Research Article

Syringic Acid Alleviates Hyperglycemia by Regulating Hepatic Key Enzymes of Carbohydrate Metabolism in Streptozotocin-induced Diabetic Rats

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ABSTRACT

Background: Diabetes mellitus is a complex metabolic disorder characterized by the development of hyperglycemia due to impaired insulin production, insulin action, or both. The persistent hyperglycemia associated with diabetes can lead to an increased risk of developing severe health problems. This study examines whether the bioactive phenolic compound Syringic Acid (SA) mitigates hyperglycemia in streptozotocin-induced diabetic rats. **Materials and Methods:** A total of 30 male Sprague-Dawley rats were utilized in the investigation, and they were split into five groups: Normal (N), Normal+Syringic Acid (N+SA), Diabetic Control (DC), Diabetic+Syringic Acid (D+SA), and Diabetic+Glimepiride (D+GM). A single dose of streptozotocin (40 mg/kg) injected intraperitoneally was used to induce diabetes. Syringic Acid (SA) was given orally once a day for 60 days at a dose of 50 mg/Kg body weight. The levels of plasma insulin, glucose, glycated haemoglobin, and the activity of carbohydrate metabolizing enzymes were examined. Results were compared with diabetic rats provided with the standard drug glimepiride (0.1 mg/kg). **Results:** Syringic acid treatment substantially lowered hyperglycemia, enhanced insulin levels, and lowered HbA_{1c}, in diabetic rats when given at a dose of 50 mg/Kg body weight. Additionally, syringic acid exhibited the ability to considerably lower the activities of fructose 1,6-bisphosphatase and glucose-6 phosphatase while significantly increasing the activities of glycolytic enzymes like pyruvate kinase and hexokinase. **Conclusion:** These results imply that syringic acid could potentially attenuate hyperglycemia in streptozotocin-induced diabetic rats by modulating carbohydrate metabolism.

Keywords: Syringic acid, Glimepiride, Hyperglycemia, Carbohydrate metabolism.

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INTRODUCTION

Diabetes mellitus is a chronic metabolic disorder that is primarily defined by hyperglycemia and results from abnormalities in insulin secretion, insulin action, or both. Diabetes remains one of the top causes of mortality, with increasing overall prevalence rates and a rising proportion of patients with associated complications. Chronic hyperglycemia, a compromised metabolism, an increase in reactive oxygen species production, and a weakened antioxidant defence system are the key factors in the emergence of diabetic complications.[1] Even though the lifespan of patients with diabetes has improved with insulin therapy and newer hypoglycemic drugs, chronic complications of the disease are on the rise.

The liver plays a significant role in carbohydrate metabolism. Diabetes deranges carbohydrate metabolism by low levels of enzymes like hexokinase and pyruvate kinase due to impaired insulin secretion. The result is an increase in hepatic glucose synthesis and

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a decrease in peripheral glucose consumption.[2] Chronic hyperglycemia can cause acute reversible metabolic and cumulative irreversible changes if prolonged. Glycation of proteins and subsequent changes in their structure and function are common mechanisms of glucose-induced damage. Further changes can lead to the formation of advanced glycation products with extensive cross-linking. They may trigger the production of free oxygen radicals, which are capable of damaging tissue and causing severe complications.[3]

Diabetes can be controlled by careful monitoring of blood glucose levels, timely administration of exogenous insulin, or consumption of oral hypoglycemic agents alongside proper exercise and diet. However, patients may suffer from several complications associated with these treatment methods. Hypoglycemic agents such as sulfonylureas cause weight gain, low blood sugar, skin rashes, and stomach upset, whereas biguanides cause dizziness, fatigue, and kidney complications. Alpha-glucosidase inhibitors, meglitinides, and SGLT 2 inhibitors cause weight gain, bloating, and hypoglycemia. These drugs are also expensive, ineffective, and have poor tolerability. Therefore, scientific attention has been paid to alternative therapies like herbal medicines.[4]

An easily accessible, affordable, and culturally acceptable form of healthcare, phytotherapy helps to manage several chronic non-communicable diseases. Phytochemicals have attracted scientific interest owing to their antioxidant, anti-inflammatory, antimutagenic, and anticarcinogenic properties. Polyphenols are secondary plant metabolites that protect plants from oxidative stress, ultraviolet radiation, and some herbivores.[5]

Syringic acid is a naturally occurring O-methylated trihydroxybenzoic acid (4-hydroxy3,5-dimethoxybenzoic acid). It is a potent bioactive phenolic compound present in many fruits and vegetables, including olives, dates, and pumpkins.[6] They are produced via the shikimic acid pathway in plants. Syringaldehyde, a natural derivative of syringic acid, is found in grapes and red wine.[7] Syringic acid is also present in some pharmacologically important fungal species, such as *Inonotus obliquus* and *Elaphomyces granula*.[8,9] Syringic acid exhibits numerous pharmacologic properties, such as significant anti-inflammatory, antibacterial, antiproliferative, antiendotoxic, antioxidant, and anticancer properties. In this study, Syringic Acid (SA), a bioactive phenolic compound, is evaluated for its effect on hyperglycemia in streptozotocin-induced diabetic rats.

MATERIALS AND METHODS

Experimental animals

This experiment was conducted using 30 male albino Sprague Dawley rats, each weighing 150-180g, that were bred in the animal house, Department of Biochemistry. All animal care was provided in accordance with the Institutional Animal Ethics Committee's authorized experimental protocol [IAEC 3-KU-02/2018-19-BCH-SM (42)] and as per the recommendations of the Committee for the Purpose of Control and Supervision of Experiments on Animals.

Experimental design

Five groups of six rats each were formed from the animal population. The groups included were;

- Normal (N) rat in - Group I
- Normal rats treated with SA, 50mg/kg body weight (N+SA) in - Group II
- Diabetic Control (DC) rats in - Group III
- Diabetic rats treated with SA, 50mg/kg body weight (D+SA)in - Group IV.[10]
- Diabetic rats treated with the standard drug glimepiride, 0.1mg/kg body weight (D+GM)in - Group V.[11]

A single intraperitoneal injection of freshly prepared STZ at a dose of 40 mg/kg body weight in 0.1M citrate buffer was used to induce diabetes in groups III, IV, and V. To treat the drug-induced hypoglycemia, 5% glucose in drinking water was given to the animals overnight. On the third day after administering STZ injections, the animals were considered diabetic if their blood glucose levels were more than 250 mg/dL. Diabetic rats were treated with syringic acid and glimepiride daily for 60 days by oral intubation. The research employed syringic acid that was purchased from Sigma Aldrich. Throughout the experiment, animals received standard pellet diets and water *ad libitum*.

Biochemical parameters

Blood glucose was measured using the glucose oxidase method,[12] glycated hemoglobin was measured using a HbA_{1c} kit from Beacon Diagnostics Pvt. Ltd., and plasma insulin was measured using the ELISA kit purchased from DRG diagnostics, Germany. The procedure outlined by Crane and Sols (1953)[13] was used to test the activity of the glycolytic enzyme hexokinase and that of pyruvate kinase by the Bucher and Pfleiderer method (1955).[14] The protocols outlined by Koide and Oda in 1959[15] and Pontremoli in 1966[16] were used in the current investigation to assess the activity of

glucose-6-phosphatase and fructose 1,6-diphosphatase, respectively.

Statistical analysis

Values were presented as the mean±standard error. One-way ANOVA was used for statistical analysis in SPSS version 17. Statistically significant differences across groups were found using Duncan's *post hoc* multiple comparison tests. Significance was accepted at $p < 0.05$.

RESULTS

Blood glucose, HbA_{1c}, and plasma insulin

In Diabetic (DC) rats compared to normal groups, blood glucose and HbA_{1c} levels were considerably higher (Figure 1). Administration of SA and glimepiride significantly reduced the levels of glucose and HbA_{1c} in comparison with diabetic rats. When compared to normal rats, plasma insulin levels were considerably lower in the diabetes group. When compared to levels found in diabetic control rats, the administration of SA and glimepiride to diabetic rats significantly elevated the amount of plasma insulin. The superior effect is shown by syringic acid administration.

Activity of hepatic glycolytic enzymes

Hexokinase (HK) and Pyruvate Kinase (PK) activity in the diabetes group were substantially lower than those in the control group ($p<0.05$). In normal and normal rats treated with SA, the activity of glycolytic enzymes were comparable. Supplementation of SA and glimepiride to diabetic rats significantly increased the activities of these enzymes when compared to untreated diabetic rats. A superior effect was shown by SA supplementation than glimepiride in diabetic rats. The results are displayed in Figure 2.

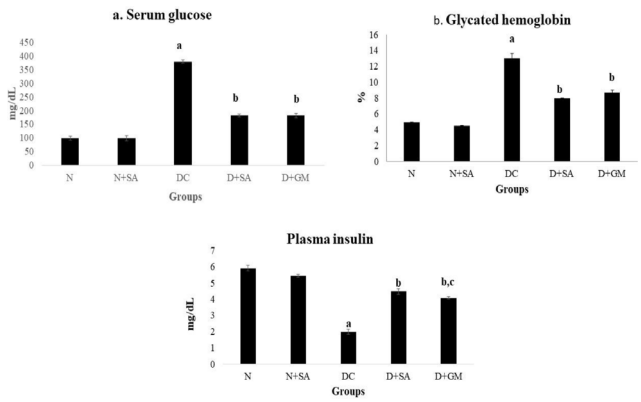

Figure 1: Serum glucose, HbA_{1c} and plasma insulin levels.

Values are expressed as mean ± SEM ($n=6$). 'a' indicates values were significantly different from N, DC is compared with D+SA and D+GM ('b' indicates values were significantly different from DC) and D+SA is compared with D+GM ('c' indicates values were significantly different from D+SA). Significance accepted at $p < 0.05$

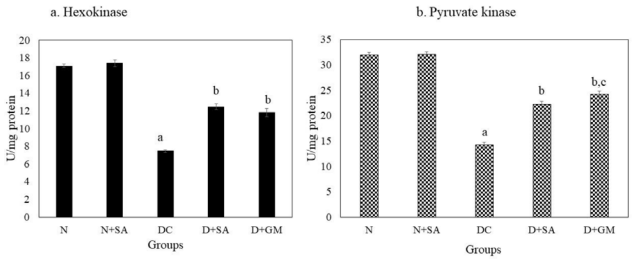

Figure 2: a. Activity of Hexokinase b. Activity of pyruvate kinase.

Values are expressed as mean ± SEM ($n=6$). 'a' indicates values were significantly different from N, DC is compared with D+SA and D+GM ('b' indicates values were significantly different from DC) and D+SA is compared with D+GM ('c' indicates values were significantly different from D+SA). Significance accepted at $p < 0.05$.

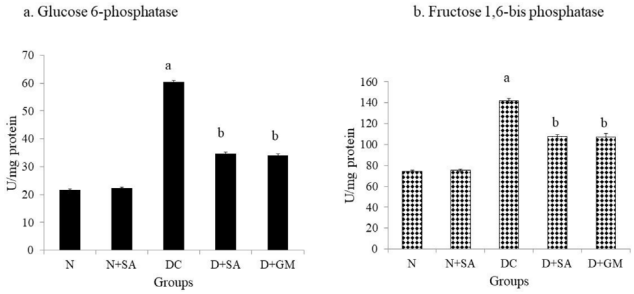

Figure 3: a. Activity of Glucose 6-phosphatase b. Activity of fructose 1,6-bis phosphatase.

Values are expressed as mean ± SEM ($n=6$). 'a' indicates values were significantly different from N, DC is compared with D+SA and D+GM ('b' indicates values were significantly different from DC) and D+SA is compared with D+GM. Significance accepted at $p < 0.05$.

Activity of hepatic gluconeogenic enzymes

When compared to normal rats, the activity of the gluconeogenic enzymes fructose-1,6-bisphosphatase (F-1,6 Pase) and glucose-6-phosphatase (G-6 Pase) were considerably higher in diabetic rats ($p<0.05$). Compared to untreated diabetic rats, the activity of these enzymes were markedly reduced after the administration of SA and glimepiride to diabetic rats. The effects were comparable in SA and glimepiride-treated groups. In both normal and normal rats treated with SA, these enzymes' activities were similar. The results are shown in Figure 3.

DISCUSSION

Chronic alterations in protein, lipid, and carbohydrate metabolism are a hallmark of diabetes mellitus. Diabetes causes persistent and chronic hyperglycemia that can damage vital organs, including the heart, liver, kidneys, nerves, and blood vessels.[17] There is increasing evidence that free radicals created by glucose oxidation and protein

glycation, as well as a compromised antioxidant defense system, is a key factor in the development of diabetes. In our study, we used the STZ-induced diabetic model that has been used for inducing diabetic complications for a long time and has undergone substantial research and review. Animal models of diabetes with STZ have been highly useful in explaining diabetic pathogenesis and in evaluating synthetic compounds, natural products, and other pharmaceutical agents that may reduce hyperglycemia. As a standard drug, we used glimepiride, which is an insulin secretagogue, to compare the effect of syringic acid on diabetic rats. Thus, the underlying mechanisms of syringic acid's pharmacological activity under diabetic conditions can be compared with those of the commercial antidiabetic medication, glimepiride.

Chronic hyperglycemia results from insufficient insulin production with or without concurrent impairment of insulin action.[18] Since haemoglobin and other proteins are glycated in response to hyperglycemia, HbA_{1c} is a widely used biochemical test for evaluating diabetes. The extent of haemoglobin glycation is influenced by the amount of glucose present in the blood.[19] Furthermore, glucose oxidation is hindered, insulin production is reduced, and insulin secretion is diminished in streptozotocin-induced diabetic rats.[20] Our results are in agreement with this as blood glucose, and HbA_{1c} levels were significantly raised and plasma insulin level was diminished in diabetic groups when compared to the normal and normal rats treated with syringic acid. There are reports that phenolic acids promote the insulin response, boost the production of glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1, and thereby regulate postprandial glycemia and decrease glucose intolerance (GLP-1).[21] In our study, in comparison to diabetic control rats, SA and glimepiride-treated diabetic rats showed lower blood glucose and glycated haemoglobin levels (Figure 1 a and b). Increased insulin production may improve glucose utilization, which in turn reduces blood glucose levels and glycosylation of haemoglobin. Our results are in line with the previous study conducted by Khanv *et al*, which revealed that gallic acid regulates glucose homeostasis by activation of AMPK pathway in streptozotocin-induced diabetes.[22] HbA_{1c} and blood sugar levels in the N and N+SA treated groups did not significantly differ from one other. SA and glimepiride showed comparable effects on diabetic rats. Furthermore, SA and glimepiride could both enhance plasma insulin levels (Figure 1c), with SA showing superior effects. When compared to the standard insulin secretagogue drug glimepiride, syringic acid has a superior effect on insulin secretion, implying that syringic acid has beneficial effects on beta cell insulin secretion, which is crucial for managing diabetes and associated complications. The results of this study are consistent with those of Muthukumaran *et al*. in 2013, who showed that syringic acid treatment had higher C-peptide levels, which might be indicative of improved proinsulin to insulin conversion. Additionally, they demonstrated that syringic acid augmented insulin secretion from beta cells.[23]

The liver plays a crucial role in glucose homeostasis. The alteration of hepatic carbohydrate metabolism contributes to the severity and progression of diabetes mellitus. In diabetes, several key enzymes involved in carbohydrate metabolism are altered. Multiple studies have shown that hyperglycemia in diabetes decreases glycolytic enzyme activity and increases gluconeogenic and glycogenolytic activity.[24] The activity of glycolytic enzymes hexokinase and pyruvate kinase in the liver are lowered during diabetes; however, the activity of gluconeogenic enzymes glucose 6 phosphatases, fructose 1-6 -bisphosphatase are elevated[25] during the diabetic condition.

These two events directly contribute to the underutilization of glucose by the liver. Hexokinase and pyruvate kinase are two key enzymes involved in the catabolism of glucose. Hexokinase and pyruvate kinase are two of the primary enzymes that are affected by partial or total insulin insufficiency. This results in impaired peripheral glucose consumption and increased hepatic glucose synthesis.[26] Small allosteric activators of the enzyme hexokinase have been demonstrated to lower blood glucose levels by increasing glucose-stimulated insulin secretion in the pancreas, increasing glucose uptake, and decreasing glucose production in the liver.[27] Hexokinase is an insulin-dependent enzyme; under diabetic conditions, the enzyme activity is reduced, resulting in a reduction in glucose oxidation by glycolysis. This contributes to the development of chronic hyperglycemia.[28] The conversion of phosphoenol pyruvate to pyruvate with the production of ATP is catalyzed by the widely distributed, rate-regulating glycolytic enzyme known as pyruvate kinase. Reduced glucose utilization is a side effect of decreased pyruvate kinase activity.[29] It was found in the current study that the activity of these glycolytic enzymes was reduced in the liver of diabetic control rats. Due to their ability to increase glucokinase activity and build up glycogen in the liver, phenolic acids may have anti-diabetic effects. Additionally, studies have shown that gallic acid's antidiabetic properties depend on its ability to promote GLUT4 translocation and induce glucose uptake.[30] In diabetic rats, SA markedly elevated the activities of pyruvate kinase and hexokinase. With

glimepiride, similar outcomes were seen. According to our results, both syringic acid and glimepiride could improve glycolysis, which is a key component of their anti-hyperglycemic effects. These findings are in agreement with those reported by Narasimhan *et al.*, 2015, who demonstrated ferulic acid's antidiabetic properties by modulating glucokinase activity in diabetic rats given a high-fat diet and fructose.

Diabetes is associated with increased gluconeogenesis, which increases blood glucose levels. Gluconeogenesis pathway enzymes, including glucose 6-phosphatase and fructose 1,6-biphosphatase, are persistently activated in the liver tissues of diabetic rats.[32] Glucose 6-phosphatase is the enzyme that catalyzes the conversion of glucose 6- phosphate to glucose in the last phase of gluconeogenesis. Under normal conditions, insulin inhibits the enzymes fructose 1, 6-bisphosphatase, and glucose 6-phosphatase so as to suppress gluconeogenesis.[33,34] The activities of these gluconeogenic enzymes were found to be increased in the diabetic control group. The increase in activity of glucose 6- phosphatase and fructose 1,6-bis phosphatase may be due to insulin insufficiency.[35,36] In addition to increased hepatic glucose synthesis, the increased Glucose-6-phosphatase activity also reduces the amount of glucose that is used by the liver.[37] In addition, elevated gluconeogenesis under diabetic condition promotes hyperglycemia, and the resulting glucose can act as a precursor for the AGE, polyol, hexosamine, protein kinase C, and other pathways that have been linked to the pathophysiology of type 2 diabetes complications.[38] In diabetic rats, the administration of SA and glimepiride reduced the activity of these gluconeogenic enzymes. These results are in agreement with the previous study conducted by Huang *et al.*, 2016 which stated that gallic acid improved hyperglycemia by improving carbohydrate metabolism in hight-fructose diet diabetic rats.[39] The anti-hyperglycemic effect of syringic acid can be thus observed via its ability to regulate the activities of glycolytic and gluconeogenic enzymes. This suggests that syringic acid could substantially lower hyperglycemia and thus can be used as a potent therapeutic molecule in the management of hyperglycemia and other complications associated with diabetes even though further studies are required to elucidate the exact mechanism underlying the role of syringic acid in regulating the enzymes of carbohydrate metabolism.

CONCLUSION

Diabetes is a chronic metabolic disease in which the body's ability to produce or respond to insulin is impaired. Diabetes prevalence is steadily rising and is especially prevalent in middle-income countries.[40] Unfortunately, the management of diabetes is not well pursued due to the lack of access to quality health care and also due to the complications and side effects associated with current therapeutic agents. In order to address this growing health challenge, scientists are focusing on phytotherapy since it is natural, effective, and non-toxic, with reduced risk of side effects. In the present study, we evaluated the effect of syringic acid, a bioactive phenolic compound in experimentally induced diabetic rats. The study clearly indicates that supplementation of SA and glimepiride treatment for 60 days modulated serum glucose, plasma insulin and glycated Haemoglobin (HbA_{1c}). Supplementation of SA and glimepiride in diabetic rats significantly increased the activities of glycolytic enzymes, viz., hexokinase and pyruvate kinase, and significantly decreased the activities of gluconeogenic enzymes such as glucose-6-phosphatase and fructose - 1,6 bis phosphatase in the liver. The findings of our study clearly indicate that SA could potentially ameliorate hyperglycemia via modulating hepatic carbohydrate-metabolizing enzymes. Thus, SA can be used as a potent candidate for the management of diabetes complications even though further research is needed for the practical implication of the same.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

DC: Diabetic control group; **GM:** Glimepiride; **HbA_{1c}:** Glycated hemoglobin; **HK:** Hexokinase; **PK:** Pyruvate kinase; **SA:** Syringic acid.

SUMMARY

Diabetes mellitus is the most prevalent metabolic disorder, mainly characterized by hyperglycemia.

Diabetes can be managed by the use of oral hypoglycemic agents but there are several side effects associated with synthetic drugs. Here comes the relevance of phytochemicals with multipharmacological properties and are relatively cheap and easily available. Syringic Acid (SA) in one such biologically active phytochemical. In the present study we evaluated the effect of SA in experimentally induced diabetic rats. The results of our study revealed that SA could ameliorate hyperglycemia as evidenced by the reduced blood glucose and glycated hemoglobin and improved insulin levels in SA treated rats. Syringic acid could also substantially modulate the activity of enzymes involved in carbohydrate metabolism including glycolysis and gluconeogenesis enzymes. The ameliorative potential of syringic acid was comparable to that of the standard drug Glimepiride. Thus it is evident from our results that SA could be used as a potent therapeutic molecule for the management of hyperglycemia and other complications associated with Diabetes mellitus.

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