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Evaluation of Anti-Hyperlipidemic Activity of Cinnamaldehyde in Triton-Induced Animal Model

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KEYWORDS

Cinnamaldehyde;

Atorvastatin;

Antioxidant;

Atherosclerosis;

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ABSTRACT:

Introduction: Hyperlipidemia is one of the major risk factors of atherosclerosis and cardiovascular diseases. Cinnamomum zeylanicum (cinnamon) is widely used in the traditional system of medicine to treat diabetes in India and exhibits antihyperlipidemic effects.

Objectives: The present study was carried out to evaluate the putative antihyperlipidemic effects of cinnamaldehyde

Methods: Male Sprague Dawley albino rats (130-150 g) were used in this study. Cinnamaldehyde was administered at different doses (10 and 30 mg/kg/day, p.o.) for 15 days in triton (single intraperitoneal dose of 100 mg/kg)-induced hyperlipidemic Sprague Dawley rats. Blood lipids and oxidative stress markers were examined in the study.

Results: It was found that oral administration of cinnamaldehyde (10 and 30 mg/kg) significantly ($P < 0.05$) restored plasma lipid concentration compared to the hyperlipidemic control group. In addition, cinnamaldehyde significantly increased GSH, and SOD levels and decreased MDA levels as compared to the hyperlipidemic control group. Administration of atorvastatin, a reference drug (10mg/kg/day, p.o.) also produced a significant ($P < 0.05$) restoration in blood lipid concentration and oxidative stress markers against triton-induced hyperlipidemic rats.

Conclusions: The results of this experimental study indicate that cinnamaldehyde possesses antihyperlipidemic effects in triton-induced hyperlipidemic rats.

1. Introduction

Hyperlipidemia, also referred to as dyslipidemia, is a primary contributor to cardiovascular disease (CVD) globally and is closely tied to a society's economic conditions. It's marked by an imbalance in serum total cholesterol and its main lipoprotein families, including low-density and high-density lipoprotein. Factors such as obesity and a diet high in fat increase the incidence of hyperlipidemia [1]. Dyslipidemia is among the most lethal disorders, responsible for one-third of all global deaths due to atherosclerosis impacting the arterial blood supply to crucial organs [2]. A 10% decrease in serum cholesterol in men aged 40 has been shown to result in a 50% reduction in cardiovascular disease within five years. Currently, synthetic hypolipidemic drugs are linked with numerous side effects, but natural remedies have demonstrated potential in safely managing various health conditions. Hyperlipidemia also accelerates the development of coronary artery disease and the progression of atherosclerosis. Lipid-lowering drugs like fibrates, statins, and bile acid sequestrants are used to treat hyperlipidemia, but they come with some side effects [3]. Natural products are viewed as the most effective option for managing hyperlipidemia. In hyperlipidemic conditions, both enzymatic and non-enzymatic antioxidative defense mechanisms, which include superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), ascorbic acid, and reduced glutathione (GSH), experience alterations. These changes result in damage caused by reactive oxygen species (ROS) [4-7]. The assessment of phytochemicals as potential new drug candidates for treating hyperlipidemia is a promising pursuit. Numerous

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inhibitors of cholesterol synthesis, such as flavonoids and dietary fiber, originate from natural sources and are effective in lowering blood cholesterol levels [8].

According to the World Health Organization, 80% of the global population depends on traditional medicines derived from plants [9]. These traditional treatments are often viewed as safer and more cost-effective than modern pharmaceuticals. The secondary metabolites of these plants yield essential chemical constituents that are effective in treating various health conditions. The therapeutic use of herbs and plant extracts has a deep-rooted historical significance. For example, early civilizations in China and India have well-documented uses for medicinal plants. However, it's crucial to remember that while these traditional medicines can provide health benefits, they should be used responsibly and under the guidance of a healthcare professional to ensure their safety and efficacy [10; 11].

Cinnamaldehyde (CA), a flavonoid, is primarily derived from the stem bark of Cinnamomum cassia and other species of the same genus. It constitutes about 98% of the essential oil from Cinnamon bark [12; 13]. CA has been identified as a potent anti-diabetic, anti-hypertensive, anticataract and anti-oxidant agent [14-18]. In this study, we assessed the anti-hyperlipidemic activity of cinnamaldehyde in Triton-induced animal model.

2. Materials and Methods

2.1. Animals

Male Sprague Dawley rats, with body weights within the range of 130-150 grams, were procured from Chakraborty Enterprises Kolkata, holding the registration number 1443/Po/11/CPCSEA. These animals were accommodated in transparent acrylic cages measuring 24x17x12 centimeters, situated in an environment meticulously regulated at 25 ± 2°C and 50 ± 5% relative humidity. The light and dark cycle was strictly maintained at a 12:12-hour ratio, with the commencement of the light phase at precisely 07:19:00 hours. Unrestricted access to a standardized nutritional regimen and water was provided. Each distinct experimental group consisted of a separate set of animals to ensure no repetition of subjects in varying experimental conditions. The Committee for Control and Supervision of Experimental Animals (CPCSEA) under reference number 228/IAEC/Pharmacy/2018 and the Institutional Animal Ethics Committee of SLT Institute of Pharmaceutical Sciences, Guru Ghasidas Central University (Reg No-994/GO/Re/S/06/CPCSEA) Bilaspur, have approved the studies and methods presented in this paper.

2.2. Chemicals & Reagents

Cinnamaldehyde, Atorvastatin, and Triton X-100, key reagents utilized in this study, were acquired from Hi Media Pvt. Ltd., Mumbai, India. Carboxymethyl cellulose (CMC; Hi Media Pvt. Ltd., Mumbai, India) served as the inert vehicle for the administration of substances to the control group. Analytical kits designed to measure plasma total cholesterol (TC), triglycerides (TG), and high-density lipoprotein (HDL) were obtained from Span Diagnostic Ltd and Labcare Diagnostic purchased from a local vendor. Additionally, cholesterol, CMC, sodium phosphate dibasic, and other analytical-grade chemicals and reagents were procured from the departmental chemical store.

2.3. Drug Preparation

A 10mg/ml stock solution of Cinnamaldehyde (10 and 30mg/kg, p. o.) and atorvastatin (10 mg/kg, p.o.) were prepared in 0.5 % CMC and stored in 2-8 ºC. A 100 mg/ml stock solution of Triton X-100 (100mg/kg; i.p.) was freshly prepared in 0.9% physiological saline. All the doses of this study were selected based on the previous study [19; 20].

2.4. Experimental Design

Male Sprague Dawley rats, with body weights ranging from 130-150 were randomly selected and categorized into normal and hyperepidemic rats. Normal rats served as the normal group and received a single dose of normal saline (10 ml/kg, i.p.). The hyperlipidemic rats were treated with a single intraperitoneal injection of a freshly prepared Triton X-100 solution (100 mg/kg) to induce hyperlipidemia [21]. Three days post saline/Triton X-100 injection, the normal group (n = 6) received 0.5% CMC (10 ml/kg/day, p.o.) for the next 15 days and hyperlipidemic rats were segregated into various groups (n = 6.). During 15 days of experimental protocol, the hyperlipidemic control group received 0.5% CMC (10

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ml/kg/day, p.o.), the atorvastatin group received atorvastatin (10mg/kg/day, p.o.), and cinnamaldehyde treated groups (T1 and T2) received cinnamaldehyde at 10 and 30 mg/kg/day (p.o.) respectively.

On the 15th day, blood samples were collected via cardiac puncture. The blood was then centrifuged at 10000 rpm for 10 minutes to separate the plasma. Plasma lipid levels, including TG, total cholesterol (TC), high-density lipoprotein (HDL), and low-density lipoprotein (LDL), were determined using enzymatic kits. Antioxidant parameters such as glutathione (GSH), superoxide dismutase (SOD), and malondialdehyde (MDA) were assessed using various methods given in previous studies [22; 23].

2.5. Statistical Analysis

Results were analyzed by using GraphPad Prizm 5.0. Data were analyzed by one-way analysis of variance (ANOVA). $P < 0.05$ considered as significant difference between multiple groups.

3. Results

The impact of Cinnamaldehyde on plasma lipid levels is presented in Table 1. When compared to the normal group, in the hyperlipidemic control group, levels of TC ($P < 0.001$), TG ($P < 0.001$), and LDL ($P < 0.01$) were found to be significantly higher, and HDL ($P < 0.001$) was found to be significantly lower. Treatments with atorvastatin, and cinnamaldehyde (10 and 30 mg/kg) in their respective group significantly restored the level of TC ($P < 0.001$), TG ($P < 0.001$), LDL ($P < 0.01$), and HDL ($P < 0.001$) as compared to the hyperlipidemic control group. These results indicate the beneficial effects of cinnamaldehyde against hyperlipidemia.

The results of the oxidative stress parameter are presented in Table 2. When compared to the normal group, in the hyperlipidemic control group, the level of GSH ($P < 0.001$) and SOD ($P < 0.001$) were found to be significantly lower and MDA level ($P < 0.001$) was found to be significantly higher. While treatments with cinnamaldehyde (10 and 30 mg/kg) significantly restored the level of GSH ($P < 0.01$), SOD ($P < 0.001$), and MDA ($P < 0.001$) as compared to the hyperlipidemic control group. Atorvastatin treatments also led to significant restoration in the level of GSH ($P < 0.001$), SOD ($P < 0.001$), and MDA ($P < 0.001$) as compared to the hyperlipidemic control group. These results indicate the antioxidant activity of cinnamaldehyde against hyperlipidemia.

Table 1. Effect of cinnamaldehyde on TC, TG, LDL, and HDL in triton-induced hyperlipidemia

Groups	TC (mg/dL)	TG (mg/dL)	LDL (mg/dL)	HDL (mg/dL)
Normal	111.6 ± 2.727	109.8 ± 4.00	54.78 ± 4.956	58.32 ± 2.789
HC	267.2 ± 4.549^{c}	268.0 ± 5.22^{c}	218.5 ± 5.006^{b}	38.26 ± 2.390^{c}
Atorvastatin	133.0 ± 5.386^{af}	129.1 ± 3.915^{af}	73.98 ± 4.532^{ae}	54.53 ± 1.863^{bf}
T1	156.6 ± 4.911^{cf}	158.7 ± 4.610^{cf}	92.28 ± 4.189^{ae}	49.64 ± 2.220^{cf}
T2	138.4 ± 5.257^{af}	139.7 ± 4.418^{cf}	78.64 ± 4.376^{ae}	53.72 ± 2.456^{bf}

Values are expressed as mean±SEM. Data were analyzed by One Way ANOVA followed by Newman-Keuls multiple comparison test, where $^{a}P < 0.05$, $^{b}P < 0.01$, $^{c}P < 0.001$ vs Normal. $^{d}P < 0.05$, $^{e}P < 0.01$, $^{f}P < 0.001$ vs hyperlipidemic control.

Table 2. Effect of cinnamaldehyde on GSH, SOD, and MDA levels

Groups	GSH (µmole/ml)	SOD (U/ml)	MDA (nmole/ml)
Normal	2.992 ± 0.1622	3.190 ± 0.1644	2.363± 0.1682
Control	1.324 ± 0.1584^{c}	1.180 ± 0.0827^{c}	3.960 ± 0.1887^{c}
Standard	2.352± 0.1807^{bf}	2.606 ± 0.1090^{bf}	2.798 ± 0.1231^{f}
T1	1.982± 0.1122^{ce}	2.280 ± 0.1126^{cf}	3.174 ± 0.1034^{f}
T2	2.094±0.17027^{ce}	2.524 ± 0.096^{bf}	2.904 ± 0.1261^{af}

Values are expressed as mean±SEM. Data were analyzed by One Way ANOVA followed by Newman-Keuls multiple comparison test, where $^{a}P < 0.05$, $^{b}P < 0.01$, $^{c}P < 0.001$ vs Normal. $^{d}P < 0.05$, $^{e}P < 0.01$, $^{f}P < 0.001$ vs hyperlipidemic control.

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4. Discussion

Hyperlipidemia is characterized by abnormally elevated levels of lipoproteins and cholesterol in the bloodstream. This condition is associated with an increase in total TC, LDL, VLDL, and TG, alongside a reduction in HDL levels. The etiology of hyperlipidemia involves a disruption in the metabolic processes governing lipid and lipoprotein regulation, which critically impacts the mechanisms of cholesterol transportation. A multitude of factors are known to influence lipid metabolism, including but not limited to, a lack of physical activity, a sedentary lifestyle, consumption of a diet high in cholesterol, excess body weight, advancing age, and hormonal imbalances [8; 23]. These factors can precipitate lipid imbalances that may culminate in atherosclerotic cardiovascular pathologies. Moreover, hyperlipidemia has been implicated in the perturbation of both enzymatic and non-enzymatic antioxidant defense systems, encompassing entities such as superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), ascorbic acid, and glutathione (GSH). The resultant imbalance can lead to oxidative stress, mediated by reactive oxygen species (ROS), inflicting damage on cellular components [17].

The compound Triton X-100 has been observed to inhibit the metabolic processing of triglyceride-rich lipoproteins, leading to acute hyperlipidemia in various animal models. This is characterized by heightened levels of plasma TG and TC, attributed to an augmented secretion of very-low-density lipoproteins (VLDL) by the liver, coupled with a subsequent decline in the catabolism of VLDL and LDL [16; 24]. The current research indicates that Triton X-100 administration results in a significant elevation of serum TC, TG, and LDL, alongside a reduction in HDL levels, corroborating findings from prior studies [6; 25]. Additionally, there was a notable decrease in the concentrations of GSH and SOD, coupled with an increase in MDA levels when compared to the baseline values observed in the normal control group.

Subsequent treatment with cinnamaldehyde, administered orally at dosages of 10 mg/kg and 30 mg/kg over 15 days, was observed to reverse the dyslipidemia profile by reducing TG, TC, and LDL levels and enhancing HDL concentrations relative to the hyperlipidemic control group. Moreover, cinnamaldehyde treatment led to an upregulation of GSH and SOD levels and a reduction in MDA levels, thereby demonstrating its potential antioxidative properties in mitigating oxidative stress associated with hyperlipidemic conditions.

The elevation of serum triglyceride levels following Triton X-100 administration is hypothesized to be a consequence of the diminished activity of lipoprotein lipase within the vascular system, which is responsible for the hydrolysis of triglycerides. The resultant hypertriglyceridemia, in conjunction with reduced uptake of fatty acids by adipose tissues, is implicated in the manifestation of HDL levels, insulin resistance, and an augmented risk for the development of atherosclerosis, as reported [26].

Diminished concentrations of HDL are significantly implicated in the etiology of atherosclerosis. Research on HDL interventions have elucidated that an elevation of HDL levels by 1% correlates with a 3% reduction in the risk of developing atherosclerotic conditions. Lecithin cholesterol acyltransferase (LCAT) plays an instrumental role in the metabolic pathways of cholesterol and HDL. Therapeutic administration of CA has been associated with a substantial increase in HDL levels, which contributes to the mitigation of atherosclerosis and the overall risk of cardiovascular diseases. It is postulated that CA may exert its beneficial effects through the activation of the LCAT enzyme, thereby enhancing the functionality of HDL in the circulatory system [27].

Elevated levels of LDL are a principal contributor to the pathogenesis of atherosclerotic plaque development. The aggregation of LDL within the extracellular matrix beneath the endothelial lining of arterial walls is well-documented [28]. Furthermore, hyperlipidemic conditions are known to induce the production of reactive oxygen species (ROS), leading to oxidative stress and subsequent tissue damage across multiple organ systems and vascular structures [29]. Treatment with CA has demonstrated a notable reduction in LDL concentrations, thereby ameliorating the hyperlipidemic state in Triton-induced models when compared to the hyperlipidemic control group. Additionally, CA therapy has been observed to inhibit the deposition of LDL in the subendothelial spaces of arteries, consequently diminishing the likelihood of atherosclerotic disease progression.

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In this detailed investigation, we delved into the properties of cinnamaldehyde, a bioactive molecule responsible for the distinctive flavor and scent of cinnamon. This compound exhibits potent antihyperlipidemic activity, which translates to its ability to significantly reduce lipid concentrations within the bloodstream. Our experimental approach involved administering cinnamaldehyde to rodent subjects that were artificially induced with elevated lipid levels via Triton treatment. The outcomes demonstrated that cinnamaldehyde effectively restored the blood lipid profile in both experimental cohorts. These lipid profile modifications are advantageous in the prophylaxis of cardiovascular diseases.

Furthermore, our study extended to the evaluation of certain non-enzymatic biomarkers indicative of oxidative stress, namely GSH, SOD, and MDA. The results indicated that cinnamaldehyde beneficially modulated these parameters by elevating GSH and SOD levels and diminishing MDA levels. Such findings underscore cinnamaldehyde's capacity to attenuate the generation of deleterious reactive oxygen species, thereby bolstering the organism's antioxidative defense system. This expanded understanding of cinnamaldehyde's pharmacological effects suggests its potential therapeutic role in the management of dyslipidemia and oxidative stress, contributing to cardiovascular health.

5. Conclusion

In our comprehensive study, we explored the effects of cinnamaldehyde, an active constituent of cinnamon, on the lipidemic profile of rodents. To induce hyperlipidemia, we utilized Triton. After this induction, we conducted a thorough analysis of various lipid fractions and antioxidant parameters within the bloodstream. Upon administering cinnamaldehyde to these hyperlipidemic rats, we observed a notable improvement in their lipid profiles, which was evidenced by a decrease in detrimental lipids and an increase in beneficial lipids. Additionally, cinnamaldehyde supplementation was found to attenuate and reduce oxidative stress within the organism. The culmination of our research indicates that cinnamaldehyde possesses the potential to mitigate cardiovascular diseases by effectively lowering the concentration of lipids in the bloodstream and bolstering the body's antioxidant defense mechanisms in rat models.

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Conflict of interest statement

We now declare that we do not possess any conflicts of interest

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