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Original Research Article

Hesperidin Recovers Lipopolysaccharide-induced Preeclampsia-like Complications in Pregnant Rat Model

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Abstract

Background: Preeclampsia is a complex and multifactorial disorder that develops during pregnancy, defined by the onset of hypertension and proteinuria, often accompanied by other systemic manifestations.
Objectives: The current study evaluated the beneficial effects of hesperidin against lipopolysaccharide (LPS)-induced preeclampsia model in pregnant rats.
Materials and Methods: In this study, the pregnant rats were induced with experimental preeclampsia by treating them with 1.0 µg/kg of LPS and then treated with hesperidin. The changes in systolic blood pressure (SBP) and urinary protein/creatinine concentrations in the rats were measured. The concentrations of angiogenic biomarkers, inflammatory biomarkers, and lipid peroxidation markers were estimated using kits. Furthermore, the effect of hesperidin on the pregnancy outcomes in pregnant rats with preeclampsia was evaluated.
Results: The result of this work indicated that hesperidin treatment effectively decreased the SBP and urinary protein/creatinine ratio and effectively regulated the changes in angiogenic biomarkers in pregnant rats with preeclampsia. Furthermore, the hesperidin treatment successfully diminished the inflammatory and oxidative stress biomarker levels and substantially improved the pregnancy outcomes in the pregnant rats with preeclampsia.
Conclusion: In conclusion, the treatment of hesperidin in pregnant rats with preeclampsia improved the abnormal phenotypes and mitigated the complications. These data indicate that hesperidin can lessen the preeclampsia condition, suggesting that it may be further promoted as a possible therapeutic agent for preeclampsia.

Keywords

Resorbed fetus, preeclampsia, hesperidin, lipopolysaccharide, hypertension, proteinuria

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Introduction

Preeclampsia is a severe pregnancy complication marked by elevated blood pressure and indications of damage to other organ systems, commonly the liver and kidneys. This disorder impacts roughly 2%–8% of pregnancies and is a primary contributor to maternal and fetal morbidity and mortality globally (Bisson et al., 2023). Preeclampsia is characterized by the emergence of hypertension and proteinuria after 20 weeks of gestation in a woman who was previously normotensive. The global prevalence of preeclampsia is 8% of all pregnancies, with the majority of instances occurring in healthy nulliparous women, where the incidence may reach 7.5%. Multiparous women conceiving with a new partner exhibit a preeclampsia risk comparable to that of nulliparous women, due to factors related to paternity change or extended interpregnancy intervals (Jaber et al., 2022). The primary cause of preeclampsia is thought to be abnormal placentation, which leads to widespread maternal endothelial dysfunction and a systemic inflammatory response. Early in pregnancy,

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placental cytotrophoblasts fail to adequately remodel the maternal spiral arteries, leading to poor placental perfusion and placental ischemia. This, in turn, results in the release of markers that cause generalized endothelial dysfunction, including anti-angiogenic factors such as soluble FMS-like tyrosine kinase-1 (sFlt-1) and diminished proangiogenic factors such as placental growth factor (PlGF) (Chantanavilai et al., 2022). Preeclampsia is a major factor in maternal and fetal morbidity and mortality. It is responsible for 25% of preterm deliveries, resulting in adverse neonatal outcomes. Women with preeclampsia are at high risk for developing hypertension, diabetes, stroke, and cardiovascular disease later in life (Beardmore-Gray et al., 2022).

The pathogenesis of preeclampsia entails a complicated interaction among placental failure, maternal endothelial dysfunction, and an exaggerated inflammatory response. The underlying pathogenic mechanisms of preeclampsia are not completely known, but current research highlights that it involves a two-stage process: an initial stage of compromised placentation, and a second stage of maternal systemic endothelial dysfunction and inflammation (Kornacki et al., 2023). The first stage of preeclampsia is believed to be related to abnormal placentation, which leads to placental ischemia and hypoxia. Impaired trophoblast invasion and spiral artery remodeling lead to reduced uteroplacental blood flow, causing placental hypoperfusion, hypoxia, and ischemia. This placental dysfunction results in the release of various factors, like anti-angiogenic proteins, into the maternal circulation, which eventually activates the second stage of the disorder (Shaw et al., 2024). The second stage of preeclampsia is characterized by maternal systemic endothelial dysfunction and inflammation. The placental factors released into the maternal circulation, including anti-angiogenic proteins, inflammatory cytokines, and adhesion molecules, contribute to generalized endothelial dysfunction and excessive maternal inflammatory response. This endothelial dysfunction manifests clinically as hypertension, proteinuria, and other organ damage, such as liver and kidney involvement (Huang et al., 2021). The activation of maternal immunity and inflammation also contributes to the development of preeclampsia. Increased pro-inflammatory markers have been observed in the maternal circulation of women with preeclampsia, suggesting an exaggerated maternal inflammatory response (Erez et al., 2022).

Despite the significant impact of preeclampsia, current management options are restricted, and the only decisive treatment is delivery of the fetus and placenta. Present treatment strategies for preeclampsia are focused on symptom control and delivery, as there are no approved pharmacological interventions to prevent or treat the underlying causes of the disease (Sakowicz et al., 2023). Anti-hypertensive drugs, like methyldopa, labetalol, and nifedipine, are often utilized to treat hypertension associated with preeclampsia, but these drugs have limited efficacy and can have adverse effects on the fetus (Mészáros et al., 2023). Due to the constraints of current treatments, researchers are investigating the possibility of plant-derived bioactive compounds as a novel therapeutic strategy for preeclampsia. These compounds have been shown to have many biological properties that could potentially address the underlying pathophysiology of preeclampsia (Ożarowski et al., 2021). Hesperidin is a bioactive flavone glycoside extensively found in citrus fruits such as sweet oranges, lemons, and other citrus plants. It has already been highlighted that hesperidin demonstrated numerous pharmacological effects, including hepatoprotective (Chen et al., 2022), anti-inflammatory (Haidari et al., 2015), anti-obesity (Ohara et al., 2015), anti-atherosclerotic (Sun et al., 2017), anti-cancer (Pandey & Khan, 2021), anti-asthma (Wei et al., 2012), nephroprotective (Sahu et al., 2013), and neuroprotective (Lim et al., 2022) effects. However, there are no reports on the beneficial effects of hesperidin on preeclampsia, a serious pregnancy-associated complication. The current study evaluated the beneficial effects of hesperidin against lipopolysaccharide (LPS)-induced preeclampsia-like model in pregnant rats.

Materials and Methods

Chemicals

The hesperidin, LPS, and others were purchased commercially from Sigma–Aldrich, USA. The diagnostic kits for biochemical markers were procured from Abcam, MyBioSource, and Elabscience, USA, respectively.

Experimental Rats and Treatment Groups

The current study employed 8–10-week-old female Sprague-Dawley rats with weights ranging from 210 to 230 g. Animals were meticulously housed in sterile enclosures, which were maintained with adequate lighting and a controlled environment. The rats were provided with unrestricted access to a standard diet and water during the study. Rats were paired overnight with active males (1:1 ratio). The vaginal spermatozoa were utilized as a biomarker to ascertain the onset of pregnancy, with the day documented as gestation day (GD) 0. The pregnant rats were allocated into four groups, each including six rats. Group I received a placebo procedure and was provided with a regular diet. Group II consisted of pregnant rats that underwent the LPS challenge. Group III consisted of LPS-induced pregnant rats treated with 25 mg/kg of hesperidin. LPS infusion was conducted in anesthetized pregnant rats on GD 5. On GD 5, 1.0 μg/kg of LPS was administered using an infusion pump (1 mL/h) through the tail vein in 1 mL of saline. Hesperidin was diluted in dimethyl sulfoxide (DMSO) and administered to the rats 30 min post-LPS delivery. On GD 18, rats were sedated with chloral hydrate (10%), and subsequently, samples were collected for further analysis. The changes in pups' weight, placenta weight, and resorbed fetuses were recorded.

Analysis of Systolic Blood Pressure (SBP) and Urinary Protein/Creatinine Levels

The changes in the SBP of the experimental rats were assessed every 3 days from 08:00 to 10:00 am using tail-cuff plethysmography. Animals were warmed to 38°C, and SBP level was meticulously monitored 15 times, with three consecutive values exhibiting a fluctuation of <6 mmHg summed to determine maternal SBP. The rat urine sample was collected every 3 days in metabolic cages. The urine protein and the urinary creatinine concentrations were assessed utilizing commercial diagnostic kits (Abcam, USA).

Analysis of Angiogenic Factors Levels

The concentrations of antigenic biomarkers, such as PlGF and sFlt-1, in both placental tissues and serum of the rats were assessed using commercial diagnostic kits. Each test was conducted with three replicates using the specifications provided by the kit's manufacturer (MyBioSource, USA).

Inflammatory and Oxidative Stress Marker Levels

The placenta tissues of the rats were analyzed for both inflammatory and oxidative stress markers, including interleukin

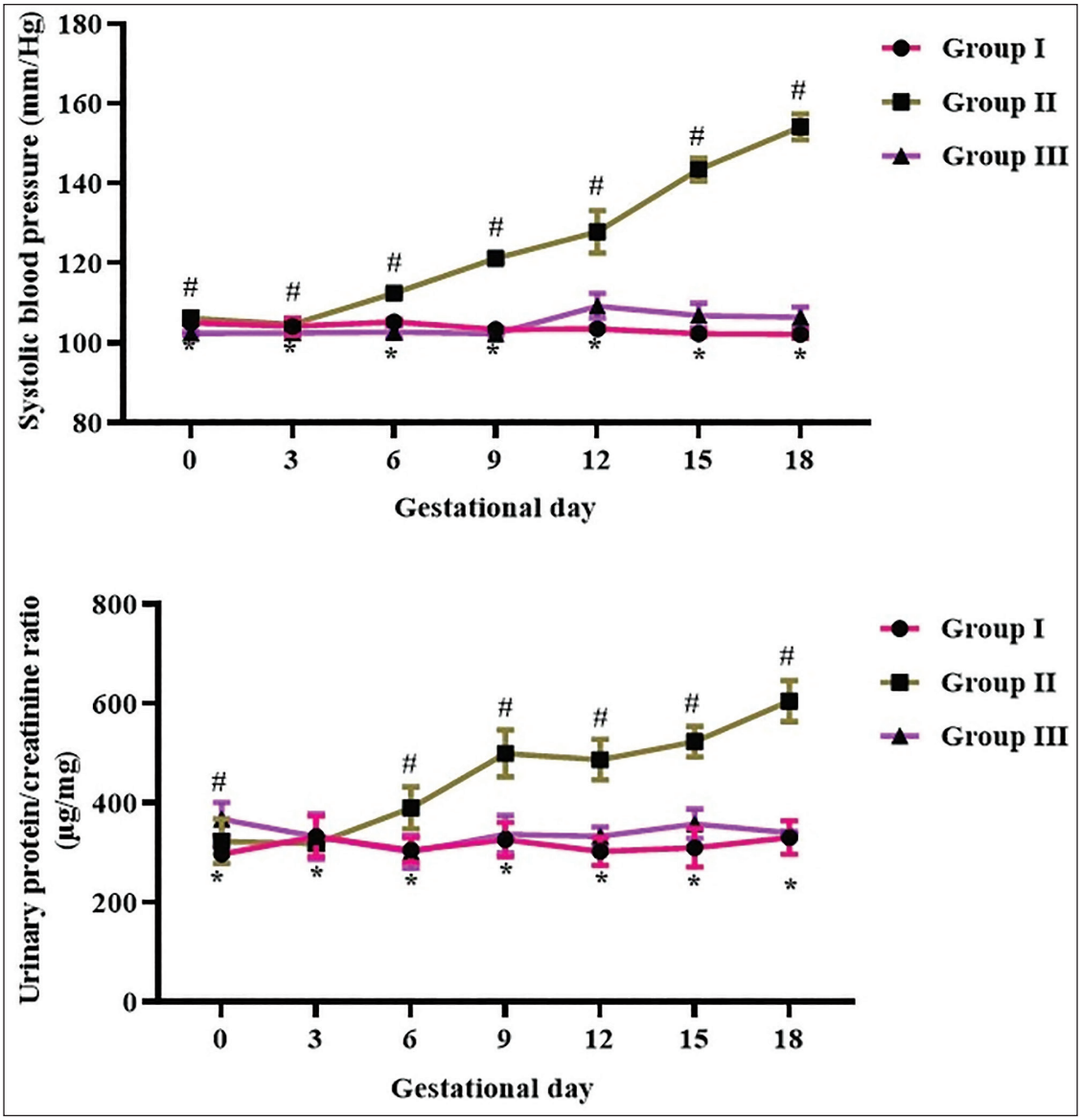


Figure 1. Effect of Hesperidin on the Systolic Blood Pressure (SBP) and Urinary Protein/Creatinine Ratio in the Experimental Rats. The Values are Presented as Mean ± Standard Deviation (SD) from Three Independent Experiments. One-way Analysis of Variance (ANOVA) and Tukey's *Post Hoc* Assay were Utilized to Ascertain the Statistical Significance Among Treatment Groups. "#" Indicates That Results are Significant at $p < .01$ Compared to the Control, and "*" Indicates that Data Are Significant at $p < .05$ Compared to the Preeclampsia-induced Group.

(IL)-6, tumor necrosis factor-alpha (TNF-α), monocyte chemoattractant protein-1 (MCP-1), and malondialdehyde (MDA) concentrations using commercially available test kits, by strictly adhering to the manufacturer's protocols (Elabscience, USA). Each test was conducted with three replicates.

Statistical Analysis

The results are presented as mean ± standard deviation (SD) from three individual studies. One-way analysis of variance (ANOVA) and Tukey's *post hoc* tests were utilized to ascertain the significance among experimental groups, with $p < .05$ being significant.

Results

Effect of Hesperidin on the SBP and Urinary Protein/Creatinine in Experimental Rats

The results of hesperidin on SBP and urinary protein/creatinine ratio were evaluated in the rats, with the outcomes depicted in Figure 1. The LPS-induced pregnant rats with preeclampsia exhibited a notable elevation in both SBP and urinary protein/creatinine ratio relative to the normal pregnant rats. However, the hesperidin treatment at a 25 mg/kg dosage effectively decreased the SBP and urinary protein/creatinine ratio in LPS-induced pregnant rats with preeclampsia.

Effect of Hesperidin on Angiogenic Biomarkers in Experimental Rats

The results of the hesperidin treatment on the concentrations of angiogenic biomarkers were evaluated in both placental tissues and serum of the experimental rats (Figure 2). The LPS-induced pregnant rats with preeclampsia exhibited a substantial increase in the PlGF and sFlt-1 in the placental tissues. However, the PlGF concentration was reduced in the serum of the LPS-induced rats. Interestingly, the treatment of hesperidin at a 25 mg/kg concentration demonstrated a remarkable decrease in both PlGF and sFlt-1 levels in the placental tissues of the rats with LPS-induced preeclampsia.

Effect of Hesperidin on Inflammatory Markers Level in Experimental Rats

Figure 3 discloses the effect of hesperidin on inflammatory biomarker levels in the experimental rats. A significant elevation in the concentrations of TNF-α, IL-6, and MCP-1 was observed in the placental tissues of the LPS-induced pregnant rats with preeclampsia when compared with normal pregnant rats. Fascinatingly, the hesperidin treatment at 25 mg/kg concentration successfully reduced the TNF-α, IL-6, and MCP-1 concentrations in the placental tissues of LPS-induced pregnant rats with preeclampsia.

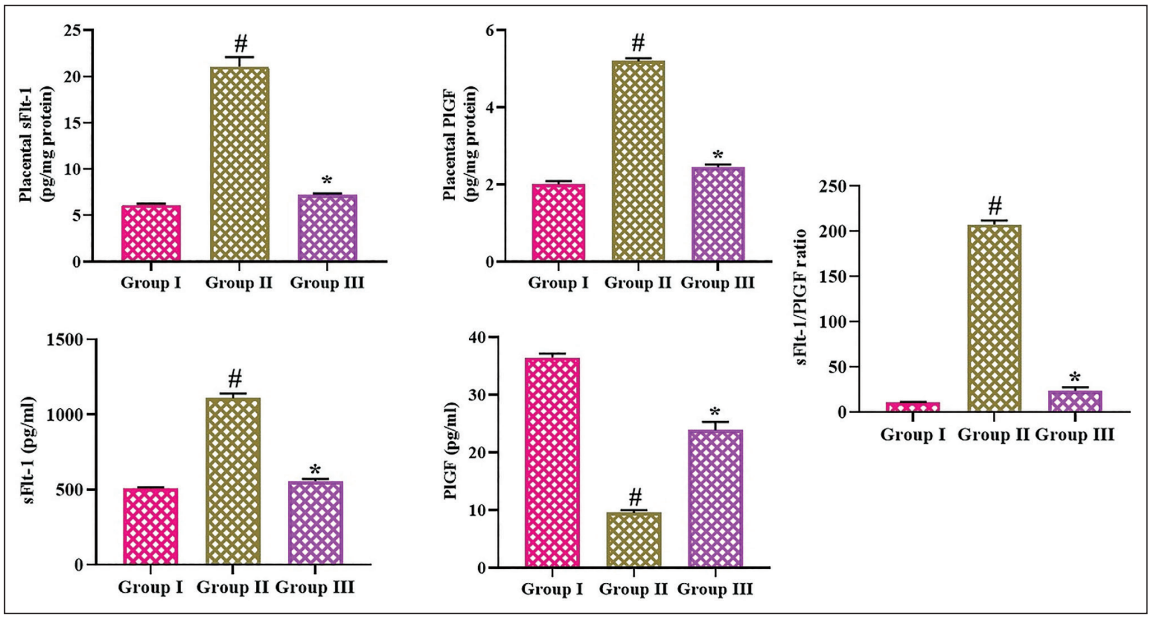


Figure 2. Effect of Hesperidin on the Angiogenic Biomarker Levels in Experimental Rats. The Values are Presented as Mean ± Standard Deviation (SD) from Three Independent Experiments. One-way Analysis of Variance (ANOVA) and Tukey's *Post Hoc* Assay were Utilized to Ascertain the Statistical Significance Among Treatment Groups. "#" Indicates That Results are Significant at $p < .01$ Compared to the Control, and "*" Indicates That Data are Significant at $p < .05$ Compared to the Preeclampsia-induced Group.

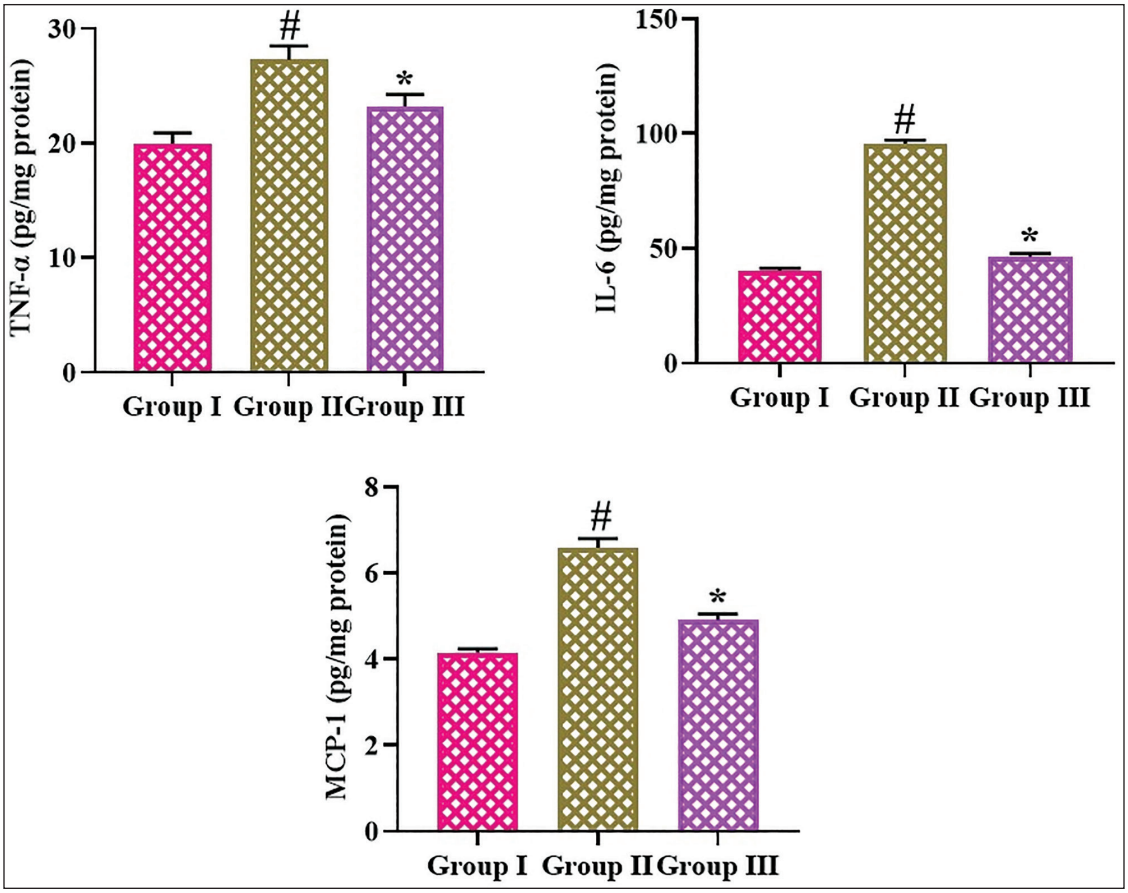


Figure 3. Effect of Hesperidin on the Inflammatory Cytokines and Chemokine Levels in Experimental Rats. The Values are Presented as Mean ± Standard Deviation (SD) from Three Independent Experiments. One-way Analysis of Variance (ANOVA) and Tukey's *Post Hoc* Assay were Utilized to Ascertain the Statistical Significance Among Treatment Groups. "#" Indicates that Results are Significant at $p < .01$ Compared to the Control, and "*" Indicates that Data are Significant at $p < .05$ Compared to the Preeclampsia-induced Group.

Effect of Hesperidin on Oxidative Stress Levels in Experimental Rats

Figure 4 illustrates the concentration of MDA, a biomarker for oxidative stress, in the experimental rats. The MDA level was drastically augmented in the placental tissues of the rats with LPS-induced preeclampsia when compared with the control. Nonetheless, a considerable reduction of MDA level was observed in the LPS-induced pregnant rats with preeclampsia in response to the 25 mg/kg of hesperidin treatment.

Effect of Hesperidin on Pregnancy Outcomes in Experimental Rats

The effect of hesperidin treatment on pregnancy outcomes in pregnant rats with LPS-preeclampsia was studied, and findings are given in Figure 5. The pregnant rats with LPS-induced preeclampsia demonstrated a considerable reduction in pups and placental weights and a subsequent elevation in the resorbed fetuses when compared with normal pregnant rats. Interestingly, the 25 mg/kg of hesperidin treatment substantially increased both pup and placental weights and subsequently reduced the resorbed fetuses in the pregnant rats with LPS-induced preeclampsia.

Discussion

Preeclampsia is a multifaceted pregnancy-related condition marked by the emergence of hypertension and proteinuria after 20 weeks of gestation. This condition poses a potential hazard to life and can result in considerable maternal and newborn morbidity and mortality. The exact cause of preeclampsia remains unclear; nevertheless, it is thought to be associated with aberrant placentation, endothelial dysfunction, and an intensified inflammatory response (Lai et al., 2021). The analysis of SBP and urinary protein/creatinine ratio is crucial in the analysis and treatment of preeclampsia. SBP, which is the pressure in the arteries during the heart's contraction, is a key diagnostic criterion for preeclampsia. Elevated SBP, defined as greater than 140 mmHg, is a

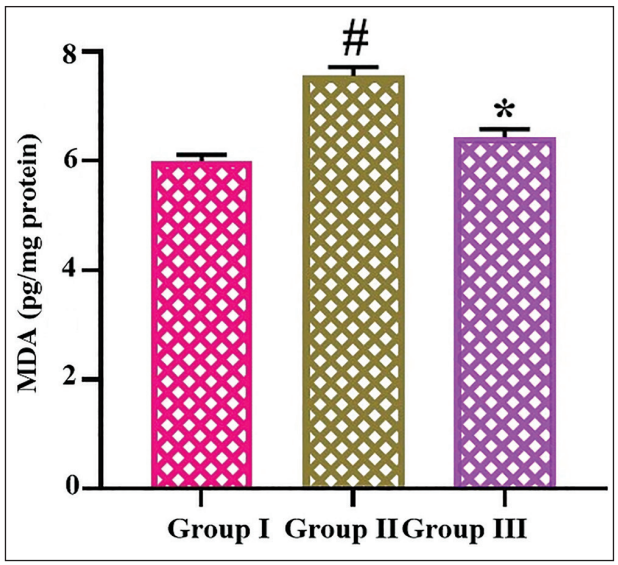


Figure 4. Effect of Hesperidin on the Oxidative Stress Levels in Experimental Rats. The Values are Presented as Mean ± Standard Deviation (SD) from Three Independent Experiments. One-way Analysis of Variance (ANOVA) and Tukey's *Post Hoc* Assay were Utilized to Ascertain the Statistical Significance Among Treatment Groups. "#" Indicates That Results are Significant at $p < .01$ Compared to the Control, and "*" Indicates That Data are Significant at $p < .05$ Compared to the Preeclampsia-induced Group.

hallmark of this condition. Additionally, the presence of significant proteinuria, as indicated by an increased urinary protein/creatinine ratio, is another essential diagnostic feature of preeclampsia (Chang et al., 2023). The analysis of these two markers can also help in understanding the progression and severity of preeclampsia. Increasing SBP and rising urinary protein/creatinine ratios may signal the advancement of more serious forms of preeclampsia, such as eclampsia, which is characterized by the onset of seizures. Early identification of high-risk patients and careful management of their condition can help reduce the risk of maternal and fetal complications associated with preeclampsia (Sharma et al., 2024). The result of this work indicated that LPS-induced pregnant rats with preeclampsia exhibited a notable elevation in both SBP and urinary protein/creatinine ratio when compared with normal pregnant rats. Interestingly, the hesperidin treatment effectively decreased the SBP and urinary protein/creatinine ratio in LPS-induced pregnant rats with preeclampsia.

Emerging evidence suggests that an imbalance in the levels of certain biomarkers, particularly PlGF and sFlt-1, may play a crucial role in the development and progression of preeclampsia (Melo et al., 2023). The placenta is pivotal in the etiology of preeclampsia, as irregularities in its development and function may result in placental hypoperfusion, hypoxia, and ischemia. These placental abnormalities have been associated with a disparity in the concentrations of pro-angiogenic and anti-angiogenic factors, specifically PlGF and sFlt-1, respectively. PlGF is a constituent of the vascular endothelial growth factor family and is essential for the development and function of placental vasculature. In contrast, sFlt-1 acts as an antagonist to PlGF and vascular endothelial growth factor, with increased levels linked to the onset of preeclampsia (Stepan et al., 2023). The analysis of PlGF and sFlt-1 levels in both placenta and serum has become a field of interest in the study of preeclampsia. Studies have shown that the levels of these biomarkers are significantly altered in women with preeclampsia compared to those of normal pregnancies. Altered PlGF and sFlt-1 levels have been observed in the placental tissues and maternal serum of women, suggesting that these imbalances may participate in the progression of the disease. The potential clinical applications of these biomarkers are vast, as they may provide valuable insights into the progression of preeclampsia (Gaccioli et al., 2023). In this study, the altered PlGF and sFlt-1 concentrations were observed in the LPS-induced pregnant rats with preeclampsia in the placental tissues and serum when compared with the control. Meanwhile, the treatment of hesperidin effectively regulated the changes in the PlGF and sFlt-1 levels in both placental tissues and serum of the rats with LPS-induced preeclampsia.

The precise etiology of preeclampsia remains incompletely elucidated; nevertheless, mounting data indicate that an exaggerated maternal systemic inflammatory response, involving activation of both the innate and adaptive immune systems, is pivotal in the disease's progression (Guan et al., 2023). In preeclampsia, increased concentrations of pro-inflammatory biomarkers in maternal circulation have been noted, potentially contributing to the widespread endothelial dysfunction and pronounced systemic inflammatory response characteristic of the maternal syndrome. Specifically, inflammatory cytokines like TNF-α and IL-6, together with the chemokine MCP-1, have been thoroughly investigated regarding the pathophysiology of preeclampsia (Miller et al., 2022). Abnormal placentation and impaired placental development early in pregnancy seem to be critical components in the onset of preeclampsia. The hypoperfused, hypoxic, or ischemic placenta may transfer various factors, including inflammatory cytokines and chemokines, into the maternal circulation, altering maternal endothelial cell function and contributing to the clinical manifestations of preeclampsia. Comprehending the role of these inflammatory biomarkers in the placental tissues of preeclamptic patients is pivotal for elucidating the underlying mechanisms of the disease (Guan et al., 2023). In this work, a considerable elevation in TNF-α, IL-6, and MCP-1 concentrations was observed in the placental tissues of the LPS-induced pregnant rats with preeclampsia when compared with normal pregnant rats. Interestingly, the hesperidin treatment successfully reduced these pro-inflammatory biomarker concentrations in the placental tissues of the LPS-induced pregnant rats with preeclampsia, which highlights its anti-inflammatory activity.

The exact etiology of preeclampsia is not completely described; mounting data suggest that increased lipid peroxidation and subsequent oxidative stress play a key role in the

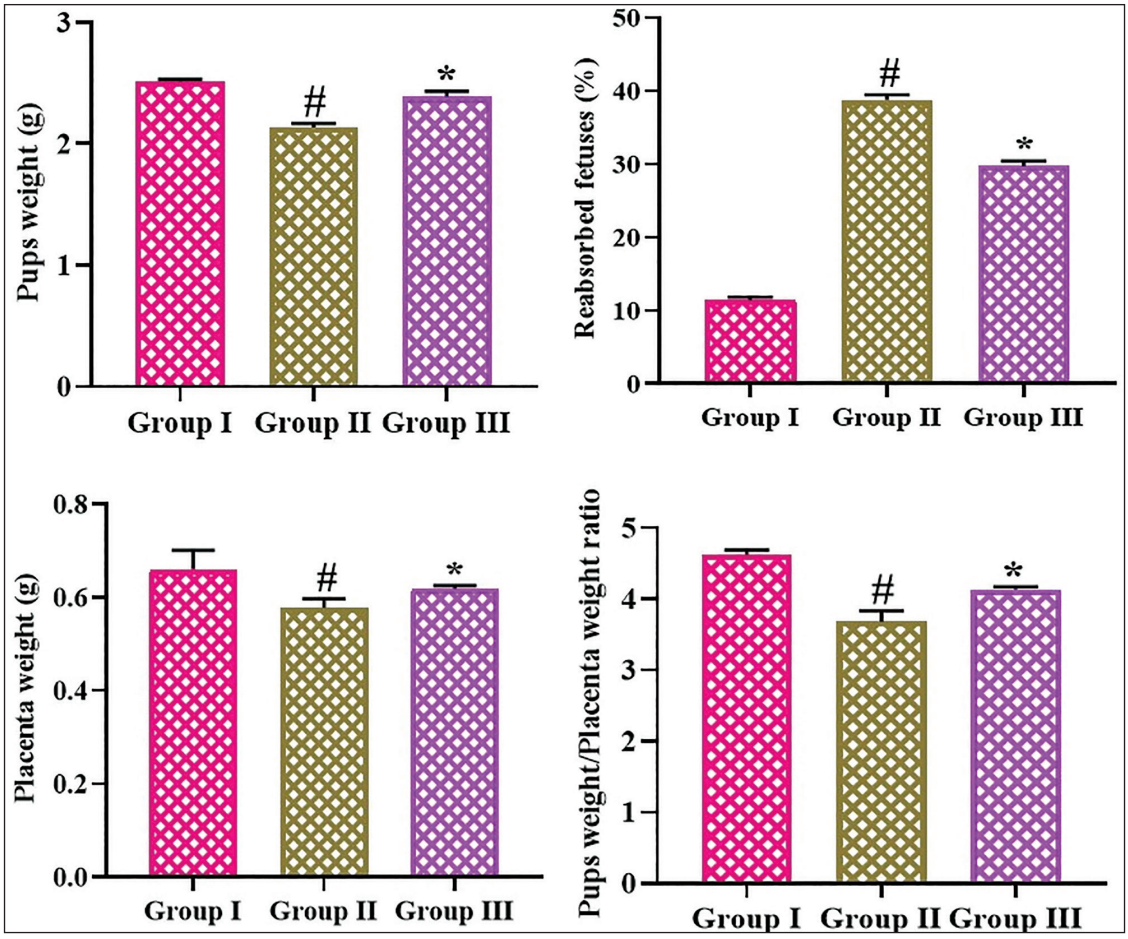


Figure 5. Effect of Hesperidin on the Pregnancy Outcomes in Experimental Rats. The Values are Presented as Mean ± Standard Deviation (SD) from Three Independent Experiments. One-way Analysis of Variance (ANOVA) and Tukey's *Post Hoc* Assay were Utilized to Ascertain the Statistical Significance Among Treatment Groups. "#" Indicates That Results are Significant at $p < .01$ Compared to the Control, and "*" Indicates That Data are Significant at $p < .05$ Compared to the Preeclampsia-induced Group.

pathophysiology of the disease (Freire et al., 2023). MDA is a reliable biomarker of lipid peroxidation, which is believed to be a crucial cause for the development of preeclampsia. Abnormal placentation and placental ischemia in preeclampsia can lead to increased oxidative stress and the release of oxidative stress markers, like MDA, into the circulation. Increased MDA levels have been consistently reported in the placental tissues of women compared to normotensive controls (Surmiak et al., 2022). Measuring the MDA concentrations in the placental tissues of preeclamptic patients can provide valuable insights into the role of oxidative stress in the pathogenesis of the disease. Understanding the connection between oxidative stress and preeclampsia may result in the advancement of novel diagnostic and therapeutic strategies (Ferreira et al., 2020). The concentration of MDA was considerably elevated in the placental tissues of the pregnant rats with LPS-induced preeclampsia. Fascinatingly, a considerable diminution in MDA level was observed in the LPS-induced pregnant rats with preeclampsia due to hesperidin treatment. These findings highlight that hesperidin can mitigate the oxidative stress response in preeclamptic conditions.

Preeclampsia poses significant maternal and fetal health risks, including increased likelihood of maternal mortality and morbidity, as well as preterm delivery and adverse neonatal outcomes (Gaccioli et al., 2017). The analysis of pregnancy outcomes, such as pup weight, placental weight, and resorbed fetuses, in experimental pregnant rats with preeclampsia is crucial for understanding the underlying mechanisms and potential interventions for this condition. Preeclampsia is thought to be primarily caused by abnormal placentation, which results in an imbalance of angiogenic factors and endothelial dysfunction. Analyzing pup weight, placental weight, and resorbed fetuses in experimental models can offer valuable insights into the impact of preeclampsia on fetal and placental development (Lin et al., 2023). For instance, reports have demonstrated that preeclampsia is often connected with diminished fetal and placental weights, as well as an increased rate of fetal resorption, likely due to compromised placental function and reduced uteroplacental

blood flow. These outcomes are crucial indicators of the severity and progression of the disease in the experimental models (Cluver et al., 2023). By evaluating these pregnancy outcomes in experimental rat models, researchers can better understand the pathogenesis of preeclampsia and identify useful therapeutic targets. This information can then be translated to clinical studies, ultimately leading to improved management strategies and better outcomes for both mothers and their babies (Farrelly et al., 2023). In the current study, the pregnant rats with LPS-induced preeclampsia demonstrated a considerable reduction in pups and placental weights and a subsequent elevation in the resorbed fetuses when compared with normal pregnant rats. Captivatingly, the hesperidin treatment substantially increased both pup and placental weights and subsequently reduced the resorbed fetuses in the pregnant rats with LPS-induced preeclampsia. These findings highlight that hesperidin can improve pregnancy outcomes in rats with preeclampsia.

Conclusion

In conclusion, the administration of LPS during pregnancy induces a preeclamptic condition in pregnant rats. The present investigation revealed elevated SBP and proteinuria, dysregulated angiogenesis, heightened oxidative stress, and negative pregnancy outcomes in the rats with preeclampsia. Interestingly, the treatment of hesperidin in pregnant rats with preeclampsia improved the abnormal phenotypes and mitigated the complications. These data indicate that hesperidin can ameliorate abnormal oxidative stress, inflammatory responses, and imbalances in angiogenic biomarkers in pregnant rats with preeclampsia, suggesting that hesperidin may be further promoted as a possible therapeutic agent for preeclampsia. Future studies can investigate the clinical efficacy and safety of hesperidin in pregnant women with preeclampsia, as well as its potential as a combination therapy with existing treatments. Additionally, research can focus on elucidating the molecular mechanisms underlying hesperidin's beneficial effects and identifying novel biomarkers for preeclampsia. This can ultimately contribute to the development of hesperidin as a therapeutic agent for preeclampsia.

Abbreviations

ANOVA: Analysis of variance; DMSO: Dimethyl sulfoxide; GD: Gestation day; IL-6: Interleukin-6; LPS: Lipopolysaccharide; MCP-1: Monocyte chemoattractant protein-1; MDA: Malondialdehyde; PlGF: Placental growth factor; SBP: Systolic blood pressure; SD: Standard deviation; sFlt-1: Soluble FMS-like tyrosine kinase-1; TNF-α: Tumor necrosis factor-alpha.

Declaration of Conflicting Interests

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

Ethical Approval

This work was approved by the Institutional Ethical Committee, the Second Affiliated Hospital of Air Force Medical University, Xi'an, Shaanxi, China.

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Informed Consent

NA.

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