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# Molecular Pharmacokinetics and Structural Docking of Phenolic Acids for Targeting NF-κB Pathway Components in Inflammation and Fibrosis: A Computational Approach Toward Therapeutic Discovery

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***Abstract***

*Inflammation and Fibrosis are critical pathological processes associated with various chronic diseases, often mediated by the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) signaling pathway. This study investigates the therapeutic potential of phenolic acids as modulators of the NF-κB pathway, aiming to identify novel ligands that can effectively interact with key components of this signaling cascade. A comprehensive computational approach was employed, utilizing molecular docking, pharmacological screening, and post-docking analysis to evaluate the binding interactions of selected phenolic acids with NF-κB and NEMO proteins. Ligands were sourced from PhytoHub and PubChem, and pharmacokinetic properties were assessed using the Swiss ADME tool, focusing on Lipinski's rule, gastrointestinal absorption, bioavailability, and potential assay interference (PAINS) and toxicity concerns (BRENK). The docking studies revealed that compounds, such as Vanilloylglycine (–6.1 kcal/mol), 2,4,6-Trihydroxybenzoic acid (–5.9 kcal/mol), and Syringic acid (–5.9 kcal/mol) exhibited strong binding affinities with NF-κB, while Hippuric Acid (–6.2 kcal/mol), Vanilloylglycine (–6.2 kcal/mol), and 4-Hydroxybenzoic acid (–6.1 kcal/mol) showed promising interactions with NEMO. The post-docking analysis showed strong interactions, such as hydrogen bonds, hydrophobic interactions, and electrostatic forces, indicating a strong and stable binding process. The pharmacological evaluations of these compounds demonstrated favorable properties, such as appropriate molecular weight, solubility, and lipophilicity, positioning them as promising candidates for further development. These findings suggest that phenolic acids could serve as effective modulators of the NF-κB pathway, potentially mitigating inflammation and fibrosis. However, experiments are needed to verify these computer-based predictions. The study's limitations include the need for in vitro and in vivo testing, as well as optimization of the compounds for improved pharmacokinetic profiles. This research underscores the potential of phenolic acids as therapeutic agents in chronic disease management, with promising future perspectives for drug development.*

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## INTRODUCTION

Cystic fibrosis (CF) is a serious inherited condition caused by changes in the CFTR gene, which results in the production of thick, sticky mucus in different organs, especially the lungs and pancreas. The buildup of mucus leads to long-term lung infections, ongoing inflammation, and worsening lung damage, greatly affecting the quality of life for those with the condition. A key factor in the inflammation seen in CF is the NF-κB signaling pathway, which controls immune

responses and inflammation. In CF, problems with the NF-κB pathway lead to the attraction of immune cells, the release of inflammation-causing signals, and the formation of scar tissue, all of which worsen the decline in lung function [1].

The persistent activation of the NF-κB pathway in CF highlights the need for targeted therapeutic strategies that can effectively mitigate inflammation and fibrosis. Current treatments mainly aim to manage symptoms and use antibiotics, but they don't target the root causes of the inflammation. Therefore, there is a pressing demand for innovative approaches that can specifically target the NF-κB pathway to reduce inflammation and improve lung function in CF patients.

Recent research has identified phenolic acids as promising candidates for therapeutic intervention due to their anti-inflammatory and antioxidant properties. These compounds, found abundantly in fruits, vegetables, and herbs, have been shown to influence the NF-κB signaling pathway, suggesting their potential role in managing chronic inflammatory conditions like cystic fibrosis. Among the key regulatory proteins in the NF-κB pathway is NEMO (NF-κB essential modulator), which plays a crucial role in the activation of NF-κB. Understanding how phenolic acids interact with NF-κB and NEMO can provide valuable insights into their therapeutic potential [2, 3].

In drug discovery, computational methods, especially molecular docking analysis, have become valuable tools for predicting how small molecules (ligands) interact with target proteins. These techniques allow researchers to explore how phenolic acids can bind to key components of the NF-κB pathway, providing a rational basis for the design of new therapeutic agents. By utilizing molecular docking studies, this research aims to elucidate the binding affinities and interaction modes of phenolic acids with NF-κB and NEMO, thereby identifying potential candidates for further development.

The objective of this study is to investigate the potential of phenolic acids as novel therapeutic agents targeting the NF-κB signaling pathway in cystic fibrosis. Through computational analysis, this research seeks to predict the binding interactions of selected phenolic acids with NF-κB and NEMO, evaluate their pharmacokinetic properties, and assess their efficacy in reducing inflammation and fibrosis. By leveraging computational tools, this study aims to contribute to the development of new treatment strategies for cystic fibrosis, ultimately improving the management of this challenging disease.

## MATERIALS AND METHODS

### Protein Retrieval

The Protein Data Bank (PDB) is an essential resource that offers access to three-dimensional structural data of biological macromolecules, facilitating the study of protein functions and interactions. In this research, we focused on two key proteins involved in the NF-κB signaling pathway: the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) protein (PDB ID: 1NFI) and the NF-κB essential modulator (NEMO) protein (PDB ID: 3RZ0). The 1NFI structure, resolved by X-ray diffraction at a resolution of 2.70 Å, represents a crucial transcription factor that regulates innate immunity [4]. The 3RZ0 structure, also determined by X-ray diffraction at a resolution of 3.00 Å, depicts NEMO, which plays a vital role in the activation of NF-κB through the IκB kinase complex. This methodology involved retrieving the structural data for both proteins from the PDB, allowing for a detailed analysis of their interactions and functions within the NF-κB signaling pathway.

### Ligand Retrieval

Phenolic acids are a group of compounds known for their anti-inflammatory and antioxidant properties, making them promising candidates for virtual screening to identify potential therapeutic agents. In drug discovery, computational techniques, like molecular docking analysis, have become important tools for predicting how small molecules (ligands) bind to target proteins [5].

### Ligand Retrieval from Databases

Phytohub (https://phytohub.eu) is a specialized database for plant-derived compounds, allowing researchers to search for ligands based on chemical structure or biological activity. Additionally,

PubChem (https://pubchem.ncbi.nlm.nih.gov) serves as a comprehensive resource for chemical information, enabling the identification of ligands using various identifiers or keywords. The canonical SMILES representations of the identified phenolic acids were retrieved from these databases for further analysis.

**Initial Compound Identification**

During the retrieval process, a total of 147 compounds were identified as potential phenolic acid metabolites. These compounds were chosen for their importance to the study and their established biological effects. The SMILES representations of these compounds were recorded to facilitate subsequent computational analyses [6].

**Duplicate Removal and Data Quality Control**

To ensure the accuracy of the dataset, duplicate entries were excluded from the initial list of compounds. After filtering, 74 distinct compounds were selected for further analysis. This selection guarantees that only relevant and distinct ligands are considered for subsequent docking studies, ensuring the integrity of the computational evaluation.

**Pharmacology Studies**

ADME stands for Absorption, Distribution, Metabolism, and Excretion, which are key pharmacokinetic properties that describe how a compound is absorbed, distributed, metabolized, and excreted by the body (http://www.swissadme.ch). ADME studies are essential for understanding the behavior of drug compounds in living organisms, providing insights into their effectiveness, safety, and bioavailability. In this study, the canonical SMILES representations of the identified phenolic acid ligands were retrieved and analyzed. The SwissADME tool was used to assess various properties, including physical and chemical characteristics, pharmacokinetics, drug-likeness, and suitability for medicinal chemistry. The compound screening was based on established criteria, including Lipinski's rule of five, gastrointestinal (GI) absorption, bioavailability, PAINS (Pan Assay Interference Compounds), and BRENK's rules [7]. These criteria help ensure that only compounds with favorable pharmacokinetic profiles are considered for further evaluation. After applying these filters, a total of 16 ligands remained for further analysis. This refined selection ensures that the compounds chosen for subsequent computational and experimental studies possess promising pharmacokinetic properties and drug-likeness.

**Protein Purification and Validation**

Protein purification is an essential process for maintaining the stability, solubility, and functional activity of proteins in drug discovery. The BIOVIA Discovery Studio is used to refine the protein structure by eliminating non-structural water molecules and extraneous heteroatoms that could disrupt further analysis. Furthermore, polar groups are introduced into the protein structure to improve its solubility, stability, and interaction capabilities. These enhancements optimize the protein's capacity to bind with potential ligands and aid in its purification, rendering it appropriate for applications in drug development [8].

**Protein Validation Using SAVES Tool**

After protein purification, the structure is validated using the SAVES Tool (saves.mbi.ucla.edu), a comprehensive online platform that incorporates five different programs for assessing protein quality. One of the primary validation techniques is ERRAT, which examines non-bonded interactions between various atom types within the protein. ERRAT produces a quality factor by comparing the protein's structural data to that of well-refined experimental structures, helping to identify any discrepancies or structural inaccuracies that could impact the protein's functional integrity. Another key validation method is PROCHECK, which assesses the stereochemical quality of the protein. PROCHECK employs the Ramachandran plot to analyze the distribution of the protein's amino acid residues based on their phi ($\phi$) and psi ($\psi$) dihedral angles. This plot classifies residues into favorable, allowed, or unfavorable regions. A high percentage of residues in the favorable region suggests a structurally stable

protein, while a significant presence in the unfavorable region may indicate potential errors in protein folding. This evaluation is crucial for confirming the accuracy and reliability of the protein structure prior to further analysis [9].

## MOLECULAR DOCKING

Molecular docking is a computer-based technique used to predict how ligands interact with their target receptor proteins, playing an essential role in the drug discovery process. In this study, molecular docking was performed using PyRx, a virtual screening tool designed for computational drug discovery. The goal was to predict how ligands bind to the target proteins NF-κB (PDB ID: 1NFK) and NEMO (PDB ID: 3RZO), as well as their binding strengths [10].

### Protein and Ligand Preparation

Initially, the structures of both the ligands and receptors underwent energy minimization to optimize their geometries and achieve stable configurations. This energy minimization process involves modifying the structures to reduce steric clashes and unfavorable interactions. Subsequently, both the ligands and receptors were converted into PDBQT format, which contains essential information, such as atomic charges and torsion angles. This format is crucial for docking simulations, as it allows for an accurate representation of ligand flexibility and interaction characteristics [11].

### Docking Setup

A grid was established around the active sites of the target proteins to ensure that the docking calculations focus on the relevant areas where ligand binding is most likely to occur. The grid centers and dimensions were meticulously defined for each protein: for NF-κB, the grid center was located at coordinates (X: 43.5987, Y: 53.4952, Z: 111.2940), and for NEMO, the coordinates were (X: 116.5429, Y: 109.0226, Z: 130.1605). These grid parameters are essential for precisely simulating how the ligands interact with the receptor proteins [12–16].

### Docking Simulation

Docking was conducted using AutoDock Vina, a popular molecular docking software recognized for its precision and efficiency. AutoDock Vina produces multiple conformations of the ligand within the receptor's active site, simulating various potential binding modes. For each ligand, nine different conformations were generated, providing a range of binding poses to investigate.

### Analysis of Docking Results

The docking results were assessed based on Root Mean Square Deviation (RMSD) and binding strength. RMSD quantifies the difference between the predicted binding poses and the reference structure, with lower values signifying a closer alignment of the ligand within the receptor's binding site. Binding affinity, measured in kcal/mol, reflects the strength of the interaction between the ligand and the receptor, with more negative values indicating stronger binding interactions.

### Post Molecular Docking

After docking, BIOVIA Discovery Studio was used to analyze the interactions between the ligands and their target proteins. The ligands with the strongest binding affinities from the docking studies were further examined for their molecular interactions within the protein's binding pocket. This process involved identifying the specific amino acid residues that participate in ligand binding and examining the nature, type, and length of these interactions. By visualizing the binding complex in both 2D and 3D, key interactions, such as hydrogen bonds, hydrophobic contacts, and electrostatic forces were evaluated. This comprehensive analysis provided insights into the stability of the ligand-protein complex, enhancing the understanding of the binding mechanisms and aiding in the selection of promising drug candidates for further development.

## RESULT

### Protein Retrieval

Protein retrieval is conducted by the RCSB PDB, and the data is provided in PDB format. Proteins can be obtained using various methods, including NMR spectroscopy, X-ray diffraction, and cryo-

electron microscopy. NF-kB B (PDB ID: 1NFI) and NEMO (PDB ID:3RZO) was obtained through the X-ray diffraction method.

**Protein Purification & Validation**

Protein purification is an essential step in molecular docking studies, ensuring that the protein is both pure and functionally active (Figure 1). The purification process includes several critical steps to prepare the protein for precise docking simulations:

**Elimination of Non-Structural Components**

- *Water Molecules:* Unnecessary water molecules that do not contribute to the protein's active site are removed.
- *Heteroatoms and Ligands:* Non-protein elements, such as metal ions and bound ligands that are not part of the protein's natural configuration, are also eliminated. These components can be addressed separately in docking simulations if needed.

**PRESERVATION OF THE A CHAIN**

**Removal of Extra Chains**

Proteins may contain additional chains due to crystallization artifacts. These extraneous chains are discarded, leaving only the biologically relevant. A chain for the docking study.

**Incorporation of Polar Hydrogen Atoms**

***Hydrogen Addition***

Polar hydrogen atoms are computationally added to fill in any missing hydrogen atoms in polar groups (such as hydroxyl, amine, and carbonyl). This step is crucial for ensuring accurate hydrogen bonding during docking simulations, as hydrogen atoms significantly influence ligand binding and protein stability.

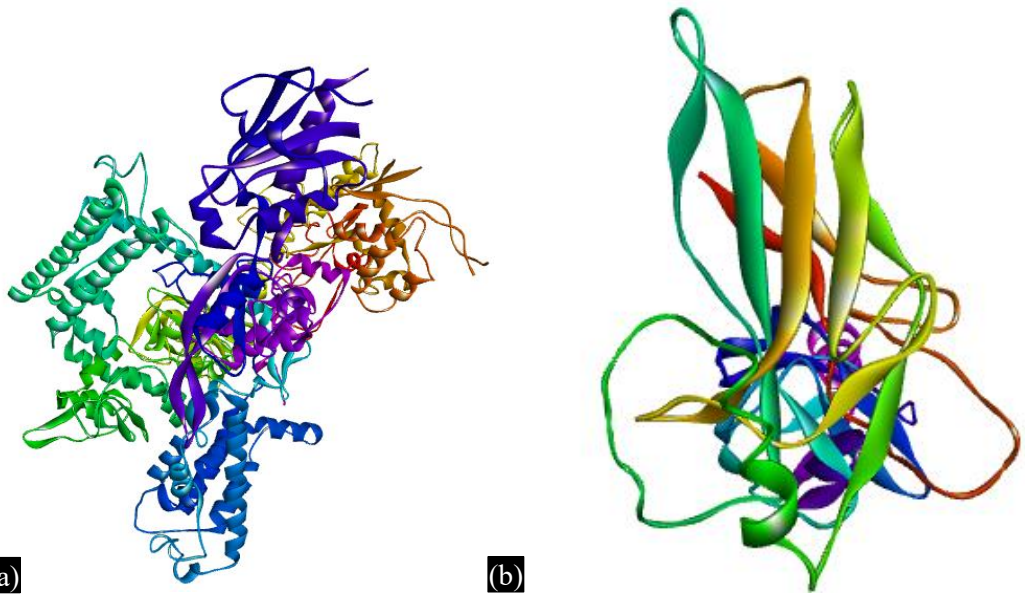



**Figure 1.** Purified structures of the target proteins (a) NF-kb B and (b) NEMO.

**THE RAMACHANDRAN PLOT ANALYSIS**

The Ramachandran plot serves as a graphical tool to illustrate the torsion angles (φ and ψ) of amino acid residues within a protein structure. It is instrumental in assessing the quality and stability of the protein by indicating which conformations are sterically permissible. This analysis is grounded in the principle that only certain combinations of these angles are energetically favorable for proper protein folding (Table 1, Figure 2).

**Regions of the Ramachandran Plot**

- *Most Favored Regions [A, B, L]:* These areas signify the angles that are frequently observed and energetically stable. A higher proportion of residues in these regions suggests a more reliable and stable protein structure.
- *Additional Allowed Regions [A, B, L, P]:* These sections denote conformations that, while less favored, remain permissible. Although they are not as optimal as the most favored regions, they still indicate stable structures.
- *Generously Allowed Regions [A, B, L, P]:* These regions represent conformations that are somewhat less favorable but still energetically viable. They may indicate potential strain or less common folding patterns.
- *Disallowed Regions:* This area corresponds to conformations that are energetically unfavorable, typically signifying issues with the protein's folding process.

NF-kB B has 73.5% of its residues positioned in the most favored regions, indicating a strong likelihood of a stable protein structure. Additionally, while there is a minor presence of 0.8% of residues in disallowed regions, the overall absence of significant numbers in these areas further underscores the quality of the model [17–19]. NEMO displays a strong structural integrity, with 83.6% of its residues situated in the most favored regions. Notably, there are 1.0% residues found in disallowed regions, which still supports the overall reliability of this protein model as shown in Figure 2.

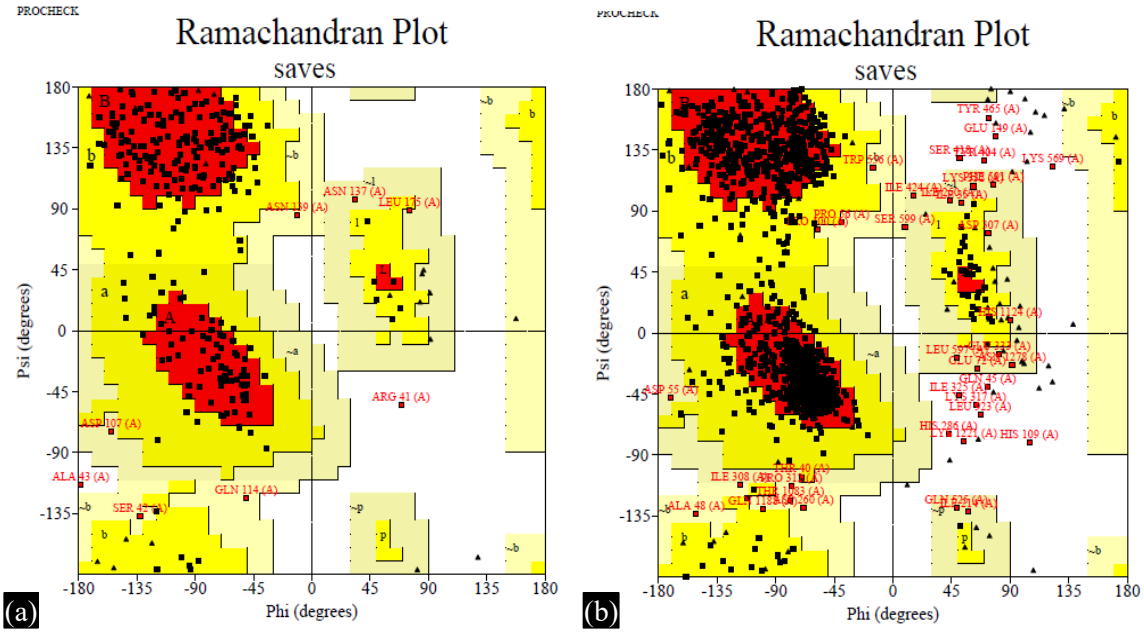



**Figure 2.** Ramachandran plots for (a) NF-kb B and (b) NEMO.

**Secondary Structure Prediction**

Secondary structure prediction focuses on identifying the local folding patterns of proteins, such as alpha helices, beta strands, and random coils. These structural elements are essential for understanding protein functionality and potential interactions with ligands. The graphical representations for NF-kB and NEMO can be found in Figure 3.

- *Alpha Helix (Hh):* This is a right-handed helical structure characterized by hydrogen bonds forming between every fourth amino acid. Alpha helices are crucial for the stability and functionality of proteins.
- *Extended Strand (Ee):* Beta strands that contribute to beta sheets, providing structural integrity and often playing a role in protein-protein interactions.
- *Random Coil (Cc):* These are flexible regions lacking a defined secondary structure, typically involved in protein flexibility or functional interactions.

NF-kB is primarily made up of 58.98% random coils, suggesting a degree of flexibility and potential areas for functional interactions. Additionally, the protein includes 11.86% alpha helices and 29.15% extended strands, both of which enhance its structural integrity. NEMO's secondary structure is primarily characterized by 41.78% alpha helices, indicating a more organized and potentially stable protein. Furthermore, it contains 12.95% extended strands and 45.27% random coils, reflecting a balance between structural elements and flexible regions.

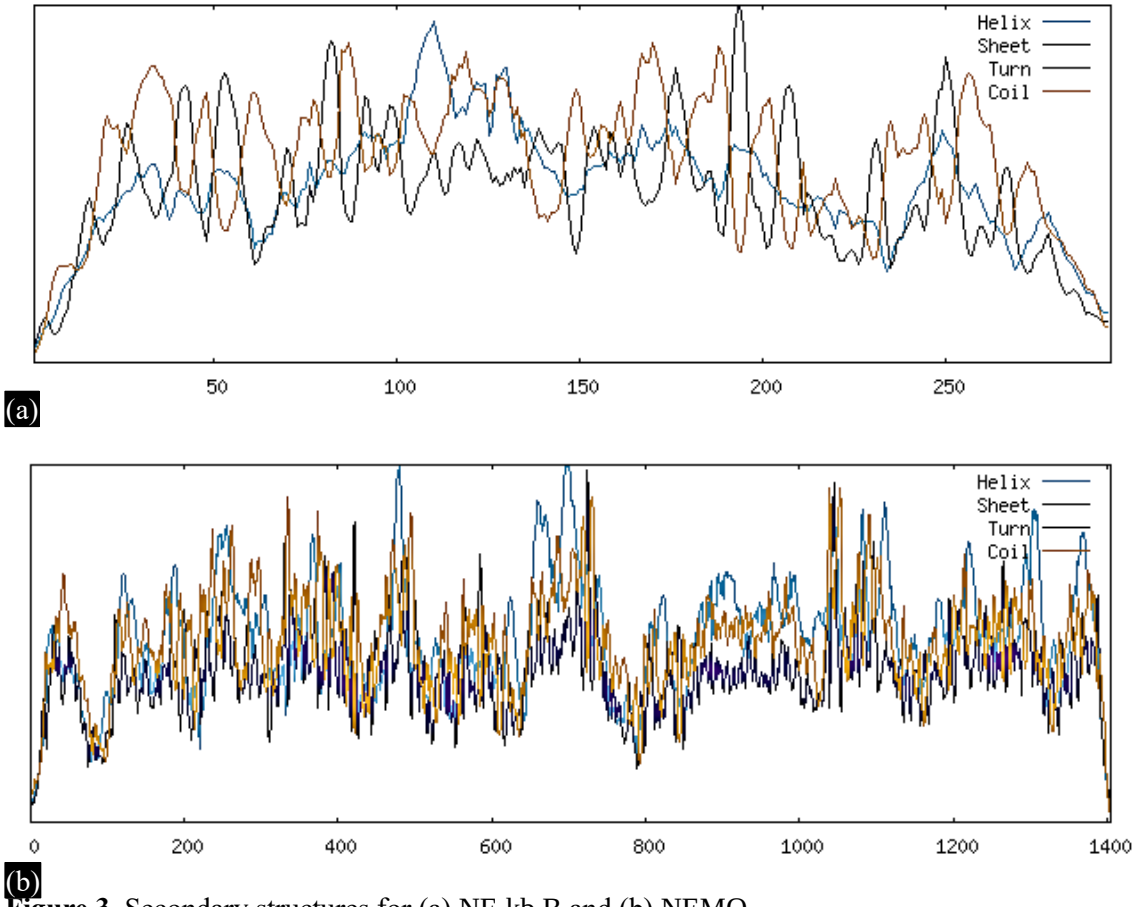



**Figure 3.** Secondary structures for (a) NF-kb B and (b) NEMO.

**ERRAT Structure Validation**

ERRAT is a software tool designed to evaluate the quality of protein models by analyzing the high-resolution environment surrounding each amino acid in the structure. The ERRAT score provides insights into the realism and accuracy of a predicted structure by comparing it to established high-resolution experimental structures.

A higher ERRAT score indicates better model quality and fewer structural problems, with scores above 80 generally regarded as acceptable for high-quality protein models (Table 1).

- NF-kB has an ERRAT score of 74.386, which is still acceptable but slightly lower than NEMO. This suggests that while the model is reasonably accurate, there may be some areas that need refinement or have slightly less optimal residue environments.
- NEMO has a score of 82.2917, indicating a strong model quality that suggests well-placed residues and minimal structural issues. This score reflects a reliable protein structure, although there may still be some areas for potential improvement [20, 21].

**Pharmacolgy Studies**

It is conducted to determine physiochemical characteristics, and an ADME (Absorption, Distribution, Metabolism, and Excretion) analysis is carried out to evaluate the ligands pharmacokinetic profiles. The

SwissADME tool offers free access to various parameters and predictive models. A few criteria, including Lipinski, GI Absorption, Bioavailability, PAINS (Pan Assay Interference Compounds), and BRENK. There were only 16 ligands remaining after following the procedure.

**Table 1.** Statistical validation analysis of structural protein.

| S.N. | Protein | RC Plot | Errat | 2D Structure |
|---|---|---|---|---|
| 1 | NF-kb B | Most favoured regions: 183 (73.5%) Additional allowed regions: 58 (23.3%) Generously allowed regions: 6 (2.4%) Disallowed regions: 2 (0.8%) | 74.386 | Alpha helix (Hh): 35(11.86%) Extended strand (Ee): 86 (29.15%) Random coil (Cc): 174 (58.98%) |
| 2 | NEMO | Most favoured regions: 1033 (83.6%) Additional allowed regions: 169 (13.7%) Generously allowed regions: 22 (1.8%) Disallowed regions: 12 (1.0%) | 82.2917 | Alpha helix (Hh): 587 (41.78%) Extended strand (Ee): 182(12.95%) Random coil (Cc): 636(45.27%) |

**Physicochemical Properties**

The physical and chemical properties of compounds are crucial for determining their potential as drug candidates. These properties significantly influence the ADME (Absorption, Distribution, Metabolism, and Excretion) processes and are critical for evaluating a compound's therapeutic potential. Key factors that help predict a compound's drug-like behavior include molecular weight (M.W.), the fraction of $sp^3$ hybridized carbons ($Csp^3$), topological polar surface area (TPSA), solubility, lipophilicity (log P), and the counts of hydrogen bond donors and acceptors. Molecular weight affects a compound's absorption and distribution within the body, while the fraction of $sp^3$ carbons indicates the compound's flexibility, which can influence its interactions with biological targets. TPSA is crucial for determining a molecule's ability to traverse biological membranes and engage with receptors. Solubility plays a vital role in absorption, whereas lipophilicity (log P) indicates how readily the compound can pass through lipid membranes. The presence of hydrogen bond donors and acceptors is important for interactions with proteins and other macromolecules in the body.

Table 2 presents the physicochemical properties of five selected ligands for NF-κB and NEMO, which are crucial for evaluating their drug-like characteristics. The molecular weight values range from 138.12 to 225.2 g/mol, indicating the size of the molecules. The fraction of sp3 hybridized carbons (Csp3) varies between 0 and 0.22, reflecting the flexibility and structural complexity of the compounds. The topological polar surface area (TPSA) values range from 57.53 to 97.99 $Å^2$, influencing the compounds' ability to cross biological membranes. Lipophilicity (Mlog P) values range from -0.16 to 0.99, suggesting the compounds' varying affinities for lipid and aqueous environments. All the ligands are expected to be soluble, suggesting they have good properties for absorption and bioavailability. These properties collectively guide the potential of these ligands as viable drug candidates.

**Table 2.** Physiochemical properties of the phenolic compounds (NF-kb protein).

| Ligand Name | Molecular Weight | Fraction Csp3 | TPSA | Lipophilicity MLOGP | Solubility (silico IT) |
|---|---|---|---|---|---|
| Vanilloylglycine | 225.2 | 0.2 | 95.86 | 0.04 | Soluble |
| 2,4,6-Trihydroxybenzoic acid | 170.12 | 0 | 97.99 | -0.16 | Soluble |
| 4-Methoxysalicylic acid | 168.15 | 0.12 | 66.76 | 0.74 | Soluble |
| Syringic acid | 198.17 | 0.22 | 75.99 | 0.49 | Soluble |
| 3-Hydroxybenzoic acid | 138.12 | 0 | 57.53 | 0.99 | Soluble |

Table 3 presents the physicochemical properties of five ligands relevant to the NF-κB and NEMO proteins. The molecular weights range from 138.12 to 225.2 g/mol, indicating variability in size. The fraction of sp3 hybridized carbons (Csp3) varies from 0 to 0.22, which influences the flexibility of the compounds. TPSA values range from 37.3 to 95.86 Å², which are important for predicting the compounds' permeability across biological membranes. The lipophilicity (Mlog P) values, spanning from 0.04 to 2.25, suggest how well these compounds can interact with lipid environments. All ligands are predicted to be soluble, indicating favorable absorption properties.

**Table 3.** Physiochemical properties of the phenolic compounds (NEMO protein).

| Ligand Name | Molecular Weight | Fraction Csp3 | TPSA | Lipophilicity MLOGP | Solubility (silico IT) |
|---|---|---|---|---|---|
| Hippuric acid | 179.17 | 0.11 | 66.4 | 0.84 | Soluble |
| Vanilloylglycine | 225.2 | 0.2 | 95.86 | 0.04 | Soluble |
| 4-Hydroxybenzoic acid | 138.12 | 0 | 57.53 | 0.99 | Soluble |
| 4-Ethylbenzoic acid | 150.17 | 0.22 | 37.3 | 2.25 | Soluble |
| Syringic acid | 198.17 | 0.22 | 75.99 | 0.49 | Soluble |

## THE LIPINSKI RULE

Lipinski's Rule of Five is a set of guidelines used to assess whether a compound has drug-like properties, based on its physical and chemical characteristics. According to this rule, a compound is considered a potential oral drug if it satisfies the following conditions:

- Molecular weight ≤ 500 Da.
- No more than 5 hydrogen bond donors.
- No more than 10 hydrogen bond acceptors.
- LogP (lipophilicity)

These guidelines are useful for assessing a compound's absorption, distribution, and bioavailability. If a compound meets most or all of these criteria, it is likely to be effective as an oral drug. SwissADME incorporates this rule in its ADME/Tox screening process, offering insights into the drug-likeness and pharmacokinetic properties of compounds, thereby assisting in the identification of promising drug candidates.

## Pharmacokinetic Properties

Pharmacokinetic properties describe how a drug interacts with the body, encompassing its absorption, distribution, metabolism, and excretion (ADME). Understanding these properties is vital for evaluating a compound's effectiveness, safety, and bioavailability. The following key parameters are essential in assessing the pharmacokinetic profile of a compound:

- *Gastrointestinal (GI) Absorption:* This refers to a compound's ability to be absorbed into the bloodstream following oral administration. High GI absorption is crucial for oral medications, indicating effective absorption from the digestive system.
- *Blood-Brain Barrier (BBB) Penetration:* This assesses whether a compound can pass through the blood-brain barrier to reach the brain. BBB penetration is significant for drugs targeting the central nervous system (CNS), but compounds that can cross this barrier may also lead to additional neurological side effects.
- *Bioavailability:* Bioavailability refers to the portion of a drug or substance taken by mouth that actually enters the bloodstream in its active form and can have an effect on the body. Higher bioavailability typically suggests a more efficient drug with enhanced therapeutic potential.
- *PAINS (Pan Assay Interference Compounds):* PAINS are compounds that frequently yield false positives in bioassays due to their tendency to interfere with testing systems. A PAINS score of 0 indicates a lower likelihood of causing assay interference.
- *Brenk's Rules:* This parameter assesses whether a compound violates established chemical principles related to toxicity or problematic structural features. A score of 0 signifies that the compound adheres to Brenk's rules, suggesting a safer chemical profile.

Table 4 presents the physicochemical properties of five ligands that are potential candidates for targeting the NF-kB protein, which is significant in various therapeutic contexts. The molecular weight of these ligands ranges from 168.15 to 225.2 g/mol, indicating a moderate size that is generally favorable for drug-like characteristics. The number of hydrogen bond acceptors varies from 3 to 5, while the number of hydrogen bond donors ranges from 2 to 4. These values are crucial as they influence the ligands' interactions with biological targets and their solubility in biological systems. The lipophilicity, measured as MlogP, shows a range from –0.16 to 0.99, suggesting that some ligands are more hydrophilic while others exhibit a higher affinity for lipid environments. All ligands are characterized by high gastrointestinal absorption, which is a positive indicator for their potential oral bioavailability. Notably, none of the ligands are predicted to cross the blood-brain barrier (BBB), which may limit their central nervous system effects but could be advantageous for targeting peripheral sites. The bioavailability values range from 0.56 to 0.85, indicating a good potential for systemic circulation after administration. Additionally, none of the ligands exhibit PAINS (pan-assay interference compounds) or BRENK (BRENK's rule of five) alerts, suggesting that they are less likely to produce false positives in biological assays and may possess a lower risk of undesirable side effects. Overall, these properties collectively suggest that these ligands have favorable characteristics for further development as drug candidates targeting the NF-kB protein, with considerations for their pharmacokinetic profiles and potential therapeutic applications.

**Table 4.** Data for the properties of lipinski rule & pharmacokinetics profile and medical chemistry (NF-kb protein).

| Ligand Name | Molecular Weight | H-Bonds Acceptor | H-Bonds Donor | Lipoph-ilicity (MlogP) | GI absor-btion | BBB | Bioavailability | Pains | Brenks |
|---|---|---|---|---|---|---|---|---|---|
| Vanilloylglycine | 225.2 | 5 | 3 | 0.04 | High | No | 0.56 | 0 | 0 |
| 2,4,6-Trihydroxybenzoic acid | 170.12 | 5 | 4 | –0.16 | High | No | 0.56 | 0 | 0 |
| 4.Methoxysalicylic acid | 168.15 | 4 | 2 | 0.74 | High | No | 0.85 | 0 | 0 |

Table 5 outlines the physicochemical properties of five ligands in relation to their potential interaction with the NF-kB protein. The molecular weights of these ligands range from 138.12 to 225.2 g/mol, reflecting a moderate variability in size that is generally favorable for drug-like characteristics. The number of hydrogen bond acceptors varies from 2 to 5, while the number of hydrogen bond donors ranges from 1 to 3. These parameters are critical as they influence the ligands' ability to form interactions with biological targets and their overall solubility in aqueous environments. The lipophilicity, measured as MlogP, shows a range from 0.04 to 2.25, indicating that some ligands are more hydrophilic while others exhibit a higher affinity for lipid environments, which can affect their absorption and distribution. All ligands show high absorption in the gastrointestinal tract, indicating they have good potential for oral bioavailability. However, only some ligands are predicted to cross the blood-brain barrier (BBB), which may limit their central nervous system effects but could be advantageous for targeting peripheral sites. The bioavailability values range from 0.56 to 0.85, indicating a good potential for systemic circulation after administration. Importantly, none of the ligands exhibit PAINS (pan-assay interference compounds) or BRENK (BRENK's rule of five) alerts, suggesting that they are less likely to produce false positives in biological assays and may possess a lower risk of undesirable side effects. Overall, these properties collectively suggest that these ligands have favorable characteristics for further development as drug candidates targeting the NF-kB protein, with considerations for their pharmacokinetic profiles and potential therapeutic applications.

**Molecular Docking**

Its goal is to determine how well a drug (ligand) matches a protein target. IT undergoes few steps like proteins are loaded, energy minimization. it is used for the stability of protein and ligand interaction,

convert from pdb to pdbqt which includes Torison's angles (rotation) and Kollman charges (neutrilizing). In order to create a grid or box that prevents atoms from misplacing. To prevent the atoms misplacing Grid/Box is generated (Table 6).

**Table 5.** Data for the properties of lipinski rule & pharmacokinetics profile and medical chemistry (NEMO protein).

| Ligand Name | Molecular Weight | H-Bonds Acceptor | H-Bonds Donor | Lipoph-ilicity (MlogP) | GI absor-btion | BBB | Bioavailability | Pains | Brenks |
|---|---|---|---|---|---|---|---|---|---|
| Hippuric acid | 179.17 | 3 | 2 | 0.84 | High | No | 0.85 | 0 | 0 |
| Vanilloylglycine | 225.2 | 5 | 3 | 0.04 | High | No | 0.56 | 0 | 0 |
| 4-Hydroxybenzoic acid | 138.12 | 3 | 2 | 0.99 | High | Yes | 0.85 | 0 | 0 |
| 4-Ethylbenzoic Acid | 150.17 | 2 | 1 | 2.25 | High | Yes | 0.85 | 0 | 0 |
| Syringic acid | 198.17 | 5 | 2 | 0.49 | High | No | 0.56 | 0 | 0 |

**Table 6.** Grid dimension in angstrom (Å) for docking.

| Protein | Grid Dimension | | |
|---|---|---|---|
| | ***X Axis*** | ***Y Axis*** | ***Z Axis*** |
| NF-kb B | X:43.5987 | Y:53.4952 | Z:111.2940 |
| NEMO | X:116.5429 | Y:109.0226 | Z:130.1605 |

The docking process generated nine unique conformations for each ligand, which were then screened and filtered using a Root Mean Square Deviation (RMSD) threshold of 0. RMSD values indicate how much the protein's backbone dihedral angles (phi and psi) deviate from their optimal conformations, with lower values signifying improved structural alignment and stability. The conformations exhibiting the highest binding affinity are presented.

Binding affinity refers to how strongly a drug molecule (or ligand) attaches to its target protein. In docking studies, binding affinity is usually expressed as a negative value (in kcal/mol), with a more negative number indicating stronger binding. For instance, a ligand with a binding affinity of –9 kcal/mol will bind more tightly to the protein than one with a binding affinity of –6 kcal/mol.

The negative value arises because the binding energy of a ligand-protein complex is generally lower than the sum of the energies of the individual components. A more negative binding affinity indicates a more stable interaction between the ligand and protein, making it less likely for them to dissociate. In drug discovery, high binding affinity often correlates with the potential effectiveness of the ligand as a binder, which can enhance its therapeutic potential. Consequently, ligands with higher negative binding affinities are frequently prioritized as promising drug candidates.

- Vanilloylglycine shows a binding affinity of -6.1 kcal/mol with NF-kb B, indicating strong binding.
- Hippuric acid shows a binding affinity of -6.2 kcal/mol with NF-kb B, indicating strong binding.

**Post-Molecular Docking Analysis**

Post-molecular analysis is conducted with BIOVIA Discovery Studio, a tool for data analysis and molecular modeling in various scientific fields. Proteins and ligands are loaded to identify their interactions, with distinct colors assigned to the A chain, ligand, and amino acids. Both 2D and 3D structures are then downloaded (Figures 4 and 5), and the bonds and of each amino acid are analyzed as shown in Table 7.

**Table 7.** Binding affinity data obtained from PyRx.

| Ligand Name | PubChem CID | Binding Affinity |
|---|---|---|
| ***Protein*** | ***NF-kb B (PDB ID:1NFI)*** | |
| Vanilloylglycine | 3083688 | –6.1 |
| 2,4,6-Trihydroxybenzoic acid | 66520 | –5.9 |
| Syringic acid | 75231 | –5.9 |
| ***Protein*** | ***NEMO (PDB ID:3RZO)*** | |
| Hippuric acid | 464 | –6.2 |
| Vanilloylglycine | 3083688 | –6.2 |
| 4-Hydroxybenzoic acid | 135 | –6.1 |

### Types of Interactions Observed

- *Electrostatic Interactions:* These interactions occur between atoms with opposite charges, such as between Aspartic acid (ASP277) and the ligand (UNK1). Electrostatic bonds are long-range interactions that assist in properly positioning the ligand within the active site. They also play a significant role in the initial binding of the ligand to the protein, thereby increasing the specificity of the interaction.
- *Hydrogen Bonds:* These interactions occur when a hydrogen atom, attached to an electronegative atom like oxygen or nitrogen, is drawn to another electronegative atom.
- For example, the hydrogen bond between Asparagine (ASN137) and (UNK1:O) is crucial for stabilizing the ligand within the protein's binding pocket. Hydrogen bonds are vital for maintaining the correct orientation of the ligand and ensuring the specificity of the interaction.
- *Hydrophobic Interactions:* These interactions take place between the nonpolar residues of the ligand and the protein. Hydrophobic regions, such as ARG73 or PRO177, to favor interactions with one another rather than with water molecules. These interactions contribute to the stability of the ligand-protein complex by reducing the exposure of nonpolar surfaces to the surrounding aqueous environment, thereby strengthening the binding.

### Visualization and Analysis

By visualizing these interactions, one can analyze the distances between interacting atoms and categorize each type of bond. The reported binding distances ranging from 1.9 to 3.7 Å for hydrogen bonds, 3.6 to 5.4 Å for hydrophobic interactions, and 4.4 Å for electrostatic interactions—demonstrate the close proximity and strength of these interactions. This comprehensive visualization aids in identifying the most stable binding poses and enhances the understanding of how ligands interact with the target protein.

For instance, the ligand UNK1 engages in several hydrophobic interactions with PRO177, TYR1365, and other hydrophobic residues. Additionally, it establishes electrostatic bonds with ASP277 and hydrogen bonds with ASN137 and LEU175, suggesting a stable and well-optimized binding configuration.

Molecular visualization offers essential insights into binding affinity, binding mode, and the types of interactions that enhance the ligand's stability within the active site. It aids in identifying potential drug candidates by demonstrating how effectively a ligand fits into the protein's binding pocket and the strength of its interactions. Additionally, these visualizations inform the optimization of ligands to enhance binding affinity, specificity, and overall drug-like characteristics (Tables 8 and 9).

## DISCUSSION

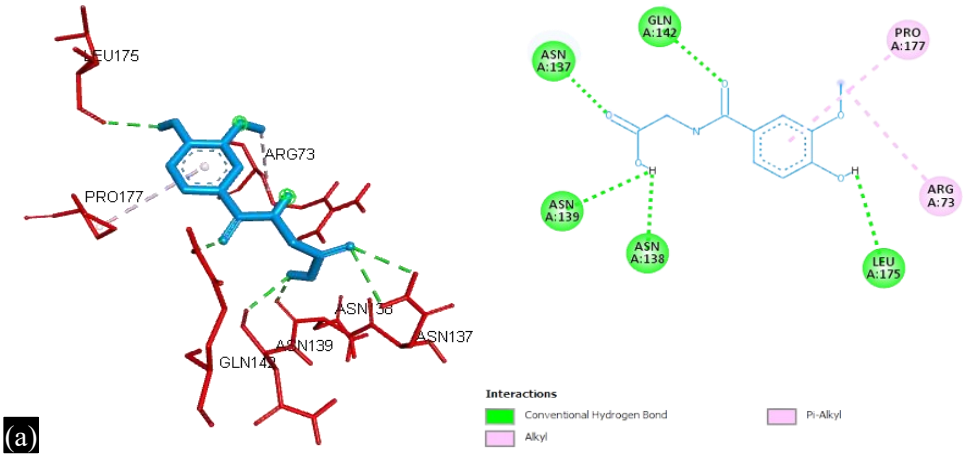
The NF-κB signaling pathway is a critical regulator of inflammation and fibrosis, playing a significant role in various chronic diseases, including cystic fibrosis. The ongoing activation of this pathway leads to the attraction of immune cells and the release of inflammatory signals, which worsen tissue damage and scar tissue formation. Due to the limitations of existing treatments, there is an urgent

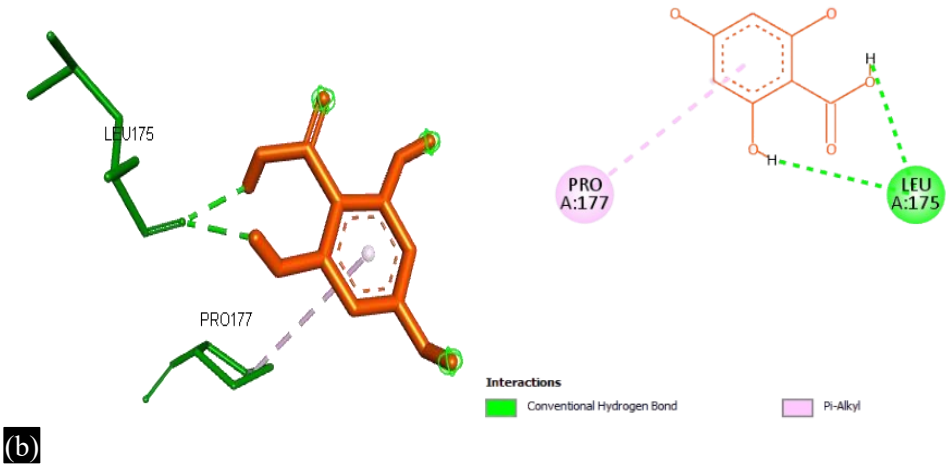
 

need for new strategies that can effectively target the NF-κB pathway. This study explored the potential of phenolic acids as modulators of NF-κB and NEMO, utilizing a computational approach to identify promising candidates for therapeutic development.

**Table 8.** The non-bond interaction for the target proteins (NF-kb B) and top ligands.

| Ligand | Name | Distance | Category |
|---|---|---|---|
| **3083688(-6.1)** | A:ASN137:HD21 – N:UNK1:O | 2.80543 | Hydrogen bond |
| | A:ASN137:HD22 – N:UNK1:O | 2.7549 | Hydrogen bond |
| | A:GLN142:HE21 – N:UNK1:O | 2.19817 | Hydrogen bond |
| | N:UNK1:H – A:ASN138:O | 2.38229 | Hydrogen bond |
| | N:UNK1:H – A:ASN139:O | 2.55539 | Hydrogen bond |
| | N:UNK1:H – A:LEU175:O | 2.67722 | Hydrogen bond |
| | N:UNK1:C – A:ARG73 | 4.54282 | Hydrophobic |
| | N:UNK1 – A:PRO177 | 5.24257 | Hydrophobic |
| **66520(–5.9)** | N:UNK1:H – A:LEU175:O | 2.3222 | Hydrogen bond |
| | N:UNK1:H – A:LEU175:O | 2.34289 | Hydrogen bond |
| | N:UNK1 – A:PRO177 | 5.00532 | Hydrophobic |
| **75231(–5.9)** | A:ARG30:HE – N:UNK1:O | 2.29794 | Hydrogen bond |
| | A:ARG30:HH21 – N:UNK1:O | 2.69502 | Hydrogen bond |
| | A:ASN190:HD21 - N:UNK1:O | 2.00742 | Hydrogen bond |
| | N:UNK1:C - A:ASN186:O | 3.59385 | Hydrogen bond |
| | N:UNK1:C – A:ARG187:O | 3.54918 | Hydrogen bond |
| | A:ASP277:OD2 – N:UNK1 | 4.49926 | Electrostatic |



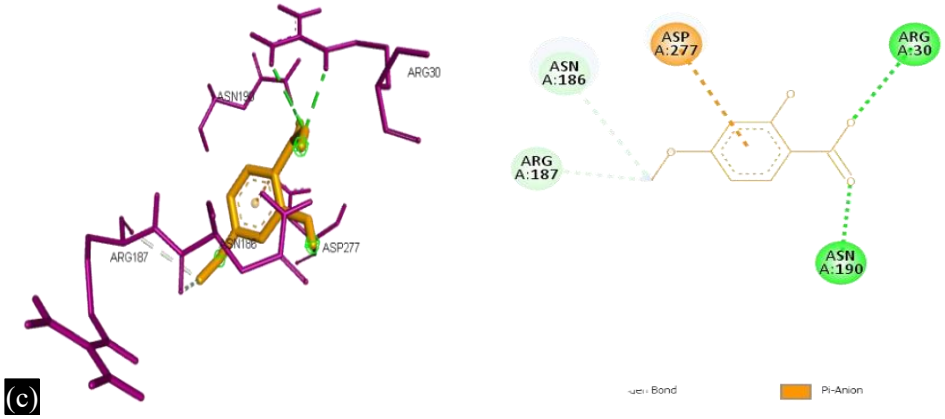



**Figure 4.** Top 3 ligands interacting with Nuclear factor-kappa B protein and its 3D, 2D interaction (a) 3083688:- Receptor protein (Red), Ligand (Blue); (b) 66520:- *Receptor protein (Green), Ligand (Orange);(c) 75231:- Receptor protein(Violet), Ligand (Golden)*.

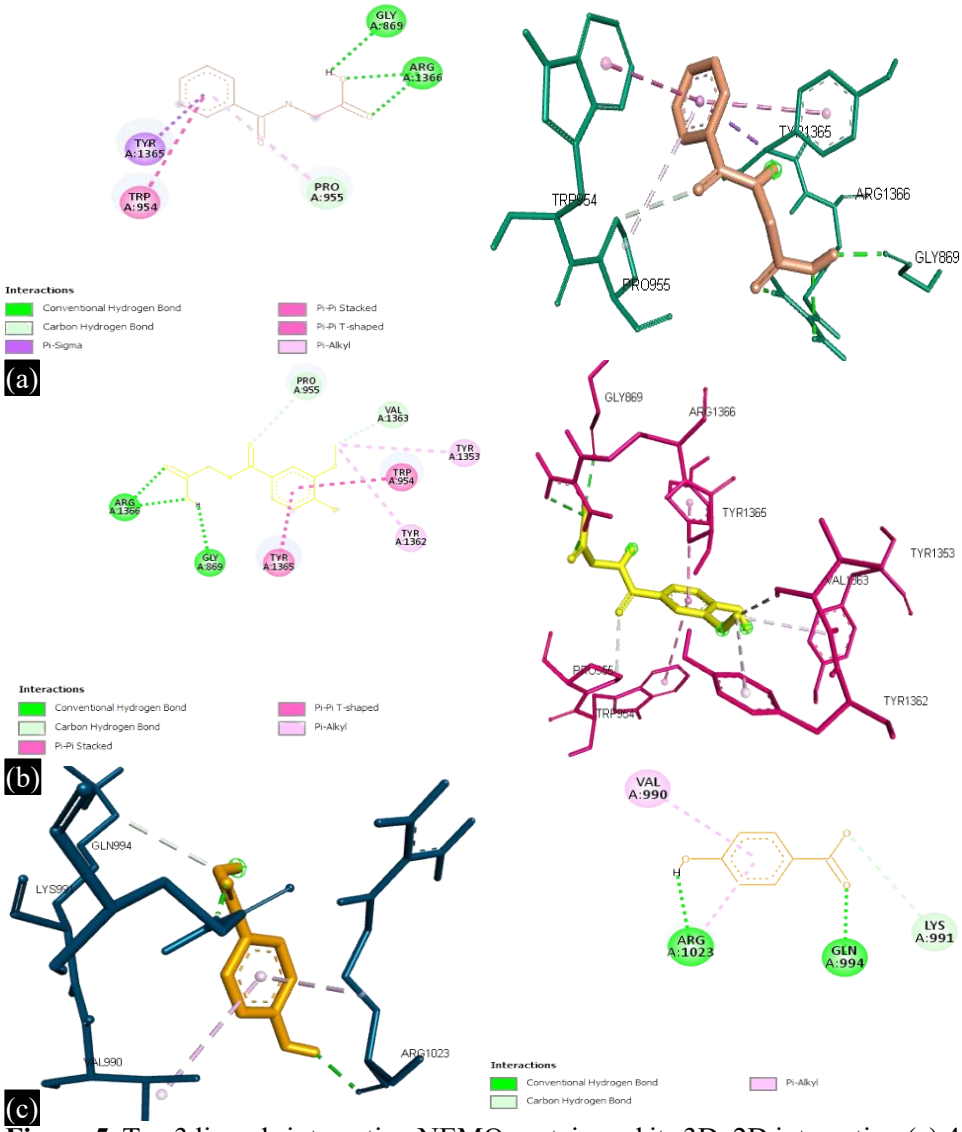



**Figure 5.** Top 3 ligands interacting NEMO protein and its 3D ,2D interaction (a) 464:- Receptor protein (Teal), Ligand (Cream); (b)3083688:- Receptor protein (Pink), Ligand (Yellow); (c)135:- Receptor protein), Ligand (Golden).

**Table 9.** The non-bond interaction for the target proteins (NEMO) and top ligands.

| Ligand | Name | Distance | Category |
|---|---|---|---|
| 464(–6.2) | A:ARG1366:HH12 – N:UNK1:O | 2.06922 | Hydrogen bond |
| | A:ARG1366:HH22 – N:UNK1:O | 2.47836 | Hydrogen bond |
| | N:UNK1:H – A:GLY869:O | 2.23061 | Hydrogen bond |
| | A:PRO955:CD – N:UNK1:O | 3.43527 | Hydrogen bond |
| | A:TYR1365:CB – N:UNK1 | 3.65857 | Hydrophobic |
| | A:TYR1365 – N:UNK1 | 5.16796 | Hydrophobic |
| | A:TRP954 – N:UNK1 | 4.76551 | Hydrophobic |
| | N:UNK1 – A:PRO955 | 5.47519 | Hydrophobic |
| 3083688(–6.2) | A:ARG1366:HH12 – N:UNK1:O | 1.96653 | Hydrogen bond |
| | A:ARG1366:HH22 – N:UNK1:O | 2.52399 | Hydrogen bond |
| | N:UNK1:H – A:GLY869:O | 2.36129 | Hydrogen bond |
| | A:PRO955:CD – N:UNK1:O | 3.34138 | Hydrogen bond |
| | N:UNK1:C – A:VAL1363:O | 3.79127 | Hydrogen bond |
| | A:TYR1365 – N:UNK1 | 4.67054 | Hydrophobic |
| | A:TRP954 – N:UNK1 | 4.76905 | Hydrophobic |
| | A:TYR1353 – N:UNK1:C | 5.45393 | Hydrophobic |
| | A:TYR1362 – N:UNK1:C | 4.8983 | Hydrophobic |
| 135(–6.1) | A:GLN994:HE22 – N:UNK1:O | 2.00782 | Hydrogen bond |
| | N:UNK1:H – A:ARG1023:O | 2.1925 | Hydrogen bond |
| | A:LYS991:CE – N:UNK1:O | 3.50622 | Hydrogen bond |
| | N:UNK1 – A:VAL990 | 5.20315 | Hydrophobic |
| | N:UNK1 – A:ARG1023 | 3.62604 | Hydrophobic |

Our molecular docking studies revealed that several phenolic acids, including Vanilloylglycine, Hippuric Acid, and 4-Hydroxybenzoic acid, exhibited strong binding affinities to NF-κB and NEMO, with binding energies ranging from –5.9 to –6.2 kcal/mol. These findings suggest that these compounds can effectively interact with key components of the NF-κB signaling cascade, potentially inhibiting its activation and downstream effects. The binding interactions were mainly driven by hydrogen bonds, hydrophobic forces, and electrical charges, all of which play a key role in stabilizing the ligand-protein complex. For instance, the presence of hydrogen bonds between the ligands and specific amino acid residues in the binding sites indicates a well-optimized fit, enhancing the likelihood of effective modulation of the NF-κB pathway.

The pharmacokinetic evaluation of the identified phenolic acids using the Swiss ADME tool demonstrated favorable properties, including compliance with Lipinski's Rule of Five, high gastrointestinal absorption, and good bioavailability. These characteristics are crucial for the development of oral therapeutics, as they indicate that the compounds are likely to be effectively absorbed and distributed within the body. The absence of PAINS and BRENK alerts in the evaluated compounds further supports their potential as safe and effective drug candidates, minimizing the risk of false positives in biological assays and potential toxicity.

The structural characteristics of the identified compounds also offer valuable clues about how they might work. For example, Vanilloylglycine contains functional groups that may facilitate hydrogen bonding with specific residues in the binding pocket of NF-κB and NEMO, enhancing its inhibitory effect. Similarly, the hydrophobic regions of these compounds suggest that they can interact with the hydrophobic areas of the proteins, contributing to the stabilization of the ligand-receptor complex. These structural characteristics are significant in optimizing the binding affinity and specificity of these compounds for their targets.

Our study highlights the importance of computational methods, such as molecular docking and pharmacological screening, in identifying potential drug candidates. These techniques allow researchers to predict the binding affinity of compounds for target proteins and screen vast compound libraries for promising candidates. By simulating ligand-receptor interactions, molecular docking helps to identify the most likely binding modes of compounds, which can be further optimized for higher potency and selectivity. This approach provides a more affordable and time-efficient alternative to traditional experimental methods, which tend to be resource-heavy.

Although the results are promising, our study has several limitations. While computational methods provide valuable insights, they are based on predictions that may not always align with real-world conditions. Experimental validation through in vitro and in vivo assays is necessary to confirm the efficacy of these compounds in modulating the NF-κB pathway and their potential therapeutic effects in chronic inflammatory diseases. Moreover, it's important to carefully assess any possible unintended side effects and the toxicity of these compounds before they can be considered safe for clinical use. In conclusion, this study underscores the potential of phenolic acids as therapeutic agents targeting the NF-κB signaling pathway to mitigate inflammation and fibrosis. The identification of novel compounds with favorable binding affinities and pharmacokinetic profiles opens new avenues for drug development in the context of chronic inflammatory diseases. Future research should focus on experimental validation, including in vitro assays to assess the anti-inflammatory effects of these compounds, as well as in vivo studies to evaluate their therapeutic potential in relevant disease models. By advancing our understanding of how these compounds interact with the NF-κB pathway, we can pave the way for the development of effective treatments for chronic inflammatory conditions.

## CONCLUSIONS

The present study highlights the therapeutic potential of phenolic acids as modulators of the NF-κB signaling pathway, offering a promising strategy to mitigate inflammation and fibrosis associated with chronic diseases, such as cystic fibrosis. By employing computational techniques, including molecular docking and pharmacological screening, we identified several compounds, such as Vanilloylglycine, Hippuric Acid, and 4-Hydroxybenzoic acid, which demonstrated strong binding affinities to key components of the NF-κB pathway. These compounds have the potential to disrupt the signaling cascade, thereby reducing pro-inflammatory cytokine production and tissue damage.

The favourable pharmacokinetic profiles of these phenolic acids, as indicated by their compliance with Lipinski's Rule of Five and high gastrointestinal absorption, further support their candidacy for therapeutic development. While the computational results are promising, it's crucial to conduct experimental tests in lab settings and living organisms to verify the effectiveness and safety of these compounds for use in clinical applications. Future research should focus on optimizing these phenolic acids for enhanced pharmacokinetic properties, assessing their biological activity in relevant disease models, and exploring their potential synergistic effects with existing anti-inflammatory therapies. The insights gained from this study lay the foundation for the development of novel therapeutic agents targeting the NF-κB pathway, contributing to improved management strategies for chronic inflammatory conditions.

## List of Abbreviations

| ***Abbreviation*** | ***Full Form*** |
|---|---|
| ADME | Absorption, distribution, metabolism, and excretion |
| BBB | Blood-brain barrier |
| BRENK | BRENK's rules |
| CF | Cystic fibrosis |
| ERRAT | Evaluation of the realism of 3D models |
| GI | Gastrointestinal |
| MLOGP | Lipophilicity (Log P) |

| | |
|---|---|
| NF-κB | Nuclear factor kappa-light-chain-enhancer of Activated B cells |
| NEMO | NF-κB essential modulator |
| PAINS | Pan assay interference compounds |
| PDB | Protein Data Bank |
| RMSD | Root mean square deviation |
| SMILES | Simplified molecular input line entry system |
| TPSA | Topological polar surface area |
| NMR | Nuclear magnetic resonance |
| RMSD | Root mean square deviation |

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