

Ameliorative Effect of Ginger on Blood Glucose Levels and Cardiac TCA Cycle Enzymes Activity in STZ Induced Diabetic Rat

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Article History	Abstract
Received: 26 June 2023 Revised: 05 Sept 2023 Accepted: 22 Oct 2023	<i>This study aimed to investigate the effects of ginger administration on altered blood glucose levels, cytosolic and mitochondrial enzymes (TCA cycle enzymes) activity in streptozotocin-induced diabetes rats. The study divided Wistar strain rats into five groups: normal control, ginger treated, diabetic control, diabetic plus ginger treated, and diabetic plus glibenclamide treated groups. The diabetic group had significantly elevated blood glucose levels, which were significantly lowered by ginger administration. The cytosolic enzyme G6PDH activity was significantly ($P<0.001$) decreased along with a significant increase in the LDH activity in diabetic rats heart tissue. The activities of SDH, MDH, GDH in the heart tissue of diabetic rats were significantly decreased, but the daily oral treatment of ginger to diabetic rats for thirty days reversed the above changes in a significant ($P<0.001$) manner. The study demonstrated that an ethanolic extract of ginger could lower blood glucose levels, improve enzyme activities and body weight in diabetic rats. This suggests that ginger extracts could be used as a cardio-protective supplement to reverse diabetic-induced complications.</i>
CC License CC-BY-NC-SA 4.0	Keywords: Diabetes, ginger, blood glucose, LDH, SDH, MDH, GDH

1. Introduction

Diabetes is widely recognized that prolonged elevated blood sugar levels, commonly known as chronic hyperglycaemia, can lead to severe harm, impaired functionality, and ultimately organ failure. This particularly holds true for vital organs such as the kidneys, nerves, heart, eyes, and blood vessels (Lai et al., 2009). Consequently, diabetes is a prominent global contributor to mortality and disability. The International Diabetes Federation (IDF) projects that the global diabetic population will reach 380 million by 2025 (Sicree et al., 2003). Over 62 million people in India are estimated to be affected by diabetes.

Mitochondria play a vital role in diabetes research as they are crucial in regulating energy balance. Various enzymes linked to NAD/NADP are intricately involved in maintaining a reduced redox state within mitochondria. This is important as it provides the necessary reducing power to generate ATP through oxidative phosphorylation (Maechler et al., 2001). The mitochondria's increased production of free radicals can harm β -cells, which are highly susceptible to these harmful molecules. Additionally, a decrease in oxygen consumption and respiratory ratio has been observed. Moreover, alloxan-induced diabetic rats have shown a reduction in pyruvate dehydrogenase activity and an increase in the NAD⁺/NADH ratio. Researchers propose that streptozotocin's ability to cause diabetes is linked to its inhibition of citric acid cycle enzymes (Devlin., 2001).

Plants and herbs harbour a vast array of bioactive phytochemicals, making them valuable resources for discovering novel drugs that are effective, safe, and affordable. These phytochemicals can potentially lead to the development of new medications. In certain difficult cases where conventional medicines have proven ineffective, herbal formulations, either on their own or in combination with oral hypoglycaemic agents, have shown positive therapeutic outcomes (Adeyi et al., 2012). In the present study we have selected a spice *Zingiber officinale*, commonly known as ginger. The pharmacological effects of ginger rhizomes are diverse and include antimicrobial, analgesic, antiulcer, anti-diabetic, cardiogenic, anti-inflammatory, immuno-stimulant, and antioxidant properties (Young et al., 2005.,

Shanmugam et al., 2010). *Zingiber officinale* rhizome contains a wide range of chemical compounds, such as (6)-gingerol, α -zingiberene, phenolic compounds, essential oils, and oleoresin resins (Van et al., 2004). These compounds are known for their antioxidant, hypolipidemic, and hypocholesteremic properties (Srinivasan et al., 1991). The objectives of this study are thus to examine the impact ginger extract on cardiac enzymes involved in mitochondrial in diabetes.

2. Materials And Methods

Animal care and maintenance

This study used male albino Wistar rats with a body weight ranging from 180 ± 200 grams. The rats were housed in clean polypropylene cages, with six rats per cage, in a hygienic environment. The room temperature was maintained at $27 \pm 2^\circ\text{C}$, and the rats were exposed to a 12-hour light and 12-hour dark cycle. The care and handling of the rats followed the guidelines of the National Institute of Nutrition, Indian Council of Medical Research, Hyderabad, India, and were approved by the Institutional Animal Ethical Committee at S.V. University, Tirupati, Andhra Pradesh. Throughout the duration of the experiment, the rats had access to standard rat pellet diet (provided by Lipton India Ltd., Mumbai, India) and water ad libitum.

Chemicals & Induction of Diabetes:

The chemicals used in the present study were of high purity (analar grade) and were obtained from reputable companies, including Fischer (Pittsburgh, PA, USA), Sigma (St. Louis, MO, USA), Ranbaxy (New Delhi, India), Merck (Mumbai, India), and Qualigens (Mumbai, India).

Diabetes was induced in healthy male Wistar albino rats, aged around 3 months, and weighing between 200-250 g. This was done by administering a single intraperitoneal injection of freshly prepared streptozotocin (STZ) at a dosage of 40 mg/kg body weight. The STZ was dissolved in ice-cold 0.1 M citrate buffer with a pH of 4.5. Prior to the injection, the rats were fasted overnight for 12-15 hours, following the protocol established by Rakiety et al. 8 hours after the STZ administration, the rats were given a 15% glucose solution for the next 24 hours to prevent hypoglycaemia. This step was necessary because STZ can cause fatal hypoglycaemia by destroying the beta cells in the pancreas, leading to excessive insulin release. To assess the development of diabetes, the fasting blood glucose levels were measured 48 hours after the STZ injection. The blood glucose levels in the rats administered with STZ were significantly higher compared to normal levels. After one week, when the diabetic condition was stabilized, rats with severe hyperglycaemia (blood glucose level ≥ 250 mg/dl) were selected for further analysis. Blood samples were collected from the tail vein for subsequent testing and analysing.

Preparation ginger extract:

The study began by purchasing fresh ginger rhizomes from the local market in August. These rhizomes were then air dried. Two kilograms of the air-dried ginger was ground into a fine powder and subjected to cold percolation with 95% ethanol for 24 hours. The extract was then collected, and more 95% ethanol was added to the ginger powder. This process of extraction was repeated three times. The three extracts were combined, filtered, and the filtrate was concentrated to dryness using a rotary evaporator under reduced pressure. The resulting ethanolic extract was air dried, resulting in a dark-brown, gelatinous substance, which was then weighed. This extract was used for the experiments without any further purification. The dose equivalent to 200 mg of extract per kg body weight was calculated and suspended in a 2% tween-80 (v/v) solution for the experiments, following the methodology described by Bhandari et al., (2005).

The rats were divided into 5 groups, six rats in each group and treated as follows:

I). Normal Control (NC): This group of rats received vehicle solution (2% of tween 80).

II) Ginger treatment (Gt): This group of rats received ginger ethanolic extract via orogastric tube for a period of thirty days at the dose of 200 mg/kg body weight.

III): Diabetic control (DC): Streptozotocin is given intraperitoneally for the induction of diabetes to this group (STZ 50 mg/kg body weight).

IV). Diabetic on Ginger treatment, (D+Gt): Diabetic rats received ginger ethanolic extract as described in group II for a period of 30 days

V): Diabetic on Glibenclamide treatment (D+Gli): Diabetic rats treated with glibenclamide 600 $\mu\text{g/kg}$ body weight in aqueous solution orally for a period of 30 days.

Analytical procedures

After undergoing a 30-day treatment, the animals were euthanized by cervical dislocation. The heart tissue was then extracted at a temperature of 4°C . Subsequently, the tissue was rinsed with ice-cold saline solution. It was then submerged in liquid nitrogen and promptly stored in a deep freezer at a temperature of -80°C in order to facilitate subsequent biochemical analysis. We conducted assays to

measure the activity of various enzymes in the cytosol and mitochondria. The activity of glucose-6-phosphate dehydrogenase (G6PD) was measured following the method developed by Lohr and Waller (1974). Lactate dehydrogenase (LDH) activity was monitored using the method modified by Prameelamma and Swami (1975), based on the technique initially described by Nachlas et al. (19). The modified version of Nachlas et al. (1960) was also used to assay the activity of mitochondrial enzymes, including succinate dehydrogenase (SDH) and malate dehydrogenase (MDH). Additionally, we determined the activity of glutamate dehydrogenase (GDH) using the method established by Lee and Lardy (1965). All enzymatic assays were performed using the crude homogenate of the heart. Blood samples were collected from all the rats before sacrifice and blood glucose levels were estimated. Body weights before and after treatment and body weights immediately after sacrifice were recorded.

Statistical Analysis:

The data were analysed by using SPSS (Version 13.5; SPSS Inc., Chicago, IL, USA) and M.S. Office Excel Software for the significance of the main effects and along with their interactions. One way analysis of variance (ANOVA) was carried out with Dunnett's multiple comparison test and differences were considered significant at $P < 0.001$.

3. Results and Discussion

Effects of Ginger Extract on Blood Glucose Levels and Body Weight Changes

The blood glucose levels in diabetic rats that were injected with streptozotocin (STZ) were significantly higher compared to normal control rats. This increase in blood glucose levels was almost three times higher even after a period of 30 days compared to the control rats. However, we observed that the administration of ginger for 30 days significantly decreased the elevated blood glucose levels in diabetic rats ($p < 0.001$). We also compared the effects of ginger extract with a standard antidiabetic reference drug called glibenclamide. Glibenclamide also showed a significant decrease in blood glucose levels ($p < 0.001$), which was comparable to the levels observed in the normal control rats (Table 1). Furthermore, we observed a significant decrease in body weight in the diabetic rats compared to the normal control rats over the course of 30 days ($p < 0.001$). However, when the diabetic rats were treated with ginger, their body weights significantly increased (Table 2).

Table 1. Effect of ginger and glibenclamide on blood glucose level in diabetic rats

Groups	Blood Glucose (mg/dl)		
	0 th day	15 th day	30day
Group I	82±1.37	86±1.028	93±2.6
Group II	85±1.26	84±1.64	80±1.87*
Group III	261±2.97	276±6.32*	268±14.4*
Group IV	267±3.98	181±6.59*	141±5.27*
Group V	269±1.65	146±7.21*	95±3.84*

All the values are mean, \pm SD of six individual observations, *significant at $p < 0.001$

Table 2: Effect of ginger and glibenclamide on body weight change in diabetic rats

Groups	Body weight(grams)		
	0 th day	15 th day	30day
Group I	193±9.58	195.5±2.64	217±14.28
Group II	198±6.94	191±8.51	189±7.95
Group III	185±2.69*	169±3.58	148±5.32
Group IV	185±6.32	176±3.7*	190±4.08
Group V	189±3.56*	185±6.98	204±0.05

All the values are mean, \pm SD of six individual observations, *significant at $p < 0.001$

Table 3: Effect of ginger and glibenclamide on heart G-6-PDH, LDH, SDH, MDH, GDH enzymes activities in the control and experimental groups

Parameter	Group I	Group II	Group III	Group IV	Group V
G-6-PDH [†]	6.32±0.18	6.55±0.06	3.89±0.09*	4.98±0.17**	4.54±0.06**
LDH [†]	3.59±0.05	3.62±0.09	5.28±0.04*	4.68±0.12**	4.27±0.12**
SDH [†]	7.86±0.12	7.94±0.09	4.97±0.08*	6.95±0.14**	6.35±0.14**
MDH [†]	6.25±0.08	6.32±0.07	4.25±0.09*	5.97±0.12**	5.21±0.10**
GDH [†]	8.37±0.19	8.57±0.05	6.01±0.06*	7.88±0.075**	7.16±0.03**

[†] (μ moles of formazan formed/mg protein/h). Value represents mean \pm SD for 6 rats per group. * $P < 0.01$ as compared to normal, nondiabetic rats' group. ** $P < 0.01$ as compared to nontreated diabetic rats

Effects of ginger Ethanolic Extract on cardiac cytosolic and mitochondrial enzymes

The activity of the cytosolic enzyme G6PDH was found to be significantly decreased ($p < 0.001$) in diabetic rats, while the activity of LDH was significantly increased. Treatment with glibenclamide, a medication commonly used to manage diabetes, showed similar effects as the daily oral administration of ginger to diabetic rats for 30 days. This reversed the changes in G6PDH and LDH activities in a significant manner ($p < 0.001$). In contrast, the activity of G6PDH and LDH remained unchanged in control rats that were treated with ginger alone.

The activities of mitochondrial enzymes (SDH, MDH, GDH) were found to be significantly decreased ($p < 0.001$) in diabetic control rats compared to normal control rats. However, in control rats treated with ginger alone, there were no significant changes observed in the activity of these enzymes. On the other hand, oral administration of ginger to diabetic rats led to a significant increase in enzyme activities compared to untreated diabetic control rats. The enzyme activities in ginger-treated diabetic rats were found to be similar to the augmentation induced by glibenclamide.

There is significant evidence suggesting that diabetes is linked to tissue damage caused by oxidative stress. This has been observed in the liver, skeletal muscle, and heart tissues of diabetic rodents induced by streptozotocin (Aragno et al., 2008). In diabetic rats, decreased oxygen utilization and respiratory percentage have been observed in the mitochondria (Puckett et al., 1979). Additionally, a study by Sener et al. reported decreased activities of citric acid cycle enzymes (Sener et al., 1990). Recent metabolomic studies on type 1 diabetes models have also reported downregulation of key tricarboxylic acid (TCA) cycle and mitochondrial proteins, as well as enzyme activities (Chowdary et al., 2010).

We observed high blood glucose levels in the diabetic rats in the present study. Streptozotocin has been found to cause diabetes mellitus. This is believed to be due to the destruction of beta cells in the islets of Langerhans, as proposed by Kavalali et al. (2002). Diabetes occurs when there is irreversible damage to the pancreatic beta cells, leading to a decrease in insulin secretion (Zhang and Tan, 2000). In streptozotocin-induced diabetes, there is a significant loss in body weight (Kamalakkannan et al., 2006), and it can result in various complications such as myocardial, cardiovascular, nervous, kidney, and urinary bladder dysfunction due to oxidative stress (Rajasekaran et al., 2005). After 30 days of supplementation with an ethanolic extract of ginger in diabetic rats, there was a significant reduction in fasting blood glucose levels compared to diabetic control rats. However, there was no significant change in fasting blood glucose levels compared to the control group. This finding supports the anti-diabetic effects of ginger extract. Many studies have reported that the phenols, polyphenolic compounds, and flavonoids present in ginger are responsible for its hypoglycemic and other pharmacological activities (Amin et al., 2006). The decrease in body weight observed in diabetic rats indicates that diabetes leads to the loss or degradation of structural proteins, which contribute to body weight (Rajkumar and Govindarajulu, 1991). The present study demonstrates that ginger treatment for 30 days has an anti-hyperglycemic effect in diabetic rats. Additionally, ginger treatment was comparable to treatment with glibenclamide, a standard hypoglycemic drug. These findings support the traditional use of ginger as a folk medicine for the treatment of diabetes.

The enzyme glucose-6-phosphate dehydrogenase (G6PDH) is an important component of the HMP shunt pathway and plays a crucial role in the diversion of glucose metabolism from glycolysis. In our study, we observed a decrease in G6PDH levels in the heart tissue of diabetic rats. These findings are consistent with previous studies that also reported lower G6PDH activity in diabetic tissues (Shanmugam et al., 2011). This decrease in G6PDH activity suggests a reduced conversion of glucose-6-phosphate dehydrogenase to 6-phosphogluconate, leading to a decrease in NADPH formation and HMP shunt activity. This decrease in G6PDH activity may be an adaptive response, cutting down the supply of NADPH for aldose reductase. These results align with earlier reports (Rajeswarareddy et al., 2012). Interestingly, in our study, we observed an increase in G6PDH activity with the administration of ginger to diabetic rats. This suggests that ginger may help reduce complications associated with diabetes. Ginger has been reported to contain many phytochemicals like phenols, flavanoids, terpenoids and other phytochemicals which are responsible for their pharmacological activities. Its dried extract contains mono-terpenes and sesquiterpenes.

The results of this study demonstrate that heart lactic dehydrogenase (LDH) activity is significantly higher in diabetic rats. Previous studies by (Ramachandran et al., 2003, Rao et al et al., 2013) have also reported increased LDH activity in diabetic rats. This increase in LDH activity may be attributed to the excessive accumulation of pyruvate during diabetic conditions. As a result, there is a higher demand for LDH to convert the excess pyruvate into lactate. The decreased availability of insulin in diabetes may contribute to the increased LDH activity. Interestingly, supplementation with ginger in diabetic rats led to a reduction in LDH activity. This inhibition of LDH activity by ginger was comparable to the effects of the anti-diabetic drug glibenclamide. Ginger compounds such as 6-gingerols and oleoresins may be

responsible for inhibiting LDH activity and contributing to the decrease in LDH activity observed in ginger-treated diabetic rats. Another study by Ansari et al., (2006). reported similar findings, showcasing the ability of ginger supplementation to decrease LDH activity in rats treated with isoproterenol. Overall, these findings suggest that ginger supplementation may have potential benefits in reducing LDH activity and potentially managing diabetes.

The current study observed a significant decrease ($p < 0.001$) in the activities of the mitochondrial marker enzymes succinate dehydrogenase (SDH) and malate dehydrogenase (MDH) in the heart of rats with streptozotocin (STZ)-induced diabetes. The enzymes mentioned are crucial for ATP production, producing 36 moles of ATPs for every mole of glucose (Berg et al., 2010). Among these enzymes, SDH and MDH are involved in the Krebs cycle, with SDH exhibiting the highest activity compared to other enzymes in the cycle. This decrease in SDH activity suggests a depressed oxidative metabolism in the mitochondria, specifically affecting the conversion of succinate to fumarate. MDH, on the other hand, plays a crucial role in the citric acid cycle by providing oxaloacetate for the formation of citrate with acetyl-CoA and generating malate, which can fuel the cytosolic gluconeogenic pathway (Murray et al., 1998). The reduced levels of MDH enzyme observed in diabetic rats indicate a decreased utilization of malate. Previous studies have also reported a decrease in SDH and MDH enzyme levels in diabetic rats (Senthilkumar et al., 2007). However, an interesting finding in this study was the amelioration of decreased SDH and MDH activities in diabetic rats treated with ginger. The increased SDH and MDH activities observed in ginger-treated diabetic rats suggest a better utilization of energy-yielding intermediates by the tricarboxylic acid (TCA) cycle. The improvement in mitochondrial marker enzymes observed in ginger-treated diabetic rats was similar to that induced by glibenclamide.

In the present study we observed GDH activity was decreased in heart tissue. The decrease in GDH activity is caused by its inhibition by elevated levels of ammonia, which acts as a product-inhibitor and reduces the enzyme's catalytic efficiency. Reddy and Rao (1991) demonstrated that increased levels of ammonia and lactate also inhibit GDH activity. The present study also reported an increase in LDH, which is consistent with lactate inhibiting GDH activity. Decreased GDH activities in heart of rats with enzyme dysfunction were attributed to the activation of lipid peroxidation (telushkin et al., 2005), indicating significant disturbances in energy metabolism and contributing to the impairment of glutamate utilization and progression of glutamate-induced toxicity. On the other hand, the increased activity of GDH observed in the present study may be due to reduced oxidative stress by ginger and an increase in mitochondrial enzymes. Ginger has been found to enhance GDH activity in diabetic rats. There are several reports on medicinal plants inhibiting GDH activity in diabetic rats, such as the normalization of mitochondrial enzymes in diabetic rats treated with *Centella asiatica* (Somara Sasikala et al., 2015).

4. Conclusion

The findings from this study suggest that the ethanolic extract derived from ginger rhizome could be effective like the anti-diabetic drug glibenclamide in preventing the diabetic-induced disturbances in cardiac cytosolic and mitochondrial enzymes. This was demonstrated by observing improved enzyme activities in diabetic rats by ginger. These results could further suggest that possible use of ginger as a nutraceutical supplement to cope with diabetic-induced detrimental effects and to protect heart tissue from damages. However, further pharmacological and biochemical researches are considered essential to find out the active constituent and its system of action to know the bioactive and ameliorative potential of the plant.

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