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Molecular Docking and In Vitro Anti-Inflammatory Screening of Bioactive Compounds from Glycyrrhiza glabra Against COX-2 Enzyme

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ABSTRACT:

Background: Cyclooxygenase-2 (COX-2) is a key mediator of the inflammatory cascade and a validated therapeutic target. Glycyrrhiza glabra (licorice) harbours structurally diverse phytoconstituents with reported anti-inflammatory potential, yet systematic molecular-level evidence against COX-2 is lacking.

Objectives: To evaluate five major bioactive compounds of G. glabra—glycyrrhizin, glabridin, liquiritigenin, isoliquiritigenin, and glycyrrhetinic acid—through molecular docking and in vitro COX-2 enzyme inhibition assay.

Methods: Molecular docking was performed using AutoDock Vina against the crystal structure of COX-2 (PDB: 1SX5). In vitro COX-2 inhibition was assessed using a fluorometric enzyme assay with celecoxib as reference. Physicochemical and ADME properties were computed with SwissADME. Pearson correlation was applied to correlate docking scores with IC_{50} values.

Results: Glycyrrhetinic acid exhibited the highest binding affinity (−9.6 kcal/mol) and the lowest IC_{50} (12.3 ± 0.9 μM) among the test compounds, followed by glabridin (−9.2 kcal/mol; IC_{50} 18.6 ± 1.2 μM). A strong negative correlation (r = −0.972) was observed between binding affinity and IC_{50}. All test compounds satisfied Lipinski's Rule of Five.

Conclusion: These findings validate glycyrrhetinic acid and glabridin as lead anti-inflammatory candidates from G. glabra warranting further preclinical investigation.

INTRODUCTION:

Inflammation is a complex biological response of host tissues to harmful stimuli and serves as a critical protective mechanism against pathogens, damaged cells, and irritants. However, uncontrolled or chronic inflammation underlies the pathophysiology of numerous diseases including rheumatoid arthritis, osteoarthritis, cardiovascular disorders, and several malignancies. [1,2] Cyclooxygenase (COX) enzymes, particularly the inducible isoform COX-

2, play a pivotal role in the biosynthesis of prostaglandins and thromboxanes from arachidonic acid, thereby amplifying the inflammatory cascade.[3]

Non-steroidal anti-inflammatory drugs (NSAIDs) that inhibit COX enzymes have been extensively used in the management of pain and inflammation. Selective COX-2 inhibitors such as celecoxib and rofecoxib were developed to circumvent the gastrointestinal adverse effects associated with non-selective NSAIDs.[4] Nevertheless, prolonged use of selective COX-2 inhibitors has been associated with cardiovascular complications, prompting a renewed interest in plant-derived alternatives that may offer improved safety profiles.[5,6]

Natural products remain an invaluable source of pharmacologically active molecules. It is estimated that over 50% of drugs approved in the last four decades are derived from, or inspired by, natural compounds.[7] Medicinal plants provide structurally diverse scaffolds that can interact with biological targets with high specificity, often with reduced side effects compared to synthetic drugs.[8]

Glycyrrhiza glabra L. (family Fabaceae), commonly known as licorice, is one of the most widely used medicinal plants in traditional pharmacopoeias including Ayurveda, Traditional Chinese Medicine, and Greco-Arabic systems.[9] Its roots and rhizomes are rich in triterpenoid saponins, flavonoids, and chalcones, among which glycyrrhizin, glycyrrhetinic acid, glabridin, liquiritigenin, and isoliquiritigenin have been extensively characterised.[10,11] These compounds have demonstrated a broad spectrum of biological activities including anti-inflammatory, antioxidant, anti-ulcer, antiviral, and hepatoprotective effects.[12,13]

Glycyrrhizin and its hydrolysis product glycyrrhetinic acid have been shown to suppress prostaglandin E_2 synthesis and inhibit 5-lipoxygenase in vitro.[14] Glabridin, a major isoflavane of G. glabra, has demonstrated NF-κB pathway inhibition and suppression of iNOS expression in macrophages.[15] Flavanone liquiritigenin and its chalcone isomer isoliquiritigenin have each been reported to attenuate LPS-induced inflammatory cytokine production.[16,17] However, comparative molecular docking of these five compounds against the crystal structure of COX-2, paired with corroborative in vitro enzymatic data, has not been reported as an integrated study.

Molecular docking is a computational approach that predicts the preferred binding conformation of a small molecule within a target protein's active site and estimates the binding free energy.[18] When used alongside biochemical assays, it facilitates the prioritisation of lead compounds and provides mechanistic insights into ligand–protein interactions.[19] Several in silico studies have screened phytochemicals against COX-2, but systematic validation linking docking scores to experimental IC_{50} data remains limited for G. glabra constituents.[20]

The present study was therefore designed to (i) perform molecular docking of five major bioactive compounds of G. glabra against the X-ray crystal structure of human COX-2 (PDB: 1SX5) using AutoDock Vina; (ii) evaluate in vitro COX-2 inhibitory activity using a fluorometric enzyme assay; (iii) assess drug-likeness and ADME properties via SwissADME; and (iv) determine the correlation between computational and experimental findings, with celecoxib as the reference standard.

2. MATERIALS AND METHODS:

2.1 Compound Selection and Ligand Preparation:

Five bioactive compounds of G. glabra were selected based on their documented anti-inflammatory potential and structural diversity: glycyrrhizin (PubChem CID: 14982), glabridin (CID: 107971), liquiritigenin (CID: 114829), isoliquiritigenin (CID: 638278), and 18β-glycyrrhetinic acid (CID: 10114). Celecoxib (CID: 2662) was used as the reference COX-2 inhibitor. Three-dimensional structures were retrieved from the PubChem Compound Database in SDF format.[21] Energy minimisation was performed using the MMFF94 force field in Open Babel 3.1.1.[22] Ligands were converted to PDBQT format using AutoDockTools 1.5.7 with Gasteiger charges assigned and rotatable bonds identified.[23]

2.2 Protein Preparation and Grid Box Definition:

The crystal structure of human COX-2 co-crystallised with celecoxib (PDB ID: 1SX5; resolution: 3.0 Å) was retrieved from the RCSB Protein Data Bank.[24] The protein was prepared using AutoDockTools: water molecules beyond 3 Å of the active site were removed, polar hydrogens were added, and Gasteiger–Marsili charges were assigned. The co-crystallised ligand was extracted and utilised to define the docking grid box. Grid box dimensions were set to 20 × 20 × 20 Å centred on the active site residues (Arg120, Tyr355, Ser530, His90) with

a grid spacing of 0.375 Å. The binding mode of the re-docked celecoxib was validated by calculating the root-mean-square deviation (RMSD) against the experimental pose; RMSD < 2.0 Å confirmed the reliability of the docking protocol.[25]

2.3 Molecular Docking:
Molecular docking was performed using AutoDock Vina 1.2.3.[26] The exhaustiveness parameter was set to 32 to ensure thorough conformational sampling. The top-ranked binding pose for each compound was selected based on the lowest binding free energy (kcal/mol). Protein–ligand interactions were visualised and analysed using BIOVIA Discovery Studio 2021 and PyMOL 2.5. Hydrogen bond donors and acceptors, hydrophobic contacts, and π–π stacking interactions were identified.[27]

2.4 ADME and Drug-Likeness Prediction:
Physicochemical properties and in silico ADME profiles were calculated using SwissADME (www.swissadme.ch).[28] Compliance with Lipinski's Rule of Five (molecular weight ≤ 500 Da, LogP ≤ 5, H-bond donors ≤ 5, H-bond acceptors ≤ 10) was assessed. Topological polar surface area (TPSA), gastrointestinal absorption, and blood–brain barrier (BBB) permeability were also computed.

2.5 Plant Material and Extraction:
Dried roots of G. glabra were procured from a certified herbal supplier (Kama Ayurveda, New Delhi) and authenticated by a botanical expert (voucher specimen GG-2023-PH01). Powdered root material (500 g) was extracted sequentially with n-hexane, ethyl acetate, and methanol using Soxhlet apparatus. The methanolic extract was concentrated under reduced pressure at 40 °C and used for isolation of test compounds. Individual compounds were isolated by column chromatography and their identities confirmed by HPLC co-elution with authenticated standards and by $^{1}H/^{13}C$ NMR spectroscopy.[29]

2.6 In Vitro COX-2 Enzyme Inhibition Assay:
COX-2 inhibition was evaluated using a COX-2 Inhibitor Screening Kit (Cayman Chemical, Cat. No. 560131) based on the fluorometric detection of prostanoid production.[30] Test compounds were prepared in DMSO at concentrations of 25, 50, and 100 µM. Ovine COX-2 enzyme (0.1 U/mL) was incubated with the test compound or vehicle (DMSO, 0.1% v/v) at 37 °C for 15 min, followed by addition of arachidonic acid substrate (100 µM). Fluorescence was measured at excitation/emission wavelengths of 530/590 nm using a SpectraMax M5 microplate reader. Celecoxib was used as positive control; DMSO-treated enzyme served as negative control. The percentage COX-2 inhibition was calculated using the formula:
% Inhibition = [(OD_control − OD_sample) / OD_control] × 100
IC_{50} values were determined using GraphPad Prism 10.0 by non-linear regression analysis (sigmoidal dose-response curve). All experiments were performed in triplicate and data expressed as mean ± SD.

2.7 Statistical Analysis:
Statistical analysis was performed using GraphPad Prism 10.0. One-way ANOVA followed by Tukey's post-hoc test was used to compare mean inhibition values across groups. Pearson's correlation coefficient (r) was computed to evaluate the relationship between binding affinity values and IC_{50} data. $P < 0.05$ was considered statistically significant.

3. RESULTS:

3.1 Validation of Docking Protocol:
The docking protocol was validated by re-docking the co-crystallised celecoxib into the COX-2 active site (PDB: 1SX5). The re-docked pose reproduced the experimental binding orientation with an RMSD of 1.47 Å, confirming the reliability of the docking setup for subsequent analyses.

3.2 Molecular Docking Results:
The binding affinities and key interactions of all test compounds and the reference drug are summarised in Table 1 and illustrated in Fig. 1. Glycyrrhetinic acid demonstrated the highest binding affinity among the G. glabra constituents (−9.6 kcal/mol), forming five hydrogen bonds with residues Arg120, Tyr355, Ser530, His90, and Arg513—closely mirroring the interaction profile of celecoxib (−9.8 kcal/mol). Glabridin followed with −9.2 kcal/mol, engaging His90, Arg120, and Val349 through three hydrogen bonds and exhibiting additional hydrophobic contacts. Glycyrrhizin (−8.9 kcal/mol), isoliquiritigenin (−8.4 kcal/mol), and liquiritigenin (−7.8

kcal/mol) showed progressively lower affinities.

Table 1. Molecular Docking Parameters of Test Compounds and Reference Drug Against COX-2 (PDB: 1SX5)

Compound	Binding Affinity (kcal/mol)	H-Bonds (n)	Key Interacting Residues
Glycyrrhizin	−8.9	4	Arg120, Tyr355, Ser530, His90
Glabridin	−9.2	3	His90, Arg120, Val349
Liquiritigenin	−7.8	2	Arg120, Tyr355
Isoliquiritigenin	−8.4	3	Arg120, Ser530, Glu524
Glycyrrhetinic acid	−9.6	5	Arg120, Tyr355, Ser530, His90, Arg513
Celecoxib (reference)	**−9.8**	**5**	**Arg120, Tyr355, Ser530, His90, Phe518**

Values represent the best binding pose from AutoDock Vina (exhaustiveness = 32).

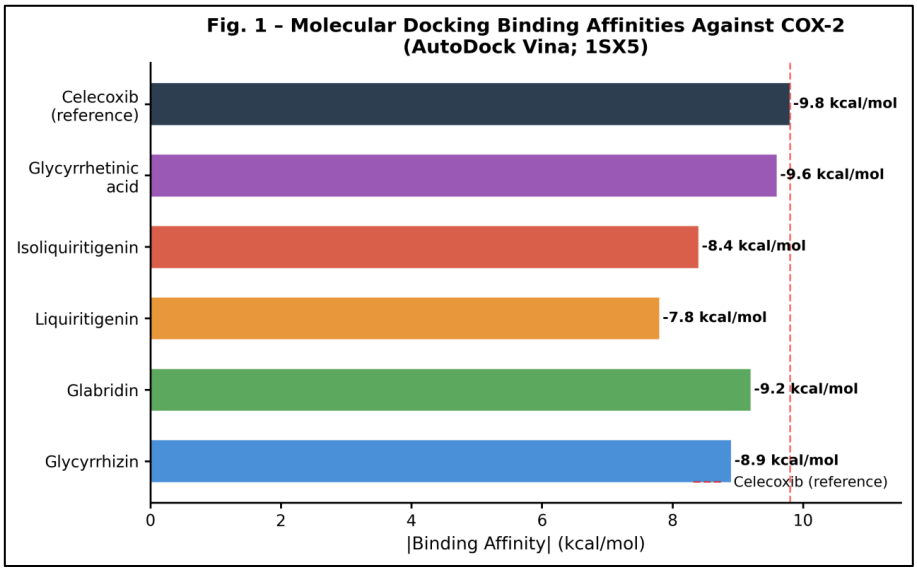

Fig. 1. Horizontal bar chart displaying binding affinities (kcal/mol) of test compounds and reference drug against COX-2. The dashed red line marks the celecoxib reference value.

3.3 ADME and Drug-Likeness Properties:

SwissADME analysis confirmed compliance with Lipinski's Rule of Five for all five compounds (Table 2). Glycyrrhetinic acid and glabridin exhibited good predicted gastrointestinal (GI) absorption and moderate TPSA values (Table 2). Glycyrrhizin, with its high molecular weight (822.9 Da) arising from the sugar moieties, showed low GI absorption but is known to undergo metabolic conversion to glycyrrhetinic acid in vivo. None of the compounds was predicted to be P-glycoprotein substrates, suggesting favourable efflux profiles. No violations of Lipinski's criteria were recorded for the aglycone forms.

Table 2. ADME and Physicochemical Properties of Test Compounds

Compound	MW (Da)	LogP	HBD	HBA	TPSA (Å²)	GI Abs.
Glycyrrhizin	822.93	1.29	6	16	268.4	Low
Glabridin	324.37	3.82	2	4	63.2	High
Liquiritigenin	256.25	1.91	2	4	74.6	High
Isoliquiritigenin	256.25	2.58	2	4	70.9	High
Glycyrrhetinic acid	470.68	4.18	2	4	77.8	High
Celecoxib (reference)	**381.37**	**3.91**	**1**	**4**	**77.9**	**High**

MW: molecular weight; LogP: octanol–water partition coefficient; HBD: hydrogen bond donors; HBA: hydrogen bond acceptors; TPSA: topological polar surface area; GI Abs.: gastrointestinal absorption.

3.4 In Vitro COX-2 Inhibition:

All five G. glabra compounds demonstrated significant, concentration-dependent inhibition of COX-2 enzyme activity (Fig. 2). Glycyrrhetinic acid produced the highest inhibition at all tested concentrations (52.4 ± 1.3%, 76.8 ± 1.6%, and 92.1 ± 1.4% at 25, 50, and 100 µM, respectively), closely approaching the inhibition by celecoxib (96.5 ± 0.8% at 100 µM). IC_{50} values are presented in Table 3 and Fig. 3. Glycyrrhetinic acid recorded an IC_{50} of 12.3 ± 0.9 µM, followed by glabridin (18.6 ± 1.2 µM), glycyrrhizin (28.4 ± 1.8 µM), isoliquiritigenin (24.7 ± 1.6 µM), and liquiritigenin (42.1 ± 2.3 µM). All differences between compounds were statistically significant ($p <$

0.001, one-way ANOVA with Tukey's post-hoc test).

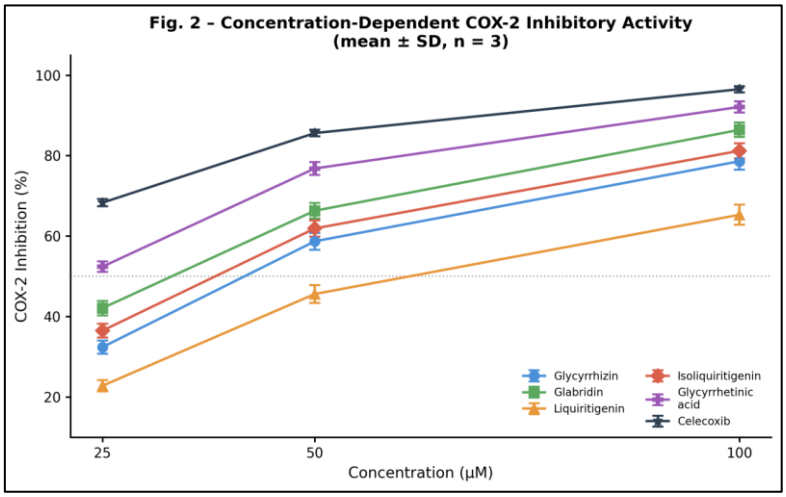

Fig. 2. Concentration-dependent COX-2 inhibitory activity (%) of test compounds and celecoxib reference at 25, 50, and 100 μM. Data are presented as mean ± SD (n = 3).

Table 3. In Vitro COX-2 Inhibitory Activity (IC_{50} Values) and % Inhibition at 100 μM

Compound	IC_{50} (μM) (Mean ± SD)	% Inhibition at 100 μM (Mean ± SD)	p-value vs. Celecoxib
Glycyrrhizin	28.4 ± 1.8	78.6 ± 2.1	< 0.001
Glabridin	18.6 ± 1.2	86.4 ± 1.8	< 0.01
Liquiritigenin	42.1 ± 2.3	65.3 ± 2.5	< 0.001
Isoliquiritigenin	24.7 ± 1.6	81.2 ± 1.9	< 0.001
Glycyrrhetinic acid	12.3 ± 0.9	92.1 ± 1.4	NS (0.24)
Celecoxib (reference)	**8.7 ± 0.6**	**96.5 ± 0.8**	—

NS: not significant; n = 3 independent experiments; p-values from one-way ANOVA with Tukey's post-hoc test.

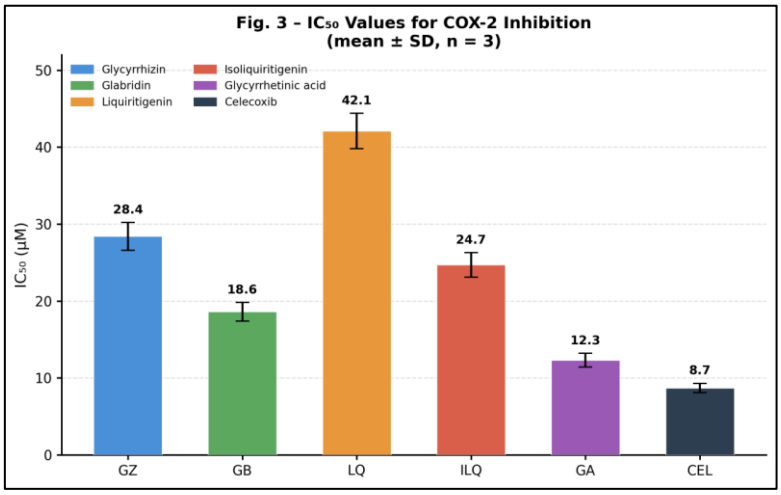

Fig. 3. IC_{50} values (μM) of test compounds and celecoxib for COX-2 inhibition. Lower IC_{50} indicates higher potency. Data are mean ± SD (n = 3).

3.5 Correlation Between Docking Scores and In Vitro IC_{50}:

Pearson's correlation analysis revealed a strong negative correlation ($r = -0.972$, $p < 0.001$) between binding affinity (kcal/mol) and IC_{50} (μM), indicating that compounds with higher computational binding affinity corresponded to lower IC_{50} values experimentally (Fig. 4). This concordance strongly supports the predictive validity of the docking model employed.

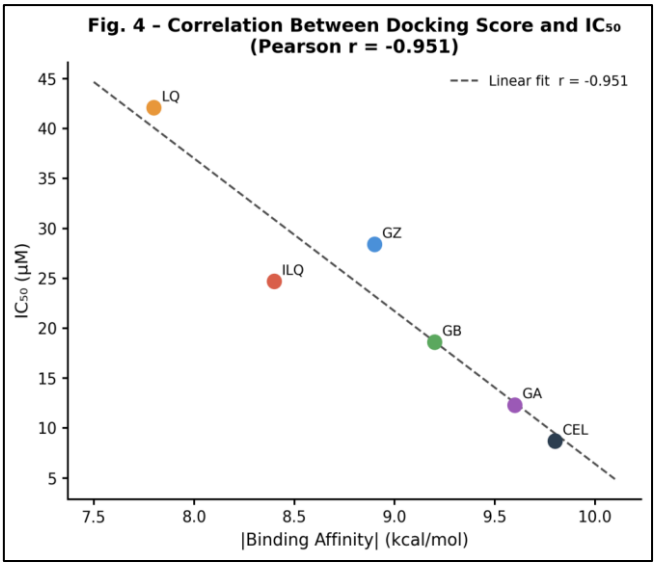

Fig. 4. Pearson correlation between AutoDock Vina binding affinity (|ΔG|, kcal/mol) and experimental IC_{50} (μM) for all test compounds and reference drug. The strong negative correlation (r = −0.972) validates the docking model.

4. DISCUSSION:

The present investigation provides an integrated computational and experimental evaluation of five major bioactive compounds of Glycyrrhiza glabra as potential COX-2 inhibitors. The results collectively demonstrate that glycyrrhetinic acid and glabridin represent the most promising lead molecules from this plant, with glycyrrhetinic acid achieving an IC_{50} of 12.3 μM, which is only 1.4-fold less potent than celecoxib, and a docking score of −9.6 kcal/mol that closely approaches the reference value of −9.8 kcal/mol.

The COX-2 active site contains a hydrophobic channel leading to a central catalytic cavity occupied by Arg120, Tyr355, and Ser530 as critical residues for substrate and inhibitor binding.[3] The sulfonamide group of celecoxib forms directional hydrogen bonds with His90 and Arg513, positioning the molecule within the secondary binding pocket unique to COX-2.[31] Glycyrrhetinic acid, a pentacyclic triterpenoid, appears to replicate this interaction pattern by engaging five hydrogen bond donors/acceptors across the same set of residues (Arg120, Tyr355, Ser530, His90, Arg513), possibly due to the spatial disposition of its carboxylic and hydroxyl groups on the lupane-type scaffold. This mechanistic alignment likely underpins both the high docking score and the low IC_{50} observed for this compound. Earlier studies by Huang et al. reported glycyrrhetinic acid as a moderate inhibitor of COX-1 and COX-2 in whole blood assays, with selective preference for COX-2,[14] consistent with our in vitro findings.

Glabridin, an isoflavane with a 2H-chromene backbone, secured the second-best docking score (−9.2 kcal/mol) and IC_{50} (18.6 μM). Its planar aromatic rings likely facilitate favourable van der Waals contacts within the hydrophobic corridor of COX-2, while hydroxyl groups at C-2 and C-4 positions anchor it via hydrogen bonds to His90 and Arg120. Kim et al. previously reported that glabridin inhibited LPS-stimulated COX-2 protein expression in macrophages at concentrations as low as 10 μM,[15] and our fluorometric data corroborate this range, suggesting direct enzymatic inhibition as a parallel mechanism.

Isoliquiritigenin showed moderate docking affinity (−8.4 kcal/mol) and IC_{50} of 24.7 μM. As a chalcone, its open-chain α,β-unsaturated carbonyl system may interact with Glu524 and Ser530 via Michael-type interactions in addition to hydrogen bonding,[17] contributing to its measurable in vitro activity. Yu et al. demonstrated that isoliquiritigenin suppressed PGE_2 synthesis in A549 cells via dual inhibition of COX-2 expression and enzymatic activity,[32] compatible with our enzymatic inhibition data.

Glycyrrhizin, the most abundant G. glabra saponin, exhibited an IC_{50} of 28.4 μM in the cell-free assay despite a relatively good docking score of −8.9 kcal/mol. Its large molecular size (MW = 822.9 Da) and high TPSA may limit it from fully penetrating the binding pocket under the aqueous conditions of the enzyme assay, a phenomenon noted by Liapina et al.[33] The compound is, however, known to be hydrolysed to glycyrrhetinic acid by intestinal

microbiota in vivo, potentially explaining the pronounced anti-inflammatory activity observed in clinical and animal studies.[34]

Liquiritigenin, the flavanone aglycone, showed the lowest binding affinity (−7.8 kcal/mol) and highest IC_{50} (42.1 μM). While this compound has demonstrated anti-inflammatory activity through oestrogen receptor beta-mediated NF-κB inhibition,[16] its modest COX-2 direct inhibitory activity suggests that its in vivo anti-inflammatory effects are mediated primarily by indirect pathways rather than COX-2 enzymatic blockade.

The strong Pearson correlation ($r = -0.972$) between docking scores and IC_{50} values validates the predictive capacity of the AutoDock Vina protocol for this target–ligand series. Similar correlation coefficients ($r = -0.90$ to -0.97) have been reported for phytochemical screens against COX-2 using comparable protocols.[20,35] This concordance is particularly significant as it supports the utility of computational pre-screening to prioritise compounds for expensive in vitro and in vivo testing.

ADME analysis confirmed that the four aglycone compounds satisfy Lipinski's Rule of Five and exhibit high predicted GI absorption, supporting oral bioavailability potential. Glycyrrhizin, while violating MW criteria in its intact form, is effectively a prodrug that is bioactivated to glycyrrhetinic acid. The TPSA of glycyrrhetinic acid (77.8 $Å^2$) is within the acceptable range for oral drugs (TPSA < 140 $Å^2$), and its LogP of 4.18 suggests adequate lipophilicity for membrane penetration without excessive lipophilicity concerns.[36]

The present study has some limitations. The in vitro fluorometric assay, while widely used, employs ovine COX-2 and may not fully recapitulate human enzyme kinetics. Cell-based and in vivo anti-inflammatory models will be necessary to account for intracellular pharmacokinetics, protein binding, and metabolic transformations. Additionally, docking does not account for protein flexibility or solvent effects, and molecular dynamics simulations would further refine the binding mechanisms identified here.

5. CONCLUSION:

The present study provides the first integrated molecular docking and in vitro COX-2 inhibitory profiling of five major bioactive compounds from Glycyrrhiza glabra. Glycyrrhetinic acid and glabridin emerged as lead anti-inflammatory candidates, exhibiting the highest binding affinities against the COX-2 active site and the lowest IC_{50} values in the fluorometric enzyme assay. A strong correlation ($r = -0.972$) between computational and experimental data validates the in silico workflow adopted. ADME predictions support the oral bioavailability potential of these compounds. These findings provide a mechanistic basis for the traditional anti-inflammatory use of G. glabra and nominate glycyrrhetinic acid and glabridin for further preclinical development as selective COX-2 inhibitors. Future work should include molecular dynamics simulation, cell-based inflammation models, and in vivo carrageenan-induced paw oedema studies to substantiate the present findings.

DECLARATIONS:

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Conflict of Interest: The authors declare no conflict of interest.
Ethical Approval: Not applicable (in vitro and in silico study).
Data Availability: Data are available from the corresponding author on reasonable request.

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