

In Silico Evaluation of *Curcuma longa* Curcuminoids as Dual (COX-2) / (5-LOX) Inhibitors

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ABSTRACT

Inflammation is a major contributor to chronic diseases, including diabetes, cancer, and cardiovascular disorders, and is regulated by the arachidonic acid cascade through cyclooxygenase-2 (COX-2) and 5-lipoxygenase (5-LOX). Conventional anti-inflammatory drugs, such as nonsteroidal anti-inflammatory drugs (NSAIDs) and selective COX-2 inhibitors, are associated with gastrointestinal, cardiovascular, and renal toxicities. Moreover, selective COX-2 inhibition may induce the "arachidonic acid shunt," increasing leukotriene production via the 5-LOX pathway. Consequently, simultaneous inhibition of COX-2 and 5-LOX represents a promising therapeutic strategy. This study employed in silico methods to evaluate the dual inhibitory potential of curcumin, demethoxycurcumin (DMC), and bis-demethoxycurcumin (BDMC) from *Curcuma longa* against COX-2 (PDB: 5F19) and 5-LOX (PDB: 7TTK), using celecoxib, ibuprofen, licofelone, and zileuton as reference drugs. Molecular docking was performed using Molegro Virtual Docker following protocol validation (RMSD < 2.0 Å), while binding interactions and pharmacokinetic properties were analysed using Discovery Studio, SwissADME, and pkCSM. Curcumin demonstrated the strongest dual inhibitory activity, with MolDock scores of -133.272 kcal/mol for COX-2 comparable to celecoxib (-138.129 kcal/mol), -143.172 kcal/mol for 5-LOX superior to zileuton (-88.474 kcal/mol), and formed hydrogen bonding, electrostatic, and hydrophobic interactions with ARG-61, GLU-465, GLN-437, and ARG-438 residues. Bis-demethoxycurcumin also exhibited favourable dual binding affinity (-127.373 and -122.126 kcal/mol for COX-2 and 5-LOX). All three curcuminoids complied with Lipinski's Rule of Five, showed good gastrointestinal absorption, and were predicted to be non-mutagenic and non-hepatotoxic, although CYP3A4 inhibition warrants further investigation. These findings identify curcuminoids, particularly curcumin, as potential candidates requiring experimental validation as dual COX-2/5-LOX inhibitors for inflammatory diseases.

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INTRODUCTION

Inflammation acts as a crucial defense mechanism induced by harmful factors such as microorganisms or tissue damage, with the goal of restoring homeostasis within the body (Alessandri *et al.*, 2013; Feehan *et al.*, 2019; Soliman *et al.*, 2025). Acute inflammation represents a fast, self-resolving response of the body to potential threats, whereas unresolved inflammation leads to chronic inflammation, a pathological process associated with severe diseases including cardiovascular disease, type 2 diabetes, cancer, rheumatoid arthritis, asthma, and neurodegenerative disorders such as Alzheimer's disease (Nathan & Ding, 2010; Chung *et al.*, 2019; Mari van de Vyver, 2023; Rafiyan *et al.*, 2023). Biochemically, inflammation is regulated by the arachidonic acid (AA) cascade. AA is released from cell membrane phospholipids following activation of phospholipase A2 and is subsequently metabolized through two principal pathways: the cyclooxygenase (COX) pathway, which yields prostaglandins (PGs) and thromboxane's responsible for pain induction and vasodilation, and the 5-lipoxygenase (5-LOX) pathway, which yields leukotrienes (LTs) involved in leukocyte recruitment and bronchoconstriction (Rudrapal *et al.*, 2023).

Dual inhibitor design has been widely researched. Elgohary *et al.* (2023) used a fragment-merging strategy to obtain thiazole/thiazolidine-clubbed pyrazoline derivatives with IC₅₀ values of 0.03–0.06 µM against COX-2 and 4.36–4.86 µM against 5-LOX. Molecules have been synthesized which combine dual COX-2/5-LOX inhibition with antioxidant activity (Bošković *et al.*, 2023), and molecular hybridization has been used to generate pyrrole-cinnamic hybrid dual inhibitors (Noti *et al.*, 2023).

Medicinal plants remain a rich and long-standing source of anti-inflammatory bioactive molecules, including polyphenols, terpenoids, alkaloids, and flavonoids (Vyshnevska *et al.*, 2023). Among Indian spices studied for dual COX-2/5-LOX inhibitory activity, Rudrapal *et al.* (2022) examined and isolated curcumin (from turmeric), capsaicin (from chili pepper), and gingerol (from ginger). Quercetin, gallotannin, and inulin have been identified in Ukrainian traditional herbs as high-affinity dual binders. *Oroxylum indicum* extract has been screened using two-dimensional liquid chromatography (Cheng *et al.*, 2022) and synthesized flavonoids have been reported to selectively inhibit COX-2 alongside 5-LOX (Idris *et al.*, 2022).

Curcuma longa L. (Zingiberaceae), commonly known as turmeric, is among the most extensively studied of these

plants. Its rhizome contains curcuminoids, the polyphenolic compounds (curcumin, Demethoxycurcumin, and bisdemethoxycurcumin) responsible for characteristic yellow color of turmeric, and essential oils comprising sesquiterpenoids such as ar-turmerone, curlone, germacrone, and zingiberene (Agboola *et al.*, 2025; Gadnayak *et al.*, 2022). Curcumin, the most abundant and pharmacologically important curcuminoid, is a biphenolic β -diketone that exists in keto–enol tautomeric equilibrium; structurally, two methoxylated phenol groups are connected by a seven-carbon chain, enabling both hydrogen bonding and hydrophobic interactions with protein targets (Singh *et al.*, 2025). Curcumin has been shown experimentally to interact with multiple inflammation-related targets, including cyclooxygenases, lipoxygenases, pro-inflammatory cytokines (TNF- α , IL-6), and the transcription factor NF- κ B, and to possess the most efficient dual COX-2/5-LOX inhibitory activity among the Indian spice constituents. Combined in vivo and in silico approaches have confirmed that curcumin potentially inhibits both COX-2 and 5-LOX in a Wistar rat model of accelerated senescence (Singh *et al.*, 2025). However, symmetrical and unsymmetrical curcumin analogues display selective COX-2 (and, in some cases, COX-1) inhibitory activity (Mohan *et al.*, 2021). Nonetheless, clinical development of curcumin has been constrained by poor bioavailability, rapid metabolism, and low aqueous solubility, prompting interest in the wider curcuminoid family and computational screening as an efficient means of prioritizing candidates before costly experimental work (Agboola *et al.*, 2025).

In silico approaches, particularly molecular docking, have become indispensable tools in early-stage drug discovery, predicting the binding orientation and affinity of small molecules within a target protein's active site and ranking these poses using a scoring function (Vyshnevskaya *et al.*, 2022; Idris *et al.*, 2022; Okoh & Aiwonegbe, 2026). ADMET (absorption, distribution, metabolism, excretion, and toxicity) profiling complements molecular docking by rapidly identifying potential pharmacokinetic liabilities (Okoh & Aiwonegbe, 2026; Ekor & Odeja 2026). The integration of Prediction of Activity Spectra for Substances (PASS), molecular docking, and ADMET profiling has been used to evaluate the anti-inflammatory potential of phytochemicals targeting 5-LOX and COX-2, with some candidates showing potential CYP3A4 inhibition and cardiotoxicity concerns (Parvin *et al.*, 2025). Similarly, ADMET profiling has been applied to assess the pharmacokinetic and toxicity characteristics of curcuma-derived 5-LOX inhibitors (Gadnayak *et al.*, 2022). Molecular dynamics (MD) simulation is frequently used to validate docking predictions by assessing the stability and flexibility of ligand–protein complexes over time (Rudrapal *et al.*, 2023; Alabi *et al.*, 2026).

Several computational studies have been carried out to investigate the anti-inflammatory activity of *Curcuma longa* constituents. Target similarity analysis, molecular docking, molecular dynamics (MD) simulation, binding energy calculations, density functional theory (DFT), and quantitative structure–activity relationship (QSAR) analysis have been integrated to evaluate curcumin, capsaicin, and gingerol, with curcumin showing the most favorable overall activity profile (Rudrapal *et al.*, 2023). Similarly, molecular docking, ADMET profiling, and MD simulation have been employed to assess the 5-LOX inhibitory potential of terpenoids present in *Curcuma* essential oil (Gadnayak *et al.*, 2022). The combination of in vitro, in vivo, and in silico approaches has also provided evidence supporting curcumin

as a dual COX-2/5-LOX inhibitor (Singh *et al.*, 2025). In another approach, bioaffinity ultrafiltration coupled with mass spectrometry and a zebrafish model was used to identify COX-2 inhibitors from turmeric (Lan *et al.*, 2024). More recently, computational analysis has been employed to investigate COX-2-inhibitory compounds from *Curcuma longa* (Agboola *et al.*, 2025). Despite this body of work, important gaps remain. Most computational investigations of turmeric phytochemicals have concentrated overwhelmingly on COX-2 or 5-LOX as single targets, with very little literature addressing simultaneous dual-target docking. Curcumin has received disproportionately more attention than the other curcuminoids, Demethoxycurcumin and bisdemethoxycurcumin. Most in silico studies on curcuminoids have relied on docking alone, without complementary ADMET or interaction-profiling analysis, and there remains no systematic comparison of the binding affinity and selectivity of the three major curcuminoids for both COX-2 and 5-LOX side by side, nor a direct benchmarking of curcuminoids against a broad panel of reference NSAIDs and dual inhibitors.

Accordingly, this study aims to evaluate the dual COX-2/5-LOX binding potential and predicted pharmacokinetic and toxicity profiles of curcumin, demethoxycurcumin and bisdemethoxycurcumin using integrated in silico approaches and selected reference anti-inflammatory drugs.

MATERIALS AND METHODS

Computational analysis and molecular docking were done on a Dell Precision 5520 laptop equipped with an Intel® Core™ i7-6820HQ operating at 2.70 GHz with a 64-bit operating system, x64-based processor, and 16 GB of RAM, running Windows 11 Pro platform.

The phytochemicals from *Curcuma longa* (turmeric) were selected on the basis of their reported anti-inflammatory pharmacological activities (Saha, 2024). The SMILES notations of curcumin, Demethoxycurcumin, bisdemethoxycurcumin, and the reference drugs (celecoxib, ibuprofen, licofelone, and zileuton) were also obtained from the PubChem data base, and their chemical structures were generated in ChemDraw 22.2.0 (64-bit), and energetically minimized to their lowest-energy conformations.

The 3D structures of the investigated ligands were retrieved from PubChem data base (<https://pubchem.ncbi.nlm.nih.gov>), while crystal structures of the target proteins relevant to inflammatory condition: COX-2 (PDB ID: 5F19), and 5-LOX (PDB ID: 7TTK), were obtained from the RCSB Protein Data Bank (<https://www.rcsb.org/pdb/>). Protein preparation prior to docking was done by removal of water molecules, addition of hydrogen atoms, and assignment of protonation states using BIOVIA Discovery Studio.

Molecular docking studies were performed using Molegro Virtual Docker (MVD), employing the MolDock docking methodology described by Thomsen & Christensen (2006). Discovery Studio 2021 was used for visualization and analysis of protein–ligand interactions. To validate the reliability and accuracy of the docking protocol, the co-crystallized ligand in each target was re-docked into its respective active site and the root mean square deviation (RMSD) between the re-docked and native poses was calculated (RMSD < 2.0 Å), with visual validation performed in BIOVIA Discovery Studio. This confirmed the efficiency of the docking approach in reproducing the experimentally observed binding modes. The binding affinities of the curcuminoids and reference drugs toward COX-2 and 5-LOX were obtained from the molecular docking simulations and

expressed as MolDock scores (kcal/mol); a more negative MolDock score corresponds to a stronger predicted binding affinity and, therefore, a greater potential for inhibitory activity.

Drug-likeness and physicochemical properties of the curcuminoids were predicted using the SwissADME web server (<https://www.swissadme.ch>) following the methodology described by Daina *et al.* (2017), with additional interpretation based on more recent reports (Er-rajy *et al.*, 2025). The pharmacokinetics and toxicity-related properties of the curcuminoids were evaluated using pkCSM web server (<https://biosig.unimelb.edu.au/pkcsm>) according to the methodology reported by Pires *et al.* (2015) and Ibrahim *et al.* (2025).

RESULTS AND DISCUSSION

Molecular Docking of the Curcuminoids and Reference Drugs against COX-2 and 5-LOX

Table 1 summarizes the MolDock scores, hydrogen bonding, electrostatic interactions, and hydrophobic contacts of the three curcuminoids and four reference drugs docked against COX-2 (PDB ID: 5F19). Curcumin emerged as the most potent curcuminoid against COX-2, with a MolDock score of -133.272 kcal/mol, forming conventional hydrogen bonds with ARG-61, GLU-465, THR-62, and GLN-461. These interactions are important for anchoring and correctly orienting the ligand within the binding site. Electrostatic interactions with LYS-546 and ARG-44 further stabilized the curcumin–COX-2 complex, reflecting favorable complementarity with the electrostatic character of the binding pocket.

Table 1: MolDock Scores and Interaction Profiles of Curcuminoids and Reference Drugs against Cyclooxygenase-2 (COX-2, PDB ID: 5F19)

S/N	Compound	MolDock Score (kcal/mol)	Hydrogen Bonds	Electrostatic Interactions	Hydrophobic Interactions
1	Curcumin	-133.272	ARG-61, THR-62	LYS-546, GLU-465, GLN-461	ALA-543, ARG-44, ARG-469, LEU-152
2	Demethoxycurcumin	-115.939	ARG-61, CYS-36, HIS-39, GLN-461, LYS-137	LYS-546	ALA-543, ARG-44, CYS-47, PRO-153
3	Bisdemethoxycurcumin	-127.373	ARG-469, ASP-125, CYS-47, HIS-39, GLN-461	—	TYR-130, LEU-152, PRO-153
4	Celecoxib	-138.129	ASN-43, CYS-47, GLY-135	ARG-469, GLN-42	ARG-44, LEU-152, PRO-153, GLU-465, LYS-468, TYR-130
5	Ibuprofen	-83.7809	GLN-372, LYS-532	—	PRO-542, TYR-373
6	Licofelone	-115.672	SER-126	GLN-372	PRO-542, HIS-122, TYR-373
7	Zileuton	-85.7846	GLN-372, SER-126, ILE-124, LYS-532, SER-121	—	SER-121

Curcumin also displayed extensive hydrophobic contacts with ALA-543, ARG-469, and LEU-152. The aromatic rings and alkyl chain of curcumin favor van der Waals interaction with these residues, and the contacts with ARG-469 and LEU-152 are particularly notable because these residues form part of the secondary hydrophobic (“side”) pocket characteristic of COX-2 that is exploited by selective inhibitors such as celecoxib (Idris *et al.*, 2022). Curcumin’s engagement of this pocket suggests it may act as a selective COX-2 inhibitor, which is relevant to minimizing the

gastrointestinal side effects associated with non-selective NSAIDs. By comparison, demethoxycurcumin (MolDock score -115.939 kcal/mol) formed hydrogen bonds with ARG-61, CYS-36, HIS-39, GLN-461, and LYS-137, an electrostatic interaction with LYS-546, and hydrophobic contacts with ALA-543, ARG-44, CYS-47, and PRO-153; bisdemethoxycurcumin (-127.373 kcal/mol) formed hydrogen bonds with ARG-469, ASP-125, CYS-47, HIS-39, and GLN-461, and hydrophobic contacts with TYR-130, LEU-152, and PRO-153.

Table 2: MolDock Scores and Interaction Profiles of Curcuminoids and Reference Drugs against 5-Lipoxygenase (5-LOX, PDB ID: 7TTK)

S/N	Compound	MolDock Score (kcal/mol)	Hydrogen Bonds	Electrostatic Interactions	Hydrophobic Interactions
1	Curcumin	-143.172	GLN-437, GLU-287	ARG-520, LYS-441	ARG-518, ARG-438
2	Demethoxycurcumin	-117.955	GLN-434, GLN-437	ARG-438	LYS-441, LEU-288

S/N	Compound	MolDock Score (kcal/mol)	Hydrogen Bonds	Electrostatic Interactions	Hydrophobic Interactions
3	Bisdemethoxycurcumin	-122.126	ASP-290	ARG-438	LYS-441, ARG-438, LEU-288
4	Celecoxib	-137.600	ARG-518, GLY-150	ARG-438	LYS-441, GLN-434, GLN-437
5	Ibuprofen	-77.2232	GLY-150	—	ARG-438
6	Licofelone	-122.558	ASP-285	ARG-246	LEU-244, LEU-288
7	Zileuton	-88.4741	GLN-437, GLN-434	ARG-438	ILE-292

Table 2 presents the corresponding docking results against 5-LOX (PDB ID: 7TTK). Curcumin again showed a strong interaction pattern, recording the most favorable MolDock score (-143.172 kcal/mol) of the three curcuminoids and forming hydrogen bonds with GLN-437 and GLU-287. These interactions are considered crucial for occupying the 5-LOX active site and, potentially, disrupting leukotriene biosynthesis. Electrostatic interactions with ARG-520 and LYS-441 further stabilized the complex, consistent with engagement of polar, electron-rich residues, while hydrophobic contacts with ARG-518 and ARG-438 indicate a mixed polar/non-polar binding mode. Because 5-LOX contains a catalytically essential non-heme iron center (Gadnayak *et al.*, 2022), the network of interactions with residues such as ARG-520 and LYS-441 surrounding this center suggests that curcumin occupies the active site in a manner likely to interfere with catalysis. Demethoxycurcumin bound 5-LOX with a MolDock score of -117.955 kcal/mol, forming hydrogen bonds with GLN-434

and GLN-437, an electrostatic interaction with ARG-438, and hydrophobic contacts with LYS-441 and LEU-288. Bisdemethoxycurcumin recorded -122.126 kcal/mol, with a hydrogen bond to ASP-290, an electrostatic interaction with ARG-438, and hydrophobic contacts with LYS-441, ARG-438, and LEU-288.

Ligand–Protein Interaction Profiles

The two-dimensional (2D) and three-dimensional (3D) ligand–receptor interaction generated in BIOVIA Discovery Studio for curcumin, demethoxycurcumin, and bisdemethoxycurcumin against both COX-2 and 5-LOX are presented in Figures 1–6. These figures visually corroborate the interaction profiles summarized in Tables 1 and 2, showing the specific hydrogen-bonding, electrostatic (pi-cation), and hydrophobic (alkyl/pi-alkyl) contacts formed by each curcuminoid within the respective active sites.

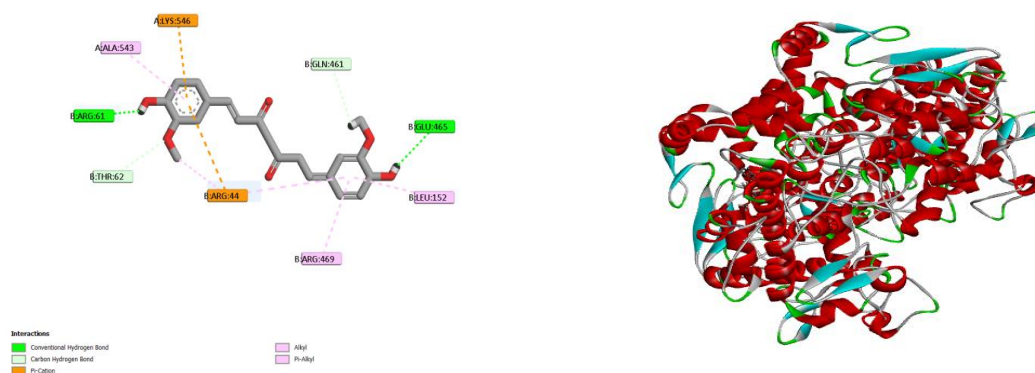


Figure 1: 2D (left) and 3D (right) interactions of curcumin within the active site of COX-2 (PDB ID: 5F19), showing conventional hydrogen bonds (ARG-61, GLU-465, THR-62, GLN-461), electrostatic (pi-cation) interactions (LYS-546, ARG-44), and hydrophobic (alkyl/pi-alkyl) contacts (ALA-543, ARG-469, LEU-152)

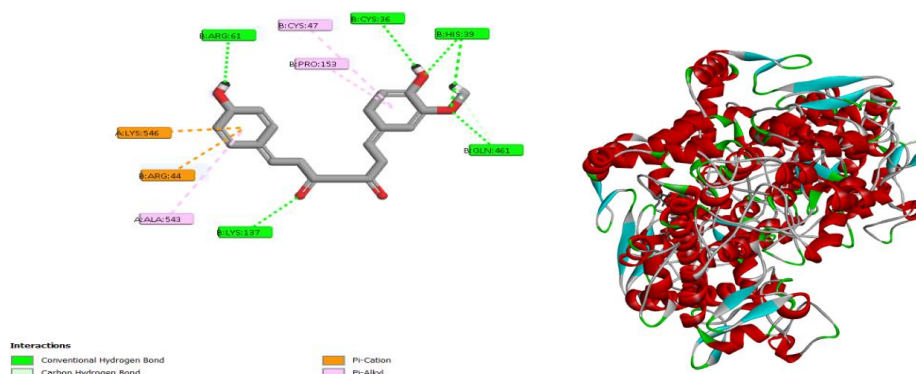


Figure 2: 2D (left) and 3D (right) interactions of demethoxycurcumin within the active site of COX-2 (PDB ID: 5F19)

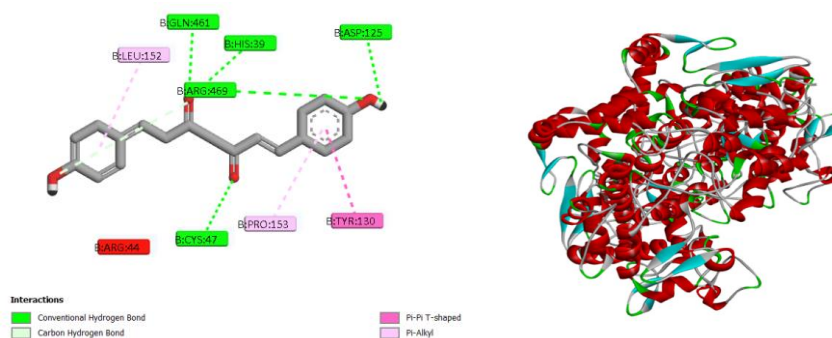


Figure 3: 2D (left) and 3D (right) interactions of bisdemethoxycurcumin within the active site of COX-2 (PDB ID: 5F19)

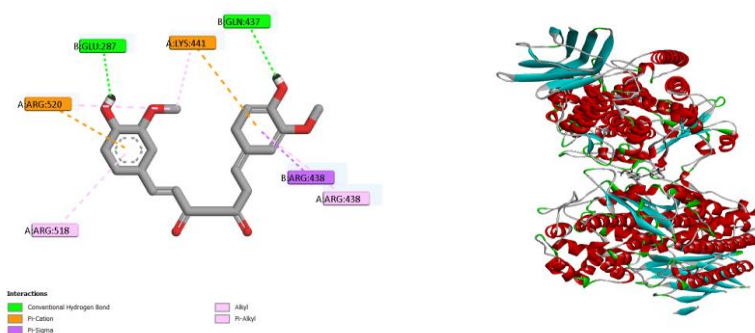


Figure 4: 2D (left) and 3D (right) interaction of curcumin within the active site of 5-LOX (PDB ID: 7TTK), showing conventional hydrogen bonds (GLN-437, GsLU-287), electrostatic (pi-cation) interactions (ARG-520, LYS-441), and hydrophobic (alkyl/pi-alkyl) contacts (ARG-518, ARG-438)

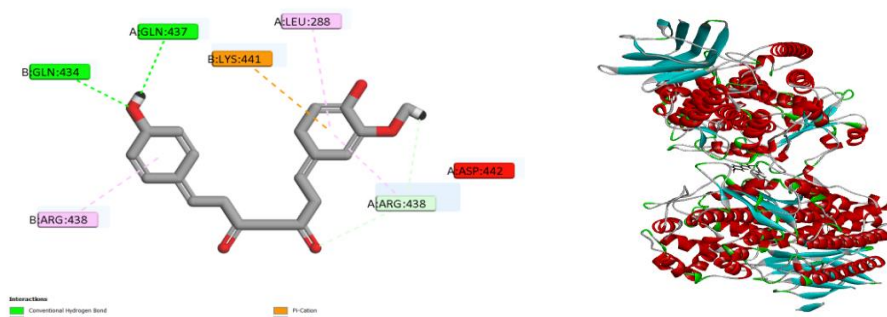


Figure 5: 2D (left) and 3D (right) interactions of demethoxycurcumin within the active site of 5-LOX (PDB ID: 7TTK)

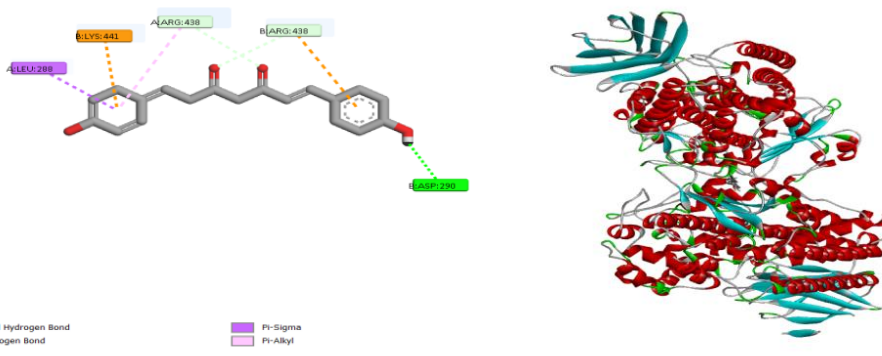


Figure 6: 2D (left) and 3D (right) interactions of bisdemethoxycurcumin within the active site of 5-LOX (PDB ID: 7TTK)

Drug-Likeness and ADMET Predictions

Absorption, Distribution, Metabolism, Excretion, and Toxicity (ADMET) profiling is a critical component of early drug discovery, providing insight into the pharmacokinetic and toxicological characteristics of candidate compounds

(Okoh & Aiwonegbe, 2026). Curcumin, demethoxycurcumin, and bisdemethoxycurcumin were evaluated for their drug-likeness and ADMET properties using SwissADME and pkCSM, and the results are presented in Table 3.

Table 3: Drug-likeness and ADMET properties of curcumin, demethoxycurcumin, and bisdemethoxycurcumin

Property	Curcumin	Demethoxycurcumin	Bisdemethoxycurcumin
Molecular weight (g/mol)	368.38	338.35	308.33
LogP	3.27	2.78	1.75
TPSA (Å ²)	93.06	83.83	74.60
Hydrogen bond donors	2	2	2
Hydrogen bond acceptors	6	5	4
Lipinski violations	0	0	0
GI absorption	High	High	High
Water solubility (log mol/L)	-4.01	-3.566	-3.38
Caco-2 permeability (log Papp × 10 ⁻⁶ cm/s)	-0.093	1.023	0.957
P-gp substrate	Yes	Yes	Yes
BBB permeation	No	No	Yes
CYP3A4 inhibition	Yes	Yes	Yes
CYP2D6 inhibition	No	No	No
Total clearance (log mL/min/kg)	-0.002	0.026	-0.008
Hepatotoxicity	No	No	No
AMES mutagenicity	No	No	No
hERG I inhibition	No	No	No

Physicochemical Properties and Lipinski's Rule of Five

Lipinski's Rule of Five is a widely used principle for predicting the oral bioavailability of drug candidates on the basis of four physicochemical properties: molecular weight (MW) ≤ 500 g/mol, LogP ≤ 5, hydrogen bond donors (HBD) ≤ 5, and hydrogen bond acceptors (HBA) ≤ 10 (Vyshnevskaya *et al.*, 2022). All three curcuminoids fully complied with these criteria, with zero violations. Curcumin (MW = 368.38 g/mol, LogP = 3.27, HBD = 2, HBA = 6) fits comfortably within all acceptable ranges, as do demethoxycurcumin (MW = 338.35 g/mol, LogP = 2.78, HBD = 2, HBA = 5) and bisdemethoxycurcumin (MW = 308.33 g/mol, LogP = 1.75, HBD = 2, HBA = 4). This complete compliance indicates favorable potential for oral absorption and membrane permeability, essential prerequisites for effective oral drugs. A clear trend toward increasing hydrophilicity is evident as molecular weight and LogP decrease from curcumin through demethoxycurcumin to bisdemethoxycurcumin.

Pharmacokinetic (ADME) Profiles

All three curcuminoids were predicted to have high gastrointestinal (GI) absorption, a desirable property for an oral anti-inflammatory agent, as it implies favorable systemic bioavailability and a higher likelihood of the compound reaching its therapeutic site of action (Nathaniel *et al.*, 2026). All three were also predicted to be P-glycoprotein (P-gp) substrates, a factor that can influence absorption and tissue distribution (Nguyen *et al.*, 2021; Mbadiko *et al.*, 2024; Coumau & Csajka, 2025).

Regarding blood–brain barrier (BBB) permeability, curcumin and demethoxycurcumin were predicted not to cross the BBB, a favorable characteristic for anti-inflammatory agents intended to act peripherally without unwanted central nervous system effects. Bisdemethoxycurcumin, by contrast, was predicted to permeate the BBB, which could be advantageous for neuro-inflammatory applications but would also warrant additional scrutiny of CNS-related side effects.

Caco-2 permeability values (log Papp in 10⁻⁶ cm/s) differed among the three compounds (-0.093, 1.023, and 0.957 for curcumin, demethoxycurcumin, and bisdemethoxycurcumin, respectively), indicating differing capacities to permeate the intestinal epithelium. Predicted aqueous solubility (log mol/L) was -4.01, -3.566, and -3.38, respectively, and predicted total clearance (log mL/min/kg) was -0.002, 0.026, and -0.008, suggesting slow-to-moderate clearance across the series.

All three curcuminoids were predicted to inhibit CYP3A4, one of the principal drug-metabolizing cytochrome P450 isoforms. CYP3A4 inhibition is clinically relevant because it can elevate the systemic exposure of co-administered CYP3A4-substrate drugs through reduced first-pass metabolism (Parvin *et al.*, 2023), and this finding indicates that the magnitude and clinical significance of such an interaction would need to be evaluated experimentally. Encouragingly, none of the three curcuminoids was predicted to inhibit CYP2D6.

Toxicity Profiles

The in silico toxicity assessment indicated a favorable safety profile for the curcuminoids relative to conventional NSAIDs. Curcumin, demethoxycurcumin, and bisdemethoxycurcumin were predicted to be non-mutagenic in the AMES test, implying a low probability of inducing DNA mutations, a key safety consideration for any candidate medicine. None of the curcuminoids was predicted to be hepatotoxic; drug-induced liver injury is a significant concern for several anti-inflammatory agents, including NSAIDs (Idris *et al.*, 2022), making this an important advantage. None of the curcuminoids was predicted to inhibit hERG, indicating a low likelihood of cardiac electrophysiological liability.

These favorable toxicity predictions are especially notable in light of the known limitations of established comparator drugs: ibuprofen, a non-selective NSAID, is associated with gastrointestinal toxicity, while celecoxib, a selective COX-2 inhibitor, carries an elevated cardiovascular risk (Rudrapal *et*

al., 2023). Licofelone, a dual COX/5-LOX inhibitor, was designed to mitigate some of these concerns but its overall safety profile remains under investigation, and zileuton, a selective 5-LOX inhibitor, carries its own distinct side-effect profile. On this basis, the curcuminoids may offer a comparatively safer therapeutic option.

Dual COX-2/5-LOX Inhibition Potential

The in silico evidence gathered in this study supports the potential of the three *Curcuma longa* curcuminoids as dual COX-2/5-LOX inhibitors of value in anti-inflammatory drug development. The combination of favorable docking scores with positive ADMET and toxicity profiles underscores the potential advantages of these natural products relative to several synthetic comparators.

Dual inhibition of the COX-2 and 5-LOX pathways is an attractive therapeutic strategy because it addresses the limitations of single-target agents: selective COX-2 inhibitors avoid gastrointestinal injury but can trigger the arachidonic acid shunt, channeling substrate toward the 5-LOX pathway and increasing inflammatory leukotriene production (Rudrapal *et al.*, 2023; Idris *et al.*, 2022), whereas simultaneous inhibition of both enzymes provides broader anti-inflammatory coverage while counteracting this shunting effect.

Curcumin was the strongest dual inhibitor among the compounds evaluated. Its MolDock score against COX-2 (−133.272 kcal/mol) was comparable to that of celecoxib (−138.129 kcal/mol), a well-established selective COX-2 inhibitor, while its binding energy against 5-LOX (−143.172 kcal/mol) markedly exceeded that of zileuton (−88.474 kcal/mol), the selective 5-LOX inhibitor used clinically. This balanced, potent activity against both targets indicates that curcumin can effectively interfere with the production of both prostaglandins and leukotrienes. Licofelone, a clinically studied dual inhibitor, recorded MolDock scores of −115.672 kcal/mol (COX-2) and −122.558 kcal/mol (5-LOX) — both less favorable than curcumin's scores against the same targets. Bisdemethoxycurcumin was also a promising dual binder, with MolDock scores of −127.373 kcal/mol (COX-2) and −122.126 kcal/mol (5-LOX). These results are consistent with the broader literature describing curcuminoids as polypharmacological agents capable of modulating multiple targets simultaneously (Nathan & Ding, 2010; Parvin *et al.*, 2023).

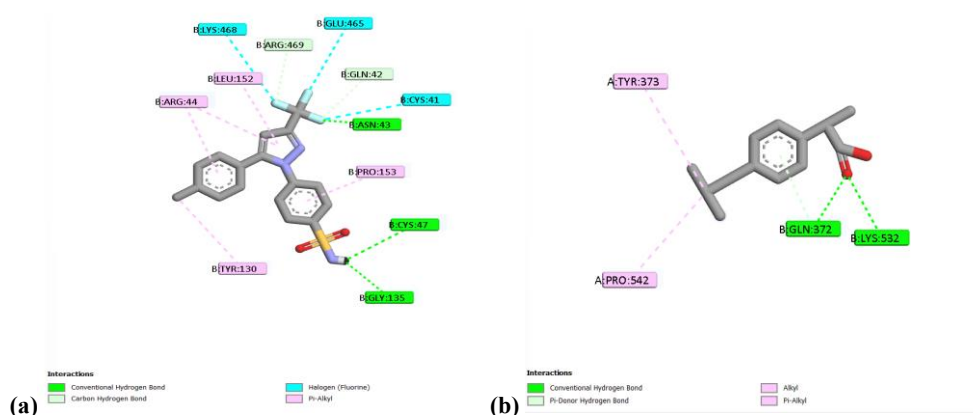
Structure–Activity Relationships among Curcuminoids

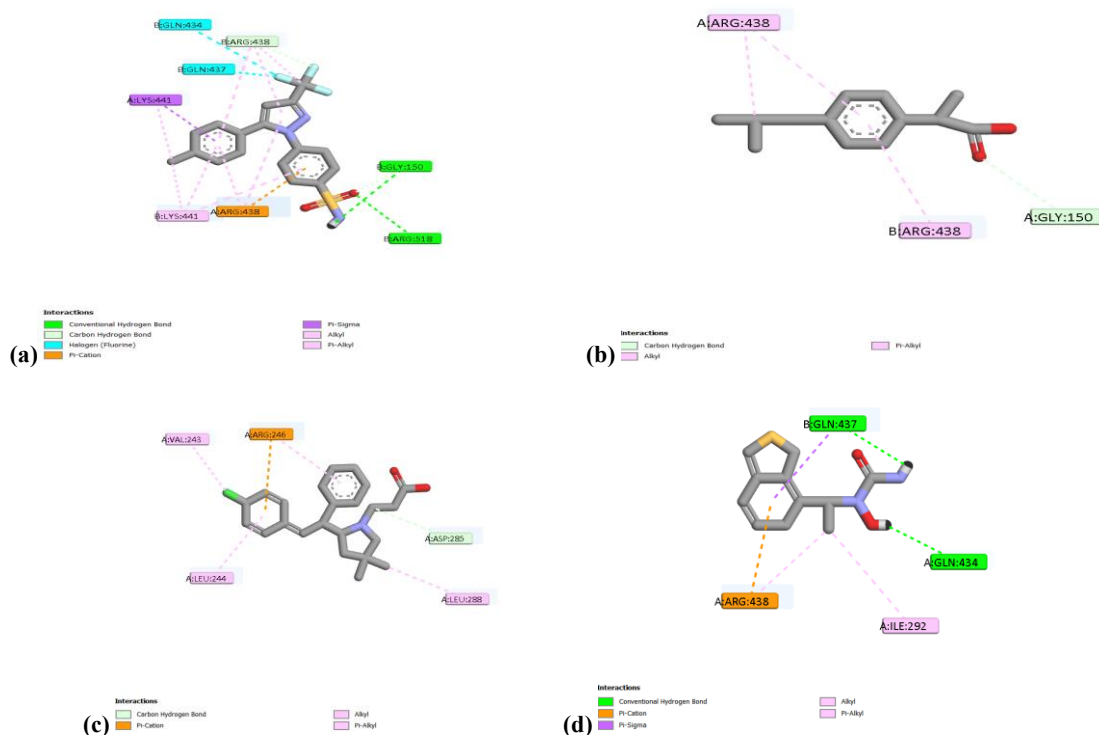
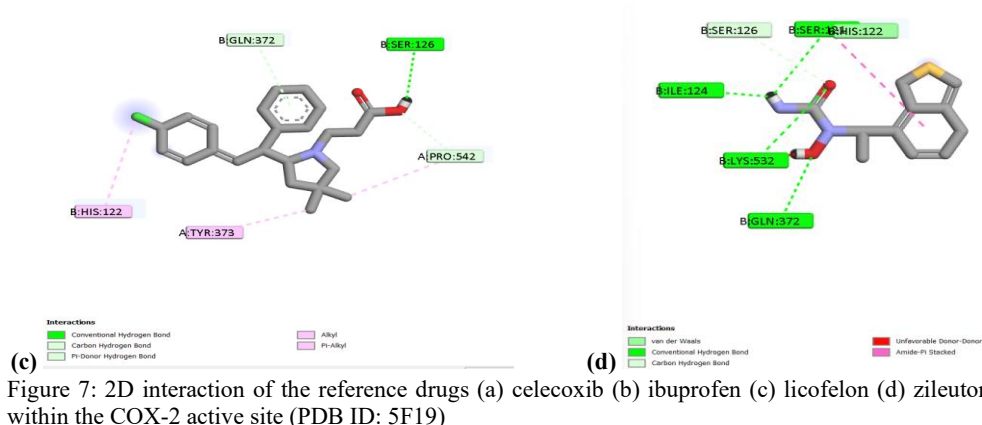
Differences in binding affinity among curcumin, demethoxycurcumin, and bisdemethoxycurcumin illustrate a clear structure–activity relationship (SAR) centered on the number of methoxy substituents on the phenolic rings: curcumin bears two methoxy groups, demethoxycurcumin one, and bisdemethoxycurcumin none.

The presence of two methoxy groups conferred on curcumin the highest binding affinity toward both COX-2 and 5-LOX, likely because these groups increase lipophilicity, favoring hydrophobic interactions within the enzyme active sites, and also modulate the electronic character of the molecule in ways conducive to optimal hydrogen bonding. The phenolic hydroxyl and β -diketone functional groups common to all three curcuminoids appear responsible for the hydrogen-bonding and electrostatic interactions observed with polar active-site residues in both COX-2 and 5-LOX (Mbadiko *et al.*, 2024). A modest decrease in COX-2 binding energy was observed on moving from curcumin (−133.272 kcal/mol) to bisdemethoxycurcumin (−127.373 kcal/mol); for 5-LOX, bisdemethoxycurcumin (−122.126 kcal/mol) also bound strongly, though not as strongly as curcumin (−143.172 kcal/mol). This pattern suggests that while the methoxy substituents in curcumin enhance binding, the shared diketone and phenolic hydroxyl groups are the principal determinants of dual-enzyme inhibitory potential across the curcuminoid series. The reduced lipophilicity of bisdemethoxycurcumin relative to curcumin (LogP 1.75 versus 3.27) may also help explain their differing binding energies.

Comparison with Standard Drugs

Benchmarking the curcuminoids against celecoxib, ibuprofen, licofelone, and zileuton helps to contextualize their therapeutic potential. The 2D interaction of these standard drugs with COX-2 and 5-LOX are shown in Fig. 7 and Fig. 8. The COX-2 binding affinity of curcumin (−133.272 kcal/mol) was very close to that of celecoxib (−138.129 kcal/mol), indicating broadly comparable predicted COX-2 inhibitory efficiency. More strikingly, curcumin's binding affinity toward 5-LOX (−143.172 kcal/mol) considerably exceeded that of zileuton (−88.474 kcal/mol). This superior dual-target profile makes curcumin an attractive candidate that can be further validated for overcoming the drawbacks associated with single-target agents.





Ibuprofen, a non-selective NSAID, showed markedly lower binding affinity toward both COX-2 (-83.7809 kcal/mol) and 5-LOX (-77.2232 kcal/mol) than the curcuminoids, indicating comparatively weaker predicted interaction with these targets. Licofelone, a dual COX/5-LOX inhibitor, recorded binding affinities of -115.672 and -122.558 kcal/mol against COX-2 and 5-LOX, respectively; curcumin outperformed licofelone against both enzymes, suggesting potentially higher inhibitory potency.

The ADMET properties of the curcuminoids further differentiate them from these reference drugs. Celecoxib, despite its high gastrointestinal absorption, may violate Lipinski's rules through excessive lipophilicity and carries cardiovascular risk (Rudrapal *et al.*, 2023), ibuprofen is well known for gastrointestinal toxicity (Idris *et al.*, 2022), licofelone, while addressing some of these issues, has its own drawbacks; and zileuton, a selective 5-LOX inhibitor, carries specific side effects of its own. All three curcuminoids satisfied Lipinski's Rule of Five, were predicted to exhibit favorable gastrointestinal absorption with no predicted mutagenic or hepatotoxic effects, suggesting potentially

favorable pharmacokinetic and safety profile that warrants further experimental validation.

CONCLUSION

Molecular docking simulations revealed that the curcuminoids investigated in this study showed strong predictive binding affinities for both COX-2 and 5-LOX. Curcumin produced the most favorable docking scores (-133.272 kcal/mol for COX-2 and -143.172 kcal/mol for 5-LOX), compared to those of several synthetic reference drugs, including the dual inhibitor licofelone and the selective 5-LOX inhibitor zileuton, under the docking conditions employed. Analysis of the molecular interactions underscored the importance of hydrogen bonding, electrostatic, and hydrophobic contacts with key active-site residues — ARG-61, GLU-465, ARG-469, and LEU-152 for COX-2, and GLN-437, GLU-287, ARG-520, LYS-441, ARG-518, and ARG-438 for 5-LOX. Drug-likeness and ADMET predictions showed that all three curcuminoids evaluated fully complied with Lipinski's Rule of Five, implying good oral bioavailability, and were predicted to

have high gastrointestinal absorption alongside a favorable toxicity profile (non-mutagenic, non-hepatotoxic). This warrants further validation towards addressing some of the side-effect concerns associated with conventional NSAIDs. CYP3A4 inhibition was, however, predicted for all three compounds and warrants further experimental investigation. The structure–activity analysis highlighted the significance of the phenolic hydroxyl and β -diketone functional groups for dual-enzyme inhibition. Overall, curcumin emerges as the most promising lead compound for further study, given its predicted superior dual-targeting profile, favorable pharmacokinetics, and safety characteristics relative to the other curcuminoids and the reference drugs evaluated. Therefore, molecular dynamics simulations, enzyme inhibition assays, cell-based studies and in vivo investigations are recommended to validate these computational findings and further assess the therapeutic potential of the compound.

Data Availability

The datasets (ligand structures, protein structures, and docking parameters) used in this study were obtained from the publicly accessible PubChem database (<https://pubchem.ncbi.nlm.nih.gov>) and the RCSB Protein Data Bank (<https://www.rcsb.org>). Further data are available from the corresponding author upon reasonable request.

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