Original Article

Hematological Impacts of Gallic Acid, Disulfiram, and Dexamethasone in a Rat Model of Lipopolysaccharide-induced Sepsis

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ABSTRACT

Background: Sepsis is a life-threatening inflammatory condition associated with severe hematological disturbances.

Objectives: This study evaluated the protective effects of dexamethasone (DEX), disulfiram (DSF), and gallic acid (GA) against lipopolysaccharide (LPS)-induced sepsis in rats.

Methods: Thirty male Wistar rats (180-200 g) were divided into six groups (n=5): a control group; an LPS (10 mg/kg) group receiving a single intraperitoneal (i.p.) injection; and four pretreatment groups. The pretreatment groups received either DEX (1 mg/kg/day, intraperitoneally (i.p), for 2 days), GA (200 mg/kg/day, orally, for 7 days), DSF (50 mg/kg/day, orally, for 3 days), or a combination of GA+DSF (200+50 mg/kg/day, orally, for 7 and 3 days, respectively). Three hours after of the last dose in pretreatment groups, LPS was administered, and blood samples were collected 20 hours post-LPS injection for hematological analysis.

Results: Administration of LPS caused significant hematological changes, including: leukopenia (mean difference: -4.99×10^3/µL, P=0.002), neutrophilia ($+6.31\times10^3$/µL, P<0.0001), lymphopenia (-9×10^3/µL, P<0.0001), thrombocytopenia (-702.8×10^3/µL, P<0.0001), and a highly significant increase in the neutrophil-to-lymphocyte (N/L) ratio (+10.2, 107 folds, P=0.001). LPS also significantly increased the red blood cell (RBC) count ($+0.914\times10^6$/µL, P=0.0063), hemoglobin (Hb) concentration (+2.04 g/dL, P=0.0029), and hematocrit (HCT) levels (+9.02%, P=0.0004). DEX significantly ameliorated the LPS-induced leukopenia and thrombocytopenia (P≤0.0001) but exacerbated neutrophilia (P≤0.0001) and the N/L ratio (P≤0.05). DSF reduced the LPS-induced changes in RBC count and Hb and HCT levels (P≤0.001–0.0001) but had minimal effects on thrombocytopenia. GA showed limited influence on the LPS-induced hematological changes but modulated HCT levels (P≤0.01). The DSF-GA combination significantly decreased the LPS-induced changes in Hb and HCT levels and the N/L (P≤0.05). Moreover, DSF and GA, both alone and in combination, demonstrated a significant reduction in RBC count, neutrophils levels, the N/L ratio, and HCT levels (P<0.05-0.0001) compared with DEX.

Conclusion: The DSF+GA combination demonstrated good efficacy in mitigating sepsis-induced hematological disruptions compared to DEX by targeting inflammation through distinct mechanisms, offering a novel therapeutic approach in the management of sepsis.

Keywords: Disulfiram (DSF), Gallic acid (GA), Hematology, Neutrophil-to-lymphocyte (N/L) ratio, Sepsis

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Introduction

Sepsis, a life-threatening condition caused by a dysregulated host response to infection, remains a major global health challenge with high mortality rates (Singer et al., 2016). The pathophysiology of sepsis involves systemic inflammation, hematological disturbances, and multi-organ failure, primarily triggered by lipopolysaccharide (LPS) from gram-negative bacterial walls (Cohen, 2002; Farkas, 2020). This inflammatory response leads to characteristic changes in blood parameters, including leukopenia/leukocytosis, anemia, and thrombocytopenia that further exacerbate organ damage (Hotchkiss et al., 2016). Current therapies, like corticosteroids (e.g. dexamethasone [DEX]) while modulating inflammation, are limited by significant side effects, including immunosuppression, hyperglycemia, and increased infection risk (Annane, 2019; Rhen & Cidlowski, 2005; Rochwerg et al., 2018). These limitations have caused an urgent need for novel therapeutic approaches with better safety profiles. Conversely, the poor outcomes of using DEX in patients have led to a high interest in the search for other effective options, especially natural and/or repurposed compounds that demonstrate anti-inflammatory, antioxidant, and/or immunomodulatory properties.

Gallic acid (GA), a natural polyphenol, has recently gained attention for its potent antioxidant and anti-inflammatory properties. GA can reduce sepsis-induced organ damage by inhibiting the NF-κB and MAPK pathways while decreasing pro-inflammatory cytokines (Alhazmi et al., 2024; Bai et al., 2021).

Disulfiram (DSF), an FDA-approved alcohol aversion therapy, recently has emerged as a promising anti-inflammatory agent in sepsis. Its mechanisms include inhibiting NETosis, reducing oxidative stress, and modulating immune cell function (Chi et al., 2022; Klimiankou & Skokowa, 2021; Wei et al., 2022; Zhang et al., 2021).

While both GA and DSF have been studied individually, no previous study has examined their combined effects on sepsis-induced hematologic disorders. The early diagnosis of sepsis facilitates the accelerated initiation of treatment. As blood parameter testing is the initial step in diagnosing any disease, including sepsis, it is particularly crucial. Changes in hematologic parameters, such as the neutrophil-to-lymphocyte (N/L) ratio, serve as important prognostic markers in sepsis (Agnello et al., 2021; de Jager CP, 2010; de Jager et al., 2012).

This study aimed to compare the effects of GA and DSF, both individually and in combination, on hematological alterations induced by LPS in a rat model. Given the limitations of corticosteroid therapy and the increasing interest in anti-inflammatory phytochemicals and drug repurposing strategies, this research evaluated and compared the hematological effects of GA, DSF, and DEX in a rat model of LPS-induced sepsis.

Materials and Methods

Animals and ethical approval

Thirty adult male Wistar rats (180-200 g) were purchased from the Laboratory Animal Center, Faculty of Veterinary Medicine, University of Tehran, Tehran, Iran. The rats were housed in cages and kept under laboratory conditions, including a 12 h-12 h light/dark cycle, in a room with controlled temperature and humidity. Food and drinking water were provided ad libitum. This study was performed in accordance with the guidelines for the care and use of laboratory animals and was approved by the Ethics Committee for Animal Research, Faculty of Veterinary Medicine, University of Tehran.

Chemicals and reagents

GA (catalog number: 149-91-7, purity 99.9%) was purchased from Merck Chemicals (Darmstadt, Germany). DSF (Antabuse, CAS number: 97-77-8) was obtained from Ortega Martinez Pharmaceutical Company (San Miguel del Arroyo, Spain). DEX ampules were obtained from Tehran Shimi Pharmaceutical Company (Tehran, Iran). LPS L6511 (catalog number: 117977-52-1) was obtained from Sigma-Aldrich. The LPS powder was first dissolved in a small amount of distilled water, and the solution was then diluted with sterile normal saline solution (NaCl, 0.9%, w/v) to achieve the target concentration. DSF and GA were accurately weighed to achieve the specified dosages. Each compound was initially dissolved in distilled water, followed by dilution with normal saline to achieve a final administration volume of 0.5 mL. The resulting suspensions were homogenized and administered to the rats via oral gavage using a standardized protocol. DEX was initially diluted to a dose of 1 mg/kg with injectable normal saline and administered intraperitoneally (i.p.) in a standard volume.

Experimental design

Animals were randomly assigned to six groups (n=5 per group).

Group 1: The control (Cont) group received normal saline solution (0.9%) orally by gavage and subsequently received a single injection (i.p.) of sterile normal saline solution (0.9%).

Group 2: The LPS group received normal saline orally by gavage and subsequently received a single injection of LPS at 10 mg/kg (i.p.).

Group 3: The DEX group received DEX (1 mg/kg, i.p.) for 2 days (Owoeye et al., 2008) , and subsequently was injected with LPS (10 mg/kg, i.p.), 1 hour after the last dose of DEX.

Group 4: The GA group received GA (200 mg/kg/day) orally by gavage for 7 days (Nikbakht et al., 2015). Three hours after the last dose, LPS was injected at 10 mg/kg (i.p.).

Group 5: The DSF group received DSF (50 mg/kg/day) orally by gavage for 3 days (Cetin et al., 2015; Zhao et al., 2022). Three hours after the last dose, LPS was injected at 10 mg/kg (i.p.).

Group 6: The GA+DSF group received GA (200 mg/kg/day) orally by gavage for 7 days and DSF (50 mg/kg/day) orally by gavage for the last 3 days. Three hours after the last dose, LPS was injected at 10 mg/kg (i.p.).

Induction of sepsis

Sepsis was induced by a single injection of LPS (10 mg/kg, i.p.) using *Salmonella typhimurium*-derived LPS (Sigma-Aldrich) dissolved in sterile saline (0.9%).

Blood sample collection

Twenty hours after LPS injection, blood samples were taken from the hearts of the rats under general anesthesia induced with ketamine (80 mg/kg) and xylazine (10 mg/kg). Blood was collected in EDTA-coated tubes for CBC analysis. After sample collection, the rats were euthanized according to the Guidelines for the Care and Use of Laboratory Animals of the Ethics Committee for Research (Ahmadi-Noorbakhsh et al., 2021).

Hematological tests

Complete blood count (CBC) parameters, including white blood count (WBC) and red blood cell (RBC) counts, Hemoglobin (Hb) concentration, hematocrit (HCT) level, and platelet (PLT) count, were analyzed via an automated hematology analyzer (Sysmex Corporation, Kobe, Japan).

Statistical analysis

Data are expressed as Mean±SD. Statistical analysis was performed using one-way ANOVA followed by Dunnett's test. A $P<0.05$ was considered statistically significant. All analyses were performed using GraphPad Prism software, version 8.4.3.

Results

Effect of LPS on hematological parameters

The WBC count was significantly decreased (mean difference: $-4.99\times10^3/\mu L$, 95% confidence interval [CI]: −8.29 to −1.69; P=0.002) by a single administration of LPS compared to the control group, indicating the development of leukopenia. Additionally, the neutrophil (Neut) count increased significantly ($+6.31\times10^3/\mu L$, 95% CI, 3.45%, 9.16%; P<0.0001), while the lymphocyte (Lymph) count decreased ($-9\times10^3/\mu L$, 95% CI, −6.79%, −11.2%; P<0.0001), suggesting an inflammatory shift (Figure 1). The N/L ratio also increased highly significantly in the LPS group compared to the control group (+10.2, 95% CI, 3.88%, 16.5%; a 107-fold increase, P=0.001). The RBC count ($+0.914\times10^6/\mu L$, 95% CI, 0.228%, 1.60%; P=0.0063), Hb concentration (+2.04 g/dL, 95% CI, 0.635%, 3.45%; P=0.0029), and HCT levels (+9.02%, 95% CI, 3.82%, 14.2%; P=0.0004) were all elevated, indicating apparent polycythemia. The PLT count in the LPS group showed a sharp decrease compared to the control group ($-702.8\times10^3/\mu L$, 95% CI, −820.8%, −584.8%; P<0.0001), which is indicative of thrombocytopenia (Figure 2).

Effect of pretreatment with DEX

Pretreatment with DEX (1 mg/kg/day for 2 days) significantly elevated the WBC count (mean difference: $+8.42\times10^3/\mu L$, 95% CI, 5.12%, 11.7%; P<0.0001), RBC count ($+1.15\times10^6/\mu L$, 95% CI, 0.460%, 1.83%; P=0.0007), and neutrophil count ($+7.26\times10^3/\mu L$, 95% CI, 4.4%, 10.1%; P<0.0001) compared to the LPS group. On the other hand, there were no significant effects on HCT and Hb levels, as well as lymphocyte count compared to the LPS group. The N/L ratio increased significantly in the DEX group compared to the LPS group (+6.57, 95% CI, 0.27%, 12.9%; 1.64 folds, P=0.0389). Furthermore, DEX significantly improved PLT count ($+450.6\times10^3/\mu L$, 95% CI, 332.6%, 568.6%; P<0.0001) compared to the LPS group (Figures 1 and 2).

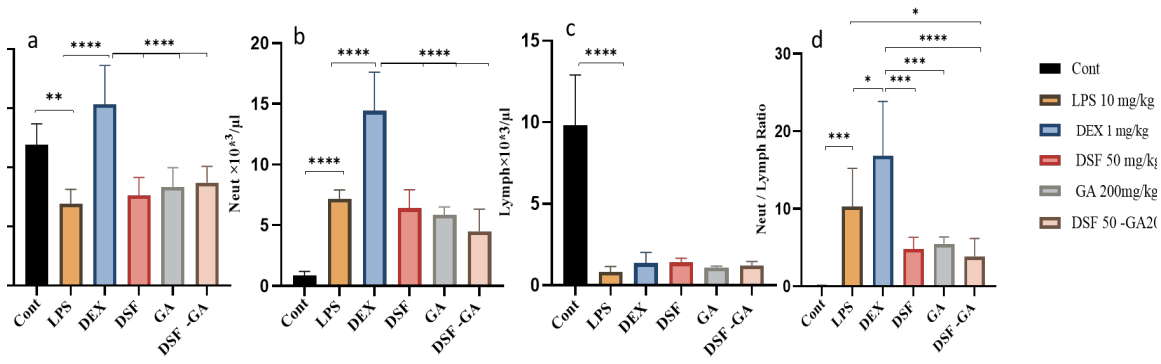

Figure 1. Effects of LPS and therapeutic interventions on leukocyte parameters

a) WBC count, b) Neutrophil count, c) Lymphocyte count, d) Neutrophil/lymphocyte ratio

Abbreviations: LPS: Lipopolysaccharide; DEX: Dexamethasone; DSF: Disulfiram; GA: Gallic acid.

*P≤0.05, **P≤0.01, ***P≤0.001, ****P≤0.0001.

Note: Data are presented as Mean±SEM.

Effect of pretreatment with DSF

DSF pretreatment (50 mg/kg/day for 3 days) also produced some significant protective effects on hematological changes induced by LPS. It slightly increased the WBC and lymphocyte counts compared to the LPS group, but the difference was not significant. Neutrophil count and the N/L ratio were not significantly reduced (Figure 1). However, DSF significantly decreased the RBC count (mean difference: −1.21×10⁶/µL, 95% CI, −1.89%, −0.522%; P=0.0004), Hb concentration (−2.38 g/dL, 95% CI, −3.78%, −0.975%; P=0.0006), and HCT levels (−11.3%, 95% CI, −16.5% −6.13%; P<0.0001) compared to the LPS group. In addition, the PLT count did not change following DSF pretreatment (Figure 2).

Effect of pretreatment with GA

GA pretreatment (200 mg/kg/day for 7 days) caused limited changes in hematological parameters. GA increased the WBC count compared to the LPS group, but this effect was not statistically significant. Neut count and the N/L ratio were not significantly reduced, and lymph count showed a slight increase (Figure 1). In addition, RBC and Hb concentrations were unaffected by pretreatment with GA, but there was a significant change in HCT levels (mean difference: −7.80%, 95% CI, −13% −2.6%; P=0.0021). The PLT count was also unchanged in the group treated with GA compared to the LPS group (Figure 2).

Effects of the combination of GA and DSF

The DSF+GA also produced significant protective effects in hematological parameters induced by LPS. The administration of DSF+GA slightly increased the WBC and lymphocyte counts compared to the LPS group, but the changes were not significant. Neutrophil count was not changed compared to the LPS group. However, the N/L ratio was significantly reduced in the DSF+GA group (mean difference: −6.40, 95% CI, −12.7%, −0.097%; 0.377-fold, P=0.0457) (Figure 1d). On the other hand, DSF+GA significantly decreased Hb concentration (−1.74 g/dL, 95% CI, −3.14% −0.333%; P=0.0118) and HCT levels (−5.24%, 95% CI, −10.4%, −0.0417; P=0.0477) in comparison to the LPS group. In addition, the PLT count did not change following DSF-GA pretreatment (Figure 2).

Comparison of the pretreated groups and the DEX group

The DSF, GA, and DSF+GA groups significantly reduced WBC and neutrophil counts compared to the DEX group (P<0.0001). However, lymphocyte count remained relatively unchanged compared to the DEX group. On the other hand, the values of the N/L ratio were significantly reduced in the DSF (P=0.0001) and GA (P=0.0003) groups, as well as in the DSF+GA group (P<0.0001) in comparison to the DEX group (Figure 1). Additionally, there were significant decreases in RBC counts in the DSF, GA, and DSF+GA groups (P<0.0001) relative to DEX. HCT levels also significantly decreased in the DSF (P<0.0001), GA (P=0.0014), and DSF+GA) P=0.033) groups. Compared to the DEX group,

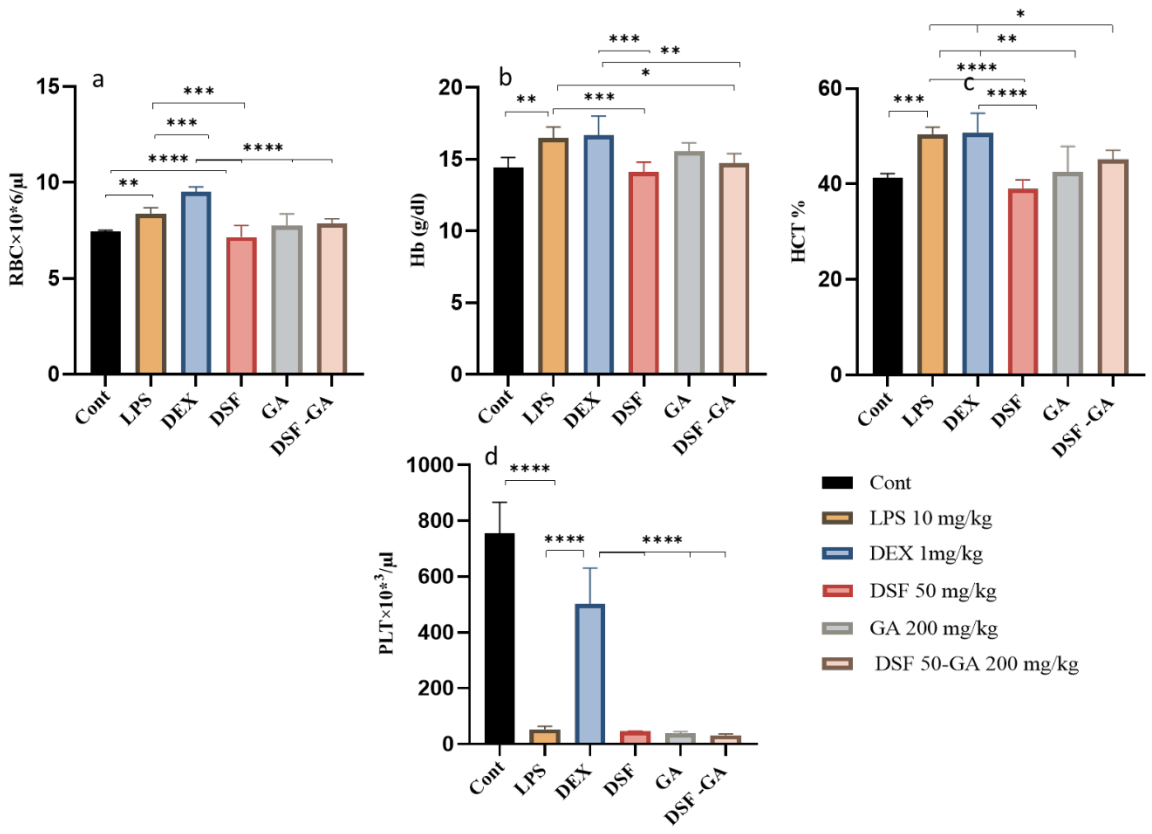

Figure 2. Effects of LPS and therapeutic interventions on erythrocyte and platelet parameters

a) RBC count, b) Hb concentration, c) HCT levels, d) PLT count

Abbreviations: LPS: Lipopolysaccharide; DEX: Dexamethasone; DSF: Disulfiram, GA: Gallic acid.

*P≤0.05, **P≤0.01, ***P≤0.001, ****P≤0.0001.

Note: Data are represented as Mean±SEM.

both DSF (P=0.0002) and the DSF-GA combination (P=0.0047) significantly decreased Hb levels. However, DEX performed significantly better than DSF, GA alone, and the DSF-GA combination in increasing PLT count (P<0.0001) (Figure 2).

Discussion

This study examined the impact of LPS-induced sepsis on hematological parameters in rats, and evaluated the protective effects of DEX, DSF, GA, and DSF+GA on LPS-induced hematological changes. The results revealed significant hematological changes following LPS injection, including leukopenia, polycythemia, and thrombocytopenia, which are well described in the pathophysiology of sepsis. Additionally, pretreatments with DEX, DSF, GA, and DSF+GA resulted in significant changes in hematological parameters, suggesting their potential for the management of sepsis. The findings are consistent with prior studies reporting that LPS can induce immune cell apoptosis and sequestration, which leads to a reduction in circulating WBC (Hotchkiss & Karl, 2003). Research has also demonstrated that leukopenia is associated with an increased risk of mortality in patients suffering from endotoxemic sepsis (Adamik et al., 2016). This elevated risk may result from decreased bone marrow production of WBC, increased destruction of immune cells because of thrombocytopenia, and neutrophil extracellular trap formation. Additionally, sensitive organs, such as the lungs may be adversely affected by sepsis due to the rapid activation of leukocytes (Belok et al., 2021). The marked decrease in WBC count (leukopenia), accompanied by increased neutrophil and decreased lymphocyte counts, indicates a systemic inflammatory response characteristic of sepsis (Farkas, 2020). Moreover, the dramatic increase in RBC count, as well as Hb concentration and HCT levels, indicates an apparent polycythemia because of hemoconcentration due to fluid loss and endothelial dysfunction (Levi

& van der Poll, 2010). These findings are consistent with the clinical presentation of sepsis, in which blood thickening and leukopenia are associated with a poor prognosis due to microcirculatory failure, increased vascular permeability, and increased interstitial fluid with subsequent impairment of oxygen delivery (Jansma, 2013). Furthermore, the profound thrombocytopenia is further evidenced by the activation of coagulation pathways and platelet consumption, which are all common features of sepsis-induced disseminated intravascular coagulation (DIC) (Gando et al., 2016; Levi & van der Poll, 2017).

Pretreatment with DEX effectively counteracted LPS-induced leukopenia by elevating WBC count, likely due to glucocorticoid-mediated demargination of leukocytes and the inhibition of apoptosis and NETosis (Jia & Zhang, 2022). The further rise in neutrophil count and the N/L ratio suggests DEX-induced granulocytosis, a well-known effect of corticosteroids (Buonacera et al. 2022; Cai et al., 2021). However, the lack of lymphocyte recovery implies immunosuppression, a critical limitation of glucocorticoid therapy in sepsis. The increase in WBC count may be linked to the anti-inflammatory effects of DEX, which prevents cytokine release and NETosis (Rhen & Cidlowski, 2005; Wang et al., 2024). The PLT count improvement also supports the effects of DEX on coagulation and inflammation previously reported (Grodzielski & Cidlowski, 2023; Mithoowani et al., 2016). The elevated RBC and HCT levels may also reflect erythropoietic effects of DEX or reduced hemolysis (King et al.,1988).

In the present study, DSF, GA, and DSF + GA showed beneficial and distinct effects on most CBC parameters without suppressing the immune system. Although the LPS-induced leukopenia was not recovered by the combination of DSF and GA, it performed very well, particularly with regard to the N/L ratio, which is an important criterion in the diagnosis and prognosis of septicemia. A retrospective study showed that the N/L ratio is a simple and readily available marker and even better at predicting bacteremia than common parameters, such as WBC and C-reactive protein levels in patients presenting to the emergency departments for infection (de Jager CP, 2010; de Jager et al., 2012).

DSF significantly reduced RBC count and Hb and HCT levels, suggesting that it may mitigate LPS-induced hemoconcentration, potentially via anti-inflammatory and anti-oxidative stress mechanisms (Skrott et al., 2019). However, its inability to normalize WBCs or the N/L ratio indicates limited anti-inflammatory efficacy of DSF compared to DEX.

It has been demonstrated that polyphenols, including GA, exert antioxidant effects primarily by inhibiting the NF-κB signaling pathway. This inhibition leads to a reduction in neutrophil activation, which can contribute to a decrease in inflammatory responses, suggesting that GA and similar polyphenolic compounds may play a significant role in modulating immune responses and protecting against oxidative stress (Chala et al., 2024; Chen et al., 2006).

In this study, DSF, GA, and DSF+GA did not significantly affect PLT count. These findings contrast with the results of Owunari et al., who reported that DSF can reduce PLT count at doses of 37.5 and 75 mg/kg over 30 days (Owunari et al., 2015). Given that we used a dose of 50 mg/kg for 3 days, the lack of significant changes in PLT count in the present study may be understandable. On the other hand, this can be viewed positively, as it suggests that at this dose and duration, DSF maintains its other beneficial effects, such as reducing inflammation, without the potential negative impact on platelet levels.

Pretreatment with GA alone caused only a small degree of protection, mostly evidenced by increasing WBC count and decreasing HCT levels, likely due to the antioxidant and anti-inflammatory effects of GA, since oxidative stress plays a critical role in hematological changes associated with sepsis (Kroes et al., 1992).

DEX performs better than DSF and GA in restoring the WBC and platelet counts underscoring its potent but non-specific immunomodulatory action. However, DSF, GA, and DSF+GA significantly lowered the N/L ratio and neutrophil count compared to DEX, implying more purposeful anti-inflammatory actions, including the inhibition of NETosis, NF-κB, or reactive oxygen species (ROS).

Conclusion

This study showed that DEX effectively restored leukocyte and platelet counts, but the exacerbation of neutrophilia and the increase in the N/L ratio raise concerns about its use in the management of sepsis. In contrast, DSF and GA, both alone and in combination, exhibited selective anti-inflammatory activity by significantly reducing neutrophil dominance, improving the N/L ratio, and modulating RBC-related parameters. These findings suggest that while DEX remains a potent acute intervention in sepsis, DSF and GA may offer a more balanced therapeutic approach by targeting inflammation through distinct pathways. Further studies are needed to investigate the optimal dosing regimens and long-term outcomes to confirm their clinical potential in the management of sepsis.

Ethical Considerations

Compliance with ethical guidelines

This study was approved by the Research Ethics Committee for Animal Research, Faculty of Veterinary Medicine, University of Tehran, Tehran, Iran (Code: IR.UT.VETMED.REC.1402.039).

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Authors' contributions

Conceptualization, study design, and final approval: All authors; Investigation and experimental procedures: Zahra Hojati; Data Collection and formal analysis: Zahra Hojati, Ali Rassouli, Farhang Sasani, and Hamidreza Javadi; Writing the original draft: Zahra Hojati and Ali Rassouli; Review and editing: Ali Rassouli and Jamileh Salar Amoli; Supervision: Ali Rassouli.

Conflict of interest

The authors declared no conflict of interest.

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