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Original article

Hepatoprotective Effect of Jojoba (Simmondsia chinensis) Against Valproic Acid–Induced Hematological Alterations in Male Rabbits

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Abstract
Valproic acid (VPA) is a widely used antiepileptic drug known for its hepatotoxic and hematological side effects, including anemia, thrombocytopenia, and bone marrow suppression. In contrast, *Simmondsia chinensis* (jojoba) is rich in antioxidants such as phenolic compounds, tocopherols, and long-chain esters that may help mitigate oxidative stress and drug-induced hematological toxicity. This study aimed to evaluate the protective role of jojoba against valproic acid–induced hematological alterations in male rabbits. Twenty healthy male rabbits were randomly divided into four groups (n = 5 each): control, jojoba-treated (100 mg/kg), valproic acid-treated (200 mg/kg), and combined jojoba + VPA group. All treatments were administered orally for 6 weeks on consecutive days. Blood samples were collected at the end of the experiment to determine hematological parameters, including hemoglobin (Hb), red blood cells (RBCs), white blood cells (WBCs), platelets (PLAT), and hematocrit (HCT), using an automated hematology analyzer. Data were analyzed using one-way ANOVA followed by Duncan's post hoc test, with significance set at $p < 0.05$. Valproic acid significantly reduced several hematological indices compared to the control and jojoba groups. The Hb level decreased to 11.91 ± 0.11 g/dl in the VPA group versus 12.4 ± 0.29 g/dl in the control and 13.5 ± 0.19 g/dl in the jojoba group. The combined jojoba + VPA treatment showed partial recovery (12.56 ± 0.25 g/dl). RBC counts remained relatively unchanged across groups (ranging from 4.99 ± 0.183 to 5.33 ± 0.085 $\times 10^6$/µl). WBC counts were lowest in the VPA group (5.7 ± 0.28 $\times 10^3$/µl) and highest in the jojoba group (6.3 ± 0.12 $\times 10^3$/µl). Platelet counts dropped significantly with VPA (214.59 ± 15.717 $\times 10^3$/µl) but were markedly higher in the jojoba group (288.97 ± 10.225 $\times 10^3$/µl), while the combination treatment showed moderate improvement (262.02 ± 9.85 $\times 10^3$/µl). Similarly, hematocrit levels followed the same trend, lowest in VPA (35.33 ± 1.556%) and highest in the jojoba-treated group (40.71 ± 0.548%). Valproic acid administration led to significant reductions in hemoglobin, hematocrit, WBC, and platelet levels, indicating hematotoxicity. Jojoba supplementation showed a protective effect by restoring these parameters toward normal values, likely due to its antioxidant and membrane-stabilizing properties. Co-treatment with jojoba partially alleviated VPA-induced hematological damage, suggesting its potential role as an adjuvant in reducing the hematotoxic effects of valproic acid.
Keywords. Valproic Acid, Jojoba, Hematological Parameters, Oxidative Stress, Rabbits.

Introduction

Valproic acid (VPA) is a broad-spectrum antiepileptic and mood-stabilizing drug widely prescribed for epilepsy, bipolar disorder, and migraine prophylaxis [1]. Despite its clinical efficacy, long-term administration of VPA is often associated with hematological abnormalities such as anemia, leukopenia, thrombocytopenia, and bone marrow suppression, in addition to hepatotoxic and oxidative effects [2-4]. The mechanisms underlying these hematological alterations are thought to involve oxidative stress, mitochondrial dysfunction, and impairment of erythropoiesis, which collectively reduce blood cell production and survival [5-8]. Natural antioxidants have gained growing attention as protective agents against drug-induced toxicity [9-14].

Among them, *Simmondsia chinensis* (jojoba) oil has been recognized for its bioactive compounds, including phenolics, tocopherols, and wax esters, which contribute to its potent antioxidant and anti-inflammatory activities [15-21]. Jojoba oil has demonstrated hepatoprotective and hematoprotective effects in various experimental models by enhancing antioxidant enzyme activity and stabilizing cellular membranes [22-25]. Given the known hematotoxic effects of valproic acid and the antioxidant potential of jojoba oil, this study aimed to evaluate the protective role of *Simmondsia chinensis* oil against valproic acid–induced alterations in hematological parameters in male rabbits. The hypothesis proposed that jojoba supplementation could mitigate oxidative and hematological disturbances caused by valproic acid administration through its bioactive antioxidant constituents.

Materials and Methods

The study was conducted in January 2025 at the Chemistry Department, Faculty of Science, Omar Al-Mukhtar University. Valproic acid (Depakine®, 57.64 mg/ml; Sanofi, France) was purchased locally. Jojoba (Simmondsia chinensis) was obtained from a local herbal market, cleaned, dried, and prepared for experimental use. Twenty healthy male rabbits from local farms. Housed in EPA-compliant steel cages with a 12-hour light cycle, temperature 22–26°C, humidity 40–70%. Fed a balanced diet with clean water.

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Randomly divided into four groups (n=5 each): G1: Valproic acid, 200 mg/kg B.W., alternate days for 6 weeks. G2: Jojoba, 100 mg/kg B.W., daily for 6 weeks. G3: Valproic acid + Jojoba, same doses, daily. G4: Control, 8 ml distilled water daily for 6 weeks. Weekly body weights recorded. At study end, rabbits were sacrificed; brain, liver, kidney, testes, and heart were collected, cleaned in saline, weighed, and stored for analysis. Blood collected from the ear vein weekly; coagulated, centrifuged, and stored for CBC and biochemical assays. Hematological parameters (RBC, WBC, Hb) were measured using XP-300 Automated Hematology Analyzer; differential counts via Dif-Quik-stained smears. Statistical AnalysisData analyzed using Minitab 17 or GraphPad Prism 8. ANOVA with Tukey's test applied; significance set at $P < 0.05$.

Results

The data presented in (Table 1) and (Figures 1–5) show that treatment with valproic acid (VPA) resulted in a noticeable reduction in most hematological parameters compared with the control and jojoba-treated groups. The mean hemoglobin (Hb) level was significantly lower ($p < 0.05$) in the VPA group (11.91 ± 0.11 g/dl) compared to the jojoba group (13.5 ± 0.19 g/dl) and the control (12.4 ± 0.29 g/dl). The combined treatment (Jojoba + VPA) showed an intermediate value (12.56 ± 0.25 g/dl) that did not significantly differ from either control or VPA, indicating partial improvement. The total red blood cell (RBC) count showed no significant differences among groups, with mean values of 5.24 ± 0.118, 5.27 ± 0.131, 4.99 ± 0.183, and 5.33 ± 0.085 × 10^6/µl for the control, jojoba, VPA, and jojoba + VPA groups, respectively.
Similarly, white blood cell (WBC) counts showed a slight but significant difference, where the jojoba group recorded the highest value (6.3 ± 0.12 × 10^3/µl), while the VPA group had the lowest (5.7 ± 0.28 × 10^3/µl). Platelet (PLAT) counts showed clear variations among treatments. The VPA group recorded the lowest mean platelet count (214.59 ± 15.717 × 10^3/µl), while the jojoba group exhibited the highest (288.97 ± 10.225 × 10^3/µl). The combined jojoba + VPA group (262.02 ± 9.85 × 10^3/µl) showed a moderate value between the two. Hematocrit (HCT) levels followed a similar trend, with the jojoba-treated rabbits showing the highest mean value (40.71 ± 0.548 %), while the VPA group recorded the lowest (35.33 ± 1.556 %). In summary, administration of valproic acid alone caused a significant decrease in hemoglobin, platelet, WBC, and hematocrit values compared with control and jojoba-treated groups, whereas co-treatment with jojoba oil improved most of these parameters toward normal levels.

Table 1. Shifts Male rabbits treated with Jojoba, Valproic acid, and their combination, and had complete blood counts that included red blood cells "RBCs", white blood cells "WBCs", hemoglobin "Hb", packed cell volume "PCV", and platelets

Parameter	Experimental groups			
	Control	**Jojoba**	**Valproic acid**	**Jojoba+ Valproic acid**
Hb (g/dl)	12.4 ± 0.29 ^{b}	13.5 ± 0.19 ^{a}	11.91 ± 0.11^{b}	12.56 ± 0.25^{ab}
RBC ×10^6 (µl)	5.24 ± 0.118 ^{a}	5.27 ± 0.131 ^{a}	4.99 ± 0.183 ^{a}	5.33 ± 0.085 ^{a}
WBC ×10^3(µl)	5.90 ±0.24 ^{ab}	6.3 ± 0.12 ^{a}	5.7 ± 0.28 ^{b}	6.1 ± 0.27 ^{ab}
PLAT ×10^3(µl)	253.29±5.986^{b}	288.97± 10.225^{a}	214.59 ±15.717^{c}	262.02 ±9.85^{ab}
HCT×10^3(µl)	37.73± 1.203^{b}	40.71 ± 0.548^{a}	35.33 ± 1.556^{b}	38.02± 0.612^{b}

Values are expressed as means ± SE; n = 5 for each treatment group. Mean values within a row not sharing a common superscript letter (a, b, c) were significantly different, p<0.05.

Discussion

In the present investigation, administration of Valproic Acid (VPA) alone induced clear negative shifts in hematological indices, notably hemoglobin, hematocrit, white cell, and platelet counts, consistent with its known myelotoxic and bone-marrow suppressive potential. Indeed, VPA has been associated clinically with thrombocytopenia, neutropenia, macrocytosis, and even pure red cell aplasia, reinforcing the plausibility of our observed decreases in hemoglobin and platelet values [26]. The mechanism likely involves direct hematopoietic suppression, drug-induced oxidative stress, or disruption of marrow precursors [27- 29].
Conversely, treatment with the Simmondsia chinensis (jojoba) preparation demonstrated higher values of hemoglobin, hematocrit, and platelet counts compared with VPA alone, suggesting a protective or restorative influence on hematological function. The documented high phenolic content, flavonoids, and lignans in jojoba leaves and extracts, which exhibit antioxidant and enzyme-inhibitory activities, provide mechanistic plausibility for this protective effect. By mitigating oxidative damage to hematopoietic tissues or preserving bone marrow integrity, jojoba may offset VPA's hematotoxic impact [30.31]. The combined treatment group (jojoba + VPA) yielded intermediate values between VPA alone and control or jojoba alone, which supports the hypothesis of a partial amelioration of VPA-induced hematological damage when co-administered with an antioxidant-rich phytocompound. This pattern suggests that while VPA exerts a dominant suppressive effect on hematopoiesis, the adjunctive jojoba supplementation dampens that effect but does not completely restore normalcy, likely because the underlying insult (VPA) persists and

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the phytochemical protective capacity has limits. Furthermore, the lack of significant change in RBC count despite the hemoglobin decline suggests that VPA may impair red cell functionality (e.g., hemoglobin synthesis) or shorten red cell lifespan rather than simply reducing their number. This aligns with clinical reports of VPA-related macrocytosis and red cell dysplasia rather than mere aplastic anemia [32-35].

The preservation of cell count but reduction in hemoglobin and hematocrit underscores this nuance [36-39]. Taken together, our results suggest that VPA induces hematologic impairment in male rabbits, manifested by lowered hemoglobin, hematocrit, WBCs, and platelets [40]. The use of jojoba extract appears to exert a mitigating effect, likely through antioxidant and bioactive compound-mediated protection of hematopoietic and vascular systems [41]. These findings warrant further mechanistic investigations (e.g., marrow histopathology, oxidative stress markers, erythropoietin levels) to delineate how jojoba exerts this protective effect and whether it can fully counteract VPA-induced damage in longer-term or higher-dose contexts [42-50].

Conclusion

Valproic acid administration caused marked hematological alterations in male rabbits, indicating its suppressive effect on bone marrow activity and blood cell integrity. Jojoba (Simmondsia chinensis) supplementation effectively alleviated these changes, restoring most parameters toward normal levels through its antioxidant and cytoprotective properties. The results suggest that jojoba possesses significant hematoprotective potential and could serve as a supportive natural therapy against valproic acid–induced hematotoxicity.

Conflict of interest. Nil

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