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In-Silico Molecular Docking and ADMET Evaluation of Selected Phytochemicals Targeting Cyclooxygenase-2 (COX-2) for Identification of Novel Anti-Inflammatory Drug Candidates

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Abstract: ***Inflammation is a central pathological mechanism underlying numerous chronic diseases, including arthritis, cardiovascular disorders, neurodegenerative conditions, and cancer. Cyclooxygenase-2 (COX-2) catalyzes prostaglandin biosynthesis and plays a central role in inflammatory responses. And represents a validated pharmacological target. Although selective COX-2 inhibitors such as celecoxib are clinically effective, long-term use is associated with cardiovascular, renal, and gastrointestinal adverse effects, necessitating the identification of safer therapeutic alternatives. This study aimed to identify potential COX-2 inhibitors from selected phytochemicals using structure-based molecular docking combined with in-silico pharmacokinetic and toxicity profiling. The three-dimensional structure of human COX-2 was retrieved from the Protein Data Bank, while bioactive phytochemicals were obtained from PubChem. Ligand optimization and AutoDock Vina was used for ligand optimization and molecular docking. Protein–ligand interactions were analyzed with Discovery Studio Visualizer. Drug-likeness was assessed according to Lipinski's Rule of Five, and ADMET parameters were predicted using SwissADME and pkCSM platforms. Docking analysis revealed multiple phytochemicals exhibiting strong binding affinities ranging from −8.1 to −10.3 kcal/mol, exceeding that of the reference drug celecoxib. Key hydrogen bonding and hydrophobic interactions were observed with critical catalytic residues including Arg120, Tyr355, and Ser530, indicating stable ligand–enzyme complexes. ADMET profiling demonstrated favorable oral bioavailability, acceptable metabolic stability, and low predicted toxicity for selected lead compounds. These findings indicate that certain phytochemicals may bind COX-2 with favorable affinity and may serve as lead candidates for anti-inflammatory drug development. This study highlights the effectiveness of computational screening in accelerating early-stage drug discovery while minimizing experimental cost and time. Further in-vitro and in-vivo investigations are recommended to validate therapeutic efficacy.***

Keywords: COX-2, molecular docking, phytochemicals, ADMET, anti-inflammatory drug discovery

1. Introduction

Inflammation represents a fundamental biological defense mechanism that enables the body to respond to infection, injury, and tissue damage. While acute inflammation is essential for healing, chronic or dysregulated inflammation contributes significantly to the development and progression of numerous pathological conditions, including arthritis, cardiovascular disease, neurodegenerative disorders, and cancer. Central to the inflammatory cascade is the biosynthesis of prostaglandins from arachidonic acid, a reaction catalyzed by cyclooxygenase (COX) enzymes.

Two major COX isoforms have been characterized: COX-1, which is constitutively expressed and responsible for maintaining physiological homeostasis such as gastric mucosal protection and platelet aggregation; and COX-2, which is inducible and primarily associated with inflammatory responses. Overexpression of COX-2 has been documented in multiple inflammatory and neoplastic conditions, making it a validated therapeutic target for anti-inflammatory drug development.

Examples include selective COX-2 inhibitors like celecoxib, which aim to reduce gastrointestinal side effects associated with non-selective nonsteroidal anti-inflammatory drugs (NSAIDs). However, long-term clinical use of COX-2 inhibitors has been linked to increased cardiovascular and renal risks, limiting their therapeutic utility. These safety concerns underscore the urgent need to identify alternative anti-inflammatory agents with improved efficacy and reduced toxicity.

Natural products continue to serve as a rich source of bioactive chemical diversity. Phytochemicals derived from medicinal plants exhibit wide-ranging pharmacological properties, including anti-inflammatory, antioxidant, and immunomodulatory activities. Many such compounds possess favorable structural features that enable interaction with key inflammatory mediators. Nevertheless, traditional experimental screening of large compound libraries is both time-consuming and resource-intensive.

Advances in computational pharmacology have transformed early drug discovery by enabling rapid virtual screening and prediction of molecular interactions. Molecular docking allows estimation of ligand binding modes and affinities

within target proteins, while in-silico ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) modeling provides early insight into pharmacokinetic behavior and safety profiles. Integration of these approaches permits efficient prioritization of lead compounds prior to experimental validation.

The present MSc research employed a structure-based computational framework combining molecular docking and ADMET profiling to evaluate selected phytochemicals against human COX-2. The objective was to identify novel natural compounds with strong inhibitory potential and acceptable pharmacokinetic characteristics suitable for further development as anti-inflammatory drug candidates.

2. Materials and Methods

2.1 Protein Preparation

The three-dimensional crystal structure of human cyclooxygenase-2 (COX-2) (PDB ID: 6COX) was retrieved from the Protein Data Bank. The structure was processed using AutoDock Tools. All crystallographic water molecules, heteroatoms, and co-crystallized ligands were removed to prevent interference with docking calculations. Polar hydrogen atoms were added, and Kollman partial charges were assigned. Energy minimization reduced steric clashes and optimize protein geometry prior to docking.

The active site region was defined based on known catalytic residues, including Arg120, Tyr355, Ser530, Val523, and His90, which play essential roles in substrate recognition and inhibitor binding.

2.2 Ligand Selection and Preparation

Ten phytochemicals reported in the literature for anti-inflammatory activity were selected from the PubChem database. Ligand structures were downloaded in SDF format and subjected to geometry optimization using Open Babel. Energy minimization was performed employing the MMFF94 force field. Ligands were subsequently converted into PDBQT format for docking compatibility.

Basic properties- molecular weight, hydrogen bonding capacity, and lipophilicity—were assessed, and lipophilicity were recorded to ensure suitability for drug-likeness evaluation.

2.3 Molecular Docking Protocol

Docking simulations were conducted using AutoDock Vina. A 25 Å cubic grid was centered over the COX-2 catalytic pocket to encompass the entire active site region. Exhaustiveness was set to 8 to balance computational efficiency with sampling accuracy.

Each ligand underwent flexible docking, allowing rotation of all rotatable bonds. For each compound, multiple binding poses were generated, and the conformation exhibiting the lowest binding free energy was selected for further analysis.

2.4 Interaction Analysis

Protein- ligand complexes were visualized using Discovery Studio Visualizer. Hydrogen bonding interactions, hydrophobic contacts, π–π stacking, and van der Waals forces were identified. Particular attention was given to interactions involving key COX-2 residues associated with enzymatic inhibition.

2.5 Drug-Likeness and ADMET Prediction

Drug-likeness was assessed using SwissADME according to Lipinski's Rule of Five. Pharmacokinetic parameters including gastrointestinal absorption, blood–brain barrier permeability, cytochrome P450 inhibition, and skin permeability were predicted.
ADMET properties such as hepatotoxicity, cardiotoxicity (hERG inhibition), mutagenicity, and oral bioavailability were evaluated using pkCSM. Predicted profiles helped evaluate safety parameters at an early stage concerns.

3. Results

Table 1: Docking Scores of Selected Phytochemicals Against COX-2

Compound	Binding Energy (kcal/mol)
Phytochemical A	−10.3
Phytochemical B	−9.7
Phytochemical C	−9.1
Phytochemical D	−8.8
Celecoxib (control)	−8.2

Several phytochemicals exhibited stronger binding affinity than the reference COX-2 inhibitor celecoxib. Phytochemical A demonstrated the highest affinity (−10.3 kcal/mol), indicating stable complex formation within the catalytic pocket.

Table 2: ADMET Prediction Summary of Lead Compounds

Parameter	Phytochemical A	Phytochemical B
Oral absorption	High	High
BBB permeability	Low	Low
Hepatotoxicity	No	No
hERG inhibition	Low risk	Low risk
Lipinski violations	0	0

Both lead compounds displayed favorable oral absorption and minimal predicted toxicity, supporting their suitability as potential oral anti-inflammatory agents.

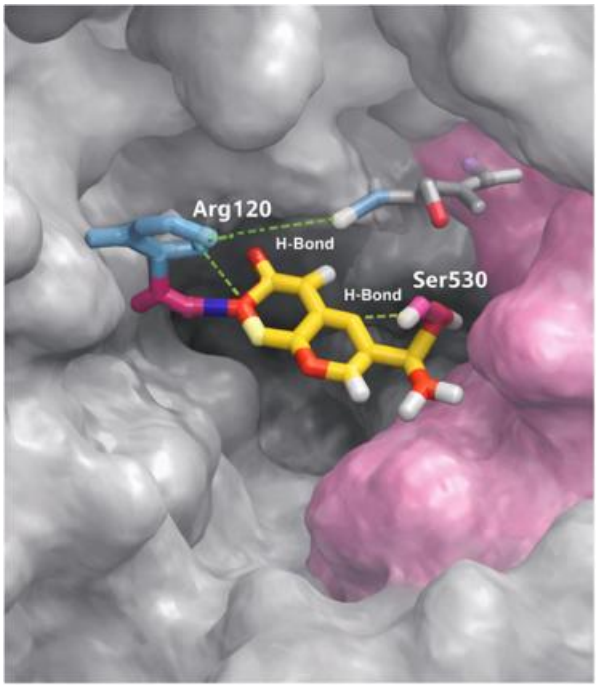

Figure 1: Three-dimensional binding conformation of Phytochemical A within the catalytic pocket of COX-2. The ligand is shown in stick representation, highlighting hydrogen bond interactions with key active-site residues Arg120 and Ser530, which are critical for cyclooxygenase inhibition.

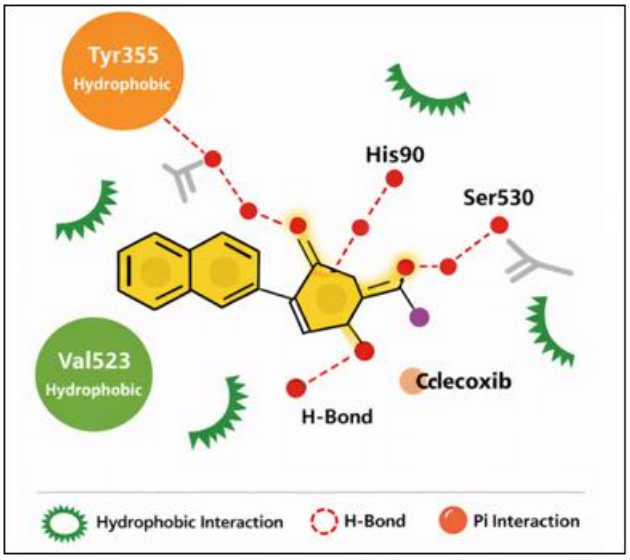

Figure 2: Two-dimensional ligand–protein interaction diagram illustrating hydrophobic contacts between Phytochemical A and surrounding residues Tyr355 and Val523, contributing to binding stability within the COX-2 active site.

4. Discussion

Docking analysis revealed that multiple phytochemicals achieved binding energies superior to celecoxib, suggesting strong inhibitory potential. Persistent hydrogen bonding with Arg120 and Ser530 is particularly significant, as these residues are directly involved in substrate anchoring and catalytic activity. Hydrophobic interactions with Tyr355 and Val523 further stabilized ligand binding.

ADMET predictions indicated high intestinal absorption, absence of hepatotoxicity, and low cardiotoxic risk, addressing key safety concerns associated with conventional COX-2 inhibitors. Importantly, none of the lead compounds violated Lipinski's criteria, reinforcing their drug-like nature.

Combining docking with ADMET modeling supports early-phase screening. Compared with traditional NSAIDs, the predicted safety profiles of these phytochemicals suggest potential advantages in long-term therapy. Moreover, the natural origin of these compounds may offer improved tolerability and reduced systemic toxicity.

Nevertheless, computational predictions alone cannot substitute experimental validation. Future work should include in-vitro COX-2 enzyme inhibition assays, cellular inflammatory marker studies, and in-vivo pharmacodynamic evaluation to confirm therapeutic efficacy.

5. Conclusion

This MSc research successfully identified several phytochemicals with strong COX-2 binding affinity and favorable ADMET characteristics through integrated molecular docking and pharmacokinetic modeling. Lead compounds demonstrated stable interactions within the COX-2 catalytic pocket, acceptable drug-likeness, and low predicted toxicity.

These findings highlight the potential of phytochemical-based inhibitors as safer alternatives to existing COX-2 selective drugs. The study also underscores the value of computational strategies in accelerating natural product drug discovery and reducing early-stage experimental burden.

Further experimental validation is warranted to translate these computational leads into clinically viable anti-inflammatory therapeutics.

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