

Molecular docking and dynamic simulation of sesamin from *Piper crocatum* Ruiz & Pav as an inhibitor of canonical NF- κ B: Potential anti-inflammatory mechanism

[Acoplamiento molecular y simulación dinámica de la sesamina de *Piper crocatum* Ruiz & Pav como inhibidor del NF- κ B canónico: Potencial mecanismo antiinflamatorio]

Siti Imroatul Maslikah^{1,3,5}, Fatchiyah², Muhammad Hermawan Widyandana^{2,5}, Muhaimin Rifa'i^{2,5}, Warsito⁴, Muhammad Sasmito Djati^{2,5*}

¹Doctoral Program, Department of Biology, Faculty of Mathematics and Natural Sciences, Brawijaya University, Malang 65145, East Java, Indonesia.

²Department of Biology, Faculty of Mathematics and Natural Sciences, Brawijaya University, Malang 65145, East Java, Indonesia.

³Department of Biology, Faculty of Mathematics and Natural Sciences, State University of Malang, Malang 65145, East Java, Indonesia.

⁴Department of Chemistry, Faculty of Mathematics and Natural Sciences, Brawijaya University, Malang 65145, East Java, Indonesia.

⁵Dewan Jamu Indonesia East Java Region, Malang 65145, East Java, Indonesia.

*E-mail: msdjati@ub.ac.id

Abstract

Context: Red betel (*Piper crocatum* Ruiz & Pav) has several fingerprint compounds with antibacterial, antifungal, anti-inflammatory, antiseptic, and antioxidant activities.

Aims: To evaluate the potential of *P. crocatum* active compound as an anti-inflammatory agent through in silico studies.

Methods: The selected active compounds of *P. crocatum*, including kaempferitin, piperbetol, sesamin, piperine, and piperbetol were used in this study. The bioactive compounds of *P. crocatum* were analyzed for drug-likeness screening using the SwissADME and then analyzed using Lipinski's rule to identify medicinal properties. The bioactive compounds of *P. crocatum* also predicted their toxicity using the web server https://tox-new.charite.de/prottox_II/. The selected ligands and NF- κ B proteins were then docked using Pyrx 0.8 software and visualized by Discovery Studio. Molecular dynamics simulation was used to obtain RMSF values using YASARA software.

Results: Kaempferitin, piperbetol, β -amyrin, and sesamin were predicted to be inactive in hepatotoxicity, carcinogenicity, mutagenicity, and cytotoxicity. Meanwhile, piperine was predicted to be active in hepatotoxicity and carcinogenicity and inactive in mutagenicity and cytotoxicity. Sesamin has a similar structure to the synthetic drug panobinostat. Sesamin has a binding affinity of -6.9 kcal/mol. While panobinostat has a binding affinity of -5.5 kcal/mol. The RMSD value showed that the compound-complex of NF- κ B-sesamin was more stable than the compound-complex of NF- κ B- drug (panobinostat).

Conclusions: Sesamin from *P. crocatum* could be considered as an anti-inflammatory agent by inhibiting NF- κ B based the *in silico* study.

Keywords: anti-inflammatory activity; *in silico*; natural medicine; *Piper crocatum*.

Resumen

Contexto: El betel rojo (*Piper crocatum* Ruiz & Pav) tiene varios compuestos de huella dactilar con actividades antibacterianas, antifúngicas, antiinflamatorias, antisépticas y antioxidantes.

Objetivos: Evaluar el potencial del compuesto activo de *P. crocatum* como agente antiinflamatorio a través de estudios *in silico*.

Métodos: En este estudio se utilizaron los compuestos activos seleccionados de *P. crocatum*, incluidos kaempferitina, piperbetol, sesamina, piperina y piperbetol. Los compuestos bioactivos de *P. crocatum* se analizaron para detectar la similitud con fármacos utilizando SwissADME y luego se analizaron utilizando la regla de Lipinski para identificar propiedades medicinales. Los compuestos bioactivos de *P. crocatum* también predijeron su toxicidad utilizando el servidor web https://tox-new.charite.de/prottox_II/. Los ligandos seleccionados y las proteínas NF- κ B se acoplaron utilizando el software Pyrx 0.8 y se visualizaron con Discovery Studio. Se utilizó la simulación de dinámica molecular para obtener los valores de RMSF utilizando el software YASARA.

Resultados: Se predijo que la kaempferitina, el piperbetol, la β -amirina y la sesamina serían inactivas en hepatotoxicidad, carcinogenicidad, mutagenicidad y citotoxicidad. Mientras tanto, se predijo que la piperina sería activa en hepatotoxicidad y carcinogenicidad e inactiva en mutagenicidad y citotoxicidad. La sesamina tiene una estructura similar al fármaco sintético panobinostat. La sesamina tiene una afinidad de unión de -6,9 kcal/mol. Mientras que el panobinostat tiene una afinidad de unión de -5,5 kcal/mol. El valor de RMSD mostró que el complejo compuesto de NF- κ B-sesamina era más estable que el complejo compuesto del fármaco NF- κ B (panobinostat).

Conclusiones: La sesamina de *P. crocatum* podría considerarse un agente antiinflamatorio al inhibir el NF- κ B según el estudio *in silico*.

Palabras Clave: actividad anti-inflamatoria; *in silico*; medicina natural; *Piper crocatum*.

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AUTHOR INFO

ORCID:

[0009-0009-3253-967X](https://orcid.org/0009-0009-3253-967X) (SIM)

[0000-0001-6241-9665](https://orcid.org/0000-0001-6241-9665) (F)

[0000-0002-1167-3177](https://orcid.org/0000-0002-1167-3177) (MHW)

[0000-0001-5731-2951](https://orcid.org/0000-0001-5731-2951) (MR)

[0000-0002-8962-819X](https://orcid.org/0000-0002-8962-819X) (W)

[0000-0002-1245-2528](https://orcid.org/0000-0002-1245-2528) (MSD)

INTRODUCTION

NF- κ B is a crucial mediator of oxidative stress, DNA damage response, and inflammation (Roberti et al., 2022). The hyper-activation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B) in a cellular system is associated with inflammation, cancer, and other human diseases. The core elements of the NF- κ B cascade might regulate the translocation and activation of the NF- κ B transcription factor (Cheemanapalli et al., 2019). Activation of NF- κ B receptors causes the production of proinflammatory cytokines that promote the inflammatory reaction. Inhibiting NF- κ B activation becomes a target to overcome the excessive inflammatory reaction (Adzic et al., 2018).

Inflammation is a positive response of the body to tissue damage to overcome the infection, repair tissue damage, and restore tissue homeostasis (Kusmardi et al., 2021). According to Bare et al. (2019), inflammation is a state of the body that results from changes in physiological processes that affect protein synthesis. Inflammation can be prevented with natural product treatment, including red betel (*Piper crocatum* Ruiz & Pav, family *Piperaceae*). Bioactive compounds in *P. crocatum*, including flavonoids, phenols, terpenoids, essential oils, polyphenolics, steroids, quinones, and alkaloids (Lister et al., 2020), can be anti-inflammatory agents in rheumatoid arthritis (Savitri et al., 2020). These bioactive compounds act as anti-inflammatory agents by regulating NF- κ B transcription factor and TNF- α expression (Alam et al., 2013). *P. crocatum* is one of the herbs that is empirically used as a traditional drug in Indonesia. *P. crocatum* has long been known to have medicinal properties to treat various diseases, including dental and oral diseases, due to strong and effective antibacterial and anti-inflammatory agents (Maslikah et al., 2023).

The pharmacological properties of *P. crocatum* could encompass a wide range of activities, such as anticancer, anti-inflammatory, antioxidant, antifungal, and neuroprotective effects (Lister et al., 2020). Understanding these properties is essential to assessing the plant's therapeutic potential for various diseases. In the context of traditional and Indigenous medical practice, studying *P. crocatum* could contribute valuable pharmacological insights that can lead to the discovery of novel therapeutic drugs. Understanding how the plant's pharmacological properties correlate with its ethnomedical uses can bridge the gap between indigenous knowledge and modern scientific approaches to drug development, potentially advancing both fields. This strategy may also lead to novel applications of this plant in modern medicine

and provide information for sustainable, plant-based treatment alternatives for a variety of illnesses.

In silico studies were conducted to predict the anti-inflammatory mechanism of *P. crocatum* on the NF- κ B receptor signaling pathway. These receptors were selected because of their downstream part of the inflammatory pathway (Kawai and Akira, 2007). When the NF- κ B receptor is activated, it will stimulate the nucleus to produce inflammatory cytokines (Banaganapalli et al., 2013). *In silico* study is a computational simulation method using specific applications and web tools to predict the activity of compounds in new drug discovery strategies. The *in silico* method involves molecular docking between the receptor and the ligand (Agamah et al., 2020). *In silico* studies have several advantages over *in-vitro* and *in-vivo* studies. *In silico* studies, compounds are effectively predicted to be considered drugs, do not require high costs, and save time.

To the best of our knowledge, there are limited studies regarding the effectiveness of *P. crocatum* as an anti-inflammatory agent, especially research based on *in silico* studies. Our preliminary research regarding the *in silico* evaluation of bioactive compound in *P. crocatum* as an anti-inflammatory agent by inhibiting the TNFR1, non-canonical NF- κ B (p52/RelB), and I κ K has been done. However, there is no research on the different mechanisms of *P. crocatum* as an anti-inflammatory agent on canonical NF- κ B. *In silico* studies investigating the anti-inflammatory potential of *P. crocatum* are novel and promising approaches to uncovering the therapeutic of this plant. Given the current lack of such studies, this area of research could offer valuable insights into the mechanisms underlying its traditional medicinal uses, identify bioactive compounds with significant anti-inflammatory activity, and provide a foundation for future drug development. Therefore, this study aimed to evaluate the potential of *P. crocatum* active compound as an anti-inflammatory agent through the interaction between *P. crocatum* active compound and canonical NF- κ B (p50/RelA). This study computationally evaluated the constituents of *P. crocatum* that possessed anti-inflammatory activities using molecular docking analysis and elucidated their molecular dynamics.

MATERIAL AND METHODS

Ligand and protein target preparation

The active compound of *P. crocatum* was retrieved from the PubChem database (<http://www.pubchem.ncbi.nlm.nih.gov/>). Then, it

Table 1. Toxicity prediction of active compound in *P. crocatum* leaf extract.

Compounds	Toxicity class	LD ₅₀ (mg/kg)	Hepatotoxicity	Carcinogenicity	Mutagenicity	Cytotoxicity
Kaempferitin	5	5,000	Inactive	Inactive	Inactive	Inactive
Piperbetol	4	1,050	Inactive	Inactive	Inactive	Inactive
β-amyryn	6	70,000	Inactive	Inactive	Inactive	Inactive
Sesamin	4	1,500	Inactive	Inactive	Inactive	Inactive
Piperine	4	330	Active	Active	Inactive	Inactive
Panobinostat	4	1,700	Inactive	Active	Active	Inactive

minimized the energy using OpenBabel integrated with PyRx software (Mawaddani et al., 2022). The structure of selected compounds, including kaempferitrin (CID: 5486199), piperbetol (CID: 10385474), piperine (CID: 638024) (Maslikah et al., 2020), β-amyryn (CID: 73145), and sesamin (CID: 72307), was downloaded from the PubChem database (<https://pubchem.ncbi.nlm.nih.gov/>). The 3-dimensional structure of the canonical NF-κB (PDB ID: 3GUT) as the target protein (Cheemanapalli et al., 2019) was obtained from <https://www.uniprot.org/>. The water molecules and contaminant ligands in the crystal structure of the protein were removed using Discovery Studio 16 software. The reference drug in this study was panobinostat (CID: 6918837), which obtained its structure from (<https://pubchem.ncbi.nlm.nih.gov/>).

Drug-likeness analysis, ADMET, and biological activities prediction

The bioactive compound of *P. crocatum* was analyzed for drug-likeness screening using the SwissADME (<http://www.swissadme.ch/>). Lipinski's rule was used to identify compounds with medicinal properties, including molecular weight (MW) 500, hydrogen binding donor (HBD) 5, hydrogen binding acceptor (HBA) 10, severe lipotoxicity (LogP) 5, and molar refractory (MR) 40–130. According to Aini et al. (2022), positive prediction satisfied at least two rules. Based on Lipinski, Egan, and Gose's rule, a chemical compound with a violation number above 0 cannot continue to be a drug candidate. If the violation number is 0, it can proceed to the molecular docking stage (Mawaddani et al., 2022). The bioactive compound of *P. crocatum* also predicted their toxicity using a web server: https://tox-new.charite.de/protox_II/. Panobinostat was used as a reference drug in this study, and also predicted their toxicity using the same web server. The canonical smiles of selected bioactive compounds of *P. crocatum* and reference drug were retrieved from PubChem (<https://pubchem.ncbi.nlm.nih.gov/>) and inserted into the PASS server (Christina et al., 2021) to predict the biological activity related to anti-inflammatory.

Molecular docking and visualization

The molecular docking process was carried out using Pyrx 0.8 software with Vina Wizard and Auto-Dock Wizard menus. Blind docking was used for molecular docking because the active site for protein binding is not yet known. The docking results between compounds and target proteins were stored in pdb format, and then the binding affinity value was recorded. The visualization of docking results was done using Discovery Studio software.

Molecular dynamic simulation

Molecular dynamics simulation was performed using the YASARA (Yet Another Scientific Artificial Reality Application) software (Wargasetia et al., 2021). The physiological conditions of the cells (37°C, pH 7.4, 1 atm, and 0.9% salt content) for 20 ns were used for system conditions. 20 ns is the duration commonly used to determine the stability of the protein-ligand complex. The simulation was run using the md_run macro program, and the results were displayed using the MD_analyze, MD_analyzeres, and MD_analyzed bind energy macro program. If the root-mean-square deviation (RMSD) value was 2, the RMSD value was valid.

RESULTS AND DISCUSSION

Prediction of ligand toxicity and drug-likeness

The toxicity analysis showed that several compounds contained in *P. crocatum* leaf extract, including kaempferitrin, piperbetol, β-amyryn, and sesamin, were predicted to be inactive in hepatotoxicity, carcinogenicity, mutagenicity, and cytotoxicity. While piperine was predicted to be active in hepatotoxicity and carcinogenicity but inactive in mutagenicity and cytotoxicity (Table 1). Panobinostat as a reference drug also predicted its toxicity and the results indicated that this drug has a risk as a carcinogen and mutagen.

Based on Lipinski, Egan, and Gose's rule, if the violation number is above 0, the compound cannot con-

tinue to be a drug candidate with molecular docking. Meanwhile, if the violation number is 0, it can proceed to molecular docking (Mawaddani et al., 2022). Based on Table 2, three compounds have a violation number of 0, including sesamin, piperine, and piperbetol. Panobinostat as a reference drug has a violation number of Lipinski, Egan, and Ghose of 0. Therefore, these compounds and panobinostat can be continued to molecular docking analysis.

Table 2. Violation analysis of active compounds in *P. crocatum* leaf extract.

Compounds	Lipinski	Egan	Ghose
Kaempferitin	3	1	4
Piperbetol	0	0	0
β-amyrin	1	1	3
Sesamin	0	0	0
Piperine	0	0	0
Panobinostat	0	0	0

The bioactive compounds of *P. crocatum* were investigated using SwissADME to assess the comparability of various drugs. Molecular weight (MW) 500, hydrogen binding donor (HBD) 5, hydrogen binding acceptor (HBA) 10, severe lipotoxicity (LogP) 5, and molar refractory (MR) 40–130 are all conditions where Lipinski's rule is used. Panobinostat was predicted to have no activity as an anti-inflammatory drug due to its lack of anti-inflammatory probability in Pass Online analysis (Table 3).

Molecular docking results

Vorinostad, romidepsin, belinostat, panobinostat, tucidinostat, azaticidin, and decitabine are a few synthetic medications for anti-inflammatory agents (Ramadass et al., 2020). Based on the similarity of the chemical structure of sesamin, panobinostat was the chemical structure most similar to sesamin (Fig. 1). The structural similarity is the presence of a benzene ring that is diffusely heterocyclic. Panobinostat structure contains indol units, and sesamin structure con-

tains 1,3-benzodioxole. Therefore, this study used panobinostat as a drug control.

Sesamin was used for molecular docking analysis as a follow-up to the prediction of anti-inflammatory drug candidates (Table 1). Sesamin [(7α,7'α,8α,8'α)-3,4:3',4'-bis(methylenedioxy)-7,9':7',9'-diepoxy]lignane belongs to the piper genus, which identified as main lignan in sesame seeds. Sesamin is converted into catechol metabolite, SC1 [(7α,7'α,8α,8'α)-3',4'-methylenedioxy-7,9':7',9'-diepoxy]lignane-3,4-diol with anti-inflammatory effect after oral administration (Dar and Arumugam, 2013).

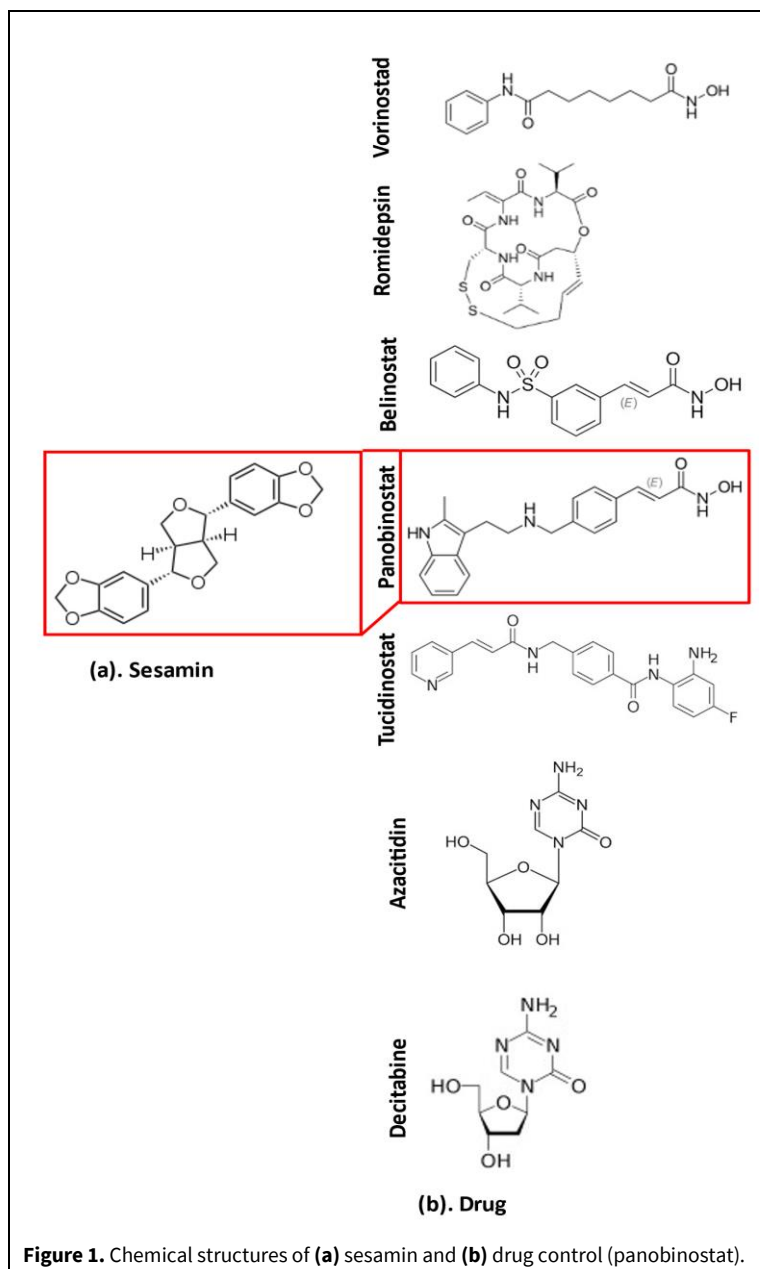
Due to their ability to bind amino acid residues, sesamin compounds have the potential to be used as NF-κB anti-inflammatory therapies (Table 4). A low-affinity value will enhance the interaction of ligands with proteins. Ligand-protein complexes are stabilized by robust ligand-protein interactions. Low hydrophobicity improves the permeability of substances on the cell membrane and is inversely correlated with the amount of hydrophobicity bonds (Sudhamalla et al., 2010). The results of molecular docking obtained sesamin compounds have a binding affinity of -6.9 kcal/mol. While panobinostat has a binding affinity of -5.5 kcal/mol (Table 4). The more negative the bond energy value, the more stable and potent the bond and affinity formed (Kharisma et al., 2021).

The potential affinity of sesamin to the target protein can be determined by comparing the bond energy formed between sesamin and the target protein to the bond energy between panobinostat and the target protein. Panobinostat binding energy to the target protein is used as a positive comparison or control to determine the stability and strength of the bond formed (Okereke et al., 2023). The energy value of sesamin is more negative than the energy of panobinostat in the validation process, so based on the bond energy value obtained shows that the sesamin compound has potential activity as an anti-inflammatory because it has a high affinity and forms hydrogen bonds with NF-κB proteins.

Table 3. Physicochemical properties and anti-inflammation probability of selected compounds from *P. crocatum* leaf extract.

Compound	MW (g/mol)	HBD	HBA	LogP	MR	Anti-inflammation probability	
						Pa	Pi
Piperbetol	386.44	1	6	1.8	104.35	0.277	0.185
Sesamin	354.35	0	6	1.98	90	0.313	0.149
Piperin	285.34	0	3	2.39	85.47	0.344	0.127
Panobinostat	349.43	4	3	2.31	103.76	-	-

MW: molecular weight; HBD: H-bond donors; HBA: H-bond acceptors; MR: molar refractivity.

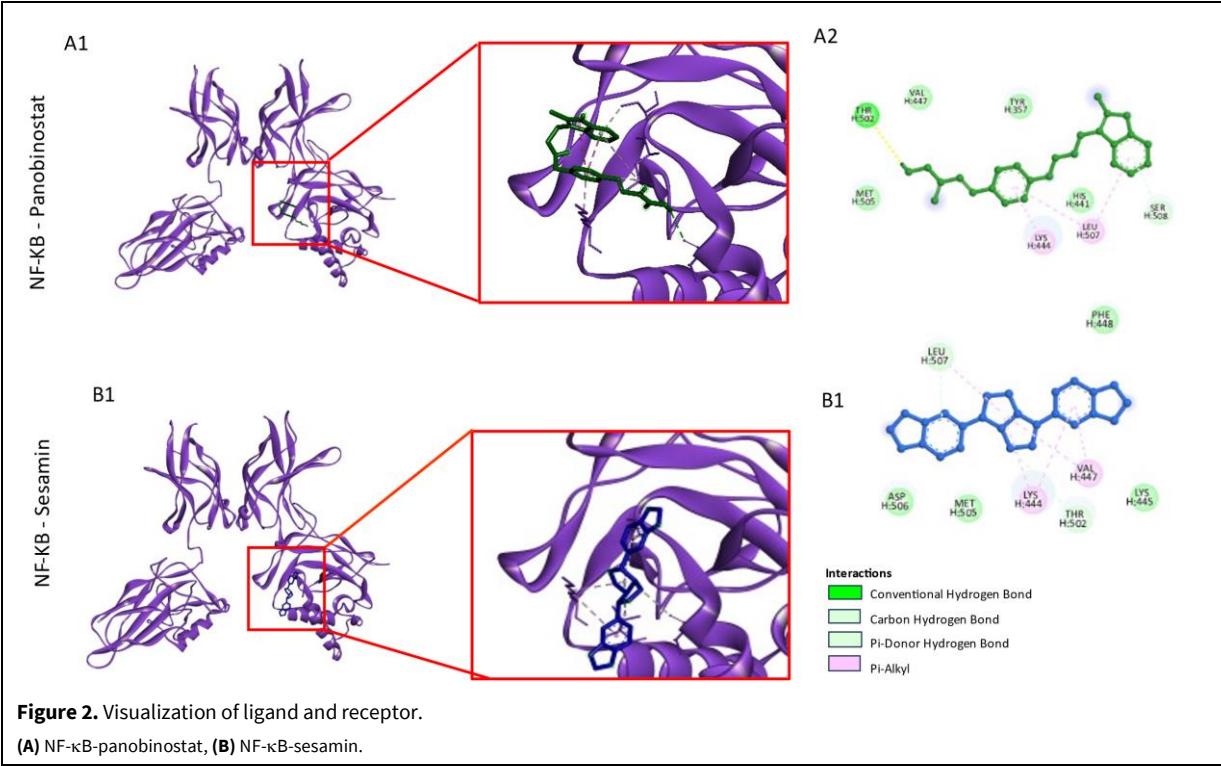


This study docked sesamin and panobinostat on NF- κ B target proteins with the same docking grid box coordinate (Fig. 2). The protein binding site is an area of protein binding to molecules and ions (ligands) that will affect the conformation and function of the protein. The binding site area involves amino acid residues that play an important role in binding with ligands (Widyananda et al., 2021). The similarity of amino acid residues involved in the binding site area of NF- κ B causes sesamin compounds to inhibit NF- κ B activity. Amino acid residues similar to drug control are LEU H: 507, MET H: 505, and LYS H: 444 (Table 4).

Based on Table 4, amino acid residues with Pi-alkyl (hydrophobic) bonds were less than those with hydrogen bonds. The residues involved in hydrophobic interactions were residues of nonpolar amino acids. Nonpolar (hydrophobic) amino acid residues tend to form clusters in the form of chain blankets in the interior of proteins. This Pi bond has higher bond energy than hydrogen bonds, so the presence of Pi bonds also increases the complex's stability and the compound's total bond energy against the enzyme receptor (Kharisma et al., 2022).

Table 4. Binding affinity and amino acid residues between ligands and protein.

Complex	Binding affinity (kcal/mol)	Interaction	Distance (Å)	Bonding categories	Donor	Acceptor
NF-κB-sesamin	-6.9	:LIG1:C - H:THR502:O	3.30696	Hydrogen bond	:LIG1:C	H-donor H:THR502:O H-acceptor
		H:LEU507:N - :LIG1	4.14375	Hydrogen bond	H:LEU507:N	H-donor :LIG1 Pi-orbitals
		:LIG1 - H:LYS444	5.47186	Hydrophobic	:LIG1	Pi-orbitals H:LYS444 Alkyl
		:LIG1 - H:VAL447	4.42693	Hydrophobic	:LIG1	Pi-orbitals H:VAL447 Alkyl
		:LIG1 - H:LEU507	5.02803	Hydrophobic	:LIG1	Pi-orbitals H:LEU507 Alkyl
NF-κB-panobinostat	-5.5	:LIG1:H - H:THR502:O	3.07603	Hydrogen bond	:LIG1:H	H-donor H:THR502:O H-acceptor
		H:SER508:OG - :LIG1	3.46425	Hydrogen bond	H:SER508:OG	H-donor :LIG1 Pi-orbitals
		:LIG1 - :LIG1	4.22769	Hydrophobic	:LIG1	Pi-orbitals :LIG1 Pi-orbitals
		:LIG1 - :LIG1	3.6634	Hydrophobic	:LIG1	Pi-orbitals :LIG1 Pi-orbitals
		:LIG1 - H:LEU507	5.47102	Hydrophobic	:LIG1	Pi-orbitals H:LEU507 Alkyl
		:LIG1 - H:LYS444	3.71697	Hydrophobic	:LIG1	Pi-orbitals H:LYS444 Alkyl



Molecular dynamic simulation

Molecular dynamic simulations are used to analyze the interaction stability between proteins and ligands (Garcia-Alonso et al., 2019). Molecular dynamics simulation is a computer simulation used to simulate the interactions between atoms or molecules as a function of time based on the parameters of physical laws. Simulation results are often described as RMSD values, which are the average number of displacement distances for each atom during the simulation, which are used to assess the stability of molecular structures.

Fig. 3A showed that the complex of NF-κB-panobinostat was indicated by blue color, and the complex of NF-κB-sesamin was indicated by green color. The RMSD of NF-κB-sesamin was more stable than NF-κB-panobinostat. RMSD of NF-κB and panobinostat showed that atoms in the protein backbone have a long displacement distance from their original position, indicating unstable fluctuations between NF-κB and the panobinostat. RMSD indicates changes in the ligand-protein complex's conformation (Jiang et al., 2019). The lower the RMSD value, the more stable the protein (Aier et al., 2016).

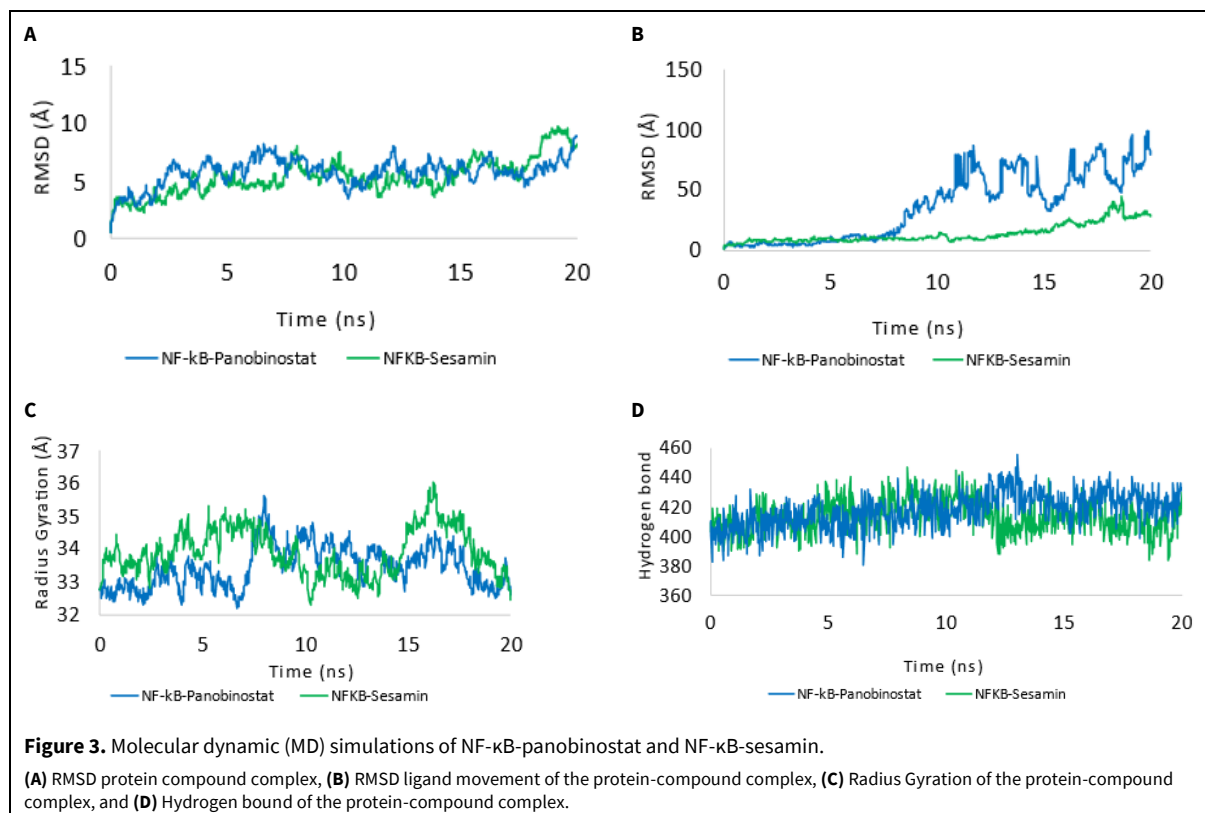


Fig. 3B showed that the RMSD ligand movement of NF-κB and drugs reaches 100 Å at the 11th nano-second. It was indicated that the ligand has been detached from the protein, and the bond between drugs and NF-κB is unstable or has very large fluctuations. Conversely, NF-κB-sesamin shows small fluctuations indicated by graphs that squeeze between ligands and proteins even though at the end of the movement, it reaches 100 Å but decreases again. The RMSD movement of sesamin was 45 Å, indicating that sesamin was more stable than NF-κB.

Fig. 3C demonstrated that the gyration radius of NF-κB and the drug (blue) was not different from NF-κB and sesamin (green), with a maximum 36 radius in Å. The radius of protein gyration is the distance of distribution of protein atoms from their central axis (Agrahari et al., 2018). The gyration radius in molecular dynamics simulations provides information about changes in protein size during the simulation (Gurram et al., 2022). Therefore, the greater the gyration radius, the greater the protein. Fig. 3C shows changes in protein gyration radius during molecular dynamics simulation of the NF-κB complex with sesamin ligands and drugs. The gyration radius in molecular dynamics simulations with drug ligands fluctuated from the beginning of the simulation to 3 ns. The gyration radius value increases to 33.75 Å, and the minimum value is 32.25 Å. Then, up to 20 ns, the gyration radius increases with a peak value of 35.5 Å. The gy-

ration radius in molecular dynamics simulations with sesamin ligands fluctuates from the beginning of the simulation to 3 ns. The gyration radius value has increased to 34.5 Å, and the minimum value is 32.75 Å. Then, up to 20 ns, the gyration radius increases with a peak value of 36 Å. The gyration radius value aligns with the RMSD analysis results, which show that the complex between proteins and ligands is dynamic during the molecular dynamics simulation time. These dynamic processes are not observed when using molecular tethering. Fluctuations in the interaction between protein ligands are important in determining the ligand's ability as an enzyme inhibitor (Bux et al., 2021). Fig. 3D shows that the number of hydrogen bonds of NF-κB-panobinostat is between 1100-1250, while the number of hydrogen NF-κB-sesamin is about 365-445, the number of hydrogen bonds. This result indicates that NF-κB and the drug are less stable than the interaction of NF-κB and sesamin.

CONCLUSION

Kaempferitrin, piperbetol, β-amyrin, and sesamin were predicted to be inactive in hepatotoxicity, carcinogenicity, mutagenicity, and cytotoxicity. Meanwhile, piperine was predicted to be active in hepatotoxicity and carcinogenicity and inactive in mutagenicity and cytotoxicity. Sesamin has a similar structure to the synthetic drug panobinostat. Sesamin has a

binding affinity of -6.9 kcal/mol. While panobinostat has a binding affinity of -5.5 kcal/mol. The RMSD value showed that the compound-complex of NF- κ B-sesamin was more stable than the compound-complex of NF- κ B-drug (panobinostat). Sesamin from *P. crocatum* can be considered an anti-inflammatory agent by inhibiting NF- κ B based on *in silico* study.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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AUTHOR CONTRIBUTION:

Contribution	Maslikah SI	Fatchiyah	Widyananda MH	Rifa'i M	Warsito	Djati MS
Concepts or ideas	x		x			
Design	x		x			
Definition of intellectual content	x	x	x			
Literature search	x					x
Experimental studies	x		x			
Data acquisition		x				x
Data analysis	x		x			
Statistical analysis	x			x		
Manuscript preparation	x		x			
Manuscript editing	x			x	x	x
Manuscript review	x	x	x	x	x	x

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