

Anti-diabetic and anti-oxidant effects of *Zingiber Officinale* on alloxan-induced and insulin-resistant diabetic male rats

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Summary: This study was designed to investigate the hypoglycaemic and anti-oxidant effects of *Zingiber officinale* on experimentally induced diabetes mellitus using alloxan and insulin resistance. Aqueous extracts of raw ginger was administered orally at a chosen dose of 500mg/ml for a period of 4 weeks to alloxan-induced diabetic and insulin resistant diabetic rats. The experimental rats exhibited hyperglycaemia accompanied with weight loss to confirm their diabetic state. Ginger effectively reduced fasting blood glucose and malonydealdehyde levels in alloxan-induced diabetic and insulin resistant diabetic rats compared to control and ginger only treated rats. Furthermore, ginger increased serum insulin level and also enhanced insulin sensitivity in alloxan-induced diabetic and insulin resistant diabetic rats compared to control and ginger only treated rats. The results of the study clearly show that dietary ginger has hypoglycaemic effect, enhances insulin synthesis in male rats and has high antioxidant activity. One of the likely mechanisms is the action of malonydealdehyde, which acts as a scavenger of oxygen radicals.

Keywords: Diabetes mellitus, Insulin resistance, *Zingiber officinale*, Malonydealdehyde.

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INTRODUCTION

Diabetes mellitus often simply considered as diabetes, is a syndrome of disordered metabolism with abnormally high blood glucose levels (Tierney, 2002). It is estimated that diabetes affect about 150 million people worldwide, and this figure is expected to be doubled in the next 20 years (Zimmet *et al.* 2001). In Africa just like in North America, 90 – 95% of all cases of diabetes mellitus are type 2 diabetes mellitus (Zimmet *et al.* 2001).

Before the discovery of insulin in the 1920s and the development of oral hypoglycaemic agents, diabetes mellitus was mainly treated by a combination of fasting, diet control and plant therapeutics (Bailey and Flatt, 1990). The efficacy of plant in diabetes required confirmation and, therefore, the WHO (World Health Organization, 1980) recommended assessment of traditional plant treatments for diabetes mellitus. Currently, several hundred plants have been reported to have beneficial effects in the treatment of diabetes (Bailey & Day, 1989; Swanston-Flatt *et al.* 1991; Gray & Flatt, 1997; Hill & Peters, 2002; Kar *et al.* 2003; Srinivasan 2005).

Plant derivatives with purported hypoglycaemic properties like *Achillea fragrantissima* (Forssk), *Ammi visnaga*, *Atriplex halimus*, *Capparis spinosa* etc have been used in folk medicine and traditional healing systems around the world e.g. Native American Indian, Jewish (Yaniv *et al.* 1987), Chinese (Covington, 2001), East Indian and Mexican (Yeh *et al.* 2003). Despite the introduction of hypoglycaemic agent from natural and synthetic sources, diabetes mellitus and its secondary complications continue to be major medicinal problem to people (Ravi *et al.*, 2005).

Ginger (*Zingiber officinale*) is a commonly used spice in the African Kitchen and has been used as spice for over 2000 years (Bartley and Jacobs, 2000). It is a perennial plant with narrow, bright green, grass-like leaves and yellowish green flowers with purple markings. It is cultivated in the tropics for its edible rhizome at about 10 months of age, with the root stocks serving culinary and medicinal purposes (Grant, 2000; Ursell 2000; Portinoi *et al.* 2003). The culinary use is as spice and food ingredient while the medicinal use includes anti-arthritis (Srivastava and Mustafa, 1989, 1992; Bliddal *et al.* 2000), anti-migraine (Mustafa and Srivastava, 1990; Cady *et al.*

2005), anti-thrombotic (Bordia *et al.* 1997; Thomson *et al.* 2002), anti-inflammatory (Thomson *et al.* 2002; Penna *et al.* 2003), hypolipidaemic (Bordia *et al.* 1997, Thomson *et al.* 2002; Bhandari *et al.* 2005; Al-Amin *et al.* 2006) and anti-nausea properties (Ernst & Pittler, 2000; Portinoi *et al.* 2003).

Research on rats suggests that ginger may be useful for treating diabetes (Kim *et al.* 2003). Studies on the hypoglycaemic, properties of ginger in animals have reported its hypoglycemic activity in both normal and Type 1 diabetic rats as well as anti-diabetic and hypolipidaemic activities (Akhani *et al.*, 2004, Al-Amin *et al.*, 2006).

Malondialdehyde (MDA) is the end-product of lipid peroxidation and the production of this aldehyde is used as a biomarker to measure the level of oxidative stress in an organism (Obboh, *et al.* 2010). Increased oxidative stress and decreased antioxidant levels are the leading cause of diabetes and diabetic complications (Jain, *et al.* 1996; Feillet – Coudray, *et al.* 1999). Literature has shown that *Zingiber officinale* exhibit anti-oxidant effects (Ghasemzadeh, *et al.* 2010; Heeba & Abd-Elghany, 2010; Stoilova *et al.* 2007) thus can be classified as a source of natural or phytochemical antioxidants (Kikuzaki and Nakatani, 1993). This is against the backdrop that antioxidation is an extremely significant activity which can be used as a preventive agent against a number of diseases (Aruoma, 1994; Basaga, 1990; Halliwell & Chirico, 1993). Some of the antioxidants are beta-carotene, ascorbic acid, terpenoids, alkaloids, and polyphenols such as flavonoids, flavones glycosides, rutin etc (Aruoma *et al.* 1997).

Several works have reported the effects of ginger (*Zingiber officinale*) in animals with experimentally induced Type I diabetes mellitus with relatively little reports on experimentally induced Type 2 diabetes mellitus using the insulin resistance mechanism. Thus this study was designed to investigate the effects of *Zingiber officinale* on experimentally induced diabetes mellitus using alloxan and insulin resistance. There have been variable reports on glycaemic properties of ginger with some reporting a small but significant blood glucose-lowering effect of ginger juice in diabetic and non-diabetic animals (Sharma and Shukla, 1977). Likewise Akhani *et al.* (2004) also observed that ginger juice exhibits hypoglycaemic activity in both normal and streptozotocin-incuded diabetic rats. Other authors like Weidner and Sigwart (2000) reported that an ethanolic extract of ginger had no effect on blood glucose levels in normal rats.

Aqueous extracts of raw ginger administered orally at a chosen dose of 500mg/ml were used in this present study since workers have previously shown

(Morakinyo, *et al.* 2008; Thomson *et al.*, 2002; Alnaqeeb *et al.*, 2003) that this route of administration is less stressful for the animals and the dose is effective and non-toxic. We hypothesized that *Zingiber officinale* will cause hypoglycaemic actions in diabetic animals and some likely mechanisms of this effect are proposed.

MATERIALS AND METHODS

Animals and Induction of Diabetes mellitus

Male Sprague-Dawley rats weighing 140 – 210 g were obtained from the Laboratory Animal Department. The animals were housed in clear polypropylene cages lined with wood chip beddings. Animals were kept under standard conditions of temperature 27°C – 30°C, with 12h light/dark cycle and were randomly divided into 6 groups. Group 1 served as control group and was fed with normal rat chow. Group 2 served as Ginger group and received 500mg of ginger extract/kg body weight (orally) daily for four weeks. The chosen dosage of 500mg ginger extract/kg body weight was previously found to be effective and non-toxic in rats (Thomson *et al.*, 2002; Alnaqeeb *et al.*, 2003).

Group 3 served as Alloxan-induced diabetic (Type 1) group and received a single dose intravenous injection of alloxan monohydrate (40 mg/kg bodyweight) (Seidel *et al.* 2003), freshly dissolved in saline into the lateral tail vein. At this dose and route of administration of alloxan monohydrate (40 mg/kg bodyweight), diabetic induction was 90% with mortality rate of 10 – 20%. Blood samples were collected from the tail vein 72 hours after alloxan injection to confirm hyperglycaemia using Dextrostix Test Strips (Bayer Corporation, U. K.) following the glucose oxidase method (Hugget & Nixon, 1957). This group of rats was diabetic for 8 weeks. Group 4 served as Alloxan-induced diabetic + ginger treated (Type 1+ginger) group; received same dose of alloxan monohydrate above and 500mg ginger extract/kg body weight as above. This group of rats was diabetic for 8 weeks but was treated with ginger for 4 weeks.

Group 5 served as Insulin resistant diabetic (Type 2) group and was fed ad libitum on a special diet containing 25% fructose mixed with 75% normal rat chow (w/w) for 4 weeks (Arikawe & Olatunji-Bello, 2004) and continued till the 12th week. At this fructose concentration, insulin resistance state was 100% with zero mortality rate. Hyperglycaemia was confirmed using Dextrostix Test Strips (Bayer Corporation, U. K.) following the glucose oxidase method (Hugget & Nixon, 1957). Group 6 served as Insulin resistant diabetic + ginger treated (Type 2 +

ginger) group; fed same special diet above and 500mg ginger extract/kg body weight as above. All animals had free access to drinking water throughout the duration of the study. Rats with blood glucose concentration above 250 mg/dl were used as Type 1 diabetic rats (Akingba & Burnett, 2001) while rats with blood glucose concentration above 200 mg/dl were used as Insulin resistant diabetic rats (Catena *et al.* 2003).

Rats were weighed weekly throughout the duration of the experiment and animals were monitored for general health during the treatment period. All the procedures were performed in accordance with the guidelines of the College Ethical Committee on the use of laboratory animals for research.

Extract Preparation

Aqueous ginger extract was prepared from the protocol established by Al-Amin *et al.* (2006). Briefly, available ginger roots purchased from local commercial sources were peeled on crushed ice and 50g ginger were cut into small pieces and homogenized in 75ml cold, sterile 0.9% NaCl in the presence of some crushed ice. The homogenization was carried out in a blender at high speed using 2 min bursts for a total of 12 min. The homogenized mixture was filtered three times through cheese-cloth (very little material was retained on the cheese cloth). The filtrate was centrifuged at 2000 relative centrifugal force for 10 min and the clear supernatant fraction was made up to 100ml with normal saline. The concentration of this ginger preparation was considered to be 500mg/ml on the basis of the weight of the starting material (50g/100ml). The aqueous extract of ginger root was stored in small samples at 4°C and used for oral administration.

Hormone Assay and Malonhydiyaldehyde Estimation

At the 8th week (Alloxan-induced), and at the 12th week (insulin resistant), the rats were anaesthetized

with ether, followed by laparotomy and blood obtained by cardiac puncture for serum Insulin measurement by radioimmunoassay in batches with control sera at both physiological and pathological levels using standard quantitative solid phase enzyme-linked immunosorbent assay (ELISA) technique with microwell kits (Syntro Bioresearch Inc., California, U. S. A.).

Serum Malonhydiyaldehyde was measured as an indicator of lipid peroxidation and by extension reactive oxygen species. Blood samples were centrifuge (2,000 rpm, 10 minutes), serum was collected and the absorbance of the pink clear supernatant was measured at $\lambda = 532$ nm in

Statistical Analysis

Results were expressed as means \pm S. E. M. The significance of differences among groups was analyzed statistically by One-way ANOVA (Analysis of Variance), followed by Student's unpaired t – test. Differences were considered statistically significant at $P < 0.05$.

RESULTS

Blood glucose

Blood glucose concentration was significantly higher ($P < 0.05$) in alloxan-induced diabetic and insulin resistant diabetic rats (260 ± 3.2 mg/dl; 212.3 ± 2.0 mg/dl) compared with control, ginger only treated, alloxan-induced diabetic + ginger treated, and insulin resistant diabetic + ginger treated rats (77.2 ± 5.2 mg/dl; 57.7 ± 11.5 mg/dl; 132.0 ± 8.3 mg/dl; and 63.0 ± 6.7 mg/dl). It was also significantly higher ($P < 0.05$) in alloxan-induced diabetic + ginger treated rats (132.0 ± 8.3 mg/dl) compared with control and ginger only treated rats (77.2 ± 5.2 mg/dl; 57.7 ± 11.5 mg/dl) while there was no significant difference in blood glucose concentration in insulin resistant diabetic + ginger rats compared with control and ginger only treated rats (Table 1).

Table 1

	Control (C)	Ginger (G)	Alloxan-induced (A)	Alloxan-induced + Ginger (A + G)	Insulin resistant (IR)	Insulin resistant + Ginger (IR + G)
Blood Glucose (mg/dl)	77.2 ± 5.2	57.7 ± 11.5	$260 \pm 3.2^{1,2}$	132.0 ± 8.3^3	$212.3 \pm 2.0^{1,2}$	63.0 ± 6.7^1
Serum Insulin (mIU/ml)	2.4 ± 0.1	$4.2 \pm 0.1^{4,5}$	$0.8 \pm 0.1^{1,3}$	2.5 ± 0.1	$1.5 \pm 0.1^{1,3}$	4.0 ± 0.1
MDA (nmol/L)	5.2 ± 0.1	4.8 ± 0.1^1	$11.3 \pm 0.1^{1,3}$	$8.2 \pm 0.1^{1,3}$	$8.4 \pm 0.1^{1,3}$	$6.3 \pm 0.1^{1,3}$

Values are mean \pm SEM. ^{1,3}p < 0.05 vs. C; G. ²p < 0.05 vs. A+G; IR+G; ^{4,5}p < 0.05 vs. C; A+G

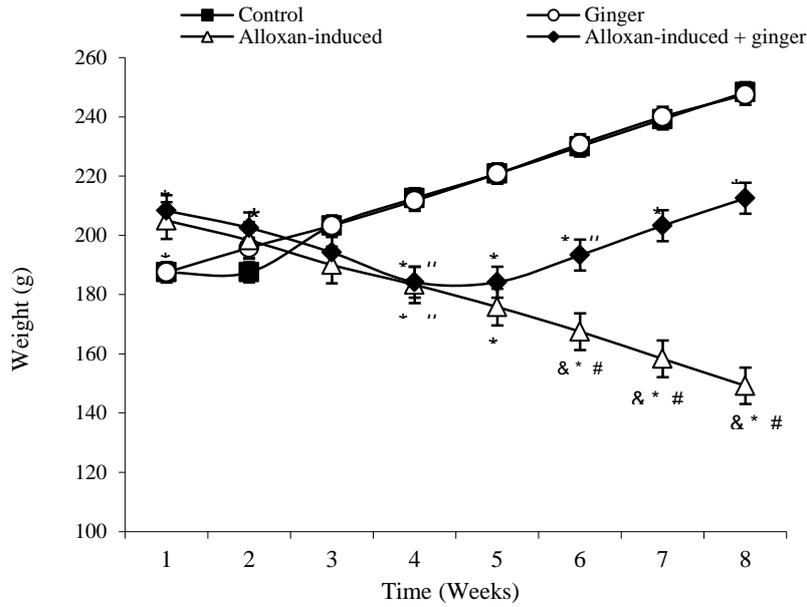


Figure 1.

Body weight in Control, Ginger, Alloxan-induced and Alloxan-induced + Ginger. *P<0.05 vs. control; #P< 0.05 vs. ginger; &P< 0.001 vs. Alloxan-induced.

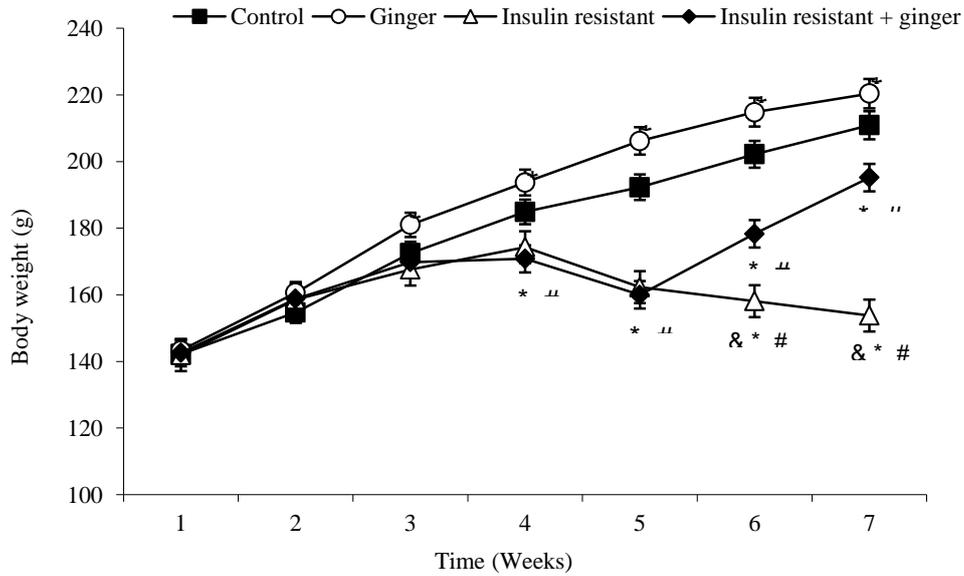


Figure 2.

Body weight in Control, Ginger, Insulin resistant and Insulin resistant + Ginger. *P<0.05 vs. control; # P < 0.05 vs. ginger; & P< 0.05 vs. Insulin resistant

Serum Concentration of Insulin (mIU/ml)

Serum concentration of insulin in control, ginger only treated, alloxan-induced diabetic, alloxan-induced

diabetic + ginger treated, insulin resistant diabetic and insulin resistant diabetic + ginger treated male rats was (2.4 \pm 0.1m IU/ml), 4.2 \pm 0.1m IU/ml, 0.8 \pm

0.1m IU/ml, 2.5 ± 0.1 m IU/ml, 1.5 ± 0.1 m IU/ml, and 4.0 ± 0.1 m IU/ml) respectively (Table 1).

Serum concentration of insulin was significantly lower ($P < 0.05$) in the alloxan-induced diabetic and insulin resistant diabetic groups compared to control, and ginger only treated groups. It was also significantly higher ($P < 0.05$) in ginger only treated group compared to control and alloxan-induced diabetic + ginger treated groups.

Serum Concentration of Malonydealdehyde (nmol/L)

Serum concentration of Malonydealdehyde (MDA) in control, ginger only treated, alloxan-induced diabetic, alloxan-induced diabetic + ginger treated, insulin resistant diabetic, and insulin resistant diabetic + ginger treated groups was (5.2 ± 0.1 nmol/L, 4.8 ± 0.1 nmol/L, 11.3 ± 0.1 nmol/L, 8.2 ± 0.1 nmol/L, 8.4 ± 0.1 nmol/L, 6.3 ± 0.1 nmol/L) respectively (Table 1).

Serum concentration of MDA was significantly higher ($P < 0.05$) in the alloxan-induced diabetic and insulin resistant diabetic groups compared to the other three groups. Likewise, it was significantly higher in the alloxan-induced diabetic + ginger treated and insulin resistant diabetic + ginger treated groups compared to the control and ginger only treated groups. However, it was significantly lower ($P < 0.05$) in the ginger only treated group compared to the control group.

Body weight

Body weight was significantly higher ($P < 0.05$) in alloxan-induced diabetic and alloxan-induced diabetic + ginger treated groups compared to the control and ginger only treated groups at the beginning of the experiment (Figure 1). This was anticipated because of the experimental duration of 8 weeks in the alloxan-induced diabetic groups and rapid weight loss in clinical type 1 diabetic state.

Body weight decreased progressively in the alloxan-induced diabetic and alloxan-induced diabetic + ginger treated groups (after alloxan monohydrate injection). This decrease was significantly lower ($P < 0.05$) at the 4th week compared to control and ginger only treated groups. Thereafter, it decreased significantly ($P < 0.05$) in alloxan-induced diabetic group compared to control and ginger only treated groups while it increased significantly ($P < 0.05$) in the alloxan-induced diabetic + ginger treated group compared to alloxan-induced diabetic group, though it was still significantly lower ($P < 0.05$) in the alloxan-induced diabetic + ginger treated group compared to the control and ginger only treated groups (Figure 1).

On the other hand, body weight increased progressively in the insulin resistant diabetic and

insulin resistant diabetic + ginger treated groups in a similar manner as observed in the control and ginger only treated groups (Figure 2) until the 6th week, after which it began to decline significantly ($P < 0.05$) till the 12th week in insulin resistant diabetic group. It however, increased significantly ($P < 0.05$) in the insulin resistant diabetic + ginger treated group compared to the insulin resistant diabetic group from the 10th week, though it was still significantly lower ($P < 0.05$) in the insulin resistant diabetic + ginger treated group compared to the control and ginger only treated groups (Figure 2).

DISCUSSION

Various plant extracts have been used as hypoglycaemic drugs, though the exact mechanisms involved have not been scientifically addressed (Grover *et al.* 2002; Rahman and Zaman, 1989; Platel and Srinivasan, 1997). Fasting blood glucose level was significantly higher in alloxan-induced diabetic and insulin resistant diabetic groups compared to the other groups (Table 1). It was also significantly higher in the alloxan-induced diabetic + ginger and insulin resistant diabetic + ginger groups compared to the control and ginger groups (Table 1). The result clearly shows that ginger has hypoglycaemic effect since the blood glucose level in the ginger and insulin resistant diabetic + ginger groups was significantly lower than that in the control group; likewise, treatment with ginger significantly decreased the fasting blood glucose level in the alloxan-induced diabetic + ginger and insulin resistant diabetic + ginger groups.

The results on fasting blood glucose level support the views that alloxan increases blood glucose in rats (Sheweita *et al.*, 2002; Raju *et al.*, 2001, Arikawe *et al.*, 2006) and that ginger exhibits hypoglycaemic effects (Al-Amin *et al.* 2006; Kadnur & Goyal, 2005; Akhani *et al.* 2004).

Serum insulin level is a crucial factor to control normal blood glucose level (Islam & Choi, 2008). It was as expected significantly lower in the alloxan-induced diabetic and insulin resistant diabetic groups compared to the other groups, while it was significantly higher in the ginger group compared to the other groups (Table 1). The result clearly shows that ginger increases serum insulin level, enhance insulin sensitivity and also decreases fasting blood glucose level. This is in line with the views of other authors (Sahebkar, 2011; Suganthi *et al.* 2007; Sekiya *et al.* 2004; Al-Amin *et al.* 2006 and Akhani *et al.*, 2004) and a likely mechanism is an increase in pancreatic secretion of insulin from the beta cells or release of bound insulin (Al-Amin *et al.*, 2006).

Serum concentration of MDA as expected was significantly higher in the alloxan-induced diabetic

and insulin resistant diabetic groups compared to the other groups. This is related to the diabetic state i.e. release of reactive oxygen species (radicals) in both experimental diabetic state. The result shows that ginger reduces MDA level since MDA level was significantly lower in the ginger group compared to the control group. Likewise MDA was lower in the alloxan-induced diabetic + ginger and insulin resistant diabetic + ginger groups compared to the alloxan-induced diabetic and insulin resistant diabetic groups respectively. Thus ginger decreases MDA concentration in normal, alloxan-induced and insulin resistant diabetic rats (Heeba and Abd-Elghany, 2010; Oboh, Akinyemi and Ademiluyi, 2010; Shanmugam *et al.* 2010; Ajith *et al.* 2008). Thus ginger acts as a scavenger of oxygen radicals and also acts as an antioxidant.

At the beginning of the experiment, the animals were grouped such that body weight was higher in animals grouped into alloxan-induced diabetic and alloxan-induced diabetic + ginger groups. This is because of the experimental duration (8 weeks) and rapid weight loss in clinical type 1 diabetic state (Figure 1). Body weight as expected progressively declined in the alloxan-induced diabetic and alloxan-induced diabetic + ginger groups till the 4th week. However, at the 3rd week, there was no significant difference in the body weight amongst all the groups (Figure 1). This was because while it body weight decreased rapidly in both alloxan-induced diabetic and alloxan-induced diabetic + ginger groups it increased progressively in the control and ginger groups.

At the 4th and 5th week, body weight was significantly lower in the alloxan-induced diabetic and alloxan-induced diabetic + ginger groups compared to the control and ginger groups though it increased slightly in the alloxan-induced diabetic + ginger group following ginger administration at the 4th week (Figure 1). This trend persisted at the 6th, 7th, and 8th week, with body weight still significantly lower in the alloxan-induced diabetic and alloxan-induced diabetic + ginger groups compared to the control and ginger groups. It was also significantly lower in the alloxan-induced diabetic group compared to the alloxan-induced diabetic + ginger group (Figure 1).

Body weight increased progressively in all the groups (Figure 2) as anticipated until the 4th week when it became significantly higher in the ginger group compared to the other groups. This trend continued till the end of the experimental period. At the 6th and 8th week, body weight declined significantly in the insulin resistant diabetic and insulin resistant diabetic + ginger groups compared to the control and ginger groups. This trend continued

for the insulin resistant diabetic group till the end of the experimental period while body weight significantly increased in the insulin resistant diabetic + ginger group from the 8th week following ginger administration till the end of the experiment.

Summarily, the body weight pattern in this study shows that ginger causes increase in body weight in normal rats and exhibited not only a leveling weight effect in diabetic animals but also has the potential to restore body weight in diabetic animals (Islam & Choi, 2008) to match that of the control group.

The results of the study clearly show that dietary ginger has hypoglycaemic effect, enhances insulin synthesis in male rats and has high antioxidant activity. One of the likely mechanisms is the action of malonydealdehyde, which acts as a scavenger of oxygen radicals. Further study is suggested on the involvement of serotonin receptors in the mechanism of action through which ginger initiate its effect.

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