



Beneficial role of ferulic acid supplementation on lipid profile status in streptozotocin-induced diabetic rats

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ABSTRACT

Background: Diabetes is a chronic metabolic disorder marked by persistent elevated blood sugar concentrations and disturbances in the metabolism of carbohydrates, lipids, and proteins. Several functional foods and naturally occurring compounds derived from plants have therapeutic potential for managing diabetes and its associated metabolic abnormalities of lipids. Ferulic acid is a bioactive compound present in numerous functional foods. It provides an extensive array of health advantages, encompassing a diverse spectrum of benefits.

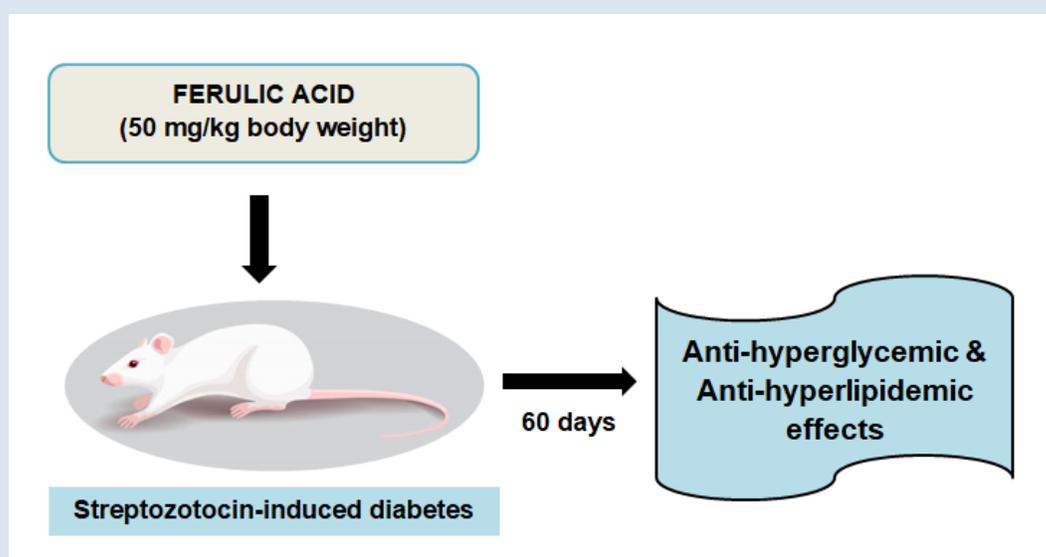
Objective: The objective of this study was to assess the effect of 50 mg/kg body weight of Ferulic acid (FA50) on the lipid profile status in diabetic rats induced with Streptozotocin (STZ).

Materials and methods: Experimental diabetes was created on male albino Sprague Dawley rats. The rats were categorized into five distinct groups- Normal (Group 1), Normal+ FA50 (Group 2), Diabetic control (Group 3), Diabetic + FA50 (Group 4), and Diabetic + Glibenclamide (Group 5). Diabetes was induced in Group 3, 4, and 5 by administering an I.P (intraperitoneal) injection of STZ (40 mg/kg body weight). Rats of groups 2 and 4 were orally administered with 50 mg of FA per rat's body weight in Kg. Group 5 was treated with Glibenclamide (5 mg/ Kg body weight) daily for two months. On the 60th day, rats from all groups were euthanized, and blood samples were gathered for the purpose of conducting biochemical assessments.

Results: The injection of STZ resulted in a significant increase in blood glucose, HbA1c, and lipid profile markers in the experimental rats. Oral administration of Ferulic acid and Glibenclamide drug to diabetic rats significantly ($P \leq 0.05$) lowered hyperglycemia, triglycerides, and total cholesterol compared to the diabetic control group. Moreover, the administration of Ferulic acid significantly increased the levels of HDL-cholesterol and regulated the Apo lipoprotein A1-Apo lipoprotein B levels.

Conclusion: The current research demonstrates the advantageous impact of Ferulic acid in improving lipid-related metabolic complications associated with diabetes.

Keywords: Nutraceuticals, Ferulic acid, Streptozotocin, Diabetes, Lipid profile



Graphical Abstract:

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INTRODUCTION

Diabetes is a prevalent metabolic disorder marked by elevated blood sugar levels [1,2]. It is associated with disturbances in carbohydrate, lipid, and protein metabolism [3]. Diabetes can lead to dyslipidemia, a condition characterized by irregularities in blood lipid levels. Typically, this entails elevated levels of triglycerides and low-density lipoprotein cholesterol (LDL-C), accompanied by decreased high-density lipoprotein cholesterol (HDL-C). This imbalance in the

lipid profile is associated with a higher likelihood of cardiovascular ailment among individuals with diabetes. Diabetic dyslipidemia is commonly seen in diabetes due to insulin-related disruptions in lipid metabolism [4]. Unregulated high blood sugar can give rise to complications such as heart disease, vision issues, kidney disease, and nerve damage [5]. The lipid particles in diabetic dyslipidemia are believed to be more likely to cause atherosclerosis [6,7].

Dietary supplements and nutraceuticals are orally consumed products that consist of various ingredients, including nutrients, minerals, plant extracts, herbs, amino acids, enzymes, or additional dietary elements [8]. The purpose of these products is to complement the diet by offering extra nutrients or promoting health benefits [9–11]. Abundant evidence supports the potent antioxidant properties and advantageous therapeutic effects of flavonoids found in the diet [12–15]. The hydroxy-cinnamates, primary components found in fruits (such as oranges), certain vegetables (like tomatoes and carrots), beverages (including beer), and grains (such as rice bran and wheat bran), exhibit significant antioxidant capacity [16]. Ferulic acid (FA), also known as 3-methoxy 4-hydroxy-cinnamic acid. FA belongs to the group of cinnamic acid derivatives and is a highly bioavailable dietary flavonoid. FA protects against liver damage caused by diabetes and serves as a remedy for inflammation, aging, and diabetes due to its anti-inflammatory, anti-aging, and anti-diabetic properties [17]. Furthermore, there is documented evidence that FA can disrupt the cascade of free radical chain reactions, thereby reducing the susceptibility to cardiovascular ailments. [18]. As such, our investigation centered on examining the impact of FA on lipid profiles in diabetes-induced rats.

MATERIALS AND METHODS

Chemicals: In this research, all chemicals employed were of analytical quality and obtained from Sigma–Aldrich, Hi-Media, and Sisco Research Laboratories.

Induction of experimental diabetes in rats: Male Sprague Dawley rats were induced with diabetes by means of intraperitoneal administration of Streptozotocin (STZ) dissolved in pH 4.5 citrate buffer at a dose of 40 mg/kg. To counteract the resultant drug-induced hypoglycemia, rats that received the STZ

injection were provided with a 20% glucose solution overnight. Rats demonstrating blood glucose levels surpassing 250 mg/dl were categorized as diabetic and subsequently included in the research. The Institutional Animal Ethics Committee granted approval for this study (Ethical sanction number: IAEC-3-KU-03/2018-19-BCH-SM (43)).

Experimental design: The rat subjects were divided into five distinct groups, each comprising six rats, and designated as follows:

1. The Normal group, in which rats received a regular diet without any treatment (N).
2. The Normal+FA50 group, composed of normal rats treated with a dose of 50 mg/kg body weight FA.
3. The third group included rats with diabetes induced by STZ, serving as the diabetic control group.
4. The Diabetic+FA50 group, consisting of STZ-induced diabetic rats administered with a 50 mg/kg body weight dosage of FA [19].
5. The Diabetic+glibenclamide group, comprising STZ-induced diabetic rats treated with glibenclamide at a dose of 5 mg/kg body weight [20].

For duration of 60 days, the rats received daily intragastric administrations of freshly prepared suspensions of FA and glibenclamide, as per their respective groups. After the completion of the treatment period, the rats underwent an overnight fasting period, following which they were sacrificed, and blood samples were collected for various analyses.

Biochemical studies: Glucose oxidase method was used to estimate blood glucose level [21]. Glycated

hemoglobin was assessed using the HbA1c kit from Beacon Diagnostics Pvt Ltd. Following the manufacturer's guidelines from AGAPPE Diagnostic Pvt Ltd, measurements for total cholesterol (TC), triglycerides (TG), HDL-cholesterol (HDL-C), LDL-cholesterol, Apo lipoprotein A1 (Apo A1), and Apo lipoprotein B (Apo B) were conducted (Agappe Diagnostics Limited, Ernakulum, Kerala).

Statistical Analysis: Analysis was carried out using GraphPad Prism 7.0, employing both one-way and two-way ANOVA. The outcomes are displayed as the mean \pm SEM ($n = 6$). Statistical significance was determined at a level of 0.05 or below ($P \leq 0.05$).

RESULTS

Body weight: Body weights of the animal groups were recorded on the initial and final days of the experimental period. The diabetic control group showed a significant decrease in body weight (123.5 ± 3.2 g) compared to the normal control rats (166.3 ± 4.5 g) at the end of the experimental period. A comparable effect was observed between N and N+FA50 groups. Body weight increased significantly in D+FA50 group (170.5 ± 3.9 g) when compared to the diabetic control group. A comparable effect was observed in the diabetic rats of both groups D+FA50 and D+G. The body weight variation of the rats at day 1 and day 60 are shown in Figure 1.

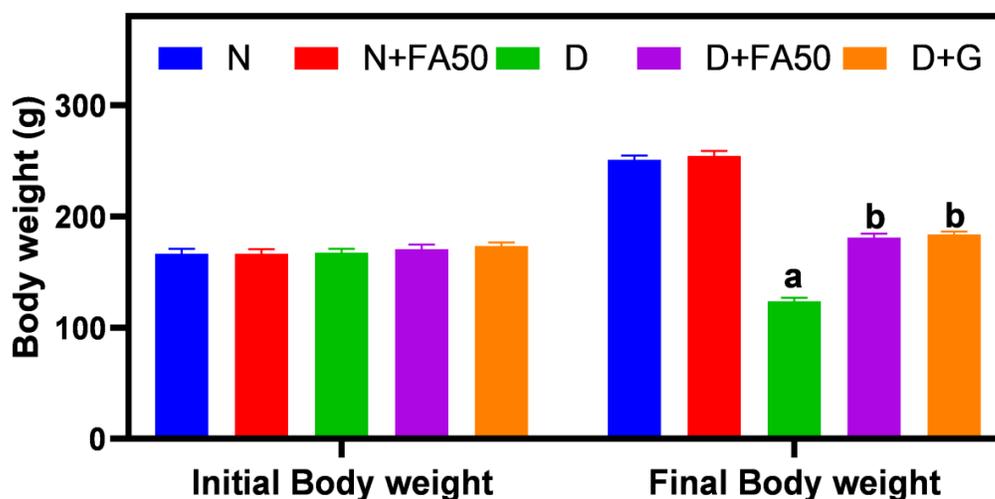


Figure 1. Change in body weight. Data is presented as the mean \pm standard error of the mean, with a sample size of six. The symbols 'a' denote significant differences from Normal, 'b' represents significant differences from diabetic control, and 'c' signifies significant distinctions between the Diabetic+FA50 and Diabetic+glibenclamide group. A significance level of $p \leq 0.05$ was employed for determining statistical significance.

Blood glucose: Rats with experimentally induced diabetes exhibited pronounced hyperglycemia, evidenced by elevated levels of glucose measuring 371.20 ± 3.58 mg/dl. Notably, the supplementation of FA50 to diabetic rats led to substantial improvement. Oral administration of FA at a dose of 50 mg/kg body

weight over the span of 60 days resulted in a significant reduction ($P \leq 0.05$) in glucose levels, reaching 178.97 ± 5.1 mg/dl by the conclusion of the treatment period (Figure 2). Comparable effects were observed between the N and N+FA50 groups.

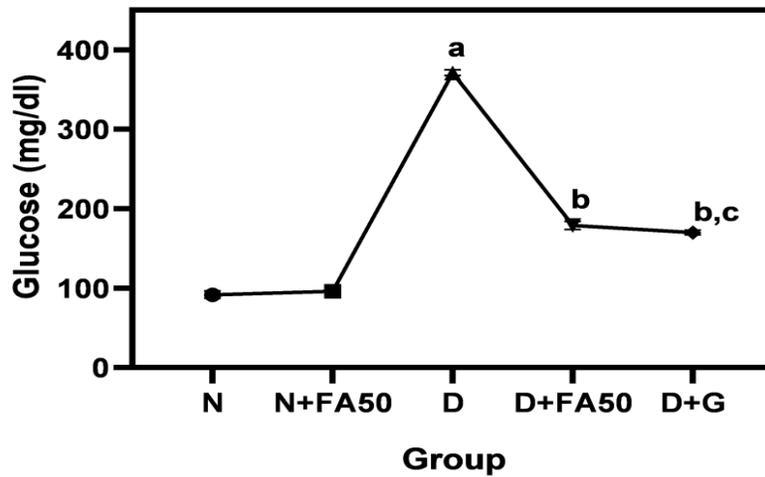


Figure 2. Blood sugar level. Data is presented as the mean \pm standard error of the mean, with a sample size of six. The symbols 'a' denote significant differences from Normal, 'b' represents significant differences from diabetic control, and 'c' signifies significant distinctions between the Diabetic+FA50 and Diabetic+glibenclamide group. A significance level of $p \leq 0.05$ was employed for determining statistical significance.

Glycated hemoglobin (HbA1c): In the diabetic control rats, there was a substantial rise in HbA1c levels ($13.93 \pm 1.45\%$) when compared to the normal groups. However, upon administering FA, the levels of glycated hemoglobin in diabetic control rats decreased notably to $7.65 \pm 0.70\%$. The visual representation of this outcome is

presented in Figure 3. Remarkably, the effect of administering FA was akin to the impact of the standard drug glibenclamide. Furthermore, both the N and N+FA50 groups exhibited a similar effect on HbA1c levels.

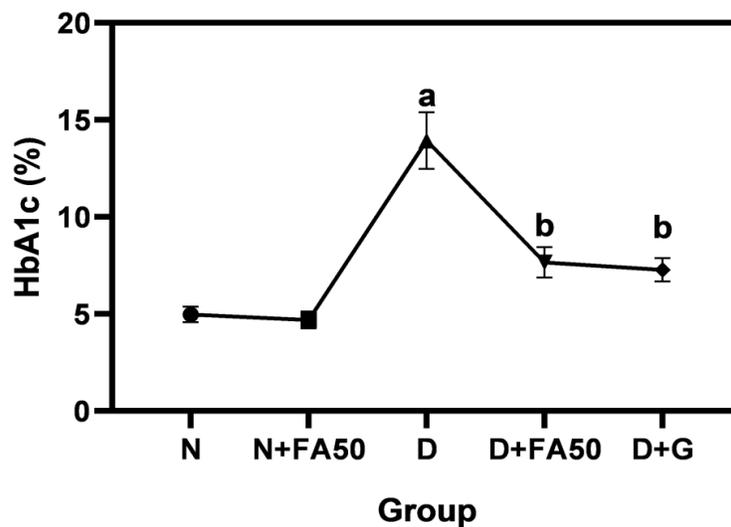


Figure 3. Glycated hemoglobin: Data is presented as the mean \pm standard error of the mean, with a sample size of six. The symbols 'a' denote significant differences from Normal, 'b' represents significant differences from diabetic control, and 'c' signifies significant distinctions between the Diabetic+FA50 and Diabetic+glibenclamide group. A significance level of $p \leq 0.05$ was employed to determine statistical significance.

Serum Total cholesterol (TC) and Triglycerides (TG):

Figure 4 illustrates the levels of TC and TG in the experimental animals at the conclusion of the study. There was a significant increase ($P \leq 0.05$) in the TC and TG levels in the diabetic group (116.64 ± 7.73 mg/dl and 95.32 ± 2.92 mg/dl) as compared to normal group (45.71

± 2.74 mg/dl and 35.38 ± 2.56 mg/dl), which was significantly decreased ($P \leq 0.05$) by glibenclamide and FA50 treated groups respectively (89.23 ± 6.08 and 76.9 ± 2.08 mg/dl) as compared with diabetic group. Both N and N+FA50 groups showed a comparable effect.

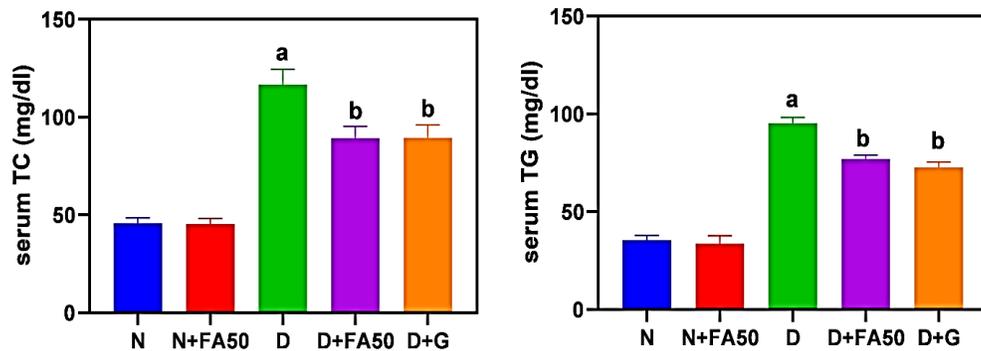


Figure 4. Serum TC and TG levels: Data is presented as the mean \pm standard error of the mean, with a sample size of six. The symbols 'a' denote significant differences from Normal; 'b' represents significant differences from diabetic control. A significance level of $p \leq 0.05$ was employed for determining statistical significance.

HDL-C & LDL-C levels: In Figure 5, a notable reduction ($P \leq 0.05$) in serum HDL-C levels among the diabetic control rats is evident when compared to the normal group. Conversely, both the glibenclamide and FA50-treated groups exhibited a noteworthy increase ($P \leq 0.05$) in serum HDL-C levels in contrast to the diabetic group. Furthermore, a substantial elevation ($P \leq 0.05$) in serum

LDL-C levels was observed within the diabetic groups when compared to the normal group. However, the D+FA50 groups demonstrated a significant decrease in serum LDL-C levels when compared to the diabetic group. It is worth noting that similar effects on HDL-C and LDL-C were observed in both the N and N+FA50 groups.

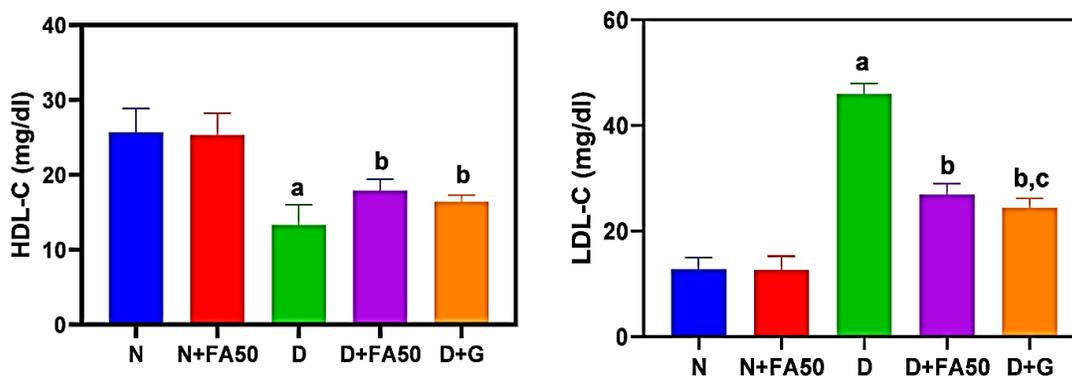


Figure 5. Serum HDL-C and LDL-C levels: Data is presented as the mean \pm standard error of the mean, with a sample size of six. The symbols 'a' denote significant differences from Normal, 'b' represents significant differences from diabetic control, and 'c' signifies significant distinctions between the Diabetic+FA50 and Diabetic+glibenclamide group. A significance level of $p \leq 0.05$ was employed to determine statistical significance.

Serum Apo A1 & Apo B: In diabetic control rats, a noteworthy decrease in Apo A1 levels ($P \leq 0.05$) was evident when contrasted with normal rats. Conversely, a significant elevation ($P \leq 0.05$) in Apo A1 levels was noted among animals treated with FA50 (50 mg/kg body weight). Meanwhile, the Apo B levels exhibited a significant increase ($P \leq 0.05$) in diabetic rats in

comparison to non-diabetic rats. However, in diabetic rats subjected to FA50 treatment, a marked reduction ($P \leq 0.05$) in Apo B levels was observed. Notably, the impact of FA50 treatment was on par with that of the standard drug glibenclamide. These outcomes are graphically depicted in Figure 6.

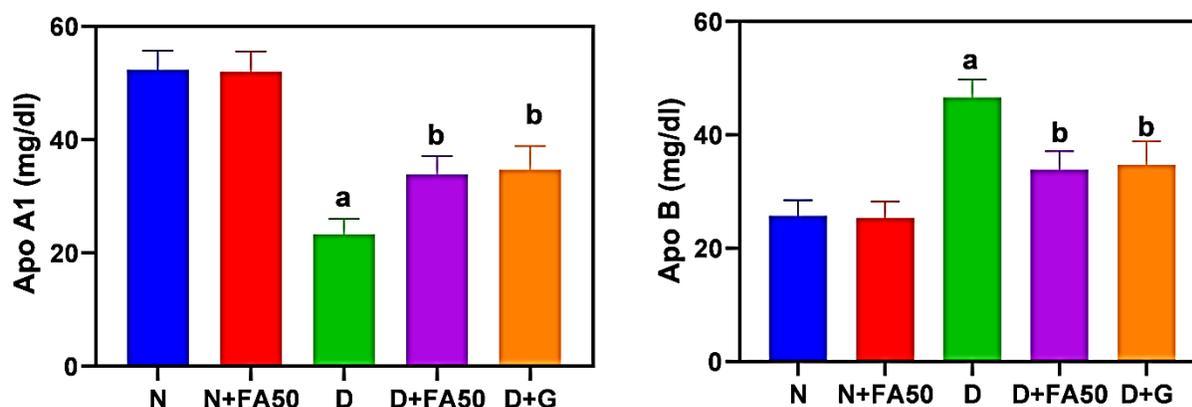


Figure 6. Serum Apo A1 and Apo B: Data is presented as the mean \pm standard error of the mean, with a sample size of six. The symbols 'a' denote significant differences from Normal; 'b' represents significant differences from diabetic control. A significance level of $p \leq 0.05$ was employed to determine statistical significance.

DISCUSSION

Diabetes is a metabolic disorder characterized by high blood sugar levels and often linked to complications arising from abnormalities in lipid levels [22]. Managing blood sugar levels through medications, lifestyle changes, and a healthy diet can help alleviate these lipid-related complications and reduce the risk of cardiovascular problems [23,24]. More than a third of diabetes patients have dyslipidemia, which includes high LDL and total cholesterol, low HDL, and high triglycerides [25]. High levels of total cholesterol are the main causes of coronary heart disease. It is widely known that people with diabetes have higher rates of hyperlipidemia and atherosclerosis. The correlation between blood sugar levels and lipid profile offers a chance for the early identification and management of lipid-related issues.

This proactive approach can effectively lower the susceptibility to cardiovascular and other conditions among individuals diagnosed with type-2 diabetes. Within this current investigation, the study aimed to ascertain the shielding influences of the phenolic phytochemical FA on the lipid profiles of diabetic rats induced by STZ. For comparative purposes, the standard antidiabetic medication, glibenclamide, was employed.

STZ stands as a widely utilized agent to induce diabetes mellitus in experimental animals [22]. Through its impact on the destruction of beta cells and subsequent reduction in insulin production, STZ administration brings forth diabetes [15]. In this context, male Sprague Dawley rats were induced into a diabetic state using an injection of 40 mg/kg of STZ, resulting in evident hyperglycemia accompanied by elevated glucose

and HbA1c levels. These findings align with the results of other investigations into STZ-induced experimental diabetes [26–28].

In our study, a 60-day supplementation of FA at a dosage of 50 mg/kg body weight exhibited a protective effect against diabetes in rats. This was achieved by effectively regulating their glucose levels. Notably, HbA1c emerges as a reliable marker for evaluating glycemic control within individuals affected by diabetes mellitus, additionally serving as a pivotal indicator for forecasting diabetes prognosis. Both FA and glibenclamide treatments contributed to decreased HbA1c levels in diabetic rats, highlighting their potential to manifest anti-hyperglycemic effects. This outcome concurs with prior investigations that have underscored the hypoglycemic efficacy of FA in diabetic rats, further corroborating the alignment between our findings and the existing body of literature [25,29].

Elevated total cholesterol levels are a prominent characteristic of diabetes mellitus, contributing significantly to both morbidity and mortality [30]. Diabetes patients often suffer from hypertriglyceridemia, which leads to vascular complications. In STZ-induced diabetic rats, hypercholesterolemia and hypertriglyceridemia are primarily caused by insulin deficiency, resulting in increased lipolysis [31]. Following the administration of FA, a notable decrease in serum cholesterol and triglyceride levels was observed in diabetic rats. The hypocholesteromic action of FA may therefore contribute to lowering cholesterol and triglyceride levels in diabetic rats by inhibiting or activating enzymes involved in cholesterol metabolism. Apolipoprotein A1 (Apo A1) and Apolipoprotein B (Apo B) are integral protein components found in distinct lipoprotein fractions [32]. Apo A1 is primarily associated with high-density lipoprotein (HDL) particles and plays a crucial role in their structure and function. It assists in the reverse cholesterol transport process, facilitating the

transport of cholesterol from peripheral tissues to the liver for excretion. On the other hand, Apo B is primarily present in low-density lipoprotein (LDL) particles and is responsible for mediating the uptake of cholesterol by cells, contributing to the formation of atherosclerotic plaques when excessively accumulated [33]. Several studies underscore Apo A1 and Apo B as notably sensitive biomarkers with potential implications for cardiovascular diseases [4,34]. The present study shows the potential of FA in maintaining these lipid markers and offering protection against complications induced by diabetes. Therefore, FA supplementation may have a beneficial effect on lipid abnormalities in diabetic rats, thereby lowering cardiovascular risk.

CONCLUSION

The injection of STZ led to a noteworthy elevation in blood glucose, HbA1c, and lipid profile markers in the experimental rats. However, when diabetic rats were orally administered Ferulic acid and Glibenclamide, it resulted in a significant reduction in hyperglycemia, triglycerides, and total cholesterol levels and notably, the administration of Ferulic acid also led to a significant increase in HDL-cholesterol levels and played a role in regulating the balance between Apo lipoprotein A1 and Apo lipoprotein B levels. These findings underscore the potential therapeutic benefits of Ferulic acid in mitigating hyperglycemia and improving lipid profiles in diabetic rats. Hence, dietary supplements rich in FA may be helpful in ameliorating diabetes-associated lipid level abnormalities and related complications.

Abbreviations: Apo A1: Apo lipoprotein A1; Apo B: Apo lipoprotein B; FA: Ferulic acid; HbA1c: Glycated hemoglobin; HDL-C: High-density lipoprotein cholesterol; LDL-C: Lowdensity lipoprotein cholesterol; STZ: Streptozotocin; TC: Total cholesterol; TG: Triglycerides

Declaration of interest: The authors report no declarations of interest.

Author's contribution: Sudha Anjali and S Mini formulated the original idea and discussed it with K G Padmakumaran Nair and Sukanta Mondal. The focus and ideas of the paper were finally agreed upon by all authors. The experiments were conducted and analysed by Sudha Anjali and S Mini conceptualized the main ideas behind the experiments. The main text of the article was written by Sudha Anjali and S Mini. The manuscript was revised and edited by S Mini and K G Padmakumaran Nair with Sukanta Mondal contributing to the editing and writing parts.

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