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Research Article

Leaf Effect of *C. Trifolia* L. as Nf-B and Tnf-A Inhibitor Compounds with *In Silico* Method

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ABSTRACT

Introduction: Infection *H. pylori* causes inflammation through various pathways to induce pro-inflammatory cytokines such as IL-1, IL-6, IL-8, and TNF-α. The transcription factor NF-kB is a crucial regulator of the immune response and inflammation and regulates many cellular processes that are important in carcinogenesis, including transformation, proliferation, angiogenesis, and metastasis. Anti-inflammatory plant *C. trifolia L* was shown to inhibit the activity of NF-B and several pro-inflammatory cytokine mediators. This study proved that the active compound from the plant's leaves, C. trifolia *L* has potential as an inhibitor of NF-B and TNF-α. **Method:** This study used a docking method with a grid box mimicking the bond between the receptor and the inhibitor control complex. **Results**: The bioactivity of Cayratria *trifolia* compounds as anti-inflammatory was shown in the inflammation parameters used, namely Interleukin 10 agonist, Interleukin agonist, Interleukin antagonist, Interleukin 6 antagonist, Interleukin 4 antagonist, Interleukin 2 agonist, Interleukin 1 antagonist, Interleukin 1b antagonist, Interleukin 10 antagonist, Interleukin 12 agonist, and Interleukin 1a antagonist. Interleukin 2 agonists showed the highest activity of all compounds. Piceid compounds showed high anti-inflammatory activity with interleukin 10 agonists, interleukin agonists, interleukin 6 antagonists, and interleukin 2 agonists. The compounds stilbenes, piceid, resveratrol, cyclopentadecane, and hentriacontane showed potency higher interleukin-6 inhibition than the other 22 compounds. These five compounds were continued for molecular docking analysis. The low bond energy is correlated with the number of bonds and the variety of interactions. The higher the number of bonds and the type of interaction, the lower the bond energy. The lower the bond energy, the stronger the interaction between the ligand and protein. **Conclusion:** Based on the prediction of anti-inflammatory bioactivity, five potential compounds were identified, namely cyclopentadecane, resveratrol, stilbenes, piceid, and hentriacontane. The five compounds bind to NFkB on the active site of the binding site with DNA, and this inhibition causes DNA to be unable to restrain NFkB transcription factors, and transcription does not occur. This proves that the active compound from the leaves of the plant *C. trifolia L* has potential as an inhibitor of NF-κB compounds. Inhibition of 6 compounds on TNF at the TNF receptor proves that the active compound from the leaves of the plant *C. trifolia L* has potential as a TNF-α inhibitor compound. The active ingredient Piceid exhibits predominant anti-inflammatory potential with lower binding energy and stronger interactions than other complexes.
Key words: *H. Pylori*, NFkB, TNF-α, *C. trifolia L, In silico.*

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INTRODUCTION

According to WHO, in 2012 showed that 17.5 million people worldwide die from cardiovascular disease. Recent studies have identified predictors of atherosclerosis, focusing on the inflammatory effects of infectious agents such as *Helicobacter Pylori (H. pylori)*. Efforts to overcome coronary artery disease (CAD) induced by *H. pylori* have not been optimal. Therefore, if the treatment of inflammation caused by *H. pylori* does not receive attention, the incidence of CAD due to *H. pylori* infection will increase.

The pathogenicity of *H. pylori* is primarily due to its various virulence components, including flagella, lipopolysaccharide (LPS), the vacuolating toxin VacA, and cytotoxin-associated gene pathogenicity island (cagPAI).[1] Infection *H. pylori* cause inflammation through various pathways for the induction of pro-inflammatory cytokines such as IL-1, IL-6, IL-8, and TNF-α. The transcription factor NF-kB is a crucial regulator of the immune response and inflammation and regulates many cellular processes that are important in carcinogenesis, including transformation, proliferation, angiogenesis, and metastasis.[2] Due to its essential role in inflammation and immunity, *H. pylori* activation and modulation of NF-B has been a topic of great interest to many researchers. NF-kB could be activated by various pro-inflammatory stimuli, including pathogenic products activating TLRs and cytokines ejected by other cells *via* canonical and non-canonical paths.[3] Three current bacterial products are essential for starting NF-kB by *H. pylori*: LPS, peptidoglycan, and CagA.[4]

To treat *H. pylori* infection currently, use a combination of antibiotics amoxicillin and clarithromycin (72.3 %) with the drug lansoprazole.[5] The use of antibiotics in *H. pylori* infection causes a decrease in cytokine levels.[6] Giving this drug also causes the bacteria to die, but the antigen that enters the body will induce atherosclerosis.

To prevent the inflammatory process, the community uses *C. trifolia L plants*.[7,8] Anti-inflammatory plant *C. trifolia L* is shown to inhibit the activity of NF-B and several pro-inflammatory cytokine mediators such as PGE2, IL-6, IL-1β, and TNF-α. Siriwatanamethanon

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N (2010)[7] showed that the methanol extract of *C. trifolia L* had an IC50 value of 83.16 in inhibiting NF-κB activity. However, the mechanism of action of plant extracts of *C. trifolia L* on the prevention of inflammation that induces endothelial dysfunction is not yet precise.

The content of all parts of *C. trifolia L* is reported to have secondary metabolites of alkaloids, steroids, terpenoids, flavonoids, and tannins.[8] The leaves contain stilbene (resveratrol, piceid, viniferin, ampelopsin) and the flavonoid cyanidin. Stems, roots, and leaves contain hydrocyanic acid and delphinidin.[8-10] The seeds and fruit contain cyanogenic components. Besides, aerial Part of this plant contains kaempferol, myricetin, quercetin, epifriedelanol and triterpenes.[8,11,12]

PURPOSE

To prove the active compound from the plant's leaves, *C. trifolia L* has the potential as an inhibitor of NF-κB compounds.

To prove the active compound from the plant's leaves, *C. trifolia L* has potential as a TNF-α inhibitor compound.

METHOD

Extraction of compound structure (ligand) and prediction of anti-inflammatory potential

A total of 27 compounds identified in *Cayratria trifolia* predicted their bioactivity as an anti-inflammatory, especially interacting with interleukins (Table 1). Prediction of bioactivity was carried out using the PASS online program. The five compounds screened for the structure were downloaded from the NCBI PubChem database, including cyclopentadecane, Resveratrol, Stilbenes, Piceid, and Hentriacontane. The 3D structure of the hentriacontane compound was modeled with the online program MolView (https://molview.org/).

Protein structure and preparation

Proteins NF-B (1a3q)[13] and TNF- (2az5)[14] were downloaded from the Protein Data Bank (PDB). Proteins were prepared by identifying the binding cavity integrated into the Molegro Virtual Docker program version 5.0.[15] active site prediction parameter, namely the molecular survey van der Waals maximum 5.

Docking simulation

The active site for NF-κB protein docking is X=13.78; Y=66.81, Z=-0.08, radius 15, and TNF-α (X=-32.52; Y=89.14, Z=42.95, radius 12). Other docking parameters are Score Function Moldock Score [Grid]; grid resolution 0.30; algorithm MolDock SE; Number of Runs 10, Max iteration 1500; max population size 50; pose generation energy threshold 100, tries 10 – 30; simplex evolution max steps 300; neighbor distance factor 1.00; multiple poses number of poses 5; energy threshold 0.00; cluster similar poses RMSD threshold 1. Docking results were analyzed using PyMol version 2.2 program. and Discovery Studio version 21.0.0.

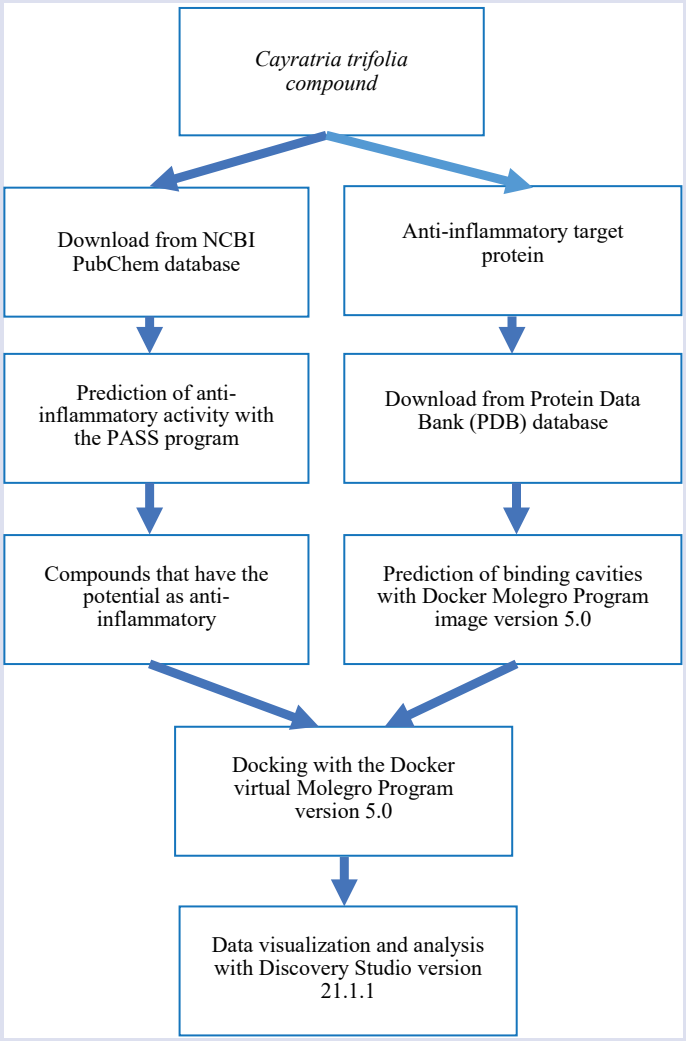


Figure 1: In silico analysis flowchart.

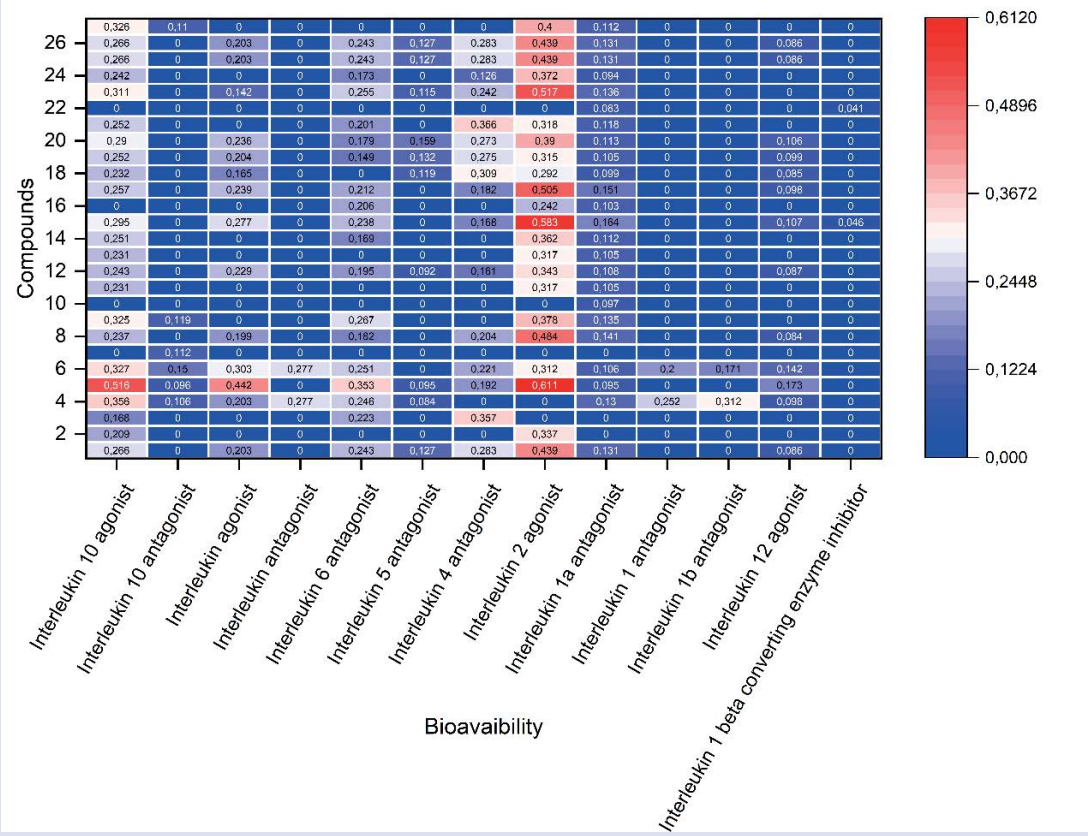


Figure 2: Anti-inflammatory activity with interleukin parameters.

Table 1: List of compounds contained in *Cayratia trifolia*.

No.	Compound	Reference	CID *
	1-pentacosanol	Sowmia 2020	92247
	finasteride	Sowmia 2020	57363
	ampelopsin	Cos et al., 2006	161557
	stilbenes	Cos et al., 2006	638088
	piceid	Cos et al., 2006	5281718
	resveratrol	Cos et al., 2006	445154
	viniferin	Cos et al., 2006	5315232
	linoleic acid	11	5280450
	Cyclopentadecane	11	67525
	9-Borabicyclo[3.3.1]nonane, 9-(2- propen-1-yloxy)-	11	534879
	3-Octadecyne	11	548889
	Ethanol, 2-(octadecyloxy)-	11	75050
	3-Octadecyne	11	548889
	9-Octadecyne	11	141998
	Hexadecanoic acid, ethyl ester	11	985
	Phytol	11	5280435
	Trans-13-Octadecenoic acid	11	6161490
	9,12-Octadecadienoic acid, ethyl ester	11	5365672
	Ethyl Oleate	11	5363269
	Octadecanoic acid, ethyl ester	11	8122
	3-Eicosene	11	5365051
	4,8,12,16-Tetramethylheptadecan-4-olide	11	567149
	Hentricontane	11	12410
	Heptadecane	11	12398
	Oxirane, hexadecyl-	11	23872
	1-Heptacosanol	11	74822
	epifriedelanol		

*CID = compound identity number obtained from PubChem NCBI Database

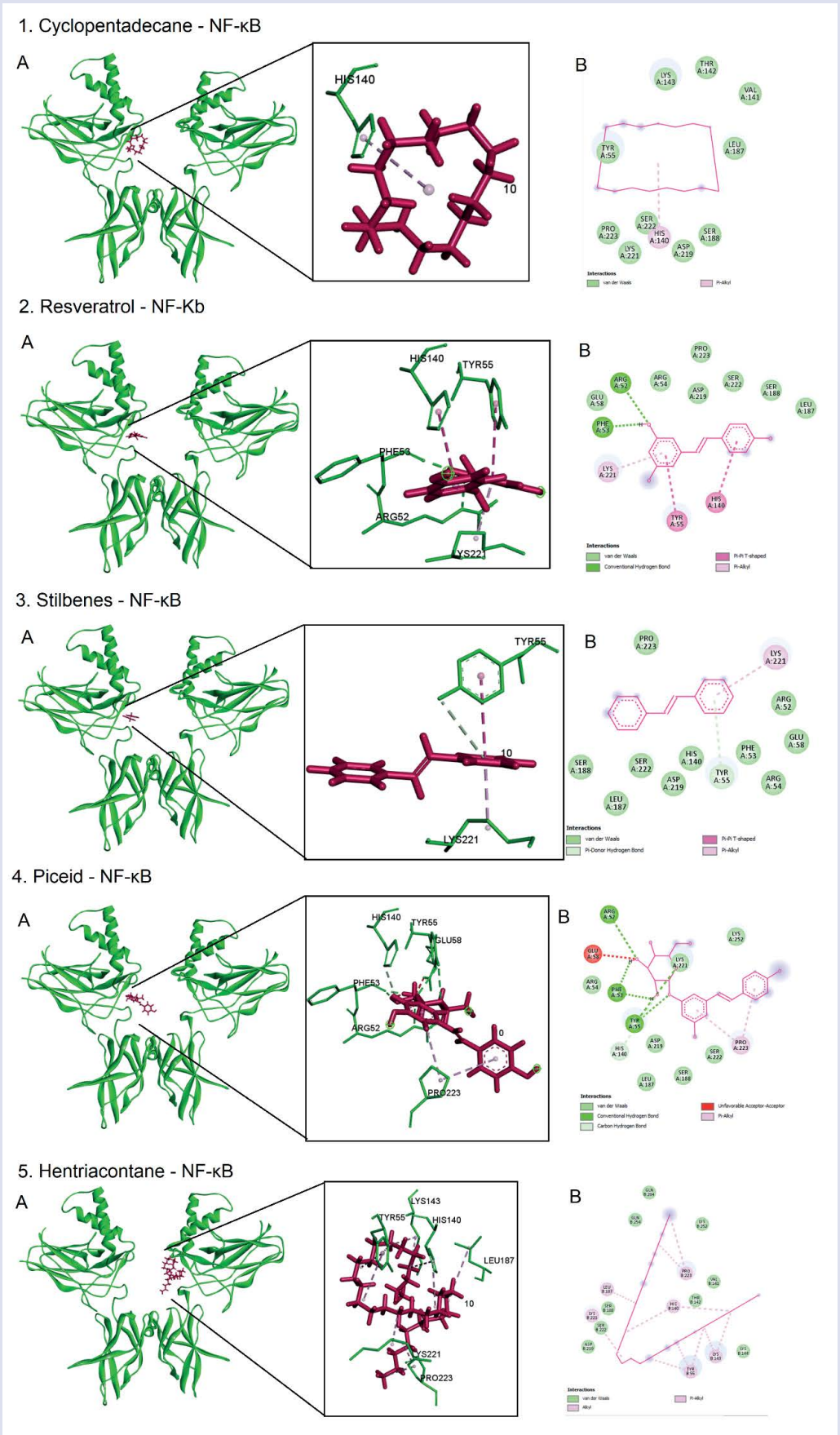


Figure 3: Interaction of *Cayratia trifolia* compounds with NF-κB protein.

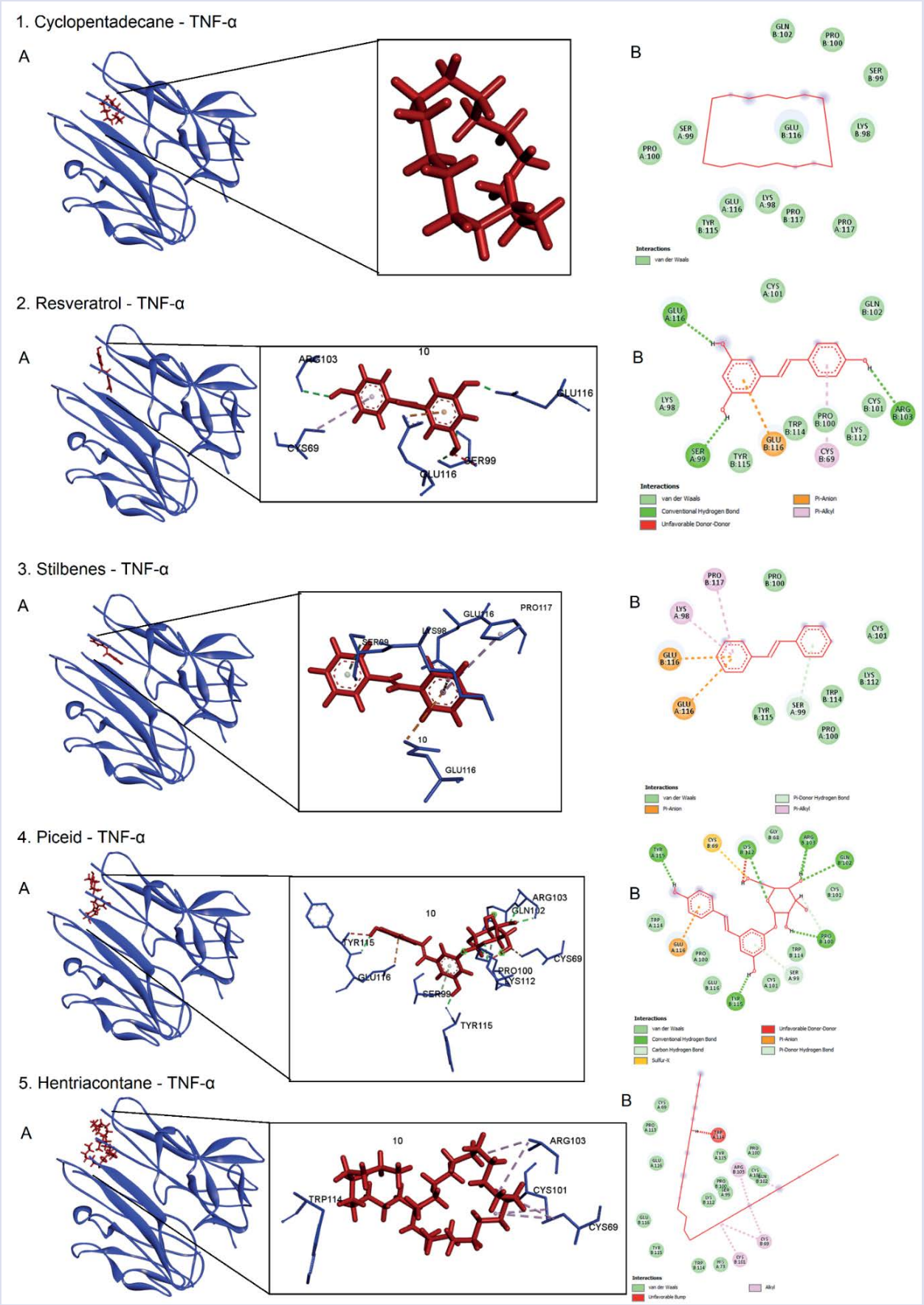


Figure 4: Interaction of *Cayratia trifolia compound* with TNF-α protein.

Table 2: Interaction of *Cayratia trifolia* compounds with NF-κB protein.

Complex Ligand - Protein	Binding Energy (kJ/mol)	Interaction	Distance (A)	Category	Type of Interaction
Cyclopentadecane - NF-κB	-170,4	A:HIS140 - :10	4,83028	Hydrophobic	Pi-Alkyl
		A:ARG52:NE - :10:O1	2,66008	Hydrogen Bond	Conventional Hydrogen Bond
		:10:H10 - A:PHE53:O	1,81098	Hydrogen Bond	Conventional Hydrogen Bond
Resveratrol - NF-Kb	-242,4	A:TYR55 - :10	4,44442	Hydrophobic	Pi-Pi T-shaped
		A:HIS140 - :10	4,73679	Hydrophobic	Pi-Pi T-shaped
		:10 - A:LYS221	3,48729	Hydrophobic	Pi-Alkyl
		A:TYR55:OH - :10	4,1498	Hydrogen Bond	Pi-Donor Hydrogen Bond
Stilbenes - NF-κB	-186,4	A:TYR55 - :10	4,36484	Hydrophobic	Pi-Pi T-shaped
		:10 - A:LYS221	3,49092	Hydrophobic	Pi-Alkyl
		A:ARG52:NE - :10:O2	3,32386	Hydrogen Bond	Conventional Hydrogen Bond
		A:TYR55:OH - :10:O1	3,17139	Hydrogen Bond	Conventional Hydrogen Bond
		A:TYR55:OH - :10:O4	2,94162	Hydrogen Bond	Conventional Hydrogen Bond
		:10:H8 - A:PHE53:O	1,62545	Hydrogen Bond	Conventional Hydrogen Bond
		:10:H10 - A:PHE53:O	1,63119	Hydrogen Bond	Conventional Hydrogen Bond
Piceid - NF-κB	-284	A:HIS140:CD2 - :10:O5	3,67398	Hydrogen Bond	Carbon Hydrogen Bond
		:10 - A:PRO223	5,42887	Hydrophobic	Pi-Alkyl
		:10 - A:PRO223	4,75723	Hydrophobic	Pi-Alkyl
		:10:H8 - :10:H10	1,86621	Unfavourable	Unfavourable Donor-Donor
		A:GLU58:OE2 - :10:O2	2,52438	Unfavourable	Unfavourable Acceptor-Acceptor
		B:LYS143 - :10	4,68578	Hydrophobic	Alkyl
		B:LYS143 - :10	4,42871	Hydrophobic	Alkyl
		B:LYS221 - :10	5,10234	Hydrophobic	Alkyl
		B:PRO223 - :10	3,96828	Hydrophobic	Alkyl
		:10:C1 - B:PRO223	4,69208	Hydrophobic	Alkyl
Hentriacontane - NF-κB	-210,6	:10 - B:LEU187	5,31876	Hydrophobic	Alkyl
		B:TYR55 - :10	4,90717	Hydrophobic	Pi-Alkyl
		B:TYR55 - :10	4,5295	Hydrophobic	Pi-Alkyl
		B:TYR55 - :10	4,926	Hydrophobic	Pi-Alkyl
		B:HIS140 - :10	4,7366	Hydrophobic	Pi-Alkyl
		B:HIS140 - :10	4,92587	Hydrophobic	Pi-Alkyl

Table 3: Interaction of Cayratia trifolia compound with TNF-α protein.

Complex Ligand - Protein	Binding Energy (kJ/mol)	Interaction	Distance (A)	Category	Type of Interaction
Cyclopentadecane - TNF-α	-172,5				
		:10:H10 - A:GLU116:OE2	1,9873	Hydrogen Bond	Conventional Hydrogen Bond
		:10:H11 - A:SER99:O	2,7608	Hydrogen Bond	Conventional Hydrogen Bond
		:10:H11 - A:SER99:OG	2,04174	Hydrogen Bond	Conventional Hydrogen Bond
Resveratrol - TNF-α	-211	:10:H12 - B:ARG103:O	2,69531	Hydrogen Bond	Conventional Hydrogen Bond
		B:GLU116:OE2 - :10	3,65954	Electrostatic	Pi-Anion
		:10 - B:CYS69	5,14083	Hydrophobic	Pi-Alkyl
		A:SER99:N - :10:H11	2,25922	Unfavourable	Unfavourable Donor-Donor
		A:GLU116:OE2 - :10	4,33369	Electrostatic	Pi-Anion
		B:GLU116:OE1 - :10	3,28542	Electrostatic	Pi-Anion
Stilbenes - TNF-α	-177,5	A:SER99:OG - :10	3,99355	Hydrogen Bond	Pi-Donor Hydrogen Bond
		:10 - A:LYS98	4,34293	Hydrophobic	Pi-Alkyl
		:10 - B:PRO117	5,28846	Hydrophobic	Pi-Alkyl
		B:GLN102:N - :10:O3	3,2046	Hydrogen Bond	Conventional Hydrogen Bond
		B:ARG103:N - :10:O3	2,61371	Hydrogen Bond	Conventional Hydrogen Bond
		B:LYS112:NZ - :10:O1	2,65088	Hydrogen Bond	Conventional Hydrogen Bond
		:10:H9 - B:ARG103:O	2,11522	Hydrogen Bond	Conventional Hydrogen Bond
		:10:H10 - B:PRO100:O	2,02621	Hydrogen Bond	Conventional Hydrogen Bond
		:10:H17 - B:TYR115:O	1,54997	Hydrogen Bond	Conventional Hydrogen Bond
Piceid - TNF-α	-295,6	:10:H22 - A:TYR115:O	2,14147	Hydrogen Bond	Conventional Hydrogen Bond
		:10:H1 - B:PRO100:O	2,46737	Hydrogen Bond	Carbon Hydrogen Bond
		B:CYS69:SG - :10:O6	3,27114	Other	Sulfur-X
		A:GLU116:OE2 - :10	3,1064	Electrostatic	Pi-Anion
		A:SER99:OG - :10	3,56791	Hydrogen Bond	Pi-Donor Hydrogen Bond
		A:TYR115:N - :10:H22	2,64875	Unfavourable	Unfavourable Donor-Donor
		B:LYS112:NZ - :10:H11	1,63949	Unfavourable	Unfavourable Donor-Donor
		B:CYS69 - :10	4,26866	Hydrophobic	Alkyl
		B:CYS69 - :10	4,94032	Hydrophobic	Alkyl
		B:CYS101 - :10	4,78313	Hydrophobic	Alkyl
Hentriacontane - TNF-α	-184,8	B:ARG103 - :10	4,32272	Hydrophobic	Alkyl
		B:ARG103 - :10	3,83176	Hydrophobic	Alkyl
		A:TRP114:HB1 - :10:H13	1,11945	Unfavourable	Unfavourable Bump

RESULTS

Cayratria trifolia compounds as an anti-inflammatory are shown in Figure 2. Inflammatory parameters used are Interleukin 10 agonist, Interleukin agonist, Interleukin antagonist, Interleukin 6 antagonist, Interleukin 4 antagonist, Interleukin 2 agonist, Interleukin 1 antagonist, Interleukin 1b antagonist, Interleukin 10 antagonist, Interleukin 12 agonist, and Interleukin 1a antagonist. Interleukin 2 agonists showed the highest activity of all compounds. Piceid compounds showed high anti-inflammatory activity with interleukin 10 agonists, interleukin agonists, interleukin 6 antagonists, and interleukin 2 agonists. The compounds stilbenes, piceid, resveratrol, cyclopentadecane, and hentriacontane showed potency higher interleukin-6 inhibition than the other 22 compounds. These five compounds were continued for molecular docking analysis.

DISCUSSION

Interaction of *Cayratia trifolia* compound with NF-κB protein

Based on the 3D view of the complex interaction of *Cayratia trifolia* with NF-B protein, four compounds, including cyclopentadecane, resveratrol, stilbenes, and piceid, showed the same binding region. In comparison, hentriacontane exhibits a different binding site. Cyclopentadecane showed one bond with the HIS140 residue with a hydrophobic interaction and yielded -170.4 kJ /mol energy. Based on a 2D view showing ten van der Waals forces. Based on the binding energy of the compound with protein NF-κB, Piceid - NF-κB < Resveratrol - NF-κB < Hentriacontane - NF-κB < Stilbenes - NF-κB < Cyclopentadecane - NF-κB. The low bond energy is correlated with the number of bonds and the variety of interactions. The higher the number of bonds and the type of interaction, the lower the bond energy. The lower the bond energy, the stronger the interaction between the ligand and protein.

Interaction of *Cayratia trifolia* compound with TNF-α protein

Cayratia trifolia with TNF- protein showed that Cyclopentadecane - TNF-α only showed van der Waals forces with -172.5 kJ/mol energy. The Piceid complex showed the lowest energy of all compounds, with a -295.6 kJ/mol bond energy. The types of bonds include hydrogen bonds, electrostatic bonds, sulfur-X, and unfavorable bonds. Resveratrol - TNF-α yields energy of -211 kJ/mol with amino acid residues GLU116, SER99, ARG103, and CYS69. Stilbenes bind to TNF- protein with electrostatic, hydrogen, and hydrophobic bonds at residues GLU116, SER99, LYS98, and PRO117, with the resulting bond energy -177.5 kJ/mol. The Hentriacontane - TNF-α complex yields bond energy of -184.8 kJ/mol. The low bond energy is correlated with the number of bonds and the variety of interactions. The higher the number of bonds and the type of interaction, the lower the bond energy. The lower the bond energy, the stronger the interaction between the ligand and protein.

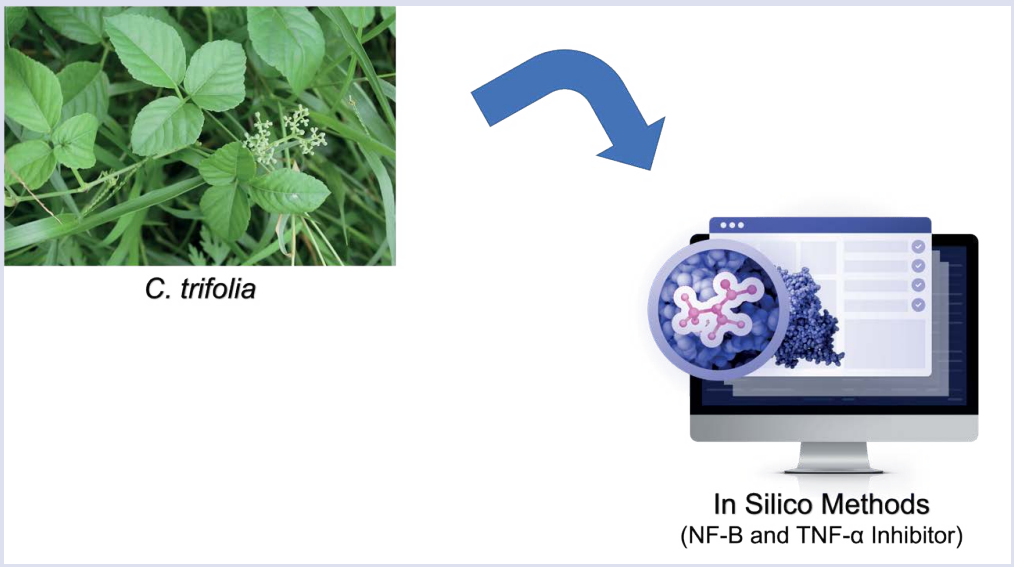
CONCLUSION

Five potential compounds were identified based on the prediction of anti-inflammatory bioactivity, namely cyclopentadecane, resveratrol, stilbenes, piceid, and hentriacontane. The five compounds bind to NFkB on the active site of the binding site with DNA. This inhibition causes DNA to be unable to restrain NFkB transcription factors, and transcription does not occur. This proves that the active compound from the leaves of the plant *C. trifolia L* has potential as an inhibitor of NF-κB compounds. Inhibition of 6 compounds on TNF at the TNF receptor proves that the active compound from the leaves of the plant *C. trifolia L* has potential as a TNF-α inhibitor compound. The active ingredient Piceid exhibits predominant anti-inflammatory potential with lower binding energies and stronger interactions than other complexes.

REFERENCES

1. Yamaoka Y. Mechanisms of disease: Helicobacter pylori virulence factors. Nat Rev Gastroenterol Hepatol. 2010;7(11):629-41.
2. Orlowski RZ, Baldwin Jr. NF-kappaB as a therapeutic target in cancer. Trends Mol Med. 2002;8:385-9.
3. Hayden MS, Ghosh S. Shared principles in NF-kappaB signaling. Cells. 2008;132:344-62.
4. Lamb A, Yamaguchi H, Chen LF. The many roads traveled by Helicobacter pylori to NF-kappaB activation. Gut Microbes. 2010;1(2):109-13.
5. Atharini YH, Probosuseno, Nugroho AE. Treatment Patterns and Clinical Outcomes in Helicobacter Pylori Infected Patients. J Pharm Man Serv. 2016;6(2):151-8.
6. Consolazio A, Borgia MC, Ferro D, Acopini F, Paoluzi OA, Crispino P, *et al.* Increased Thrombin Generation and Circulating Levels of Tumour Necrosis Factor-a in Patients with Chronic Helicobacter pylori-positive Gastritis. Aliment Pharmacol Ther. 2004;20(3):289-94.
7. Siriwatanametanon N, Fiebich BL, Efferth T, Prieto JM, Heinrich M. Traditionally Used Thai Medicinal Plants: In Vitro Anti-inflammatory, Anticancer and Antioxidant Activities. J Ethnopharmacol. 2010;130(2):196-207.
8. Feriadi E, Muhtadi A, Barliana MI. Galing (Cayratia trifolia L.): A Study of Biological, Phytochemical and Pharmacological Activities. Pharm Sci Health Magazine. 2018;4(2):1-5.
9. Roat C, Ramawat KG. Elucitor-Induced Accumulation of Stilbenes in Cell Suspension Cultures of Cayratia trifolia. Plant Biotechnol Rep. 2009.
10. Roat C, dan M Saraf. Isolation and Screening of Resveratrol Producing Endophytes from Wild Grape Cayratia trifolia. Int J Adv Agr Sci Technol. 2017;4(11).
11. Perumal PC, Sundaran S, Prabhakaran P, Balasubramanian V, Palanirajan A, Thangarajan S, *et al.* Isolation, Structural Characterization and In Silico Drug-Like Properties Prediction of a Natural Compound from The Ethanolic Extract of Cayratia trifolia. Pharmacognosy Res. 2014;7(1):121-5.
12. Ragasa CY, Adiel IB, Emelina HM, Chien-Chang S. Chemical Constituents of Cayratia trifolia L. Der Pharma Chem. 2014;6(6).
13. Cramer P, Larson CJ, Verdine GL, Müller CW. Structure of the human NF-κB p52 homodimer-DNA complex at 2.1 A resolution. EMBO J. 1997;16(23):7078-90.
14. Qaiser H, Saeed M, Nerukh D, Ul-Haq Z. Structural insight into TNF-α inhibitors through combining pharmacophore-based virtual screening and molecular dynamic simulation. J Biomol Struc Dynam. 2021;39(16):5920-39.
15. Bitencourt-Ferreira G, de Azevedo WFJ. Molegro Virtual Docker for Docking. Methods Mol Biol. 2019;2053:149-67.
16. Preston RC, Jakob RP, Binder FPC, Sager CP, Ernst B, Maier T. E-selectin ligand complexes adopt an extended high-affinity conformation. J Mol Cell Biol. 2016;8(1):67-72.
17. Somers W, Stahl M, Seehra JS. 1.9 Å crystal structure of interleukin 6: Implications for a novel mode of receptor dimerization and signaling. EMBO J. 1997;16(5):989-97.
18. Wang JH, Pepinsky RB, Stehle T, Liu JH, Karpusas M, Browning B, *et al.* The crystal structure of an N-terminal two-domain fragment of vascular cell adhesion molecule 1 (VCAM-1): A cyclic peptide based on the domain 1 C-D loop can inhibit VCAM-1-α4 integrin interaction. Proc Natl Acad Sci U S A. 1995;92(12):5714-8.

GRAPHICAL ABSTRACT



ABOUT AUTHORS

Judya Sukmana: He is a doctoral student from Faculty of Medicine, Airlangga University Indonesia. He is also a lecturer at Hang Tuah University Indonesia. Recently, his research topic about the active compound from the leaves of the plant C. trifolia L has potential as inflammatory in silico methods.

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