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-κB 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 Cayratia 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 agonist, 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 antagonists, and interleukin 2 agonists. The compounds stilbenes, piceid, resveratrol, cyclopentadecane, and hentriacontane showed potent 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 NFκB 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 NFκB 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.

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 cytotoxic-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.3 Anti-inflammatory plant C. trifolia L is shown to inhibit the activity of NF-B and several pro-inflammatory cytokine mediators such as PG2, IL-6, IL-1β, and TNF-α. Sirivatanamethanon

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

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

### PURPOSE

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

To prove the active compound from the plant's leaves, *C. trifolia* 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 *Cayratia 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-κB (1a3q) and TNF-α (2az5) 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. 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.

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**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   | 1-pentacosanol                                 | Sowmia 2020 | 92247 |
| 2   | finasteride                                    | Sowmia 2020 | 57363 |
| 3   | ampolopsin                                     | Cos et al., 2006 | 161557 |
| 4   | stilbenes                                      | Cos et al., 2006 | 638088 |
| 5   | piceid                                        | Cos et al., 2006 | 5281718 |
| 6   | resveratrol                                    | Cos et al., 2006 | 445154 |
| 7   | viniferin                                      | Cos et al., 2006 | 5315232 |
| 8   | linoleic acid                                  | 11          | 5280450 |
| 9   | Cyclopentadecane                               | 11          | 67525 |
| 10  | 9-Borabicyclo[3.3.1]nonane, 9-(2-propen-1-yloxy)-octadecene | 11          | 534879 |
| 11  | Octadecyl-3-ylol                              | 11          | 548889 |
| 12  | Ethanol, 2-octadecyloxy-3-ylol                  | 11          | 75050 |
| 13  | Octadecyl-3-ylol                               | 11          | 548889 |
| 14  | Octadecyl-9-ylol                               | 11          | 141998 |
| 15  | Hexadecanoic acid, ethyl ester                 | 11          | 985   |
| 16  | Phytol                                        | 11          | 5280435 |
| 17  | Trans-13-Octadeconoic acid                     | 11          | 6161490 |
| 18  | 9,12-Octadecadienoic acid, ethyl ester         | 11          | 5365672 |
| 19  | Ethyl Oleate                                   | 11          | 5363269 |
| 20  | Octadecanoic acid, ethyl ester                 | 11          | 8122  |
| 21  | 3-Eicosene                                     | 11          | 5365051 |
| 22  | 4,8,12,16-Tetramethylheptadecano-4-olide       | 11          | 567149 |
| 23  | Hendricontane                                  | 11          | 12410 |
| 24  | Heptadecane                                   | 11          | 12398 |
| 25  | Oxirane, hexadecyl-                           | 11          | 23872 |
| 26  | 1-Heptacosanol                                 | 11          | 74822 |

*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.
| Complex Ligand - Protein | Binding Energy (kJ/mol) | Interaction | Distance (Å) | Category | Type of Interaction |
|-------------------------|-------------------------|-------------|--------------|----------|--------------------|
| Cyclopentadecane - NF-κB | -170,4 | A:HS140 - :10 | 4,83028 | Hydrophobic | Pr-Alkyl |
|                         |             | A:ARG52:NE - :10:O1 | 2,66008 | Hydrogen Bond | Conventional Hydrogen Bond |
|                         |             | :10:H10 - A:PHES3:O | 1,81098 | Hydrogen Bond | Conventional Hydrogen Bond |
| Resveratrol - NF-Kb     | -242,4 | A:TYR55 - :10 | 4,44442 | Hydrophobic | Pr-Pi T-shaped |
|                         |             | A:HS140 - :10 | 4,73679 | Hydrophobic | Pr-Pi T-shaped |
|                         |             | :10 - A:LYS221 | 3,48729 | Hydrophobic | Pr-Alkyl |
|                         |             | A:TYR55:OH - :10 | 4,1498 | Hydrogen Bond | Conventional Hydrogen Bond |
| Stilbenes - NF-κB       | -186,4 | A:TYR55 - :10 | 4,36484 | Hydrophobic | Pr-Pi T-shaped |
|                         |             | :10 - A:LYS221 | 3,49092 | Hydrophobic | Pr-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:PHES3:O | 1,62545 | Hydrogen Bond | Conventional Hydrogen Bond |
|                         |             | :10:H10 - A:PHES3:O | 1,63119 | Hydrogen Bond | Conventional Hydrogen Bond |
|                         |             | A:HS140:CD2 - :10:O5 | 3,67398 | Hydrogen Bond | Carbon Hydrogen Bond |
|                         |             | :10 - A:PRO223 | 5,42887 | Hydrophobic | Pr-Alkyl |
|                         |             | :10 - A:PRO223 | 4,75723 | Hydrophobic | Pr-Alkyl |
|                         |             | :10:H8 - :10:H10 | 1,86621 | Unfavourable | Unfavourable Donor-Donor |
|                         |             | :10:H10 - :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 | 4,95284 | Hydrophobic | Alkyl |
|                         |             | :10:C1 - B:PRO223 | 4,69208 | Hydrophobic | Alkyl |
| Henriciacontane - NF-κB | -210,6 | :10 - B:LEU187 | 5,31876 | Hydrophobic | Alkyl |
|                         |             | B:TYR55 - :10 | 4,90717 | Hydrophobic | Pr-Alkyl |
|                         |             | B:TYR55 - :10 | 4,5295 | Hydrophobic | Pr-Alkyl |
|                         |             | B:TYR55 - :10 | 4,926 | Hydrophobic | Pr-Alkyl |
|                         |             | B:HS140 - :10 | 4,7366 | Hydrophobic | Pr-Alkyl |
|                         |             | B:HS140 - :10 | 4,92587 | Hydrophobic | Pr-Alkyl |

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

| Complex Ligand - Protein | Binding Energy (kJ/mol) | Interaction | Distance (Å) | 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 |
|                         |             | :10:H12 - B:ARG103:O | 2,69531 | Hydrogen Bond | Conventional Hydrogen Bond |
|                         |             | B/GLU116:OE2 - :10 | 3,65954 | Electrostatic | Pt-Anion |
|                         |             | :10 - B:CY69 | 5,14083 | Hydrophobic | Pr-Alkyl |
|                         |             | A:SER99:N - :10:H11 | 2,25922 | Unfavourable | Unfavourable Donor-Donor |
|                         |             | B/GLU116:OE2 - :10 | 4,33369 | Electrostatic | Pt-Anion |
|                         |             | B/GLU116:OE1 - :10 | 3,28542 | Electrostatic | Pt-Anion |
|                         |             | B:GLN102:N - :10:O3 | 3,99355 | Hydrogen Bond | Pr-Donor Hydrogen Bond |
|                         |             | :10 - A:LYS98 | 4,34293 | Hydrophobic | Pr-Alkyl |
|                         |             | :10 - B:PRO117 | 5,28846 | Hydrophobic | Pr-Alkyl |
|                         |             | B:GLN102:N - :10:O3 | 3,2046 | Hydrogen Bond | Conventional Hydrogen Bond |
|                         |             | B:ARG103:N - :10:O3 | 2,61731 | Hydrogen Bond | Conventional Hydrogen Bond |
|                         |             | B:LYS12: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 |
|                         |             | B:TYR115:O - :10 | 1,54997 | Hydrogen Bond | Conventional Hydrogen Bond |
|                         |             | B:TYR115:O - :10 | 2,14147 | Hydrogen Bond | Conventional Hydrogen Bond |
|                         |             | :10:H12 - B:ARG103:O | 2,46737 | Hydrogen Bond | Carbon Hydrogen Bond |
|                         |             | B:CY69:SG - :10:O6 | 3,27114 | Other | Sulfur-X |
|                         |             | A:GLU116:OE2 - :10 | 3,1064 | Electrostatic | Pt-Anion |
|                         |             | A:SER99:OG - :10 | 3,56791 | Hydrogen Bond | Pr-Donor Hydrogen Bond |
|                         |             | A:TYR115:N - :10:H22 | 2,64875 | Unfavourable | Unfavourable Donor-Donor |
|                         |             | B:LYS12:NZ - :10:H11 | 1,63949 | Unfavourable | Unfavourable Donor-Donor |
|                         |             | B:CY69 - :10 | 4,26866 | Hydrophobic | Alkyl |
|                         |             | B:CY69 - :10 | 4,94032 | Hydrophobic | Alkyl |
| Henriciacontane - TNF-α | -295,6 | B:CY69:SG - :10:O6 | 3,27114 | Other | Sulfur-X |
|                         |             | A:GLU116:OE2 - :10 | 3,1064 | Electrostatic | Pt-Anion |
|                         |             | B:SER99:OG - :10 | 3,56791 | Hydrogen Bond | Pr-Donor Hydrogen Bond |
|                         |             | A:TYR115:N - :10:H22 | 2,64875 | Unfavourable | Unfavourable Donor-Donor |
|                         |             | B:LYS12:NZ - :10:H11 | 1,63949 | Unfavourable | Unfavourable Donor-Donor |
|                         |             | B:CY69 - :10 | 4,26866 | Hydrophobic | Alkyl |
|                         |             | B:CY69 - :10 | 4,94032 | Hydrophobic | Alkyl |
|                         |             | B:TRP114:HB1 - :10:H13 | 1,11945 | Unfavourable | Unfavourable Bump |

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

Cayratia 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 agonist. 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-xB, Piceid -NF-xB < Resveratrol - NF-xB < Hentriacontane - NF-xB < Stilbenes - NF-xB < Cyclopentadecane - NF-xB. 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 TNF-α yields energy of -211 kJ/mol with amino acid residues GLU116, electrostatic, sulfur-X, and unfavorable bonds. Resveratrol - NF-κB showed one bond with the HIS140 residue with a -295.6 kJ/mol bond energy. 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 NFκB on the active site of the binding site with DNA. This inhibition causes DNA to be unable to restrain NFκB 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-xB 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.

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