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Evaluation of Curcumin as NF-κB Inhibitor for Breast Cancer Therapy Using in Silico Approach

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ABSTRACT

Purpose of the study: This study aims to evaluate the potential of curcumin as a breast cancer therapeutic agent by analyzing its ability to inhibit NF-κB activation using an *in silico* approach, specifically through molecular docking to assess absorption and interaction with the target protein.

Methodology: This study used a quantitative experimental method with molecular docking as an *in silico* approach. Tools included a Lenovo laptop (Intel® Inside™, Windows 10 Pro). Software used: PyRx 0.8 (with AutoDock Vina), YASARA, PyMOL, and Discovery Studio 2019. Ligand data were obtained from PubChem; protein from Protein Data Bank. Lipinski's Rule was applied for drug-likeness screening.

Main Findings: Curcumin showed a binding affinity of -6.2 kcal/mol to NF-κB with RMSD < 2.00 Å. Visualization confirmed hydrogen bonds at ASN 32 and ASN 47, and hydrophobic pi-alkyl interactions at ALA 34 and ARG 50. Lipinski's Rule of Five was fulfilled, indicating good oral drug-likeness and potential as an NF-κB inhibitor in breast cancer therapy.

Novelty/Originality of this study: This study offers new insights into the potential of curcumin as a natural NF-κB inhibitor for breast cancer therapy through a comprehensive *in silico* approach. By combining molecular docking, visualization, and drug-likeness analysis, it advances current knowledge by highlighting curcumin's binding efficiency and pharmacological feasibility, supporting its development as an alternative anticancer candidate.

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1. INTRODUCTION

Cancer is one of the major global health issues, with increasing prevalence and mortality rates each year. This trend is observed across various regions of the world, including Indonesia. According to data from the *Global Burden of Cancer (GLOBOCAN)* released by the *World Health Organization (WHO)*, there are 14.87 cancer cases per 100,000 people globally, with a mortality rate of 9.38 per 100,000 and a five-year prevalence rate of 345.9 per 100,000 people [1], [2]. It is estimated that by 2030, the number of cancer-related deaths will continue to rise significantly [3], [4].

In general, cancer refers to a group of diseases characterized by the uncontrolled growth of abnormal cells, which can spread to other tissues in the body. Among the various types of cancer, breast cancer is the most

commonly diagnosed worldwide. According to GLOBOCAN 2020 data, breast cancer ranks first in terms of the highest number of cases and is the second leading cause of cancer-related deaths globally [1], [5].

Breast cancer is caused by the proliferation of abnormal cells in breast tissue that form a lump [6], [7]. Although the majority of cases occur in women, this type of cancer can also affect men [8], [9]. The exact cause of breast cancer remains unknown due to its multifactorial nature [10]-[12]. One important biological indicator involved in the cancer process is the activation of *Nuclear Factor Kappa Beta* (NF-κB) [13]. NF-κB activation is known to contribute to cell proliferation, inhibition of apoptosis, and various inflammatory responses [14]-[16]. NF-κB is a transcriptional protein that serves as a key regulator in inflammation, immune response, wound healing, and apoptosis [17]-[19]. Under normal conditions, NF-κB resides in the cytoplasm in an inactive form and becomes active upon release from its inhibitor complex [20]-[22].

Various studies have investigated compounds with the potential to inhibit NF-κB activation, one of which is curcumin. Curcumin, or diferuloylmethane, is the main bioactive compound found in *Curcuma longa*, a plant from the Zingiberaceae family [21]-[24]. Curcumin has long been recognized for its wide range of pharmacological activities, including anti-inflammatory, antioxidant, antimutagenic, anticarcinogenic, antidiabetic, and antiviral properties [25]-[27]. The therapeutic potential of curcumin in cancer treatment has been extensively studied, particularly regarding its role as an NF-κB inhibitory agent [28], [29].

However, curcumin exhibits low stability in the body, which necessitates various approaches to enhance its bioactivity. One of the emerging strategies is the use of *in silico* methods to design and evaluate compound interactions with molecular targets [30], [31]. *In silico* approaches are considered efficient as they can reduce the use of experimental animals, save time, and lower research costs [32], [33]. One technique widely used in this approach is *molecular docking*, which simulates the interaction between ligand molecules (active compounds) and receptors (target proteins) both visually and quantitatively [34], [35].

Molecular docking enables the analysis of a compound's affinity and orientation toward relevant target proteins. This technique is widely applied in modern biomedical research to identify and develop new drug candidates [36], [37]. The results of docking simulations can provide insight into the strength of molecular interactions and the potential of compounds to inhibit or activate specific biological targets.

Several previous studies have demonstrated the potential of curcumin as a therapeutic candidate for breast cancer through the inhibition of the Nuclear Factor Kappa Beta (NF-κB) signaling pathway. Farghadani and Naidu [38] highlighted that curcumin can disrupt multiple key signaling pathways—including NF-κB—in hormone-independent and triple-negative breast cancer (TNBC) subtypes, resulting in reduced proliferation, metastasis, and angiogenesis. Another study by Panda et al. [39] designed curcumin-derived hybrid compounds that exhibited higher affinity toward cancer-related target proteins, including NF-κB, while also improving the stability and biological activity of curcumin through molecular docking and in vitro assays. These findings reinforce the potential of curcumin as an NF-κB pathway inhibitor. However, most studies have focused on partial protein models (e.g., the p50 or p65 subunit individually), without comprehensively evaluating the interaction of curcumin with the complete NF-κB complex (p50/p65) in an integrated manner.

Furthermore, although several studies have developed curcumin derivatives or nanoparticle-based formulations to improve its stability, in silico investigations into the pharmacokinetic and toxicity profiles (ADME/Tox) of curcumin remain limited. In addition, current curcumin research tends to focus predominantly on the triple-negative breast cancer (TNBC) subtype, while other subtypes such as luminal and HER2-positive have not been extensively explored at the molecular level. Therefore, a critical research gap exists that needs to be addressed—namely, the necessity for molecular interaction analyses of curcumin with the complete NF-κB complex structure, accompanied by evaluations of its pharmacokinetic characteristics and therapeutic potential across various breast cancer subtypes.

Based on this background, this study aims to evaluate the potential of curcumin in inhibiting NF-κB activation as a target for breast cancer therapy through an *in silico* approach. The specific objectives of this research are: (1) to examine the potential of curcumin as a drug candidate for breast cancer therapy, and (2) to analyze the absorption capability and interaction of curcumin with NF-κB protein using the *molecular docking* method.

2. RESEARCH METHOD

2.1 Research Type

This study is a quantitative experimental research, in which the researcher manipulates one or more independent variables, controls other relevant variables, and observes the effects of the manipulation on the dependent variable. This experimental study aims to determine whether curcumin compounds can act as inhibitors of the NF-κB (Nuclear Factor Kappa Beta) protein in breast cancer cells using the software applications PyRx 0.8, Discovery Studio, YASARA, and PyMOL. The study involves two types of variables:

independent and dependent. The independent variable refers to the conformational forms of the bonds formed between the ligand and the protein, while the dependent variable pertains to the docking interaction between the ligand molecules and receptor molecules.

This research was conducted in Samata, Gowa Regency, South Sulawesi, using a Lenovo laptop equipped with an Intel® Inside™ processor and operating on Windows 10 Pro. The compound and receptor explorations were carried out using data obtained from the Protein Data Bank (PDB) and PubChem databases.

2.2 Research Instruments

The tools used in this study include hardware, a set of Lenovo Laptops with Intel® InsideTM processors using Windows 10 Pro and several software, namely PyRx 0.8, Discovery Studio 2019, YASARA and Pymol. The materials used in this study are the 2D structure of the test ligand in the form of curcumin and the 3D structure of the Nf-Kb protein.

2.3 Data Processing and Analysis Techniques

Data processing and analysis in this study were conducted through an *in silico* approach using molecular docking methods to evaluate the potential of curcumin compounds in inhibiting the activation of NF-κB proteins. The analysis stages began with ligand and receptor preparation, followed by molecular docking, docking validation, and visualization and interpretation of molecular interactions. Additionally, a drug-likeness analysis was conducted to assess the pharmacological feasibility of curcumin as a drug candidate based on Lipinski's Rule of Five.

Ligand preparation was carried out by downloading the 2D structure of curcumin from the PubChem database and saving it in SDF format. The structure was then optimized and converted into PDBQT format using Open Babel in the PyRx 0.8 application. Subsequently, the target protein NF-κB was retrieved from the Protein Data Bank (PDB) and prepared using YASARA software by removing non-essential residues such as water molecules and co-crystallized ligands, then saved in pdbqt format.

The molecular docking process was performed using AutoDock Vina within the PyRx 0.8 interface. The interaction between the curcumin ligand and the NF-κB protein was analyzed to obtain binding affinity values (expressed in kcal/mol), indicating the strength of interaction between the compound and the target protein. Docking results were visualized using PyMOL and Biovia Discovery Studio 2019 to generate 3D and 2D interaction representations and identify amino acid residues involved in bond formation.

Docking validation was carried out by calculating the Root Mean Square Deviation (RMSD) between the native structure and the re-docked structure. An RMSD value of less than 2.0 Å indicates that the docking method is valid and applicable for compound evaluation. The final stage involved interpretation of the docking results, including affinity values, types of interactions (hydrogen bonding, hydrophobic, and electrostatic interactions), and analysis of the binding site location.

To assess the pharmacokinetic feasibility of the compound, a screening was also performed based on Lipinski's Rule of Five, which includes molecular weight, number of hydrogen bond donors and acceptors, logP value, and molar refractivity. Compounds meeting at least three out of the five criteria are considered to have drug-like properties. The following represents the technical workflow of data processing and analysis carried out in this study:

Table 1. Workflow of Data Processing and Analysis Techniques

No.	Stages	Brief Description
1.	Ligand Preparation	Curcumin structure downloaded from PubChem, optimized with Open Babel, saved in PDBQT format
2.	Receptor Preparation	NF-κB protein downloaded from PDB, cleaned in YASARA, saved in PDBQT format
3.	Molecular Docking	Performed with AutoDock Vina via PyRx, generating ligand affinity values to proteins
4.	Interaction Visualization	Using PyMOL and Discovery Studio to display structures and bonds in 3D and 2D
5.	Docking Validation	Using RMSD values; the method is considered valid if RMSD < 2.0 Å
6.	Data Interpretation	Analysis of binding sites, affinity energy, and types of ligand-protein binding interactions
7.	Drug-Likeness Screening	Using Lipinski's rule to assess the feasibility of compounds as drug candidates

With these stages, the data generated from the docking process can be analyzed comprehensively both from the aspect of the compound's affinity for the target protein and from the side of the possibility of the

compound to be developed as a drug. The results of this analysis are the basis for drawing conclusions about the potential of curcumin in inhibiting NF-κB as a target for breast cancer therapy.

3. RESULTS AND DISCUSSION

Curcumin compound is one of the compounds contained in turmeric plants that has the potential to be an inhibitor of NF-Kb in cancer cells. The results of Molecular docking research, the stages of ligand-protein docking obtained the following results.

3.1. Molecular Docking Results

Molecular docking is a study that uses computational methods to determine the interaction and binding of a compound with a receptor on a target protein. The results of this study are in the form of affinity scores and visualization in the form of 3D and 2D ligand and receptor interactions. A good affinity value is one that has the lowest score below the reference control ligand. This shows that the ligand can bind to the receptor easily and does not require much energy to bind. Furthermore, using the PyMOL and Discovery Studio applications to see the types of bonds and interactions in the form of visualization. Protein Data Bank (PDB) is a collection of data for structural biology. Where on this site we can study the structure of DNA, proteins and viral capsids by downloading PDB files. All samples collected are collected from experimental data such as (X-Crystallography, NMR etc). We can download it on the site https://www.rcsb.org (Inbio Indonesia., 2005) The target protein downloaded on the site https://www.rcsb.org will be used as a receptor. The file is downloaded in the form of a "pdb" file, in this study the target protein used as a receptor is NF Kb or Nuclear Factor Kaffa Beta with the protein code 2DBF. Based on data on the site https://www.rcsb.org/structure/2DBF has a Ramachandran outliers value of 2.0% which can be used as a target receptor seeing the color in the percentile ranks does not tend to red.

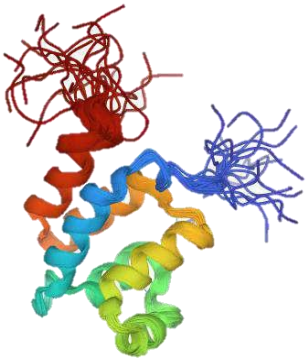


Figure 1. 3D structure of the NF-Kb protein with the code (2DBF)

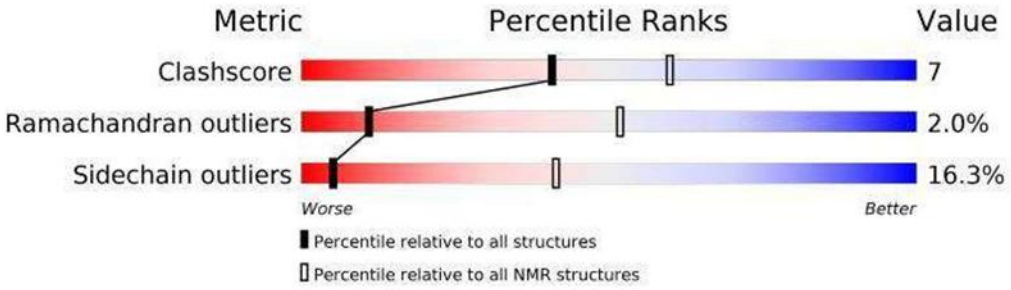


Figure 2. wwPDB validation of NF-Kb protein with code (2DBF)

The next step is to prepare the protein data using the Yasara application. This stage is important because basically the molecules have the same residue composition in the protein file, so several molecules contained in the protein need to be deleted to take only 1 molecule. The residues that need to be deleted here are residues that are considered inhibitory residues (water compounds) and native ligand compounds (native ligands), to avoid the possibility of the test ligand attaching to the interfering molecule. The prepared file is saved in the form of "pdb" with the storage format "mol2-sybylmol2" adjusted to the protein code "2DBF.pdb". The following are the NF-Kb target macromolecules selected after the preparation process.

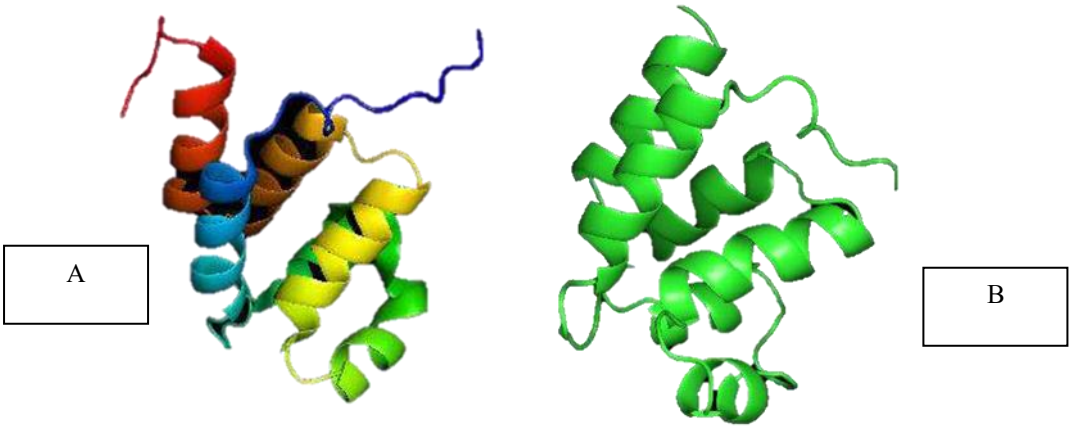
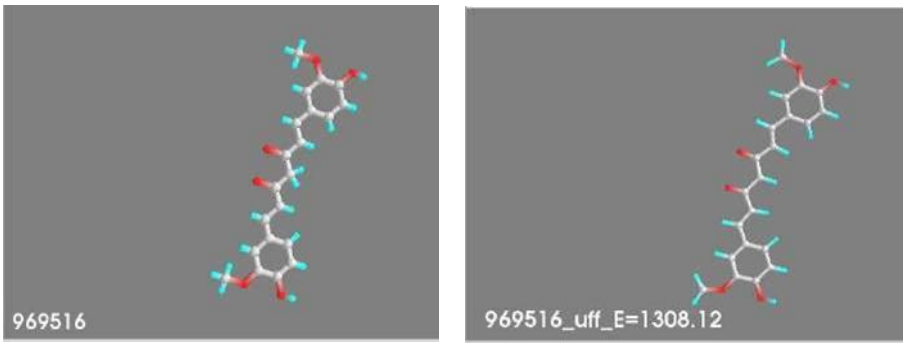


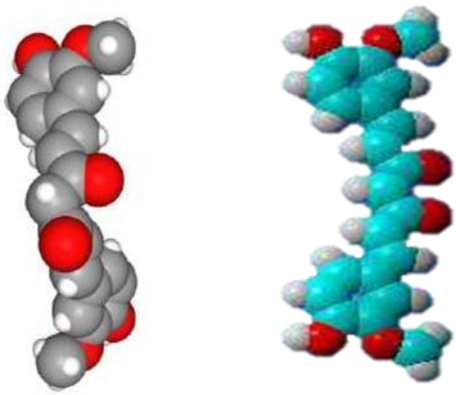
Figure 3. Macromolecular structure of Nuclear Factor Kaffa Beta (2DBF) PyMOL visualization (a) Macromolecular structure of Nuclear Factor Kaffa Beta (2DBF) before preparation (b) Macromolecular structure of Nuclear Factor Kaffa Beta (2DBF. Pdb) after preparation

Preparation of the test ligand downloaded from the site https://pubchem.ncbi, will be used as a ligand. The file is downloaded in the form of a "2D" file in the "SDF" format. This ligand preparation aims to reduce the activation energy of the ligand and adjust it to a format that can be accepted by the docking application. Preparation data can be saved in the "pdbqt" format. The following is the test ligand after preparation.



a b

Figure 4. Curcumin Test Ligand PyRx Visualization (a) curcumin test ligand before preparation (b) curcumin test ligand after preparation



a b

Figure 5. Curcumin Test Ligand Space-Filling Visualization (a) Curcumin ligand before preparation Space-Filling visualization PubChem (b) Curcumin ligand before preparation Space-Filling visualization PyMOL

Ligand and target protein docking using the PyRx application with AutoDock Vina, taking into account the interaction value at the binding site, namely the ΔGbind value or free energy. The following are the binding affinity results from the docking of the test ligand curcumin and the NF-Kb receptor.

Table 2. Binding Affinity Results from PyRx

No.	Protein	Ligand	Binding Affinity (kcal/mol)	RMSD
1.	NF-kappa B p105	Curcumin	-6.2 kcal/mol	< 2.00

Ligand-protein interactions can be visualized using the Pymol application to determine the shape match between the ligand and protein. This also includes the ligand's anchoring residues and the resulting bond shape. Discovery Studio is used to visualize the interaction between the ligand and the target protein. The following is an example of the interaction between the two:

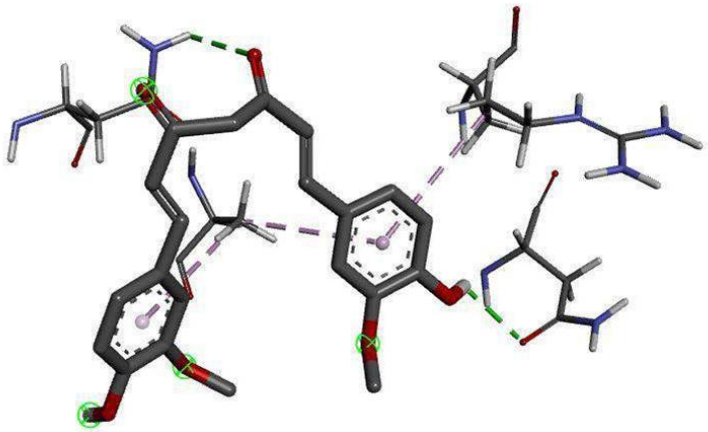


Figure 6. 3D Ligand-Receptor Interaction Discovery Studio Visualization

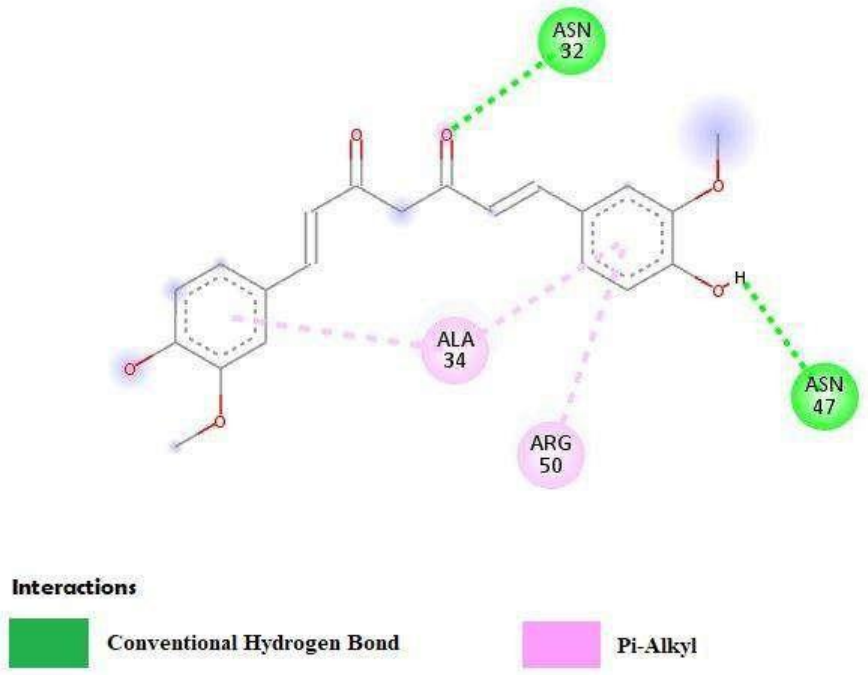


Figure 7. 2D Ligand-Receptor Interaction Discovery Studio Visualization

Table 3. Color Descriptions in PyMOL Visualization

Atom Name	PyMOL Color
Hydrogen	Green
Carbon	White
Oxygen	Red
Sulfur	Orange
Pi-Sigma	Purple
Alkyl	Light Purple
Nitrogen	Blue

The best docking results will be uploaded to iitd.res.in/software/drugdesign/lipinski.jsp, carried out by analysis using Lipinski's rules of five to determine whether the compound can be absorbed by the body or not. The following are the results of Lipinski's rules of five.

Table 4. Lipinski's Rule of Five Results

No.	Parameter	Curcumin
1.	Molecular Mass	368
2.	Hydrogen Bond Donors	2
3.	Hydrogen Bond Acceptors	6
4.	Log P	3.369898
5.	Molar Refractivity	102.016571

Breast cancer develops from breast tissue and is an invasive cancer that most commonly affects women. Signs of this cancer include changes in breast shape, lumps, nipple discharge, and small red scales on the skin. Risk factors for breast cancer include female gender, obesity, lack of physical activity, alcohol use, hormone-releasing therapy during menopause, ionizing radiation, and menstrual cycles that are too early or too late [40]. The macromolecule selection was based on previous research showing that NF-κB acts as a transcription factor, regulating the expression of several genes that can suppress apoptosis and stimulate tumor cell progression [41]. Protein selection was based on the outlier RAMachanran value and previous research. Protein data were downloaded from the RSCB Protein Data Bank, with the code "2DBF." The protein identity of 2DBF is the structure of the nuclear factor NF-κB p105 subunit molecule in humans (Homo sapiens) obtained using solution NMR (Nuclear Magnetic Resonance). Ligand selection was based on the benefits of turmeric, based on several sources related to its curcuminoid content, namely curcumin [23]. Curcumin can inhibit several molecules involved in inflammation, including tumor necrosis factor [42]. Curcumin compounds were downloaded from PubChem in 2D format and saved in SDF format. The ligand preparation process using the PyRx application in the Open Babel feature aims to minimize the ligand to obtain a structural conformation with lower energy than before minimization, thus facilitating the docking process.

Protein preparation using the Yasara application aims to remove control ligands and water molecules bound to macromolecules, as these can interfere with the docking process [43]. Docking was performed using the PyRx application in the Autodock vina feature by entering the prepared protein and ligand using the "pdbqt" format. The docking process yields binding affinity, binding affinity, and conformation values for the prepared ligands. The ligand with the lowest binding affinity and best binding is then saved in "sdf" format and later opened in the Pymol application to view the position and orientation of the docked ligand. Discovery Studio continues to view the amino acids bound to the ligand and the amino acid bond distances in 3D and 2D.

The docking results between the receptor ligands yielded a Root Mean Square Deviation (RMSD) value in the protein, and a value <2.00Å is considered valid, indicating good conformational precision [44]. The RMSD value is used to indicate the success of the docking process and the validation of the docking program, as well as to demonstrate the compatibility between an atom in one conformation and an atom of the same element in another conformation [45]. Binding affinity is a measure of a drug's ability to bind to a receptor. The smaller the binding affinity value, the higher the affinity between the receptor and the ligand, and vice versa, the larger the binding affinity value, the lower the affinity between the receptors [46].

The Lipinski test results showed a mass of 368 Da, 2 hydrogen bond donors, 6 hydrogen bond acceptors, log P 3.369898, and a molar refractivity of 102.016571. These results fulfill Lipinski's rule, where the mass and molecular weight are ≥500 Da, indicating that the drug can diffuse through cell membranes in the body. The larger the molecule, the slower it is to diffuse across the membrane, so the molecular weight is limited to ≥500 g/mol [47]. A hydrogen bond donor of ≤ 5 and a hydrogen bond acceptor of ≤ 10 affect the permeability of the cell membrane, where the drug must cross the membrane, and the membrane is crossed passively by the drug that diffuses across the nonpolar membrane, so oral drugs do not need to interact too strongly with water.

The number of hydrogen bonds in donors and acceptors correlates with the biological activity of a ligand/drug, so the number of donors and acceptors is limited [48]. The log P value indicates solubility in fat (hydrophobic) or water (hydrophilic), with a range of values ≤ 5. The ligand should not be too negative because it cannot pass through the lipid bilayer membrane, and it should not be too positive because the molecule becomes more hydrophobic. Hydrophobic properties indicate a high level of toxicity because it will be retained longer in the lipid bilayer and distributed more widely in the body, resulting in reduced binding selectivity to the target enzyme [49].

The results of the binding of curcumin ligand and NF-Kb receptor visualized with Discovery Studio can be seen in Figures 6 and 7. Hydrogen bonds are visible, indicated in green at ASN 32 and ASN 47, and pi-alkyl bonds are formed, indicated in light purple, classified as hydrophobic bonds at ALA 34 and ARG 50 [50]. The

presence of hydrophobic bonds allows hydrophobic interactions to occur in the ligand and receptor binding process and increases the hydrophobic interactions of the ligand in the receptor binding pocket [51].

This study presents a novel approach to investigating the molecular interaction between curcumin and the NF-κB target protein (2DBF) through molecular docking using various computational tools such as PyRx, PyMOL, Discovery Studio, and validation through Lipinski's Rule of Five. The key novelty lies in the detailed identification of specific hydrogen bonds (ASN 32 and ASN 47) and pi-alkyl bonds (ALA 34 and ARG 50), highlighting the strong potential of curcumin as an anticancer agent through enhanced hydrophobic interactions within the receptor binding pocket. Additionally, the multi-faceted visualization and analysis offer a comprehensive understanding of ligand conformation and its potential biological affinity toward inflammation-related target proteins.

The findings of this study have significant implications for the early-stage development of curcumin-based drug candidates targeting NF-κB, a key factor in cancer cell progression, particularly in breast cancer. The validation through Lipinski's parameters indicates that curcumin possesses favorable pharmacokinetic properties for oral drug development. Furthermore, this research supports the use of cost-effective and time-efficient in silico approaches as a preliminary step in drug discovery, providing a solid foundation for future in vitro and in vivo studies to evaluate the real-world efficacy of curcumin in biological systems. The main limitation of this study lies in its reliance on in silico molecular docking methods, which do not account for the dynamic complexities of biological systems. Additionally, the binding affinity results and interactions observed require further validation through in vitro and in vivo experiments to confirm their therapeutic potential.

4. CONCLUSION

Based on the results of this study, it can be concluded that curcumin has potential as a breast cancer drug, as demonstrated through the Lipinski's Rule of Five test, with results meeting the criteria: molecular weight of 369 g/mol (≤ 500 g/mol), hydrogen bond donors (HBD) totaling 2 (≤ 5), hydrogen bond acceptors (HBA) totaling 6 (≤ 10), and a log P value of 3.369898 (< 5). The molecular weight indicates that curcumin is capable of penetrating cell membranes, the HBD and HBA values suggest that the compound can passively traverse membranes, while the log P value reflects its hydrophobic nature, which, if too high, may increase toxicity potential. Therefore, it is recommended that this research be continued with molecular dynamics simulations to gain deeper insights into the stability and dynamic interactions of the curcumin-target protein complex.

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