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Anti-inflammatory Activity of *Tectona grandis* Linn. F. Extract Against TNF-α using In Vivo and Silico Methods

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ABSTRACT

Tumor necrosis factor-alpha (TNF-α), a cytokine involved in inflammation, plays a critical role in inflammatory processes, particularly in synovial cells. Therefore, TNF-α represents a promising target for anti-inflammatory interventions. This study investigates the anti-inflammatory potential of *Tectona grandis* leaf extract by evaluating its ability to inhibit TNF-α activity. To identify bioactive compounds from the extract that may interact with the TNF-α receptor, molecular docking simulations were employed. In vivo experiments were conducted using different doses of the extract (100, 200, and 300 mg/kg body weight), and TNF-α levels were quantified to assess the anti-inflammatory effect. At a dose of 300 mg/kg, TNF-α levels were significantly reduced to 0.358 µg/L, indicating superior anti-inflammatory activity compared to the lower doses (0.539 µg/L at 100 mg/kg and 0.433 µg/L at 200 mg/kg). Molecular docking simulations revealed two bioactive compounds, Phaeophorbid A and (132S, 17S, 18S)-132-Hydroxy-20-Chloro-Ethylpheophorbide A, which demonstrated strong binding affinities (-5.4 kcal/mol and -5.2 kcal/mol, respectively) and interacted with the TNF-α receptor through hydrogen bonds and hydrophobic interactions. These results underscore the potential of *Tectona grandis* as a source of novel anti-inflammatory agents, suggesting its value in the development of therapeutic strategies targeting TNF-α in inflammation-related disorders.

***Keywords*:** Inflammatory; LC-MS; *Tectona grandis* Linn.F.; TNF- α

INTRODUCTION

The collection of cells, materials, and pathways that shield cells from external invaders is known as the immune system. The immune system consists of two main pillars of protection against pathogens: innate immunity and adaptive immunity.[1] Innate immunity is characterized by its rapid, non-specific response that acts within minutes to hours, providing the first line of defense. Adaptive immunity, on the other hand, is antigen-dependent and involves a more specific and memory-based response following exposure to antigens. These two types of immunity work synergistically to maintain homeostasis and prevent disease.[2] Any disruption in this balance can result in conditions such as immunodeficiency disorders, autoimmune diseases, or chronic inflammation.[3]

Inflammation is one of the body's natural defense mechanisms to combat invading pathogens. However, chronic

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inflammation can lead to serious health issues, including metabolic disorders, cardiovascular diseases, and cancer.[4] Tumor Necrosis Factor-Alpha (TNF-α), a pro-inflammatory cytokine, plays a critical role in the inflammatory response. Targeting TNF-α has emerged as a therapeutic strategy to modulate inflammatory pathways.[5] Recent research has highlighted the importance of identifying natural compounds capable of inhibiting TNF-α to address chronic inflammation.

Tectona grandis Linn F., commonly known as teak, has been widely used in traditional medicine for various ailments.[6] While the pharmacological properties of teak leaves, such as anti-ulcer, anti-anemia, antibacterial, and wound-healing effects, have been reported, their specific role in targeting inflammatory mediators like TNF-α remains underexplored.[7,8,9] This presents a significant research gap, as the anti-inflammatory potential of teak leaves, particularly in the context of chronic inflammation, has not been fully investigated. Furthermore, although secondary metabolites such as quinones, flavonoids, phenolics, and tannins are known for their pharmacological activities, it is critical to establish their specific contribution to TNF-α inhibition.[10]

In this study, we aim to explore the anti-inflammatory activity of Tectona grandis Linn. F. teak leaf extract, focusing on its ability to inhibit TNF-α. The novelty of this research lies in combining in vivo and in silico approaches to validate the inhibitory effects of teak leaf extract on TNF-α and other pro-inflammatory cytokines. Through molecular docking and experimental testing, we seek to identify active compounds that can serve as potential anti-inflammatory agents. Our findings are expected to provide new insights into the therapeutic potential of teak leaves and their role in managing chronic inflammatory conditions.

METHODS

Plant collection and extraction

The leaves of *Tectona grandis* were collected from Southeast Sulawesi, Indonesia. The plant species were identified and verified at the Biology Laboratory, Halu Oleo University, ensuring that the correct plant species was used for the study.

The leaves of *Tectona grandis* were separated from impurities through a wet-sorting process, washed, thinly sliced, and air-dried before being pulverized. The powdered leaves were then weighed and subjected to maceration with 70% ethanol solvent for three cycles of 24 hours each. The extract was concentrated using a rotary evaporator to obtain a thickened extract.

In vivo study

The anti-inflammatory effect of the *Tectona grandis* leaf extract was assessed by measuring the volume of edema in the paws of mice induced with 1% carrageenan. The edema volume was calculated by measuring the difference in paw volume before and after carrageenan injection.[11,12]

The blood samples were collected by cardiac puncture, placed in EDTA-coated tubes, and stored at 2–8°C. The blood plasma was separated by centrifugation at 2000–3000 rpm for 15 minutes. The TNF-α levels in the plasma were measured using an ELISA kit, following the manufacturer's instructions.[13,14]

After the addition of the stop solution (50 µL), the color change from blue to yellow was monitored, and TNF-α levels were quantified using an ELISA reader at a wavelength of 450 nm.

Data collection and analysis

In vivo data were presented as the mean TNF-α levels, with comparisons made between the experimental and control groups. The results were analyzed statistically using One-Way ANOVA, with a significance level set at $p < 0.05$.

Ethical considerations

This study was approved by the Ethics Committee of the Faculty of Medicine, Halu Oleo University, under the ethical

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clearance number 049/UN.29.17.1.3/ETIK/2023.

In silico study

Molecular docking simulations were performed to predict the binding affinity of compounds in the teak leaf extract to the Tumor Necrosis Factor-Alpha (TNF-α) receptor. The 3D structure of TNF-α (PDB code 7JRA) was obtained from the RCSB Protein Data Bank.[15]

The structure was refined using BIOVIA Discovery Studio 2020 by removing water molecules, solvents, and associated ligands. The 3D structures of the compounds from *Tectona grandis* leaves were retrieved from PubChem and prepared using AutoDock Tools 1.5.6. Prior to docking, hydrogen atoms were added to the TNF-α structure, and the ligand structures were assigned Kollman and Gasteiger charges.[16,17]

The docking simulations were performed using AutoDock Vina, with a grid size of 15 Å and a spacing of 0.375 Å.[18] The docking validation was performed by ensuring that the Root Mean Square Deviation (RMSD) of the ligand was less than 2 Å, in line with previously established procedures.[19] The docking results were visualized and analyzed using BIOVIA Discovery Studio 2020.

RESULTS AND DISCUSSION

Activity anti-inflammatory

Maserate from the maceration process was placed in a container and evaporated using a rotary vacuum evaporator set to 50°C. This produced an extract that was thick, reddish-dusky in color, and had a distinctive scent. Additionally, the extracted thick was found to have a weight and yield of 254.14 g.

The mice's foot were subplantarly injected with 0.1 ml of 1% carrageenan suspension as an inducer, as part of the artificial edema technique employed in this study. All mice were starved for 10–12 hours prior to treatment. Every mouse was weighed and its left foot marked. Its left foot was then placed into a Plethysmometer, a device used to measure edema volume, and the initial volume (V0) of the foot was noted. Next, a 1% (w/v) carrageenan solution was sub-plantar injected into each mouse's foot. Using a plethysmometer, the amount of edema that developed after 30 minutes was calculated and recorded as the volume of the mouse's soles (Vt). Measurements were again taken until the 120th minute after the test animals were administered the test solution by their grouping: negative control, positive control, and control dose of extract (100 mg/kgBW, 200 mg/kgBW, and 300 mg/kgBW).

The treatment group did not have a discernible decrease in edema, as seen by the mice's legs' average swelling at 120 minutes, which was 0.733 mm. This demonstrates that administering Na-CMC is unable to reduce inflammation. Diclofenac Natrium has strong anti-inflammatory properties and works by blocking the cyclooxygenase enzyme (COX-1 and COX-2), which prevents the release of inflammatory mediators. This is why the positive control showed a reduction in edema with an average of 0.160 mm at 120 minutes. In order to prevent inflammation, such as prostaglandins.[20,21]

With a mean swelling value of 0.213 mm at 120 minutes, the dose of teak leaf ethanol extract in the treatment group (300 mg/kgBW) reduced edema more than other extracts and nearly as much as the positive control, diclofenac sodium. With a mean swelling value of 0.418 mm and 0.318 mm, the treatment group receiving 100 doses of teak leaf ethanol extract mg/kgBW and 200 mg/kgBW demonstrated a lesser reduction in edema. Following the measurement of mouse paw edema volume in each test group, the data was statistically analyzed using the Shapiro-Wilk normality test, which revealed that each test group's data distribution was normally distributed with a ρ value > 0.05.

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The group control positive was as high as 54.225%, the group extract was as high as 45.086 %, the extract 200 mg/KgBW was as high as 37.045%, the extract 100 mg/KgBW was as high as 25.251 %, and the group control negative was at zero percent. These percentages represent the average inhibition of inflammation from the largest down to the smallest, in that order. In excellent extracts, the group extract with the highest percentage of inflammation inhibition is 300 mg/KgBW. Considering that the inhibition group control is nearly at a positive percentage. Because there is content on the teak leaves, the larger the value of the ability to block inflammation, the greater the suppression of inflammation that happens. Alkaloids, tannins, terpenoids, saponins, and flavonoids are examples of secondary metabolite chemicals that have anti-inflammatory properties.[22,23]

The anti-inflammatory properties of flavonoids are similar to those of diclofenac sodium in that they can prevent inflammation by blocking pro-inflammatory enzymes including lipoxygenase (LOX) and cyclooxygenase (COX), which are involved in the production of leukotrine. In addition to impeding the metabolism of sour arachidonic acid, which reduces prostaglandin synthesis, flavonoids also inhibit secretory enzymes. Mediators of inflammation are called lysosomes. Inhibition of mediators that cause inflammation This may prevent the inflammatory process's proliferation.[24,25]

Enzyme-linked immunosorbent assay (ELISA) results of TNF-α examination, which is a quantitative study demonstrating antigen-antibody response through color change obtained with the use of conjugate-related enzymes and substrate enzymes.[26,27] The samples utilized to measure TNF-α levels were previously centrifuged blood plasma containing EDTA. Next, the ELISA reader method will be used to measure the plasma levels of TNF-α. In the activity testing of the teak leaf (*Tectona grandis* Linn F.) extract, the mean TNF-α rate was achieved with a value of 0.71 µg/L in the control negative group and 0.130 µg/L in the group treated with diclofenac sodium. Group therapy one leaf teak extract dose of 100 mg/kgBB equals 0.539 µg/L; two leaf teak extracts dosed at 200 mg/kgBB equals 0.433 µg/L; and three leaf teak extracts dosed at 300 mg/kgBB equals 0.358 µg/L in a group therapy. TNF-α levels are notable in all test groups compared to the normal group. With every increase in concentration, relative returns fall. The control negative, Na-CMC, is inert or neutral and has no ability to reduce TNF-α levels, indicating the highest levels of TNF-α. Conversely, when diclofenac sodium is administered, the lowest levels of TNF-α, specifically on control positive, are observed. Because of its ability to inhibit cyclooxygenase enzymes (COX-1 and COX-2), diclofenac sodium has a strong anti-inflammatory effect. This means that it can prevent the release of prostaglandins and other inflammatory mediators, as well as TNF-α, a cytokine that promotes inflammation.[28,29]

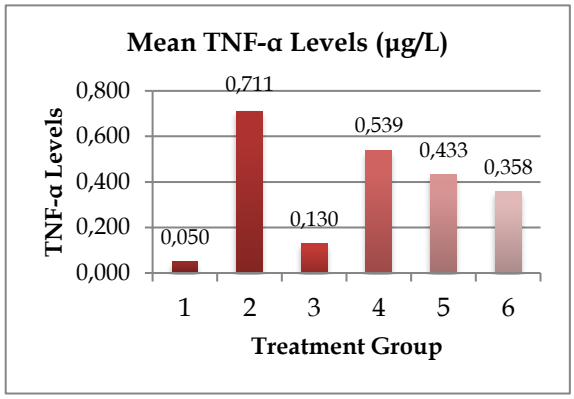

Figure 1. TNF-α levels in all treatment groups

The 300-dose group mg/kgBW, which had a value of more than 0.358 µg/L low from group control negative, was the extract group that had the lowest levels of TNF-α. Still, more all from the positive group control diclofenac sodium, This demonstrates the anti-inflammatory properties of teak leaf extract at large dosages. Because there is a greater amount of lots content compound metabolism with anti-inflammatory activity in taller dose samples. Flavonoids have the ability to

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significantly lower levels of the pro-inflammatory cytokine TNF-α because their flavonoid content inhibits IkB kinase, preventing IkB degradation and preventing activation of NF-kB, which controls the expression of genes coding for pro-inflammatory cytokines and prevents an increase in TNF-Ά levels.[4,30,31]

Therefore, by examining the reduction of TNF-α levels, teak leaf extract (*Tectona grandis* Linn. F.) has an impact on inflammation models. The ideal dosage of teak leaf ethanol extract (*Tectona grandis* Linn F.) can lower TNF-α levels in mice. Carrageenan is induced at a dosage of 300 mg/kgBW of extract.

Simulation molecular docking

For the TNF-α target, all compounds exhibited binding energies more negative than diclofenac (-4.0 kcal/mol), ranging from -3.6 kcal/mol to -5.4 kcal/mol (Table 1). Among these, Phaeophorbid A and (132S, 17S, 18S)-132-Hydroxy-20-Chloro-Ethylpheophorbide A demonstrated strong affinities toward TNF-α, with binding energies of -5.4 kcal/mol and -5.2 kcal/mol, respectively.

Additionally, a shift in the binding pose of diclofenac relative to TNF-α was observed when compared to VGY, as indicated by differences in interactions. The VGY compound exhibited hydrogen bonding with Leu160 and hydrophobic interactions with Leu60 and Tyr62 (Figure 2A). In contrast, diclofenac did not form hydrogen bonds but established hydrophobic interactions with Lys14 and Ile158 in the active site of TNF-α (Figure 2B).

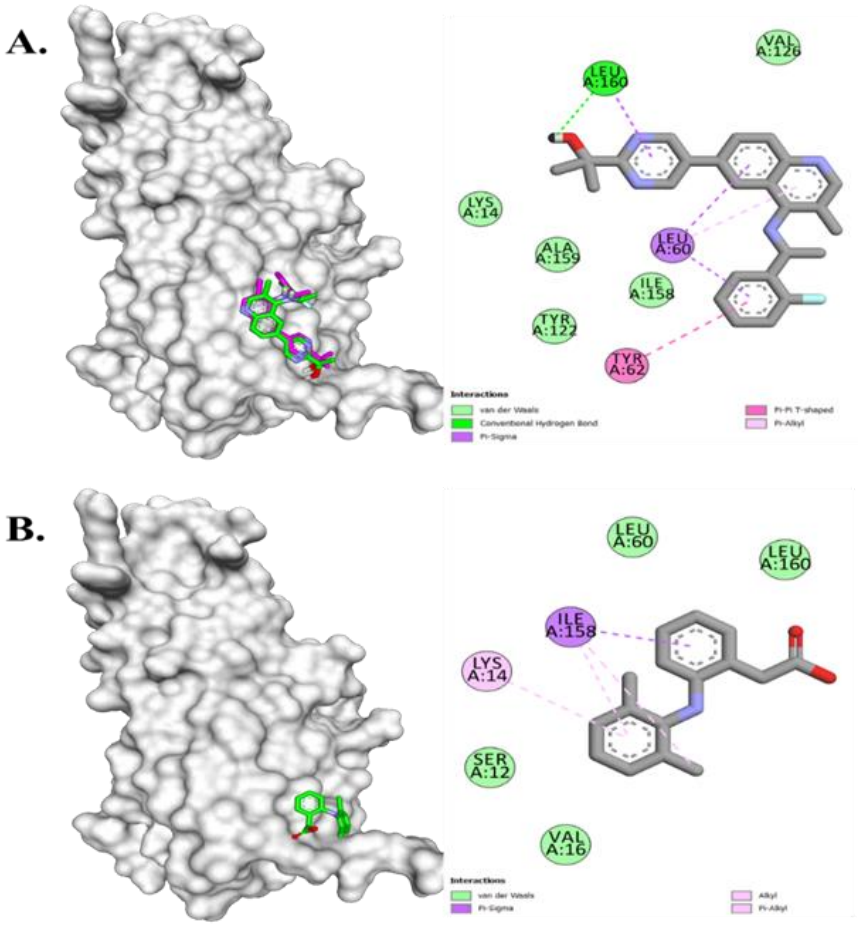

Figure 2. Binding poses and molecular interactions of (A) the crystallographic structure of VGY (green) overlay with the redocking structure (pink) with an RMSD value of 0.897 Å, and (B) the structure of diclofenac in the active site of TNF-α.

Table 1. Summary of the binding energy and molecular interactions of compounds from teak leaf against TNF-α

Compound	Binding Energy (kcal/mol)	Hydrogen Bond	Hydrophobic Interactions
VGY (nature ligand)	-5.2	Leu160	Leu60, Tyr62
Diclofenac sodium	-4.0		Lys14, Ile158
Phaeophorbid A	-5.4		Leu60, Tyr122, Val126, Ile158, Leu160
(132S, 17S, 18S)-132-Hydroxy-20-Chloro-Ethylpheophorbide A	-5.2	His18	Lys14, Leu60, Tyr62, Ile158, Leu160
7-Hydroxycoumarin glucoside	-4.6	Tyr122	Tyr62
(S)-2-(4-(ethyl((2-methyl-4-oxo-3,4-dihydroquinazolin-6-yl)methyl)amino)benzamido) -pentanedioic acid	-4.6	Ser12	Leu60, Ile158
Dichrostachine F	-4.5	Leu160	Leu60, Ile158
Norartocarpetin	-4.2		Leu60, Tyr62
Pexacerfont	-4.2	Ser12	Lys14, Leu160
Aloxistatin	-3.6	Tyr122	Leu60, Tyr62

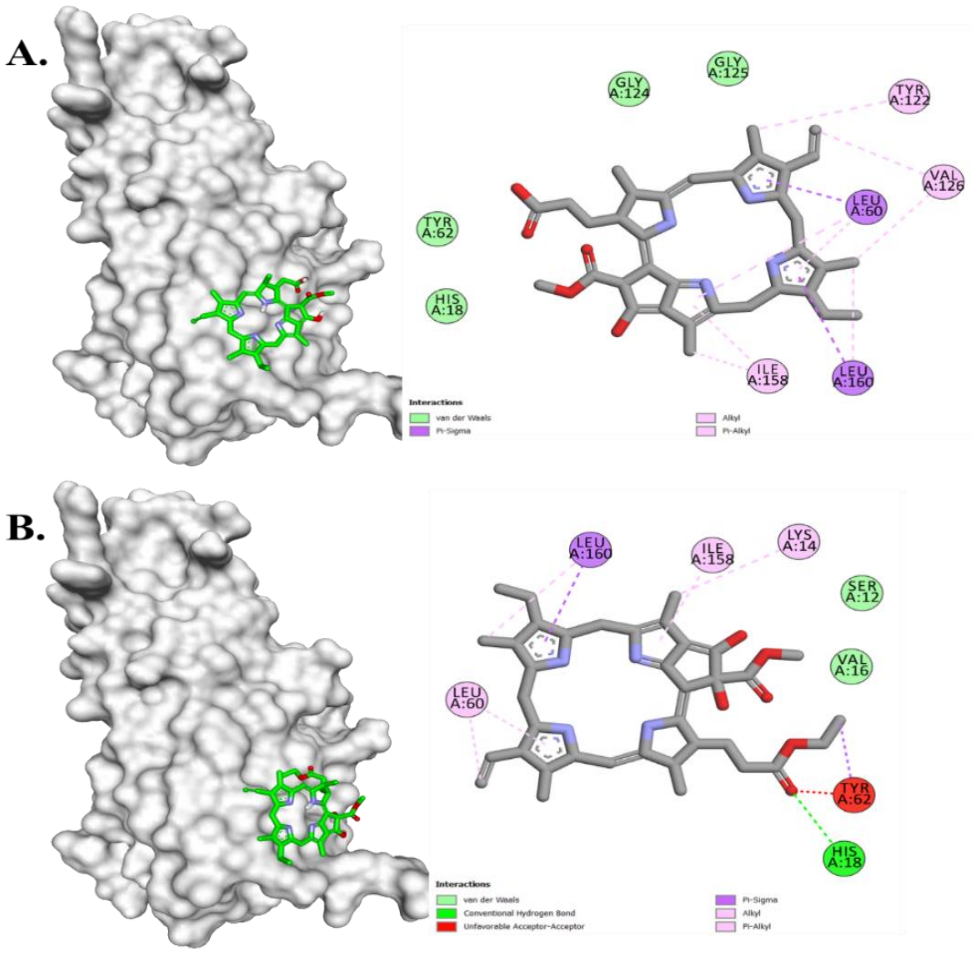

Figure 3. Binding poses and molecular interactions of (A) Phaeophorbid A and (B) (132S, 17S, 18S)-132-Hydroxy-20-Chloro-Ethylpheophorbide A against TNF-α

Phaeophorbid A and (132S, 17S, 18S)-132-Hydroxy-20-Chloro-Ethylpheophorbide A exhibited interaction profiles similar to VGY, indicating their ability to bind to the active site of TNF-α. The methyl groups and cyclopentane rings of both compounds predominantly formed hydrophobic interactions with residues Leu60, Tyr62, Tyr122, Val126, Ile158, and Leu160 (Figures 3A and 3B). Notably, the carbonyl group of (132S, 17S, 18S)-132-Hydroxy-20-Chloro-Ethylpheophorbide A formed a hydrogen bond with His18.

This study reveals the ability of Phaeophorbid A and (132S, 17S, 18S)-132-Hydroxy-20-Chloro-Ethylpheophorbide A, derived from *Tectona grandis* leaves, to establish hydrogen bonds and hydrophobic interactions with TNF-α. These interactions may significantly disrupt the receptor's binding site. Based on these findings, it can be inferred that the binding of these compounds to the TNF-α monomer could potentially inhibit the formation of its trimer, which is essential for inflammatory signaling.[15,16,32]

This computational study highlights the potential of two compounds derived from *Tectona grandis leaves*, Phaeophorbid A and (132S, 17S, 18S)-132-Hydroxy-20-Chloro-Ethylpheophorbide A, which play a significant role in anti-inflammatory effects. Molecular-level interaction studies are highly valuable for developing effective anti-inflammatory therapies. The ability of these compounds to bind strongly to TNF-α provides critical insights, suggesting their potential as promising candidates for the development of anti-inflammatory drugs.

CONCLUSION

This study highlights the potential of *Tectona grandis* leaves as a valuable source of bioactive compounds with significant anti-inflammatory properties. The metabolites found in the extract ethanol of these leaves exhibit promising anti-inflammatory effects by effectively reducing TNF-α levels and interfering with receptor interactions. Additionally, Phaeophorbid A and (132S, 17S, 18S)-132-Hydroxy-20-Chloro-Ethylpheophorbide A from this plant demonstrated the strongest binding affinities (-5.4 kcal/mol and -5.2 kcal/mol, respectively), forming hydrogen bonds and hydrophobic interactions that disrupt TNF-α receptor activity. These findings lay the groundwork for the development of anti-inflammatory therapeutics derived from *Tectona grandis* leaves.

Conflict of Interest

The authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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