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THE EFFECT OF COMBINED PROPOLIS EXTRACT AND VITAMIN E SUPPLEMENTATION ON IL-10 AND CRP

Pengaruh Kombinasi Ekstrak Propolis dan Vitamin E Terhadap Kadar IL-10 dan CRP

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ABSTRACT

A high-fat diet induces oxidative stress and systemic inflammation, characterized by decreased the effects of propolis extract and vitamin E on IL-10 and CRP levels in male Wistar rats induced by a high-fat Interleukin-10 (IL-10) and increased C-Reactive Protein (CRP). This study aimed to evaluate diet. An experimental post-test only control group design was used, involving 30 rats divided into five groups: healthy control, high-fat diet control, vitamin E, propolis extract, and combination treatment. Interventions were administered for 14 days. Serum IL-10 and CRP levels were measured using ELISA and analysed using one-way ANOVA. The results showed that propolis extract and vitamin E significantly increased IL-10 levels ($p < 0.05$), indicating an improved anti-inflammatory response. However, CRP levels did not show significant differences among groups ($p > 0.05$). In conclusion, both treatments enhanced anti-inflammatory activity through IL-10 modulation but did not significantly affect CRP levels.

Keywords: *CRP, High-fat diet, IL-10, Propolis extract, and Vitamin E*

ABSTRAK

Diet tinggi lemak diketahui dapat memicu stres oksidatif dan inflamasi sistemik yang ditandai dengan penurunan sitokin antiinflamasi Interleukin-10 (IL-10) serta peningkatan C-Reactive Protein (CRP). Penelitian ini bertujuan untuk mengevaluasi pengaruh pemberian ekstrak propolis dan suplementasi vitamin E terhadap kadar IL-10 dan CRP pada tikus Wistar jantan yang diinduksi diet tinggi lemak. Penelitian ini menggunakan desain eksperimental dengan rancangan post-test only control group. Sebanyak 30 ekor tikus jantan galur Wistar (Rattus norvegicus) dibagi secara acak ke dalam lima kelompok, yaitu kontrol sehat, kontrol diet tinggi lemak, kelompok vitamin E, ekstrak propolis, dan kombinasi vitamin E–propolis. Perlakuan diberikan selama 14 hari. Pengukuran kadar IL-10 dan CRP serum dilakukan menggunakan metode ELISA. Data dianalisis menggunakan uji one-way ANOVA yang dilanjutkan dengan uji post hoc LSD. Hasil penelitian menunjukkan bahwa pemberian ekstrak propolis dan vitamin E, baik secara tunggal maupun kombinasi, mampu meningkatkan kadar IL-10 secara signifikan ($p<0,05$). Namun, kadar CRP tidak menunjukkan perbedaan yang bermakna secara statistik antar kelompok perlakuan ($p>0,05$). Kesimpulannya, pemberian ekstrak propolis dan vitamin E dapat memodulasi respon imun antiinflamasi melalui peningkatan IL-10, namun belum berpengaruh signifikan terhadap CRP.

Kata kunci: *CRP, Diet tinggi lemak, Ekstrak propolis dan vitamin E, IL 10*

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INTRODUCTION

Inflammation is the body's physiological response to harmful stimuli such as infection, tissue injury, or oxidative stress, and this condition can be exacerbated when the body is exposed to a high-fat diet. A high-fat diet triggers increased oxidative stress, lipid accumulation, and activation of pro-inflammatory pathways, leading to an imbalance between inflammatory and anti-inflammatory mediators, thus triggering systemic inflammation. (Rahmawati, 2024; Norhaizan, 2022) The imbalanced immune response resulting from long-term exposure to a high-fat diet contributes to obesity, insulin resistance, metabolic disorders, and accelerates tissue damage through increased sustained inflammation (Balancic, A, 2025; Khedmatgozar, 2021)

A high-fat diet is a major factor in triggering systemic inflammation through increased visceral fat accumulation, oxidative stress, and immune cell activation that leads to the release of pro-inflammatory cytokines. This condition leads to increased levels of C-Reactive Protein (CRP), an inflammatory marker that increases when the immune response is activated in both acute and low-grade chronic inflammation and is closely associated with the risk of metabolic, cardiovascular, and degenerative diseases.6 Interleukin-10 (IL-10) As an anti-inflammatory cytokine, it plays an important role in inhibiting the production of pro-inflammatory cytokines and suppressing macrophage activation so that the immune response remains balanced (Khedmatgozar,2021; Ling,2020; Ashworth,2023) The imbalance characterized by high CRP and decreased IL-10 due to exposure to a high-fat diet causes prolonged inflammation, increased oxidative stress, and tissue damage which ultimately worsens metabolic dysfunction and increases susceptibility to various chronic diseases (Ashworth, 2023; Walton, 2025; Balancic. A, 2025)

Propolis and vitamin E have long been used as anti-inflammatory agents, both singly and in combination, with synergistic potential in suppressing inflammatory responses. Various studies have shown that propolis, which is rich in flavonoids, phenolics, and caffeic acid phenethyl ester (CAPE), can reduce the expression of pro-inflammatory mediators such as TNF-α, IL-6, and CRP and increase IL-10 through modulation of the NF-κB and MAPK pathway (Mohamed, 2023; Figueiredo, 2023; Hussaana,2021) Vitamin E has antioxidant activity through its ability to neutralize free radicals and protect cell membranes from lipid peroxidation. It is also known to inhibit NF-κB activation, which lowers CRP, and supports IL-10 regulation under oxidative stress conditions. Although both have anti-inflammatory effects, their use alone often does not provide optimal results because propolis predominantly suppresses proinflammatory mediators, while vitamin E focuses more on controlling oxidative stress. The increase in IL-10 and the decrease in CRP may not be optimal. The combination of propolis and vitamin E is thought to provide a synergistic effect, with propolis suppressing inflammatory pathways and vitamin E strengthening antioxidant defences, thus achieving a more effective balance between IL-10 and CRP (Haleagrahara, 2020; Hashem, 2023; Schneider, 2025)

The combination of propolis and vitamin E has greater synergistic potential than either single dose, as both have complementary mechanisms of action in suppressing oxidative stress and inflammatory responses.[14] Propolis contains flavonoids and phenolic acids that act as powerful antioxidants and can suppress the production of proinflammatory cytokines, while vitamin E is a major lipophilic antioxidant that protects cell membranes from free radical damage. The synergy between the two is expected to improve immune system regulation, reduce inflammatory biomarkers, and provide a more optimal protective effect against various pathological conditions related to chronic inflammation. Based on this background, this study was conducted to evaluate the effectiveness of the combination of propolis extract and vitamin E on IL-10 and CRP levels in male Wistar rats (Rattus norvegicus) induced by a high-fat diet. It is hoped that the results of this research will be able to provide scientific evidence regarding the potential synergy of the two antioxidant agents in suppressing inflammation, so that it can become the basis for developing alter-

native therapies based on natural ingredients for the prevention and management of metabolic diseases (Tsurumaki,2019; Bastian,2025; Harahap,2020)

MATERIALS AND METHODS

This study was an experimental research using a post-test only control group design involving 30 male Wistar rats (*Rattus norvegicus*) acclimatized at the Integrated Biomedical Laboratory, Faculty of Medicine, Universitas Islam Sultan Agung (UNISSULA), Semarang. The sample size was determined using Federer's formula $(t-1)(n-1) \geq 15$ (t-1)(n-1) \geq 15 $(t-1)(n-1) \geq 15$, resulting in six animals per group, and samples were allocated using simple random sampling. The animals were randomly divided into five groups: a healthy control group, a negative control group induced with a high-fat diet, a treatment group receiving vitamin E, a treatment group receiving propolis extract, and a treatment group receiving a combination of both. The high-fat diet consisted of standard feed and raw quail egg yolk administered for 14 days. Ethical approval for this study was obtained from the Research Ethics Committee of the Faculty of Medicine, UNISSULA. The independent variables were propolis extract and vitamin E, while the dependent variables were serum interleukin-10 (IL-10) and C-reactive protein (CRP) levels. Propolis extract was administered orally at a dose of 36 mg/kgBW/day and vitamin E (d-α tocopherol) at a dose of 12 mg/kgBW/day for 14 days, while the combination group received both at the same respective doses. Blood samples were collected on day 15 via the retro-orbital plexus after 12 hours of fasting, and serum IL-10 and CRP levels were measured using the ELISA method. Data were analyzed using appropriate parametric or nonparametric statistical tests based on data distribution, with a significance level set at $p < 0.05$.

DATA ANALYSIS

Parametric statistical analysis was applied to evaluate differences in serum IL-10 and CRP levels among the experimental groups. Prior to hypothesis testing, the data were assessed for normality and homogeneity of variance to ensure that the assumptions for parametric testing were met. Since the data were normally distributed and homogeneous, comparisons between the six groups were performed using a one-way analysis of variance (ANOVA).

One-way ANOVA was used to determine whether there were statistically significant differences in mean IL-10 and CRP levels among the healthy control, high-fat diet control, vitamin E, propolis extract, and combination treatment groups. When a significant difference was identified ($p < 0.05$), post hoc analysis using the Least Significant Difference (LSD) test was conducted to determine pairwise differences between groups.

The analysis showed a significant difference in IL-10 levels among groups, indicating that the interventions had a measurable effect on anti-inflammatory response. In contrast, no significant difference was observed in CRP levels, suggesting that the treatments did not significantly influence systemic inflammation as measured by CRP.

RESULTS AND DISCUSSION

RESULT

C-Reactive Protein (CRP) Level Test Results

The average CRP levels in each group, along with the results of the analysis of data normality, homogeneity of variance, and the intergroup mean difference test, are shown in Fig.

Table I. Mean and Standard Deviation (Mean ± SD), Normality Test (Shapiro-Wilk), Homogeneity of Variance Test (Levene), and Difference Test for CRP

Statistik	K1	K2	K3	K4	K5
Mean	1.790	1.816	1.660	1.968	2.030
Std. Deviation	0.179	0.258	0.210	0.371	0.147
Saphiro-Wilk	0.340*	0.431*z	0.395*	0.698*	0.344*

Statistik	K1	K2	K3	K4	K5
Levene			0.092*		
One-Way ANOVA Robust			0.170*		

Shapiro-Wilk test* is significantif p > 0.05, the Levene test** is significant if p > 0.05, and the Robust test*** is significant if p < 0.05.

The study found that the highest CRP levels were in group K5, at 2.0300 ± 0.14782 ng/mL, and the lowest in group K3, at 1.6600 ± 0.21071 ng/mL. The Shapiro-Wilk test for CRP levels in the five groups yielded a p value > 0.05, indicating normal CRP levels. CRP levels across the five measurements were also homogeneous, as indicated by the Levene test p value of 0.092, or p>0.05. The requirements for normal data distribution and homogeneity of variance were met, so the comparison of mean CRP levels between the five groups was analyzed using a one-way ANOVA test, which yielded a value of 0.170 (p < 0.05), which was not significant.

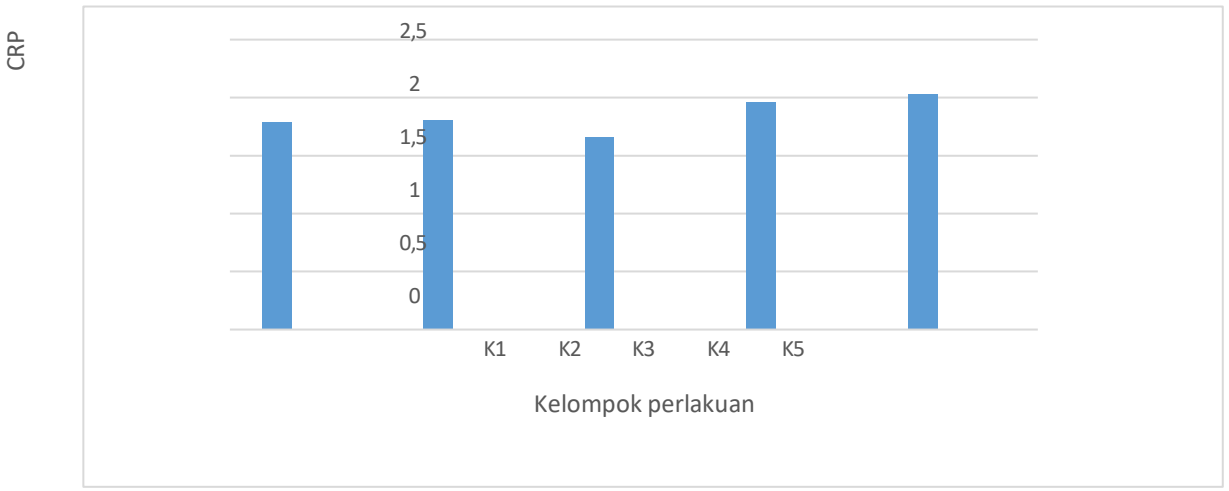

Figure 1. Bar Chart of CRP Levels Across Groups

IL-10 (Interleukin-10) Level Examination Results

The average IL-10 levels in each group, along with the results of the analysis of data normality, homogeneity of variance, and the test for differences in mean levels between groups, are shown below:

Table II. Mean and Standard Deviation (Mean ± SD), Uji Normalitas

Statistik	K1	K2	K3	K4	K5
Mean	67.50	46.66	68.01	75.21	77.67
Std. Deviation	6.41	7.62	8.34	9.19	16.67
Saphiro-Wilk	0.742*	0.751*	0.227*	0.197*	0.231*
Levene			0.264*		
One-Way ANOVA			0.001***		

(*Shapiro-Wilk*), Test of Homogeneity of Variance (Levene's Test) and Analysis of Differences in IL-10 levels (pg/ml) Across Treatment Groups

The Shapiro-Wilk test* is significant if p > 0.05, the Levene test** is significant if p > 0.05, and the Robust test*** is significant if p < 0.05.

The study found that the highest IL-10 levels were in group K5 at 77.6740 ± 16.67947 pg/mL, and the lowest in group K2 at 46.6620 ± 7.62566 pg/mL. The Shapiro-Wilk test for IL-10 levels in all five groups yielded a p-value > 0.05, indicating normal IL-10 levels.

IL-10 levels across all five measurements were also homogeneous, as indicated by a Levene's p-value of 0.264, or p>0.05. The requirements for normal data distribution and homogeneity of variance were met, so the comparison of mean IL-10 levels between the five groups was analyzed using a one-way ANOVA test. The IL-10 levels were significant between groups K1, K2, K3, K4, and K5.

Tabel III. Results of the LSD Post-Hoc Analysis Conducted to Determine Differences in IL-10 Levels Between Groups (Post-Hoc Test* significant if p < 0.05)

Kelompok	K2	K3	K4	K5
K1	0.005*	0.938	0.251	0.135
K2		0.004*	0.000*	0.000*
K3			0.283	0.154
K4				0.710

The results of the post hoc test on IL-10 levels differentiated between the two treatment groups, showing a significant difference between groups K1 and K2 (p = 0.005). Group K2 also showed a significant difference compared to groups K3, K4, and K5 (p < 0.05). Conversely, no significant difference was found between groups K1 and K3, K4, and K5 (p > 0.05), or between groups K3, K4, and K5 (p > 0.05). These results indicate that IL-10 levels in the treatment groups were relatively similar and significantly different from group K2.

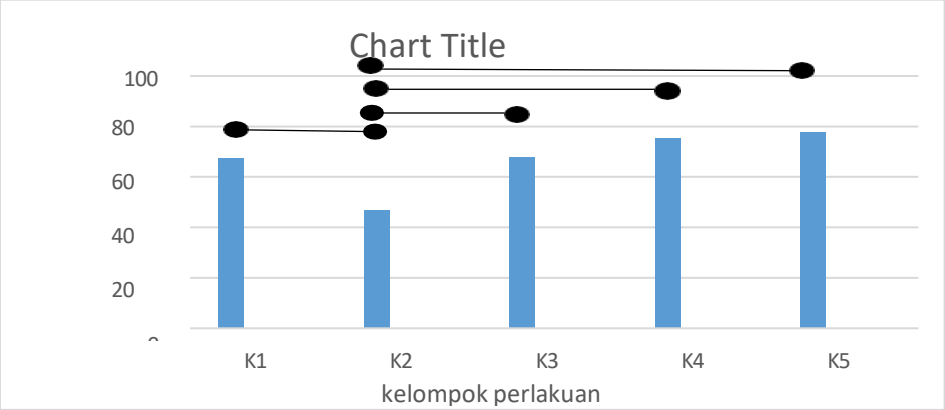

Figure II. *the LSD Post Hoc Analysis to Determine Differences in IL-10 Levels Among Groups (Post Hoc test is considered significant if p < 0.05)**

The chart showed that all groups experienced an increase in body weight during the intervention period, with the high-fat diet control group (K2) exhibiting the greatest weight gain, while the treatment group receiving a combination of propolis extract and vitamin E (K5) showed the lowest increase, indicating a potential role of these interventions in controlling weight gain induced by a high-fat diet. The lipid profile analysis revealed that K2 had the highest levels of total cholesterol, triglycerides, and LDL, whereas the propolis (K4) and combination (K5) groups demonstrated lower lipid levels, suggesting hypolipidemic effects that may reduce metabolic inflammation risk. No significant differences in C-reactive protein (CRP) levels were observed among groups (p > 0.05), indicating that the administered doses and duration were insufficient to elicit a measurable systemic anti-inflammatory effect. In contrast, interleukin-10 (IL-10) levels differed significantly among treatment groups (p < 0.05), reflecting enhanced anti-inflammatory immune modulation, likely mediated through the antioxidant and immunomodulatory properties of propolis and vitamin E, and supporting IL-10 as a more sensitive marker than CRP for detecting nutraceutical-induced immunoregulatory effects.

DISCUSSION

The results of this study showed that C-Reactive Protein (CRP) levels did not differ significantly among the treatment groups ($p > 0.05$), although the highest mean value was observed in the combination group (K5) and the lowest in the vitamin E group (K3). The normality and homogeneity tests confirmed that the data were normally distributed and homogeneous, validating the use of one-way ANOVA. The absence of significant changes in CRP suggests that the administration of propolis extract and vitamin E for 14 days was insufficient to modulate systemic inflammatory markers. CRP is an acute-phase protein that is relatively stable and typically elevated in more severe or chronic inflammatory conditions, making it less sensitive to short-term interventions. (Daleprane, 2023; Ouyang, 2020; Saraiva, 2020)

In contrast, Interleukin-10 (IL-10) levels showed significant differences among groups ($p < 0.05$), with the highest levels observed in the combination group (K5) and the lowest in the high-fat diet group (K2). Post hoc LSD analysis indicated that K2 differed significantly from the treatment groups (K3, K4, and K5), suggesting that a high-fat diet suppresses anti-inflammatory responses. The increase in IL-10 levels in the treatment groups reflects the immunomodulatory effects of propolis and vitamin E. (Tsurumaki,2019; Bastian,2025; Harahap,2020)

Mechanistically, propolis contains flavonoids and phenolic compounds with antioxidant and anti-inflammatory properties, while vitamin E protects cell membranes from oxidative damage. Their combination likely exerts a synergistic effect in reducing oxidative stress and enhancing anti-inflammatory immune responses through increased IL-10 production (Khedmatgozar,2021; Ling,2020; Ashworth,2023)

Additionally, the high-fat diet group exhibited greater weight gain and a poorer lipid profile, whereas the treatment groups, particularly the combination group, showed improved lipid profiles. This suggests potential hypolipidemic effects of propolis and vitamin E, which may help reduce the risk of metabolic inflammation (Magnavacca,2022; Roziana,2022; Koga, 2019)

Overall, IL-10 appears to be a more sensitive biomarker than CRP in detecting the anti-inflammatory effects of nutraceutical interventions. Therefore, propolis extract and vitamin E have potential as supportive agents in modulating anti-inflammatory immune responses. However, further studies with longer intervention durations and optimized dosages are needed to evaluate their effects on systemic inflammatory markers such as CRP. (Dewi,2024; Bastian,2022)

CONCLUSION

Administration of propolis extract and vitamin E, either individually or in combination, did not produce a statistically significant effect on C-reactive protein (CRP) levels in high-fat diet–induced male Wistar rats ($p > 0.05$). In contrast, propolis extract and vitamin E significantly increased interleukin-10 (IL-10) levels ($p < 0.05$), with the highest IL-10 concentrations observed in the group receiving the combined treatment. These findings indicate that propolis extract and vitamin E play a more prominent role in enhancing the anti-inflammatory IL-10 response than in reducing the acute systemic inflammatory marker CRP under the conditions and duration of this study.

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