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Original Article

Molecular Docking Investigation of *Caffeic Acid Phenethyl Ester* (CAPE) Interaction with IL-6 and TNF-α for Anti-Inflammatory Potential

Investigasi Docking Molekuler Interaksi *Caffeic Acid Phenethyl Ester* (CAPE) dengan IL-6 dan TNF-α untuk Potensi Anti-inflamasi

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Abstract

Inflammation is a physiological response to tissue injury mediated by pro-inflammatory cytokines, including interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α). Although conventional anti-inflammatory drugs are effective, their long-term use is associated with adverse effects, prompting interest in safer natural alternatives. *Caffeic acid phenethyl ester (CAPE)*, a major bioactive constituent of propolis, has been reported to exhibit anti-inflammatory properties. This study aimed to investigate the interaction of CAPE with IL-6 and TNF-α using molecular docking to evaluate binding affinity and molecular interactions. Docking simulations were performed to predict the binding behavior of CAPE and compare it with diclofenac sodium as a reference compound. CAPE exhibited binding affinities of −5.1 kcal/mol against TNF-α and −5.0 kcal/mol against IL-6, whereas diclofenac sodium showed slightly stronger binding affinities of −5.5 kcal/mol and −5.2 kcal/mol, respectively. In addition, CAPE shared several interacting residues with the reference compound, suggesting a similar binding orientation within the active sites of both proteins. These findings indicate that CAPE possesses favorable binding characteristics toward TNF-α and IL-6. However, the obtained binding affinities represent preliminary predictions of ligand–protein interactions and require further validation through molecular dynamics simulations and experimental studies. This study provides molecular insights into the anti-inflammatory potential of propolis-derived compounds and supports their further exploration as natural lead compounds for anti-inflammatory drug development.

Abstrak

Peradangan adalah respons fisiologis terhadap cedera jaringan yang dimediasi oleh sitokin pro-inflamasi, termasuk interleukin-6 (IL-6) dan faktor nekrosis tumor-alfa (TNF-α). Meskipun obat anti-inflamasi konvensional efektif, penggunaan jangka panjangnya dikaitkan dengan efek samping, sehingga mendorong minat pada alternatif alami yang lebih aman. *Caffeic acid phenethyl ester (CAPE)* konstituen bioaktif utama propolis, telah dilaporkan menunjukkan sifat anti-inflamasi. Studi ini bertujuan untuk menyelidiki interaksi CAPE dengan IL-6 dan TNF-α menggunakan penambatan molekuler untuk mengevaluasi afinitas pengikatan dan interaksi molekuler. Simulasi penambatan dilakukan untuk memprediksi perilaku pengikatan CAPE dan membandingkannya dengan natrium diklofenak sebagai senyawa referensi. CAPE menunjukkan afinitas pengikatan sebesar −5,1 kkal/mol terhadap TNF-α dan −5,0 kkal/mol terhadap IL-6, sedangkan natrium diklofenak menunjukkan afinitas pengikatan yang sedikit lebih kuat, yaitu −5,5 kkal/mol dan −5,2 kkal/mol. Selain itu, CAPE memiliki beberapa residu yang berinteraksi dengan senyawa referensi, menunjukkan orientasi pengikatan yang serupa di dalam situs aktif kedua protein tersebut. Temuan ini menunjukkan bahwa CAPE memiliki karakteristik pengikatan yang menguntungkan terhadap TNF-α dan IL-6. Namun, afinitas pengikatan yang diperoleh merupakan prediksi awal interaksi ligan-protein dan memerlukan validasi lebih lanjut melalui simulasi dinamika molekuler dan studi eksperimental. Studi ini memberikan wawasan molekuler tentang potensi antiinflamasi senyawa turunan propolis dan mendukung eksplorasi lebih lanjut sebagai senyawa utama alami untuk pengembangan obat antiinflamasi.

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INTRODUCTION

Inflammation is a fundamental protective mechanism that the body initiates in response to tissue damage, preventing further injury and supporting recovery [1]. This process begins with cellular disruption, leading to the release of phospholipids such as arachidonic acid, which is subsequently converted into inflammatory mediators including leukotrienes, prostaglandins, and thromboxanes by cyclooxygenase and lipoxygenase enzymes. Among these mediators, pro-inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) play pivotal roles in orchestrating immune responses and regulating both acute and chronic inflammation [2,3].

IL-6 activates inflammatory signaling pathways, induces the synthesis of acute-phase proteins, and supports T-cell proliferation and B-cell differentiation. TNF-α serves as an early mediator by promoting the production of additional pro-inflammatory cytokines and triggering endothelial activation, which increases vascular permeability. Dysregulated levels of these cytokines have been linked to increased disease severity and adverse clinical outcomes, highlighting the importance of precise modulation to prevent excessive inflammation [4,5].

Conventional anti-inflammatory drugs, such as nonsteroidal anti-inflammatory agents, are effective but are often associated with gastrointestinal, renal, and cardiovascular side effects. This limitation has driven growing interest in natural alternatives that offer comparable efficacy with lower risk profiles. Propolis, a resinous substance produced by bees, contains bioactive compounds such as flavonoids and caffeic acid phenethyl ester (CAPE) [6–8]; Idacahyati et al., 2020). CAPE has been shown to inhibit prostaglandin synthesis, enhance immune cell phagocytosis, and promote tissue repair [9]. Its ability to inhibit cyclooxygenase-2 (COX-2), a key enzyme in inflammatory pathways, further supports its potential as a natural anti-inflammatory agent [10].

Despite these promising findings, the precise molecular interactions of CAPE with key inflammatory cytokines, particularly IL-6 and TNF-α, remain poorly characterized. Understanding these interactions is critical for elucidating the mechanisms underlying CAPE's anti-inflammatory effects and for optimizing its therapeutic application. Addressing this gap is particularly urgent given the increasing prevalence of inflammatory disorders and the need for safer, more effective treatments.

Although CAPE has been extensively reported to exhibit anti-inflammatory effects through inhibition of NF-κB activation, suppression of COX-2 expression, and regulation of oxidative stress pathways, most previous studies have mainly focused on cellular mechanisms and downstream inflammatory mediators. Several studies have demonstrated the anti-inflammatory activity of CAPE in various disease models. However, information regarding its direct molecular interactions with major pro-inflammatory cytokines, particularly IL-6 and TNF-α, remains limited. Furthermore, comparative studies evaluating CAPE against conventional anti-inflammatory drugs at the molecular level are still scarce. Therefore, elucidating the binding behavior of CAPE toward these cytokines is important to better understand its mechanism of action and support the development of propolis-derived anti-inflammatory agents.

To the best of our knowledge, this study is among the few investigations that simultaneously evaluate the interaction of CAPE with both IL-6 and TNF-α using molecular docking and compare its binding characteristics with diclofenac sodium as a reference compound. This approach provides molecular insights into the anti-inflammatory potential of CAPE and may support the development of safer natural therapeutic agents. Therefore, this study aims to evaluate the anti-inflammatory potential of caffeic acid phenethyl ester by investigating its molecular interactions

with IL-6 and TNF-α using docking simulations. The research seeks to provide mechanistic insights into CAPE's activity, contributing to the development of novel, safe, and effective herbal-based therapies for managing inflammation.

METHODS

This study employed an in silico molecular docking approach to investigate the interactions of caffeic acid phenethyl ester (CAPE) with target proteins interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α). The workflow included ligand and protein retrieval, structural preparation, docking simulations, and interaction analysis.

Tools and Materials

Tools. The study utilized a combination of hardware, software, and online servers. Hardware included a Lenovo laptop (model 1A02S74R) with Intel Core i5-1035G1 CPU @ 1.00 GHz, 4 GB RAM, and Windows 11 Pro 64-bit. Software and online resources included AutoDockTools 1.5.7 (Morris et al., 2009), BIOVIA Discovery Studio Visualizer 2021, PyRx 0.9.9, PyMOL, PubChem, RCSB Protein Data Bank, and PLIP (Protein-Ligand Interaction Profiler) [11].

Materials. The 3D structure of caffeic acid phenethyl ester (CAPE) was obtained from PubChem (https://pubchem.ncbi.nlm.nih.gov/) as shown in Figure 1. The target protein structures were obtained from the Protein Data Bank (PDB), including IL-6 (PDB ID: 1ALU) and TNF-α (PDB ID: 6OP0). PDB ID 1ALU was selected because it represents the crystal structure of human IL-6 with sufficient resolution and has been previously used in molecular docking studies involving inflammatory targets. Similarly, PDB ID 6OP0 was chosen because it corresponds to human TNF-α complexed with a co-crystallized ligand, allowing identification and validation of the active binding site through redocking analysis [12,13].

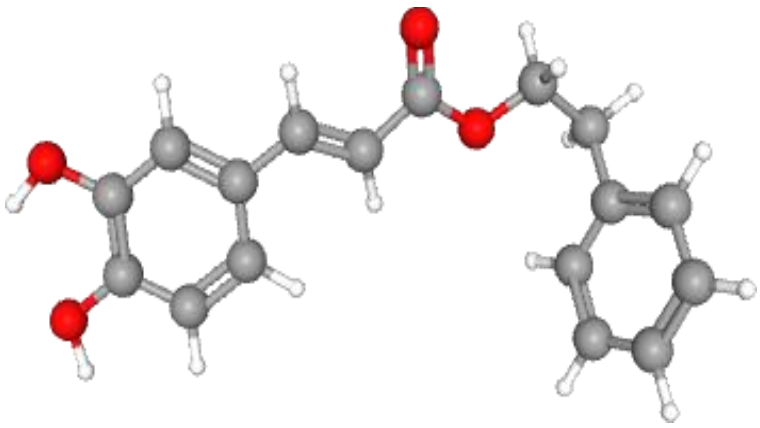


Figure 1. Caffeic Acid Phenethyl Ester (CAPE) in 3D struture

Research Procedure

Step I: Retrieval and Preparation of Protein Structures

The IL-6 and TNF-α protein structures were retrieved from the PDB database. Protein preparation involved removing water molecules, ions, and irrelevant ligands using AutoDockTools 1.5.7 to focus on the active binding domains for molecular docking. Chain selection was performed to isolate the biologically relevant protein chains used for docking analysis. The co-crystallized ligands were retained during the validation process and subsequently removed before ligand docking. Polar hydrogen atoms and Gasteiger charges were added, and the prepared receptors were saved in PDBQT format.

Step II: Validation of Docking Method

Docking validation was conducted by redocking the native ligand into the prepared target protein. The method was considered valid if the root-mean-square deviation (RMSD) was ≤ 2 Å, ensuring reliable docking parameters for subsequent ligand testing.

Step III: Retrieval and Preparation of CAPE Structure

The 3D structure of CAPE was obtained from PubChem and visualized using BIOVIA Discovery Studio Visualizer 2021. The ligand was prepared for docking, including optimization and conversion to compatible file formats. Ligand geometry optimization and energy minimization were performed prior to docking to obtain a stable conformation suitable for interaction analysis. The optimized ligand structure was converted into PDBQT format using AutoDockTools 1.5.7.

Step IV: Molecular Docking Simulation

Molecular docking simulations were performed using AutoDock Vina version 1.5.7 implemented in PyRx version 0.9.9. Grid box parameters were defined according to the binding pocket of the co-crystallized ligand identified during redocking validation. For TNF-α (6OP0), the grid center coordinates were x = -13.917, y = -1.482, and z = 19.021, with dimensions of 15 × 15 × 15 Å. For IL-6 (1ALU), the grid center coordinates were x = -7.677, y = -12.743, and z = 0.048, with dimensions of 12 × 12 × 12 Å. Docking calculations were performed with an exhaustiveness value of 8, generating nine binding poses for each ligand. The docking pose exhibiting the lowest binding energy and an orientation consistent with the active binding site was selected as the best pose for further analysis. Visualization and interaction analyses were carried out using PyMOL, Discovery Studio Visualizer 2021, and the PLIP webserver.

Step V: Analysis of Molecular Docking Interactions

Binding affinities for each docking pose were analyzed using AutoDock Vina 1.5.7, with the lowest energy conformations considered the best. Poses were clustered in PyRx based on structural similarity. Protein-ligand interactions, including hydrogen bonds, hydrophobic interactions, π-π stacking, and electrostatic interactions, were identified. Further quantitative analysis was conducted using the PLIP webserver, reporting all non-covalent interactions, distances, interaction energies, and 3D visualizations.

Data Analysis

The best docking pose was selected based on the lowest binding affinity value and its consistency with the active site residues identified during redocking validation. Docking results were evaluated primarily through binding affinity scores and interaction types. Conformational analysis, energy calculations, and quantitative interaction data from PLIP provided detailed insights into the molecular interactions between CAPE and the target proteins.

RESULT AND DISCUSSION

Target Protein Preparation

Target protein preparation was conducted to obtain optimized receptor structures suitable for molecular docking simulations. Proper protein preparation is a critical step in molecular docking studies because inaccuracies in receptor structures may significantly affect binding affinity predictions and ligand–receptor interaction profiles [14]. In this study, the target proteins analyzed were TNF-α (PDB ID: 6OP0) and IL-6 (PDB ID: 1ALU). Caffeic acid phenethyl ester (CAPE) was used as the test compound, while diclofenac sodium was employed as a reference compound because of its well-established anti-inflammatory activity and widespread clinical use. Although diclofenac primarily

exerts its therapeutic effects through cyclooxygenase (COX) inhibition rather than direct inhibition of IL-6 or TNF-α, it was included as a comparator to provide a benchmark for evaluating the relative binding behavior of CAPE toward these inflammatory targets.

Macromolecular chain separation was performed as the initial step in receptor preparation to isolate the biologically relevant protein chains. The separated receptor structures were saved in .pdb format and subsequently optimized using AutoDockTools. During optimization, water molecules were removed and hydrogen atoms were added to each amino acid residue. Removal of crystallographic water molecules is necessary because they may introduce artificial hydrogen bonding and reduce docking accuracy if not properly treated [15].

Hydrogen atoms were added to ensure accurate modeling of hydrogen bonding interactions and proper protonation states during docking simulations. Furthermore, Gasteiger charges were assigned to maintain electrostatic stability and improve docking reliability. Electrostatic interactions play an essential role in ligand binding and significantly influence docking scoring functions [16]. The optimized receptor structures (Figure 2) were then saved in .pdbqt format and used for docking validation and molecular docking simulations. The systematic preparation of TNF-α and IL-6 receptors ensured that the docking protocol provided a reliable representation of ligand–protein interactions and supported accurate prediction of CAPE binding behavior toward inflammatory target proteins.

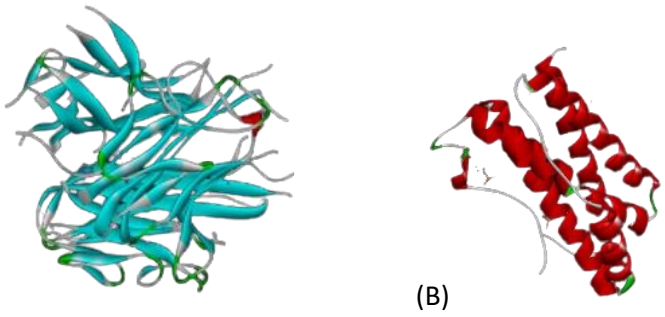


Figure 2. Prepared structures of IL-6 (A) and TNF-α (B) target proteins used for molecular docking analysis.

Docking Method Validation

Validation of the molecular docking method was conducted to ensure the accuracy and reliability of the docking protocol prior to evaluating the binding affinity of the test compounds toward the inflammatory target proteins. The validation process used the root mean square deviation (RMSD) parameter, which measures the structural deviation between the crystallographic conformation of the native ligand and the redocked pose. RMSD is widely accepted as an indicator of docking accuracy because it reflects how well the docking protocol can reproduce the experimentally observed ligand–protein interactions [17].

A docking protocol is generally considered reliable when the RMSD value is less than 2 Å, indicating that the predicted ligand orientation closely matches the experimental crystallographic structure [18]. In this study, validation was performed by redocking the native ligands into the active sites of the inflammatory target proteins TNF-α (PDB ID: 6OP0) and IL-6 (PDB ID: 1ALU). The native ligand used for TNF-α was A7A [(R)-{1-[(2,5-dimethylphenyl)methyl]-6-(1-methyl-1H-pyrazole-4-yl)-1H-benzimidazol-2-yl}(pyridin-4-yl)methanol], while the native ligand for IL-6 was TLA (L(+)-tartaric acid). The redocking results produced RMSD values of 0.943 Å for TNF-α and 1.666 Å for IL-6, both of which fall within the acceptable validation range.

Method validation was carried out by redocking the native ligands into their respective binding sites [19]. The docking results were analyzed using Discovery Studio 2021 and visualized with PyMOL. The RMSD values obtained were 0.943 Å for TNF-α and 1.666 Å for IL-6, both of which meet the accepted validation criteria. These results confirm that the docking parameters used in this study were reliable and suitable for docking simulations of the test compound. The docking validation results are presented in Table 1.

Table 1. Molecular docking validation results for TNF-α and IL-6 based on root mean square deviation (RMSD) values.

Ligand	Protein Target	Grid Center	Grid Box Dimensions (Å)	RMSD (Å)
A7A / R)-{1-[(2,5-dimethylphenyl)methyl]-6-(1-methyl-1H-pyrazole-4-yl)-1H-benzimidazol-2-yl}(pyridin-4-yl)methanol	TNF- α : 6OP0	x = -13.917 y = -1.482 z = 19.021	x = 15 y = 15 z = 15	0.943
TLA / L(+)-TARTARIC ACID	IL-6 : 1ALU	x = -7.677 y = -12.743 z = 0.048	x = 12 y = 12 z = 12	1.666

These RMSD values indicate that the docking parameters used in this study were capable of accurately reproducing the binding poses of the native ligands within the active sites of TNF-α and IL-6. Therefore, the docking protocol can be considered valid and suitable for predicting the binding interactions and affinity of the tested compounds. The validated docking method increases the reliability of subsequent molecular docking simulations and supports the interpretation of ligand–protein interaction results

Ligand Preparation

Ligand preparation is an important step in molecular docking studies because the accuracy of docking results depends on the quality of the ligand structure used in the simulation. In this study, the three-dimensional structure of caffeic acid phenethyl ester (CAPE) was obtained from the PubChem Compound database (CID: 5281787). PubChem is a widely used public chemical database that provides reliable structural and physicochemical information for bioactive compounds, including natural products and phytochemicals, making it suitable as a source of ligand structures in computational drug discovery studies [20].

The structure was downloaded in .sdf format and converted using AutoDock tools to generate a .pdb file for docking analysis. The CAPE structure was downloaded in Structure Data File (.sdf) format and subsequently converted into Protein Data Bank (.pdb) format using AutoDock Tools to ensure compatibility with the docking software. Proper ligand preparation, including file format conversion and structural optimization, is essential to obtain accurate predictions of ligand–protein interactions and binding affinity[21].

After conversion, the ligand structure was visualized using Discovery Studio Visualizer to verify the molecular geometry and structural integrity prior to docking simulations. Visualization helps ensure that the ligand structure is correctly prepared and free from structural errors that could affect docking results. A well-prepared ligand structure improves docking reliability and enhances the accuracy of predicted binding interactions with the target proteins[22].

Molecular Docking Analysis

The molecular docking analysis provided binding affinity values and interaction profiles between ligands and the target proteins TNF-α and IL-6. Binding affinity values reflect the strength and stability of ligand with receptor complexes and are commonly used as preliminary indicators of biological activity in structure-based drug design. More negative binding energy values indicate stronger molecular interactions and greater stability of the ligand–receptor complex, suggesting a higher probability of biological activity [23].

All tested ligands, including caffeic acid phenethyl ester (CAPE), diclofenac sodium, and native ligands, showed negative binding affinity values, indicating that the interactions with TNF-α and IL-6 receptors occurred spontaneously under simulated conditions. Docking analysis against TNF-α demonstrated that diclofenac sodium exhibited the strongest binding affinity with a value of −5.5 kcal/mol, whereas CAPE showed a binding affinity of −5.1 kcal/mol. Similarly, docking analysis against IL-6 showed that diclofenac sodium produced a binding affinity value of −5.2 kcal/mol, while CAPE demonstrated a slightly lower binding affinity of −5.0 kcal/mol. The comparison of binding affinity values between CAPE and diclofenac sodium is presented in Table 2.

Table 2. Comparison of Binding Affinities of CAPE and Diclofenac Sodium Against Target

Protein Target	Compound	Binding Affinity (kcal/mol)
TNF-a	Diclofenac sodium	-5.5
	Caffeic Acid Phenethyl Ester	-5.1
IL-6	Diclofenac sodium	-5.2
	Caffeic Acid Phenethyl Ester	-5.0

Although diclofenac sodium exhibited slightly lower binding energies than CAPE, the differences between both compounds were less than 1 kcal/mol. Such differences are generally considered relatively small and suggest comparable interaction stability. According to Ferreira et al. (2024), compounds exhibiting differences below 1 kcal/mol may possess similar binding behavior within the receptor cavity [24].

Although CAPE exhibited binding affinity values comparable to those of diclofenac sodium, the values obtained (approximately −5 kcal/mol) should be interpreted as preliminary predictions of ligand–protein interactions rather than direct evidence of anti-inflammatory activity. Molecular docking provides only an estimation of binding propensity and does not necessarily reflect biological efficacy. Therefore, these findings indicate the potential ability of CAPE to interact with TNF-α and IL-6, which should be further confirmed through molecular dynamics simulations and experimental studies. CAPE contains aromatic rings and polar functional groups that enable both hydrophobic and electrostatic interactions, which are known to contribute significantly to ligand stabilization within protein binding sites. Previous studies have reported that CAPE exhibits anti-inflammatory activity through modulation of inflammatory mediators and inhibition of pro-inflammatory signaling pathways, supporting the relevance of the docking results obtained in this study [9].

Visualization of Molecular Docking Interactions

Visualization of molecular docking interactions revealed distinct interaction patterns between caffeic acid phenethyl ester (CAPE), diclofenac sodium, and the inflammatory target proteins TNF-α and IL-6 (Figure 3). In the TNF-α receptor, diclofenac sodium formed hydrogen bonds with LEU120C and SER60C, accompanied by hydrophobic interactions involving LEU57C, TYR59C, and TYR151C (Figure 3B). Similarly, CAPE interacted with TNF-α through key residues including LEU120C and TYR59C, suggesting that CAPE occupies a binding region comparable to that of the reference compound (Figure 3A).

For the IL-6 receptor, no hydrogen bond interactions were observed for either CAPE or diclofenac sodium. However, both compounds established hydrophobic interactions with residues LEU178A, ARG179A, and ARG182A, which are considered important contributors to ligand stabilization within the binding cavity (Figure 3C and 3D). The presence of shared interacting residues indicates that CAPE exhibits a binding orientation similar to that of diclofenac sodium and may potentially modulate inflammatory pathways through comparable molecular interactions.

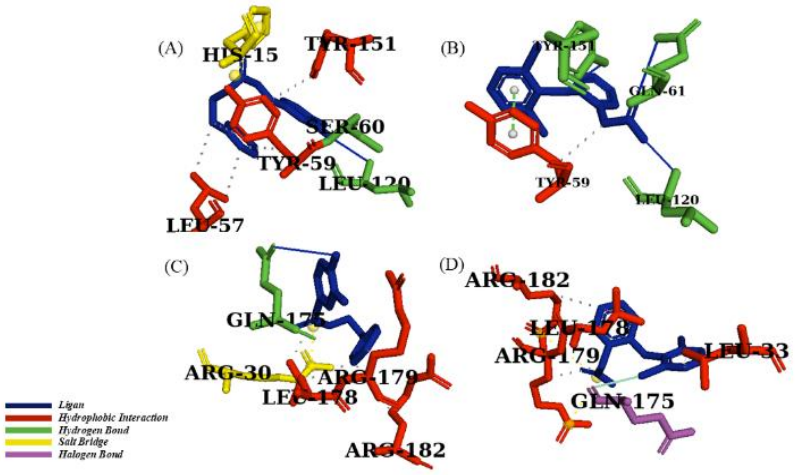


Figure 3. Molecular interaction profiles of caffeic acid phenethyl ester (CAPE) and diclofenac sodium with inflammatory target proteins. (A) CAPE–TNF-α, (B) Diclofenac sodium–TNF-α, (C) CAPE–IL-6, and (D) Diclofenac sodium–IL-6. Hydrogen bonds and hydrophobic interactions are shown to illustrate the binding patterns within the active sites of the target proteins.

These interactions indicate stable accommodation of the ligand within the TNF-α binding pocket. CAPE exhibited a comparable interaction pattern, particularly with residues LEU120C and TYR59C, suggesting that CAPE occupies a similar binding region within the active site. The presence of shared interacting residues indicates structural compatibility between CAPE and the TNF-α binding pocket and suggests the possibility of competitive binding within this region. Similar molecular docking studies have demonstrated that phytochemical compounds are capable of interacting with TNF-α through comparable amino acid residues, supporting their potential as anti-inflammatory agents[25].

In the IL-6 receptor, hydrogen bond interactions were not observed for CAPE or the reference ligand. However, hydrophobic interactions were detected involving residues LEU33A, LEU178A, ARG179A, and ARG182A. CAPE shared several interacting residues with the reference ligand, particularly LEU178A, ARG179A, and ARG182A, indicating a similar binding orientation within the IL-6 interaction cavity. Hydrophobic interactions play an important role in stabilizing ligand–protein complexes and may significantly contribute to binding stability even in the absence of hydrogen bonding interactions. Molecular docking studies have shown that non-covalent interactions such as hydrophobic contacts are essential determinants of ligand stability within protein binding sites[26].

The interaction patterns observed in both TNF-α and IL-6 receptors indicate that CAPE forms stable non-covalent interactions dominated primarily by hydrophobic contacts. Although the binding affinity values of CAPE were slightly lower than those of diclofenac sodium, the similarity of interacting residues suggests that CAPE interacts with

key regions involved in inflammatory signaling. IL-6 and TNF-α are well-recognized inflammatory mediators frequently targeted in molecular docking studies for anti-inflammatory drug discovery, and their inhibition is associated with modulation of inflammatory pathways[13].

From a structural perspective, the aromatic rings and ester functional groups of CAPE enable hydrophobic and π-related interactions within the binding pockets, contributing to stabilization of ligand–receptor complexes. These findings suggest that CAPE demonstrates a consistent interaction profile toward both TNF-α and IL-6, supporting its potential as a natural anti-inflammatory candidate. Overall, the docking results provide a molecular-level explanation for the anti-inflammatory activity of CAPE and indicate that this compound may serve as a promising lead compound for further anti-inflammatory drug development.

LIMITATION

This study was limited to an in silico molecular docking approach to evaluate the interaction of caffeic acid phenethyl ester (CAPE) with IL-6 and TNF-α target proteins. Nevertheless, molecular docking provides an important preliminary insight into ligand–receptor interactions and binding affinity prediction. Further studies involving molecular dynamics simulations and experimental approaches (in vitro or in vivo) are recommended to confirm and extend the findings of this study.

CONCLUSION

This study demonstrated that caffeic acid phenethyl ester (CAPE) is capable of interacting with the inflammatory target proteins TNF-α and IL-6, exhibiting binding affinity values comparable to those of diclofenac sodium and sharing several key interacting residues within the binding sites. These findings suggest that CAPE possesses favorable binding characteristics and may contribute to the modulation of inflammatory pathways. However, the binding affinity values obtained from molecular docking represent preliminary predictions of ligand with protein interactions and should not be considered direct evidence of anti-inflammatory activity. Therefore, CAPE may serve as a promising natural lead compound for anti-inflammatory drug development, although further molecular dynamics simulations and experimental studies are necessary to validate its biological efficacy and therapeutic potential.

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AUTHOR CONTRIBUTION STATEMENT

KAAKS: Conceptualization, Methodology, Software; **AN**: Data curation, Writing Original draft preparation; **AN**: Visualization, Investigation; **PMK**: Supervision; **KAAKS**: Software, Validation; **PMK**: Writing- Reviewing and Editing.

CONFLICT OF INTEREST DECLARATION

The authors declare no conflict of interest.

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