ORIGINAL ARTICLE

Effects of Extra Virgin Olive Oil and Virgin Coconut Oil Combination on Hematologic Profiles in a Rat Model of Preeclampsia

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ABSTRACT

Preeclampsia is a hypertensive disorder of pregnancy marked by systemic inflammation, oxidative stress, and endothelial dysfunction. Extra-virgin olive oil (EVOO) and Virgin Coconut Oil (VCO) are natural antioxidants with potential therapeutic benefits. This study aims to determine the effect of EVOO, VCO, and their combination on blood pressure and hematologic profiles in a preeclampsia-induced rat model using N-nitro-L-arginine methyl ester (L-NAME). A total of 25 pregnant Wistar rats were divided into five groups: negative control (PBS), positive control (L-Name 75 mg/kgBW), EVOO (4.5 mL/kg BW/day), VCO (4.45 mL/kg BW/day), and EVOO+VCO (2.25 mL each/ kg BW/day). The treatment was given orally from gestational day 1, and L-NAME was injected intraperitoneally from day 9 to 18 of gestation. The data were statistically analyzed using one-way ANOVA. Results showed that the EVOO+VCO group reduced systolic and diastolic blood pressure more than the positive control and single-treatment groups ($p<0.001$). Hematological parameters also differed significantly ($p<0.001$): hemoglobin (12.34 ± 0.67 g/dL), erythrocyte count (6.29 ± 0.52 × 10^6/µL), and platelet count (1310.80 ± 67.33 × 10^3/µL) increased, whereas leukocyte count decreased (8.06 ± 0.37 × 10^3/µL). Erythrocyte indices also improved. Overall, combined EVOO and VCO showed greater protective effects than either treatment alone, suggesting potential benefit for blood pressure control and hematological disturbances associated with preeclampsia.

Keywords: Preeclampsia; Extra Virgin Olive Oil; Virgin Coconut Oil; Antioxidant; blood pressure; Hematologic Profile.

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Introduction

Preeclampsia is a severe pregnancy condition and a major contributor to maternal and perinatal morbidity and mortality worldwide. The American College of Obstetricians and Gynecologists (ACOG) defines it as new-onset hypertension that develops after 20 weeks of pregnancy and is accompanied by proteinuria or, in its absence, evidence of target-organ failure [1]. A recent global meta-analysis found a combined prevalence of 4.43% of all pregnancies [2]. In Indonesia, preeclampsia remains an important cause of maternal death, and severe complications such as pulmonary edema, renal injury, and Hemolysis. These data highlight the need for preventive strategies during pregnancy, including the evaluation of adjunctive therapies that may reduce the risk of preeclampsia, while underscoring the importance of clinically relevant targets for intervention [3].

Preeclampsia is characterized by abnormal placentation, leading to placental hypoxia, angiogenic imbalance, and endothelial dysfunction. Hypoxia increases soluble endoglin (sEng), which inhibits TGF-β signaling, reduces nitric oxide (NO) production, and promotes vasoconstriction and impaired angiogenesis [4]. Experimental studies have shown that N-nitro-L-arginine methyl ester (L-NAME)-induced pregnant rats reproduce key features of human preeclampsia, including hypertension, proteinuria, vascular

injury, and an elevated sFlt-1/PlGF ratio, making this a well-established model for investigating disease pathogenesis and potential therapeutic interventions [5].

Preeclampsia is associated with hematologic alterations resulting from endothelial dysfunction, systemic inflammation, and coagulation abnormalities. Women with preeclampsia exhibit reduced platelet counts, while inflammatory markers, such as the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR), are significantly elevated and correlate with disease severity [6],[7]. These findings highlight the role of hematologic dysregulation in preeclampsia and support its therapeutic relevance.

Natural antioxidants with potential to counteract oxidative stress include extra virgin olive oil (EVOO) and virgin coconut oil (VCO) [8]. EVOO is rich in monounsaturated fatty acids and polyphenols, which reduce reactive oxygen species (ROS), improve endothelial function, lower blood pressure, and decrease the risk of cardiovascular complications associated with preeclampsia [9], [10]. According to Massaro et al., the high polyphenol content of EVOO contributes to reduced blood pressure through its antioxidant effects and improved endothelial function in hypertensive patients [11]. VCO contains medium-chain fatty acids and phenolic compounds with antioxidant and anti-inflammatory properties that scavenge free radicals and suppress inflammatory mediators such as nitric oxide (NO), TNF-α, and IL-6 [12]. In addition, a study by Utari et al. reported that although the protective effect of VCO against doxorubicin cardiotoxicity was lower than that of EVOO, the combination of the two showed a synergistic ability to suppress free radical formation and restore the balance of the antioxidant system, making it safe and potentially useful as an adjunctive therapy [13].

The complementary bioactive profiles of VCO, which is dominated by medium-chain fatty acids and anti-inflammatory phenolic compounds, and EVOO, which is rich in polyphenols with potent antioxidant activity, may result in additive effects that outperform using each oil alone. Therefore, the purpose of this study was to assess the effects of extra virgin olive oil, virgin coconut oil, and their combination on hematological parameters (hemoglobin, erythrocytes, leukocytes, platelets, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and mean corpuscular hemoglobin concentration (MCHC) and systolic and diastolic blood pressure in a rat model of L-NAME-induced preeclampsia.

METHODS

Instruments

The primary instruments used in this study included an animal balance (Ohaus Corporation, USA), a non-invasive blood pressure measurement system (CODA®, Kent Scientific Corporation, USA), an EDTA blood collection tube (Vaculab®, China), and a hematology analyzer (Exigo H400®, Boule Medical AB, Sweden).

Materials

The EVOO and VCO used in this study were standardized products with Certificates of Analysis (COAs). L-NAME from Sigma Aldrich and phosphate buffer solution (PBS), dipstick test, Aqua for injection, and standard animal feed.

Experimental Animals

A total of 25 female Wistar rats weighing 190-210 g were used in this study. The animals used for standard laboratory purposes were obtained from the animal house at the Faculty of Pharmacy, Universitas Andalas. The rats were in early pregnancy (day 0) after being mated with male white rats at a 3:1 ratio. All animals were healthy, exhibited normal behavior, and had not been previously used in any research studies. The animals were acclimatized for one week prior to treatment and were housed under standard laboratory conditions with free access to standard animal feed and water. All procedures were carried out in accordance with the European Council Directive on the Laboratory Animal Care and Use of Laboratory Animals (86/609/EEC). The protocol used in this study was authorized by the Faculty of Pharmacy's Research and Ethics Committee (No. 122/UN16.10.D.KEPK-FF/2024).

Experimental design

An experimental controlled study with repeated blood pressure measurements and endpoint hematological assessment was conducted. A total of 25 pregnant Wistar rats were randomly allocated into five

groups (n = 5 per group). The sample size was determined using the Federer formula for completely randomized experimental designs, (t − 1) (n − 1) ≥ 15, where t is the number of treatment groups and n is the number of animals per group. With five groups (t = 5) and five animals per group (n = 5), the calculation yielded (5 − 1) (5 − 1) = 16, satisfying the minimum requirement for an adequate sample size. The pregnant Wistar rats were randomly allocated into five experimental groups (n = 5 per group) as follows:

1. Normal group (received PBS as vehicle control)
2. Negative control group (received L-NAME at a dose of 75 mg/200 g BW intraperitoneally (i.p) on days 9-18 of pregnancy to induce preeclampsia-like symptoms)
3. Treatment Group 1 (received L-NAME (75 mg/200 g BW, i.p.) and EVOO at 4.45 mL/kg BW orally once daily)
4. Treatment Group 2 (received L-NAME (75 mg/200 g BW, i.p.) and VCO at 4.45 mL/kg BW orally once daily)
5. Treatment Group 3 (received L-NAME (75 mg/200 g BW, i.p.) and a combination of EVOO and VCO (2.25 mL/kg BW each) orally once daily)

Blood Pressure Measurement

Blood pressure was measured three times during pregnancy: on days 7, 15, and 18. Measurements were taken before and after L-NAME injection, and after administration of the test preparation. The procedure for measuring blood pressure in rats using a non-invasive blood pressure monitor (CODA, Kent Scientific Corporation) was conducted in the Pharmacology Laboratory of the Faculty of Pharmacy, Universitas Andalas.

Urine Protein Examination

Urine protein examinations were performed three times during pregnancy: on day 7, day 15, and day 18. A 24-hour urine sample was collected in a metabolic cage and tested with a dipstick to detect protein.

Hematological Parameter Examination

Blood sampling was performed on day 19. The test animals were sacrificed following anesthesia. Blood was then collected via surgical cardiac puncture by inserting a needle into either the left or right ventricle. A total of 1 mL of blood was collected and placed in an EDTA vacutainer tube. From this sample, 20 µl of blood was examined using a hematology analyzer. The hematological parameters measured included erythrocyte count, hemoglobin concentration, hematocrit, MCV, MCH, MCHC, leukocyte count, and platelet count.

Data Analysis

The research data, including systolic and diastolic blood pressure, proteinuria levels, and hematological parameters, were statistically analyzed using IBM SPSS Statistics 25. The data were analyzed using one-way Analysis of Variance (ANOVA). If the test results showed a p-value <0.05, indicating a statistically significant. When significant differences were found, post hoc analysis was conducted using Duncan's Multiple Range Test.

RESULT AND DISCUSSION

Effect of EVO and VCO on Blood Pressure and Protein Levels

Blood pressure (systolic and diastolic) and urine protein levels were measured at three time points – gestational day 7, 15, and 18 for all groups. Measurements taken on day 7 provided baseline values before any treatment was given. By day 15, the assessments were used to confirm whether preeclampsia had been successfully induced during the second trimester in the negative control group. Measurements on day 18 provided information on the effectiveness of the test preparations in reducing elevated blood pressure and improving the hematological profile.

Figure 1 illustrates the changes in systolic blood pressure across the five treatment groups. Overall, the negative control group showed the greatest increase in systolic blood pressure throughout the observation period. On day 15, this group's systolic blood pressure peaked before declining slightly on day 18, but remained higher than the other groups. The normal group maintained the lowest systolic blood pressure at all time points with minimal fluctuation, reflecting a stable physiological state without induced hypertension.

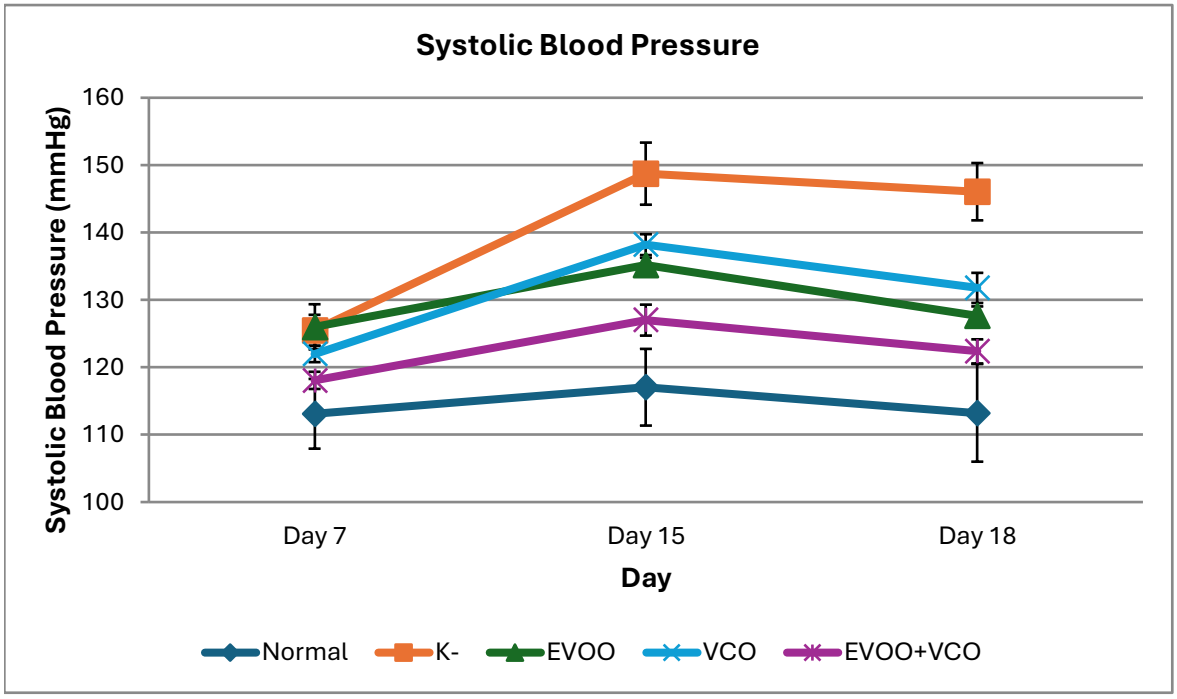

Figure 1. Comparison of Systolic Blood Pressure Among Treatment Groups.

EVOO and VCO administration each showed a moderate systolic blood pressure-lowering effect compared to the negative control. Both groups experienced a slight increase on day 15, followed by a decrease on day 18, indicating a positive blood pressure response after continued treatment. The EVOO+VCO combination group showed a more consistent reduction profile than the single treatments. Despite a slight increase on day 15, the systolic blood pressure of this group remained lower than that of those treated with EVOO or VCO alone. On day 18, the combination group showed blood pressure values that were nearly as low as those of the normal group, suggesting a potential additive effect of the two oils in lowering systolic pressure.

Statistical analyses were conducted using IBM SPSS Statistics version 25. The results of the One-Way ANOVA indicated a highly significant difference among the experimental groups ($p < 0.001$). Subsequent analysis employing Duncan's test demonstrated that the negative control group at day 15 presented a mean systolic blood pressure that was significantly higher than that of the other groups. These findings confirm the successful establishment of a preeclampsia model in mice, induced by L-NAME beginning on day 9 of gestation.

In contrast, the treatment groups receiving EVOO and VCO both fell within the same statistical subset and showed no significant difference between them. However, their mean systolic blood pressure was lower than that of the negative control group, suggesting that administering EVOO and VCO at a dosage of 4.45 mL/kg BW per day can effectively lower systolic blood pressure. Notably, the combined treatment group (EVOO+VCO) demonstrated greater efficacy in lowering systolic blood pressure by day 15 compared to the individual EVOO and VCO groups, as well as the negative control group.

Further assessment of systolic blood pressure on day 18 was conducted using One-Way ANOVA, which again yielded a statistically significant p-value (<0.001). The subsequent Duncan post hoc analysis showed that the EVOO and VCO treatment groups had mean systolic blood pressure values that did not differ significantly. In contrast, the EVOO+VCO combination group demonstrated the greatest reduction in systolic blood pressure, with values falling within the normal range.

Figure 2 illustrates changes in diastolic blood pressure across all treatment groups on days 7, 15, and 18. The negative control group had the highest diastolic

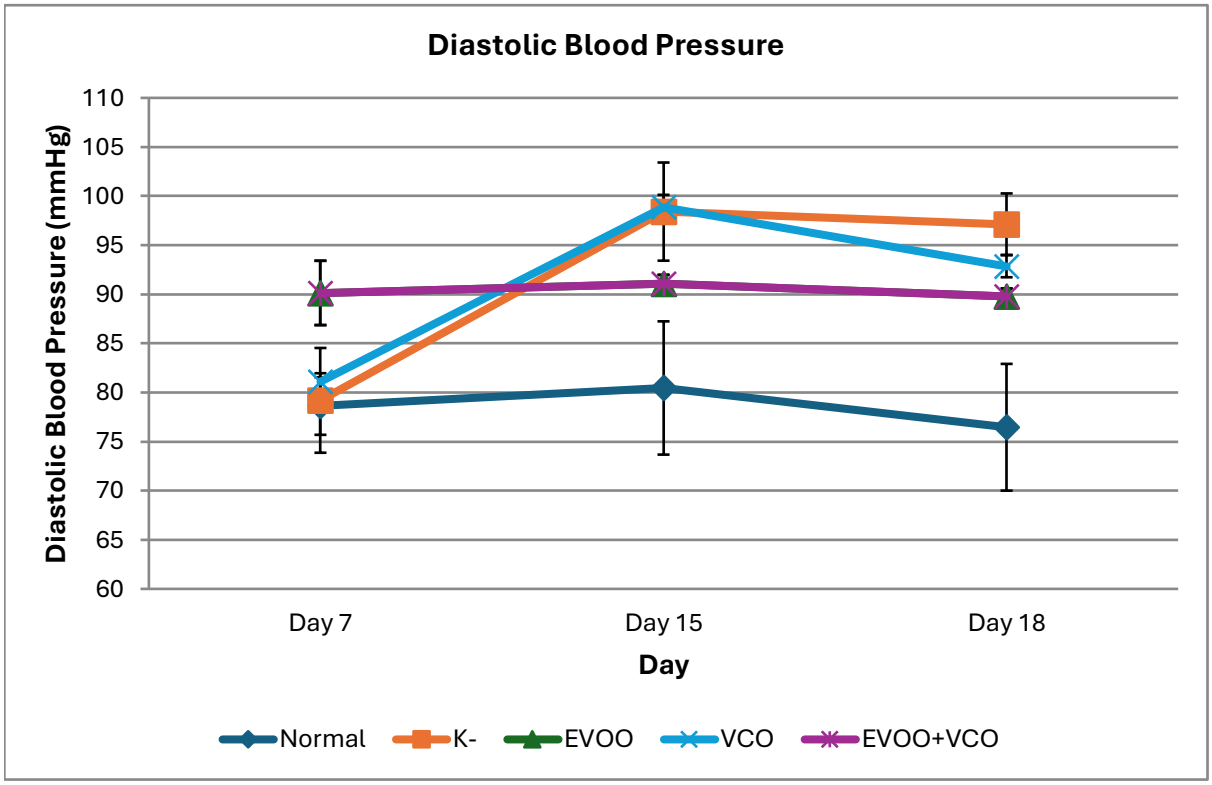

Figure 1. Comparison of Diastolic Blood Pressure (mmhg) Among Treatment Groups.

pressure throughout the observation period, with a sharp increase until day 15, followed by a slight decline on day 18. In contrast, the normal control group maintained the lowest value and remained relatively stable. The EVOO, VCO, and combination treatment groups showed a pattern of moderate increase on day 15, followed by a decline on day 18. The EVOO+VCO combination appeared to provide a more consistent reduction effect than either treatment alone.

A statistical analysis using One-Way ANOVA revealed a significant effect of each treatment on diastolic blood pressure in L-NAME-induced rats. Results from Duncan's further test indicated that the L-NAME-induced negative control group exhibited significantly lower diastolic blood pressure than all other treatment groups. In contrast, the groups receiving EVOO and VCO separately showed no significant differences. However, the combination of EVOO and VCO resulted in a significantly greater reduction in diastolic blood pressure than either treatment alone. Additionally, the diastolic values in the combination group approached those of the normal group, although they remained significantly different.

On day 18 of the measurement, a similar pattern of results was observed. The combination of EVOO and VCO produced a more significant reduction in diastolic blood pressure than either EVOO or VCO alone. These findings suggest a potential synergistic effect between EVOO and VCO in reducing diastolic blood pressure in the L-NAME-induced preeclampsia model.

As shown in **Table 1**, proteinuria levels varied among treatment groups during pregnancy. Normal rats consistently showed negative proteinuria at all observation points. Rats treated with a combination of EVOO and VCO generally maintained low proteinuria levels, particularly on days 15 and 18. In contrast, animals receiving EVOO or VCO alone showed a gradual increase in proteinuria over time. The negative control group demonstrated a clear progression toward moderate-to-severe proteinuria by day 18. Overall, these findings also indicate that the combined EVOO and VCO treatment provided better protection against proteinuria progression in this experimental model of preeclampsia

Table 1. Effects of EVOO, VCO, and their combination on Proteinuria Levels (mg/dL) in Pregnant Rats Model of Preeclampsia

Group	Day 7	Day 15	Day 18
Normal	-	-	-
Normal	-	-	-
Normal	-	-	-
Normal	-	-	-
Normal	-	-	-
Combination of EVOO and VCO	-	-	-
Combination of EVOO and VCO	-	-	-
Combination of EVOO and VCO	-	-	-
Combination of EVOO and VCO	-	-	-
Combination of EVOO and VCO	-	+	+
EVOO	-	-	-
EVOO	-	-	-
EVOO	-	+	+
EVOO	-	+	+
EVOO	-	+	+
VCO	-	-	-
VCO	-	-	-
VCO	-	+	-
VCO	-	+	+
VCO	-	+	+
Negative Control	-	+	+
Negative Control	-	+	+
Negative Control	-	+	+
Negative Control	-	+	++
Negative Control	-	++	++

Notes: Proteinuria was graded as follows: negative (−), no detectable protein; positive (+), >0.3 g/L; and strongly positive (++), >1.0 g/L

Table 2 summarizes changes in hematological parameters following administration of EVOO, VCO, or their combination. The negative control group induced with L-NAME exhibited marked hematological disturbances compared to the normal group, including significant reductions in red blood cell count, hemoglobin (HGB), hematocrit (HCT), and erythrocyte indices, accompanied by an increase in white blood cell (WBC) count and a decrease in platelet (PLT) levels. These alterations reflect anemia, systemic inflammation, and hematological dysfunction associated with oxidative stress and endothelial impairment commonly observed in preeclampsia.

Administration of EVOO or VCO alone resulted in partial improvement of hematological parameters. Both treatments increased RBC, HGB, HCT, MCV, MCH, and MCHC compared to the positive control, indicating recovery of erythropoiesis and red blood cell integrity. Improvements in platelet counts and reductions in leukocyte levels were also observed, suggesting reduced inflammation and protection against thrombocytopenia.

Notably, the combination of EVOO and VCO demonstrated the most consistent and pronounced corrective effects. This group showed greater normalization of erythrocyte parameters and red blood cell indices, with values approaching those of the normal group, indicating improved red cell morphology and hemoglobin content. In addition, the combination group exhibited the most substantial reduction in WBC count, suggesting a stronger anti-inflammatory response, and

Table 2. Effects of EVOO, VCO, and their combination on Hematologic Parameters

Hematologic Paramater	Mean ± SD of blood parameter values					
	Normal Control	Negative Control	EVOO	VCO	EVOO+ VCO	Mean
RBC (×10^6/µL)	7.45 ± 0.24d	5.08 ± 0.09a	5.66 ± 0.03b	5.48 ± 0.16b	6.29 ± 0.52c	5.99 ± 0.88
WBC (×10^3/µL)	5.32 ± 0.66a	18.52 ± 3.73c	11.10 ± 0.63b	12.92 ± 0.53 b	8.06 ± 0.38a	11.18 ± 4.88
PLT (×10^3/µL)	1,415.00±83. 77	469.40 ±52.49a	890.80 ± 111.93c	672.20 ± 88.10b	1,310.80 ± 67.34d	949.64 ± 376.23
HGB (g/dL)	14,14 ± 0.81d	9.30 ± 0.98a	11.12 ± 0.24b	10.46 ± 0.21b	12.34 ± 0.68c	11.47 ± 1.80
HCT (%)	32.86 ± 2.25d	23.74 ± 2.18a	26.74 ± 0.40b	25.73 ± 0.32b	30.00 ± 0.99c	27.81 ± 3.57
MCV (fL)	50.10 ± 0.53a	43.26 ± 0.87c	46.88 ± 0.19b	46.60 ± 0.46b	47.98 ± 0.82a	46.92 ± 2.35
MCH (pg)	20.30 ± 0.12a	18.48 ± 0.12d	19.04 ± 0.19b	18.97 ± 0.15c	19.78 ± 0.06b	19.30 ± 0.72
MCHC (g/dL)	40.56 ± 0.27a	43.92 ± 0.26d	41.37 ± 0.42b	42.54 ± 0.34c	40.44 ± 0.13a	41.07 ± 0.90

Note: RBC = erythrocyte; WBC = leukocytes; PLT = platelets; HGB = hemoglobin; HCT = hematocrit; MCV = mean cell volume; MCH = mean cell hemoglobin; MCHC = mean cell hemoglobin concentration. Different superscript letters (a, b, c, d) indicate statistically significant differences for each hematologic parameter, as determined by Duncan's multiple-range test ($p<0.05$).

the highest recovery in platelet levels, reflecting better preservation of vascular and hemostatic balance.

Statistical analysis revealed significant differences among groups for all hematological parameters ($p < 0.001$), with different superscript letters indicating significant differences according to Duncan's multiple-range test. Overall, these findings suggest that the combined administration of EVOO and VCO offers superior protection against hematological disturbances induced by preeclamptic conditions compared to single-oil treatments, likely due to the additive effects of antioxidants, anti-inflammation, and membrane stabilization.

This study demonstrates that administering EVOO, VCO, or their combination improves blood pressure, proteinuria, and hematological profiles in an L–NAME–induced rat model of preeclampsia. The L-NAME model is widely used to simulate preeclamptic conditions[14]. L-NAME is a nitric oxide synthase (NOS) inhibitor that affects vascular tone. Administration of L-NAME in the negative control group induced hypertension by inhibiting NO production, leading to endothelial dysfunction, hypertension, renal impairment, and systemic inflammation [15], [16]. In this context, the observed improvements indicate that EVOO and VCO play a protective role against key pathophysiological features of preeclampsia.

Administration of EVOO and VCO significantly reduced blood pressure, with the most pronounced effect observed in the combination group. EVOO contains phenolic compounds that help reduce the risk of cardiovascular disease. EVOO is rich in polyphenols and flavonoids. Among the main bioactive molecules belonging to the secoiridoid group are oleuropein and oleocanthal, while the phenylethanoid group includes tyrosol and hydroxytyrosol. That compound has been shown to enhance endothelial function by increasing NO bioavailability and reducing reactive oxygen species [17], [18].

Meanwhile, VCO contains medium-chain fatty acids and phenolic compounds that may contribute to vascular protection by reducing lipid peroxidation [19]. A study by Nurul-Iman et al. demonstrated that phenolic compounds stimulate endothelial nitric oxide (NO) release, leading to vasodilation and a subsequent decrease in blood pressure. Polyphenolic components have also been shown to prevent low-density lipoprotein (LDL) oxidation and to increase antioxidant levels in rats [20]. The greater blood pressure reduction observed in the combination group suggests an additive effect that restores endothelial homeostasis more effectively.

Hematological abnormalities are frequently observed in preeclampsia and are associated with oxidative stress, endothelial dysfunction, and systemic

inflammation. In the L-NAME-induced group, significant reductions in RBC count, hemoglobin, hematocrit, and erythrocyte indices were observed, indicating anemia associated with preeclampsia. These findings are consistent with previous reports linking preeclampsia to oxidative damage and hematological disturbances [21]. Treatment with EVOO and VCO was associated with improvements in these hematological parameters, suggesting a protective effect on erythrocyte status. The combination group exhibited values closest to those of the normal group, indicating a greater improvement in hematological profiles than either treatment alone.

The leukocyte count was significantly elevated in the L-NAME-induced group, consistent with the systemic inflammatory response commonly observed in preeclampsia. Administration of EVOO and VCO was associated with lower leukocyte counts, with the greatest reduction observed in the combination group. These findings suggest a potential anti-inflammatory effect, although inflammatory mediators were not directly measured in this study. Previous studies have reported that polyphenols in EVOO may modulate inflammatory signaling pathways, including NF-κB [22], while VCO contains lauric acid and phenolic compounds that have demonstrated antioxidant and immunomodulatory activities in experimental models [23], [24]. Therefore, the observed reduction in leukocyte count may reflect attenuation of inflammatory responses, although this mechanism requires further confirmation.

Thrombocytopenia is another important hematological manifestation of preeclampsia and is associated with endothelial dysfunction and coagulation abnormalities. In this study, L-NAME induction reduced platelet counts, whereas administration of EVOO and VCO was associated with significantly higher platelet counts. The combination group showed the greatest improvement, suggesting better preservation of hematological status during preeclampsia. Previous studies have suggested that the antioxidant and anti-inflammatory properties of EVOO and VCO may help maintain endothelial function and reduce platelet consumption [25]. Overall, the greater improvement observed in the combination group suggests that the bioactive constituents of EVOO and VCO may exert complementary effects, although further mechanistic studies are needed to confirm this possibility.

Several limitations of this study should be acknowledged. First, proteinuria was assessed using a urine dipstick test, which provides only semiquantitative results and is less accurate than quantitative laboratory methods. Therefore, the proteinuria findings should be interpreted with caution. Second, biomarkers of oxidative stress, inflammation, and nitric oxide bioavailability, including malondialdehyde (MDA), superoxide dismutase (SOD), nitric oxide (NO), tumor necrosis factor-α (TNF-α), and interleukin-6 (IL-6), were not directly measured. Consequently, the proposed mechanisms underlying the protective effects of EVOO and VCO remain speculative and are based on evidence from previous studies rather than direct experimental confirmation. Future studies incorporating quantitative proteinuria assessment together with molecular and histopathological analyses are warranted to further elucidate the mechanisms of action. Despite these limitations, the present findings provide experimental evidence supporting the potential of combined EVOO and VCO supplementation as a protective strategy against preeclampsia-related complications.

CONCLUSION

Based on the findings, it can be concluded that oral administration of a combination of EVOO and VCO exerts protective effects against hematological disturbances induced by preeclampsia. The combination was effective in reducing blood pressure, lowering proteinuria, and normalizing blood parameters, including erythrocyte count, hemoglobin, hematocrit, leukocytes, and platelets, as well as improving erythrocyte indices. These additive effects are likely attributed to the antioxidant and anti-inflammatory properties of bioactive compounds present in both oils. Therefore, the combination of EVOO and VCO holds potential as a supportive therapeutic strategy for managing preeclampsia.

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