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Hypolipidemic, Antioxidant and Anti-atherosclerogenic Effect of Catalpol in Hypercholesterolemic Induced Rats

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ABSTRACT

Background: Atherosclerosis, oxidative stress and hyperlipidemia are major risk factors in the pathogenesis of cardiovascular diseases. Cardiovascular diseases are public health problem all over world and constitute more than 17 million deaths in a year. Catalpol is well-known is an iridoid glucoside found in the roots of Rehmanniaglutinosa and known to have several protective effect against diabetic encephalopathy, neurotoxicity and hyperglycemia. The present study was aimed to analyze the hypolipidemic, anti-atherosclerogenic and antioxidant effect of catalpol in hyperlipidemic induced rats.

Methods: Rats were grouped into normal control, hyperlipidemic, hyperlipidemic + 10 mg/kg of catalpol, hyperlipidemic + 20 mg/kg of catalpol and hyperlipidemic + 10 mg/kg of simvastatin. Treatment was administered orally for 45 consecutive days.

Result: Hyperlipidemic rats treated with catalpol and simvastatin significantly reduced excessive body weight gain. Lipid peroxidation was reduced 36.4% and 115.2% at 10 and 20 mg/kg of catalpol. Hyperlipidemic rats treated with catalpol and simvastatin significantly improved the catalase, glutathione peroxidase (Gpx), superoxide dismutase (SOD) and reduced glutathione (GSH) in the serum to the near normal range, whereas HMG-CoA reductase, total cholesterol, liver enzymes in the liver tissues were reduced significantly. Furthermore, catalpol treatment reduced the serum level triglycerides, total cholesterol, low-density lipoprotein (LDL) and very low-density lipoprotein (VLDL) and increased the high-density lipoprotein (HDL). Taking all these data together, catalpol supplementation appears to function as an anti-hyperlipidemic agent in Triton WR 1339-induced hyperlipidemic rats.

Key words: Anti-oxidant, Catalpol, Hyperlipidemia, Lipoproteins, Lipid peroxidation.

INTRODUCTION

Atherosclerosis, oxidative stress and hyperlipidemia are major risk factors in the pathogenesis of cardiovascular diseases (Fidele *et al.,* 2017; Men *et al.,* 2024; Devi *et al.,* 2023). A cardiovascular disease is public health problem all over world and constitutes more than 17 million deaths in a year (Roth *et al.,* 2020). Researchers have reported that the diabetes, obesity, hypercholesterolemia, sedentarity and high blood pressure are directly associated with cardiovascular diseases (Powell-Wiley *et al.,* 2021; Wang *et al.,* 2024; Khalid *et al.,* 2019). Researchers have reported that the reduced level of the cholesterol high density lipoprotein (HDL-c) and increased triglycerides, total cholesterol and cholesterol of the low density lipoprotein (LDL-c) are associated with dyslipidemia (Hermans and Valensi, 2018; Bao *et al.,* 2018). Higher level of total cholesterol and of plasma LDL-c plays a vital role in the development of atherosclerosis (Lu *et al.,* 2022; Luo *et al.,* 2024). Several researchers have well reported that the atherosclerosis and renal failure are due to hypercholesterolemia (Shrestha *et al.,* 2021; Ramalingam *et al.,* 2024). Researchers have reported that the reduction of magnitude of cardiovascular diseases is directly associated with reduction of LDL-c (Feng *et al.,* 2023; Zhao *et al.,* 2021).

Catalpol is well-known is an iridoid glucoside found in the roots of *Rehmanniaglutinosa* (Bhattamisra *et al.,* 2019). Several researchers have reported the protective effect against diabetic encephalopathy, neurotoxicity and hyperglycemia (Fu *et al.,* 2023). Anti-inflammatory and anti-oxidative effects of catalpol have been reported in hypercholesterolemic rabbits (Liu *et al.,* 2023). Earlier anti-atherosclerotic effect of catalpol in diabetic rabbits (Liu *et al.,* 2016) was reported. However, there is no direct investigation on anti-atherosclerogenic effect of catalpol in diet induced hypercholesterolemic rats. As discussed above, there is a significant gap in the current literature on eath mortality ratio that exist for catalpol's antiatherosclerosis properties for diet induced hypercholesterolemic rat models and is associated with their relevant literature. About its other models, not much has been investigated in detail, but we do understand its preventive properties. This study

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attempts to close the gap by establishing and examining its hypolipidemic and antioxidant activities alongside antiatherosclerosis activities.

MATERIALS AND METHODS

Rats

Male albino rats (190-210 g) were obtained from the animal house of Qinghai Province Cardiovascular and Cerebrovascular Disease Specialist Hospital, Qinghai, China. They were kept in polycarbonate cages under a 12-h light/dark cycle with standard atmospheric conditions. Rats were allowed free access to water and food. The experiments followed the institutional guidelines for the care and use of rats.

Experimental induction of hyperlipidemia

Experimental hyperlipidemia was induced according to previously reported method (Sikarwar and Patil, 2012). Briefly, triton WR 1339 (200 mg/kg) non-ionic surfactant was prepared in normal saline and administered intraperitoneally to over-night fasted rats to induce hyperlipidemia.

Experimental groups

Thirty male rats were grouped into normal control (group I), hyperlipidemic (control; group II), hyperlipidemic + 10 mg/kg of catalpol (group III), hyperlipidemic + 20 mg/kg of catalpol (group IV) and hyperlipidemic + 10 mg/kg of simvastatin (group V). The treatment was administered orally for 45 consecutive days. Rats were carefully observed daily for mortality and clinical symptoms. At the end of 45 days, rats were euthanized following standard ethical guidelines using isoflurane anesthesia. Euthanasia was performed by placing the rats in a sealed chamber filled with 4-5% isoflurane vapour until unconsciousness was achieved, followed by cervical dislocation to ensure humane termination. Blood and liver tissues were collected immediately for biochemical investigations.

Determination of body weight

Body weight was measured at baseline and subsequently recorded at 15-day intervals during the 45-day treatment period. The changes in body weight served as an indicator of the metabolic and physiological impact of the treatments. This methodology ensured a systematic evaluation of the hypolipidemic, antioxidant and anti-atherosclerogenic effects of catalpol in hyperlipidemic rats.

Determination of anti-oxidant markers

Determination of superoxide dismutase (SOD) activity was carried out by the addition of serum (0.1 ml), nitro blue tetrazolium (0.3 ml), phosphate buffer (1.2 ml) and NADH (0.2 ml). Reactant product was measured at 560 nm using formula:

$$\text{SOD activity (\%)} = \frac{\text{Absorbance of control - Absorbance of sample}}{\text{Absorbance of control}} \times 100$$

Where,

Control = Represents the reaction without SOD.

Determination of catalase activity was carried out by the addition of 500 µl of serum, 500 µl of TiOSO4, 500 µl of phosphate buffer and 500 µl of water in the reaction tube. The reactant product was measured at 420 nm using formula:

$$\text{Enzyme activity (Units/L)} = \frac{\Delta\text{Abs} \times \text{Total assay volume}}{\Delta t \times \varepsilon \times l \times \text{Enzyme sample volume}}$$

Where,

Δt= Time of incubation (min).

ΔAbs= Change in absorbance.

ε = Extinction coefficient of substrates in units of M^{-1} cm^{-1}).

I = Cuvette diameter (1 cm).

Reduced glutathione (GSH) level was measured according to Ellman's reaction. The reactant product was determined at 412 nm (Khan *et al.,* 2005). Glutathione peroxidase (Gpx) activity was measured at 340 nm using formula:

$$C/1000 = (OD2 - OD1)/13{,}600 \times E1 \times 5/2 \times [(C: \text{mmol/ glutathione (mg/dl)}]$$

OD1 = First absorbance measured at 412 nm.

OD2 = Second absorbance measured after adding Ellman's reagent.

Determination of lipid peroxidation

Lipid peroxidation level in the serum was determined as malondialdehyde (MDA) level *via* determining the thiobarbituric acid reactive species (TBARS) as indicator of lipid peroxidation. The end product of lipid peroxidation was measured at 534 nm.

Determination of liver HMG-CoA reductase and total cholesterol

HMG-CoA reductase activity and total cholesterol in the liver tissue homogenate was measured according to previously described method (Baskaran *et al.,* 2015).

Determination of liver enzymes

Serum level of alanine aminotransferase (AST) and aspartate aminotransferase (AST) activities were determined according to previously reported method (Zarei *et al.,* 2015).

Determination of lipid profile

Serum level of total cholesterol, triglycerides and high-density lipoprotein (HDL) were measured according to previously described method (Maruthappan and Shree, 2010).

Statistical analysis

The study used Student's t-test to compare two independent groups and ANOVA to assess differences across multiple treatment groups, including various catalpol doses and simvastatin. The t-test is suitable for simple comparisons, while ANOVA efficiently handles multiple group analyses, reducing type I error. Values are

represented as the mean ± standard error of the mean. A significance level of P<0.05 was applied to determine statistical significance.

RESULTS AND DISCUSSION

Hypercholesterolemia has been linked in numerous studies to diseases like atherosclerosis and renal failure. This pathology is characterized by the production of atherosclerotic plaque, which is essential for arterial constriction and the ischemic events that follow (Hu and Feng, 2017; Chen *et al.,* 2025). Numerous studies have shown that lowering LDL-c levels considerably reduces the risk and severity of cardiovascular illnesses. Additionally, new studies show that fibrosis linked to non-alcoholic fatty liver disease (NAFLD) can increase cardiovascular risks, highlighting the complex connection between metabolic dysregulation and the development of atherosclerosis (Shen *et al.,* 2023; Chen *et al.,* 2024).

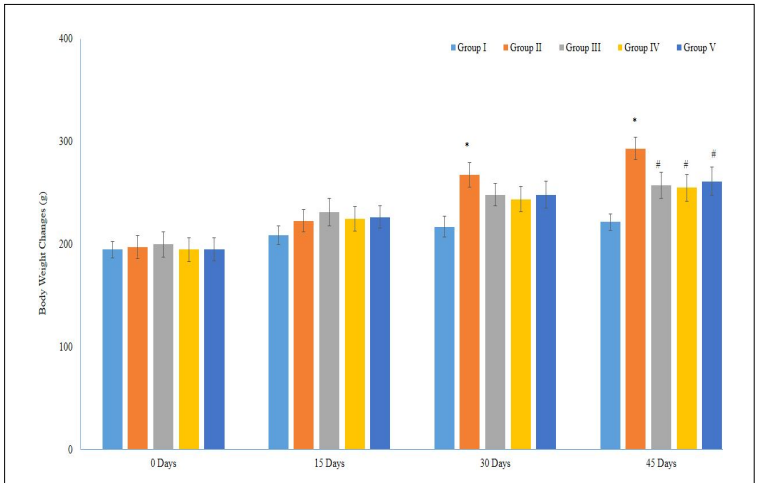
This study evaluated the hypolipidemic, antioxidant and anti-atherosclerogenic effects of catalpol in Triton WR 1339-induced hyperlipidemic rats, a well-established model for hyperlipidemia (Zarzecki *et al.,* 2014). Triton WR 1339-induced hyperlipidemia mimics the pathophysiological lipid imbalances observed in cardiovascular diseases, which are a global health concern contributing to over 17 million deaths annually.

The weight changes in the control group over the 45 days period was not significant. On the other hand, the hyperlipidemic group had significant weight gains of 13%, 35% and 48.6% for the 15, 30 and 45-day period. The 10 mg/kg and 20 mg/kg doses of catalpol treatment led to weight gain mitigation to 15.7% and 15.5% at 15 days, 24.2% and 25.2% at 30 days and 28.7% and 31% at 45 days, respectively (* <0.05, Fig 1). Simvastatin-treated rats also similarly gained weight with 15.4%, 27.2% and 33.9% at the same intervals. These findings suggest that catalpol reduces hyperlipidemia-induced weight gain as well and has an effect similar to simvastatin (Tucker and Soslowsky, 2016).

This construct of the autonomic system is regarded to be conditioned by hyperlipidemia associated changes in alteration of serum antioxidant enzyme attributes activities including catalase (59.6%), superoxide dismutase (SOD, 55,5%), glutathione peroxidase (Gpx, 61.9%) and glutathione (GSH, 66.5%). Treatment with catalpol at doses of 10 mg/kg and 20 mg/kg brought back significantly these enzyme activities with catalase increasing by 36.4 and 115.2, SOD by 46.5 and 98.5, Gpx by 20.8 and 116.7 cpm, respectively, in GSH dby 64 and 172, respectively (*P <0.05, Table 1). Simvastatin is another compound that determined significant gains in antioxidative enzyme activities. The lipid peroxidation which is remarkably increased in hyperlipidemic rats was significantly decreased after treatment with catalpol at both doses and simvastatin (*P<0.05, Table 2). This data confirms the previous results, which are bolstered by catalpol's antioxidative effect (Zhu *et al.,* 2016).

The administered dosage of catalpol played a critical role in the treatment of hyperlipidermic rats, as it significantly improved their lipid profiles. Serum total cholesterol levels that were elevated by 282.4% were lessened by catalpol doses of 10 mg/kg and 20 mg/kg, which reduced the serum cholesterol by 17.6% and 63% respectively (which is significant with a P value of less than .05). The triglyceride levels increased by 283.8% were diminished by 43.5% with a catalpol dose of 20 mg/kg (*<0.05, Table 3). Moreover, simvastatin and catalpol showed comparable results where simvastatin increased HDL-C levels by 9.5% and 23.5% while reducing LDL-C and VLDL-C levels by over 50%. These results offer insights regarding the potential role of catalpol in the management of dyslipidemia.

The atherogenic indices that are known to be a cardiovascular risk are significantly reduced with catalpol



Rats were supplemented with 10 and 20 mg/kg of catalpol for 45 days through oral route. The body weight changes were recorded every 15 days of treatment interval. #P<0.05 vs. control rats. *P<0.05 vs. normal rats. N: 6.

Fig 1: Effect of catalpol on body weight changes in hyperlipidemic rats.

Table 1: Effect of catalpol supplementation on antioxidant markers in the serum of hyperlipidemic rats.

Markers	Group I	Group II	Group III	Group IV	Group V
Catalase (U/mg of protein)	45.4±3.2	18.4±1.6**	25.1±2.2$^{\#}$	39.6±3$^{\#\#}$	42.5±3.1$^{\#\#}$
SOD (U/mg of protein)	58.9±4.1	26.2±1.5***	38.4±2.1$^{\#}$	52±3.5$^{\#\#}$	53.4±4.2$^{\#\#}$
Gpx (nmol/ml)	0.63±0.04	0.24±0.01**	0.29±0.01$^{\#}$	0.52±0.03$^{\#\#}$	0.58±0.04$^{\#\#}$
GSH (nmol/ml)	0.75±0.05	0.25±0.02**	0.41±0.03	0.61±0.05$^{\#\#}$	0.68±0.04$^{\#\#}$

**P <0.01, ***P <0.001, $^{\#}P$ <0.05 and $^{\#\#}P$ <0.01.

Table 2: Effect of catalpol supplementation on lipid peroxidation, lipid profile and liver enzymes in the serum of hyperlipidemic rats.

Markers	Group I	Group II	Group III	Group IV	Group V
MDA (nmol/ml)	4.1±21	18.5±52.1***	13.1±12.2$^{\#}$	6.64±3.6$^{\#\#}$	5.65±2.15$^{\#\#}$
Total cholesterol (mg/dl)	74.6±5.5	285.3±19.1***	235.2±15.4$^{\#}$	105.7±8.6$^{\#\#}$	81.8±5.4$^{\#\#}$
Triglycerides (mg/dl)	85.4±6.3	327.8±21***	261.7±15$^{\#}$	185.2±10.2$^{\#\#\#}$	123.5±9.3$^{\#\#\#}$
HDL-TC (mg/dl)	38.5±2	30.6±1.8**	33.5±2.2	37.8±2.1$^{\#}$	42.3±2.1$^{\#}$
VLDL-TC (mg/dl)	18.5±1.1	94.3±6.4***	63.1±3.5	41.6±2$^{\#\#}$	33.7±1.8$^{\#\#}$
LDL-TC (mg/dl)	23.7±1.8	105.4±6.9***	72±5$^{\#}$	45.8±2.2$^{\#\#}$	31.5±2$^{\#\#}$
HMG-CoA reductase (Mevalonate ratio)	2.95±0.18	1.2±0.1***	1.7±0.12$^{\#}$	2.5±0.2$^{\#\#}$	2.8±0.2$^{\#\#\#}$
Total cholesterol (mg/g)	11.5±1.1	46.2±2.6**	35.1±2.2$^{\#}$	19.2±1.5$^{\#\#\#}$	14.4±1.3$^{\#\#\#}$
ALT (U/l)	44.4±2.1	89.1±3.5***	73.2±4.2$^{\#}$	53.6±4.4$^{\#\#\#}$	49.5 3.5$^{\#\#}$
AST (U/l)	211.7±15	294.5±17.7**	263.4±17	228.4±19$^{\#\#}$	215.1±11$^{\#\#}$

**P <0.01, ***P <0.001, $^{\#}P$ <0.05, $^{\#\#}P$ <0.01 and $^{\#\#\#}P$ <0.001

treatment (Lumu *et al.,* 2023). These protective effects against atherosclerosis are aligned with previous results oncatalpol's ability to lipid peroxidation in diabetic and hypercholesterolemic patients (Liu *et al.,* 2016).

In comparison to the control, catalpol restored hepatic activity of HMG-CoA reductase by an average of 41.7% and 108.3% with doses of 10 mg/kg and 20 mg/kg, respectively. These dosages were somewhat lower than the restoration provided by simvastatin, which was 133.3% (*< 0.05, Table 2). The higher dose of catalpol also increased liver enzyme levels (ALT and AST) by over 20% which indicates hepatotoxicity at higher concentrations (*<0.05, Table 2). Proceeding this indicates that effectiveness and harm operate on a self-serving scale proportionate to dosage.

Limitation and future perspective

It is important to recognize the limitations of the current investigation. Translational investigations are necessary because the study was carried out in diet-induced hypercholesterolemic rats, which might not accurately reflect the complexity of cardiovascular illnesses in humans. Future research into catalpol's interactions with lipid metabolism and oxidative stress pathways is necessary since, despite its encouraging hypolipidemic, antioxidant and anti-atherosclerogenic properties, the underlying molecular processes were not examined. The extremely brief 45-day study period made it difficult to evaluate long-term safety and therapeutic results. Additionally, the possible hepatotoxicity seen at larger dosages emphasizes how crucial it is to carry out dose-response studies in order to determine the ideal therapeutic range. Human clinical investigations to confirm catalpol's effectiveness and safety as well as comparisons with other lipid-lowering medications to further understand its related effectiveness and long-term studies to evaluate sustained outcomes. These advancements will provide comprehensive insights into catalpol's potential as a therapeutic agent for cardiovascular diseases.

CONCLUSION

This study confirms that catalpol effectively reduces hyperlipidemia, oxidative stress and atherosclerosis in triton WR 1339-induced hyperlipidemic rats. Catalpol significantly improved antioxidant enzyme activity, reduced lipid peroxidation and normalized lipid profiles by lowering triglycerides, cholesterol, LDL and VLDL while increasing HDL levels. These findings highlight catalpol's potential as a therapeutic agent for managing hyperlipidemia and reducing cardiovascular disease risk.

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Informed consent

All animal procedures for experiments were approved by the Committee of Experimental Animal care and handling techniques were approved by the Animal Care Committee of Qinghai Province Cardiovascular and Cerebrovascular Disease Specialist Hospital, Xining, Qinghai, China.

Conflict of interest

The authors declare that there are no conflicts of interest regarding the publication of this article. No funding or sponsorship influenced the design of the study, data collection, analysis, decision to publish, or preparation of the manuscript.

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