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Protective Effect of Resveratrol on Isoproterenol-Induced Myocardial Damage in Male Rats

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A r t i c l e i n f o.

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ABSTRACT

This study evaluated the cardioprotective effects of resveratrol against isoproterenol-induced myocardial infarction in male Sprague-Dawley rats. Forty rats were randomly divided into four groups: control, resveratrol-treated, isoproterenol-treated, and a combined treatment group. Resveratrol was administered orally at 20 mg/kg/day, while isoproterenol was given intraperitoneally at 100 mg/kg. The results revealed that isoproterenol significantly increased serum levels of oxidative stress markers (MDA), inflammatory cytokine (TNF-α), triglycerides, cholesterol, and cardiac enzymes (CK-MB, cTnI, LDH), while reducing total antioxidant capacity (T-AOC) ($P \leq 0.05$). esveratrol treatment significantly mitigated these alterations, restoring antioxidant levels and reducing lipid and enzyme elevations. The combination treatment group showed intermediate values, indicating a partial protective effect. In conclusion, resveratrol demonstrates promising cardioprotective properties through its antioxidant, anti-inflammatory, and lipid-lowering actions, suggesting its potential as a preventive agent against oxidative and inflammatory cardiac damage.

Introduction

Isoproterenol (ISO) is a member of the class of medications known as beta-adrenergic agonists as a strong heart stimulant that raises cardiac output and heart rate and causes the smooth muscles in the uterus, lungs, and gastrointestinal tract to relax, and it improves blood flow to the extremities. Also, it enhances the heart's electrical signal transmission and is administered intravenously to treat cardiac arrhythmias in life-threatening emergencies (Hassanien, 2020).

Isoproterenol raises cytosolic cAMP by activating beta-adrenergic receptors. Circulating hormones or medications are the initial messengers to engage with beta-adrenergic receptors on the extracellular surface of target cells when there is beta-adrenergic agonist action (Wong et al., 2017). According to research, isoproterenol can cause cardiomyocyte damage that is comparable to that caused by myocardial infarction, ischaemia, cardiac stress, and cardiomyopathy (Zhou et al., 2020).

Isoproterenol increases lipid deposition in the myocardium and also increases augmented lipid breakdown, which can lead to myocardial necrosis (Suchal et al., 2016). The contributing factors for altered vascular function in isoproterenol-induced myocardial infarction are elevated serum triglycerides and elevated serum and tissue cholesterol salts (Godugu et al., 2018).

These natural products and herbal plants are gaining widespread use in order to treat a myriad of diseases and remove toxins that have been stored up in the body. Being active chemicals in plant extracts, like polyphenols, they can effectively inhibit reactive oxygen species (ROS), one of the main factors causing most serious diseases. Additionally, researchers and physicians are looking towards natural antioxidant testing as a secure step in contrast to artificial chemicals (Agarwal et al., 2025).

Resveratrol is a polyphenol found in peanuts, peanut butter, grapes, berries, and nuts. Plants produce compounds called phytoalexins in response to fungal or bacterial infection. Resveratrol is one of the most important of these compounds, which work to enhance the plant's resistance to harmful external factors. It was first found in grapevines (Vitis vinifera) in 1976, where they established that leaf tissue synthesizes it in response to fungal infection or UV light exposure (Azargoonjahromi et al., 2025). Resveratrol is a valuable chemopreventive and therapeutic agent that finds application in the management of an extensive variety of disorders. It exerts anti-cancer activity against different cancers in different ways (Mozafaryan et al., 2025). It also has antioxidant, anti-inflammatory, and anti-diabetic effects on various cell types. As a strong free radical scavenger, it manifests anti-aging and chronic disease preventive effects by inhibiting a myriad of pathways, including oxidative stress and apoptosis (Yi et al., 2025).

The protective effects of resveratrol are attributed to a range of biological targets and may lead to new therapeutic approaches to heart failure, metabolic syndrome, atherosclerosis, and ischaemia. Due to this, the use of resveratrol as a dietary supplement that promotes health is quickly gaining ground in the market of today (Laghari et al., 2025). Antioxidant resveratrol can be used to cure reactive oxygen species that can damage macromolecules and initiate signalling cascades of various inflammatory mediators. Resveratrol can postpone and/or avert oxidative stress-related diseases and cellular injury. Cells may experience apoptosis as a result of overwhelming oxidative stress-induced damage (Hong et al., 2025). Thus, according to the physiological parameters, the current study was planned to use resveratrol for the protection of the heart against isoproterenol-induced myocardial infarction in male albino rats.

Materials and methods

Animals used in the Study

This study was conducted for two months in the Department of biology animal house at the University of Anbar's College of Education for Pure Sciences. Forty mature male Sprague Dawley albino rats were used in the study. They were three to four months old and weighed between 200 and 300 g. Following an examination by a specialised veterinarian, the animals were placed in metal-covered, specifically made plastic cages measuring 64 by 15.5 by 30 cm, which were used to develop rats. For this experiment, the animals were housed in a lab with adequate ventilation, a temperature of 22 ± 2 C, and 13:11 hours of natural light and dark.

The Experiment Design

The animals were split up into four groups based on comparable weights, with ten animals in each group: Group 1 (Control): Distilled water (1 mL/kg) was administered orally. Group 2 (Resveratrol): Given 2 ml of resveratrol daily for 21 days at a level of 20 mg/kg. Group 3: received an intraperitoneal injection of isoproterenol (100 mg/kg) for two consecutive

days. Group 4 (Isoproterenol + Resveratrol): Oral doses of resveratrol (20 mg/kg/day) and isoproterenol (100 mg/kg) were administered on days 20 and 21 following the initiation of resveratrol for 21 days.

Collecting blood samples

The animals were starved for 24 hours, and the following day they were put under anesthesia with an intraperitoneal dosage of 0.1 ml/100 g of ketamine/xylazine. We took blood directly from the heart using a 5-mL sterile, disposable syringe. The blood was centrifuged at 3,000 rpm for 15 minutes in plain tubes. Before biochemical testing, the serum was stored at -20°C in white tubes after being separated using micropipettes. Every sample's data was recorded.

Assay of Oxidative Stress and Antioxidants

The level of (T-AOC and MDA) in blood serum was estimated using a ready-made test kit provided by the American company Elabscience, using the colorimetric method on a spectrophotometer.

Measurement of the level of Tumor Necrosis Factor Alpha (TNF-α) in the blood serum:

Using an ELISA Microplate Reader and a pre-made test kit from the American company Elabscience (www.elabscience.com, **No:** E-EL-H0109), serum TNF-α levels were determined using the Sandwich ELISA technique.

Risk Factors

The concentration of triglycerides and cholesterol in the blood serum was estimated using the analysis kit provided by the French company Biolabo (Allain et al., 1974; Fossati et al., 1982)

Heart function test

A kit from Ichroma (Geodudanji 1-gil, Dongnae-myeon, Chuncheon-si, Gangwon-do, Republic of Korea) was used to quantify the concentration of serum troponin (cTnI). A kit from Biolabo France was used to measure the levels of CK-MB [Soldin et al., 1999]. By adopting the [Friedman et al., 1997] approach, which involves converting pyruvate to lactate in the presence of NADH, the activity of lactate dehydrogenase (LDH) was discovered.

Statistical Analysis

The data of three independent experiments were collected and statistically analyzed using one-way analysis of variance (one-way ANOVA), followed by Duncan's honestly significant difference (HSD). Probability $p \leq 0.05$ indicated statistically significant differences.

Result and discussion

Estimation of oxidation balance and antioxidants in blood serum

Table 1 shows that isoproterenol (ISO) and resveratrol (RES) affect oxidative stress and antioxidants. Male rats injected with (ISO) had a highly significant increase in MDA activity at the level ($P \leq 0.05$) when compared to the control group. In contrast, the second group dosed with resveratrol showed a significant decrease, and the fourth group of rats dosed with Resveratrol and injected with (ISO) showed a significant decrease. Isoproterenol (ISO) and Resveratrol (RES) affect oxidative stress and antioxidants. In our current study, we observe a significant increase in antioxidant effectiveness at the level ($P \leq 0.05$) in male white rats orally dosed with Resveratrol compared to the control group. Conversely, the third group injected with ISO showed a significant decrease in antioxidant effectiveness, with results of, while the fourth group of rats orally dosed with resveratrol and injected with ISO showed a significant increase in antioxidant effectiveness.

Table (1): The effect of resveratrol on the level of oxidative stress (MDA) and total antioxidant capacity (T-AOC) in the blood serum of male rats treated with isoproterenol.

		Control	RES	ISO	ISO+RES
MDA nmol/ml	**Mean± SD**	**a 7.62 ± 0.984**	**b 5.77 ± 0.988**	**c 16.66 ± 0.847**	**a 8.175± 1.036**
T-AOC µmol/ml	**Mean± SD**	**a 49.29± 3.000**	**b 56.81± 3.330**	**c 31.96± 2.760**	**a 47.52± 2.778**

Mean values n=10, within a column not sharing a common superscript letter (a, b, and c) were significantly different, p ≥ 0.05.

Effect of resveratrol on the level of TNF-α in the serum of male rats treated with isoproterenol

Figure (3) shows a significant increase in the level of (TNF-α) activity at the level (P ≤ 0.05) in the G3 of male rats injected with (ISO), where the ratio reached (56.02±3.763) pg/ml compared to the control group (33.47±2.554) pg/ml. On the other hand, a significant decrease is observed in the G2 group dosed with resveratrol, where the results were (33.03±3.597) pg/ml, while a significant decrease is observed in the G4 group dosed orally with Resveratrol and injected with (ISO) where the results were (37.63±3.084) pg/ml.

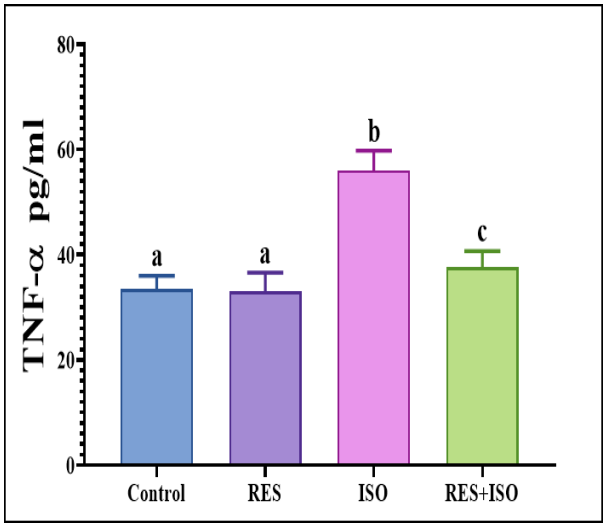

Fig.(1) The effect of resveratrol on the level of tumor necrosis factor alpha (TNF-α) in the blood serum of male rats treated with isoproterenol.
-Values are expressed as means±SE; n=10 for each treatment group; means in each column with different superscript letters are significantly different (p≥0.05).

Biochemical Assay

Results of the level of cholesterol and triglycerides in the blood serum of male rats.

Table 2 shows that the results showed a significant decrease at the level (P ≤ 0.05) for both cholesterol and triglycerides in group 2 of male rats that were orally dosed with Resveratrol compared with the control group. While in the group 3 that was intravenously injected with (ISO), a significant increase was observed at the level (P≤ 0.05) for both cholesterol and triglycerides compared to group 4, which was orally dosed with Resveratrol and intravenously injected with (ISO) where a significant decrease was observed for both cholesterol and triglycerides and the results.

Table 2: The effect of resveratrol on the activity of cholesterol and Triglycerides in the blood serum of male rats treated with isoproterenol.

		Control	RES	ISO	ISO+RES
Cholesterol mg/dl	Mean± SD	a 80.34± 6.829	b 69.00± 7.414	c 129.6± 6.393	d 69.25 ± 7.745
Triglycerides mg/dl	Mean± SD	a 56.12 ± 9.370	b 33.74± 6.967	c 152.0± 10.81	a 57.67± 7.633

Mean n=10 values within a column not sharing a common superscript letter (a, b, and c) were significantly different, p ≤ 0.05.

Effect of resveratrol on cardiac functions in the blood serum of male rats treated with isoproterenol

Figures (2), (3) and (4) show the results from male white rats' serum for the concentration of the following enzymes (cTNL) (CK-MB) (LDH). The results showed a significant decrease at the level of probability (P ≤ 0.05) in the group treated orally with Resveratrol second, and the results were as follows: ng/ml (0.071±0.258) U/L (12.49±121.9) U/L (21.80±100.5), respectively, compared to the control group ng/ml (0.067±0.284) U/L (15.45±137.6) U/L

(27.21±176.7), respectively. While the third group, intravenously injected with (ISO), had a significant rise, as results were ng/ml (0.069±1.076), U/L (20.89±315.6), U/L (28.99±446.9), respectively, in comparison to the fourth group, administered Resveratrol orally and intravenously injected with (ISO), as results were ng/ml (0.077±0.352), U/L (19.15±143.4), U/L (21.38±206.3), respectively.

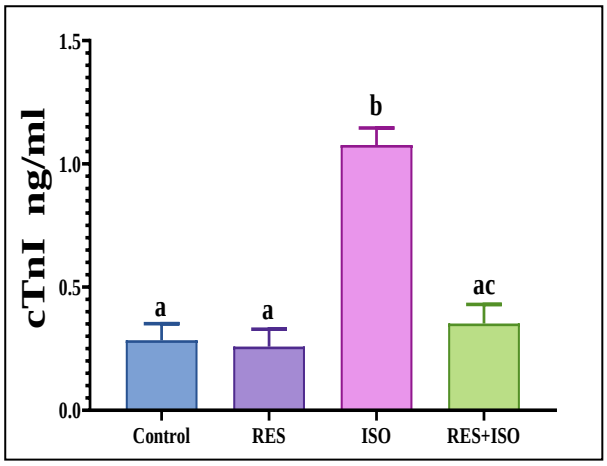

Fig.2 The effect of resveratrol on the level of cTnl in the blood serum of male rats treated with isoproterenol

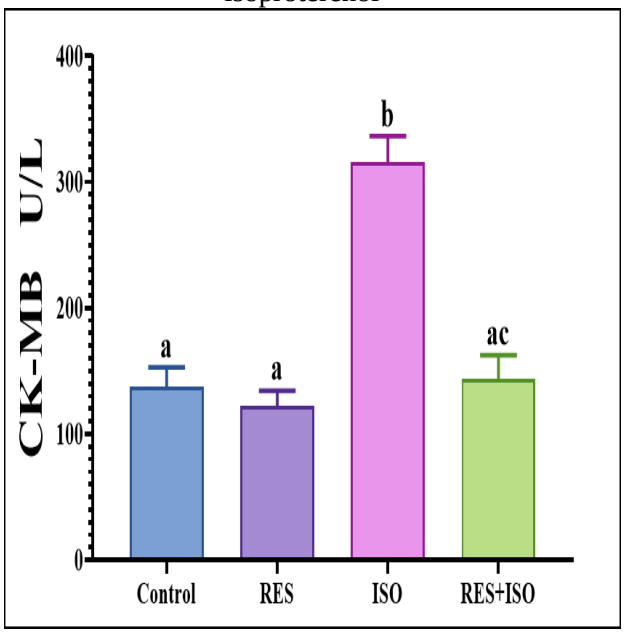

Fig. 3 The effect of resveratrol on the level of CK-MB in the blood serum of male rats treated with isoproterenol

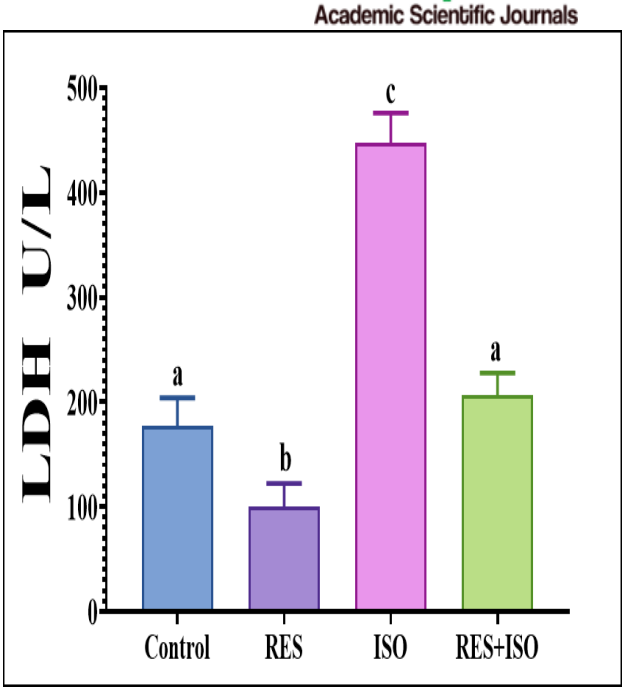

Fig.4. The effect of resveratrol on the level of LDH in the blood serum of male rats treated with isoproterenol

discussion

Cardiomyopathy is a major health concern, and since oxidative stress is a key factor in the pathophysiology of cardiac damage, treatment with bioactive antioxidants is believed to be a feasible way to prevent pathological changes and maintain heart function, the administration of ISO causes oxidative stress and necrotic damage to the hearts of laboratory rats, reactive oxygen species (ROS) generation and/or antioxidant depletion are the causes of oxidative stress and the pathophysiology of myocardial infarction (MI) [Estep et al., 2025; Padmanabhan et al., 2025]. Increased ROS levels in ISO-induced myocardial infarction result in endothelial dysfunction, damage to cardiomyocytes, mitochondrial dysfunction, inhibition of several enzymes that affect metabolism, inflammatory cytokine release, and increased apoptosis [Arandhara et al., 2025].

Several studies have linked the heart injury caused by ISO injection to lipid peroxidation. This study agrees with Cebova et al. (2025) that the high MDA levels and insufficient antioxidant levels combined to cause severe oxidative stress in mice (Figure 1). Because myocardial infarction causes metabolic disruptions that enhance the formation of reactive oxygen species (ROS), mice with myocardial infarction have greater levels of oxidative stress. In addition to ATP depletion

processes, lipid peroxidation of cell membranes, partial damage, and loss of elasticity, these ROS are extremely harmful to cardiac cells and can result in myocardial necrosis and death [Chang et al., 2025].

Malondialdehyde (MDA), which increases lipid peroxidation and tissue damage, was found to be present at higher concentrations in animals exposed to ISO. The cardiac cell membranes are then gravely and fatally damaged as a result. Cellular oxidative damage and tissue degeneration, including cardiac tissue, follow from this [Pop et al., 2025]. It is crucial to remember that free radical activity surpasses the antioxidants' ability to neutralize or eradicate them in pathological situations. Malondialdehyde and lipid peroxidation levels rise as a result, leading to oxidative stress, which in turn weakens the membranes of myocardial cells, activates genes that lead to mutations, promotes the development of malignant tumours, and so forth [Chandimali et al., 2025].

In this study, the significant decrease in oxidative stress indicators and the increase in total antioxidant levels in the blood of rats given ISO were evidence of resveratrol's antioxidant action. These results show that resveratrol treatment improves antioxidant status while reducing lipid peroxidation and hyperlipidemia. Notably, administering resveratrol significantly increased antioxidant levels, indicating that it could strengthen the body's defenses against free radicals. This results in agreement with the study by Chai et al. (2025), the significant increase in antioxidants in the serum of rats treated with resveratrol, compared to the group treated with isoproterenol, further proves the antioxidant potential of resveratrol against isoproterenol-induced oxidative cardiotoxicity in rats. Additionally, as a pure polyphenol, resveratrol showed free radical scavenging capabilities [Fiod Riccio et al., 2020].

These results show that resveratrol have a strong antioxidant capacity that guards the heart against oxidative injury. These alterations made us consider that reduced MDA was the reason for the enhanced antioxidant levels. Resveratrol's activity, which suppressed the generation of free radicals in cardiac muscle and consequently safeguarded cell membranes against oxidative injury, was the reason behind these alterations. Because they are antioxidants, polyphenolic compounds like resveratrol may also be reducing agents, hydrogen donors, and scavengers of single oxygen atoms, which prevents the formation of free radicals and minimizes oxidative stress to heart muscle tissue.

Triglyceride and cholesterol in the serum of isoproterenol-treated male albino rats were elevated when compared to the control group. This is consistent with research that discovered that isoproterenol degrades lipid profiles [Shanmugasundaram et al., 2025]. Rats treated with isoproterenol had decreased insulin sensitivity and an inhibition of fatty acid, triglyceride, and hepatic cholesterol synthesis. According to [Mahajan et al., 2025], it also promotes the absorption of cholesterol via the gut by changing the concentration of the intestinal monolayer structure.

However, the oxidative stress induced by injecting isoproterenol may be the cause of the triglyceride elevation in the blood in rats. It may lead to inhibition of insulin release because free radicals kill pancreatic beta cells, and insulin deficiency lowers the activity of the enzyme lipoprotein lipase that hydrolyzes triglycerides to glycerol and fatty acids. The liver produces excess very low-density lipoprotein (VLDL) when insulin deficiency triggers the mechanism of lipolysis in fat tissue, releasing free fatty acids for energy use [Kaur et al., 2025]. Cholesterol gets deposited on the inner walls of the arteries, as a result of which it damages the lining cells of the arteries as well as other tissue cells. Elevated blood cholesterol and free radicals enhance the body's vulnerability to oxidation [Roy et al., 2023].

Elevated troponin T levels and the activity of LDH and CK-MB are sensitive indicators of growing myocardial injury. The amounts of these cellular enzymes in serum or plasma indicate changes in the cellular permeability and/or the functional integrity of the plasma membrane [Joseph et al., 2025]. The present study found that rats administered isoproterenol had significantly elevated blood levels of troponin T and both enzyme activities, indicating a change in the integrity of the cardiac membrane. The symptoms of these repercussions included the release of these enzymes into the circulation and necrosis of the heart's cells (Table 1). Increased oxidative stress is one recognised mechanism for cellular necrosis, including cardiac fibre necrosis. The increase in the aforementioned enzymes in the ISO-treated group may be due to the oxidative stress caused by lipid peroxidation, which breaks down the endoplasmic reticulum and most cell membranes, and the exposure to ISO, which raises free radical levels [Chen et al., 2025].

The resveratrol injection in the current study was able to decrease the elevated levels of these cardiac markers to normal, signifying that resveratrol is a cardioprotective and useful treatment. This finding revealed that resveratrol may be able to prevent isoproterenol-induced damage to the heart. This is likely due to increased oxygen radical scavenging activity and reduction of lipid peroxidation-mediated damage. From these results, resveratrol has the potential to protect the heart against oxidative stress and associated diseases.

The increase in CK-MB enzyme activity is because of structural changes in the myocardium during the development of ISO injection-induced ischaemic heart disease, leading to fibrosis of the ischaemic region. The changes in structure are associated with an increase in serum concentration of cardiac proteins like the CK-MB enzyme. These proteins are discharged from the cardiac fibres into the blood after dissolving the cardiac fibres, contractile proteins, and sarcoplasmic reticulum. These proteins are present in greater amounts when the membranes of the damaged cardiac cells get less permeable [Asaikumar et al., 2019].

Also, recent studies have demonstrated that the diagnosis of acute myocardial infarction and the forecast of the likelihood of future myocardial infarction rely more on the estimation of troponin T (cTnI), a contractile protein of low molecular weight that is not generally found in serum but is discharged once myocardial necrosis takes place [Damen et al., 2025].

According to our current study findings, the pre-treated group with resveratrol showed significantly reduced activity of these enzymes, which would have helped in preserving the heart cell membrane integrity. Anti-inflammatory and antioxidant activities of resveratrol prevent cardiovascular diseases like myocardial infarction and heart attack and death due to heart disease by safeguarding cardiac cell membrane from ISO-induced oxidative stress. This reduces the amount of enzymes in the blood by suppressing their release. Resveratrol also enhances cardiovascular health by reducing blood pressure, cholesterol, and blood clotting risk, as stated by [Peng et al., 2025].

Isoproterenol administration could lead to myocarditis, which is reflected in the release of multiple cytokines, including TNF-α, and increased reactive oxygen species (ROS). Isoproterenol-induced myocarditis has been reported to raise the ROS and pro-inflammatory cytokine levels significantly [Zhang et al., 2025]. The primary field of research on the potential therapeutic application of anti-inflammatory medications in myocarditis and related outcomes has been evidence of inflammatory processes in the pathogenesis of cardiomyopathy. Resveratrol has been reported to modulate cellular behavior in the case of inflammation since it acts as an antioxidant.

Resveratrol lowered TNF-α in isoproterenol-induced myocarditis in rats according to this study. Polyphenols have anti-inflammatory activity when oxidative stress occurs, according to a number of recent experimental studies. Resveratrol treatment has been found to lower the increase in the level of tumor necrosis factor alpha (TNF-alpha) in LPS-induced acute respiratory distress syndrome in rats [Chen et al., 2025]. In addition, resveratrol inhibited TNF-α gene expression [Bai et al., 2025]. These results suggest that resveratrol may be a potential nutritional supplement that is effective in lowering myocardial inflammation in situations where oxidative stress is beyond limit.

Conclusion

The results show that resveratrol considerably protects male rats' hearts against isoproterenol-induced deleterious effects. The effect of such was through increased cardiac enzymes and lipid parameters, decreased markers of oxidative stress and inflammation, and overall enhanced antioxidant activity. These findings are evidence that resveratrol is able to prevent or treat oxidative stress-induced cardiomyopathy by several mechanisms, including its anti-inflammatory, antioxidant, and anti-hyperlipidaemic actions. The findings recommend clinical and experimental research to determine the efficacy and mechanism of action of this compound on a wider scale.

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التأثير الوقائي للريسفيراترول على تلف عضلة القلب الناجم عن الأيزوبروترينول في ذكور الفئران

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الملخص

أجريت هدفت هذه الدراسة الى تقييم التأثير الوقائي للريسفيراترول ضد احتشاء عضلة القلب المحدث بالأيزوبروتيرينول في ذكور فئران . شملت الدراسة 20 فأرًا، تتراوح أعمارهم بين 3 و4 أشهر، ويزنون من 200 إلى 250 جرامًا، وقُسِّموا عشوائيًا إلى أربع مجموعات. تلقت المجموعة الأولى (المجموعة الضابطة) 1 مل من الماء المقطر. عوملت المجموعة الثانية (ريسفيراترول) 20 ملغ/كغ عن طريق الفم بجرعة 2 مل يوميًا. تم إعطاء المجموعة الثالثة (إيزوبروتيرينول) 100 ملغ/كغ عن طريق الحقن البريتوني (IP). المجموعة الرابعة عوملت (ريسفيراترول + إيزوبروتيرينول) ريسفيراترول عن طريق الفم (20 ملغ/كغ/يوم) لمدة 21 يومًا. بعد الريسفيراترول، تلقوا حقنة 100 ملغ/كغ من ISO عن طريق الحقن البريتوني في اليومين 20 و21 من علاج الريسفيراترول لمدة 21 يومًا. أظهرت النتائج أن الإيزوبروتيرينول تسبب في ارتفاع ملحوظ في مؤشرات الإجهاد التأكسدي (MDA)، والالتهاب (TNF-α)، والدهون الثلاثية، والكوليسترول، وإنزيمات القلب (CK-MB، cTnI، LDH)، وانخفاض إجمالي نشاط مضادات الأكسدة (T-AOC). في المقابل، أدى العلاج بالريسفيراترول إلى انخفاض ملحوظ في هذه المؤشرات، مما أدى إلى انخفاض مستويات المؤشرات المرتفعة وعودة مضادات الأكسدة إلى مستوياتها الطبيعية، مما يشير إلى تأثير الريسفيراترول في منع الضرر التأكسدي والالتهابي. أظهرت المجموعة التي عولجت بكلا الدوائين قيمًا متوسطة، مما يشير بقوة إلى التأثير الوقائي للريسفيراترول ضد السمية الناجمة عن الإيزوبروتيرينول. وختامًا، تشير النتائج الحالية إلى أن جزيء الريسفيراترول المرشح للوقاية من اعتلال عضلة القلب وتحسين وظائف القلب في حالات الإجهاد التأكسدي والالتهابي، يعود إلى تأثيراته المضادة لفرط شحميات الدم، ومضادات الأكسدة، والالتهابات.

الكلمات المفتاحية: الريسفيراترول؛ الإيزوبروترينول؛ الإجهاد التأكسدي؛ الالتهاب؛ إنزيمات القلب.