RESEARCH ARTICLE

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Synergistic Effect of Propolis Extract and Vitamin E on TNF-α Reduction in High Fat Diet–Induced Rats

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Background: High-fat diet (HFD) can lead to a low-grade inflammatory state in the body called meta-inflammation. Propolis and Vitamin E are proven to act as antiinflamatories by inhibiting the NF-Kβ pathway, inhibiting lipid peroxidation, and scavenging free radicals. TNF-α is a biomarker for the analysis of acute pro-inflammatory cytokines. This study aimed to determine the effect of propolis extract and vitamin E on TNF-α responses in HFD-induced rats.

Materials and methods: A randomized controlled trial with post-test only with control group design. Thirty Wistar rats were acclimatized for 7 days, prior to randomization into five groups that are C group (standard diet), T1 group (HFD 2 mL of quail eggs/day), T2 group (HFD + vitamin E 12mg /200 g of rat BW/day), T3 group (HFD + propolis extract 36 mg /200 g of rat BW/day), and T4 group (HFD + vitamin E 6 mg/200 g of rat BW/day + propolis extract 18 mg/200 g of rat BW/day). All intervention were administered orally for 14 days. TNF-α were measured from periorbital blood sample on day 15th using ELISA.

Results: TNF-α highest levels was found in HFD group (T1) on 90.53±10.48 ng/L and the lowest was found in propolis group (T3) on 68.21±3.97 ng/L. Combination group (T4) has TNF-α levels on 68.46±15.39ng/L. One way ANOVA showed significant differentiation $p<0.05$.

Conclusion: Propolis extract and vitamin E significantly reduced TNF-α levels on HFD induced rats, either in single form or in combination. This shows their rule as anti-inflammatory agent.

Keywords: *high fat diet, propolis extracts, TNF-α ,vitamin E*

Introduction

Inflammation is a coordinated body process that occurs as a result of the body's response to infection, bacteria or external substances and is characterized by an increase in pro-inflammatory cytokines.[1] A high-fat diet is a risk factor for inflammation that creates a leaky gut condition, thus creating a condition of intestinal dysbiosis.[2] A high-

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fat diet activates the nuclear factor kappa beta (NF-kβ) inflammatory pathway through an increase in toll like receptor-4 (TLR4) in the cell membrane, resulting in an increase in pro-inflammatory cytokines such as tumor necrosis factor-α (TNF-α).[3] TNF-α is one of the cytokines that is crucial for immunity.[4] Propolis itself has been shown to play a role in reducing TNF-α through inhibition of the NF-Kβ pathway, influencing fat cell differentiation, increasing adiponectin and decreasing leptin and having a strong scavenging effect in capturing free radicals produced by long-term consumption of a high-fat diet.[5] Vitamin E as a fat-soluble vitamin plays a very important role in preventing lipid peroxidation due to free radicals. The combination of propolis and vitamin E allows for a better anti-inflammatory effect compared to single administration.[6]

A high-fat diet given continuously causes the body to experience a continuous low-level inflammatory condition, called meta-inflammation, which is characterized by an increase in pro-inflammatory cytokines such as TNF-α, IL-6, C-reactive protein (CRP). TNF-α is produced by macrophages and adipocytes, the concentration of both increases along with the increase in the percentage and distribution of fat tissue in the body.[3] TNF-α will increase when cell damage occurs, has an important role in fat metabolism, where TNF-α is able to inhibit lipoprotein lipase (LPL) both at the mRNA and protein levels, and is also able to inhibit the expression of fat tissue differentiation regulators.[7] This meta-inflammatory condition causes various health problems such as type II diabetes mellitus, NAFLD, cardiovascular disease, stroke, and cancer if not addressed.[8] Projections for 2025 estimate that approximately 167 million people will suffer from health issues due to overweight or obesity, contributing to the chronic disease. A study of the adult populations in Indonesia revealed a high prevalence of obesity and central obesity, at 23.1% and 28%, respectively, linked to increased risk of diabetes and hypertension.[9] Research on propolis and vitamin E has been ongoing for decades.1 Data show that propolis for 14 days can function as an anti-inflammatory by reducing TNF-α levels in rats, through its active ingredient CAPE (Caffeic Acid Phenetyl Ester).[10] Vitamin E has a dosage range that needs to be considered because when given in high doses it turns into a prooxidant.[7] The recommended daily dose vitamin E for rats is 18 ppm (27- 50 IU/kg BW rats). Study showed that vitamin E dose to rats more than 90 ppm/day increase the risk of oxidative stress and anxiety.[11] The combination of propolis and vitamin E at a lower dose is expected to reduce the toxicity of vitamin E. Research on the effects of vitamin E as an anti-inflammatory has also been conducted extensively.[12] This shows that there is potential synergy in the use of propolis and vitamin E.

There are several studies about combination of propolis extract and vitamin E as anti-inflamatory, but none on high fat diet. Newest research about combination propolis extract and Vitamin E against toxicity of ALCl3 in albino mice showed that propolis 50 mg/kg BW and vitamin E 150mg/kg BW 21 days significantly lowering lipid profile and hepar enzim.[13] This study aims to analyze the effects of a combination of propolis and vitamin E on TNF-α levels in rats induced by a high-fat diet. The results obtained from this study are expected to provide strong evidence of the anti-inflammatory effects of propolis and vitamin E. Both propolis and vitamin E have anti-inflammatory effects, influence fat metabolism, are readily available, and are affordable.[11] The combination of propolis and vitamin E at lower doses is also expected to reduce the toxicity of vitamin E.[13]

Materials and methods

Experimental Design

The experimental animals used were 30 Wistar rats (Rattus norvegicus), aged 10-12 weeks with weight 180-220 g. Rats were acclimatized with room temperature 25±2°C for 7 days. Rats were placed in groups in metal-barred cages. All rats labs were certified, obtained from Department of Agriculture, Food and Fisheries, Karanganyar No.008/SKKH/XI/2025.

Rats were divided into five groups. Group C received only standard diet. Group T1 received HFD 2 mL of quail egg yolk/day. Group T2 received HFD and 12 mg/200 g rat BW/day of vitamin E. Group T3 received HFD and 36mg/200 g rat BW/day of propolis extract. Group T4 received HFD, 18mg/200 g rat BW/day of propolis extract and 6mg/kg rat BW/day of vitamin E. The establishment of this research protocol was based on previous studies investigating the combination of propolis and vitamin E.[13] All intervention were administered orally for 14 days , once daily. Quail egg yolks were given in the morning and propolis extract and vitamin E were given in the afternoon. Rat stomach capacity is approximately 3,4 mL-5 mL.14 To avoid overloading, the administration of drugs and feed is divided. TNF-α was measured from periorbital blood sample on day 15th using ELISA (Figure 1).

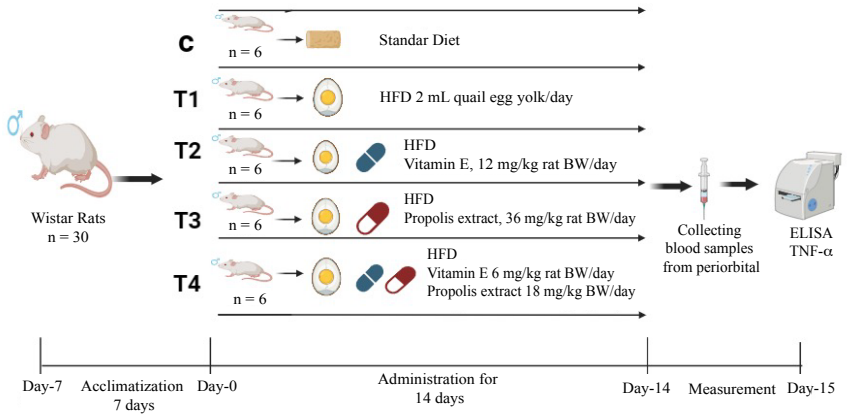

Figure 1. Schematic diagram of study design and timeline. Created in https://BioRender.com access on March 12th 2026).

High Fat Diet Induction

The high-fat diet used quail egg yolk at a dose of 2 mL/day. Quail eggs yolks were used because they contain high cholesterol (844 mg/100g) compared to other poultry eggs.[15] The quail eggs have low PUFA/SFA ratio and higher ω-6/ω-3 ratio so that it is pro-inflammatory.[15] The quail eggs were given using tube once a day to HFD groups for 14 days.

Preparation of Propolis Extract and Vitamin E

The propolis extract used was CMCE Propolis with trade name PropoelixTM, from PT Harmoni Dinamika Indonesia, Bogor, Indonesia. CMCE (Continous Multistage Countercurrent Extraction) was a method of propolis extraction that produce high levels of bioactive compunds. The CMCE extraction methods is a modern extraction method, by removing all the wax and resin subtances in propolis, thus producing only bioactive substance extracts.[10] Propolis extract dose using 36 mg/200 g of rat BW/day (T3) and 18 mg/200 g of rat BW/day (T4). The vitamin E used was a 100 IU α-tocopherol preparation from Natur-E (PT. Darya Varia Laboratoria Tbk, West Java, Indonesia). The dosage used was 12mg/200g rat BW/day (T2) and 6mg/200g rat BW/day (T4).

Sampling and Measurement of TNF-α

The equipment used includes a sterile serum tube, a blood tube, and sterile cotton. Blood is drawn from the ophthalmic vein at the corner of the mouse's eye, then gently rotated slightly. Approximately 2 mL of blood is collected in a special tube. Sterile cotton is used to clean any remaining blood in the mouse's eye. Measurement of TNF-α was carried out using ELISA Kit (Cat.No.E0764Ra, BT LAB Bioassay Technology Laboratory, China).

Statistical Analysis

Data analysis was performed using SPSS software version 26.0. Data obtained from TNF-α measurements were tested for homogeneity and normality using the Shapiro-Wilk test and Levene's test. If the data were normally distributed and homogeneous, then continued using One-way ANOVA data analysis. Post-Hoc Test was conducted to determine which groups were significantly different. The decision to accept or reject the hypothesis is based on $p<0.05$ which is statistically significant.

Results

Reduction of TNF-α Levels in Treatment Groups

The highest TNF-α levels were found in T1 with a value of 90.53±10.48 ng/L. The lowest TNF-α levels were found in T3 with a value of 68.21±3.97 ng/L. The difference in mean TNFα levels showed fairly homogeneous data variation between study groups (Table 1). The Shapiro-Wilk normality test showed that the TNF-α level data in C to T4 had p>0.05. This indicates that the TNF-α level data in the group was normally distributed. The results of the homogeneity of variance test using the Levene test obtained $p = 0.370$ ($p>0.05$). This means that the data variance in the TNF-α group was homogeneous. The results of the difference test for more than 2 treatment groups (One Way ANOVA) showed a significant difference in TNF-α levels $p = 0.012$ ($p<0.05$).

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Table 1. Results of mean analysis, normality test, homogeneity test and difference test more Than 2 groups on TNF-α levels in various treatment groups.

Variables	Group					
	C	T1	T2	T3	T4	Sig. (*p*)
TNF-α levels (ng/L)						
Mean	70.43	90.53	69.98	68.21	68.46	
Std. Deviation	9.46	10.48	9.47	3.97	15.39	
Shapiro-Wilk	0.481*	0.234*	0.332*	0.812*	0.107*	
Levene						0.370**
One-way ANOVA						0.012***

Shapiro-Wilk* test is significant if $p>0.05$, the Levene test ** is significant if $p>0.05$, One Way ANOVA *** test is significant if $p<0.05$.

Significant Differences in TNF-α Levels Indentified by Post Hoc Analysis

Post Hoc showed a significant difference between groups T1 with T2, T3 and T4 (Figure 2). TNF-α levels did not differ significantly between T2 with T3 and T4, as well as between groups T3 and T4 did not differ significantly.

Discussion

High-fat diets produce high levels of free fatty acids in circulation.[8] Adipocytes and adipose tissue store a number of fat cells, including triglycerides and cholesterol, and function as active endocrine organs and immune cells (Immune standpoint).[7] High levels of free fatty acids will activate toll-like receptor complex 4 (TLR4) and stimulate the release of pro-inflammatory cytokines such as TNF-α.[16] Quail egg yolks, as a high-fat diet, have advantages of high cholesterol content (844 mg/100gr), low PUFA/SFA ratio and higher ω-6/ω-3 ratio so that it is pro-inflammatory.[15] The highest TNF-α levels were found in T1, at 90.53±10.48 ng/L.

Inflammation in a high-fat diet is also a manifestation of increased oxidative stress caused by the formation of ROS during hypoxic tissue growth.[17] Decreased blood flow to adipose tissue causes tissue hypoxia, thereby increasing the process of angiogenesis in order to increase oxygen supply to the tissue.[18] This process will also increase pro-inflammatory cytokines. These pro-inflammatory mediators would attract macrophages infiltration to the extracellular matrix. Macrophages could digest and store lipid as atherosclerotic foam cell that also produces TNF-α that eventually exaggerate the inflammatory condition. Moreover, in adipose tissue, macrophages could express a large amount of NOS2 and TNF-α that have a contribution to inflammation.[19]

A high-fat diet also affects the gut microbiota, by altering gut microbiota interactions, changing its composition, and increasing pathogenic bacteria that increase lipopolysaccharide (LPS).[17] A high-fat diet will increase chylomicrons, which in turn increase lipopolysaccharide

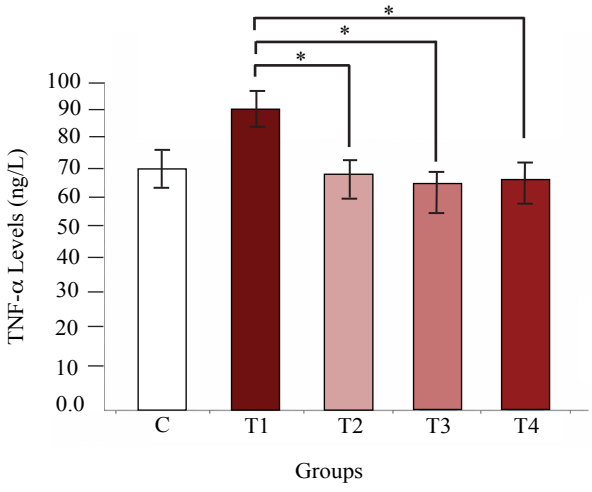

Figure 2. Results of the LSD post hoc analysis donducted to determine the difference in TNF-α levels. Post hoc is significant if $p<0.05$.

that will penetrate the intestinal epithelium and enter the blood circulation, causing endotoxinemia and inflammation. The chylomicron-LPS complex also increases intracellular pressure and decreases the integrity of tight junction, making basement membrane rupture more likely.[17] This also leads to increased membrane permeability, endotoxinemia, and increased proinflammatory cytokines such as TNF-α.[18] Increased adipose tissue also increases oxidative stress. The increase in ROS caused by a high-fat diet is activated through pathways such as NADPH oxidase (NOX) and protein kinase C (PKC). Increased ROS result in lipid peroxidation, protein carbonylation, and a decrease in endogenous antioxidants such as glutathione (GSH).[17]

Vitamin E has a strong scavenger effect, scavenging free radicals and reducing ROS in the body.[6] Vitamin E plays a role in suppressing inflammation by maintaining the intestinal membrane, preventing endotoxinemia and systemic inflammation.[20] Vitamin E plays a role in inhibiting the NF-Kβ pathway, which in turn produces pro-inflammatory cytokines, preventing or minimizing inflammation.[20] Several meta-analytical studies have demonstrated the effect of vitamin E in reducing metabolic syndrome.[21] Research on vitamin E with a dose 1.8 IU/200 g BW of rats for 4 weeks has been shown to be able to withstand oxidative stress and reduce inflammation.[22] This is inline with the result where vitamin E can inhibit the increase of TNF-α in group T2 and T4.

Propolis extract inhibits the TLR4 and NF-Kβ pathways so that pro-inflammatory cytokines are not formed.1 The lowest TNF-α levels were found in T3 at 68.21±3.97 ng/L and the highest in T1 at 90.53±10.48 ng/L. Statistically, the one-way ANOVA test of propolis extract against TNF-α was significant (p<0.05). Propolis extract is a natural resinous complex produced by bees, which contains bioactive flavonoids such as chrysin, luteolin, apigenin and kampferol, phenolic acids such as CAPE, coumaric acid, as well as minerals and vitamins. Its biological activities are anti-inflammatory, antioxidant, antibacterial, immunomodulatory, antiviral, anti-caries and anti-cancer.[23] The role of propolis extract in lipid metabolism results in propolis playing a role in reducing pro-inflammatory cytokines such as TNF-α.[24] This proves that propolis extract is able to work well in terms of suppressing the production of acute pro-inflammatory cytokines, such as TNF-α in high fat diet-induced rats.

The combination of vitamin E and propolis extract in T4 also showed synergy. TNF-α levels in T4 were nearly identical to those in T2 and T3, at 68.46±15.39. The half-dose of T2 and T3 was intended to reduce vitamin E toxicity, which, when administered in large amounts, can act as a prooxidant.[25] This combination was also given because administering both simultaneously would increase the effectiveness of each active ingredient.[13] Based on the results of T4, it can be concluded that the combination of propolis extract and vitamin E given in moderate doses also has the effect of reducing the pro-inflammatory cytokine TNF-α.

We acknowledge the limitations of this study. Other biomarker of inflammation should also be investigated in the future. IL-6 and CRP may serve as a parameter proinflammatory effect of propolis and vitamin E during the chronic phase of HFD-induced inflammation This study placed one group of rats in one cage, making it difficult to measure the amount of food left over from each individual. This means that each rat may have received a different amount of food, which could have affected their inflammatory status. Sampling in this study was only conducted at the end (post-test only). This means that the condition of the rats before treatment is unknown. This study did not account for the physical activity of the rats, which in the cage would have affected their body weight and inflammatory status. Physical activity may reduce inflammation in the rat's body.[26]

Conclusion

Quail egg yolk as high fat diet leads inflammations, characterized by an increase of TNF-α serum levels in rats body. Propolis extract and vitamin E significantly reduced TNF-α levels on HFD induced rats, either in single form or in combination. This shows their rule as anti-inflammatory agent.

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Authors' Contributions

NA conceptualized and designed the research; conducted data collection; NA, JWW and HS performed data analysis;

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NA drafted the manuscript and prepared the figures; JWW, HS, assisted in interpreting the results. All authors contributed to critical revisions of the manuscript.

Ethical Statement

Ethical clearance was obtained from Ethical Commision Medical Faculty Sultan Agung University No 554/XI/2025/ Komisi Bioetik. This research is conducted at IBL Medical faculty, Sultan Agung University, Semarang, Indonesia.

Conflict of Interest

The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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