

Significant Impact of Ginger Extract on Oxidative stress Markers and Lipid Peroxidation in Diabetic Male Albino Rats

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ABSTRACT: The role of oxidative stress has been reported in various diabetes complications. This study's objective was to determine whether ginger supplementation at a dose of 200 mg/kg body weight was beneficial at protecting diabetic rats produced by the drug streptozotocin (STZ). Adult male albino rats weighing 180–200 g were given STZ (40 mg/kg body weight) intraperitoneally to develop diabetes. Glibenclamide (600 g/kg body weight) was the recommended medication. Blood glucose, uric acid, MDA concentration, and Xanthine oxidase (XOD) activity were all greater in diabetic rats' brain homogenates. They found that the brain tissue had lower amounts of ascorbic acid, glutathione, and GST activity. We found that diabetic rats given oral supplementation of ginger extracts and glibenclamide had lower MDA, uric acid content, XOD activity and higher levels of GST, ascorbic acid, and GSH in the brain as well as higher body weight. Since ancient times, ginger or *Zingiber officinale* has been used as a herbal remedy to cure a variety of diseases. Recent research has shown ginger's promise as a diabetic mellitus therapy. These finding suggest that ginger extract therapy has a protective effect against the progression of diabetes through reducing oxidative stress and brain oxidative stress.

Keywords: Ginger, STZ, Diabetes, Blood glucose, XOD, GST, Brain.

INTRODUCTION

The global prevalence of diabetes in adults according to a report published in 2013 by the IDF 382 million people, the number is expected to rise beyond 592 million by 2035 with a global prevalence (Preguiça *et al.*, 2020). Diabetes mellitus-related hyperglycemia is an endocrine disease that is either brought on by insulin resistance or by insufficient insulin release by pancreatic cells (Vats *et al.*, 2004). In persons with diabetes mellitus, prolonged hyperglycemia increases the production of free radicals (Szkudelski, 2001) by non-enzymatic protein glycation and glucose oxidation, which impairs cellular processes and damages membranes through oxidation (Valko *et al.*, 2007). Reactive oxygen species (ROS) generation and STZ-induced diabetes mellitus work hand in hand and result in oxidative damage (Cade, 2008). Chronic and persistent hyperglycemia causes high levels of oxidative stress in diabetics and experimental animal models, which impairs the immune system's

antioxidative defenses, promotes poor GSH metabolism, and lowers ascorbic acid levels (Rajasekaran *et al.*, 2005). Recent reports indicate that diabetic complications are associated with overproduction of free radicals and accumulation of lipid peroxidation by-products (Mancino *et al.*, 2011). In therapeutic plants, antioxidants, tannins, and flavonoids are usually found in high quantities. Most of this research focuses on naturally derived products of plant origin which are capable of reducing blood glucose levels (Patel *et al.*, 2012). The current study suggests that plant medicines' capacity to function as antioxidants may be essential to their capacity to have a hypoglycemic impact on persons with diabetes mellitus. One of the most well-known spices in the world, ginger has been used for its health benefits since ancient times. Ginger has been recommended for usage in Ayurveda as a analgesic effect (Young *et al.*, 2005) digestive aid, anti-inflammatory agent, circulatory stimulant, diaphoretic, astringent, appetite stimulant, and diuretic Jiang *et al.* (2006). Ginger is reported to have

hypoglycaemic, and hypolipidemic pharmacological effects on human health (Kondeti *et al.*, 2011). The anti-inflammatory and anti-oxidant properties in ginger help relieve various inflammatory disorders like gout, osteoarthritis, and rheumatoid arthritis. Ginger provides considerable pain relief caused by inflammation and help decrease swelling (Habib *et al.*, 2008). Traditional medicine also makes use of dried ginger rhizomes to treat a range of human illnesses. In this study, we looked at how ginger extract treatment affected brain oxidative stress and lipid peroxidation in streptozotocin-induced diabetic rats.

MATERIEL AND METHODS

Animals. The current study used in Albino male rats (Wistar strain) that were 3 months old (180-200 g). 30 animals were used in this study. The rats were fed a regular pellet diet and had unlimited access to water. They were housed in clean, dry polypropylene cages in animal houses that were adequately ventilated and had a cycle of 12 hours of light and 12 hours of darkness. To avoid circadian rhythm-induced changes, all tests were performed between 8 and 10 a.m. The animal ethics committee at the university approved the study, and all procedures for handling and using lab animals were followed.

Ginger ethanolic extract preparation. The ginger rhizomes were purchased locally in Tirupati (AP, India) in September and Dr. Madhva Chetty, a botanist at S.V. University, identified and verified their authenticity. The department receives a voucher specimen with the ID number 1556. The herb's air-dried rhizomes weighing two kilos were mechanically ground into a fine powder and extracted over a 24-hour period using cold percolation and 95% ethanol. After the extract was recovered, the extraction process was resumed by adding 95% ethanol and more ginger powder. Three times, this procedure repeated itself. The three extracts were combined, mixed, filtered, and the filtrate was then concentrated at condensed pressure in a rotary evaporator until it was dry. After being air dried, the ethanolic extract produced 80 g of a dark brown, gelatinous extract of dried ginger rhizomes. Without additional purification, the ethanolic extract in its raw form was employed for the studies. For the experiment, a calculated dose suspended in a 2%, v/v Tween 80 solution equal to 200 mg of the crude extract per kg of body weight was used.

Induction of diabetes. A single intraperitoneal injection of 1 ml/kg body weight of streptozotocin solution (STZ solution) containing 40 mg/ml of STZ solution was given to groups III and IV. As a result of the large pancreatic insulin release caused by streptozotocin, rats were given oral 20% glucose (5–10 ml) after 6 hours after injection over the following 48 hours to prevent hypoglycemia. Over the course of the trial, neither mortality nor any other negative effects

were noticed at the measured dose. Rats that had diabetes (high blood glucose levels, 200–300 mg/dL) and displayed glycosuria and hyperglycemia were chosen for the experiment after one week.

Experimental design. Rats of the same age group (3 months) were divided into 5 groups, six rats in each group, and were treated as follows:

- Group I- Normal control (NC): Six rats were received the 0.9% NaCl / kg bodyweight via
- Orogastric tube for a period of 30 days.
- Group II - Diabetic control (DC): Six rats were used as diabetic control rats by giving the fasted animals intraperitoneal injections of STZ (40 mg/kg b.w.).
- Group III - Diabetic Control and Ginger Treatment (DC+Gt): For 30 days, this group of rats received the same STZ and ginger treatments as those in groups 2 and 4.
- Group IV (Gt): For 30 days, normal rats were given an ethanolic extract of ginger (200 mg/kg body weight).
- 5. Group V (DC+Glb): Diabetic animals treated with 600 μ g/kg b.w. day of glibenclamide for 30days. Glibenclamide is a type of diabetes medication known as a sulfonylurea antidiabetic agent. This is a chronic metabolic disorder marked by a lack of insulin, a pancreatic hormone that regulates blood sugar levels. We are comparing efficacy with ginger-treated diabetic rats using glibenclamide as a standard drug in this study.

Tissue collection and Analytical procedures. After the 30-day treatment period, the animals were killed by cervical dislocation and the brain tissues were extracted at 4°C. The tissues were washed with ice-cold saline following a liquid nitrogen immersion and quick storage at -80°C for subsequent biochemical analysis. The chosen parameters, such as MDA levels, uric acid content and XOD activity, ascorbic acid, GSH, and GST activity, were monitored using the techniques of Ohkawa *et al.* (1979); Martinek (1970); Srikanthan and Krishnamurthy (1955); Omaye *et al.* (1970); Theodorus *et al.* (1981); Habig *et al.* (1974). A glucometer from Accucheck was used to measure blood sugar levels (Roche – Germany). The changes in body weight were accounted for by tracking the body weights of all experimental groups over a 30-day period.

Chemicals. The following research organisations provided the chemicals for the current study: Fisher (Pittsburgh, PA, USA), Sigma (St. Louis, MO, USA), Ranbaxy (New Delhi, India), Merck (Mumbai, India), and Qualigens (Mumbai, India).

Statistical Analysis. To determine the significance of the main effects (factors), treatments and their interactions, data were subjected to analysis of variance (ANOVA) and Duncan's multiple comparison tests using the SPSS (Version 13.5; SPSS Inc., Chicago, IL, USA) and M.S. Office, excel software. $P < 0.001$ was used to determine statistical significance.

RESULTS

Effect of ginger on the blood glucose levels and body weight changes. According to the findings of the current study, diabetic rats' body weight decreased and

their blood glucose levels sharply increased. However, diabetic rats receiving nutritional ginger therapy had lower blood glucose levels and gained weight (Table 1).

Table 1: Blood glucose levels and body weight changes in STZ-induced rats followed by ginger and glibenclamide treatment.

Groups	Blood glucose (mg/dl)		Body weight (g)	
	0 th Day	30 th Day	0 th Day	30 th Day
Group I (NC)	82 ± 1.12	97 ± 2.7	189 ± 9.66	209 ± 13.89
Group III (DC)	261 ± 3.53*	254 ± 14.3*	186 ± 2.73*	149 ± 6.69
Group IV (DC + Gt)	252 ± 3.09**	125 ± 5.14	184 ± 6.32	197 ± 4.23**
Group II (Gt)	84 ± 1.36	86 ± 1.87	197 ± 7.07	89 ± 7.01
Group V (DC + Gli)	259* ± 1.87**	94 ± 3.69**	189 ± 3.12	204 ± 2.14**

All the values are mean ± SD of six individual observations.

Values are significant compared to normal control (*P < 0.001) and diabetic control (** < 0.01).

Effect of ginger on oxidative stress markers and MDA levels in STZ-induced diabetic rats. Significant (p < 0.001) increases in MDA, uric acid content, and XOD activity were seen in diabetic rats, while significant (p < 0.001) decreases were observed in ascorbic acid, GSH content, and GST activity. When ginger was administered to diabetic rats, MDA, uric acid content, XOD activity significantly decreased, ascorbic acid content, GSH content, and GST activity were significantly increased (P < 0.001), indicating that the antioxidant enzyme system has been restored to levels that are close to normal (Figs. 1-6).

DISCUSSION

According to the current investigation, STZ-induced hyperglycemia in diabetic rats was accompanied by oxidative brain damage. There is a need for safer and more effective medications because the pharmacological regimens now used to manage diabetes mellitus have some limitations. In this investigation, we used STZ-induced diabetic rats to investigate the idea that ginger protects against hyperglycemia-induced oxidative stress in the brain. In the present study we observed high blood glucose levels in diabetic rats. Previous reports suggested that (Ghudhaib *et al.*, 2018) STZ induced diabetes, which may be due to beta cells destruction Islets of Langerhans (Kavalali *et al.*, 2002). By irreversible destruction of pancreatic beta cells diabetes is arises, this causing reduction of insulin secretion (Zhang and Tan 2000). Supplementation with ginger to diabetic rats they showed low blood glucose levels. Many secondary plant metabolites, including flavonoids, terpenoids, and a variety of others, have hypoglycemic effects in diverse experimental animal models (Grover *et al.*, 2000). Numerous researchers have claimed that chemicals found in ginger, such as 6-gingerol, polyphenolic compounds, tannins, flavonoids, and triterpenoids, have pharmacological effects that can lower blood sugar levels (Young *et al.*, 2005) (Table 1). We found that the body weight of diabetic rats had reduced. Diabetes has been linked to both dehydration

and weight loss. This demonstrates the polyphagic state, weight loss caused by increased tissue protein breakdown (Kamalakkannam and Prince 2006), protein waste as a result of the lack of access to carbohydrates as an energy source, dehydration, and catabolism of fats and proteins (Al-Attar *et al.*, 2007). Ginger was given orally for 30 days to STZ diabetic rats, which increased body weight. This might be because the hyperglycemic condition in diabetic rats was better controlled. (Table 1).

In the present study MDA levels were decreased in diabetic rats. It may be during diabetic condition the anti-oxidant system inefficient (Rastogi *et al.*, 2008). This could be as a result of the brain having an excessive amount of fatty acids that are prone to oxidation (Carney *et al.*, 1991). It is well known that certain parts of the brain are significantly richer in iron. Iron is a metal that, in its free state, is catalytically implicated in the creation of damaging oxygen free radical species (Nistico *et al.*, 1992). In diabetes mellitus, diminished antioxidant scavenger systems can increase oxidative stress in the cell, which can cause lipid peroxidation (Safinaz, 2008). This increased MDA content was triggered by ginger extract. Similar reports were found in the brain regions of diabetic rats, the elevated level of MDA was significantly decreased in animals treated with *Pimpinella tirupatiensis*. (Veera Nagendra Kumar, 2021). This hypothesis suggests that the antioxidant properties of flavonoids found in ginger root, which in turn operate as potent superoxide radical scavengers and singlet oxygen quenchers, may be responsible for the protective effects of ginger root extracts.

Uric acid is the most rich aqueous antioxidant, particularly effective in quenching the superoxide anion and hydroxyl radicals (Yu *et al.*, 1994). Recent antioxidant biochemistry investigations have found that uric acid is among the finest free radical scavengers. In the present study, uric acid levels were increased in the brain tissue of diabetic treated rats. In this context a marked increase in uric acid in diabetic animals, were reported by Yassin *et al.* (2019). The total inhibitory

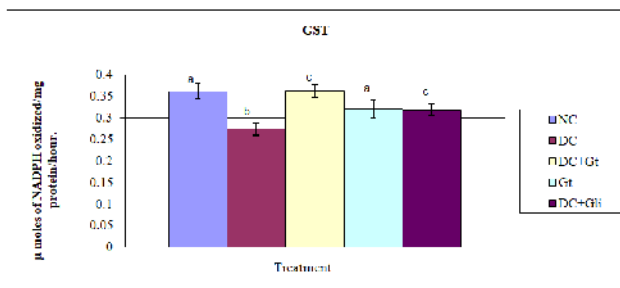
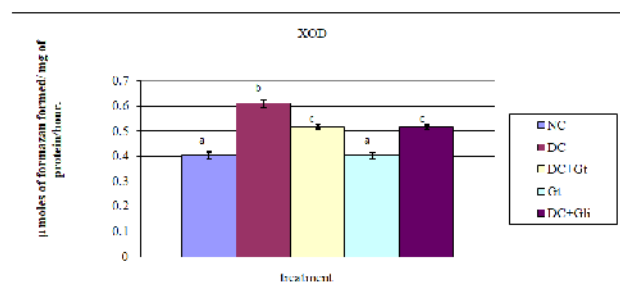
action against oxidative stress can surely be significantly impacted by uric acid, which is also a potent iron chelator according to research by Davies *et al.* (1986). In the current study we observed ascorbic acid was decreased in diabetic rats. Anupama *et al.* (2012) reported similar results in the diabetic rat brain respectively. Such a fall in level of vitamin C could be due to the increased utilization of vitamin C in the deactivation of increased level of ROS or due to decrease in GSH level, since GSH is required in recycling of vitamin C.

The xanthine oxidase activity was significantly elevated in diabetic treated rats. Increased XOD activity from xanthine, which is formed during the breakdown of ATP and reoxygenation, results in the production of oxygen radicals and uric acid (McCord, 1985). It is possible that Xanthine oxidase activity increased the levels of uric acid in the brains of diabetic rats, which is compatible with the critical functions of uric acid as a free radical scavenger and a single oxygen quencher. Treatment with ginger extract decreased uric acid levels; this result may have been brought about by a decline in Xanthine oxidase activity. There are several ways that oxygen free radicals can form inside of cells. It is known that xanthine oxidase is a substantial generator of oxygen free radicals. Xanthine oxidase can be produced from xanthine dehydrogenase either reversibly or irreversibly in pathological conditions. According to (Tubaro *et al.*, 1980), xanthine oxidase catalyses the oxidation of hypoxanthine and xanthine to uric acid and creates $O_2 \bullet$ - Hydrogen peroxide produced from $O_2 \bullet$ - could be transformed into highly reactive $\bullet OH$, causing oxidative stress. When diabetic rats were given glibenclamide and ginger extract, the activity of Xanthine oxidase was reduced. This might be because there is less ATP degradation, less purine metabolism, which results in a low xanthine profile, and, lower amounts of hypoxanthine, which are required for strong XOD activity. However, with ginger treatment in diabetic treated groups XOD activity was decreased. This may be due to the counter action of ginger compounds like gingerols, shogals and other pharmacological compounds of ginger as they have the capacity to reduce the free radical toxicity. The decreased XOD activity with ginger treatment in alcohol treated rats is in agreement with the earlier reports (Rajeswara Reddy *et al.*, 2013). By converting radicals into vitamin A, vitamin E, and GSH, it also functions as a co-antioxidant. In the current investigation, we found that diabetic rats' brains had fewer vitamins C. Similar findings were found in the diabetic rat brain by Anupama *et al.* (2012). Such a decrease in vitamin C levels may be caused by increased vitamin C use in the deactivation of elevated ROS or by a decline in GSH levels, as GSH is necessary for the recycling of vitamin C (Sunil *et al.*, 2009). Another hypothesis is that hyperglycemia inhibits ascorbic acid and its cellular transport (Chirico *et al.*, 1987). As a result, a rise in glucose concentration

may decrease the body's natural antioxidants like vitamin C (Rotruck *et al.*, 1973). In this work, ginger therapy was shown to prevent declines in tissue GSH and ascorbic acid concentrations due to its extra function in scavenging free radicals in diabetic rats and therefore lowering the utilisation of GSH and ascorbic acid (Chatterji *et al.*, 1991). Ginger's antioxidant chemical content may be to responsibility for this.

We have seen a marked decrease in GSH levels and GST activity in the brain during diabetes. Reduced glutathione, a potent free radical scavenger GSH found within the islet of β -cell, is crucial in preventing the β -eventual cell's demise following partial pancreatectomy (McLennan *et al.*, 1991). Due to increased consumption caused by oxidative stress, GSH levels are decreasing (Kadah, 2019). Depletion of the GSH content may potentially have an impact on the GST activity. The increased GSH concentration in the brains of the rats given ginger and glibenclamide may have prevented oxidative damage to the cell membrane by regulating the redox status of the proteins in the membrane (Inove *et al.*, 1987). Treatment with ginger significantly potentiates above enzyme activities and the results are in agreement with the previous reports (Sangi and Elwahab 2017). The increase in GSH and GST levels brought on by diabetes in diabetic rats receiving ginger treatment raises the possibility of an adaptive response to oxidative stress.

Future Outlook and Perspective. Clinical outcomes for the diabetes and metabolic syndrome pandemic in poor countries can be derived from ginger's ancient usage in herbal therapy. Numerous studies on ginger can be validated by current pharmacological research that is pertinent to the management of diabetes. Studies on the biological impacts' mechanisms help us comprehend the aspects that contribute to ginger's safety.



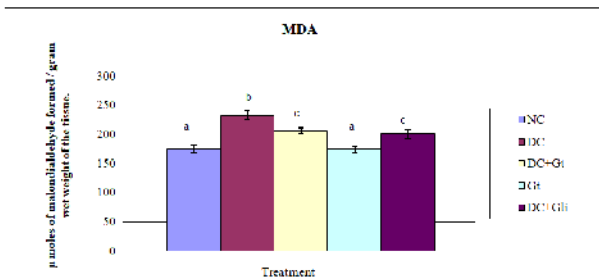


Fig. 1-3. Status of XOD, GST activity and MDA content in the brain of Normal Control (NC), Diabetic control (DC), Diabetic rats treated with Ginger extract (DC+Gt), Control rats treated with ginger extract (Gt), Diabetic rats treated with Glibenclamide. Each vertical bar represents the mean \pm SD (n=6). Top of the vertical bars having the same letter do not differ significantly at $p < 0.001$.

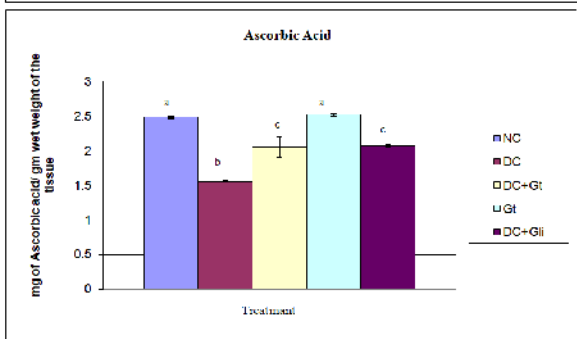
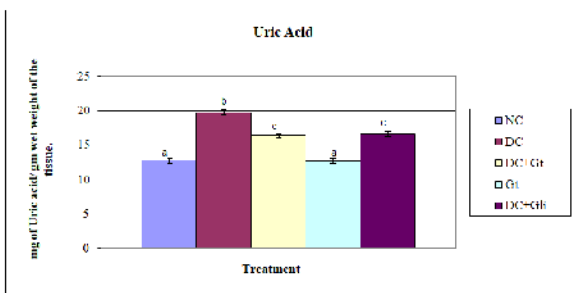
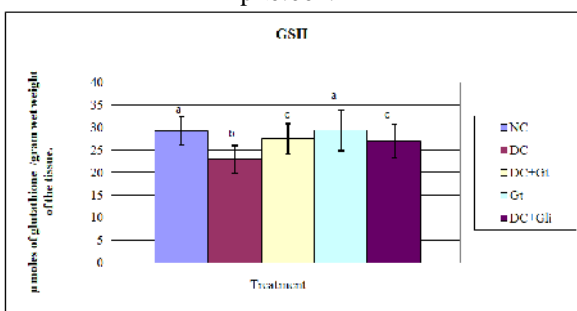


Fig. 4-6. Changes in GSH, Uric acid and ascorbic acid in the brain Normal Control (NC), Diabetic control (DC), Diabetic rats treated with ginger extract (DC+Gt), Control rats treated with ginger extract (Gt), Diabetic rats treated with Glibenclamide. Each vertical bar represents the mean \pm SD (n=6). Top of the vertical bars having the same letter do not differ significantly at $p < 0.001$.

CONCLUSION

The results of this investigation suggested that ginger could improve the health and metabolic efficiency of diabetic rats. Because of this, ginger could be used to make natural diabetes treatments. Considering that ginger has antioxidant and anti-diabetic characteristics, it may be clinically useful in the control of human diabetes.

Conflict of Interests. None.

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