Original Article

Effects of Resveratrol on Blood Parameters of Dexamethasone-induced Hypercortisolism in a Rat Model

Masumeh Rezaei[1], Shahin Hassanpour[2*], Ehsan Khaksar[3]

1. Faculty of Veterinary Medicine, SR.C, Islamic Azad University, Tehran, Iran.
2. Department of Basic Veterinary Sciences, SR.C., Islamic Azad University, Tehran, Iran.
3. Department of Veterinary Clinical Sciences, Ga.B, Islamic Azad University, Garmsar, Iran.

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ABSTRACT

Background: Glucocorticoid-induced hypercortisolism, a common complication of prolonged dexamethasone use, disrupts metabolic and endocrine homeostasis. Current therapeutic strategies remain limited, necessitating novel interventions. Resveratrol, a polyphenol with anti-inflammatory and antioxidant properties, shows potential in modulating glucocorticoid signaling.

Objectives: This study investigated the of efficacy resveratrol in mitigating dexamethasone-induced hypercortisolism in a rat model.

Methods: Twenty-four male Wistar rats were obtained from the Pasteur Institute of Iran and randomly allocated to four groups: (1) untreated control; (2) hypercortisolism induction via oral dexamethasone (100 µg/kg) for 4 weeks; (3) co-administration of dexamethasone (100 µg/kg) and ketoconazole (5 mg/kg) for 4 weeks; and (4) co-administration of dexamethasone (100 µg/kg) and resveratrol (80 mg/kg) for 4 weeks. Serum biomarkers, including cortisol, glucose, triglycerides, cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), creatinine, and total protein (TP) were then analyzed.

Results: Neither ketoconazole nor resveratrol significantly altered body weight in hypercortisolemic rats (P=0.45). Dexamethasone and dexamethasone-ketoconazole administration elevated serum cortisol, whereas resveratrol attenuated serum cortisol levels (P=0.022). Dexamethasone increased serum glucose, cholesterol, triglycerides, and low density lipoprotein (LDL) levels (P=0.011), while reducing HDL (P=0.014) and TP levels. Resveratrol reversed the changes in these blood parameters (P=0.027).

Conclusion: Resveratrol attenuates the biochemical alterations associated with experimental hypercortisolism, underscoring its potential utility as a therapeutic agent in the management of hypercortisolism disorders.

Keywords: Biochemical parameters, Dexamethasone, Hypercortisolism, Resveratrol, Rat

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*** Corresponding Author:**
Shahin Hassanpour, Assistant Professor.
Address: *Department of Basic Veterinary Sciences, SR.C., Islamic Azad University, Tehran, Iran.*
Phone: *+98 (21) 44868560*
E-mail: *s.hassanpour@srbiau.ac.ir*

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Introduction

Glucocorticoids, of which cortisol is the main form in humans, are steroid hormones secreted by the adrenal cortex that play fundamental roles in metabolic homeostasis, immune response regulation, and stress adaptation (Ahmed et al., 2014). These hormones regulate glucose metabolism, inhibit inflammation, and influence neuroendocrine functions through genomic and nongenomic mechanisms (Ataee et al., 2016; Baghaei Naeini et al., 2023). Their secretion is tightly controlled by the hypothalamic-pituitary-adrenal (HPA) axis, in which corticotropin-releasing hormone (CRH) and adrenocorticotropic hormone (ACTH) stimulate cortisol synthesis in a cascade, while a dynamic equilibrium is maintained through negative feedback (Ahmed et al., 2014). Dysregulation of the HPA axis caused by chronic stress, neoplasia, or exogenous administration of glucocorticoids can lead to hypercortisolism (Cushing's syndrome) with the manifestation of abnormal and persistent cortisol levels (Bowles et al., 2015). Chronic hypercortisolism involves various body organs and body systems, causing metabolic disorders (visceral obesity and insulin resistance), cardiovascular complications (hypertension and atherosclerosis), musculoskeletal atrophy, and immunosuppression with an increased risk of infection (Brummelte et al., 2006). Hypercortisolism can lead to glucose disorders as a result of increased gluconeogenesis, decreased insulin production, increased insulin resistance, and increased serum low-density lipoprotein (LDL) levels (Cai et al., 2015). In addition, it exacerbates neurobehavioral diseases, including cognitive disorders and mood swings (de Fatima Silva et al., 2022) and accelerates osteoporosis by disrupting osteoblast activity (Dias et al., 2016). Understanding the interplay among glucocorticoid signaling, HPA axis integrity, and systemic pathologies is essential for effectively managing the diverse manifestations of elevated cortisol and optimizing therapeutic approaches.

In addition to its adverse effects on behavior and physiology, hypercortisolism has significant effects on patients' blood biochemical factors. Its effects on biochemical parameters of blood include increased serum levels of glucose, cholesterol, triglycerides, total protein (TP), and LDLs, while serum levels of beneficial factors, such as high-density lipoproteins (HDLs) are reduced in patients with hypercortisolism (El-Sonbaty et al., 2019).

Current pharmacological strategies for the management of hypercortisolism face several limitations, including lack of specificity, inconsistent efficacy, and significant toxicity (Farzaei et al., 2018, Finnell et al., 2017). For example, cortisol synthesis inhibitors, such as ketoconazole and metyrapone may cause off-target effects, like hepatotoxicity or the accumulation of mineralocorticoid precursors (Ge et al., 2016). Adrenolytic agents, such as mitotane require long-term use and are associated with the risk of systemic toxicity (Gu et al., 2019). Targeted therapies for ACTH hypersecretion, such as pasireotide are also effective in limited populations or result in metabolic complications, such as hyperglycemia (Hakami et al., 2021). Pharmacologic treatments generally do not result in durable remission, with relapse frequently observed after cessation. These agents also have limited clinical utility due to causal-dependent ineffectiveness (Brummelte et al., 2006). Given the lack of standardized treatment guidelines and the need for close patient monitoring, the development of more targeted therapies to improve long-term outcomes, management of hypercortisolism, and its associated complications is urgently needed.

Resveratrol is a natural polyphenol found in red wine, grapes, berries, peanuts, and dark chocolate, and has multiple biological functions that may be beneficial in metabolic diseases. It is known for its antioxidant and anti-inflammatory properties and improves mitochondrial function, lipid oxidation, and insulin sensitivity through the activation of sirtuin 1 (SIRT1) and adenosine monophosphate-activated protein kinase (AMPK) (He et al., 2017; Herman et al., 2020). It reduces oxidative stress (such as that caused by superoxide and hydroxyl radicals) and levels of proinflammatory cytokines (such as TNF-α and IL-6) (Herman et al., 2020; Huang et al., 2020). Evidence regarding the effects of resveratrol on metabolic parameters, including lipid profiles and glucose regulation, remains inconclusive, with studies reporting variable degrees of efficacy (Jothie Richard et al., 2016; Kumar et al., 2007).

In the study by Zhou et al., resveratrol reduced serum lipid and triglyceride levels and hepatic cholesterol levels compared with controls in hyperlipidemic rats (Zhou et al., 2014). In the study by Richard et al. (2016) and Kumar et al. (2007) daily oral administration of resveratrol significantly reduced LDL, triglyceride, and cholesterol levels in experimentally obese female rats. Despite limited human data, experimental studies indicate that this compound may exert beneficial effects on obesity, type 2 diabetes, and cardiovascular disease through mechanisms, such as enhancing endothelial

function, suppressing lipogenesis, and inhibiting hepatic gluconeogenesis (Jothie Richard et al., 2016; Kumar et al., 2007). Overall, resveratrol has significant potential as an adjunct strategy in the management of metabolic diseases, but further research is needed to determine its precise therapeutic role.

Because hypercortisolism has deleterious and dangerous effects on blood parameters, including lipid and glucose profiles, and resveratrol has shown promising protective effects against these changes in previous studies, the present study aimed to investigate the therapeutic potential of resveratrol for some serum parameters in a rat model of experimental hypercortisolism. To our knowledge, no previous study has investigated this topic.

Materials and Methods

Twenty-four adult male MNRI Wistar rats (mean body weight: 180±5 g) were obtained from the Pasteur Institute of Iran and acclimated to standard conditions (regulated temperature: 22±1 ˚C; relative humidity: 55±5%; photoperiod: 12 h light/12 h dark) in a pathogen-free vivarium environment. Pelleted food and drinking water were provided ad libitum. Random assignment to four experimental groups (n=6 per group) was performed in accordance with the National Institutes of Health ethical guidelines for the welfare of laboratory animals. Ethical approval for the study was granted by the Research Ethics Committee of Islamic Azad University, Science and Research Branch, Tehran, Iran.

The experimental groups were as follows: (1) Control group: age-matched rats without receiving any intermediate compound; (2) Glucocorticoid elevation model: daily oral administration of dexamethasone (100 µg/kg; suspended in 1% aqueous ethanol vehicle, Iran hormone Co.) for 28 days; (3) Ketoconazole-receiving group: oral administration of dexamethasone (100 µg/kg) and ketoconazole (5 mg/kg; Jalinous Co.) for 28 days; and (4) Resveratrol-receiving group: simultaneous oral administration of dexamethasone (100 µg/kg) and resveratrol (80 mg/kg; ≥98% purity, Sigma Aldrich, USA) for 28 days (Lacroix et al., 2015).

Chronic glucocorticoid exposure protocol: Hypercortisolism was induced by chronic administration of dexamethasone. This substance was dissolved in a hydrophobic vehicle (1% ethanol) and administered in drinking water (75–100 µg/mL) for 28 days (Herman et al., 2020). The pathophysiological assessment included three phenotypic signs: (1) increased visceral fat, measured as peritoneal fat mass, (2) progressive loss of body weight, and (3) HPA axis suppression, confirmed by decreased blood cortisol levels (Nishiyama et al., 2022).

Biochemical analyses: After phenotypic evaluation, the rats were subjected to terminal anesthesia (sodium pentobarbital, 50 mg/kg, intraperitoneal injection). Blood samples were collected and centrifuged (3000 g, 15 min, 4 ˚C). Serum cortisol was measured using a quantitative luminescence immunoassay (Nishiyama et al., 2022) with a commercial kit from Ideal Tashkhis Atiyeh. Glucose was measured using the glucose oxidase-peroxidase method (Richard et al., 2011). The lipid profile was assessed by measuring triglycerides using the glycerol-3-phosphate oxidase method and cholesterol using the cholesterol oxidase method (Rodríguez Castaño et al., 2019, Salehi et al., 2018). LDL and HDL were measured using the surfactant-based and polyethylene glycol precipitation methods, respectively (Sanders et al., 2018; Schoettl et al., 2018). TP was measured using the Biuret reaction (Shuker et al., 2022), and creatinine was measured using the alkaline picrate method with a commercial kit from Pars Pars Azmoon (Smets et al., 2010).

Statistical analysis: The normality of the data distribution was assessed using the Shapiro–Wilk test. Homogeneous parametric data were analyzed using one-way ANOVA followed by Tukey's post hoc test. Data analysis was performed using SPSS software, version 21. Results are presented as Mean±SE, and statistical significance was set at $P<0.05$.

Results

Treatment with resveratrol or ketoconazole had no significant effect on body weight (P=0.46) (Figure 1). Resveratrol significantly reduced serum cortisol levels with those in the dexamethasone and ketoconazole-treated groups (P=0.022) (Figure 2). Regarding metabolic indices, resveratrol attenuated the dexamethasone-induced increase in serum glucose (P=0.032) (Figure 3) and prevented increases in serum triglycerides, total cholesterol, and LDL in the dexamethasone-treated groups (P=0.011) (Figures 4, 5, and 6). Interestingly, resveratrol reversed the decrease in serum HDL, although its levels did not increase significantly compared with those in the dexamethasone group (P=0.014) (Figure 7). In addition, resveratrol ameliorated dexamethasone-induced changes in serum creatinine and TP levels (P=0.027) (Figure 8 and 9).

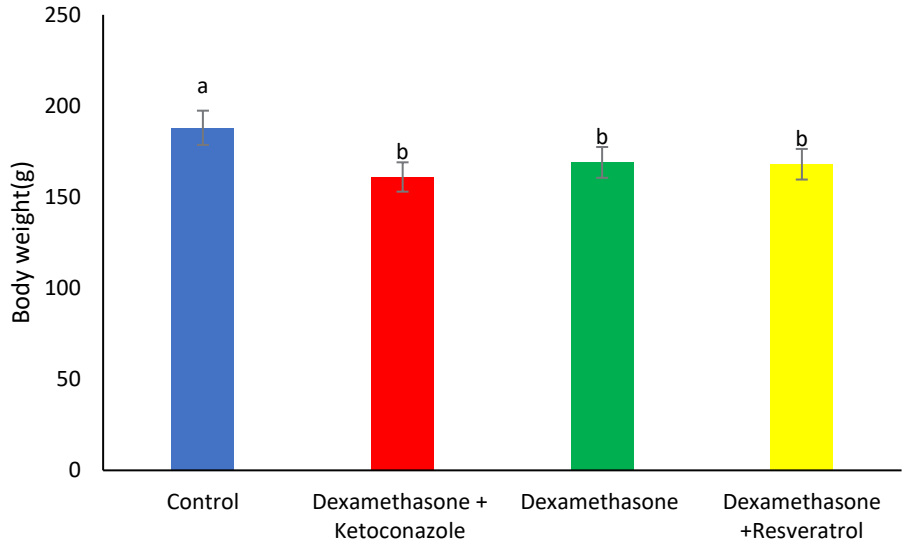


Figure 1. Effects of ketoconazole and resveratrol on body weight in dexamethasone-induced hypercortisolism rats

Note: Data are expressed as Mean±SE. Different letters (a-b) indicate significant differences between treatments (P<0.05).

Discussion

Dexamethasone analogs are commonly used as synthetic glucocorticoids to induce hypercortisolism (Cushing's syndrome) in rodents and reproduce the hallmark clinical, endocrine, and metabolic features of this disorder (El-Sonbaty et al., 2019). In the present study, resveratrol, a polyphenol with anti-inflammatory and antioxidant properties, effectively reduced hypercortisolism and its associated metabolic disturbances compared to dexamethasone. Hypercortisolism significantly disrupts blood biochemical profiles. Our findings showed increased serum levels of cortisol, glucose, cholesterol, triglycerides, and LDL, along with decreased HDL

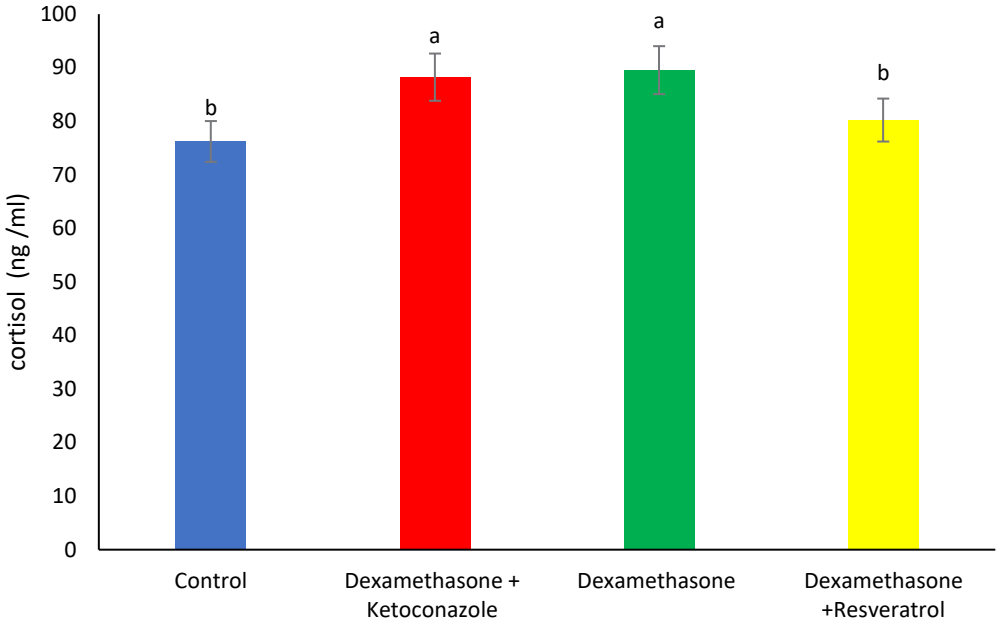


Figure 2. Effects of ketoconazole and resveratrol on serum cortisol levels in dexamethasone-induced hypercortisolism rats

Note: Data are expressed as Mean±SE. Different letters (a-b) indicate significant differences between treatments (P<0.05).

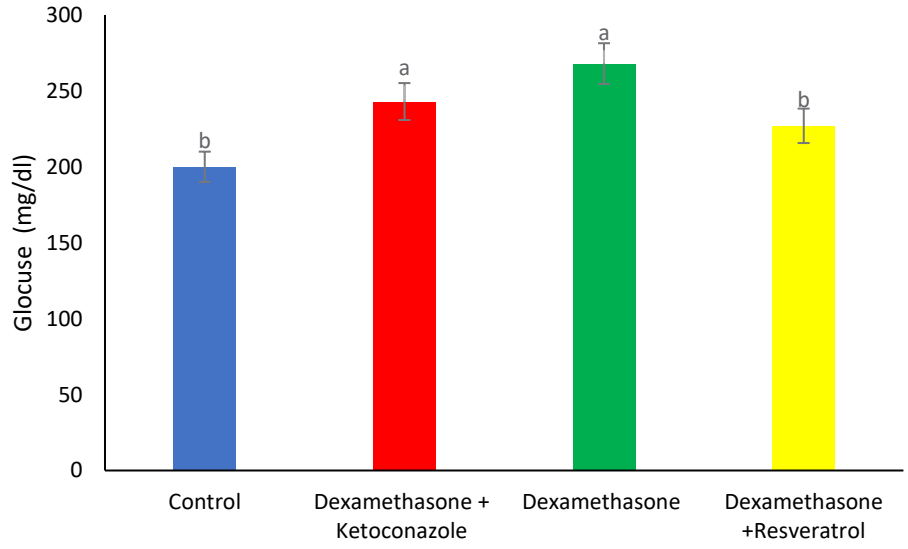


Figure 3. Effects of ketoconazole and resveratrol on serum glucose levels in dexamethasone-induced hypercortisolism rats

Note: Data are expressed as Mean±SE. Different letters (a-b) indicate significant differences between treatments (P<0.05).

and TP levels in Wistar rats. Chronic administration of dexamethasone sodium phosphate (100 µg /kg) mimics key features of human hypercortisolism/Cushing's syndrome, including glucose intolerance, insulin resistance, dyslipidemia, hepatic lipid accumulation, and adipose tissue redistribution (Nemati et al., 2017). These metabolic abnormalities are consistent with the clinical observations in Cushing's syndrome, which is characterized by impaired glucose absorption, hyperlipidemia, and hypertension, and suggest glucocorticoid-induced dysregulation of carbohydrate and lipid metabolism (Nishiyama et al., 2022). Prolonged hypercortisolemia, accompanied by worsening insulinopenia, points to a potential direct or indirect cytotoxic effect of cortisol on pancreatic β-cells within the islets of Langerhans (Richard et al., 2011). Mechanistically, the reduced rates of glucose clearance and replacement in individuals with Cushing's syndrome reflect reduced peripheral glucose utilization,

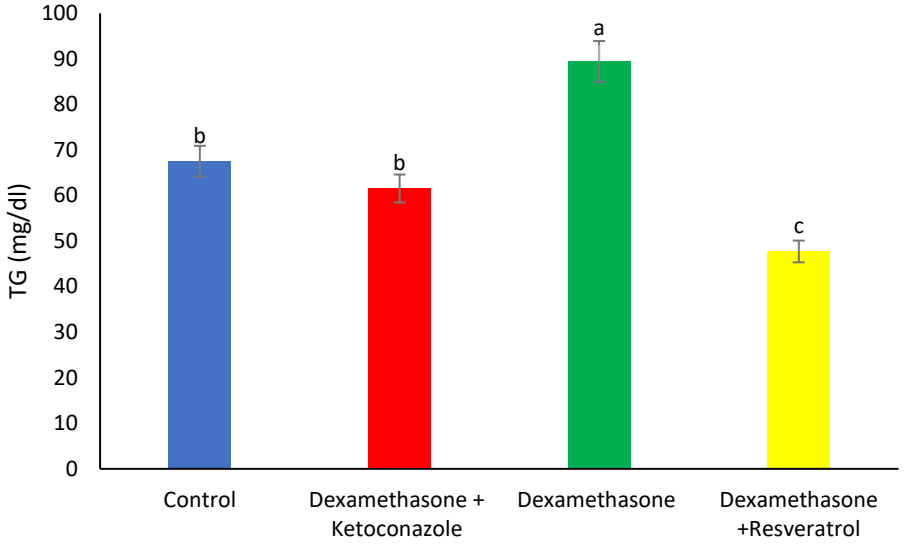


Figure 4. Effects of ketoconazole and resveratrol on serum triglyceride levels in dexamethasone-induced hypercortisolism rats

Note: Data are expressed as Mean±SE. Different letters (a-c) indicate significant differences between treatments (P<0.05).

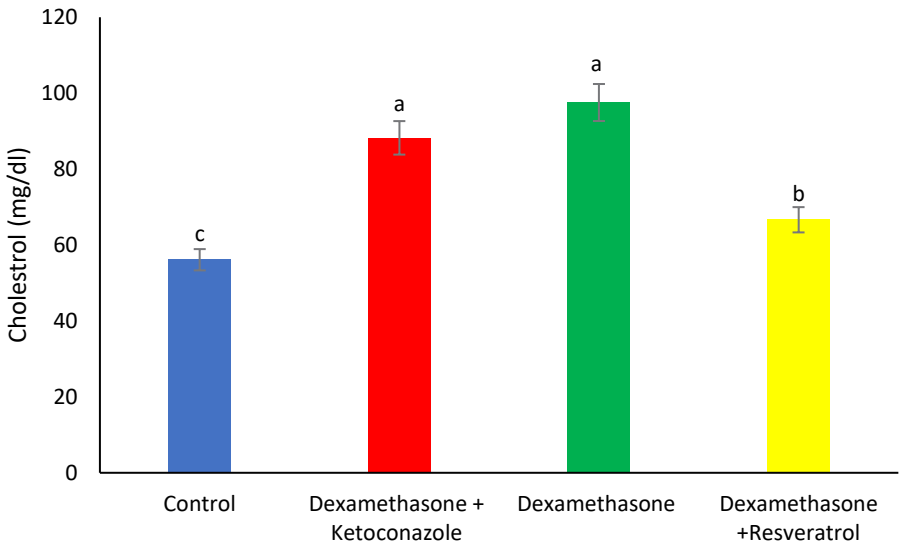


Figure 5. Effects of ketoconazole and resveratrol on serum cholesterol levels in dexamethasone-induced hypercortisolism rats

Note: Data are expressed as Mean±SE. Different letters (a-c) indicate significant differences between treatments (P<0.05).

compensatory hyperinsulinemia, and impaired suppression of hepatic glucose production, despite systemic insulin resistance (Xu et al., 2010). Glucocorticoids also enhance hepatic lipogenesis and increase very low-density lipoprotein (VLDL) secretion by increasing the expression of acetyl-CoA carboxylase and fatty acid synthase (Wu et al., 2017).

In the present study, resveratrol effectively attenuated dexamethasone-induced metabolic disturbances and reduced serum glucose, cholesterol, triglycerides, and LDL levels, while restoring HDL and TP levels. These findings contrast with in vitro reports indicating that resveratrol stimulates cortisol production in adrenocortical cells (Wang et al., 2013), but align with in vivo studies demonstrating corticosterone-lowering effects of this compound in both stressed (Shuker et al., 2022; Wu et al., 2017; Xu et al., 2010) and non-stressed rodent models (Salehi et al., 2018). These discrepancies may be attributed to methodological differences, including the type of experimental model used and the dosing regimens applied (Rodríguez Castaño et al., 2019). The therapeutic poten-

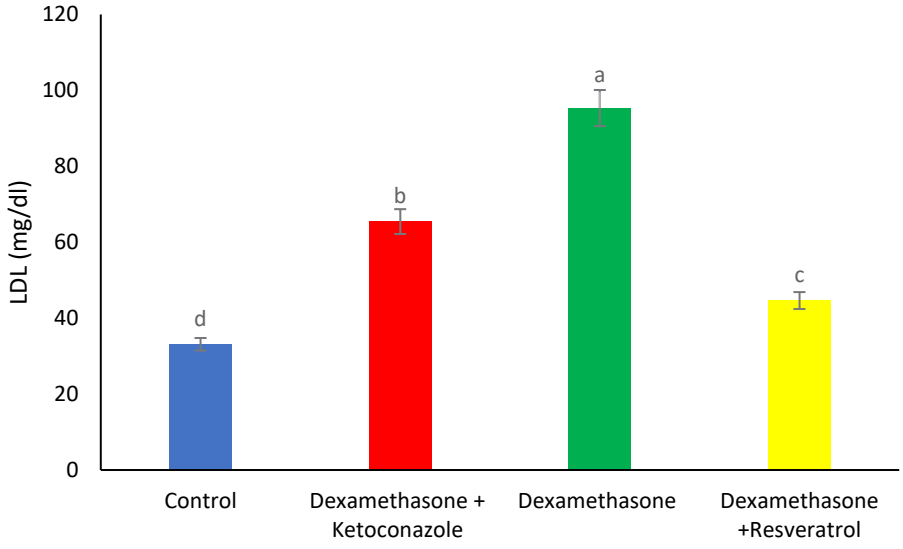


Figure 6. Effects of ketoconazole and resveratrol on serum LDL levels in dexamethasone-induced hypercortisolism rats

Note: Data are expressed as Mean±SE. Different letters (a-d) indicate significant differences between treatments (P<0.05).

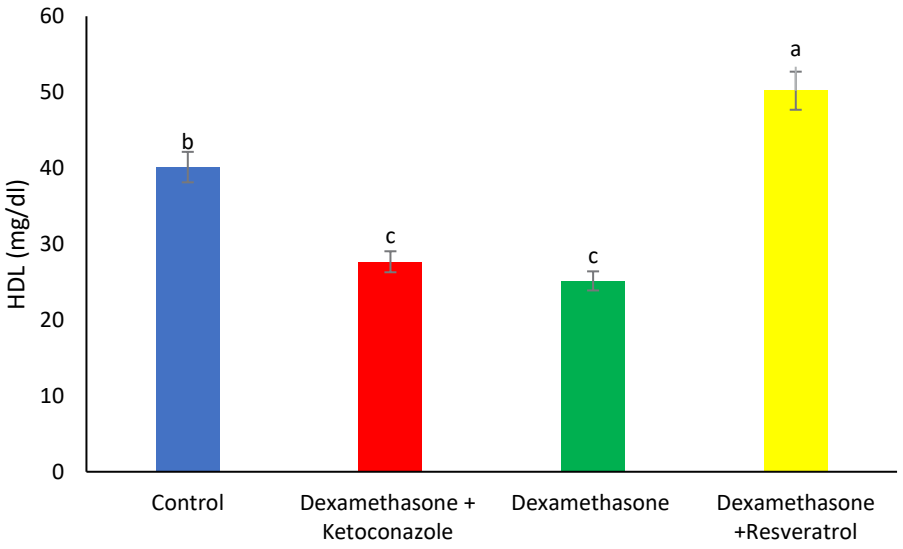


Figure 7. Effects of ketoconazole and resveratrol on serum HDL levels in dexamethasone-induced hypercortisolism rats

Note Data are expressed as Mean±SE. Different letters (a-c) indicate significant differences between treatments (P<0.05).

tial of resveratrol likely involves modulating HPA axis activity, suppressing neuroinflammatory pathways (such as NLRP3/NF-κB), or restoring hippocampal Wnt/β-catenin signaling, thereby ameliorating HPA and hypothalamic-pituitary-thyroid (HPT) axis dysfunction in metabolic and psychiatric settings (Unno et al., 2013). Furthermore, abnormal HPA axis activity in hypercortisolism exacerbates neuroinflammation by increasing brain proinflammatory cytokines (Sanders et al., 2018), a process that is likely inhibited by the anti-inflammatory properties of resveratrol. These multifaceted mechanisms hold promise for a role for resveratrol in counteracting glucocorticoid-induced metabolic and endocrine pathologies. However, several limitations require attention. First, the short treatment duration limits conclusions regarding the long-term efficacy or safety of resveratrol in chronic hypercortisolism. Second, although serum cortisol levels and metabolic markers were measured, direct measurement of insulin, ACTH, or glucocorticoid receptor activity in specific tissues could have more precisely elucidated the pathways involved in

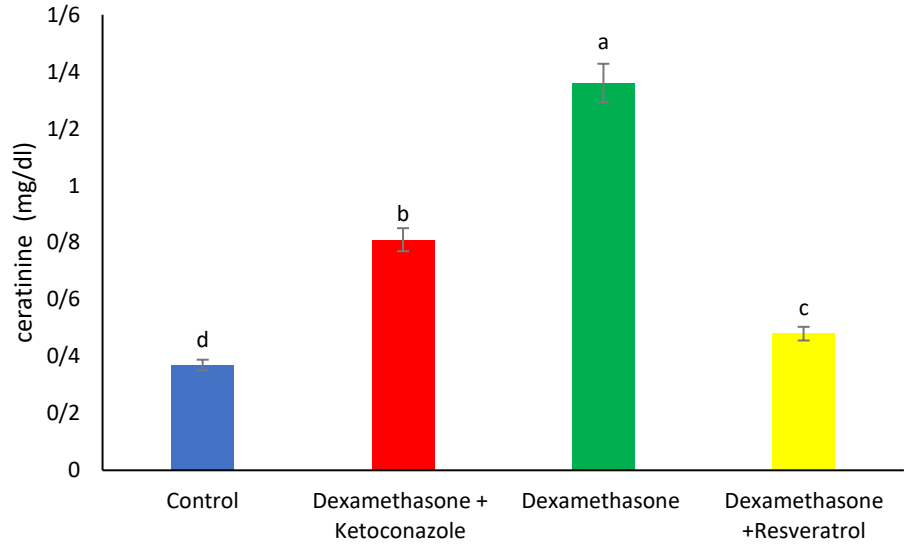


Figure 8. Effects of ketoconazole and resveratrol on serum creatinine levels in dexamethasone-induced hypercortisolism rats

Note: Data are expressed as Mean±SE. Different letters (a-d) indicate significant differences between treatments (P<0.05).

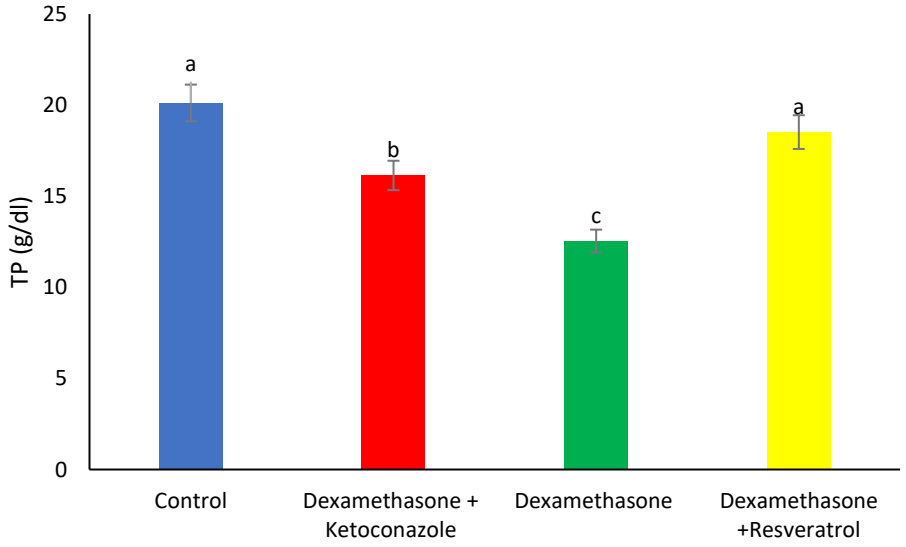


Figure 9. Effects of ketoconazole and resveratrol on serum TP levels in dexamethasone-induced hypercortisolism rats

Note: Data are expressed as Mean±SE. Different letters (a-c) indicate significant differences between treatments (P<0.05).

resveratrol's action. Third, the lack of dose-response data for resveratrol makes it difficult to optimize its therapeutic window. Finally, the translational relevance of findings from rodent models to humans is unclear, as interspecies differences in HPA axis regulation and glucocorticoid metabolism may influence the results.

Conclusion

The present study demonstrates that resveratrol effectively attenuates dexamethasone-induced hypercortisolism and blood parameters in rats, providing new insights into the therapeutic potential of this compound in cortisol-related disorders. The most important advantages of this study include the comprehensive assessment of hormonal and metabolic parameters, the use of a standard rodent model that mimics the clinical features of hypercortisolism, and the elucidation of the dual ability of resveratrol to regulate cortisol levels and improve dyslipidemia, hyperglycemia, and hypoproteinemia. Furthermore, the use of ketoconazole as a comparator highlights the specificity of resveratrol's cortisol-lowering effect, as ketoconazole paradoxically exacerbated hypercortisolism in this model. Future research should focus on long-term in vivo studies, mechanistic analyses of the interaction of resveratrol with glucocorticoid signaling pathways, and clinical trials to validate its efficacy in human Cushing's syndrome. Addressing these shortcomings will advance our understanding of the therapeutic potential of resveratrol and improve strategies to mitigate glucocorticoid-induced metabolic and endocrine disorders.

Ethical Considerations

Compliance with ethical guidelines

All ethical principles are considered in this article.

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Authors' contributions

Data collection, and writing the original: Masumeh Rezaei: supervision, methodology, statistical analysis, review and editing: Shahin Hassanpour; Advisory support: Ehsan Khaksar.

Conflict of interest

The authors declared no conflict of interest.

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