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CARDIOPROTECTIVE ACTIVITY ON ORYZANOL IN INSULIN RESISTANCE IN RATS

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Abstract

Cardiovascular diseases (CVDs) are a leading cause of morbidity and mortality worldwide, with insulin resistance (IR) being a major metabolic risk factor. This study investigated the cardioprotective potential of γ-oryzanol in dexamethasone-induced insulin-resistant rats subjected to isoproterenol-induced myocardial toxicity. Forty-two male Wistar rats were divided into seven groups, including normal control, insulin-resistant control, cardiotoxic control, combined insulin resistance and cardiotoxicity, oryzanol alone, oryzanol-treated, and standard drug (propranolol) groups. Serum biochemical parameters, lipid profile, cardiac injury markers (SGOT, SGPT, LDH), and myocardial oxidative stress markers (TBARS, GSH, SOD, CAT) were assessed. Histopathological analysis of heart tissue was performed to evaluate structural alterations. Isoproterenol administration significantly increased TBARS, SGOT, SGPT, LDL, VLDL, and triglyceride levels while reducing GSH, SOD, and CAT, indicating oxidative stress and cardiotoxicity. Treatment with γ-oryzanol significantly restored antioxidant enzyme levels, reduced lipid peroxidation, improved serum lipid profile, and normalized cardiac biomarkers. Histopathology revealed well-preserved myocardial architecture in oryzanol-treated rats compared to isoproterenol-treated controls, confirming its cardioprotective effect. These findings suggest that γ-oryzanol exerts significant cardioprotective activity in insulin-resistant rats through antioxidant, lipid-lowering, and myocardial protective mechanisms. Thus, γ-oryzanol may represent a potential nutritional therapeutic agent for preventing or mitigating cardiovascular complications associated with metabolic disorders.

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Introduction

Pharmacology, the science that explores interactions between drugs and biological systems, forms a critical foundation for modern medicine, pharmacy, nursing, dentistry, and veterinary science. Its scope spans from elucidating molecular mechanisms of drug action to evaluating the safety of chemical agents and developing therapies for major human diseases. Despite significant progress in drug discovery and mechanistic understanding, the complexity of biological systems continues to present new challenges that demand innovative research and therapeutic strategies. Among the most pressing global health concerns are cardiovascular diseases (CVDs), which remain the leading cause of morbidity and mortality worldwide [1-3].

Cardiovascular diseases encompass a broad spectrum of disorders affecting the heart and vasculature, including coronary artery disease, myocardial infarction, arrhythmias, hypertensive heart disease, heart failure, congenital defects, and inflammatory heart conditions [4]. According to international health statistics, CVDs account for nearly one-third of all global deaths, surpassing the burden of infectious, nutritional, maternal, and perinatal conditions combined. The progression of these disorders is often insidious, with early symptoms ranging from fatigue and dizziness to chest pain, dyspnea, and edema, ultimately leading to life-threatening complications such as myocardial infarction or stroke. Major risk factors include smoking, hypertension, hyperlipidemia, obesity, diabetes, family history, physical inactivity, and stress, many of which are modifiable through lifestyle and therapeutic interventions [5-8].

Among the metabolic abnormalities that heighten CVD risk, **insulin resistance (IR)** plays a central role. IR, characterized by impaired cellular responsiveness to insulin, leads to compensatory hyperinsulinemia, dyslipidemia, endothelial dysfunction, and chronic inflammation. These metabolic derangements accelerate atherosclerosis, promote oxidative stress, and disrupt vascular homeostasis [9]. Tissue-specific insulin resistance in adipose tissue, liver, muscle, and vascular endothelium contributes to enhanced free fatty acid flux, increased hepatic very-low-density lipoprotein (VLDL) synthesis, and the development of the atherogenic lipid triad-hypertriglyceridemia, low HDL cholesterol, and small dense

LDL particles. Consequently, insulin resistance is a defining feature of the metabolic syndrome and a major predictor of premature cardiovascular events [10-12].

Growing evidence suggests that **nutritional therapy** plays a critical role in mitigating cardiovascular risk, particularly in individuals with metabolic disturbances. Diets rich in fruits, vegetables, nuts, whole grains, and functional foods have been associated with reduced incidence of hypertension, diabetes, obesity, and CVD [13-14]. Bioactive compounds such as polyphenols, carotenoids, omega-3 fatty acids, flavonoids, arginine, vitamins, and plant sterols exert diverse cardioprotective effects through antioxidant, anti-inflammatory, lipid-lowering, vasodilatory, and anti-atherogenic mechanisms [15-16]. Among these, **γ-oryzanol**, a mixture of ferulic acid esters predominantly found in rice bran oil, has gained attention for its potent antioxidant properties, ability to modulate lipid metabolism, and potential to reduce serum cholesterol and inhibit early atherosclerotic changes. Its stability, synergism with tocopherols, and multifunctional physiological effects make γ-oryzanol a promising candidate for functional food formulations aimed at cardiovascular health [17].

Given the rising global prevalence of CVD and metabolic disorders, there is an urgent need to explore safe, effective, and accessible nutritional strategies that complement existing pharmacological therapies. This manuscript focuses on the potential cardioprotective role of γ-oryzanol within the broader context of nutrition-mediated modulation of cardiovascular risk, particularly in relation to insulin resistance–associated metabolic disturbances [18].

Aim and Objectives

Aim

The present study aims to investigate the cardioprotective potential of γ-oryzanol against isoproterenol-induced cardiotoxicity in dexamethasone-induced insulin-resistant rats**,** with emphasis on its antioxidant, anti-hyperlipidemic, and myocardial protective actions.

Objectives

1. **To induce insulin resistance** in rats using dexamethasone and assess the impact of γ-oryzanol on metabolic alterations associated with insulin resistance.
2. **To evaluate the cardioprotective effect of γ-oryzanol** in isoproterenol-induced cardiotoxicity in insulin-resistant rats.
3. **To assess myocardial protection** by evaluating the following parameters:
    - **Restoration of serum biochemical markers** associated with cardiac injury and metabolic dysfunction.
    - **Reduction of oxidative stress**, assessed by TBARS and related lipid peroxidation biomarkers.
    - **Enhancement of endogenous antioxidant defense systems**, including enzymatic and non-enzymatic antioxidants.
    - **Preservation of myocardial structure**, confirmed through histopathological examination of cardiac tissue.

Materials and Methods

1 Drugs and Chemicals

The major drugs and analytical-grade chemicals used in the study are listed below:

- **Oryzanol**-Sigma Aldrich Life Sciences, Bangalore
- **Dexamethasone**-Kaneka Corporation
- **Isoproterenol**-Glenmark Generics S.A
- **Heparin sodium**-Biological E. Ltd., Hyderabad
- **Sodium lauryl sulfate, Trichloroacetic acid, Nitro blue tetrazolium, Pyridine, n-Butanol, Sodium chloride, Triton-X** – Molychem, Mumbai
- **Acetic acid**-Thermofisher Scientific Pvt. Ltd., Mumbai
- **Thiobarbituric acid** – HiMedia Labs, Mumbai
- **Phosphate buffers, DTNB, Sodium pyrophosphate, Phenazine methosulfate, NADH**-Sigma Aldrich Life Sciences, Bangalore
- **Other routine analytical reagents** were obtained from certified chemical suppliers.

2. Instruments

- **UV-Visible Spectrophotometer** (Shimadzu UV-1800)
- **Research Centrifuge** (Remi Instruments Ltd., Mumbai)
- **Tissue Homogenizer** (Rajendra Electronics, Remi Instruments Division)
- **Incubator** (Remi Instruments, Mumbai)

3. Experimental Animals

Forty-two male Wistar albino rats (180–200 g, 3 months old) were obtained from the Institutional Animal House. Animals were housed in polypropylene cages under controlled temperature (23 ± 2 °C), humidity (50 ± 5%), and a 12-h light/dark cycle. Standard pellet diet and water were provided *ad libitum*. Rats were acclimatized for 7 days prior to experimentation.

All experimental procedures were approved by the Institutional Animal Ethics Committee (CPCSEA Reg. No: 1220/a/08/CPCSEA).

4. Experimental Design

Forty-two rats were divided into **seven groups (n = 6)** and treated for **12 days**:

- **G1 – Normal Control:** Distilled water
- **G2 – Insulin-resistant Control:** Dexamethasone (10 mg/kg, i.p.) for 10 days
- **G3 – Cardiotoxic Control:** Isoproterenol (85 mg/kg, i.p.) for 2 consecutive days
- **G4 – Insulin resistance + Cardiotoxicity:** Dexamethasone + Isoproterenol
- **G5 – Oryzanol alone:** Oryzanol (100 mg/kg, p.o.)
- **G6 – Oryzanol treated group:** Dexamethasone + Isoproterenol + Oryzanol (100 mg/kg, p.o.)
- **G7 – Standard drug:** Dexamethasone + Isoproterenol + Propranolol (10 mg/kg, i.p.)

Animals were sacrificed on day 13 under light ether anesthesia. Blood was collected for serum biochemical analysis. Hearts were isolated, rinsed with ice-cold saline, and divided for biochemical assays and histopathology.

5. Biochemical Estimations

Serum Cardiac Biomarkers

- Lactate Dehydrogenase (LDH)
- Aspartate Aminotransferase (AST)
- Alanine Aminotransferase (ALT)

(Estimated by Reitman and Frankel colorimetric method.)

Metabolic Parameters

- Blood glucose (GOD-POD method)
- Total cholesterol (CHOD-POD method)
- Triglycerides (GPO-Trinder method)
- HDL-cholesterol (PEG-precipitation method)
- LDL-cholesterol (calculated)

6. Antioxidant Parameters in Heart Tissue

Heart tissue (10% homogenate in phosphate buffer, pH 7.4) was used to estimate:

- **Superoxide Dismutase (SOD)** – Kakkar et al. method
- **Catalase (CAT)** – Aebi method
- **Reduced Glutathione (GSH)** – Ellman's method
- **Lipid Peroxidation (TBARS/MDA)** – Ohkawa et al. method

7. Histopathology

Heart tissues were fixed in 10% buffered formalin, processed, embedded in paraffin, sectioned at 5 µm, and stained with hematoxylin and eosin (H&E). Cardiac morphology was examined under a light microscope for structural alterations [19-20].

8. Statistical Analysis

All data were expressed as mean ± SEM. Statistical analysis was performed using one-way ANOVA followed by Dunnett's multiple comparison test using GraphPad Prism version 5.01. Differences were considered statistically significant at $p < 0.05$.

Results

Effect of Oryzanol on Serum Biochemical Parameters

Serum levels of blood glucose, total cholesterol, HDL, LDL, VLDL, triglycerides, SGOT, and SGPT were evaluated in all experimental groups. Throughout the study, no mortality was observed in any group.

Serum Blood Glucose

A significant decrease ($p < 0.001$) in blood glucose levels was observed in Group VI (Oryzanol + Dexamethasone + Isoproterenol) and Group VII (Propranolol standard group) when compared with the normal, dexamethasone, isoproterenol, and combined (Group IV) disease controls. This indicates that oryzanol effectively improved glucose metabolism in insulin-resistant and cardiotoxic conditions.

Table 01: Effect of Oryzanol on Blood Glucose, Total Cholesterol, HDL, LDL, VLDL, Triglycerides, SGOT, and SGPT

Treatment group	Glucose (mg/dL)	TCH (mg/d L)	TG (mg/dL)	HDL (mg/dL)	LDL (mg/dL)	VLDL (mg/dL)	SGOT (mg/dL)	SGPT (mg/dL)
Group I	82.00±8.567	53.17 ±1.01 4	147.3±2. 71	6.50± 0.76	12.67±1. 40	32.50± 0.88	54.00±2. 309[a]	46.88±1.4 7
GroupII	81.67±7.365	49.67 ±2.77	215±3.91 b	3.0±0. 85	14.67±0. 61	45.67± 1.05	139.2±1. 04[b]	106.5±1.3 3[b]
GroupIII	85.17±0.833	51.67 ±3.89	173.8±4. 37[b]	5.16± 0.6	22.67±1. 62	39.00± 2.80	107.3±1. 54[b]	175.8±1.2 7[b]
GroupIV	99.67±3.48	63.17 ±1.30 2	237±2.49 b	6.66± 0.55	25.17±1. 16[b]	50.83± 1.79[b]	112.8±1. 95[b]	162.5±2.4 0[b]
GroupV	84.00±1.065	55.83 ±2.44	186.3±0. 88a	6.00± 0.73	14.5±0.1 6	38.33± 1.85	40.00±8. 12	54.83±1.0 14
Group VI	53.17±1.108 a	58.00 ±2.29	169.2±2. 48[a]	8.50± 0.76	15.17±1. 108[a]	44.33± 2.97	57.67±1. 90[a]	59.83±2.3 86[a]
Group VII	36.33±1.256 a	59.67 ±1.58	155.3±1. 02[a]	13.33 ±0.88	15.33±1. 52[a]	40.33± 1.07	63.83±2. 253[a]	71.17±2.2 7[a]

All values are expressed as mean ± SEM. Statistical analysis was performed using one-way ANOVA followed by Tukey's multiple comparison test. *a*p < 0.001 vs Group IV; *b*p < 0.001 vs Group I.

Effect of Oryzanol on Serum Biochemical Parameters

Blood glucose, total cholesterol, HDL, LDL, VLDL, triglycerides, SGOT, and SGPT levels were estimated in serum. The results are presented in Table 5.1 and the corresponding graphs.

Serum Blood Glucose

A significant decrease (p < 0.001) in blood glucose levels was observed in Groups VI and VII when compared with Groups I, II, III, and IV.

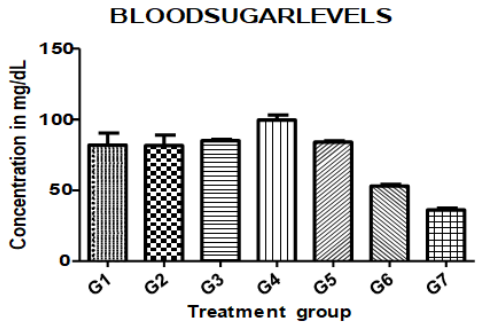

Figure o1.Effect of Oryzanolon blood glucose levels

Serum Level of Total Cholesterol

There was no significant difference in total cholesterol levels among the experimental groups.

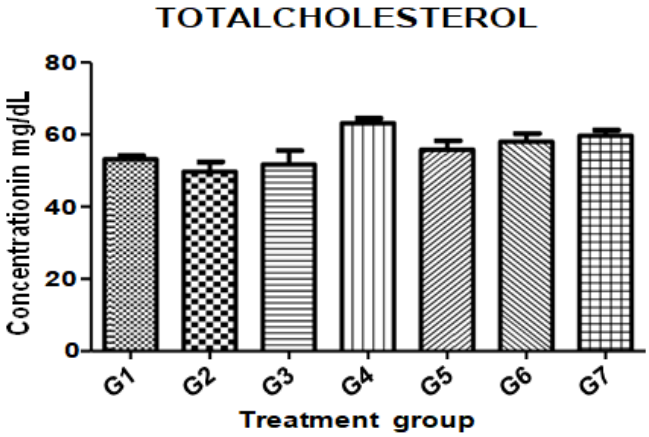

Figure 02: Effect of oryzanolon total cholesterol.

Serum Level of Triglycerides

There was a significant increase (p < 0.001) in triglyceride levels in Groups II, III, and IV when compared with Group I. A significant decrease (p < 0.001) in triglyceride levels was observed in Groups V, VI, and VII when compared with Groups II and III.

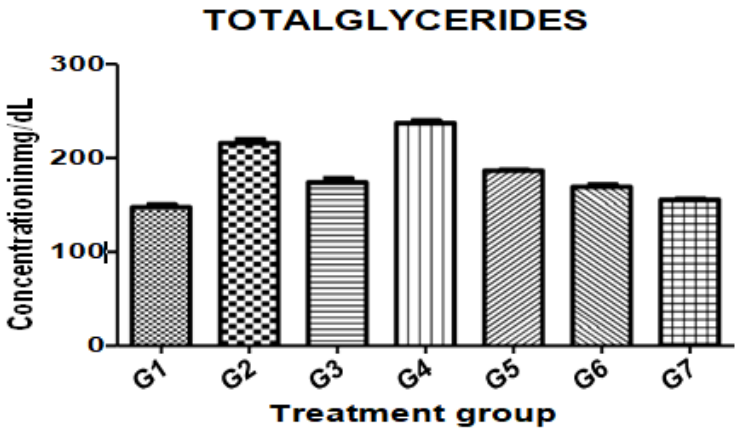

Figure 03: Effect of oryzanolon Totalglycerides levels

Serum Level of LDL

There was a significant increase (p < 0.001) in LDL levels in Group IV compared to Group I. A significant decrease (p < 0.001) in LDL levels was observed in Groups VI and VII compared to Group IV.

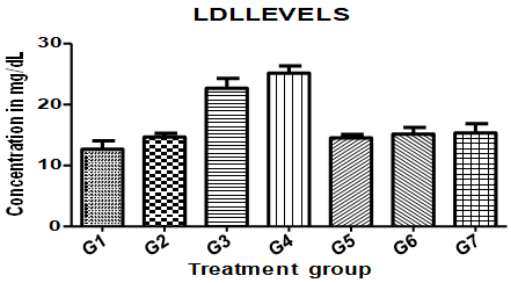

Figure 04.Effect of oryzanol onLDL levels

Serum Level of HDL

There was no significant difference in serum HDL levels among the groups.

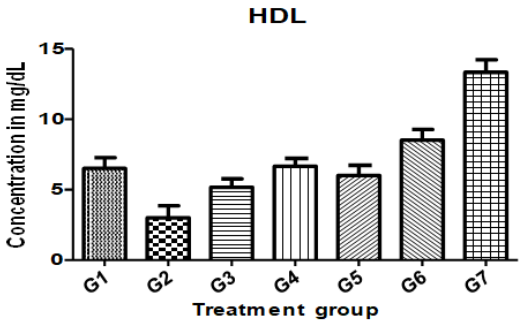

Figure 05.Effectof oryzanolon HDL levels

Serum Level of VLDL

There was a significant ($p<0.001$) increase in serum VLDL levels in Group 4 compared to Group 2.

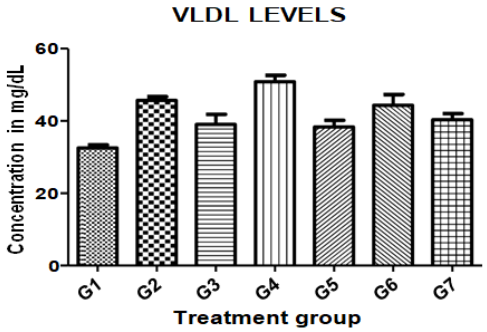

Figure 06.Effect of oryzanolonVLDL levels

Serum Levels of SGOT

There was a significant increase ($p < 0.001$) in SGOT levels in groups 2, 3, and 4 compared to group 1. Conversely, there was a significant decrease ($p < 0.001$) in SGOT levels in groups 6 and 7 compared to groups 2, 3, and 4.

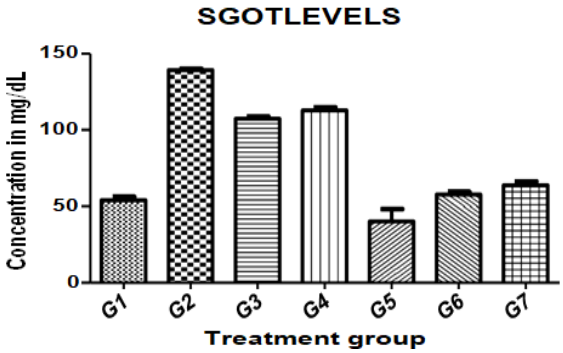

Figure 07 Effect of oryzanol on SGOT levels

Serum Levels of SGPT

There was a significant increase ($p < 0.001$) in SGPT levels in groups 2, 3, and 4 compared to group 1. Conversely, there was a significant decrease ($p < 0.001$) in SGPT levels in groups 6 and 7 compared to groups 2, 3, and 4.

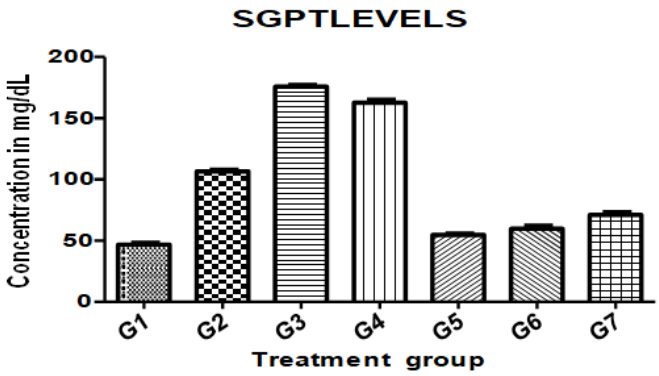

Figure: 08 Effect of oryzanol on SGPT levels

Effect of Oryzanol on TBARS, GSH, SOD, and CAT in Myocardial Tissue

Thiobarbituric acid reactive substances (TBARS), reduced glutathione (GSH), superoxide dismutase (SOD), and catalase (CAT) levels were estimated in myocardial tissue homogenates. The results are presented in Table 02, and the levels of TBARS, GSH, SOD, and CAT are also graphically illustrated.

Table 02: Oxidative stress and antioxidant parameters across experimental groups.

Treatment Group	TBARS (nmol/g wet wt)	GSH (µg/g wet wt)	SOD (I.U/mg protein)	Catalase (I.U/mg protein)
Group I	59.78±0.21	5.5±0.45	63.5±0.22	857.9±2.08
Group II	109.9±0.25[a]	7.8±0.02[a]	36±0.89[a]	515±36.87[a]
Group III	109.6±2.36[a]	4.8±0.07	25.78±0.15[a]	390.9±34.88[a]
Group IV	116.4±4.99[a]	5.8±0.07	24.15±0.57[a]	450.1±30.0[a]
GroupV	87.38±1.42	5.8±0.08	55.16±0.57	862±0.0
GroupVI	87.73±3.34[b]	5.7±0.02	53.34±1.69[b]	814.1±4.98[b]
GroupVII	71.27±2.27[b]	11.9±0.22[b]	56.81±0.14[b]	826.8±20.06[b]

All values are expressed as mean ± SEM. Statistical analysis was performed using one-way ANOVA followed by Dunnett's test.
a $P < 0.0001$ vs Group I; **b** $P < 0.0001$ vs Group IV; **c** $P < 0.001$ vs Group IV.

Group descriptions:

- **Group I (Normal control):** Rats received distilled water for 10 days.
- **Group II:** Rats received distilled water for 10 days and were treated with dexamethasone (10 mg/kg, i.p.).
- **Group III:** Rats received distilled water for 10 days and were treated with isoproterenol (85 mg/kg, two consecutive days, i.p.).
- **Group IV:** Rats received distilled water and were treated with dexamethasone (10 mg/kg, i.p.) plus isoproterenol (85 mg/kg, two consecutive days, i.p.).
- **Group V:** Rats received distilled water and oryzanol (100 mg/kg).
- **Group VI:** Rats received dexamethasone (10 mg/kg, i.p.) and isoproterenol (85 mg/kg, i.p.) along with oryzanol (100 mg/kg).
- **Group VII:** Rats received dexamethasone (10 mg/kg, i.p.) and isoproterenol (85 mg/kg, i.p.) along with propranolol (10 mg/kg, i.p.).

Effect on TBARS

There was a significant increase ($P < 0.001$) in TBARS levels in Groups II, III, and IV compared with Group I, indicating enhanced lipid peroxidation. In contrast, Groups V, VI, and VII showed a significant decrease ($P < 0.0001$) in TBARS levels compared with Groups II and IV, demonstrating attenuation of oxidative stress

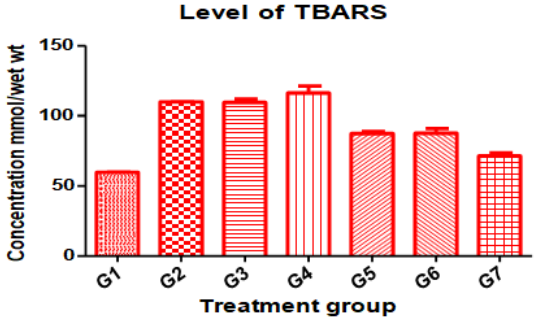

Figure 09: Effect of oryzanol on TBARS levels

Effect of Reduced Glutathione (GSH)

There was a significant increase ($P < 0.001$) in GSH levels in Group II compared with Group I. In addition, Group VII showed a further significant increase ($P < 0.0001$) in GSH levels when compared with Group II.

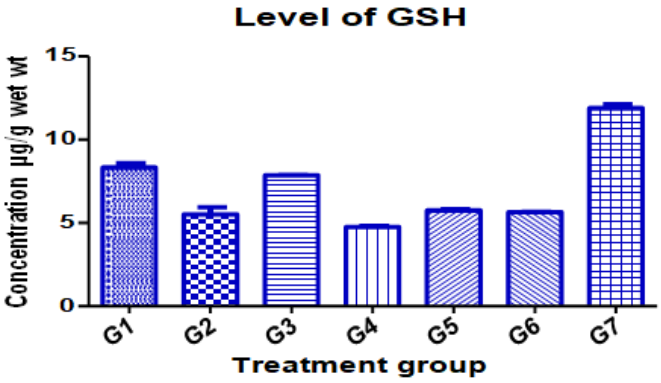

Figure 09: Effect of Reduced Glutathione levels

Effect of Oryzanol on Superoxide Dismutase (SOD)

There was a significant decrease ($P < 0.001$) in SOD levels in Groups II, III, and IV compared with Group I. A significant increase in SOD levels was observed in Groups VI and VII when compared with Groups III and IV, indicating the restorative effect of oryzanol.

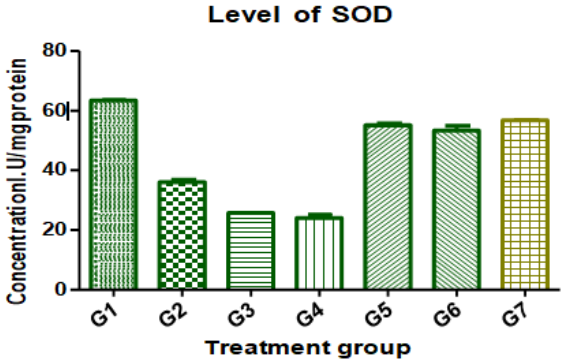

Figure 10: Effect of oryzanolon SOD levels

Effect of Oryzanol on Catalase (CAT)

There was a significant decrease ($P < 0.001$) in catalase levels in Groups II, III, and IV compared with Group I. A significant increase ($P < 0.001$) in catalase levels was observed in Groups VI and VII when compared with Groups II, III, and IV, indicating the protective effect of oryzanol.

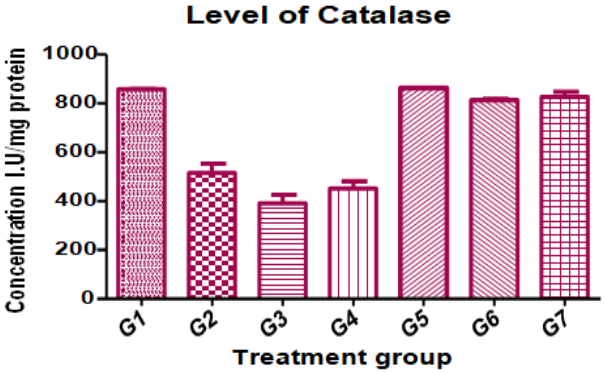

Figure 11: Effect of oryzanol on CAT levels

Discussion

The present study was aimed at assessing the cardioprotective effect of oryzanol in insulin-resistant rats. Myocardial ischemia, a major cause of morbidity and mortality, occurs when there is an imbalance between myocardial oxygen demand and supply. Prolonged ischemia leads to angina pectoris and eventually myocardial cell death due to insufficient blood flow [21]. Oxidative stress plays a key role in cardiotoxicity. It is characterized by an increase in TBARS (thiobarbituric acid-reactive substances) and a decrease in endogenous antioxidants such as superoxide dismutase (SOD), catalase (CAT), and reduced glutathione (GSH). Excessive formation of oxygen free radicals overwhelms the natural antioxidant defenses, leading to tissue injury. This pattern was evident in the toxic (isoproterenol-treated) group, where oxidative stress and cardiotoxicity were successfully induced [22-23].

In this study, isoproterenol administration significantly increased lipid peroxidation, as indicated by elevated TBARS levels. TBARS is a well-recognized marker of oxidative damage resulting from ROS-mediated attack on myocardial polyunsaturated fatty acids. The reduced TBARS levels in the drug-treated groups suggest that oryzanol effectively inhibited ROS-induced lipid peroxidation and mitigated oxidative stress [24].

Endogenous antioxidants (GSH, SOD, and CAT) protect myocardial tissue from free radical–induced damage. A marked depletion of these enzymes was observed in the isoproterenol-treated group, reflecting a compromised antioxidant defense system. These findings are consistent with earlier reports on isoproterenol-induced cardiotoxicity [25].

In contrast, rats treated with oryzanol showed a significant restoration of GSH, SOD, and CAT levels toward normal, indicating the antioxidant and cardioprotective effects of oryzanol. Additionally, lipid profile analysis demonstrated a decrease in TGL, TCH, LDL, and VLDL levels with a corresponding increase in HDL, suggesting improved lipid metabolism and inhibition of cholesterol biosynthesis [26].

Histopathological studies further supported the biochemical findings. Isoproterenol-treated hearts showed myocardial fiber damage and inflammatory cell infiltration. In contrast, oryzanol-treated groups displayed well-preserved myocardial architecture with minimal or no inflammation, confirming the protective effect of oryzanol against isoproterenol-induced cardiotoxicity [27].

Conclusion

In conclusion, the present research demonstrates the protective effect of oryzanol against myocardial toxicity. The findings support the hypothesis that oryzanol exhibits significant cardioprotective activity in insulin-resistant rats, thereby justifying its potential use in the management of heart diseases such as heart failure associated with diabetic conditions. The protective role of oryzanol may be attributed to its ability to reduce oxidative stress, enhance endogenous antioxidant activity, restore cardiac marker levels, and improve the lipid profile.

Acknowledgement

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Conflicts of Interest

The authors declare no conflicts of interest.

Author Contribution

Both contribute equally

Financial Support

None

Ethical Considerations

Ethical approved taken from the Annamacharya College of Pharmacy, Rajampete, Kadapa.

Informed Consent

Not Applicable

References

1. Astra LI, Hammond R, Tarakji K, Stephenson LW. Doxorubicin-induced canine CHF: advantages and disadvantages. J Card Surg. 2003;18:301–6.
2. Bardi E, Bobok I, Olah AV, Kappelmayer J, Kiss C. Anthracycline antibiotics induce acute renal tubular toxicity in children with cancer. Pathol Oncol Res. 2007;13:249–53.
3. Mayfield J. Diagnosis and classification of diabetes mellitus: new criteria. Am Fam Physician. 1998;46:46–8.
4. Chronic hepatitis C is associated with peripheral rather than hepatic insulin resistance. Gastroenterology. 2010;138(3):932–41.
5. Hypercortisolism and insulin resistance: comparative effects of prednisolone, hydrocortisone, and dexamethasone on insulin binding of human erythrocytes. J Clin Endocrinol Metab. 1982;55(5):910–5.
6. Laakso M, Kuusisto J. Insulin resistance and hyperglycemia in cardiovascular disease development. Nat Rev Endocrinol. 2014;10:293–302.
7. Kahn BB, Flier JS. Obesity and insulin resistance. J Clin Invest. 2000;106:473–81.
8. Gavrilova O, et al. Surgical implantation of adipose tissue reverses diabetes in lipoatrophic mice. J Clin Invest. 2000;105:271–8.
9. McFarlane SI, et al. Insulin resistance and cardiovascular disease. J Clin Endocrinol Metab. 2001;86(2).
10. Howard G, et al. Insulin sensitivity and atherosclerosis. Circulation. 1996;93:1809–17.
11. Bazzano LA, Serdula MK, Liu S. Dietary intake of fruits and vegetables and risk of cardiovascular disease. Curr Atheroscler Rep. 2003;5:492–9.
12. Houston MC. Nutraceuticals, vitamins, antioxidants, and minerals in the prevention and treatment of hypertension. Prog Cardiovasc Dis. 2005;47:396–449.
13. Britton G. Structure and properties of carotenoids in relation to function. FASEB J. 1995;9:1551–8.
14. Di Mascio P, Kaiser S, Sies H. Lycopene as the most effective biological carotenoid singlet oxygen quencher. Arch Biochem Biophys. 1989;274:532–8.
15. Arab L, Steck S. Lycopene and cardiovascular disease. Am J Clin Nutr. 2000;71:1691S–5S.
16. Kohlmeier L, Hastings SB. Epidemiologic evidence of a role of carotenoids in cardiovascular disease prevention. Am J Clin Nutr. 1995;62:1370S–6S.
17. Rao AV, Agarwal S. Role of antioxidant lycopene in cancer and heart disease. J Am Coll Nutr. 2000;19:563–9.
18. Agarwal S, Rao AV. Tomato lycopene and its role in human health and chronic diseases. CMAJ. 2000;163:739–44.
19. Dugas TR, Morel DW, Harrison EH. Impact of LDL carotenoid and alpha-tocopherol content on LDL oxidation by endothelial cells in culture. J Lipid Res. 1998;39:999–1007.
20. Fuhrman B, Elis A, Aviram M. Hypercholesterolemic effect of lycopene and β-carotene is related to suppression of cholesterol synthesis and augmentation of LDL receptor

activity in macrophage. Biochem Biophys Res Commun. 1997;233:658–62.
21. Manach C, Scalbert A, Morand C, Rémésy C, Jimenez L. Polyphenols: food sources and bioavailability. Am J Clin Nutr. 2004;79:727–47.
22. Scalbert A, Williamson G. Dietary intake and bioavailability of polyphenols. J Nutr. 2000;130:2073S–85S.
23. Gutteridge JM, Halliwell B. Free radicals and antioxidants in the year 2000: a historical look to the future. Ann NY Acad Sci. 2000;899:136–47.
24. Scalbert A, Manach C, Morand C, Remesy C, Jimenez L. Dietary polyphenols and the prevention of diseases. Crit Rev Food Sci Nutr. 2005;45:287–306.
25. WHO/FAO. Diet, nutrition, and the prevention of chronic diseases. Geneva: World Health Organization; 2003.
26. Vita JA. Polyphenols and cardiovascular disease: effects on endothelial and platelet function. Am J Clin Nutr. 2005;81:292S–7S.
27. Keen CL, Holt RR, Oteiza PI, Fraga CG, Schmitz HH. Cocoa antioxidants and cardiovascular health. Am J Clin Nutr. 2005;81:298S–303S.