

Pharmacological Effects of *Garcinia kola* Seed Powder on Blood Sugar, Lipid Profile and Atherogenic Index of Alloxan-induced Diabetes in Rats

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Abstract: Objective: The pharmacological effects of *Garcinia kola* seed Powder (GKP) on blood sugar, lipid profile and atherogenic index of diabetic rats were studied. **Materials and Methods:** Thirty male albino Wistar rats were divided into six groups of five animals per group. The first two groups: non-diabetic control and non-diabetic treated were normal animals and orally given normal saline and 600 mg kg⁻¹ b.wt. GKP respectively. The last four groups which were made diabetic using alloxan monohydrate had one diabetic untreated group, that received normal saline and three diabetic treated groups which received 300, 600 and 900 mg kg⁻¹ b.wt. of GKP orally, respectively. At a single dose of treatment, blood was collected through tail vein puncture and blood glucose concentration measured with glucometer at 0, 2, 4, 6 and 8 h after which it was continued for 21 days. At the end of the treatment period, the animals were sacrificed and blood collected via cardiac puncture from where serum was recovered for lipid profile analysis. **Results:** GKP treatment significantly lowered blood glucose and improved lipid profile and atherogenic index of diabetic rats. This investigation therefore portrays GKP as an antidiabetic, antilipidemic and anti-atherogenic agent with a tremendous potential to protect against coronary heart disease.

Key words: *Garcinia kola*, lipid profile, atherogenic index, antidiabetic, antilipidemic

INTRODUCTION

Diabetes mellitus is among the most common disorder in developed and developing countries (Makund *et al.*, 2008). The disease is increasing rapidly in most parts of the world (Kumar *et al.*, 2008). In 2000, according to WHO, at least 171 million people worldwide suffer from diabetes which corresponds to 2.8% of population (Wild *et al.*, 2004), this figure is expected to double in the year 2030. Hyperglycaemia in diabetic patients is associated with alterations in glucose and lipid metabolism and modification in liver enzyme levels (Jenson and Stender, 1998). Diabetes mellitus is consistently characterized by abnormalities in lipid profile (Andallu *et al.*, 2009) and an increase in atherogenic index (Mazumder *et al.*, 2009). Diabetes mellitus has been recognized as a major risk factor for Cardiovascular Diseases (CVD), such as atherosclerosis, heart attacks, stroke etc. (Mazumder *et al.*, 2009). About 75% of deaths among men and 57% of death among women with diabetes are attributable to CVD (Moller, 2004). The use of plants in traditional medical practice has a long drawn history and remains the mainstay of primary health care in most of the third world (Prescott-Allen and Prescott-Allen, 1982). Traditional medicines are used by

about 60% of the world population in both developing and developed countries (Mythilypriya *et al.*, 2007).

Garcinia kola Heckle otherwise called bitter kola belongs to the family Guttiferae and found mainly in the tropical rain forest region of Central and West Africa, (Uko *et al.*, 2001). It is predominant in rainforest belt of southern Nigeria (Agada and Braide, 2009). The seeds are edible and are consumed as adjuvant to the true kola (*Cola nitida*) and for medicinal purposes (Braide, 1989). *Garcinia kola* plant is a wonder plant because every part of it has been found to be of medicinal importance. *Garcinia kola* is used in folklore remedies for the treatment of ailments such as liver disorders, diarrhoea, laryngitis, bronchitis and gonorrhoea (Adesina *et al.*, 1995). The seed is masticatory and used to prevent and relieve colic, chest colds and cough and can as well be used to treat headache (Ayensu, 1978). It is also used in treatment of jaundice, high fever and purgative (Iwu *et al.*, 1990); stomach ache and gastritis (Ajebesone and Aina, 2004); cirrhosis and hepatitis (Okwu, 2005). Its antifungal (Okwu and Morah, 2007) and antimicrobial effects (Adeboye *et al.*, 2008) has also been established. Pharmacological treatment of diabetes mellitus is based on use of insulin and oral hypoglycaemic agents. However, these approaches do not restore

normoglycaemia in most patients and in most cases becomes less effective with time. Moreover, continuous use of the synthetic anti-diabetic drugs causes side effects and toxicity (Luo *et al.*, 2004). The need to discover and develop more effective hypoglycaemic and antiatherogenic agents with minimum side effects becomes apparent. This study therefore sets out to evaluate the biochemical and pharmacological effects of *Garcinia kola* seed on blood glucose, lipid profile and atherogenic index in alloxan-induced diabetic rats and to ascertain whether or not it could protect against Coronary Heart Disease (CHD) secondary to diabetes.

MATERIALS AND METHODS

Plant material: Fresh *Garcinia kola* seeds were purchased from Watt Market, Calabar, Nigeria in September 2010. They were identified and authenticated by Mr. Frank Apejoye, a botanist at the Botany Department of the University of Calabar. Voucher samples (No. 176) were kept in the herbarium of Botany Department for reference purposes.

Preparation of seed samples: The outer testa of each *Garcinia kola* seed was removed washed and air dried for about 24 h. Each seed was cut into small pellets with kitchen knife and the resulting pellets were subsequently dried in an electric oven for 12 h at 40°C. The dry seed pellets were ground to fine powder using manual grinder and then sieved with 10 µm sieve. The resulting powder aliquots were used for phytochemical analysis and the remaining reconstituted with normal saline to obtain suspensions of appropriate concentration for oral administration.

Phytochemical screening: A portion of the powder was subjected to phytochemical analysis using Trease and Evans (1983) and Harborne (1983) methods to test for alkaloids, tannins, flavonoids, saponins and cardiac glycosides. The intensity of the coloration determines the abundance of the compound.

Test for alkaloids: Exactly 0.5 g of *Garcinia kola* seed powder was dissolved in 5 mL of 1% HCl on steam bath. 1 mL of the filtrate was treated with drops of Dragendorff's reagent. Turbidity or precipitation was taken as indicative of the presence of alkaloids.

Test for tannins: About 5 g of *Garcinia kola* seed powder was dissolved in 20 mL of distilled water and filtered. Drops of FeCl₃ was added. The production of a blue-black or blue-green precipitate was indicative of tannins.

Test for flavonoids: A 0.2 g of *G. kola* seed powder was dissolved in 2 mL of methanol and heated. A chip of magnesium metal was added to the mixture followed by the addition of a few drops of concentrated HCl. The occurrence of a red or orange colouration was indicative of flavonoids.

Test for saponins: The ability of saponins to produce frothing in aqueous solution and to hemolysed red blood cells was used as screening test for those compounds. About 0.5 g of GKP was shaken with water in a test tube. Frothing which persists on warming was taken as preliminary evidence for presence of saponins. The blood haemolysis test was performed on those extracts that frothed in water and was taken as further evidence for the presence of saponins.

Test for cardiac glycosides: About 0.5 g of *G. kola* seed powder was dissolved in 2 mL of glacial acetic acid containing one drop of 1% of FeCl₃. This was underlaid with concentrated sulphuric acid. Brown ring was seen at the interface and indicated the presence of deoxy sugar characteristic of cardiac glycosides.

Acute toxicity (LD₅₀) studies: Acute toxicity test was done using probit method. Thirty five male mice weighing between 24.8-25.5 g were used. The test was carried out by single oral administration of GKP in normal saline at doses of 0, 100, 500, 1500, 3000, 5000 and 6000 mg kg⁻¹ to different groups of mice (5 mice per group). Mortality and general behaviour was observed continuously for one, three and intermittently for the next six hours and again at 24 and 48 h. The parameters observed were gross behavioural changes, grooming, alertness sedation, loss of righting reflex, tremors and convulsions. The LD₅₀ of *Garcinia kola* seed powder was found to be 6741.43 mg kg⁻¹ and doses up to 900 mg kg⁻¹ b.wt. were found to be safe. All doses used in this study were carefully chosen to exclude the lethal dose.

Laboratory animals: Thirty male albino rats weighing about 240-250 g were purchased from the animal unit of the department of pharmacology, University of Calabar. The animals were kept in cages to acclimatize with conditions of the animal housing facility with ambient temperature 26-28°C and adequate ventilation for two weeks and fed with standard growers mash (Vita Feeds Nig. LTD. and clean water *ad libitum*.

Induction of diabetes mellitus: A single dose freshly prepared alloxan monohydrate (Sigma, St Louis MO, USA) in normal saline at a dose 150 mg kg⁻¹ b.wt. (Ebong *et al.*, 2008) was injected intra-peritoneally into the rats. Blood

samples collected by tail vein tapping were monitored for glucose levels, using a glucometer. After 72 h rats that had blood glucose level above 200 mg dL⁻¹ were considered diabetic and selected for the study.

Experimental design: The thirty male albino rats were divided into six groups of five rats per group. Animals in all groups received, by gavage, the following:

- **Non-diabetic control:** Received normal saline (0.5 mL kg⁻¹)
- **Non-diabetic treated group:** Received 600 mg kg⁻¹ of *Garcinia kola* seed (GKP)
- **Diabetic control:** Received normal saline (0.5 mg kg⁻¹)
- **Diabetic treated I:** Received 300 mg kg⁻¹ of GKP
- **Diabetic treated II:** Received 600 mg kg⁻¹ of GKP
- **Diabetic treated III:** Received 900 mg kg⁻¹ of GKP

The blood glucose levels of all animals were monitored after zero, two, four, six and eight hours of oral administration of a single dose of placebo and GKP suspension. The administration was then continued twice daily for every 12 h (6.00 a.m. and 6.00 p.m.) for 21 days. The blood glucose and body weight changes were also monitored every three days during the period.

Collection and analysis of samples: At the end of the 21-day period, the animals were fasted for 12 h, anaesthetized with chloroform and then sacrificed and blood collected by cardiac puncture. Blood was collected into non heparinised sample tubes and allowed to clot for two hours and later centrifuged at 3000 rpm for 10 min, after which serum was recovered for analysis.

Serum glucose level was determined by GOD-PAP method based on Barham and Trinder (1972), Total cholesterol and HDL-cholesterol was determined by CHOD-PAP method based on NCEP/ATPIII (2001), Triglyceride by GPO-PAP method based on Tietz (1995), VLDL and LDL-cholesterol based on Friedwald *et al.* (1972). Atherogenic index was determined using the following formula:

$$\text{Atherogenic Index (AI)} = \frac{\text{Total cholesterol}}{\text{HDL-cholesterol}}$$

$$\text{Protection against CVD (\%)} = \frac{\text{AI of diabetic control-AI of diabetic treated group}}{\text{AI of diabetic control group}}$$

Statistical analysis: Data were collected and analysed by ANOVA using Statistical Package for Social Science (SPSS) software for windows and post hoc testing was performed for inter-group comparison using the Least

Significant Difference (LSD). All data were expressed as Means±Standard error of the mean (SEM). The p-value<0.05, 0.01 and 0.001 were considered significant.

RESULTS

Phytochemical studies: Table 1 showed the result of the phytochemical screening carried out on *Garcinia kola* seed powder. *G. kola* was found to contain glycosides, flavonoids, tannins and saponins, while alkaloids were not detected.

Effects of *Garcinia kola* seed powder (GKP) on blood glucose concentration of diabetic and non-diabetic rats: Blood glucose changes were monitored at 0, 2, 4, 6, 8 h after oral administration of a single dose of GKP as shown in Table 2. The diabetic controls had their blood glucose increased significantly (p< 0.001) compared to the normal controls while treatment with GKP produced a dose-dependent significant reduction (p<0.05, 0.01 and 0.001) compared to the diabetic controls.

Effects of *Garcinia kola* seed powder (GKP) on serum lipid profile of diabetic and non-diabetic rats: The effect of GKP on serum lipid profile is shown in Table 3. The HDL-cholesterol of diabetic control rats was significantly (p<0.001) reduced compared to the normal control. Treatment with various doses of GKP increased significantly (p< 0.001) HDL-C of diabetic treated group in a dose dependent manner. The highest dose of GKP also produced the most significant increase (p<0.001) compared to the normal control. The HDL-C of non diabetic treated group was significantly (p<0.01) increased compared to the non diabetic control group. The Total Cholesterol (TC), Triglycerides (TG), very low density lipoprotein cholesterol (VLDL-c), atherogenic index and low density lipoprotein cholesterol (LDL-c) of diabetic control animals were significantly (p<0.001) increased compared to the non diabetic control. Treatment with GKP attenuated these increases significantly (p<0.001) in a dose dependent fashion compared to the diabetic control, achieving the most favourable reduction in the highest dose of GKP. The TG and VLDL-C of non diabetic treated group was significantly (p<0.001 and 0.01) reduced, respectively compared to non diabetic control.

Table 1: Phytochemical studies

Components	Presence
Alkaloids	-
Glycoside	++
Flavonoids	++
Tannins	+
Saponins	++

+: Present, -: Not present

Table 2: Effects of *Garcinia kola* seed powder (GKP) on blood glucose concentration of diabetic and non diabetic rats

Treatment	Blood glucose concentration (mg dL ⁻¹) at various times (h) after oral dosing with GKP				
	0	2	4	6	8
Non diabetic control (GKP, 0 mg kg ⁻¹)	77.90±2.65	77.41±2.44	76.96±2.45	76.17±2.35	73.10±1.77
Non Diabetic treated (GKP, 60 0 mg kg ⁻¹)	74.39±4.69	73.74±4.66	74.92±4.75	65.29±2.33	64.66±2.11
Diabetic control (GKP, 0 mg kg ⁻¹)	432.40±14.32***	434.60±12.42***	433.89±7.69***	431.22±13.78***	440.12±14.78***
Diabetic treated I (GKP, 300 mg kg ⁻¹)	454.04±15.99***	432.22±12.20***	415.39±9.55***	364.27±20.44***,c	307.03±3.28***,c
Diabetic treated II (GKP, 600 mg kg ⁻¹)	442.70±12.83***	406.48±8.94***,a	359.29±9.18***,c	319.39±7.33***,c	272.59±11.55***,c
Diabetic treated III (GKP, 900 mg kg ⁻¹)	445.27±21.83***	396.61±6.60***,b	320.00±7.49***,c	246.34±11.64***,c	232.04±7.06***,c

***p<0.001 significantly different from non diabetic controls; *p<0.05, ^bp<0.01, ^cp<0.001 significantly different from diabetic controls

Table 3: Effects of *Garcinia kola* seed powder (GKP) on serum lipid profile of diabetic and non diabetic rats

Treatment	Conc. (mg dL ⁻¹)				
	HDL-C	TC	TG	VLDL-C	LDL-C
Non diabetic control (GKP, 0 mg kg ⁻¹)	50.82±0.93	75.50±1.11	83.14±1.26	16.63±0.25	8.03±0.60
Non diabetic treated (GKP, 600 mg kg ⁻¹)	55.01±1.29**	77.34±1.73	71.52±1.25***	14.30±0.25**	8.02±0.83
Diabetic control (GKP, 0 mg kg ⁻¹)	27.05±1.32***	199.07±1.35***	157.06±1.14***	31.41±0.23***	140.53±1.71***
Diabetic treated I (GKP, 300 mg kg ⁻¹)	35.84±0.71***,c	166.50±5.86***,c	120.63±1.03***,c	24.33±0.35***,c	104.53±1.34***,c
Diabetic treated II (GKP, 600 mg kg ⁻¹)	51.72±0.95 ^c	120.31±1.43***,c	129.56±1.47***,c	25.91±0.30***,c	40.73±0.75***,c
Diabetic treated III (GKP, 900 mg kg ⁻¹)	59.25±1.15***,c	75.96±0.85 ^c	88.46±3.27 ^{bc}	18.44±1.22 ^{bc}	5.93±0.35 ^c

*p<0.05, **p<0.01, ***p<0.001 significantly different from non diabetic controls, ^cp<0.001 significantly different from diabetic controls

Table 4: Effect of GKP on atherogenic index and protection against CVD

Treatment	Atherogenic index	Protection (%)
Non-diabetic control (GKP, 0 mg kg ⁻¹)	1.49±0.02	79.84
Non-diabetic treated (GKP, 600 mg kg ⁻¹)	1.41±0.02	80.92
Diabetic control (GKP, 0 mg kg ⁻¹)	7.39±0.30***	0.00
Diabetic treated I (GKP, 300 mg kg ⁻¹)	4.65±0.15***,c	37.08
Diabetic treated II (GKP, 600 mg kg ⁻¹)	2.79±0.45***,c	62.25
Diabetic treated III (GKP, 900 mg kg ⁻¹)	1.28±0.03 ^c	82.68

***p<0.001 significantly different from non diabetic controls. ^cp<0.001 significantly different from diabetic controls

Effect of GKP on atherogenic index and protection against CVD:

The atherogenic index of diabetic control was significantly (p<0.001) increased compared to non-diabetic control. Oral administration with GKP attenuated this significantly (p<0.001) in a dose dependent manner. In a similar development, protection against CVD appeared to be dose dependent as the group that has the highest dose of GKP, had about 82.68 protection; the highest in all group (Table 4).

DISCUSSION

Phytochemical analysis of GKP showed that it contains flavonoids, tannins, saponins, cardiac glycosides and does not contain alkaloids at all. These findings agree with the report of Adegboye *et al.* (2008). Alloxan induces diabetes by damaging the insulin-secreting cells of the pancreas leading to hyperglycaemia (Lenzen, 2008). The observation in this study was in line with previous research finding, in that fasting levels glucose at 0, 2, 4, 6 and 8 h of alloxan diabetic untreated rats was significantly higher than in non-diabetic rats. This observed increase in glucose levels have been reported in diabetic untreated rats (Iwu *et al.*, 1990; Ebong *et al.*, 2008; Mohammed *et al.*, 2009). Alloxan

induces damage and death of pancreatic islet cells in experimental animal models, causing diabetes and decreasing or stopping insulin secretion. The cytotoxic action of alloxan is mediated by reactive oxygen species, alloxan and the products of its reduction, dialuric acid; establish a redox cycle with the formation of super oxide radicals. These radicals undergo dismutation to hydrogen peroxide. Then highly reactive hydroxyl radicals are formed by Fenton reaction. The action of reactive oxygen species with a simultaneous massive increase in cytosolic calcium concentration causes rapid destruction of β-cells, hence precipitating experimental diabetes mellitus (Lenzen, 2008). Oral administration of different doses of *Garcinia kola* seed powder (GKP) significantly reduced the increased glucose level in diabetic animals following treatment. This observation is in accord with the report of Iwu *et al.* (1990) and Adaramoye and Adeyemi (2006). Both reported the hypoglycaemic effect of GKP in normoglycemic rats as observed in this work. The reduction of glucose concentration could partly be that the biflavonoid of GKP promoted entry of glucose into cells, stimulation of glycolytic enzymes and glycogenic enzymes or inhibiting the glucose 6-phosphatase in the liver and subsequently reducing the release of glucose in blood. Naringenin another flavonone similar to kolaviron of *Garcinia kola*, has been implicated in eliciting its hypoglycaemic effect by an extra-hepatic action, possibly by stimulating glucose utilization in extra hepatic tissues or increasing the expression of insulin receptors in the liver plasma membranes (Pinnet *et al.*, 2004). Since kolaviron is structurally similar to naringenin, it could exert its action through this mechanism. This reduction is however dose-dependent as the 900 mg kg⁻¹ dose recorded the greatest reduction and almost brought the

glycaemic state to normal at the end of the treatment period. Hyperlipidemia is a known complication of diabetes mellitus (Merzouk *et al.*, 2004) and this co-exists with hyperglycemia which is characterized by increased levels of cholesterol, triglycerides and phospholipids and changes in lipoproteins (Bagdade *et al.*, 1991). Diabetes is also often associated with increased dyslipidaemia (Daniel *et al.*, 2003). At the end of the 21 day study period it was observed that serum TC, TG, VLDL-cholesterol, LDL-cholesterol levels and atherogenic index of alloxan-diabetic rats were significantly increased when compared to the normal control, while the serum HDL-cholesterol of diabetic rats were significantly reduced when compared to normal control. The observation is consistent with the reports of previous researchers (Ahmed *et al.*, 2010; Andallu *et al.*, 2009). The abnormally high concentration of serum lipids was mainly due to increase in the mobilization of Free Fatty Acids (FFA) from peripheral tissue due to activation of the hormone sensitive lipase during insulin insufficiency. Lack of insulin in diabetes is also known to be associated with increased synthesis of cholesterol which may be due to increased activity of HMG CoA reductase (Ahmed *et al.*, 2010). Insulin resistance in diabetic rats could increase the hepatic uptake of fatty acids released by lipolysis of adipose tissue, the intrahepatic synthesis of triglycerides and the over production and secretion of VLDL particle that, in turn, leads to increased plasma levels of TG (Daniele *et al.*, 2010). HDL-cholesterol is the smallest of the lipoprotein species containing approximately 20% cholesterol ester and very little triglyceride. It is strongly and independently related to CHD. Unlike LDL, the relationship is inverse, a low HDL being an important predictor of CHD and high HDL level protecting against CHD. A decrease in turnover has been implicated in diabetes mellitus. Some authors have suggested that non-enzymatic glycosylation of HDL accelerates its catabolism and same mechanism is thought to be involved for the low level of HDL observed in alloxan-diabetic rat in this study (Witztum *et al.*, 1982). LDL-cholesterol concentration has strongly and positively been linked to risk of atherosclerosis and other CHDs. *In vitro* studies have shown a decreased fractional catabolic rate of LDL from diabetic patients and there is also evidence suggesting that *in vivo* non-enzymatic glycosylation of LDL may result in decreased LDL-clearance (Howard, 1987). In the present study, GKP orally administered to diabetic rats after the 21-day period reduced significantly the serum TC, LDL-cholesterol, TG, VLDL-cholesterol and the atherogenic index in the diabetic treated group compared to the diabetic control and this reduction was dose related. This observation is in line with previous finding

by Adaramoye and Adeyemi (2006). The underlying mechanism of lipid lowering effect of GKP could be by inhibition of lipid absorption due to the presence of saponin and tannin in GKP (Ram *et al.* 1997; Ahmed *et al.*, 2010) or inhibition of cholesterol esterase, activation of fatty acid synthase, acetyl-CoA carboxylase and production of triglyceride precursors such as acetyl-CoA and glycerol phosphate (Sharmila *et al.*, 2007). Another plausible mechanism of lipid lowering by GKP could be modulated by the flavonoid content. Flavonoids from plants have been variously implicated in the reduction of lipids by inhibiting hepatic HMG-CoA reductase (Jung *et al.*, 2006). Flavonoids decreased the triacylglycerols and total cholesterol in blood of rats (Miyake *et al.*, 1998). The decrease of LDL levels may occur due to the reduction of VLDL and increased hepatic depuration of LDL precursors (Knett *et al.*, 2002). What this goes to show is that oral administration of GKP facilitates lipid metabolism and hence can be antiatherogenic. This is evidenced in this study as treatment reduced atherogenic index (TC/HDL-C) in a dose-dependent manner of diabetic treated groups, achieving the most favourable reduction at the highest dose. Such reduction has been reported in previous works where plants and their extracts containing similar phytoconstituents reduced the atherogenic indexes in diabetic rats (Gupta *et al.*, 2009). Increase in serum HDL-cholesterol in diabetic treated group is of course an improvement of antiatherogenicity. This is an advantage since HDL-cholesterol is responsible for transportation of cholesterol from peripheral tissues to the liver for metabolism. Thus anti-atherogenic effect is of course mediated by the HDL increase. HDL-cholesterol exerts part of its anti-atherogenic effect by counteracting LDL oxidation (Adaramoye *et al.*, 2008). It also inhibits oxidation of LDL by transition metal ions, but also prevents 12-lipoxygenase-mediated formation of lipid hydroperoxides (Nofer *et al.*, 2002). It would therefore be appropriate to suggest that GKP administration has a strong antiatherogenic potential and hence could be cardioprotective and reduce the risk of CHD occasioned by diabetes mellitus.

CONCLUSION

Dose dependent reduction in blood glucose level, improvement in lipid profile together with a dose dependent attenuation of the atherogenic index by GKP depicts that GKP could be used as an antidiabetic agent with potent cardioprotective effect and this effect may attributed to a variety of phytoconstituents present in *Garcinia kola* seeds.

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