al., 2025).

ADME and Drug-Likeness Analysis

The pharmacokinetic characteristics of the selected *Asclepias syriaca* phytochemicals were evaluated using the SwissADME web tool to predict their potential as orally active anti-inflammatory agents (Muthukrishnan et al., 2024). Key parameters such as gastrointestinal absorption, distribution profile, and blood–brain barrier permeability were examined, as these factors play crucial roles in determining systemic availability and therapeutic efficiency (Cornelissen et al., 2023). Each compound was also analyzed for possible interactions with the major cytochrome P450 isoenzymes, including CYP2C19, CYP2C9, CYP2D6, and CYP3A4, to predict their metabolic pathways and likelihood of enzyme-mediated interactions (Iacopetta et al., 2023).

Rather than providing absolute pharmacokinetic values, these in silico predictions offer indicative trends regarding the compounds' metabolic stability and oral bioavailability (Komura et al., 2023). The findings were further assessed for compliance with Lipinski's and Veber's rules, which define the physicochemical parameters favorable for oral drug-likeness (Caminero et al., 2023; Krishnan et al., 2025). Overall, this analysis provides preliminary insight into the pharmacokinetic suitability of *A. syriaca* phytochemicals, identifying compounds that may serve as promising candidates for further biological evaluation (Withana et al., 2025).

Visualization of Ligand-Protein Interactions

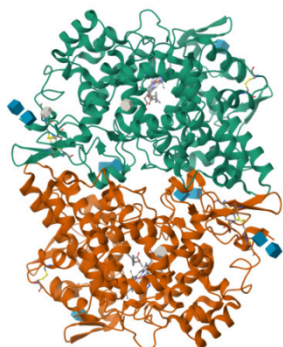
To gain a deeper insight into how the selected ligands interacted with their respective protein targets, molecular docking outputs were carefully analyzed using Discovery Studio Visualizer 2025 (Rao et al., 2023). The evaluation went beyond numerical docking scores, focusing instead on how well each compound fitted into the binding pocket and the stability of its orientation within the site (Meng et al., 2011). The formation of hydrogen bonds between the ligand and active-site residues was closely examined, as these interactions played a major role in maintaining the binding stability of the complex. For every protein studied, the ligand pose that showed the best predicted affinity was explored in a three-dimensional view to verify proper alignment within the active site (Nasief et al., 2017). Additionally, two-dimensional interaction plots were created to clearly display the amino acid residues taking part in binding, allowing for straightforward comparison across different protein–ligand complexes (Stierand et al., 2011).

3. Results

Docking Results for COX1

The strongest interaction was achieved by **daidzin**, with a binding energy of **−10.6 kcal/mol** and an estimated **K_i of 0.0168 μM** . **Genistin** exhibited a closely comparable affinity (−10.3 kcal/mol; **K_i = 0.0279 μM**), indicating that both compounds were favourably accommodated within the

(c)



(d)

Molecular Docking Protocol

The 34 selected polyphenolic ligands were uploaded in SDF format and converted into PDBQT with the help of PyRx's OpenBabel interface (Keerthana & Sivaraj, 2026). In addition, all the ligands were energy-minimized using the Universal Force Field before actual docking to obtain optimized conformers and reduce distortions arising from strained geometries (Belbachir et al., 2025).

Refined receptor structures for JAK1, JAK2, 5-lipoxygenase (5-LOX), and cyclooxygenase-1 (COX-1) were imported into PyRx v0.9.8 for the purpose of molecular docking (Rekha et al., 2020). Each PDB file was converted into PDBQT format using the macromolecule preparation module of AutoDock, where missing polar hydrogens were added and partial charges of Gasteiger were assigned to the proteins, thereby ensuring that all proteins are consistently prepared for docking (Forli et al., 2016). Non-essential elements like crystallographic water molecules, co-crystallized ligand, counterions, and other heteroatoms had already been removed in earlier steps to obtain biologically relevant receptor structures (Alamri et al., 2024).

A blind-docking approach was adopted for all receptors, in which grid boxes were extended to completely engulf the entire surface of the protein, allowing the exploration of putative binding regions beyond annotated active sites (Roomi et al., 2025). In PyRx, the vina wizard automatically defined and readjusted the dimensions of the grid to completely cover the macromolecule (Rakib et al., 2021). All docking simulations were executed using default settings in AutoDock Vina with an exhaustiveness of 8, generating up to 10 poses per ligand, and an energy window of 4 $\text{kcal} \cdot \text{mol}^{-1}$ (Pham et al., 2022).

The binding free energy (ΔG , $\text{kcal} \cdot \text{mol}^{-1}$) values generated through PyRx were utilized to interpret the interaction strength between each ligand and the target receptors (Fukunishi et al., 2012). From these data, the inhibition constant (K_i) was estimated using the thermodynamic relationship:

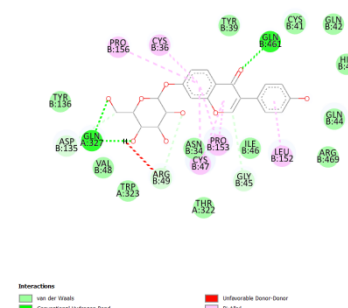
COMPUTATIONAL MOLECULAR DOCKING AND SIMULATION-BASED ASSESSMENT OF ANTI-INFLAMMATORY PROPERTIES OF ASCLEPIAS SYRIACA PHYTOCHEMICALS.

receptor's active site. In contrast, the weakest interactions were observed for **vanillic acid** (−5.9 kcal/mol), **sinapinic acid** (−5.8 kcal/mol), and **benzoic acid** (−5.8 kcal/mol), reflecting less effective binding within the active pocket (Khan et al., 2018).

Table 3. Docking scores and inhibition constants (Ki) of ligands from *Asclepias syriaca* phytochemicals against COX-1 (PDB ID: 1EQG).

Ligand	kcal/mol	Ki (μM)	Ligand	kcal/mol	Ki (μM)
Daidzin	−10.6	0.0168	Resveratrol	−7.9	1.606
Genistin	−10.3	0.0279	Chlorogenic acid	−7.5	3.156
Catechin	−9.4	0.1275	Esculetin	−7.2	6.906
Naringenin	−9.3	0.151	Caffeic acid	−6.8	10.293
Apigenin	−9.2	0.1788	Juglone	−6.6	14.429
Cyanidin	−9.2	0.1788	Protocatechuic acid	−6.4	20.227
Ellagic acid	−9.0	0.2506	p-Coumaric acid	−6.4	20.227
Epicatechin	−8.8	0.3513	4-Hydroxybenzoic acid	−6.3	23.948
Epigallocatechin	−8.7	0.4159	Gallic acid	−6.3	23.948
Kaempferol	−8.7	0.4159	Syringic acid	−6.1	33.571
Luteolin	−8.5	0.583	trans-Cinnamic acid	−6.0	39.747
Myricetin	−8.5	0.583	Salicylic acid	−5.9	47.06
Delphinidin	−8.4	0.6903	Vanillic acid	−5.9	47.06
Quercetin	−8.4	0.6903	Sinapinic acid	−5.8	55.718
Taxifolin	−8.3	0.8173	Benzoic acid	−5.8	55.718

Figure 2. 2D interaction structure of Daidzin bound to COX-1.



COMPUTATIONAL MOLECULAR DOCKING AND SIMULATION-BASED ASSESSMENT OF ANTI-INFLAMMATORY PROPERTIES OF ASCLEPIAS SYRIACA PHYTOCHEMICALS.

Quercetin	-9.2	0.18	Protocatech uic acid	-6.1	34
Delphinidin	-9	0.24	Gallic acid	-6.1	34
Naringenin	-9	0.24	Syringic acid	-5.9	48
Genistin	-8.9	0.3	4-Hydroxybenzoic acid	-5.9	48
Taxifolin	-8.9	0.3	Salicylic acid	-6.2	29
Cyanidin	-8.8	0.39	Benzoic acid	-5.7	67
Daidzin	-8.8	0.39	Vanillic acid	-6	40
Epigallocatechin	-8.7	0.43	Juglone	-7.8	1.9
Epicatechin	-8.5	0.6	Resveratrol	-7.8	1.9
Luteolin	-8.5	0.6	Esculetin	-7.2	5
Myricetin	-6.6	15	Catechol	-5.1	180

Figure 4. 2D interaction structure of Ellagic acid bound to JAK1.

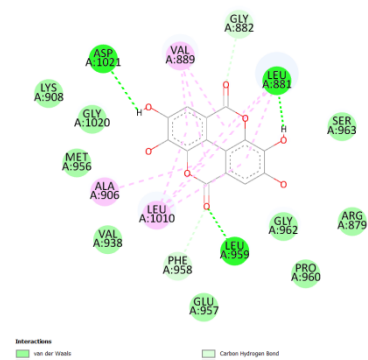
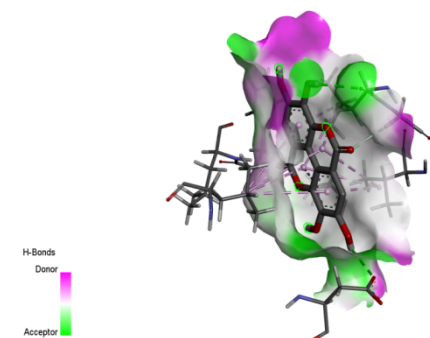


Figure 5. 3D interaction structure of Ellagic acid bound to JAK1.



Docking Results for JAK2

The strongest interaction was observed with **ellagic acid**, showing a binding energy of **-9.9 kcal/mol** and an estimated **Ki of 0.037 μ M**. **Daidzin** exhibited a comparable affinity (-

9.7 kcal/mol; Ki = 0.05 μ M), suggesting favourable accommodation within the receptor's active site. In contrast, the weakest interactions were recorded for **vanillic acid** (-5.8 kcal/mol), **4-hydroxybenzoic acid** (-5.6 kcal/mol), and **benzoic acid** (-5.6 kcal/mol), reflecting less effective binding within the active pocket (Rekha et al., 2020).

Table 5. Docking scores and inhibition constants (Ki) of ligands from *Asclepias syriaca* phytochemicals against JAK2 (PDB ID: 3KRR).

Ligand	kcal/mol	Ki (μ M)	Ligand	kcal/mol	Ki (μ M)
Ellagic acid	-9.9	0.037	Chlorogenic acid	-8.2	1.4
Daidzin	-9.7	0.05	Resveratrol	-7.7	4
Genistin	-9.6	0.062	Juglone	-7.4	7.9
Luteolin	-9.4	0.09	Esculetin	-6.9	24
Apigenin	-9.1	0.18	Caffeic acid	-6.7	35
Quercetin	-9.0	0.22	Sinapinic acid	-6.5	52
Taxifolin	-9.0	0.22	p-Coumaric acid	-6.4	64
Kaempferol	-8.9	0.3	trans-Cinnamic acid	-6.3	76
Naringenin	-8.9	0.3	Gallic acid	-6.0	122
Catechin	-8.6	0.44	Protocatech uic acid	-6.0	122
Delphinidin	-8.6	0.44	Salicylic acid	-6.0	122
Epicatechin	-8.6	0.44	Syringic acid	-5.9	148
Cyanidin	-8.5	0.54	Vanillic acid	-5.8	180
Epigallocatechin	-8.5	0.54	4-Hydroxybenzoic acid	-5.6	250
Myricetin	-8.7	0.36	Benzoic acid	-5.6	250

Figure 6. 2D interaction structure of Ellagic acid bound to JAK2.

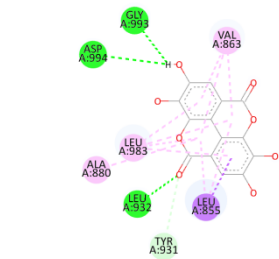
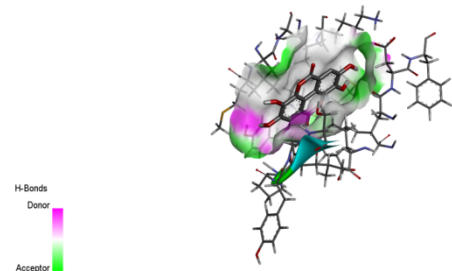


Figure 7. 2D interaction structure of Ellagic acid bound to JAK2.



Docking Results for 5-LOX

The strongest interaction was observed with **Daidzin**, which registered a binding energy of **−8.7 kcal/mol** and an estimated **Ki of 0.41 μM**. **Genistin** showed a comparable affinity (**−8.7 kcal/mol; Ki = 0.41 μM**), suggesting favourable accommodation within the receptor’s active site. In contrast, the weakest interactions were observed for **benzoic acid** (−5.9 kcal/mol), **sinapinic acid** (−5.7 kcal/mol), and **syringic acid** (−5.1 kcal/mol), indicating less effective binding within the pocket (Sajid et al., 2024).

Table 6. Docking scores and inhibition constants (Ki) of ligands from *Asclepias syriaca* phytochemicals against 5-LOX (PDB ID: 3O8Y).

Ligand	kcal/mol	Ki (μM)	Ligand	kcal/mol	Ki (μM)
Daidzin	−8.7	0.41	Taxifolin	−7.5	4.6
Genistin	−8.7	0.41	Chlorogenic acid	−7.3	6.7
Luteolin	−8.6	0.5	Resveratrol	−7.3	6.7
Apigenin	−8.4	0.71	p-Coumaric acid	−6.8	18
Catechin	−8.3	0.88	Caffeic acid	−6.7	22

Epicatchin	−8.3	0.88	Vanillic acid	−6.7	22
Quercetin	−8.3	0.88	trans-Cinnamic acid	−6.6	29
Cyanidin	−8.0	1.8	Protocatechuic acid	−6.5	37
Ellagic acid	−8.0	1.8	Gallic acid	−6.4	45
Kaempferol	−8.0	1.8	4-Hydroxybenzoic acid	−6.3	57
Delphinidin	−7.9	2.3	Salicylic acid	−6.3	57
Epigallocatechin	−7.9	2.3	Juglone	−6.0	115
Esculetin	−7.9	2.3	Benzoic acid	−5.9	150
Myricetin	−7.9	2.3	Sinapinic acid	−5.7	215
Naringenin	−7.9	2.3	Syringic acid	−5.1	600

Figure 8. 2D interaction structure of Ellagic acid bound to JAK2.

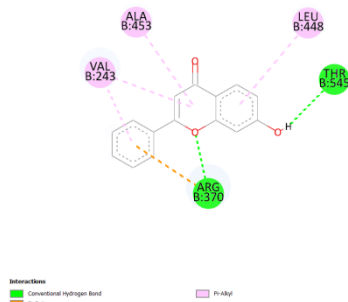
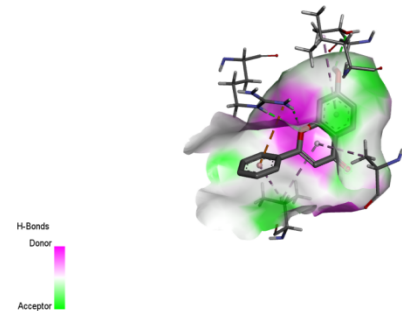


Figure 9. 3D interaction structure of Ellagic acid bound to JAK2.



Multi-Target Analysis

A comparative docking analysis was conducted for six major phytochemicals **daidzin**, **ellagic acid**, **genistin**, **luteolin**,

catechin, and kaempferol against four inflammation-associated proteins: **COX-1, JAK1, JAK2, and 5-LOX** (Ahmad et al., 2023). Among the screened compounds, **daidzin, ellagic acid, and genistin** consistently ranked among the strongest binders across the targets (Alfei et al., 2019). **Daidzin** showed the highest affinity for **COX-1** (**−10.6 kcal/mol**), while **ellagic acid** exhibited strong interactions with both **JAK1** (**−10.0 kcal/mol**) and **JAK2** (**−9.9 kcal/mol**), highlighting their potential as broad-spectrum anti-inflammatory modulators (Khan et al., 2025).

Compounds such as **luteolin, kaempferol, and catechin** demonstrated moderate yet consistent multi-target activity, with docking energies ranging from **−8.0 to −9.4 kcal/mol** across all proteins. These results suggest that they may contribute to simultaneous regulation of COX- and JAK-mediated inflammatory pathways (Pathak et al., 2018).

A selective interaction pattern was observed for **kaempferol**, which showed slightly weaker affinity toward 5-LOX (**−8.0 kcal/mol**) compared to other targets. Overall, the docking results identify **daidzin, ellagic acid, and genistin** as the most versatile candidates with strong cross-target interactions, whereas the remaining compounds displayed moderate or target-specific binding, indicating their potential role in managing inflammatory responses (Ayorinde et al., 2025).

Table 7: Multi-target docking affinities (kcal/mol) of selected phytochemicals against COX-1, JAK1, JAK2, and 5-LOX

Ligand	COX-1 (kcal/mol)	JAK1 (kcal/mol)	JAK2 (kcal/mol)	5-LOX (kcal/mol)
Daidzin	−10.6	−8.8	−9.7	−8.7
Ellagic acid	−9.0	−10.0	−9.9	−8.0
Genistin	−10.3	−8.9	−9.6	−8.7
Luteolin	−8.5	−9.4	−9.4	−8.6
Catechin	−9.4	−8.7	−8.6	−8.3
Kaempferol	−8.7	−9.3	−8.9	−8.0

Pharmacokinetic and ADME Insights

SwissADME analysis was performed to evaluate the pharmacokinetic profiles, drug-likeness, and ADME suitability of the six selected phytochemicals: **daidzin, ellagic acid, genistin, luteolin, catechin, and kaempferol** (Daina et al., 2017). Parameters assessed included gastrointestinal (GI) absorption, blood–brain barrier (BBB) permeability, cytochrome P450 (CYP) inhibition, and compliance with Lipinski’s and Veber’s rules (Yusuf et al., 2025).

Non-glycosylated flavonoids **ellagic acid, luteolin, kaempferol, and catechin** exhibited generally favourable pharmacokinetic characteristics. Most showed high GI absorption and no violations of Lipinski’s rules, indicating potential for good oral bioavailability. Additionally, luteolin, kaempferol, and catechin satisfied Veber’s criteria, suggesting effective membrane permeability (Ojuka et al., 2025).

In contrast, glycosylated molecules **daidzin and genistin** displayed lower GI absorption, non-permeability across the

BBB, and violations in Veber’s rules, likely due to their higher topological polar surface area (TPSA) and increased molecular size from sugar moieties. These properties may limit passive diffusion and oral bioavailability (Lu et al., 2004).

Across all compounds, none were predicted to cross the BBB, implying minimal central nervous system penetration, which is favourable for peripherally targeted anti-inflammatory therapies. CYP inhibition analysis indicated that aglycone flavonoids particularly **luteolin, kaempferol, and catechin** may inhibit CYP2D6 or CYP3A4, suggesting possible drug–drug interaction risks, though experimental validation is needed (Shimazu et al., 2021).

Overall, the ADME profiles suggest that non-glycosylated flavonoids are the most promising candidates for further anti-inflammatory drug development, whereas glycosylated compounds may require structural optimization or formulation strategies to improve pharmacokinetic performance (Hasnat et al., 2024).

Table 8: Molecular Properties of Selected Phytochemicals.

S. N. O	COM NAME	Formula	Molecular weight	Num. heavy atoms	Num. H-bond acceptors	Num. H-bond donors
1	Daidzin	C ₂₁ H ₂₀ O ₉	416.38 g/mol	30	9	5
2	Ellagic acid	C ₁₄ H ₆ O ₈	302.19 g/mol	22	8	4
3	Genistin	C ₂₁ H ₂₀ O ₁₀	432.38 g/mol	31	10	6
4	Luteolin	C ₁₅ H ₁₀ O ₆	286.24 g/mol	21	6	4
5	Catechin	C ₁₅ H ₁₄ O ₆	290.27 g/mol	21	6	5
6	Kaempferol	C ₁₅ H ₁₀ O ₆	286.24 g/mol	21	6	4

Table 9: Pharmacokinetic and Drug-Likeness Properties

S. N. O	COM NAME	GI absorption	BBB permeant	CYP2C19 inhibitor	CYP2C9 inhibitor	CYP2D6 inhibitor	CYP3A4 inhibitor	Lipinski	Veber

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1	Daidzin	Low	No	No	No	No	No	Yes ; 0 violation	No; 1 violation on: TP SA >1 40
2	Ellagic acid	High	No	No	No	No	No	Yes ; 0 violation	No; 1 violation on: TP SA >1 40
3	Genistin	Low	No	No	No	No	No	Yes ; 1 violation	No; 1 violation on: TP SA >1 40
4	Luteolin	High	No	No	No	Yes	Yes	Yes ; 0 violation	Yes
5	Catechin	High	No	No	No	No	No	Yes ; 0 violation	Yes
6	Kaempferol	High	No	No	No	Yes	Yes	Yes ; 0 violation	Yes

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4. Discussion

Daidzin, an isoflavone glycoside abundant in soybeans, legumes, and fermented foods, is known for its antioxidant and anti-inflammatory activities. These properties correspond with the multi-target interactions observed in this study, where daidzin exhibited strong affinities toward inflammation-related proteins. Its binding energies ranged from -8.7 to -10.6 kcal/mol, suggesting its potential to modulate COX- and JAK-mediated inflammatory signalling pathways (Ahmad et al., 2024).

Ellagic acid, a polyphenolic compound found in berries, pomegranates, and walnuts, is recognized for its antioxidant and anti-inflammatory effects. The stable binding profiles observed here, with docking energies from -8.0 to -10.0 kcal/mol, support its potential to reduce oxidative stress and regulate inflammatory responses through JAK and COX inhibition (Sharifi-Rad et al., 2022).

Catechin, abundant in green tea, cocoa, and several fruits, is reported for its anti-inflammatory and antioxidant effects. Its consistent binding across all selected targets, ranging from -8.3 to -9.4 kcal/mol, highlights its ability to modulate multiple inflammation-related signalling cascades (Nain et al., 2022).

Luteolin, present in parsley, celery, and chamomile, is known for anti-inflammatory and immunomodulatory activities. Docking trends in this study, with affinities from -8.5 to -9.4 kcal/mol, suggest luteolin can influence cytokine-mediated pathways and COX- and JAK-dependent inflammatory mechanisms (Huang et al., 2023).

Kaempferol, found in tea, broccoli, and spinach, possesses anti-inflammatory and antioxidant properties. Its docking energies ranged from -8.0 to -9.3 kcal/mol, reflecting strong interactions with multiple inflammation-associated proteins and supporting its potential role in controlling oxidative and inflammatory stress (Alrumaihi et al., 2024).

Genistin, the glycosylated form of genistein present in soybeans and legumes, has reported antioxidant and anti-inflammatory activities. Despite its sugar moiety, genistin showed meaningful interactions with JAK1, JAK2, and 5-LOX, with binding energies ranging from -7.5 to -9.6 kcal/mol, indicating potential relevance in regulating stress- and cytokine-linked pathways (Goh et al., 2022).

Overall, the multi-target docking behaviour of these phytochemicals aligns with their known anti-inflammatory properties. The results suggest that these compounds may act as broad-spectrum modulators of inflammatory signalling, highlighting their potential as candidates for the development of natural anti-inflammatory agents. Further experimental validation is warranted to confirm their therapeutic relevance.

5. Conclusion

An integrated computational approach was employed to evaluate the anti-inflammatory potential of phytochemicals from *Asclepias curassavica* (*Asclepias syriaca*) against four inflammation-associated proteins: COX-1, JAK1, JAK2, and 5-LOX. Molecular docking analysis identified ellagic acid, daidzin, luteolin, catechin, kaempferol, and genistin as notable multi-target binders, displaying strong affinities across the selected protein panel. Among them, ellagic acid, daidzin, and luteolin demonstrated the most favourable

binding characteristics, indicating their potential to modulate key inflammation-linked signalling pathways.

Pharmacokinetic and SwissADME evaluation revealed that non-glycosylated phytochemicals particularly ellagic acid, luteolin, kaempferol, and catechin exhibited better oral bioavailability, higher gastrointestinal absorption, and overall drug-likeness. In contrast, glycosylated compounds such as daidzin and genistin showed lower absorption and violated major drug-likeness parameters due to their higher polarity and molecular weight. These findings suggest that the aglycone forms of *Asclepias syriaca* flavonoids possess more favourable pharmacokinetic profiles for potential therapeutic applications.

Overall, the combined docking and ADME results indicate that several phytochemicals in *A. curassavica* hold promise as lead molecules for the development of multi-targeted anti-inflammatory agents. Further experimental validation through in vitro and in vivo studies is essential to establish their efficacy and therapeutic relevance, supporting potential applications in pharmaceutical research and human health.

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