Molecular Docking and ADMET Analysis of Bioactive Compounds from *Vitex trifolia* as Potential COX-2 Anti-Inflammatory Agents

Analisis Docking Molekuler dan ADMET Senyawa Bioaktif dari *Vitex trifolia* sebagai Agen Antiinflamasi Potensial COX-2

Hanif Hibatulloh[1], Zulpakor Oktoba[2]*, Atri Sri Ulandari[2], Muhammad Iqbal[2], Recky Patala[3]

[1]*Bachelor of Pharmacy Study Program, Faculty of Medicine, Universitas Lampung, Bandar Lampung, Lampung, 35145, Indonesia*

[2]*Department of Pharmacy, Faculty of Medicine, Universitas Lampung, Bandar Lampung, Lampung, 35145, Indonesia*

[3]*Pharmacy Study Program, Faculty of Mathematics and Natural Sciences, Universitas Tadulako, Palu, Central Sulawesi, 94148, Indonesia*

ABSTRACT

Legundi (*Vitex trifolia*) has been reported to exhibit anti-inflammatory activity; however, the specific bioactive compounds responsible for this effect remain unclear. This study aimed to evaluate the anti-inflammatory potential of bioactive compounds from *V. trifolia* against cyclooxygenase-2 (COX-2; PDB ID: 5KIR) using an in silico molecular docking approach, along with the analysis of their pharmacokinetic and toxicity profiles. The results showed that persicogenin exhibited the lowest binding affinity of -9.2 kcal/mol and formed hydrogen bonds with key amino acid residues, namely THR 212, HIS 207, and TYR 385. ADMET prediction results indicated that persicogenin met the drug-likeness criteria for an oral drug candidate, demonstrated good intestinal absorption (HIA: 92.29%), high membrane permeability (Caco-2 permeability > 0.9), low volume of distribution (VDss < 0.45), inhibitory activity against CYP2C19 and CYP3A4, and no hepatotoxic potential. These findings suggest that persicogenin may serve as an anti-inflammatory agent.

ABSTRAK

Tumbuhan legundi (*Vitex trifolia*) dilaporkan memiliki aktivitas antiinflamasi; namun, senyawa bioaktif spesifik yang berperan dalam aktivitas tersebut masih belum sepenuhnya diketahui. Penelitian ini bertujuan untuk mengevaluasi potensi senyawa bioaktif yang terdapat pada tumbuhan *V. trifolia* sebagai agen antiinflamasi terhadap protein target COX-2 dengan kode PDB 5KIR melalui molecular docking secara in silico serta menganalisis profil farmakokinetik dan toksisitasnya. Hasil menunjukkan bahwa senyawa persicogenin memiliki nilai afinitas terendah, yaitu $-9,2$ kkal/mol, dengan ikatan hidrogen pada residu THR 212, HIS 207, dan TYR 385. Prediksi ADMET menunjukkan bahwa senyawa tersebut memenuhi parameter sifat mirip obat (drug-likeness) sebagai kandidat obat oral, memiliki absorpsi usus yang baik (HIA 92,29%), permeabilitas membran yang tinggi (Caco-2 $> 0,9$), volume distribusi yang rendah (VDss $< 0,45$), berpotensi menghambat enzim CYP2C19 dan CYP3A4, serta tidak berpotensi hepatotoksik. Hasil studi ini menunjukkan bahwa persicogenin berpotensi sebagai agen antiinflamasi.

*Corresponding author:

Zulpakor Oktoba (zulpakor.oktoba@fk.unila.ac.id)

1. INTRODUCTION

Inflammation is a protective immune response to various harmful stimuli, including pathogens, cellular damage, toxic compounds, and radiation. This response functions to eliminate harmful stimuli and initiate tissue repair mechanisms. The clinical signs of inflammation include redness (*rubor*), swelling (*tumor*), heat (*calor*), pain (*dolor*), and loss of tissue function (*functio laesa*) (Chen et al., 2018). In Indonesia, several diseases involving inflammatory processes have shown relatively high prevalence rates, including asthma (2.4%), cancer (1.79%), heart disease (1.5%), chronic kidney disease (0.38%), joint disorders (7.3%), acute respiratory infections (9.3%), pneumonia (4.0%), and diabetes mellitus (1.5%) (Kemenkes RI, 2018). Therefore, pharmacological intervention using anti-inflammatory agents is commonly required to control excessive inflammatory responses.

Anti-inflammatory drugs are used to suppress or reduce inflammatory processes. In general, these drugs are classified into two major groups: steroidal and nonsteroidal anti-inflammatory drugs. Nonsteroidal anti-inflammatory drugs (NSAIDs) exert their effects by targeting the cyclooxygenase (COX) enzyme, which is involved in the biosynthesis of prostaglandins from arachidonic acid (Clària, 2003; Putri et al., 2024). The COX-2 isoenzyme plays a crucial role in the inflammatory pathway by catalyzing the conversion of arachidonic acid into prostaglandins, which are key mediators of inflammation and help prevent physiological disturbances associated with cytokine imbalance in the immune system. Consequently, COX-2 has become a major target in the development of more selective anti-inflammatory agents (Loka & Kodariah, 2022).

Legundi (*Vitex trifolia*) is one of the medicinal plants that has long been used by Indonesian communities. This plant has been reported to possess various pharmacological activities, including anti-inflammatory, antioxidant, anticancer, and hepatoprotective effects (Ankalikar & Viswanathswamy, 2017; Silalahi & Asra, 2024). Previous studies evaluating the anti-inflammatory activity of *V. trifolia* have been conducted using in vivo carrageenan-induced edema models in Wistar rats and in vitro ELISA-based assays for COX-2. The ethanol extract of *V. trifolia* leaves was tested at doses of 200, 400, and 800 mg/kg body weight. The extract exhibited COX-2 inhibition of 8%–22% and suppressed rat paw edema by 40%–46%. These effects were reported to be comparable to those of the reference drug celecoxib (Ifora et al., 2022).

One of the major challenges in evaluating bioactive compounds with potential biological activity is that experimental testing is often time-consuming and costly. These limitations can be addressed through computational approaches, including in silico molecular docking. Molecular docking is a method used in computer-aided drug design (CADD) to predict the interaction of a compound with a target protein by estimating its binding conformation and binding energy (Hasan et al., 2022). This study aimed to identify the anti-inflammatory potential of bioactive compounds from legundi (*V. trifolia*) against the COX-2 target protein using an in silico molecular docking approach. The molecular docking results were further evaluated by analyzing absorption, distribution, metabolism, excretion, and toxicity (ADMET) profiles. ADMET evaluation can provide important information on oral bioavailability, cellular permeability, metabolism, elimination, and toxicity, which are essential pharmacokinetic and toxicological characteristics of a drug candidate.

However, the specific bioactive compounds responsible for the anti-inflammatory activity of *V. trifolia* and their molecular interactions with COX-2 have not been extensively explored using computational approaches such as molecular docking and ADMET prediction.

2. METHODS

2.1. Materials and Instruments

This study used an Asus K389J2A1 laptop equipped with an Intel(R) Celeron(R) N4020 CPU @ 1.10 GHz, 8 GB RAM, and 256 GB ROM. The software used in this study included Windows 11, MGL Tools 1.5.7 (Molecular Graphics Laboratory, The Scripps Research Institute, USA), AutoDock Vina 1.1.2 (The Scripps Research Institute, USA), ChemDraw Professional 15.0 (PerkinElmer Informatics Inc., USA), BIOVIA Discovery Studio Visual 2025 (Dassault Systèmes BIOVIA, USA), and the pkCSM web server for ADMET prediction. The study examined 10 compounds isolated from legundi (*V. trifolia*), namely artemetin, casticin, vitexilactone, maslinic acid, vitexin, isovitexin, persicogenin, luteolin, penduletin, and chrysosplenol-D (El-Kousy et al., 2012; Li et al., 2005; Wee et al., 2020). The ligand structures were obtained from PubChem. The target protein, COX-2 (PDB ID: 5KIR), was downloaded from the Protein Data Bank in .pdb format.

2.2. Ligand Preparation

The test ligands were drawn and energy-minimized using Chem3D 15.0 and then saved in .pdb format. Ligand preparation was then continued using AutoDockTools 1.5.7. During ligand preparation, hydrogen atoms were added, nonpolar hydrogens were merged, Gasteiger charges were assigned, and torsional bonds were defined. The prepared ligands were subsequently saved in .pdbqt format (Forli et al., 2016).

2.3. Receptor Preparation

The protein structure was opened in BIOVIA Discovery Studio Visual 2025 to remove water molecules and separate the protein from its native ligand. The separated protein and native ligand were saved in PDB format. Protein preparation was then continued using AutoDockTools 1.5.7. During protein preparation, polar hydrogen atoms were added, Gasteiger charges were assigned, and

nonpolar hydrogens were merged. The prepared protein was then saved in .pdbqt format (Forli et al., 2016).

2.4. Docking Validation

Docking validation was performed using AutoDock Vina, with a root mean square deviation (RMSD) value of < 2.0 Å considered acceptable. The native ligand was re-docked into the target protein by defining the active-site coordinates and the grid box dimensions corresponding to the binding-site pocket. The validation process was initiated by setting the grid box size to 40 × 40 × 40 Å with center coordinates of x = 24.456, y = 40.257, and z = 3.487, corresponding to the active site of the native ligand on the target protein (Forli et al., 2016).

2.5. Molecular Docking

The structures of the test compounds, which had previously undergone energy minimization, were prepared as ligands following the procedure described above. Molecular docking between the test compounds as ligands and the COX-2 protein (PDB ID: 5KIR) as the macromolecular target was performed using the Windows command line with the commands vina --config config.txt --out out.pdbqt --log log.txt and vina_split.exe --input out.pdbqt --ligand ligand_out, using the same settings as those applied in the docking validation step (Forli et al., 2016).

2.6. ADMET Prediction

The pharmacokinetic and toxicity profiles of the compounds showing the best docking activity were predicted using canonical SMILES obtained from PubChem. These data were then analyzed using the pkCSM web server.

3. RESULTS AND DISCUSSION

3.1. Docking Validation Results

Docking validation was performed by re-docking the native ligand into the target protein. The native ligand, rofecoxib, was re-docked into the COX-2 target protein (PDB ID: 5KIR) using a grid box size of 40 × 40 × 40 Å and center coordinates of x = 24.456, y = 40.257, and z = 3.487. The overlay of the ligand before and after docking is shown in **Figure 1**. The docking validation yielded a root mean square deviation (RMSD) value of 0.2360 Å.

The RMSD value indicates the degree of conformational similarity, and a value of < 2.0 Å is generally considered acceptable. The smaller the RMSD value, particularly when it approaches 0, the better the agreement between the docked structure and its reference structure (Hasan et al., 2023; Sari et al., 2020). The validation results indicated that the docking method was reliable because the RMSD value was < 2.0 Å; therefore, molecular docking of the test compounds was considered feasible.

3.2. Molecular Docking Results

Among the 10 tested compounds, two compounds showed the most favorable binding affinities, namely persicogenin (−9.2 kcal/mol) and luteolin (−9.0 kcal/mol). These binding affinity values were relatively close to that of rofecoxib, suggesting that the tested compounds may exhibit comparable interaction strength with the COX-2 active site, which served as the native and reference ligand, with a binding affinity of −10.4 kcal/mol.

The binding affinity obtained from docking reflects the strength of the interaction between the ligand and the receptor. A more negative binding affinity indicates a stronger and more stable ligand-receptor interaction. This finding is also consistent with the study by Chen et al. (2007), which reported the anti-inflammatory activity of luteolin.

The observed binding affinity was influenced by the interactions formed, such as hydrogen bonds, hydrophobic interactions, and electrostatic interactions, all of which may increase the stability of the ligand-receptor complex. As shown in **Table 1**, persicogenin and luteolin formed several hydrogen bonds with amino acid residues at the active site of COX-2. The native ligand (rofecoxib) in **Figure 2** formed hydrogen bonds with HIS 90 and ARG 513, whereas persicogenin in **Figure 3** and luteolin in **Figure 4** interacted with different amino acid residues. Persicogenin formed hydrogen bonds with THR 212, HIS 207, and TYR 385. Notably, TYR385 is a key catalytic residue in the COX-2 active site that plays an important role in prostaglandin synthesis, whereas luteolin formed hydrogen bonds with THR 206, THR 212, and PHE 210. These interactions contributed to the stability of the ligand complex. Complex stability generally increases with the number of favorable interactions formed. Accordingly, a greater number of interactions may result in a more negative binding affinity value (Sururi et al., 2023).
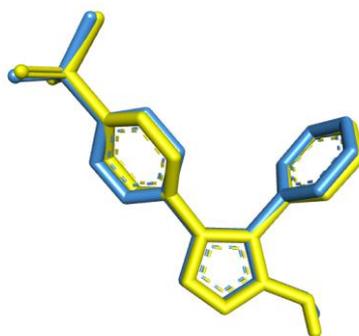

Figure 1. Ligand before docking (yellow) and ligand after docking (blue).

**Table 1.** Molecular docking results of the two best-performing compounds.

Compound	Binding affinity (kcal/mol)	Hydrogen-bonding residues	Hydrogen-bond distance (Å)	Other interacting residues
Rofecoxib (native ligand)	-10.40	HIS 90, ARG 513	2.35, 2.30	VAL 349, SER 353, VAL 523, ALA 527, PHE 518, LEU 352
Persicogenin	-9.20	THR 212, HIS 207, TYR 385	1.95, 2.12, 2.37	HIS 386, ALA 202, LEU 391, PHE 518, HIS 207
Luteolin	-9.00	THR 206, THR 212, PHE 210	2.96, 2.34, 2.47	HIS 386, HIS 207, ALA 202
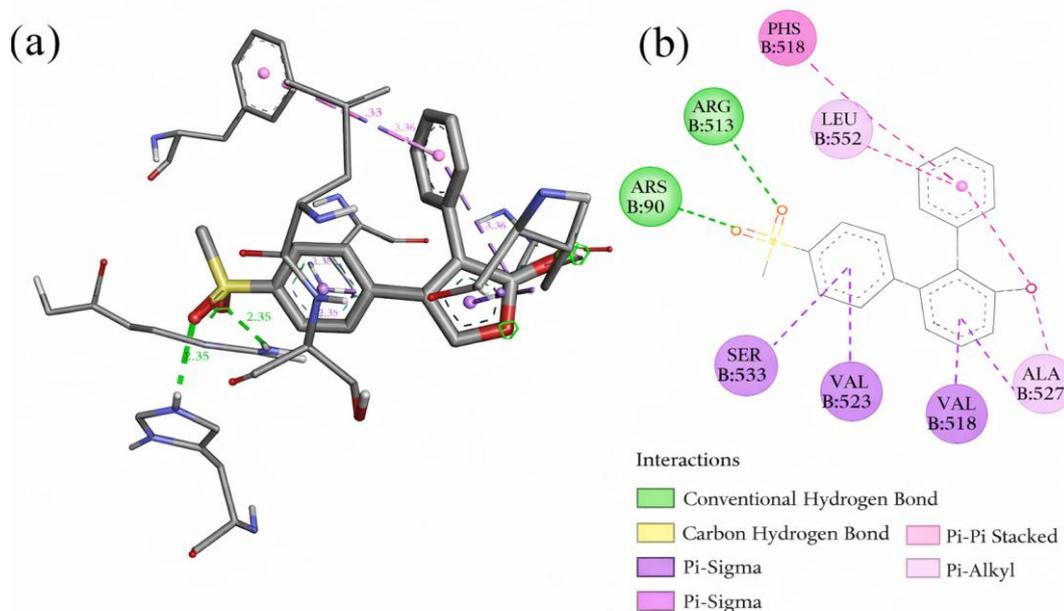
Figure 2. Three-dimensional (a) and two-dimensional (b) visualization of the interaction between the native ligand (rofecoxib) and the receptor (PDB ID: 5KIR).
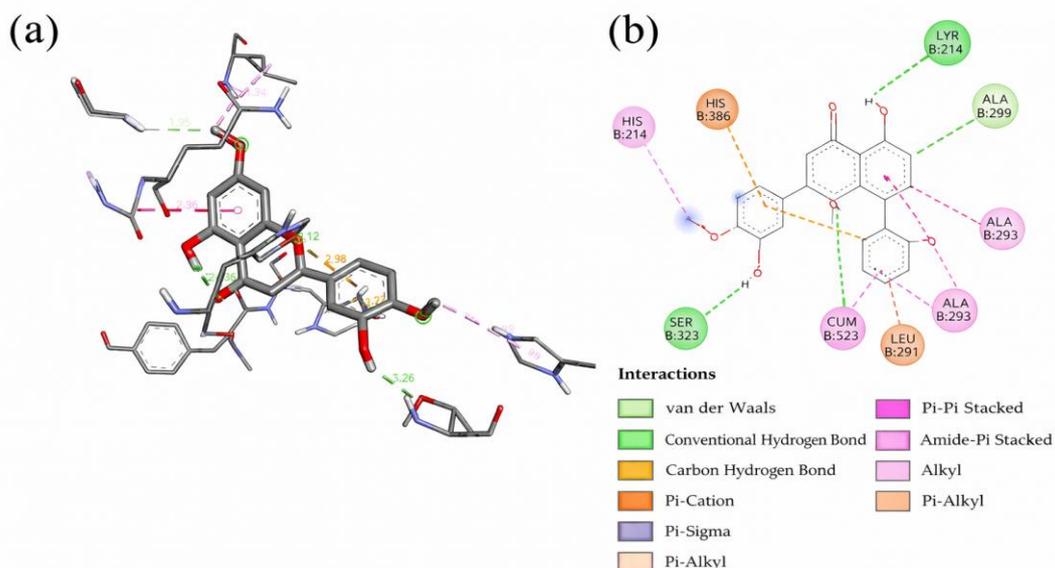
Figure 3. Three-dimensional (a) and two-dimensional (b) visualization of the interaction between persicogenin and the receptor (PDB ID: 5KIR).
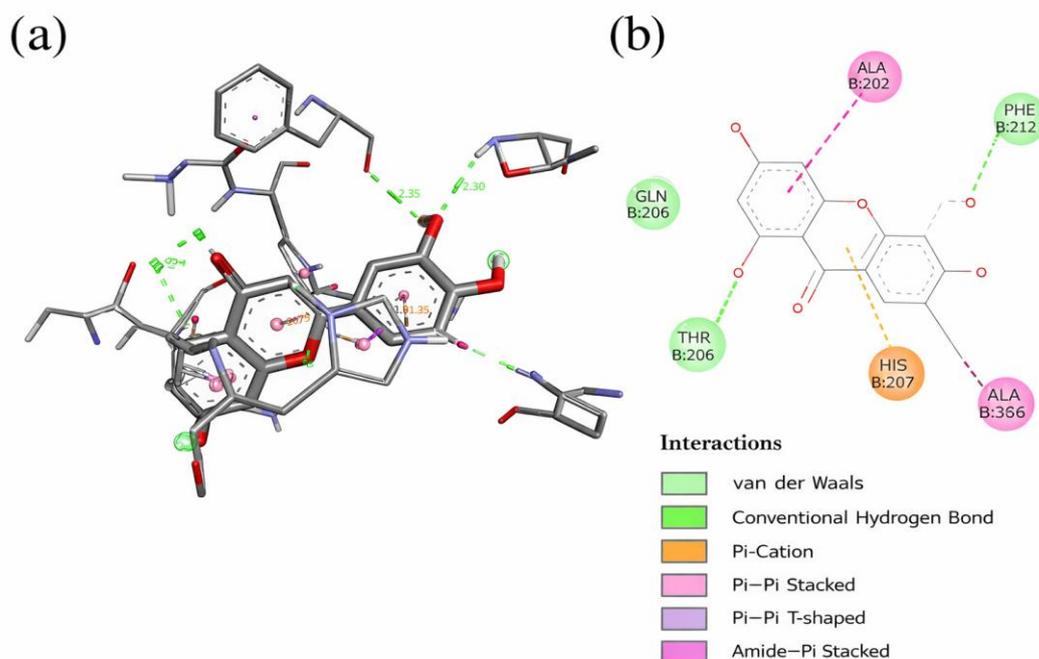
Figure 4. Three-dimensional (a) and two-dimensional (b) visualization of the interaction between luteolin and the receptor (PDB ID: 5KIR).

3.3. Drug-Likeness Evaluation Based on Lipinski's Rule of Five

Drug candidate evaluation is commonly performed through the analysis of drug-likeness and absorption, distribution, metabolism, excretion, and toxicity (ADMET) profiles. Drug-likeness is generally assessed based on Lipinski's rule of five, whereas ADMET prediction provides information on oral bioavailability, cellular permeability, metabolism, elimination, and toxicity, which are important characteristics of a drug candidate (Nusantoro & Fadlan, 2020).

Table 2 shows that all three compounds complied with Lipinski's rule of five. Lipinski's rule of five is commonly used to evaluate the drug-likeness of a compound based on physicochemical parameters that influence oral bioavailability. The LogP parameter reflects the hydrophobicity of a molecule. Excessively high values indicate pronounced hydrophobicity and may increase toxicity, whereas excessively low values indicate hydrophilicity that may limit permeation across lipid membranes. In addition, compounds with a molecular weight above 500 Da generally diffuse poorly across cell membranes. The numbers of hydrogen bond donors and acceptors also influence absorption, because greater hydrogen-bonding capacity requires more energy for membrane permeation (Weni et al., 2020).

3.4. ADMET Prediction Results

The ADMET prediction results are shown in **Table 3**. In terms of absorption-related properties, rofecoxib, persicogenin, and luteolin showed acceptable water solubility values (> -6 log mol/L). In addition, all three compounds showed human intestinal absorption values above 80%, indicating good intestinal absorption.

For distribution, rofecoxib and persicogenin showed VDss values below 0.45 log L/kg, indicating low distribution volumes and suggesting that these compounds tend to remain in plasma. In contrast, luteolin showed a higher VDss value above 0.45 log L/kg, suggesting broader distribution into tissues. Persicogenin also showed high Caco-2 membrane permeability (> 0.9 log Papp in 10^{-6} cm/s).

Metabolic parameters were evaluated using cytochrome P450 isoforms, including CYP substrates (CYP2D6 and CYP3A4) and CYP inhibitors (CYP1A2, CYP2C19, CYP2C9, CYP2D6, and CYP3A4) (Pires et al., 2015). The prediction results indicated that rofecoxib may act as a CYP3A4 substrate and as an inhibitor of CYP1A2, CYP2C19, and CYP2C9. Luteolin was predicted to inhibit CYP1A2 and CYP2C9, whereas persicogenin was predicted to inhibit CYP2C19 and CYP3A4. Both test compounds were predicted not to interact with CYP substrate isoforms.

Total clearance reflects the combined excretion of a compound through the liver and kidneys. Luteolin showed a higher total clearance value than persicogenin, but a slightly lower value than the reference compound rofecoxib. These results indicate that rofecoxib had the highest total clearance among the three compounds. In terms of toxicity, persicogenin and luteolin were predicted to be non-hepatotoxic, whereas rofecoxib was predicted to have hepatotoxic potential. Overall, the results presented in Tables 2 and 3 indicate that persicogenin demonstrated the most favorable balance between binding affinity and predicted pharmacokinetic and toxicity properties among the tested compounds.

Table 2. Prediction results based on Lipinski's rule of five.

Compound	MW (Da)	LogP	HBD	HBA	Molar refractivity	Compliance
Rofecoxib (native ligand)	300	3.638499	0	4	83.810982	Yes
Persicogenin	316	2.821499	2	6	81.634079	Yes
Luteolin	286	2.125199	4	6	72.478676	Yes

Table 3. ADMET prediction results

Parameter	Rofecoxib (native ligand)	Persicogenin	Luteolin
Water solubility (log mol/L)	-4.217	-3.441	-3.094
Human intestinal absorption (%)	98.413	92.299	81.130
VDss (log L/kg)	-0.619	-0.034	1.153
Caco-2 permeability (log Papp in 10^{-6} cm/s)	1.289	0.999	0.096
CYP substrate	Yes	No	No
CYP inhibition	Yes	Yes	Yes
Total clearance (log mL/min/kg)	0.888	0.106	0.495
Hepatotoxicity	Yes	No	No

4. CONCLUSION

This in silico study suggested that bioactive compounds from *V. trifolia* may exert anti-inflammatory potential through inhibition of the COX-2 target protein. Among the tested compounds, persicogenin exhibited the most favorable binding affinity (-9.2 kcal/mol) and was supported by favorable predictions based on Lipinski's rule of five and ADMET profiling. The ADMET results indicated that persicogenin met the criteria of Lipinski's rule of five as a potential oral drug candidate, showed good intestinal absorption, low distribution volume, high membrane permeability, inhibitory potential against CYP2C19 and CYP3A4, and no predicted hepatotoxicity. Overall, persicogenin demonstrated the most promising characteristics as a potential COX-2 inhibitor among the tested compounds. However, this study was limited to computational analysis; therefore, further in vitro and in vivo studies are required to validate the anti-inflammatory activity and safety of these compounds.

AUTHOR CONTRIBUTIONS

Conceptualization, Z.O. and H.H.; methodology, Z.O.; validation, H.H. and R.P.; formal analysis, A.S.U.; investigation, A.S.U. and H.H.; resources, H.H.; data curation, H.H.; writing—original draft preparation, H.H. and A.S.U.; writing—review and editing, Z.O. and M.I.; visualization, R.P. and H.H.; supervision, Z.O.; project administration, Z.O.; funding acquisition, Z.O. All authors have read and agreed to the published version of the manuscript.

INSTITUTIONAL REVIEW BOARD STATEMENT

Not applicable.

INFORMED CONSENT STATEMENT

Not applicable.

DATA AVAILABILITY STATEMENT

No new data were created or analyzed in this study. Data sharing is not applicable.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

DECLARATION OF GENERATIVE ARTIFICIAL INTELLIGENCE (AI) USE

The authors declare that no generative AI or AI-assisted technologies were used in the preparation or writing of this manuscript. All contents were produced entirely by the authors without any automated assistance.

REFERENCES

Ankalikar, A., & Viswanathswamy, A. H. (2017). Effect of leaves of *Vitex trifolia* Linn. on different stages of inflammation. *Indian Journal of Pharmaceutical Education and Research, 51*(3), 461–471. https://doi.org/10.5530/ijper.51.3.74

Chen, C. Y., Peng, W. H., Tsai, K. D., & Hsu, S. L. (2007). Luteolin suppresses inflammation-associated gene expression by blocking NF-κB and AP-1 activation pathway in mouse alveolar macrophages. *Life Sciences, 81*(23–24), 1602–1614. https://doi.org/10.1016/j.lfs.2007.09.028

Chen, L., Deng, H., Cui, H., Fang, J., Zuo, Z., Deng, J., Li, Y., Wang, X., & Zhao, L. (2018). Inflammatory responses and inflammation-associated diseases in organs. *Oncotarget, 9*(6), 7204–7218. https://doi.org/10.18632/oncotarget.23208

Clària, J. (2003). Cyclooxygenase-2 biology. *Current Pharmaceutical Design, 9*(27), 2177–2190. https://doi.org/10.2174/1381612033454054

El-Kousy, S., Mohamed, M., & Mohamed, S. (2012). Phenolic and biological activities of *Vitex trifolia* aerial parts. *Life Science Journal, 9*(2), 671–677.

Forli, S., Huey, R., Pique, M. E., Sanner, M. F., Goodsell, D. S., & Olson, A. J. (2016). Computational protein-ligand docking and virtual drug screening with the AutoDock suite. *Nature Protocols, 11*(5), 905–919. https://doi.org/10.1038/nprot.2016.051

Hasan, R., Cholashotul I'anah, F., Resvita, R., & Bahi, R. R. (2022). Docking molekuler senyawa potensial daun kelor (*Moringa oleifera*) terhadap reseptor folat. *Journal of Innovation Research and Knowledge, 2*(2), 519. https://doi.org/10.53625/jirk.v2i2.2918

Hasan, R., Herowati, R., & Pamudji Widodo, G. (2023). Molecular docking and pharmacokinetic prediction of potential compounds from *Luffa acutangula* as antidiabetic candidates. *Pharmaceutical Journal of Indonesia, 20*(1), 71–76. https://doi.org/10.30595/pharmacy.v0i0.16066

Ifora, I., Putri, A., & Oktavia, S. (2022). *Vitex trifolia* as cyclooxygenase-2 inhibitors in anti-inflammatory drug discovery. *International Journal of Pharmaceutical and Bio-Medical Science, 2*(10), 400–406. https://doi.org/10.47191/ijpbms/v2-i10-03

Kemenkes RI. (2018). *Laporan nasional Riset Kesehatan Dasar (Riskesdas)*. Badan Penelitian dan Pengembangan Kesehatan RI.

Li, W. X., Cui, C. B., Cai, B., Wang, H. Y., & Yao, X. S. (2005). Flavonoids from *Vitex trifolia* inhibit cell cycle progression at G2/M phase and induce apoptosis in mammalian cancer cells. *Journal of Asian Natural Products Research, 7*(4), 615–626. https://doi.org/10.1080/10286020310001625085

Loka, K. D. P., & Kodariah, R. (2022). Inflamasi kronis pada kolon: Tinjauan dari aspek COX-2 dan IL-10. *Pratista Patologi, 7*(2), 1–5.

Nusantoro, Y. R., & Fadlan, A. (2020). Analisis sifat mirip obat, prediksi ADMET, dan penambatan molekular isatinil-2-aminobenzoilhidrazon dan kompleks logam transisi Co(II), Ni(II), Cu(II), Zn(II) terhadap BCL2-XL. *Akta Kimia Indonesia, 5*(2), 114–126. https://doi.org/10.12962/j25493736.v5i2.7881

Pires, D. E. V., Blundell, T. L., & Ascher, D. B. (2015). pkCSM: Predicting small-molecule pharmacokinetic and toxicity properties using graph-based signatures. *Journal of Medicinal Chemistry, 58*(9), 4066–4072. https://doi.org/10.1021/acs.jmedchem.5b00104

Putri, F. S., Arief, M. J., & Rusli, R. (2024). Uji aktivitas antiinflamasi akut ekstrak etanol dan ekstrak air daun telang (*Clitoria ternatea* L.) dengan induksi karagenan. *Jurnal Mandala Pharmacon Indonesia, 10*(1), 151–156. https://doi.org/10.35311/jmpi.v10i1.467

Sari, I. W., Junaidin, J., & Pratiwi, D. (2020). Studi molecular docking senyawa flavonoid herba kumis kucing (*Orthosiphon stamineus* B.) pada reseptor α-glukosidase sebagai antidiabetes tipe 2. *Jurnal Farmagazine, 7*(2), 54. https://doi.org/10.47653/farm.v7i2.194

Silalahi, M., & Asra, R. (2024). *Vitex trifolia* (Botani, metabolit sekunder, dan bioaktivitasnya). *Jurnal Pro-Life, 11*(2), 96–110. https://doi.org/10.33541/pro-life.v11i2.5813

Sururi, A. M., Wati, A., & Kartika Maharani, D. (2023). Studi in silico: Potensi senyawa katekin dan turunannya dari teh hijau sebagai inhibitor HGF serta profil toksisitasnya. *UNESA Journal of Chemistry, 12*(2), 57–63. https://doi.org/10.26740/ujc.v12n2.p57-63

Wee, H. N., Neo, S. Y., Singh, D., Yew, H. C., Qiu, Z. Y., Tsai, X. R. C., How, S. Y., Yip, K. Y. C., Tan, C. H., & Koh, H. L. (2020). Effects of *Vitex trifolia* leaf extracts and phytoconstituents on cytokine production in human U937 macrophages. *BMC Complementary Medicine and Therapies, 20*, Article 91. https://doi.org/10.1186/s12906-020-02884-w

Weni, M., Safithri, M., & Seno, D. S. H. (2020). Molecular docking of active compounds *Piper crocatum* on the alpha-glucosidase enzyme as antidiabetic. *Indonesian Journal of Pharmaceutical Science and Technology, 7*(2), 64–72. https://doi.org/10.24198/ijpst.v7i2.21120