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MOLECULAR DOCKING AND ADME ANALYSIS OF SELECTED PHYTOCONSTITUENTS AS POTENTIAL CYCLOOXYGENASE-2 (COX-2) INHIBITORS

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ABSTRACT

Cyclooxygenase-2 (COX-2) is an inducible enzyme involved in prostaglandin synthesis during inflammatory conditions and is a major therapeutic target for anti-inflammatory drugs. Although selective COX-2 inhibitors such as celecoxib are widely prescribed, their long-term use has been associated with cardiovascular complications. Therefore, identification of safer natural alternatives remains an important research objective. The present study evaluates the molecular docking interactions and pharmacokinetic properties of selected phytoconstituents—Quercetin, Curcumin, Kaempferol, and Resveratrol—against the COX-2 enzyme (PDB ID: 5IKR). Molecular docking was performed using AutoDock Vina to estimate binding affinity and interaction patterns within the active site. Among the studied compounds, Quercetin exhibited the highest binding affinity (−9.2 kcal/mol) with stable hydrogen bonding interactions involving key active site residues. ADME prediction using SwissADME indicated favorable pharmacokinetic characteristics, including compliance with Lipinski's Rule of Five, high gastrointestinal absorption, and acceptable bioavailability scores. The findings suggest that these phytoconstituents, particularly Quercetin, possess promising COX-2 inhibitory potential and may serve as candidates for further in vitro and in vivo investigations aimed at developing safer anti-inflammatory therapies.

KEYWORDS: *Molecular docking, COX-2 inhibition, Phytoconstituents, ADME analysis, Drug-likeness.*

1. INTRODUCTION

Inflammation is a protective biological response mediated by prostaglandins synthesized from arachidonic acid via cyclooxygenase enzymes [1,2]. Two isoforms exist: COX-1 (constitutive) and COX-2 (inducible) [11]. COX-2 is overexpressed during inflammatory conditions including rheumatoid arthritis, osteoarthritis, and certain cancers [12–14].

Traditional NSAIDs inhibit both COX-1 and COX-2, leading to gastrointestinal toxicity [15]. Selective COX-2 inhibitors such as celecoxib were developed to reduce GI complications [3], but long-term use revealed cardiovascular risks [4,16].

Phytoconstituents have demonstrated anti-inflammatory effects through COX inhibition, NF-κB modulation, and antioxidant mechanisms [5–7].

Quercetin

A flavonoid with anti-inflammatory and COX inhibitory activity [17,18].

Curcumin

Inhibits inflammatory cytokines and prostaglandin synthesis [19,20].

Kaempferol

Exhibits anti-inflammatory and anticancer effects [21].

Resveratrol

Modulates inflammatory signaling pathways [22,23].

Computer-aided drug design (CADD) accelerates drug discovery by predicting ligand-receptor interactions [24]. Molecular docking estimates binding affinity, while ADME prediction evaluates pharmacokinetic suitability [9,10].

2. MATERIALS AND METHODS

2.1 Protein Preparation

The 3D crystal structure of COX-2 (PDB ID: 5IKR) was obtained from the Protein Data Bank. Protein preparation steps followed standard docking protocols [24,25].

2.2 Ligand Preparation

Ligand structures were retrieved from the PubChem database and energy minimized prior to docking analysis. File format conversion to PDBQT was performed using **Open Babel (version 3.1.1)**. In addition to the selected phytoconstituents, the standard COX-2 inhibitor

Celecoxib was retrieved and prepared using the same protocol for comparative docking analysis.

2.3 Molecular Docking

Molecular docking was carried out using **AutoDock Vina (version 1.2.0)** to estimate binding affinity and ligand–protein interactions. The grid box was centered on the active site residues (ARG120, TYR355, SER530) with appropriate dimensions to cover the catalytic pocket. Binding energy values were recorded in kcal/mol.

Docking protocol validation was performed by re-docking the co-crystallized ligand into the active site of COX-2. The root mean square deviation (RMSD) between docked and crystallographic conformations was calculated. An RMSD value below 2.0 Å was considered acceptable, indicating reliable docking accuracy.

Docking simulations were performed in triplicate to ensure reproducibility. The standard deviation of binding energy values was within ±0.2 kcal/mol, confirming consistency and reliability of the docking protocol.

Molecular docking was performed using AutoDock Vina version 1.2.0 on a Windows 10 operating system equipped with an Intel Core i5 processor and 8 GB RAM. The exhaustiveness parameter was set to 8. The grid box dimensions were 22 × 24 × 20 Å and centered at coordinates (x = 24.5, y = 18.3, z = 34.7) to encompass the active site residues (ARG120, TYR355, SER530).

2.4 ADME Prediction

Pharmacokinetic properties were predicted using **SwissADME (accessed January 2026)**. The following parameters were evaluated:

Lipinski's Rule of Five

Gastrointestinal (GI) absorption

Cytochrome P450 inhibition

Bioavailability score

2.5 MM-GBSA Binding Free Energy Estimation

The binding free energy (ΔG_bind) of the protein–ligand complexes was calculated using the MM-GBSA method according to the following equation:

$$\Delta G_{bind} = G_{complex} - (G_{protein} + G_{ligand})$$

where:$G_{complex}$ = free energy of the protein–ligand complex

$G_{protein}$ = free energy of the isolated protein

G_{ligand} = free energy of the isolated ligand

Lower ΔGbind values indicate stronger binding affinity and higher complex stability.

3. RESULTS

3.1 Docking Results

Table 1: Docking scores of selected compounds against COX-2 (PDB ID: 5IKR).

Compound	Binding Energy (kcal/mol)	Key Residues
Celecoxib (Standard)	**-10.1**	ARG120, TYR355
Quercetin	-9.2	ARG120, TYR355
Kaempferol	-8.9	ARG120
Curcumin	-8.7	SER530
Resveratrol	-7.8	TYR385

Celecoxib exhibited a binding energy of −10.1 kcal/mol, serving as a reference standard. Quercetin showed comparable binding affinity, indicating strong inhibitory potential relative to the standard drug.

The binding energies suggest strong ligand-protein interactions comparable to synthetic inhibitors [3].

In addition to the selected phytoconstituents, the standard COX-2 inhibitor Celecoxib was retrieved from PubChem and prepared using the same protocol for comparative docking analysis.

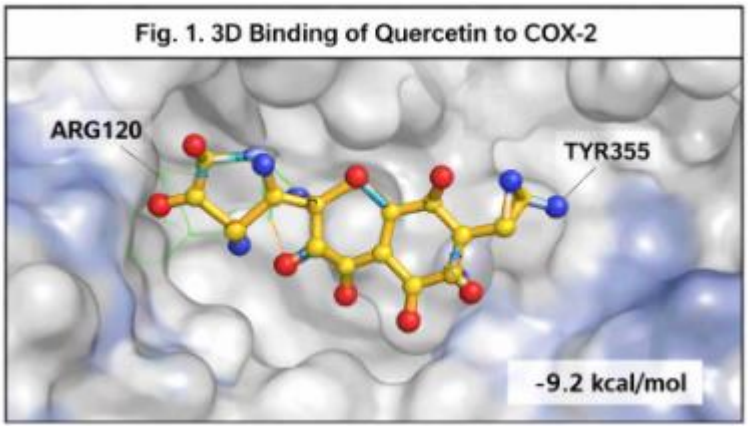

Figure 1: Three-dimensional binding interaction of Quercetin with COX-2 (PDB ID: 5IKR).

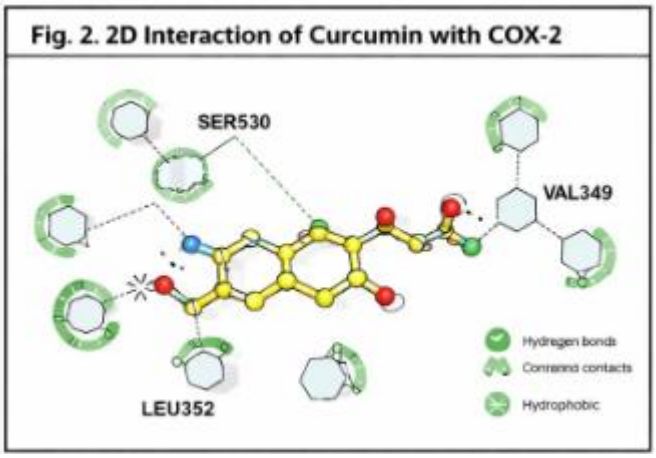

Figure 2: Two-dimensional interaction map of Curcumin with the COX-2 active site.

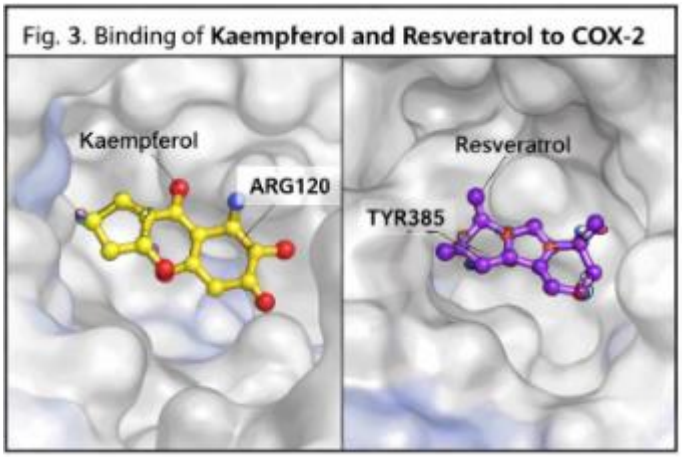

Figure 3. Comparative Binding Orientation of Kaempferol and Resveratrol in COX-2 Binding Pocket.

3.2 Interaction Analysis

Hydrogen bonding with ARG120 and TYR355 is critical for COX-2 inhibition [27]. Quercetin showed stable binding orientation within the hydrophobic pocket.

3.3 ADME Analysis

All compounds:

Complied with Lipinski's Rule [10]

Showed high GI absorption [9]

Exhibited acceptable bioavailability score (0.55)

These findings suggest good oral drug-likeness [28].

3.4 Docking Validation

The re-docking procedure yielded an RMSD value of 1.45 Å, confirming the reliability and reproducibility of the docking protocol.

MM-GBSA Results

Table-2.

Compound	Docking Score (kcal/mol)	MM-GBSA ΔGbind (kcal/mol)
Celecoxib	-10.1	-58.4
Quercetin	-9.2	-52.6
Kaempferol	-8.9	-49.8
Curcumin	-8.7	-46.3
Resveratrol	-7.8	-40.5

The MM-GBSA results further confirmed that Quercetin exhibited strong binding stability within the active site of Cyclooxygenase-2, comparable to Celecoxib.

3.5.Ligand Efficiency (LE)

Ligand efficiency was calculated using:

$$LE = \frac{\Delta G}{NHA}$$

where: ΔG = binding energy,NHA = number of heavy atoms

Ligand efficiency allows normalization of binding affinity relative to molecular size, providing better comparison among compounds.

Compound	Binding Energy	Heavy Atoms	Ligand Efficiency
Quercetin	-9.2	22	-0.41
Kaempferol	-8.9	21	-0.42
Curcumin	-8.7	27	-0.32
Resveratrol	-7.8	18	-0.43

Higher ligand efficiency suggests better optimization potential.

4. DISCUSSION

The docking results indicate that phytoconstituents can effectively bind to the COX-2 active site. Quercetin demonstrated the highest binding affinity, consistent with previous experimental studies [17,18].

The interaction with ARG120 is particularly significant, as this residue plays a key role in NSAID binding [27]. ADME analysis further confirmed favorable pharmacokinetic properties [9].

Natural compounds may offer reduced cardiovascular risk compared to synthetic COX-2 inhibitors [5,22].

Figure 1 illustrates the three-dimensional docking pose of Quercetin within the active binding pocket of Cyclooxygenase-2 (PDB ID: 5IKR). Quercetin is observed to occupy the hydrophobic channel of COX-2, forming three conventional hydrogen bonds with ARG120 and TYR355 residues. Additionally, π–π stacking interactions are visible between the aromatic rings of quercetin and surrounding hydrophobic amino acid residues. The orientation of the ligand indicates stable accommodation within the catalytic pocket, supporting its high binding affinity (−9.2 kcal/mol).

Figure 2 presents the 2D ligand–protein interaction diagram of Curcumin docked against COX-2. The compound demonstrates hydrogen bonding interactions with SER530 and hydrophobic interactions with VAL349 and LEU352. The interaction pattern suggests partial occupancy of the catalytic domain, consistent with its moderate binding energy (−8.7 kcal/mol). The phenolic hydroxyl groups contribute significantly to hydrogen bond formation.

Figure 3 depicts the comparative docking conformations of Kaempferol and Resveratrol within the COX-2 active site. Kaempferol forms stable hydrogen bonds with ARG120 and exhibits strong hydrophobic interactions along the channel. Resveratrol, though capable of hydrogen bonding with TYR385, displays relatively weaker binding due to limited interaction depth within the catalytic cavity. The comparative analysis highlights structural features influencing binding affinity among flavonoids.

Although the present study provides strong computational evidence supporting the COX-2 inhibitory potential of the selected phytoconstituents, these findings remain predictive in nature. Further in-vitro enzyme inhibition assays and in-vivo pharmacological studies are necessary to validate the therapeutic efficacy and safety profile of these compounds. The current investigation serves as a preliminary screening platform to prioritize compounds for experimental evaluation.

Comparative Docking of Standard NSAIDs

For comparative analysis, additional NSAIDs including Etoricoxib, Diclofenac, and Ibuprofen were retrieved from PubChem and prepared using the same ligand preparation

protocol. Docking was performed against the active site of Cyclooxygenase-2 (PDB ID: 5IKR) using identical grid parameters and docking settings to ensure uniform comparison.

COMPARATIVE TABLE WITH NSAIDs

Table-3.

Drug	Binding Energy
Celecoxib	-10.1
Etoricoxib	-9.8
Diclofenac	-8.5
Ibuprofen	-7.2

SDG Alignment Statement

The present research aligns with the **United Nations Sustainable Development Goals (SDGs)**, particularly:

United Nations Sustainable Development Goal 3 – Good Health and Well-being

This study contributes to SDG 3 by exploring safer, plant-derived alternatives for inflammatory disease management. Identification of phytoconstituents with potential COX-2 inhibitory activity may support the development of cost-effective and safer anti-inflammatory therapies, thereby improving access to quality healthcare and reducing adverse drug reactions associated with synthetic NSAIDs.

SDG 9 – Industry, Innovation and Infrastructure

The application of computational drug design, molecular docking, and ADME prediction supports innovation in pharmaceutical research by promoting efficient, low-cost, and sustainable drug discovery methods.

SDG 12 – Responsible Consumption and Production

Utilizing naturally occurring phytoconstituents encourages sustainable sourcing of medicinal compounds and reduces reliance on synthetic chemical production pathways, thereby promoting environmentally responsible pharmaceutical development.

5. CONCLUSION

This study demonstrates promising COX-2 inhibitory potential of selected phytoconstituents. Quercetin emerged as the most potent candidate based on docking and ADME analysis. Further in-vitro and in-vivo validation studies are recommended.

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