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Resveratrol alleviates hyperlipidemia, inflammation, and oxidative stress in poloxamer 407-induced hyperlipidemic adult Wistar rats

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Abstract: Poloxamer 407 (Pol-407) is widely used to induce hyperlipidemia, leading to dysregulated lipid metabolism and increased cardiovascular risk. This study investigated the therapeutic potential of resveratrol in mitigating Pol-407-induced hyperlipidemia and associated oxidative and inflammatory stress. Twenty-five Wistar rats were divided into five groups (n=5 per group) as follows: Group 1 (normal control), Group 2 (Pol-407-only), Groups 3, 4, and 5, administered resveratrol at doses of 20, 40, and 80 mg/kg, respectively. The study lasted for 21 days. The experimental animals were anaesthetized and killed. Blood samples and cardiac tissues were collected and used for biochemical assessment. Resveratrol treatment demonstrated a significant ($P<0.05$) dose-dependent improvement in lipid profiles, reducing total cholesterol, triglycerides, and low-density lipoprotein (LDL), while increasing high-density lipoprotein (HDL) levels. Resveratrol administration significantly ($P<0.05$) lowered atherogenic and Castelli's risk indices, restoring cardiovascular balance. Antioxidant defenses were strengthened, evidenced by reduced malondialdehyde (MDA) levels and improved superoxide dismutase (SOD), and catalase (CAT) activity. Resveratrol mitigated inflammation by decreasing tumor necrosis factor-alpha (TNF-α) and increasing interleukin-10 (IL-10). Cardiac brain-derived neurotrophic factor levels (BDNF) were significantly ($P<0.05$) restored in the resveratrol-treated groups, suggesting improved cardiac protection. These findings highlight resveratrol's potential use against hyperlipidemia-induced oxidative and inflammatory stress, reinforcing its lipid-regulating, antioxidant, and anti-inflammatory activities.

Keywords: poloxamer 407, hyperlipidemia, resveratrol, oxidative stress, inflammation

INTRODUCTION

Hyperlipidemia is a major cardiovascular disease (CVD) risk factor [1]. The excessive accumulation of lipids in the bloodstream leads to the formation of atherosclerotic plaques, which can impede blood flow and trigger inflammatory processes [2]. Systemic inflammation and oxidative stress are pivotal factors in the pathogenesis of hyperlipidemia, a condition characterized by elevated levels of lipids in the blood, which can lead to atherosclerosis and other cardiovascular diseases [3]. Hyperlipidemia can be induced experimentally using various models, one of which is the Poloxamer 407 (P-407) experimental model known for its ability to mimic the metabolic syndrome observed in humans [4,5]. This model effectively causes hyperlipidemia by disrupting lipid metabolism through the inhibition of lipoprotein lipase activity, leading to increased plasma triglyceride levels and promoting systemic inflammation [6]. Research has shown that Pol-407 can induce hyperlipidemia rapidly, making it an effective model for evaluating the effects of potential therapeutic agents. For example, studies have reported that Pol-407 treatment in rats leads to significant alterations in lipid profiles within 24 h, providing a clear window for assessing the impact of interventions like resveratrol [7]. The P-407-induced hyperlipidemia model is particularly valuable for studying the mechanisms of lipid metabolism and the role of dietary interventions, such as resveratrol, in modulating these processes.

Resveratrol, a polyphenolic compound found naturally in various plants, especially grapes, berries, and peanuts, has garnered considerable attention in recent

years for its potential health benefits [8]. This compound is primarily known for its antioxidant properties and its ability to modulate inflammatory pathways [9,10], making it a subject of interest in the context of several chronic diseases, including cardiovascular diseases, diabetes, and obesity-related conditions [11]. Resveratrol's mode of action involves several biological pathways. It is known to activate sirtuins, a group of proteins that play a crucial role in cellular regulation, including responses to inflammation and stress [12,13]. By activating NAD-dependent deacetylase sirtuin-1 (SIRT1), resveratrol has been shown to downregulate pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), thus attenuating inflammatory responses [14]. For instance, a study by Liu et al. [15] reported that resveratrol administration significantly reduced serum levels of triglycerides and total cholesterol in high-fat diet-induced obese mice, along with a decrease in serum inflammatory markers. This suggests that resveratrol may serve as a potential therapeutic agent in the management of hyperlipidemia-related complications.

Utilizing the Poloxamer 407-induced hyperlipidemic model allows for a controlled examination of resveratrol's effects on lipid metabolism and inflammation, providing valuable insights into its potential activity [16]. This model is particularly effective in mimicking human metabolic disorders, thereby enhancing the relevance of findings to human health [17]. P-407 administration has been shown to affect adipokine levels, leading to an increase in leptin and a decrease in adiponectin [18]. Given the rising incidence of hyperlipidemia and the limitations of current treatment options, exploring natural compounds like resveratrol offers a promising avenue for therapeutic intervention [19]. Resveratrol has demonstrated promising effects in mitigating hyperlipidemia and its associated complications. In hyperlipidemic rat models induced by P-407, significant increases in plasma cholesterol and triglycerides, along with alterations in lipid-regulating enzymes, were observed [20]. Resveratrol supplementation in rats with metabolic syndrome, induced by a high-fat, high-fructose diet, exhibited protective effects against hepatic steatosis, oxidative stress, and inflammation. It improved lipid profiles, enhanced insulin sensitivity, and modulated the expression of genes involved in lipid metabolism [21]. In cholesterol-fed rats, resveratrol effectively reduced serum and hepatic lipid levels and increased bile acid excretion. It demonstrated antioxidant properties by decreasing thiobarbituric acid reactive substances (TBARS) levels and enhancing antioxidant enzyme activities [22]. These findings strongly suggest resveratrol's potential as a therapeutic approach for hyperlipidemia and related metabolic disorders.

The role of brain-derived neurotrophic factor (BDNF) in cardiac health under hyperlipidemic conditions remains underexplored. While studies have linked hyperlipidemia to inflammation, few have examined the specific interplay between interleukin-10 (IL-10) suppression and TNF-α elevation in Pol-407-induced models. By investigating its effects on systemic inflammation and oxidative stress in a well-established animal model, this study aims to contribute to understanding resveratrol's potential effect on lipid metabolism.

MATERIALS AND METHODS

Ethics statement

All experimental protocols were executed in strict adherence to the institutional regulations for animal well-being. This project received ethical clearance from the Ahmadu Bello University Committee for the Ethical Use of Animals (Approval No. ABUCAUC/2024/085).

Materials

Poloxamer-407 (Lutrol F127; BASF, Ludwigshafen, Germany). Weighing machine (model: XY100C, no. 1404273, Changzhou Xingyun), measuring tape, and a ruler. Vis Spectrophotometer S23A (Axiom, UK), TNF-α (ER1393), rat catalase (CAT) (ER0264), were obtained from FineTest (Wuhan, China), reduced glutathione (GSH) Colorimetric Assay Kit (Elabscience, China, E-BC-K030). Total cholesterol (Cat. No. EU2634), triglycerides (Cat. No. ER2150), high-density lipoprotein (Cat. No. ER1035), and low-density lipoprotein (Cat. No. ER0311) were measured using kits from FineTest (Fine Biotech), Wuhan, China.

Animal handling and care

Twenty-five adult Wistar rats weighing 150 and 180 grams were obtained from the animal facility at the

Department of Human Physiology, Ahmadu Bello University in Zaria, Nigeria. The animals were kept in transparent plastic cages for an acclimatization period of two weeks, with unrestricted access to commercial feed and water. All applicable international, national, and/or institutional guidelines for the care and use of animals were followed.

Induction of hyperlipidemia

Pol-407 was used to induce hyperlipidemia at a dose of 500 mg/kg intraperitoneally twice a week for 3 weeks. Before the administration, Pol-407 was dissolved in distilled water and refrigerated overnight to facilitate its dissolution. It was injected into the abdominal cavity at a dose of 500 mg/kg, between 10:00 a.m. and 11:00 a.m. [23]. Resveratrol was administered 2 h after Pol-407 injection. Needles and syringes used for administration were cooled to prevent gelation inside the syringe during injection [24].

Experimental design

A total of 25 rats were allocated into five groups (n=5 per group) by random selection. Group 1 served as the normal control and received distilled water. Group 2, the negative control, was given Pol-407 throughout the study without additional treatment. Groups 3, 4, and 5 received daily oral resveratrol doses of 20, 40, and 80 mg/kg, respectively, for 21 days. Resveratrol was dissolved in deionized water with 0.05% Tween 80 on the day of the treatment [25]. The 20 mg/kg dose of resveratrol was adopted from Oliveira et al. [25] and modified in this study to higher doses of 40 and 80 mg/kg to study the dose-dependent effect of resveratrol.

Blood sample and heart tissue collection

After fasting overnight, the animals were anaesthetized by an intraperitoneal injection of 75 mg/kg ketamine and 10 mg/kg xylazine [26]. Blood samples were then drawn through cardiac puncture and collected in plain tubes. The heart was removed and rinsed in a cold phosphate buffer solution. A portion was homogenized (0.01 M, pH 7.4; using 9 mL of phosphate buffered saline (PBS) per 1 g of tissue), centrifuged at 5,000 ×g for 10 min, and used for biochemical analysis.

Biochemical assays

Total cholesterol, triglycerides, HDL, and LDL parameters were measured according to the manufacturer's manual using the following kits from FineTest (Fine Biotech), Wuhan, China: serum total cholesterol (Cat. No.: EU2634), triglycerides (Cat. No.: ER2150), HDL (Cat. No. ER1035), and LDL (Cat. No. ER0311).

Atherogenic index, Castelli's risk indices I and II

The atherogenic index (AI) was estimated using the relationship: Log [TG/HDL-c]. Castelli's risk index 1 (CRI-I) was measured using the mathematical relationship: TC/HDL. Castelli's risk index II (CRI-II) was estimated using the relationship LDL/HDL as described [27].

Assessment of oxidative stress biomarkers

MDA concentration was determined using the method by Ohkawa et al. [28]; GSH levels were measured with a commercial assay kit (E-BC-K030 Elabscience, China), SOD activity according to the method by Misra and Fridovich [29], and CAT activity using Claiborne's method [30]. Protein concentrations were quantified with the Bradford assay using Coomassie Brilliant Blue G-250 [31] and bovine serum albumin as the standard. Absorbance readings were taken with a Vis Spectrophotometer S23A (Axiom UK).

Assessment of inflammatory biomarkers

Serum and cardiac tissue levels of TNF-α, IL-10, and BDNF were measured using commercially available rat-specific ELISA kits: TNF-α (ER1393), BDNF (ER0008), and IL-10 (ER0033) (all from Fine Test, Wuhan, China), following the manufacturer's instructions.

Measurement of abdominal circumference, thoracic circumference, and body length

The abdominal (AC) and thoracic circumferences (TC) were determined using a measuring tape anterior to the forefoot and immediately behind the foreleg. The body length was measured as distance from the nose to anus [32]. All measurements were taken with the animal in an anaesthetized state.

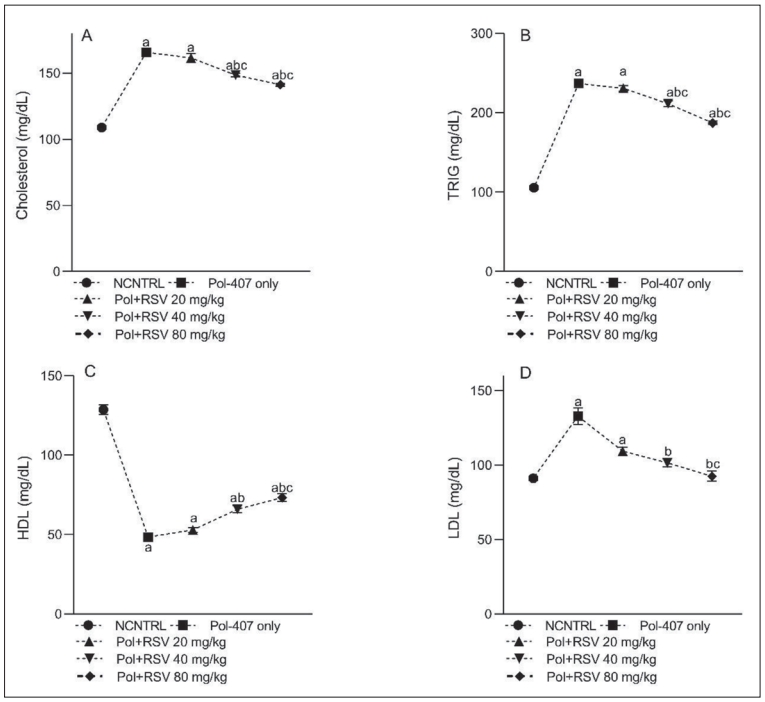

Fig. 1. Serum cholesterol (**A**), triglycerides (**B**), HDL (**C**), and LDL (**D**). Pol – Poloxamer, NCNTRL – normal control, RSV – resveratrol. [a]P<0.05 vs NCNTRL; [b]P<0.05 vs Pol-407-only; [c]P<0.05 vs Pol+resveratrol 20 mg/kg.

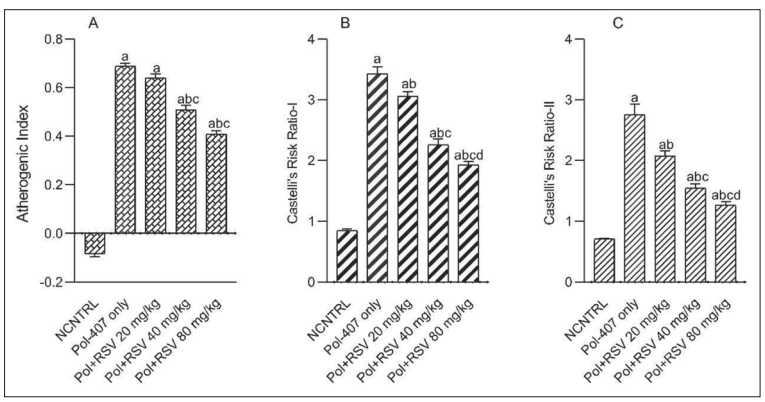

Fig. 2. Atherogenic index (**A**), Castelli's Risk Ratio I (**B**), HDL Castelli's risk index II. Pol – Poloxamer, NCNTRL – normal control, RSV – resveratrol. [a]P<0.05 vs NCNTRL; [b]P<0.05 vs Pol-407-only; [c]P<0.05 vs Pol+resveratrol 20 mg/kg; [d]P<0.05 vs resveratrol 80 mg/kg.

Data analysis

The quantitative findings of this study are reported as the mean±SEM. Statistical evaluations were performed using IBM SPSS version 23. To ascertain intergroup variations, a one-way ANOVA was initially employed. Tukey's post hoc test was used for pairwise comparisons where the ANOVA yielded significant results. A significance level of P<0.05 was predetermined for all statistical tests.

RESULTS

Serum cholesterol, triglyceride, HDL, and LDL

Fig. 1 shows the effect of resveratrol on the lipid profile of hyperlipidemic animals. In Fig. 1A and B, the cholesterol and triglyceride levels were significantly higher (P<0.05) in the Pol-407-only, and other resveratrol-treated groups compared to the normal control (NCNTRL). In the groups receiving 40 and 80 mg/kg resveratrol, cholesterol was significantly reduced compared to the Pol-407-only and the resveratrol 20 mg/kg groups. HDL (Fig. 1C) was significantly (P<0.05) lowered in the Pol-407 and all resveratrol-treated groups compared to the NCNTRL. LDL was significantly (P<0.05) elevated in the Pol-407-only group compared to the NCNTRL (Fig. 1D). At 40 and 80 mg/kg resveratrol, LDL was significantly reduced compared to the Pol-407-only group.

Atherogenic index, CRI-I and -II

Fig. 2 shows the effect of resveratrol on the atherogenic index (AI), Castelli's risk indices I and II (CRI-I and -II). The AI (Fig. 2A) was significantly raised (P<0.05) in the Pol-407 and resveratrol-treated groups compared to the NCNTRL. In the groups given resveratrol at 40 and 80 mg/kg, the AI was significantly (P<0.05) reduced compared to the NCNTRL and Pol-407 groups. The CRI-I and -II were significantly increased (P<0.05) in the Pol-407-only and all resveratrol-treated groups compared to the NCNTRL. Treatment with resveratrol significantly decreased CRI-I and -II in a dose-dependent fashion compared to the Pol-407-only group.

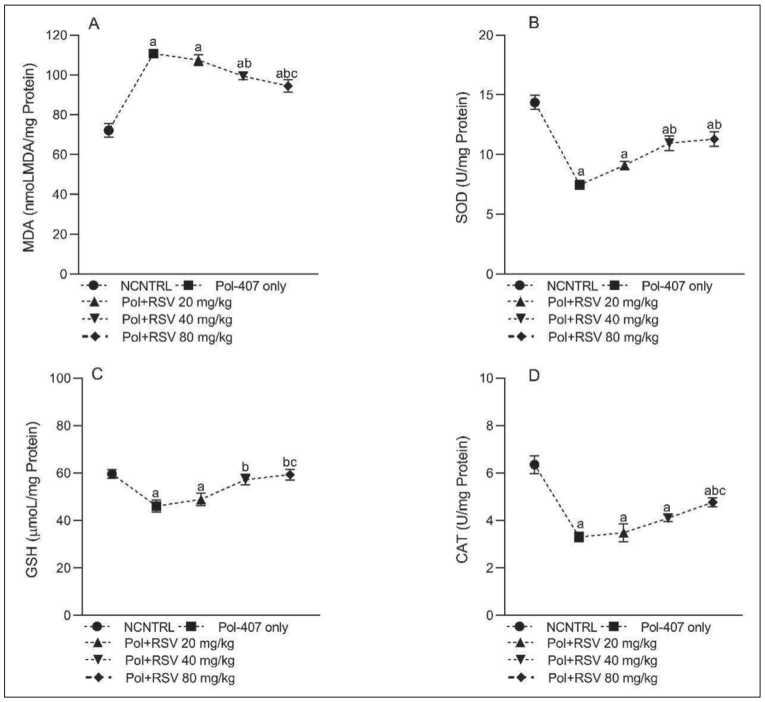

Fig. 3. MDA (**A**), SOD (**B**), GSH (**C**), CAT (**D**). Pol – Poloxamer; NCNTRL – normal control; RSV – resveratrol. [a]P<0.05 vs NCNTRL; [b]P<0.05 vs Pol-407-only; [c]P<0.05 vs Pol+resveratrol 20 mg/kg.

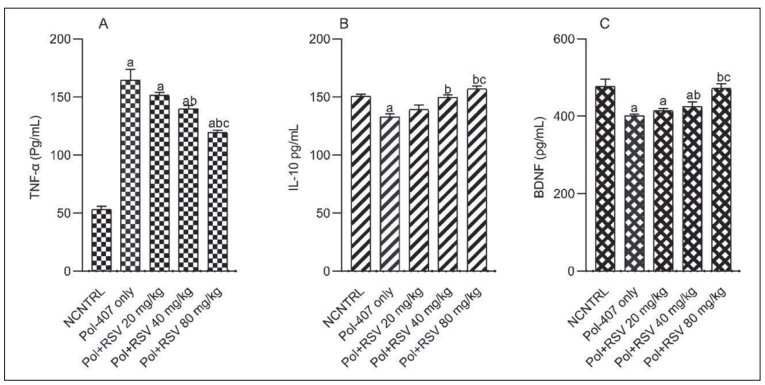

Fig. 4. Serum TNF-α (**A**); IL_10 (**B**); BDNF (**C**). Pol – Poloxamer; NCNTRL – normal control; RSV – resveratrol. [a]P<0.05 vs NCNTRL; [b]P<0.05 vs Pol-407-only; [c]P<0.05 vs Pol+resveratrol 20 mg/kg; [d]P<0.05 vs resveratrol 80 mg/kg.

Cardiac tissue oxidative stress biomarkers

Fig. 3 shows the effect of resveratrol on cardiac oxidative stress biomarkers. MDA was significantly increased (P<0.05) in the Pol-407-only group and the resveratrol-treated groups compared to the NCNTRL (Fig. 3A). MDA was significantly (P<0.05) reduced in the resveratrol-treated groups at 40 and 80 mg/kg compared to the Pol-407-only group. In the group given resveratrol at 80 mg/kg, MDA was significantly (P<0.05) lower when compared to the group given resveratrol at 20 mg/kg. SOD in Fig. 3B was significantly reduced (P<0.05) in the Pol-407-only group and all the resveratrol-treated groups compared to the NCNTRL. Treatment with resveratrol at 40 and 80 mg/kg significantly (P<0.05) raised SOD level compared to the Pol-407-only group. The level of GSH (Fig. 3C) was significantly (P<0.05) reduced in the Pol-407-only and resveratrol 40 mg/kg compared to the NCNTRL. Treatment with resveratrol 40 and 80 mg/kg significantly (P<0.05) increased GSH compared to the Pol-407-only group. Compared to the resveratrol 20 mg/kg group, GSH was increased significantly (P<0.05) in the group that received 80 mg/kg resveratrol. CAT was significantly (P<0.05) reduced in all the groups compared to the NCNTRL (Fig. 3D). In the group given resveratrol at 80 mg/kg, CAT was significantly (P<0.05) higher compared to the Pol-407-only and resveratrol 20 mg/kg-treated groups.

Serum TNF-α, IL-10, and BDNF

Fig. 4 shows the effect of resveratrol on TNF-α, IL-10, and BDNF. Serum TNF-α was significantly (P<0.05) higher in all the groups compared to the NCNTRL group (Fig. 4A). However, this was significantly (P< 0.05) dose-dependently lowered in the groups that received 40 and 80 mg/kg resveratrol. IL-10 was significantly lower (P<0.05) in the Pol-407-only group compared to the NCNTRL group (Fig. 4B). In the resveratrol 40 and 80 mg/kg groups, IL-10 was significantly (P<0.05) higher compared to the Pol-407-only group. Although BDNF was significantly lower in the Pol-407-only and 20 and 40 mg/kg resveratrol groups when compared to the NCNRTL, the treatment with 40 and 80 mg/kg resveratrol significantly (P<0.05) increased it compared to the Pol-407-only group.

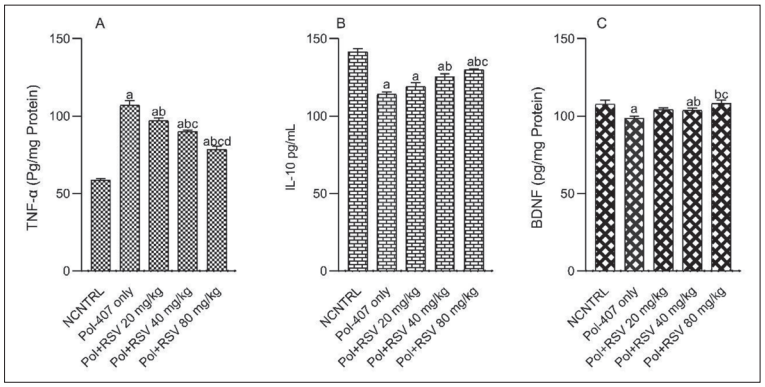

Fig. 5. TNF-α (**A**); IL-10 (**B**), BDNF (**C**). Pol – Poloxamer, NCNTRL – normal control, RSV – resveratrol. [a]P<0.05 vs NCNTRL; [b]P<0.05 vs Pol-407-only; [c]P<0.05 vs Pol+resveratrol 20 mg/kg; [d]P< 0.05 vs resveratrol 80 mg/kg.

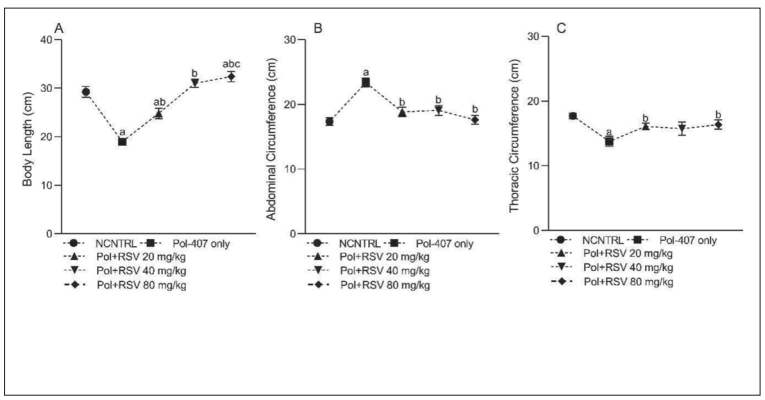

Fig. 6. Body length (**A**); abdominal circumference (**B**); thoracic circumference (**TC**). Pol – Poloxamer, NCNTRL – normal control, RSV – resveratrol. [a]P<0.05 vs NCNTRL; [b]P<0.05 vs Pol-407-only; [c]P<0.05 vs Pol+resveratrol 20 mg/kg

Tissue TNF-α, IL-10, and BDNF

Fig. 5 shows the effect of resveratrol on cardiac inflammatory biomarkers. TNF-α was significantly (P<0.05) higher in all groups compared to the NCNTRL (Fig. 5A). Treatment with resveratrol significantly (P<0.05) reduced TNF-α in a dose-dependent fashion. IL-10 was significantly lower (P<0.05) in all the groups compared to the NCNTRL (Fig. 5B). In the 40 and 80 mg/kg resveratrol-treated groups, IL-10 was significantly (P<0.05) increased dose-dependently when compared to the Pol-407-only group. BDNF was significantly (P<0.05) reduced in the Pol-407-only, and in the resveratrol 40 mg/kg group compared to the NCNTRL group. However, treatment with 40 and 80 mg/kg resveratrol significantly improved BDNF compared to the Pol-407-only group.

Body length (BL), abdominal circumference (AC), thoracic circumference (TC)

Fig. 6 shows the effect of resveratrol on the BL, AC, and TC. BL was significantly (P<0.05) decreased in the Pol-407-only and resveratrol 20 mg/kg groups compared to the NCNTRL (Fig. 6A. In all the resveratrol-treated groups, BL was significantly (P<0.05) higher compared to the Pol-407-only group, the increase being significantly (P<0.05) higher in the resveratrol 80 mg/kg group compared to the other resveratrol-treated groups. The AC was significantly (P<0.05) higher in the Pol-407-only group compared to the NCNTRL (Fig. 6B). The treatment with resveratrol significantly (P<0.05) reduced the AC compared to the Pol-407-only group. TC was significantly (P<0.05) lower in the Pol-407-only group compared to the NCNTRL group (Fig. 6C), while it increased significantly (P<0.05) in the groups that received 20 and 80 mg/kg resveratrol.

DISCUSSION

Studies suggest that Pol-407 induces hyperlipidemia by altering lipid metabolism, which leads to elevated cholesterol and triglyceride levels [5,34]. This aligns with the present study, which shows significantly elevated cholesterol and triglycerides in the Pol-407-only group compared to the NCNTRL. Serum HDL and LDL were significantly higher and lower, respectively, in the Pol-407-only group compared to the NCNTRL. This shows a higher risk of cardiovascular disease in the hyperlipidemic control group. Together, high LDL and low HDL create an unfavorable lipid profile, increasing the risk of heart disease, stroke, and other complications [35]. In the groups treated with resveratrol, total cholesterol and triglycerides were significantly reduced compared to the Pol-407-only group. Resveratrol can suppress the activity of enzymes involved in cholesterol production, leading to reduced levels of total cholesterol [36]. It promotes the breakdown of cholesterol and triglycerides, improving overall

lipid balance [37]. The action of resveratrol could also have been via its antioxidant and anti-inflammatory activity, as observed in the present study. By reducing oxidative stress and inflammation, resveratrol helps protect blood vessels and supports healthy cholesterol levels [38]. Resveratrol has been shown to enhance liver enzyme activity, which plays a crucial role in cholesterol regulation [39]. Resveratrol influences enzymes involved in lipid regulation, promoting the synthesis of HDL [40,41]. The higher HDL observed in the resveratrol-treated groups in the present study could have been via its influence on paraoxonase-1 (PON-1), which is associated with HDL and helps protect against oxidative damage [42]. Additionally, resveratrol may affect AMP-activated protein kinase (AMPK), a crucial regulator of lipid metabolism. Activation of AMPK can lead to increased HDL production and improved cholesterol transport [43].

The CRI-I and -II and the AI are simple ratios that can be calculated from the lipid profile values of a subject and have been used as screening tools to identify increased cardiovascular risk [44]. The AI in the Pol-407-only treated group in this study was significantly higher compared to the NCNTRL. A higher AI in Pol-407-induced hyperlipidemic rats in the present study suggests an increased risk of cardiovascular disease and atherosclerosis. Pol-407 disrupts lipid metabolism, leading to elevated triglycerides and reduced HDL cholesterol, which directly influence the AI [44]. Castelli's indices were significantly raised in the Pol-407-only group compared to the NCNTRL. Pol-407 disrupts lipid metabolism, leading to excessive accumulation of low-density lipoprotein (LDL) and total cholesterol, which raises CRI-I and -II [44]. Treatment with resveratrol lowered AI, CRI-I, and -II compared to the Pol-407-only group. This action of resveratrol could be explained by the reduced total cholesterol, triglycerides, and LDL observed in the resveratrol-treated groups. Resveratrol reduces the risk of cardiovascular diseases. These findings agree with Akbari et al. [45].

The cardiac MDA was significantly higher in the Pol-407-only group compared to the NCNTRL. Pol-407-induced hyperlipidemia increases protease activity in the heart and liver, contributing to lipid oxidation and tissue damage [20]. Pol-407 disrupts normal lipid metabolism, causing excessive accumulation of cholesterol and triglycerides in the bloodstream and tissues. Elevated lipid levels contribute to oxidative stress, producing reactive oxygen species (ROS) that damage lipids, proteins, and DNA [46]. As observed in the present study, treatment with resveratrol significantly reduced MDA levels in both serum and cardiac tissue. The action of resveratrol on MDA levels could be explained by the reduced hyperlipidemia within the group and improved antioxidant enzymes. Hyperlipidemia reduces the activity of antioxidant enzymes such as catalase and superoxide dismutase, making tissues more vulnerable to oxidative damage [47]. The presence of excess lipids can trigger inflammation, further exacerbating oxidative damage and lipid peroxidation [48]. Therefore, the decrease in inflammation observed with resveratrol treatment may have contributed to the reduction in lipid peroxidation.

The antioxidants were significantly reduced in the Pol-407-only group compared to the control. High levels of lipids, especially LDL cholesterol, can become oxidized, triggering oxidative stress. This means that harmful free radicals accumulate in the body, depleting the available antioxidants that work to neutralize them [49]. Excessive lipids also contribute to chronic inflammation, which further increases oxidative stress [42]. This ongoing cycle continuously consumes and depletes antioxidants, as observed in this study. Therefore, the significant enhancement of antioxidant levels observed with resveratrol treatment in the present study may be attributed to its mitigating effects on excess lipids, lipid peroxidation, and inflammation.

Raised lipid levels stimulate macrophages to release TNF-α, a key pro-inflammatory cytokine [50]. TNF-α levels were significantly elevated in the Pol-407-only group compared to the NCNTRL group, indicating a heightened inflammatory response in this group. This may have resulted from disrupted lipid metabolism, leading to excessive lipid accumulation that, in turn, triggered an inflammatory response [51]. TNF-α promotes systemic inflammation and contributes to vascular dysfunction, which is commonly observed in hyperlipidemia [52]. IL-10 levels were significantly lower in the Pol-407-only group compared to the NCNTRL in the present study. Elevated lipid levels trigger an inflammatory cascade, leading to the suppression of IL-10 production [53]. In our study, resveratrol administration reduced inflammation by

improving IL-10 and reducing TNF-α. The reduced TNF-α in the group given resveratrol may have been due to its inhibition of nuclear factor kappa B (NF-κB), a key regulator of inflammation that drives TNF-α production [54]. It has also been reported to activate SIRT1, a protein that reduces inflammatory cytokine expression, including TNF-α [55], as observed in this study. As a potent antioxidant, resveratrol neutralizes free radicals and prevents lipid-induced inflammation [56]. In the present study, resveratrol administration led to an increase in IL-10 levels, which may have contributed to the inhibition of TNF-α production [57]. Cardiac BDNF was significantly reduced in the Pol-407-only group compared to the NCNTRL. Excess lipids contribute to chronic inflammation and oxidative stress, which can impair BDNF signaling in the heart [58]. Additionally, hyperlipidemia disrupts vascular function, reducing BDNF expression in endothelial cells, which play a role in cardiac health [59]. The significant increase in cardiac tissue BDNF observed in the resveratrol-treated group may be attributed to reductions in oxidative stress, hyperlipidemia, and inflammation, thereby enhancing BDNF expression.

The significant decrease in BL observed in the Pol-407-only group suggests altered body development, potentially resulting from lipid metabolism disturbances. Therefore, the effect of resveratrol on BL in this study may be related to its ability to mitigate lipid abnormalities. A higher abdominal circumference in hyperlipidemic rats is typically an indicator of visceral fat accumulation, which is strongly linked to metabolic disorders and cardiovascular risks. In hyperlipidemia, excess lipids, especially triglycerides and LDL cholesterol, are stored in abdominal adipose tissue, leading to increased central obesity [60]. Thus, the significant increase in AC in the Pol-407-only group is consistent with the observed excess lipids. The action of resveratrol on both the AC and TC suggests it could be involved in fat redistribution in hyperlipidemia.

CONCLUSION

Resveratrol treatment demonstrated significant protective effects, mitigating lipid abnormalities, oxidative stress, and inflammation. Resveratrol administration improved total cholesterol, triglyceride, HDL, and LDL levels, thereby reducing cardiovascular risk. Resveratrol enhanced antioxidant defenses, restored the anti-inflammatory marker IL-10, suppressed the pro-inflammatory cytokine TNF-α, and maintained cardiac BDNF expression, indicating its protective role against hyperlipidemia-induced tissue damage. These findings underscore resveratrol's potential for managing hyperlipidemia and related cardiovascular complications by supporting its antioxidant, anti-inflammatory, and lipid-regulating effects.

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Author contributions: Conceptualization, MJ, and AII; methodology, AII; software, MJ; validation, AII and MJ; formal analysis, AII; investigation, MJ; resources, MJ; data curation, AII; writing – original draft preparation, AII; writing – review and editing, AII; visualization, MJ; supervision, AII; project administration, MJ. Both authors have read and agreed to the published version of the manuscript.

Conflict of interest disclosure: The authors declare no conflict of interest

Data availability: The data presented in this study are openly available at: https://doi.org/10.5281/zenodo.15649744

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