

Hypoglycemic Activity of Methanolic Fruit Pulp Extract of *Adansonia digitata* on Blood Glucose Levels of Alloxan Induced Diabetic Rats

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Abstract: This study was carried out to evaluate the hypoglycemic properties of the methanolic extract of *Adansonia digitata* fruit pulp on blood glucose. Forty eight of the rats were randomly distributed into six. Group one served as the normal control and Group two rats were administered with alloxan (150 mg/kg) intraperitoneally and served as the diabetic control. Groups 3, 4 and 5 were intraperitoneally administered with alloxan (150 mg/kg) and orally administered with methanolic extract of *Adansonia digitata* fruit pulp (100, 200 and 300 mg/kg) once daily for 4 weeks. Group six rats were intraperitoneally administered with alloxan (150 mg/kg) and orally administered with chlorpropamide (84 mg/kg) once daily for 4 weeks. The serum concentration of glucose of all the rats in each group was determined after the 14th and 28th dose of treatment. There was significant ($p < 0.001$) reduction of serum glucose in the three groups of rats administered with methanolic extract of *Adansonia digitata* fruit pulp at second and fourth week of the treatment. The group of animal treated with chlorpropamide (84 mg/kg) also showed significant ($p < 0.001$) reduction of serum glucose compared to most effective dose of the methanolic extract (300 mg/kg) during the second and fourth week of the treatment. The result of qualitative phytochemical analysis of methanolic extract of *Adansonia digitata* fruit pulp indicated the presence of glycosides, flavonoids, tannins, saponins, terpenoids and steroids. This result suggests that the methanolic fruit pulp extract of *Adansonia digitata* possess antidiabetic effect on alloxan induced diabetic rats.

Keywords: *Adansonia digitata*, alloxan, hypoglycemic activity, phytochemicals

INTRODUCTION

Diabetes mellitus is a group of metabolic disorders characterized by hyperglycemia and defective metabolism of glucose and lipids (Chevenne and Fonfrède, 2007). Diabetes is not a single disease rather it is a heterogeneous group of syndromes characterized by an elevation of blood glucose caused by relative or absolute deficiency of insulin. Diabetes was estimated to affect 177 million people worldwide in 2000 and this figure is projected to increase to 300 million by 2025 (Chevenne and Fonfrède, 2007). Diabetes mellitus is one of the world's most devastating human diseases. WHO (1980) estimate of the people affected by this disease worldwide was put at 230 million and it is projected to become 235 million by 2035, thus putting human population in midst of epidemic of diabetes (Chevenne and Fonfrède, 2007). Diabetes is a chronic condition which the body cannot properly convert food into energy and is associated with long-term complications that affect almost every part of the body (Bluestone *et al.*, 2010). The condition often leads to problems such as: blindness, heart and blood vessel disease, Stroke, kidney failure, amputation and nerve damage (McCarthy and Frognel, 2002). Diabetes can

be divided into two main groups based on their requirements of insulin: insulin dependent diabetes mellitus (Type 1) and non-insulin dependent diabetes mellitus (Type 2). Type 1, known as juvenile onset or Insulin Dependent Diabetes Mellitus (IDDM); it manifests before 20 years of age (Cantrill, 1999) and its origin is usually ascribed to autoimmune disorder that destroys the beta cells of islet of Langerhans that are responsible for insulin production in the body. Individuals with this form of Type 1 diabetes often become dependent on insulin for survival eventually and are at risk for ketoacidosis (Willis *et al.*, 1996). Markers of immune destruction, including islet cell autoantibodies and/or autoantibodies to insulin are present in 85-90% of individual with Type 1 diabetes mellitus (Verge *et al.*, 1996). Type 2 diabetes mellitus is a chronic progressive disease typified by a loss of glycaemic control over time as the insulin secreting pancreatic beta cells lose their ability to compensate for the prevailing levels of insulin sensitivity. The hyperglycemia of type 2 diabetes is associated with an increased risk of micro vascular (retinopathy, neuropathy, nephropathy) and macro vascular (myocardial infarction, stroke) events.

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Orthodox treatment of diabetes mellitus includes a modification of life style, such as diet and exercise and the use of insulin and/or oral hypoglycaemic drugs. These pharmacologic agents target increased insulin secretion, decreased hepatic glucose production and increased sensitivity to insulin (Gray and Flatt, 1999). Management of this disease with insulin and/or oral hypoglycaemic agents has certain drawbacks (University Group Diabetes Program, 1974). Many traditional plant treatment for diabetes exist (Gray and Flatt, 1999) out of which few have received scientific or medical scrutiny and WHO (1980), has recommended that traditional plant treatment for diabetes warrant proper evaluation.

Baobab (*Adansonia digitata* L.) is a deciduous tree and belongs to the plant family called *Bombacaceae*. Baobab contains a number of substances usually employed for the treatment of numerous diseases in the African traditional medicine and for that reason it is also named "the small pharmacy" (Obizoba and Anyika, 1994). Baobab is used in folk medicine as an antipyretic or febrifuge to overcome fevers. Both leaves and fruit pulp are used for this purpose. Fruit pulp and powdered seeds are used in cases of dysentery and to promote perspiration (i.e., a diaphoretic) (Sibibe *et al.*, 2002). Baobab fruit pulp has traditionally been used as an immunostimulant, anti-inflammatory, analgesic, antipyretic, febrifuge and astringent in the treatment of diarrhoea and dysentery (Al-Qarawi *et al.*, 2003). The fruit pulp has been evaluated as a substitute for improved western drugs (Al-Qarawi *et al.*, 2003). The aqueous extract of baobab fruit pulp exhibited significant hepatoprotective activity and, as a consequence, consumption of the pulp may play an important part in human resistance to liver damage in areas where baobab is consumed (Al-Qarawi *et al.*, 2003).

Taking cognizance that the pulp fruits of *Adansonia digitata* are traditionally consumed as a food sources as well as for medicinal purposes, such as management of diabetes mellitus in Hausland, this study evaluated the hypoglycemic activity of the methanolic extract on blood glucose levels of alloxan induced diabetic rats. This has become necessary in view of high carbohydrate contain of the pulp (Magdi, 2004). As part of nutritional therapy, diabetic patients are advised to avoid high carbohydrate diets. Hence evaluation of hypoglycaemic activity becomes imperative in order to establish any therapeutic benefit in the used of pulp in the management of diabetes mellitus in Hausaland.

MATERIALS AND METHODS

The study was conducted at Bayero University Kano, Nigeria in October, 2012.

Plant materials: The fruit pulps of *Adansonia digitata* were collected from kawo market, Kaduna State, Nigeria. The plant was identified and authenticated by a

specialist and deposited at the Herbarium Section in the Department of Biological Sciences, Bayero University Kano, Nigeria, where a voucher specimen has been deposited.

Extract preparation: The fruit pulps were broken, air dried and then crushed with a pestle and mortar and then sieved to obtain the powder and remove the seeds. The powdered sample was soaked in methanol for 48hrs. The extract was obtained by filtration using a Whatman filter paper No. 1. The methanol was evaporated using rotary evaporator. Solutions of the extract were prepared freshly for the study.

Chemical used: All chemicals are of analytical grade obtained from Sigma (St. Louis USA) unless otherwise stated.

Phytochemical Screening: The phytochemical screening of the crude extract of *Adansonia digitata* was carried out in order to ascertain the presence of its constituents utilizing standard methods (Sofowora, 1993).

Acute toxicity study: The procedure was followed by using OECD guidelines (organization of economic cooperation and development) for acute toxicity of chemical No 425 (OECD, 2008). Six female rats weighing 120g were used for the study, the doses of the methanolic extract of *Adansonia digitata* fruit pulp administered were 2000mg/kg and 5000mg/kg and the extract was administered orally to rats which were fasted overnight with water. Body weights of the rats before and after treatment were noted. Any changes in skin and eyes and mucous membrane and also respiratory, were observed and also sign of tremors, convulsion, salivation, diarrhoea, sleep and coma were noted. The onset of toxicity and signs of toxicity also noted for 14 days.

Experimental animals and alloxan induction: White albino rats weighing 160-240 g were purchased from the animal room of biological sciences department, Bayero University, Kano State. The rats were maintained under standard laboratory conditions and were allowed free access to both food and water throughout the period of the experiment.

Stock solution of alloxan was prepared by dissolving alloxan monohydrate (0.9 g) in distilled water (6 cm³) and diabetes was induced by single intraperitoneal injection of alloxan monohydrate (150 mg/kg). The volume of the solution containing 150 mg/kg given to each rat was determined by its weight. After a period of two days, the rats with blood glucose level greater than 200 mg/dL were considered diabetic and used for this research work.

Experimental design: Forty eight of the rats weighing (160-240 g) were used for testing antidiabetic effect.

Forty rats were divided into five groups after alloxan induction as follows: -

- Group 1 (8) :** Normal rats
- Group 2 (8) :** Diabetic control rats
- Group 3 (8) :** Diabetic rats given fruit pulp extract (100 mg/kg) once dai
- Group 4 (8) :** Diabetic rats given fruit pulp extract (200 mg/kg) once daily
- Group 5 (8) :** Diabetic rats given fruit pulp extract (300 mg/kg) once daily
- Group 6 (8) :** Diabetic rats given chlorpropamide (84 mg/kg) once daily

Determination of blood glucose level: Blood samples of the rats were collected by cutting the tail tip of the rats for blood glucose determination before administration of the extract, after administration of the extract for 14 days and after administration of the extract for 28 days. Determination of the blood glucose level was carried out using Glucose Oxidase Method (Barham and Trinder, 1972) and results were reported in mg/dL.

Statistical analysis: The data was statistically analysed using GraphPad Instat3 Software (2000) version 3.05 by GraphPad Inc. Data are presented in Mean±Std. Statistical significance was accepted at a level of p<0.05 and below.

RESULTS

Phytochemical analysis: The result of qualitative phytochemical analysis of methanolic extract of *Adansonia digitata* fruit pulp indicated the presence of the following phytochemicals; glycosides, flavonoids, tannins, saponins, terpenoids and steroids (Table 1).

Acute toxicity study: The acute toxicity of methanolic extract of *Adansonia digitata* fruit pulp was evaluated in two phases. In the first phase, the group was orally administered with 2000 mg/kg of the extract and no mortality was recorded. In the second phase the group was administered with 5000 mg/kg of the extract and

Table 1: Summary of phytochemical constituents present in extract of *Adansonia digitata* fruit pulp

Constituents	Inference
Alkaloids	-
Glycosides	+
Flavonoids	+
Tannin	+
Saponins	+
Terpenoids	+
Steroids	+
Antraquinones	-

- : means absent + : means present

no mortality was recorded. Observation of the groups for 14 days does not show any sign of toxicity. In the current study, the extract could be declared practically non toxic since the LD₅₀ is greater than 5000 mg/kg.

Antidiabetic study: The Antidiabetic activity of the methanolic extract of *Adansonia digitata* fruit pulp was determined in rats administered orally with the extract for 14 and 28 days once daily.

The result obtained after 14th dose of treatment with the extract (Table 2) has shown a significantly higher (p<0.001) serum level of glucose in diabetic control rats when compared with the normal control rat. The three groups orally administered with different doses of the extract (Table 2) had their serum levels of glucose significantly lower (p<0.001) when compared to diabetic control rats, but higher than that of the normal control rats. The serum level of glucose in chlorpropamide treated rats was found to be significantly lower (p<0.001) when compared to the three groups orally administered with different doses of the extract (Table 2).

In the 28th dose of treatment the serum level of glucose was found to be significantly higher in diabetic control rats (p<0.001) when compared to normal control rats (Table 2). The three groups orally administered with different doses of the extract had their serum levels of glucose significantly lower (p<0.001) when compared to diabetic control rats, but higher than that of the normal control rats (Table 2). The serum level of glucose, in chlorpropamide treated rats was found to be significantly lower (p<0.001) when compared to the three groups orally administered

Table 2: Serum glucose level (in mg/dl) in alloxan induced diabetic rats before administration of extract, after 14th and 28th dosage of oral administration with methanolic fruit pulp extract of *Adansonia digitata* and Chlorpropamide

Groups	Before Administration	After administration	
		14 th Day	28 th day
Normal control	95.48±5.88	92.00±4.24	94.44±3.91
Diabetic control	258.18±2.75*	277.78±2.12*	283.13±1.41*
MFPEAD(100mg/kg)	249.23±2.42*	227.50±2.80*	205.81±3.92 ^a *
MFPEAD(200mg/kg)	251.23±3.33*	195.56±3.95 ^a *	167.78±3.65 ^a *
MFPEAD(300mg/kg)	256.08±4.98*	152.22±1.68 ^a *	138.96±0.89*
CP (84mg/kg)	252.28±3.75*	130.00±2.36*	121.78±1.54*

Values with asterisk in each column are significantly different at p<0.001 compared to normal control; Values bearing superscript (a) in each column are significantly different at p<0.001 compared to diabetic control and chlorpropamide; MEPEAD: Methanolic Fruit Pulp Extract of *Adansonia digitata*; CP: Chlorpropamide

with different doses of the extract (Table 2). There is significant difference in normal control ($p < 0.01$) when compared to the group administered with 84mg/kg of chlorpropamide (Table 2).

DISCUSSION

Insulin mediation of glucose in take by the cells is a critical step in maintaining glucose homeostasis and in clearing the postprandial glucose load (Defronzo *et al.*, 1985; Kruszynska and Olefsky, 1996). Historical records provide a reservoir of basic information on the use of traditional medicine in the management of diabetes mellitus with plant extracts (Bailey and Day, 1989; Swanston-Flatt *et al.*, 1991; Gray and Flatt, 1997, 1999; Srinivasan, 2005). One of such part is the stem of *Adansonia digitata* in the management of streptozocin induced Diabetes mellitus in rat.

Though hypoglycaemic potential of *Adansonia digitata* stem in Streptozocin-Induced Diabetic Wistar Rats (Tanko *et al.*, 2008) has been established, there is paucity of information about the anti hyperglycaemic effect of the pulp widely consumed and used in the management of diabetes mellitus in Hausaland. *Adansonia digitata* pulp is rich in flavanoids, vitamin C and Procyanidins (Kaboré *et al.*, 2011; Shahat, 2006). Intestinal sodium glucose transporter-1 (SGLT-1) was suggested to be involved in the absorption of quercetin glucosides (Cermak *et al.*, 2004). Hence they competitively inhibit sodium (Na^+) dependent mucosal uptake of the non-metabolisable glucose analogue methyl- α -D-glucopyranoside via SGLT-1 using rat mid-jejunum, whereas quercetin (aglycone) and rutin had no effect (Cermak *et al.*, 2004). Similarly, conjugated flavanoids such as Quercetin-3Glycosides have the tendency of inhibiting Na^+ -independent, non-saturable uptake of glucose by SGLT-1 (Cermak *et al.*, 2004). Flavonoids, glycosides also stimulate the secretion of insulin in β -cells of pancreas (Hii and Howell, 1985).

The detection of flavonoids in the extract can also be linked to the blood glucose lowering property by inhibiting intestinal absorption. Furthermore, flavonoids inhibit glucose-6-phosphatase activity in the liver thereby suppressing gluconeogenesis and glycogenolysis and consequently reduce the hyperglycaemia (Chen *et al.*, 1998). Many reports on herbal remedy for diabetes show that flavonoids exhibit anti-oxidant properties. The free radical scavenging ability of many flavonoids-containing extracts has been postulated as the mechanism which affords relief in many distressful diseased conditions of the body such as diabetes mellitus (Tiwari, 2004). Procyanidins isolated from fruit pulp of *Adansonia digitata* are class of proanthocyanidins (condensed tannins). In recent years, attention has been paid to polyphenolic procyanidins as a result of their antioxidant, radical scavenging, antiviral and anti-HIV activities (Shahat *et al.*, 2002; Saint-Cricq de Gaulejac *et al.*, 1999).

Polymers and oligomers from proanthocyanidins of Persimmon inhibit digestive enzymes such as α amylase and α glucosidase enzymes in addition to preventing the formation of advanced glycation products (Lee *et al.*, 2007). Hence, it is likely that the proanthocyanidins in the pulp may have as well reduce the glycaemic index of the food consumed with pulp by acting on the carbohydrate digestive enzymes such as α amylase and α glucosidase

Flavonoid and terpenes isolated from the other antidiabetic medicinal plants have been found to stimulate secretion of insulin (Marles and Farnsworth, 1995). Quercetin an important flavonoid is also found in the pulp (Mueller and Mechler, 2005). It increases insulin secretion by enhancing hepatic glucokinase activity (Matschinsky *et al.*, 2006). Effect of the flavonoids, quercetin and ferulic acid on pancreatic β -cells leading to their proliferation and secretion of more insulin have been proposed by Mahesh and Menon (2004) and Balasubashini (2003) as the mechanism by which they reduced hyperglycaemia. The flavonoids present in *Adansonia digitata* may also be acting similarly thereby decreasing the high blood glucose levels of alloxan induced-diabetic rats. The extract might also exert its effect by bringing about hypoglycemic effects due to the presence of insulin-like substance in it, thus stimulating the β cells to produce more insulin. Furthermore the phytochemicals might also exert their blood glucose lowering ability by retarding necrosis of the pancreatic β -cells or by partially recovering the destroyed β -cells of the pancreas.

The significant increase in serum glucose level in diabetic control rats compared to normal control rats is as a result of damage of the pancreatic beta cells by the effect of alloxan. Alloxan monohydrate is one of the chemical used to induce diabetes mellitus. It induces diabetes by damaging insulin secreting cells of the pancreas leading to hyperglycaemia (Szudelski, 2001). In alloxan induced diabetes, there is selective necrosis of the β -cells of islet of langerhans in the pancreas so that insulin production is totally or partially inhibited, depending on the concentration of the alloxan (Etuk, 2010).

Although the precise mechanism of alloxan-induced diabetes remains unclear, there is increasing evidence that it involves the degeneration of islet b-cells by accumulation of cytotoxic free radicals. The action of reactive oxygen species causes rapid destruction of *beta* cells (Szudelski, 2001). One of the targets of the reactive oxygen species is DNA of pancreatic islets. Its fragmentation takes place in *beta* cells exposed to alloxan (Takasu *et al.*, 1991). Following its administration, alloxan is concentrated in the islets and in the liver, where it is reduced to dialuric acid. This acid is unstable in aqueous solutions and undergoes oxidation back to alloxan, accompanied by generation of O_2^- , hydrogen peroxide and hydroxyl

radicals by Fenton reaction. The liver contains high Super Oxide Dismutase (SOD), catalase and glutathione peroxidase activities, which can scavenge these free radicals. On the contrary, the islet cells have low concentrations of these enzymes and are vulnerable to the cytotoxic effects of the free radicals. It is reported that increase in islet cell SOD activity can prevent or decrease alloxan toxicity (Halliwell and Gutteridge, 1989). A significantly lower ($p < 0.001$) mean serum level of glucose was observed in the diabetic rats during the fourth week when compared to the first two weeks of oral treatment. However, it can be inferred that the methanolic fruit pulp extract of *Adansonia digitata* produces its most potent antidiabetic effect at the highest dose (300 mg/kg) and after four weeks of treatment. Chlorpropamide has shown to be effective therapy for diabetes. There was significant difference ($p < 0.001$) in the level of blood glucose in the group treated with Chlorpropamide (diabenase) 84 mg/kg when compared with the diabetic control rats these can be attributed to its ability in lowering blood glucose or retarding the necrosis caused by alloxan. It also acts by stimulating insulin release from beta cells, these shows that diabetic produced from this instance was moderate rather than severe. This implies the presence of some functional secreting beta cells in the islet of langerhans (Gyang and Day, 1989). Chlorpropamide on the other hand was found to exert a significantly higher ($p < 0.001$) antidiabetic activity when compared to the most effective dose of the extract (300 mg/kg).

Therefore the finding of this study indicated that the methanolic extract of *Adansonia digitata* fruit pulp exert its antidiabetic effect by lowering blood glucose in alloxan induced diabetic rats.

CONCLUSION

The result obtained in this study indicated that though *A. digitata* pulp may be very rich in carbohydrate, but still possesses the potential to be used in the management of diabetes mellitus. The presence of certain phytochemicals may have overcome the negative effect of high carbohydrate content of the pulp. It is likely that polymers of tannins and flavanoids in the pulp may have the potential of reducing intestinal absorption of glucose, inhibit carbohydrate digestion and increase hepatic activity of glucokinase. The ability of 300 mg/kg weight of methanolic extract to lower serum glucose comparable to chlorpropamide supports the traditional use of *A. digitata* fruit pulp extract for controlling hyperglycemia in diabetics in Hausaland.

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