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Therapeutic Potentials of Acarbose and Protocatechuic Acid in Streptozotocin- Induced Diabetic Rats

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Abstract

Diabetes mellitus is a global health concern due to its escalating prevalence. The use of acarbose as a sole treatment for diabetes cannot treat oxidative stress which occur during chronic hyperglycaemia. However, Protocatechuic acid (PCA), a natural phenolic compound, can help reduce oxidative stress linked to type 2 diabetes. This study aimed to assess the effects of Acarbose and Protocatechuic acid on diabetic rats induced with streptozotocin, to evaluate their combined potential in treating diabetes. Forty rats were divided into five groups, each with eight rats. Group 1 was the normal control group, while Groups II to V were the treatment groups. Diabetes was induced in the treatment groups using a 50 mg/kg dose of streptozotocin injected into the abdomen. Group II, the diabetic group, received only distilled water. Group III was given acarbose (25 mg/kg), Group IV received PCA (100 mg/kg), and Group V was treated with a combination of acarbose (25 mg/kg) and PCA (100 mg/kg). Treatment lasted 14 days, with regular measurements of blood glucose levels and rat weights. On the 15th day, the rats were sacrificed and blood samples were taken for biochemical analysis. Results shows significant ($p < 0.05$) decrease in (body weight, Hepatic glucose, insulin, specific activity of some glucose metabolizing enzymes, HDL-cholesterol, also, significant ($p < 0.05$) increase in (Fasting blood glucose, Cholesterol, Triglyceride level) in STZ-induced rats when compared to normal control. After treatments with acarbose and protocatechuic acid in treatment groups, resulted in significant ($p < 0.05$) increase in (body weight, Hepatic glucose, insulin, specific activity of some glucose metabolizing enzymes, HDL-cholesterol and significant ($p < 0.05$) decrease in (Fasting blood glucose, Cholesterol,

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Triglyceride level) when compare to diabetic control and the increment is comparable to normal. It is therefore, concluded that acarbose and protocatechuic acid treatment of diabetic rats may have improved or enhanced pancreatic islet regeneration, increasing insulin secretion while inhibiting oxidative damage associated with diabetics, leading to an improvement in the management of diabetes.

Keywords: Acarbose, Protocatechuic acid, streptozotocin-induced diabetic rats, Diabetes

INTRODUCTION

Diabetes mellitus (DM) is a long-term condition caused by problems with insulin production and/or how the body uses insulin, leading to high blood sugar (American Diabetes Association, 2021). There are two common types: type 1 diabetes, where the body makes less insulin, and type 2 diabetes, where the body doesn't respond well to insulin and has cell dysfunction (American Diabetes Association, 2021). Diabetes is marked by high blood sugar due to issues with insulin secretion or action (Powers, 2017).

The rising prevalence of diabetes across all age groups, genders, races, and economic backgrounds is a major global health concern (Robert and Al Darwish, 2020). Type 1 Diabetes Mellitus (T1DM) makes up 5–10% of all diabetes cases. It happens when the immune system attacks and destroys the beta cells in the pancreas, leading to a lack of insulin (Gadah, 2020). Acarbose is a common medication used to treat type 2 diabetes (Shahwan *et al.,* 2022). It works by inhibiting alpha-glucosidase in the digestive system that break down carbohydrates into simple sugars, slowing down the absorption of glucose into the bloodstream after a meal (Singh, 2022).

Protocatechuic acid (PCA) is a phenolic acid found in nature and is a member of the group of hydroxybenzoic acids (Saleem, 2022). It is known for its anti-inflammatory and anti-cancer properties, making it a promising compound for medical and pharmaceutical use (Banez *et al.,* 2021). This study aims to evaluate the therapeutic potential of acarbose and protocatechuic acid in diabetic rats induced with streptozotocin. The specific goals are to measure the rats' fasting blood sugar levels, weight changes, liver glucose levels, serum insulin levels, the activity of glucose-metabolizing enzymes, and the levels of certain lipid profile parameters in the rats.

MATERIALS AND METHODS

Materials

Acarbose is a product of Bayer Pharmaceutical Private Limited, Panchkula, Haryana, India. All other chemicals and reagents used were of analytical grade.

Assay Kits

Glucometer was a product of MDSS GmbH schiffgraben 41,30175 Hannover, Germany. Assay kit for Insulin is product of Elabscience Biotechnology Company Limited, Texas, United States of American. Assay kits for hepatic glucose, Cholesterol, Bilirubin, Triayglyceride, HDL-Cholesterol, Albumin, Urea, Sodium, Potassium, Alkaline phosphatase, Alanine aminotransferase, and Aspartate aminotransferase were products of Fortress Diagnostic Limited, United Kingdom.

Experimental animals

Forty female albino rats, each weighing around 188.52 ± 2.51g, were obtained from the Animal House at the Department of Biochemistry, University of Ibadan, Nigeria. The rats were given

one week to adjust before the experiment began. They were then divided into five groups of eight and kept in individual cages under normal environmental conditions.

Experimental induction of diabetes

Diabetes was induced in the rats with a single injection of streptozotocin (50mg/kg body weight) into the abdomen using a freshly prepared citrate buffer (0.1 M, pH 4.5) after they fasted overnight (Abdulghafoor *et al.,* 2021). Blood glucose levels were measured 72 hours after the injection using a glucometer. Rats with blood glucose levels of 5.6 mmol/L or higher were considered diabetic and selected for the study (Vishwakarma *et al.,* 2022).

Experimental design

The rats were randomly divided into five groups of eight and were given different treatments as shown in Table 1.

Table 1: Experimental design

Category	Treatments/ Dosage
Group I	Normal (1 mL of distilled water)
Group II	Diabetic control (induced diabetes and 1 mL of distilled water)
Group III	Diabetic + acarbose (25 mg/kg body weight)
Group IV	Diabetic + protocatechuic acid (100 mg/kg body weight)
Group V	Diabetic + protocatechuic acid (100 mg/kg) +acarbose (25 mg/kg)

The treatments were given as 1ml dosage for 14 days

Animal sacrifice and blood Sample Collection

The treatment lasted for 14 days, and the animals were sacrificed on the 15th day. The rats were anesthetized using diethyl ether fumes. Once they were unconscious, their jugular veins were cut to collect blood samples in sterile bottles. The blood was then centrifuged at 3000 rpm for 15 minutes to separate the serum, which was stored in a refrigerator for laboratory analysis (Yakubu *et al.,* 2009).

Preparation of tissues homogenates

The tissue homogenates were made following the method by Yakubu *et al.* (2009). The livers and kidneys were collected and dried with blotting paper. To prepare the homogenates, 1 gram of tissue was mixed with 10 mL of 6.7 mM potassium phosphate buffer at pH 7.4 and ground using a mortar and pestle. The homogenates from the livers and kidneys were then centrifuged at 3000 rpm for 10 minutes to get a clear liquid on top, and biochemical tests were performed within 24 hours of preparation.

Biochemical assay

Hepatic glucose, serum insulin and glucose metabolizing enzymes

The hepatic glucose level was measured using the GOD-PAP method, as modified by Jendrassik and Grof in 1938. Serum insulin levels were measured using a microplate immune enzymometric assay kit, following the manufacturer's instructions based on the principles from Tierz (1990). Hexokinase activity was tested using the method described by Trinder *et al.* (1969). Glucose-6-phosphate dehydrogenase activity was assessed using the method by Brandstrup *et al.* (1957), and fructose 1, 6-bisphosphatase activity was measured according to Gancedo and Gancedo (1971).

Lipid profile parameters

Total cholesterol in the serum was measured using the method outlined by Fredrickson et al. (1967). High-density lipoprotein (HDL) levels were determined using the method from Baggio

and Bragagnolo (2006). Triglycerides in the serum were measured according to the method described by Tierz (1990).

Data Analysis

The data generated from the study was presented as mean ± standard error of the mean five (5) replicates, and was subjected to one-way Analysis of Variance (ANOVA) with the aid of graph pad prisms version 9.0 statistical software (Graph pad software, inc., San Diago, California, United States). Differences was considered statistically significant at $p < 0.05$.

RESULTS

Effects of Acarbose and Protocatechuic Acid on Body Weight in Diabetic Rats Induced by Streptozotocin

The body weight of the rats significantly ($p < 0.05$) decreased in all groups after STZ administration. However, after induction and treatment, the body weight significantly ($p < 0.05$) increased following the administration of Acarbose, Protocatechuic acid, and their combination (Table 2).

Effect of Acarbose and Protocatechuic acid on fasting blood glucose level of streptozotocin induced diabetic rats

The fasting blood glucose levels of the rats increased ($p < 0.05$) significantly in all groups after STZ administration. However, after induction and treatment, the levels significantly decreased ($p < 0.05$) following the administration of Acarbose, Protocatechuic acid, and their combination (Table 3).

Effect of Acarbose and Protocatechuic acid on hepatic glucose and insulin concentration of streptozotocin induced diabetic rats.

Hepatic glucose and insulin levels significantly ($p < 0.05$) decreased after the administration of STZ. However, their levels increased ($p < 0.05$) significantly following treatment with Acarbose, Protocatechuic acid, and their combination (Table 4).

Table 2. Effect of Acarbose and Protocatechuic acid on body weight of streptozotocin-induced diabetic rats

Groups	Body Weights (g)			
	Day 0	Day 3	Day 7	Day 14
Distilled water (Control)	174.3±1.77 [a]	175.3±0.66 [a]	180.0±3.50 [a]	184±3.20[a]
STZ + Distilled water	179.0±2.52 [a]	157.7±1.45 [b]	149.7±0.33 [b]	153± 0.60 [b]
STZ + 25mg/kg Acarbose	208.0±4.16 [a]	189.7±5.81 [b]	187.3±3.60 [b]	208±0.88 [a]
STZ + 100mg/kg Protocatechuic Acid	190.7±3.93 [a]	158.3±0.88 [b]	163.0±1.50 [c]	183±0.60 [a]
STZ + Acarbose and Protocatechuic Acid	186.0±1.16 [a]	148.3±1.67 [b]	164.0±0.01 [c]	179±3.90[a]

Data are expressed as means of five determinants ±SEM. Values with different superscript are significantly different ($p < 0.05$)

Table 3. Effect of Acarbose and Protocatechuic acid on fasting blood glucose level of streptozotocin- induced diabetic rats.

Groups	Fasting blood glucose (mmol/L)			
	Day 0	Day 3	Day 7	Day 14
Distilled water (Control)	3.53± 0.09 [a]	3.37± 0.12 [a]	3.57±0.15 [a]	3.47±0.09 [a]
STZ + Distilled water	3.43± 0.09 [a]	26.90 ± 1.78 [b]	27.20±1.45 [b]	24.50±0.45 [b]
STZ + 25mg/kg Acarbose	2.70± 0.10 [b]	20.83± 0.60[b]	7.06±2.20 [a]	5.53±0.44 [c]
STZ + 100mg/kg Protocatechuic Acid	3.93± 0.03 [c]	28.43± 1.37[b]	23.60±0.84 [b]	16.77±0.37 [d]
STZ + Acarbose and Protocatechuic Acid	3.23± 0.03 [a]	27.17± 0.82 [b]	17.03±0.07 [b]	5.20±0.35 [a]

Data are expressed as means of five determinants ±SEM. Values with different superscript are significantly different ($p < 0.05$).

Table 4: Effect of Acarbose and Protocatechuic acid on hepatic glucose and insulin concentration of streptozotocin -induced diabetic rats.

Groups	Hepatic glucose concentration(mg/dl)	Insulin concentration(mg/dl)
Distilled water (Control)	62.33±3.90[a]	8.31±0.72[a]
STZ + Distilled water	27.42±0.60[b]	5.05±0.72[b]
STZ + 25mg/kg Acarbose	57.67±3.30 [c]	7.30±0.11[c]
STZ + 100mg/kg Protocatechuic Acid	63.43±1.60 [a]	7.22±0.70[c]
STZ + Acarbose and Protocatechuic Acid	62.14±2.00[a]	7.72±0.40[c]

Data are expressed as means of five determinants ±SEM. Values with different superscript are significantly different ($p < 0.05$).

Effect of Acarbose and Protocatechuic acid on some glucose metabolizing enzymes of streptozotocin induced diabetic rats.

The activity levels of glucose-6-phosphate dehydrogenase, hexokinase, and fructose 1,6-bisphosphate showed a significant (p <0 .05) decreased after STZ was given. However, these enzyme activities significantly ($p < 0.05$) increased in the treatment groups and became similar to those in the normal control group (Table 5).

Effect of Acarbose and Protocatechuic acid on level of lipid profile parameter of streptozotocin induced diabetic rats.

After STZ was administered, cholesterol and triacylglyceride levels went up significantly ($p < 0.05$), while HDL cholesterol significantly ($p < 0.05$) decreased. However, with treatment, cholesterol and triacylglyceride levels significantly ($p < 0.05$), decreased, and HDL cholesterol increased, bringing these values close to normal levels (Table 6).

Table 5: Effect of Acarbose and Protocatechuic acid on some glucose metabolizing enzymes of streptozotocin- induced diabetic rats.

Groups	specific activities of Glucose Metabolizing Enzymes (U/L/mgprotein)		
	G6PDH	Hexokinase	Fructose 1,6-Bisphosphatase
Distilled water (Control)	110.4±4.6 [a]	5.84±0.98 [a]	12.21±0.22[a]
STZ + Distilled water	52.54±2.85 [b]	2.75±0.25 [b]	9.013±068 [b]
STZ + 25mg/kg Acarbose	117.7±0.434 [a]	3.96±0.33 [a]	12.80±0.46 [a]
STZ + 100mg/kg Protocatechuic Acid	114.3±1.13 [a]	4.14±0.25 [a]	12.75±0.49 [a]
STZ + Acarbose and Protocatechuic Acid	107.6±1.95 [a]	4.269±0.55 [a]	13.85±0.06 [a]

Data are expressed as means of five determinants ±SEM. Values with different superscript are significantly different ($p < 0.05$).

Table 6: Effect of Acarbose and Protocatechuic acid on some lipid profile parameters of streptozotocin- induced diabetic rats.

Groups	Lipid Profile Parameters (mmo1/L)		
	Cholesterol concentration	Triacylglycerol concentration	HDL-cholesterol concentration
Distilled water (Control)	24.99±0.22 [a]	3.93±0.22 [a]	8.29±0.30 [a]
STZ + Distilled water	34.68±1.1[b]	5.47±0.06[b]	5.83±0.50 [b]
STZ + 25mg/kg Acarbose	26.71±1.60 [a]	4.03±0.04 [a]	7.95±0.60 [a]
STZ + 100mg/kg Protocatechuic Acid	24.75±1.60 [a]	3.83±0.04 [a]	6.94±0.13 [c]
STZ + Acarbose and Protocatechuic Acid	26.82±0.00 [a]	3.75±0.43 [a]	8.31±0.32 [a]

Data are expressed as means of five determinants ±SEM. Values with different superscript are significantly different ($p < 0.05$).

DISCUSSION

Body weight refers to the total mass of an organism, typically measured in kilograms or pounds, and is influenced by factors such as muscle mass, fat tissue, and overall health (Burridge *et al.,* 2022). In individuals with diabetes, the loss or breakdown of structural proteins due to altered metabolism can result in a significant decrease in body weight (Dilworth *et al.,* 2021). This happens because diabetes often leads to insulin resistance, which disrupts the body's ability to properly utilize glucose, causing the body to break down muscle tissue and fat for energy. As a result, a noticeable decrease in body weight is commonly observed in diabetic individuals, especially when blood glucose levels are poorly controlled. Recent study has demonstrated that several anti-diabetic drugs boost the effects of insulin, either by enhancing the insulin production from the pancreatic islets of Langerhans cells or by using processes outside the pancreas to reduce hepatic glucose production and correct insulin resistance (Kalra *et al.*, 2021). This present study, experimental diabetes was established in the rats intraperitoneally when injected with streptozotocin. Streptozotocin is a toxin that specifically destroys pancreatic beta cells, resulting in an inadequate supply of the hormone insulin. After the third day of treatment, the fasting blood glucose levels were measured, showing that all the rats had high glucose levels, indicating they had diabetes. This high blood sugar remained throughout the 14-day treatment period, just like in the untreated diabetic rats. However, when diabetic rats were treated with acarbose, protocatechuic acid, or both, their body weight significantly increased after initially decreasing, likely due to the positive effects of these drugs.

In comparison to the untreated diabetic group, fasting blood glucose levels significantly decreased across all treatment groups, which may indicate that acarbose can improve peripheral glucose absorption and insulin sensitivity. In comparison to the separate treatments of acarbose and protocatechuic acid alone, the combination therapy of acarbose and protocatechuic acid had a greater effect in reducing fasting blood glucose levels (Uuh and Segura, 2022).

Hepatic glucose concentration refers to the amount of glucose stored in the liver. The liver plays an important role in controlling blood sugar levels by storing glucose when there's excess and releasing it when the body needs energy. This helps maintain stable blood sugar levels and ensures the body has a steady supply of energy (Qaid and Abdelrahman, 2016). The liver absorbs excess glucose and converts it to glycogen through a process known as glycogenesis, which helps to reduce blood glucose levels. There are various factors for the lower hepatic glucose levels in diabetic rats compared to normal controls, one of which may be the liver's decreased ability to synthesise glycogen. Diabetes affects the normal process of storing glucose as glycogen in the liver, which ultimately leads to lower hepatic glucose levels. Issues like insulin resistance or inadequate insulin production interrupt this process. (Laurenti and colleagues, 2021). The significant increase in insulin concentration across treatments groups may imply a significant improvement in glycaemic control in diabetic rats. as reported by Bamosa *et al.* 2010.

The decrease in the activity of enzymes like G6PDH, F-1,6-BPase, and Hexokinase in the untreated diabetic group might be due to a lack of insulin, caused by the destruction of insulin-producing cells in the pancreas by streptozotocin. However, the treatment groups showed an increase in enzyme activity, which was within the normal range, likely due to the beneficial effects of the drugs. This finding supports the results of Sellamuthu *et al.* (2014). The significant rise in cholesterol and triacylglyceride levels in the untreated group could be because insulin plays a key role in regulating fat metabolism, including the breakdown and storage of triacylglycerides (Zhang *et al.,* 2022). Insulin deficiency also affect various enzyme and processes involved in lipid metabolism. Insulin normally inhibits enzyme lipoprotein lipase which breakdown triacylglyceride in circulating lipoproteins thereby reducing their level (Kersten, 2017). In untreated diabetes, lack of insulin prevents efficient utilization of glucose as energy source leading to increase in breakdown of fats (lipolysis) and elevated production of triacylglyceride in the liver, which also lead to elevated level of cholesterol (Farooqi, and O'Rahilly, 2006). The reduced level of triacylglyceride and cholesterol across the treatment groups may be due to improved insulin secretion across the treatment groups which might be due to beneficial effect of the drugs.

The significant increase in the level of HDL-cholesterol across the treatment groups which may contribute to its cardioprotective effects of the drugs. Elevated levels of HDL-cholesterol have been consistently linked to a decreased risk of cardiovascular disease. Higher levels of HDL-cholesterol are associated with cardiovascular outcomes, including a lower incidence of coronary artery disease and reduced risk of atherosclerosis (Rader and Hovingh, 2014).

CONCLUSION

Acarbose and protocatechuic acid treatment of diabetic rats may have improved and enhanced pancreatic islet regeneration, increasing insulin secretion while inhibiting oxidative damage associated with diabetics, leading to an improvement in the management of diabetes. Acarbose is ineffective in treating oxidative stress brought on by persistent hyperglycaemia, which is a complication of diabetes. Acarbose and protocatechuic acid work together to

significantly lower glucose levels and decrease oxidative damage related to diabetes. To further ascertain their efficacy, investigation on the synergistic mechanism of action acarbose and protocatechuic acid in reducing oxidative stress and hyperglycaemia in diabetes.

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