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Original Research Article

In Silico Evaluation of Quercetin and CAPE as Potential Anti-Inflammatory Agents Targeting COX-2

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ABSTRACT

Propolis, has emerged as a promising candidate in this regard due to its active compounds, such as quercetin and caffeic acid phenethyl ester (CAPE).[7,8] These compounds exhibit anti-inflammatory, making propolis a potential alternative to conventional nonsteroidal anti-inflammatory drugs (NSAID). This study evaluates the anti-inflammatory potential of quercetin and CAPE, compounds from propolis, through in silico analysis focusing on cyclooxygenase-2 (COX-2) inhibition. Toxicity predictions, molecular docking, and molecular dynamics simulations were used to assess their safety and efficacy. The COX-2 structure (PDB ID: 4PH9) was retrieved from the Protein Data Bank, and ligands (quercetin, CAPE, ibuprofen, aspirin, and vanillin) were prepared for docking. Toxicity assessments were conducted using PROTOX II and pkCSM, including AMES, LD50, skin sensitization, and hepatotoxicity tests. Molecular docking was performed using Dock 6.8, and protein-ligand interactions were validated by RMSD. Molecular dynamics simulations were carried out with Amber22, including energy minimization, solvation, and stability evaluation via RMSD, RMSF, and MM-GBSA calculations. Toxicity predictions indicated that quercetin and CAPE are safe, with negative results in mutagenicity, skin sensitization, and hepatotoxicity tests, and LD50 values supporting their therapeutic potential. Molecular docking showed strong binding of quercetin (-51.4 kcal/mol) and CAPE (-53.3 kcal/mol) to COX-2, outperforming ibuprofen and aspirin. Molecular dynamics simulations revealed stable protein-ligand interactions, with low RMSD (0.3–0.4 Å) and RMSF values, indicating high stability. MM-GBSA calculations confirmed the strong binding of quercetin (-35.4 kcal/mol) and CAPE (-33.0 kcal/mol). Quercetin and CAPE exhibit strong COX-2 binding and stability, alongside favorable safety profiles, supporting their potential as anti-inflammatory agents for further clinical investigation.

Keywords: Propolis, Quercetin, Caffeic Acid Phenethyl Ester, Anti-inflammatory, Cyclooxygenase-2

Introduction

Dental diseases affect approximately 3.5 billion people globally, with dental caries being the most prevalent condition across all age groups, according to the World Health Organization (WHO).[1] The prevalence of dental caries is alarmingly high, affecting 90.2% of children aged 5 years and 95% of individuals aged 65 years or older.[2,3] These statistics underscore the urgent need to address oral health issues, particularly pain and inflammation caused by bacterial infections, trauma, heat, or chemical irritants.[4]

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Nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen and aspirin are commonly used to manage pain and inflammation through inhibition of the cyclooxygenase (COX) enzyme.[5] However, their use is associated with gastrointestinal side effects, primarily due to nonselective inhibition of COX-1, which reduces protective prostaglandins in the gastrointestinal tract.[6] Selective COX-2 inhibitors, which target inflammation without disrupting COX-1 physiological functions, offer a promising alternative but remain limited in availability. Therefore, there is a pressing need for safer and more effective anti-inflammatory agents. Propolis, a natural substance produced by bees, has emerged as a promising candidate in this regard due to its active compounds, such as quercetin and caffeic acid phenethyl ester (CAPE).[7,8] These compounds exhibit anti-inflammatory, antibacterial, and antioxidant properties, making propolis a potential alternative to conventional NSAIDs.[9]

This study employs an *in silico* approach to evaluate the anti-inflammatory potential of quercetin and CAPE, focusing on their ability to inhibit the COX-2 enzyme. *In silico* methods, including molecular docking and molecular dynamics simulations, are invaluable tools in drug discovery, offering cost-effective insights into molecular interactions and mechanisms.[10,11] Toxicity testing predicts the safety profiles of the compounds, while molecular docking evaluates their binding affinity to COX-2. Molecular dynamics simulations provide

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further insights into the stability and behavior of these interactions under physiological conditions.[12] This research aims to identify and characterize novel COX-2 inhibitors with high efficacy and safety profiles, contributing to the development of alternative therapeutic agents for managing inflammation and pain.

Materials and Methods

Macromolecule preparation

The target protein, cyclooxygenase-2 (COX-2), was retrieved from the Protein Data Bank (PDB) using its PDB ID code 4PH9. The structure with the highest resolution was selected to ensure greater accuracy in the simulations. The downloaded PDB file of COX-2 was saved for subsequent analyses.[13,14]

Ligand preparation

The molecular structures of the candidate ligands, quercetin and caffeic acid phenethyl ester (CAPE), were obtained from the PubChem database in .sdf format, along with their SMILES sequences for parameterization. The control ligands, ibuprofen and aspirin, were also downloaded from PubChem in the same format, alongside their SMILES sequences. Additionally, vanillin, a component of propolis, was downloaded as a negative control ligand, also from PubChem in .sdf format.

Toxicity prediction

Toxicity evaluations were conducted using the PROTOX II and pkCSM tools. Several toxicity tests were performed, including the AMES test for mutagenicity, LD_{50} test to estimate lethal doses, skin sensitization test to evaluate potential allergenicity, and hepatotoxicity test to assess liver toxicity. The results provided insights into the safety of the ligands for further in-silico studies.

Molecular docking

Molecular docking simulations were performed using Dock 6.8 software. The protein structure (COX-2, PDB ID: 4PH9) was prepared using Chimera 1.16. A simulation grid was generated using the SHOWBOX and GRID programs, taking into account van der Waals and electrostatic interactions. The docking procedure was validated through redocking, ensuring an RMSD deviation of less than 2.0 Å.[15] Ligand structures were optimized using the MMFF94 force field, and interactions were visualized using the PLIP web tool to identify key binding interactions and hydrogen bonds between the ligands and COX-2.

Molecular dynamic simulation

Molecular dynamics (MD) simulations were conducted using Amber22 software to assess the stability of the interactions between the COX-2 protein and the ligands. The protein structure (COX-2, PDB ID: 4PH9) was obtained from the Protein Data Bank, and cysteine residues were converted to CYX to comply with AMBER22 standards. Protonation was carried out at pH 7.4 using the H^{++} server. Candidate ligands were parameterized with AMBER22's `parmchk` tool, and the system was neutralized with counterions and solvated in an octagonal box using OPC water molecules. Energy minimization was performed using steepest descent and conjugate gradient methods, with restraints gradually relaxed on backbone and side-chain residues.[13,14]

Results and Discussion

The AMES test results confirm that quercetin, CAPE, ibuprofen, and vanillin are non-mutagenic, indicating they do not have the potential to induce DNA mutations. The median lethal dose (LD_{50}) values classify the compounds into toxicity categories: quercetin and ibuprofen fall into category 3 (highly toxic), vanillin into category 4 (moderately toxic), and CAPE into category 5 (slightly toxic). Despite their classification, quercetin and ibuprofen remain safe for oral use at appropriate dosages, with their recommended daily doses significantly below their acute toxicity thresholds (Table 1).

Skin sensitization testing revealed that quercetin, CAPE, aspirin, and vanillin are non-sensitizing, meaning they do not trigger allergic skin reactions. Ibuprofen, however, tested positive for skin sensitization, indicating potential for allergic reactions with topical exposure.

In the development of new drug compounds, it is essential to ensure that the candidate molecules not only bind effectively to their target receptors and exhibit favorable pharmacokinetic properties but also demonstrate safety and non-toxicity in biological systems. Toxicity prediction is therefore a critical step in drug development.[17] Computational methods for toxicity evaluation, as employed in this study, provide a time-efficient and cost-effective alternative to traditional animal testing, aligning with the principles of reducing, refining, and replacing animal use in research.

Hepatotoxicity, a critical indicator of systemic drug toxicity, was assessed due to its frequent manifestation in early-stage drug development.[18] None of the compounds tested—quercetin, CAPE, ibuprofen, aspirin, or vanillin—showed hepatotoxicity, suggesting minimal risk of liver damage. Overall, quercetin and CAPE from propolis exhibit a favorable safety profile alongside ibuprofen and vanillin. The computational toxicity evaluations suggest low risk of acute toxicity for all compounds, supporting their potential use as therapeutic agents, provided dosing guidelines are carefully adhered to.

The docking method employed in this study was validated by redocking the native ligand onto the protein structures obtained from the Protein Data Bank (PDB). Validation was assessed using Root Mean Square Deviation (RMSD) and visual pose comparison parameters.[19] RMSD quantifies the deviation between experimental and predicted ligand poses by comparing atom positions.[20] An RMSD value of <2.0 Å is widely accepted as a benchmark for docking success.[19] The validation process yielded an RMSD of 1.5 Å, confirming the reliability of the docking protocol and its suitability for subsequent virtual screening in drug discovery.[21] Lower RMSD values reflect higher accuracy, demonstrating that the docking method can predict ligand poses consistent with experimental data.

Table 1: Toxicity assessment of selected propolis components

Component	AMES	LD_{50} (mg/kg)	LD_{50} Class	Skin Sensitisation	Hepatotoxicity
Quercetin	Negative	159	3	NO	NO
CAPE	Negative	5000	5	NO	NO
Ibuprofen	Negative	299	3	YES	YES
Aspirin	Negative	250	3	NO	No
Vanillin	Negative	1000	4	NO	NO

In this study, molecular docking simulations were performed to evaluate the interactions of quercetin and CAPE, two propolis components, with the COX-2 enzyme. COX-2, derived from *Mus musculus*, has a resolution of 1.81 Å, ensuring high structural quality.[22] To avoid interference during docking simulations, water molecules were removed, enhancing the accuracy of ligand-receptor interaction analyses.

Molecular docking evaluates binding affinity and predicts ligand interactions within the protein's active site using a defined grid box. The grid box dimensions were 40 × 40 × 40, with coordinates X: 14.0, Y: 23.0, and Z: 25.5. Docking simulations included quercetin, CAPE, vanillin, aspirin (standard reference), and ibuprofen, focusing on parameters such as hydrogen bond count, binding affinity, and RMSD. Low RMSD values (≤2 Å) further validated docking accuracy.[23]

Binding affinities represent the strength of ligand-receptor interactions, with lower values indicating stronger binding. Table 2 presents the binding affinities of the tested compounds, with quercetin (-51.4 kcal/mol) and CAPE (-53.3 kcal/mol) demonstrating higher affinities compared to aspirin (-39.5 kcal/mol) and vanillin (-31.9 kcal/mol). Ibuprofen (-48.4 kcal/mol), a known anti-inflammatory drug, also showed slightly lower binding affinity than quercetin and CAPE.

Table 2 presents the binding affinities of the tested compounds, with

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quercetin (-51.4 kcal/mol) and CAPE (-53.3 kcal/mol) demonstrating higher affinities compared to aspirin (-39.5 kcal/mol) and vanillin (-31.9 kcal/mol). Ibuprofen (-48.4 kcal/mol), a known anti-inflammatory drug, also showed slightly lower binding affinity than quercetin and CAPE.

Docking results were visualized using the Protein Ligand Interaction Profile (PLIP) web tool in both 2D and 3D formats (Figure 1). This visualization identified key amino acid residues involved in ligand binding and interactions, including hydrogen bonds, hydrophobic forces, and electrostatic interactions within 8 Å. Both quercetin and CAPE formed hydrogen bonds with TYR355 and exhibited hydrophobic interactions with other critical residues (Table 3).

Table 2: Molecular docking test results

Target	*Compounds*	Binding affinity (kcal/mol)	RMSD
COX-2	Quercetin	-51.4	0
	CAPE	-53.3	0
	Ibuprofen	-48.4	0
	Aspirin	-39.5	0
	Vanillin	-31.9	0

Table 3: Visualization results of the bond

Target Proteins	Ligand	Types Of Bonds	Amino Acids
COX-2	*Quercetin*	Hydrogen	Tyr355 Ser530
		Hydrophobic	Val350 Leu353 Phe519 Val523
	Cape	Hydrogen	Tyr355 His90
		Hydrophobic	Leu353 Leu385 Tyr386 Phe519 Val523
		Pi-Pi Stacking	Trp388
	Ibuprofen	Hydrogen	Tyr355
		Hydrophobic	Val350, Leu360 Trp388 Ala528
		Salt Bridges	Arg120
	Aspirin	Hydrogen	Tyr355
		Hydrophobic	Val350 Leu353 Phe519 Val523 Ala528 Leu532
		Salt Bridges	Arg120
	Vanillin	Hydrogen	Ser530
		Hydrophobic	Leu353 Phe519

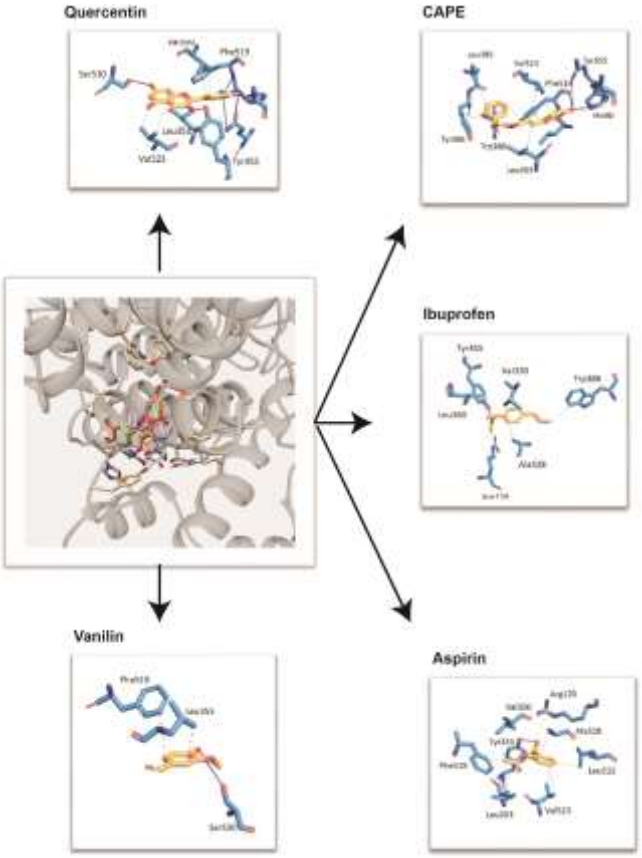

Figure 1: Visualization results of the bonds formed between quercetin, CAPE and comparison compounds ibuprofen, aspirin and vanillin against COX-2.

The molecular docking analysis revealed that quercetin and CAPE interact with COX-2 in a manner comparable to ibuprofen, suggesting their strong potential as anti-inflammatory agents. These results support the hypothesis that quercetin and CAPE could serve as competitive inhibitors of COX-2.

Molecular dynamics (MD) simulations were performed to examine the dynamic and flexible interactions between proteins and ligands, which are not fully captured during docking. This approach provides insights into the stability of these interactions under near-physiological conditions. The simulation workflow involved generating topology and coordinate files for the ligands, forming a complex with the COX-2 enzyme, and conducting solvation, neutralization, energy minimization, equilibration, and production steps. Each stage ensured system accuracy and stability, enabling the detailed analysis of interaction dynamics through parameters such as Root Mean Square Deviation (RMSD), Root Mean Square Fluctuation (RMSF), and Molecular Mechanics-Generalized Born Surface Area (MM-GBSA) free energy calculations.

RMSD measures the average displacement of backbone atoms (C, N, and O) relative to the reference structure, offering a quantitative assessment of conformational changes in the protein and ligand throughout the simulation.[16] It tracks shifts in secondary structures, such as helices and beta-sheets, as well as residues within the active site.

RMSD values were plotted over the 50 ns simulation period, as shown

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in Figure 2, and provide insight into molecular stability. Molecular dynamics simulations were conducted for 50 ns on protein-ligand systems (COX-2: Ibuprofen, COX-2:Aspirin, COX-2:Quercetin, and COX-2:CAPE). RMSD analysis revealed that system stability was achieved around 20 ns and maintained through the end of the simulation. Average RMSD values from 20 to 50 ns were 1.5 Å for ibuprofen, 0.6 Å for aspirin, 0.3 Å for quercetin, and 0.4 Å for CAPE.

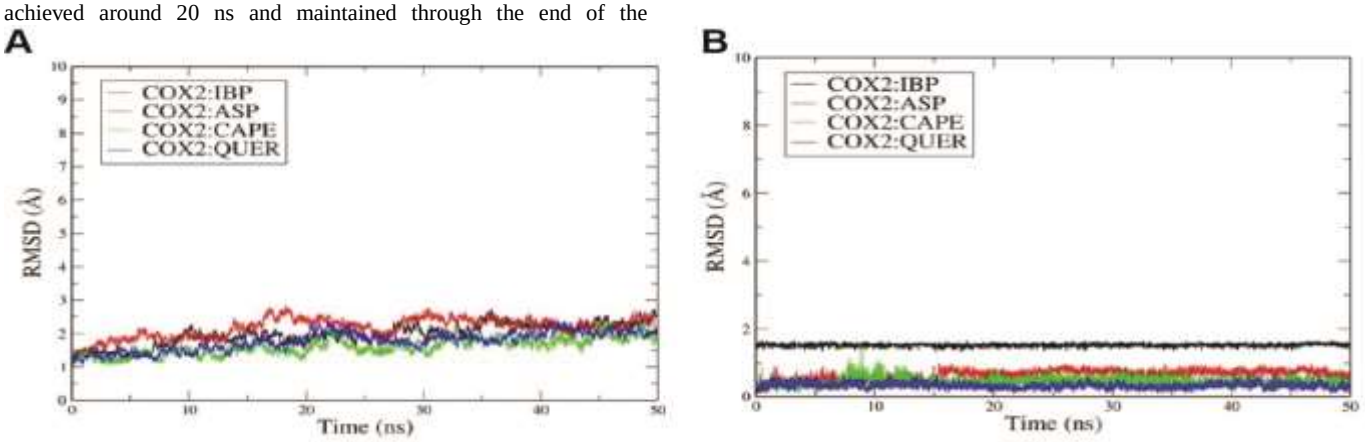

Figure 2: RMSD graph of each system for 50 ns: (A) Backbone and (B) ligand.

The initial rise in RMSD indicates structural adjustments in the enzyme and ligand optimization at the binding site, while stable RMSD values demonstrate the attainment of optimal protein-ligand conformations. The consistently low RMSD values for quercetin and CAPE suggest superior stability compared to ibuprofen and aspirin. Key residues, including HIS90, ARG120, TYR355, TYR385, TRP387, ARG513, GLU524, SER530, and LEU531, exhibited minimal fluctuations, indicating stable interactions with ligands (Figure 3). The RMSF results further confirm that quercetin and CAPE maintain stable interactions with COX-2, contributing to the overall stability of the complexes. The binding free energies for ibuprofen and aspirin were -35.7 kcal/mol and -25.23 kcal/mol, respectively, while quercetin and CAPE demonstrated comparable or better affinities with values of -35.4 kcal/mol and -33.0 kcal/mol, respectively (Table 4).

Table 4: Free binding energy prediction

Compound	Docking score	Free energy bind (ΔG)
Ibuprofen	-48.48	-35.7213±2.7835
Aspirin	-39.54	-25.2355±6.5280
CAPE	-53.38	-33.0759±3.2055
Quercentin	-51.40	-35.4447±3.4917

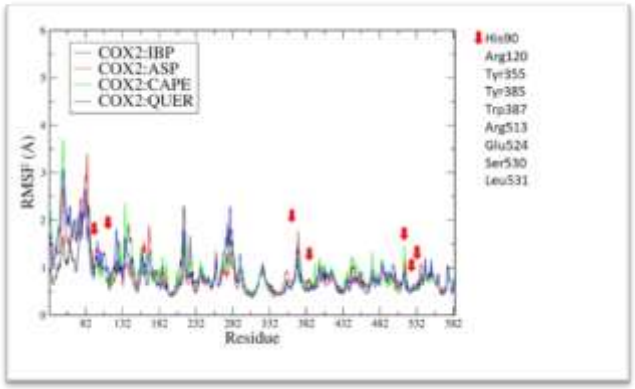

Figure 3: RMSF graph of ibuprofen, aspirin, quercetin, and CAPE

MD simulations revealed stable interactions between quercetin, CAPE, and the COX-2 enzyme, supported by low RMSD, low RMSF for active site residues, and favorable ΔG values. These results suggest that quercetin and CAPE exhibit strong potential as COX-2 inhibitors with stability and binding affinities comparable to or better than ibuprofen and aspirin, positioning them as promising candidates for anti-inflammatory drug development. RMSD values, essential for evaluating docking accuracy, were consistently low across all compounds (≤2 Å), indicating robust agreement between predicted and experimental ligand conformations.[24,25] These results position quercetin and CAPE as strong candidates for COX-2 inhibition, with affinities comparable to or exceeding those of aspirin and ibuprofen.

Docking results were visualized using the Protein Ligand Interaction Profile (PLIP) web tool in both 2D and 3D formats (Figure 1). This visualization identified key amino acid residues involved in ligand binding and interactions, including hydrogen bonds, hydrophobic forces, and electrostatic interactions within 8 Å. Both quercetin and CAPE formed hydrogen bonds with TYR355 and exhibited hydrophobic interactions with other critical residues (Table 3). These interactions are consistent with known COX-2 binding site studies, highlighting residues crucial for hydrogen bonding at the active site.[26]

RMSF measures the average positional fluctuations of individual residues over time, providing residue-level insights into flexibility and interaction stability.[27] Residues involved in binding interactions typically exhibit low RMSF values, reflecting their stability and active participation at the binding site.[28] Key residues, including HIS90, ARG120, TYR355, TYR385, TRP387, ARG513, GLU524, SER530, and LEU531, exhibited minimal fluctuations, indicating stable interactions with ligands (Figure 3). These residues form the binding pocket and are critical for ligand binding, as supported by their low RMSF values.[13] The RMSF results further confirm that quercetin and CAPE maintain stable interactions with COX-2, contributing to the overall stability of the complexes. The MM-GBSA method was employed to calculate the binding free energy (ΔG), which reflects the affinity of ligands for the receptor. Lower ΔG values indicate stronger binding interactions.[29] The binding free energies for ibuprofen and aspirin were -35.7 kcal/mol and -25.23 kcal/mol, respectively, while quercetin and CAPE demonstrated comparable or better affinities with values of -35.4 kcal/mol and -33.0 kcal/mol, respectively (Table 4).

Conclusion

The findings from this study provide compelling evidence that quercetin and CAPE, key components of propolis, are promising candidates for anti-inflammatory drug development targeting COX-2. Toxicity evaluations confirmed their safety, showing negative results for mutagenicity, skin sensitization, and hepatotoxicity. Despite being classified as highly toxic based on LD_{50} values, their safe therapeutic use is supported at recommended doses. Molecular docking simulations revealed that quercetin and CAPE exhibit strong binding affinities to COX-2, surpassing those of ibuprofen and aspirin, with significant hydrogen bonding and hydrophobic interactions at critical active site residues. Molecular dynamics simulations further validated these

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interactions, demonstrating stable protein-ligand complexes with low RMSD and RMSF values, indicating minimal fluctuations and high conformational stability. Additionally, MM-GBSA free energy calculations confirmed their strong binding affinities, comparable to or better than existing anti-inflammatory drugs. Collectively, these results highlight the potential of quercetin and CAPE as effective and safe COX-2 inhibitors, warranting further investigation through in vitro and in vivo studies to advance their clinical development.

Conflict of Interest

The authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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