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## Effects of *Plumeria alba* Roots Hydro Alcoholic Extract on some Parameters of Type 2 Diabetes

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### ABSTRACT

In Togo folk medicine, water infusion of *Plumeria alba* (Apocynaceae) root has a reputation for the local management and treatment for type 2 diabetes. The present study was investigated to evaluate the effect of *Plumeria alba* hydro alcoholic extract on some markers of metabolic syndrome in type 2 diabetes (hyperlipidemia, glucose intolerance, obesity) and atherogenic index. This syndrome was induced by high fructose and fat diet in male Wistar rat. The rats received fructose and fat diet (10 mL kg<sup>-1</sup> per day) during 35 days; at the 21st day to the 35th day, 30 min before, they received distilled water for high fructose and fat diet control group, metformin 100 mg kg<sup>-1</sup> per day or extract 250 and 500 mg kg<sup>-1</sup> per day for treatment group. The normal control group received only distilled water during the experiment. After 5 weeks of experiment, fasting blood glucose, body weight gain, intra abdominal grease, serum triglycerides (TG), total cholesterol levels and atherogenic index in treated groups were significant ( $p < 0.01$ ) lower than that of high-fructose diet control group. However rats in treated group were found to have a significant ( $p < 0.01$ ) increase of serum HDL cholesterol level. In the oral glucose tolerance test, rats in treated group had a significant ( $p < 0.001$ ) reduction of blood glucose level during 180 min after glucose load, indicating that *Plumeria alba* root improved glucose tolerance. In conclusion, our plant can prevent metabolic syndrome induced by high fructose diet and cardiovascular diseases in type 2 diabetes. These results justify the use of *Plumeria alba* traditionally in the treatment of diabetes.

**Key words:** *Plumeria alba*, fructose, diabetes, lipid, atherogenic index

### INTRODUCTION

Type 2 diabetes has become a major health problem in both developed and developing countries (Li *et al.*, 2006). Diabetes mellitus is a serious metabolic disease affecting major populations worldwide. According to the World Health Organization, diabetes mellitus affects approximately 171 million people worldwide and the number is expected to reach to 552 million in 2030 (IDF, 2011). Lifestyle in industrialized societies such as high caloric-diet and sedentary lifestyle are the fundamental causes of this fast-spread epidemic (Zimmet *et al.*, 2001; Friedman, 2003). An improved postprandial hyperglycemic peak is one of the main therapeutic targets in diabetic patients. Treatment of hyperglycemia or hyperlipidemia in diabetes involves diet control, exercise and the use of hypoglycemic or lipid-lowering diets and drugs. Obesity is a common chronic disorder of carbohydrate and fat metabolism which is characterized by excessive fat deposition in adipose tissue and other internal organs such as liver, heart, skeletal muscle and pancreatic islet (Ahima, 2006). This increasing trend can be attributed to chronic alcoholism, excessive eating

habits and sedentary lifestyle (Ahima, 2006). Consequent to the increasing obesity prevalence is a dramatic increase in the prevalence of obesity-associated diseases such as cholelithiasis, dyslipidaemia, type 2 diabetes mellitus and ischaemic heart disease (Woo *et al.*, 2008). *Plumeria alba*, belonging to the family Apocynaceae, is a tall tree of Togo flora, measuring about 12 and 1 m in height and girth, respectively. Despite long historical and current use of the water decoction of *Plumeria alba* roots in the local management of antidiabetic, there is a dearth of scientific reports on the therapeutic potential of this plant in the management of obesity, hyperlipidaemia and hyperglycemia. This formed the basis for the current study which is aimed at investigating the anti-obesity and antihyperlipidemic effects 250 and 500 mg kg<sup>-1</sup> of *Plumeria alba* in hyperlipidemic rat models. The effect of *Plumeria alba* on the Atherogenic Index (AI) was also investigated.

## MATERIALS AND METHODS

**Collection of plant material:** *Plumeria alba* roots were collected from the garden of the Teaching Hospital Sylvanus Olympio of Lomé, Togo. A specimen was identified by the Laboratory of Botany and Plant Ecology (Faculty of Science/University of Lomé) and retained in the department herbarium under number 8035.

**Preparation of extract:** The roots were washed, dried under air-conditioning and reduced to powder with electric mill (Thomas Scientific™, 3375-E20). The powder was cold extracted with ethanol 95% water mixture (80:20) for 72 h. The crude extracts were filtered and evaporated under vacuum at 45°C using a rotary evaporator Büchi R210. The yield of the extraction was 11.34%.

**Animals:** Male Wistar rats weighing 150-200 g were used in this study. The animals were housed in colony cages (7 rats per cage), under standard laboratory conditions (24°C, 30-70% humidity, 12 h light/dark cycle) and had free access to standard commercial diet and tap water. All animal experiments were conducted under strict institutional ethical guidelines.

**Chemicals:** The D-fructose and the cholesterol (Sigma France) and lard were used in this study. Cholesterol total, HDL-cholesterol and total triglycerides were estimated using standardized Labkit. The antioxidant activity of *Plumeria alba* is measured by using the 2, 2-diphenyl-1-picrylhydrazyl (DPPH) (Sigma France).

**Fructose lard cholesterol mixture:** The 6 g of fructose and 1 mL of Tween 80 were dissolved in distilled water to have 50 mL of a solution. The 4 g of cholesterol was dissolved in 50 mL of lard. The two solutions were mixed to have an emulsion which is administered at a dose of 10 mL kg<sup>-1</sup>.

**Experimental design:** A protocol of 35 days was used; animals were randomly assigned into five groups of seven each as given below.

**Group I as normal control (C):** Rats received distilled water (10 mL kg<sup>-1</sup> per day) during 35 days; at the 21st day to the 35th day 30 min before, they received distilled water again (5 mL kg<sup>-1</sup> per day).

**Group II as hyperlipidemic control (HC):** Rats received mixture (10 mL kg<sup>-1</sup> per day) during 35 days; at the 21st day to the 35th day 30 min before, they received distilled water (5 mL kg<sup>-1</sup> per day).

**Group III (PA 250):** Rats received mixture (10 mL kg<sup>-1</sup> per day) during 35 days; at the 21st day to the 35th day 30 min before, they received extract 250 mg kg<sup>-1</sup> per day in a volume of 5 mL kg<sup>-1</sup> per day.

**Group IV (PA 500):** The rats received mixture (10 mL kg<sup>-1</sup> per day) during 35 days; at the 21st day to the 35th day 30 min before, they received extract 500 mg kg<sup>-1</sup> per day in a volume of 5 mL kg<sup>-1</sup> per day.

**Group V (Met):** The rats received mixture (10 mL kg<sup>-1</sup> per day) during 35 days; at the 21st day to the 35th day 30 min before, they received metformin 100 mg kg<sup>-1</sup> per day in a volume of 5 mL kg<sup>-1</sup> per day.

The substances were administered by gavages during the experimentation, animals body weight was measured at the first, 7, 14, 28 and 35th day. Blood glucose level the first, 15 and 28th day.

**Oral glucose tolerance test (OGTT):** At the end of experimental period (35 days), the 12 h fasted animals were subjected to oral glucose tolerance test. The 80% glucose solution was introduced directly into the stomach by gavages at a dose of 4 g kg<sup>-1</sup> b.wt to conscious rats. Blood glucose level was determined at 0 (before glucose administration), 30, 60, 120 and 180 min after glucose administration using One Touch Ultra 2 glucometer.

**Sample collection:** After OGTT, blood was collected from rats with capillary tube from retino-orbital plexus of the animals in dry tube. The samples were centrifuged at 3000 g for 15 min and the serum obtained was aliquoted and frozen for serum total Cholesterol (Ch), HDL-Cholesterol (HDL-Ch) and triglycerides (TG) dosage using commercial Kit (Labkits).

After blood collection, the animals were killed by cervical decapitation. The body was cut open. and intra abdominal grease were dissected and were weighed.

**Determination of Atherogenic Index (AI):** Atherogenic index (AI) were calculated as: LDL-c (mg dL<sup>-1</sup>)/HDL-c (mg dL<sup>-1</sup>) (Abbott *et al.*, 1988).

Serum LDL-c was estimated using Friedlmann's equation:

$$\text{LDL-cholesterol} = \frac{\text{Total cholesterol} - [\text{HDL-cholesterol} + \text{Total triglycerides}]}{5}$$

### Antioxidant activities

**DPPH assay:** The free radical scavenging activity of *Plumeria alba* was measured *in vitro* using 1, 1-diphenyl-2-picryl-hydrazyl (DPPH) assay according to Sharma and Bhat (2009) with slight modification. The 100 mmol L<sup>-1</sup> solution of DPPH in 100% methanol was prepared and 1.5 mL of this solution was added to 0.25 mL of the extract dissolved in methanol at different concentrations. The mixture was shaken and allowed to stand at room temperature for 30 min and the absorbance was measured at 517 nm using spectrophotometer. The IC<sub>50</sub> value of the extract was compared with that of quercetin which was used as standard.

**Statistical analysis:** GraphPad Prism software 4.0 was used to analyse results. Data were expressed as Mean±Standard error of mean (n = 7). The difference between groups was determined with ANOVA; Tukey test was used to compare two groups. A probability level of  $p < 0.05$  was taken to indicate a significant difference between means.

## RESULTS

**Effect of the extract on the evolution of the basal glycemia during the experiment:** There was no significant variation in the blood glucose concentrations of control group (C) throughout the experimental period. HC group showed a significant increase of blood glucose levels at the 15th days and at the 35th day. The blood glucose level of the treated groups showed a significant reduction ( $p < 0.001$ ) at the end of experiment compared to HC group (Table 1).

**Effect of the extract on the glucose tolerance in control, lard fructose fed and treatment groups:** The analysis of the glucose tolerance test and the comparison between Areas Under the Curve (AUC) of glycemia during 180 min from control and experimental groups show that fructose fed rats developed glucose intolerance. The AUC of glucose during OGTT of HC group was elevated by 22% ( $p < 0.001$ ) compared to group control. The AUC of glucose in treated groups (PA 250, PA 500 and Met) was significantly lower than that of group HC showing an improved glucose tolerance (Fig. 1).

**Effect of the extract on the body weight and the intra abdominal grease in control, high fructose fed and treatment groups:** The rats fed with high-fructose diet showed an increase in body weight as compared to the normal control (C) group at the 7th day to the 35th day ( $p < 0.001$ ). It was found that the variation of the body weight was significantly ( $p < 0.01$ ) reduced by the extract (PA 250, PA 500) and the reference drug (Met) as compared to Hyperlipidemic Control (HC) group between the 28th day to the 35th day (Fig. 2). After 5 weeks of the experiment, rats fed with a high fructose diet (HC) showed also a significant increase of intra abdominal grease, as compared to normal control group ( $p < 0.001$ ). The extract at the dose of 250, 500 mg kg<sup>-1</sup> day<sup>-1</sup> and metformin at the dose of 100 mg kg<sup>-1</sup> day<sup>-1</sup> reduced significantly ( $p < 0.001$ ) the intra abdominal grease compared to the high-fructose diet group (Fig. 3).

**Effect of the extract on serum lipids and atherogenic index in control, lard fructose fed and treatment groups:** Table 2 shows that repeated daily oral treatment with fructose-lard-cholesterol caused significant ( $p < 0.05$ ) and dose-related elevations of serum triglycerides (TG) and Total Cholesterol (TC). the effect of repeated oral administration of 250 and 500 mg kg<sup>-1</sup> body

Table 1: Effect of the extract on the evolution of the basal glycemia during the experiment

Groups	Days		
	D <sub>0</sub>	D <sub>15</sub>	D <sub>35</sub>
C	79.142±2.676	76.714±1.304	82.285±2.997
HC	80.000±2.329	91.571±1.674***	110.714±3.227***
PA 250 mg kg <sup>-1</sup>	85.142±3.568	91.857±3.050***	91.571±1.770*###
PA 500 mg kg <sup>-1</sup>	81.142±3.425	90.428±4.069***	97.142±1.805***###
Met (100 mg kg <sup>-1</sup> )	83.142±2.272	87.142±2.443*	106.000±2.058***

Data are expressed as Mean±SEM (n = 7). \*\*\* $p < 0.001$  vs. C, ### $p < 0.001$  vs. HC, ## $p < 0.01$  vs HC, \* $p < 0.05$  vs. C

Table 2: Effect of the extract on serum lipid and AI in control , high fat diet and treated groups

Groups	Lipid parameters				
	TG	TC	HDLc	LDL-c	AI
C	0.431±0.032	0.470±0.027	0.245±0.016	0.138±0.018	0.921±0.086
HC	0.710±0.029***	0.582±0.031#	0.297±0.017	0.144±0.038	1.001±0.160
PA 250 (mg kg <sup>-1</sup> )	0.367±0.015###	0.494±0.017	0.381±0.015***##	0.038±0.014##*	0.324±0.062***###
PA 500 (mg kg <sup>-1</sup> )	0.442±0.025*	0.500±0.017*	0.351±0.012#	0.051±0.012*#	0.422±0.052**
Met 100 (mg kg <sup>-1</sup> )	0.354±0.015*	0.477±0.017	0.388±0.016***##	0.027±0.005***##	0.167±0.032***###

Data are expressed as Mean±SEM (n = 7). #p<0.05, ##p<0.01, ###p<0.001 vs. HC, \*p<0.05, \*\*\*p<0.001 vs. C, AI: Atherogenic index, TG: Triglycerides, TC: Cholesterol total, HDL-c: Cholesterol high density lipoprotein, LDL: Low density lipoprotein

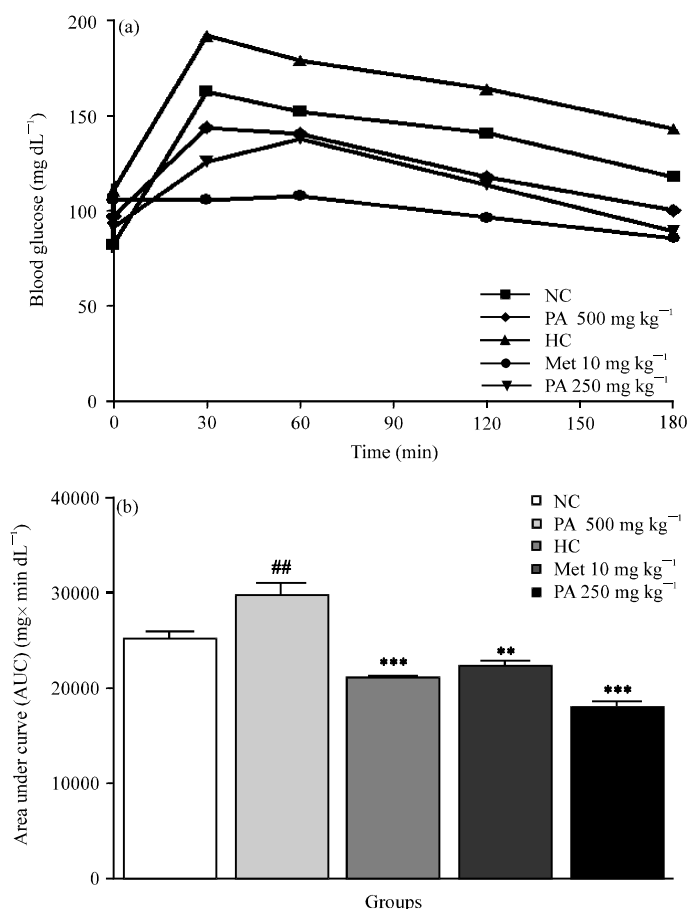


Fig. 1(a-b): Effect of the extract on the glucose tolerance test in rats (a) Blood glucose level and (b) Area Under the Curve (AUC). The high fructose diet was administered for 35 days to rats and drugs daily for 14 days at the 21st to 35th. A 80% glucose solution was introduced directly into the stomach by gavages at a dose of 4 g kg<sup>-1</sup> body weight to conscious rats. Blood glucose level was determined at 0 (before glucose administration), 30, 60, 120 and 180 min after glucose administration using One Touch Ultra 2 glucometer. The data was expressed as Mean±SEM. (n = 7) and evaluated by ANOVA followed by Tukey's test at 5% \*\*p<0.01; \*\*\*p<0.001 vs. HC, ###p<0.01 vs. C

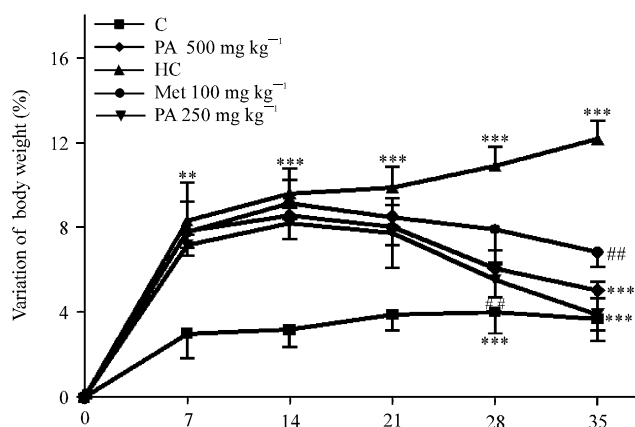


Fig. 2: Effect of the extract on the variation of body weight. The high fructose diet was administered for 35 days to rats and drugs daily for 14 days at the 21st to 35th. Animals body weight was measured at the 1, 7, 14, 28 and 35th day to evaluate animals weight gain during the experiment. The data was expressed as Mean $\pm$ SEM (n = 7) and evaluated by ANOVA followed by Tukey's test at 5%. \*\*p<0.01, \*\*\*p<0.001 vs. C, ##p<0.01, ###p<0.001 vs. HC

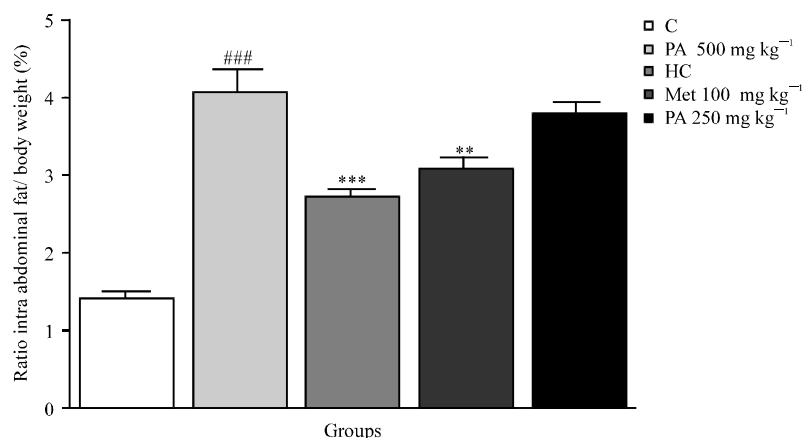


Fig. 3: Effect of the extract on the ratio intra abdominal grease/body weight. The high fructose diet was administered for 35 days to rats and drugs daily for 14 days at the 21st to 35th day. At the end of the experiment, the intra abdominal grease were collected and reported to the body weight for each animal. The data was expressed as Mean $\pm$ SEM (n = 7) and evaluated by ANOVA followed by Tukey's test at 5%. \*\*\*p<0.001 vs. C, ###p<0.001, ##p<0.01 vs. HC

weight of *Plumeria alba* reduced significantly serum lipids (TC and TG) and atherogenic index (p<0.01) compared to HC group; while causing an increase on serum HDL-c (p<0.001).

**Antioxidant activity:** Data in Table 3 show that *Plumeria alba* extract reduced DPPH to a yellow coloured product in concentration dependent manner. The IC<sub>50</sub> value of the extract was compared with quercetin which was used as standard. It is 28, 10 mg mL<sup>-1</sup> for the extract and 21,8  $\mu$ g mL<sup>-1</sup> for quercetin.

Table 3: DPPH reducing effect of *Plumeria alba* hydro-alcoholic extract

Value of extract	DPPH	
	<i>P. alba</i>	Quercetin ( $\mu\text{g mL}^{-1}$ )
CI50	28.10	21.8

## DISCUSSION

In the present study, the antidiabetic and antihyperlipidemic effects of 250-500 mg kg<sup>-1</sup> of *Plumeria alba* in normal and experimental models of hyperlipidemia were investigated.

Dietary fructose is a monosaccharide which can induce metabolic disorders including glucose intolerance, hypertension and dyslipidemia which have pathophysiologic importance for the development of diabetes and atherosclerosis (Schaefer *et al.*, 2009). Our results are consistent with previous studies (Suwannaphet *et al.*, 2010; Bakoma *et al.*, 2011; Adeneye, 2012) which found that consumption of high-fructose diets markedly induces an increase in glycemia associated with dyslipidemia and consequently a reduction of insulin sensitivity as glucose intolerance.

The oral administration of a glucose load of 4 g kg<sup>-1</sup> to Hyperlipidemic Control (HC) rats produced an increase in the serum glucose level during 180 min, This suggest that there was glucose intolerance and a reduction of glucose-induced insulin secretion.

A significant increase in the incremental AUC of glucose concentrations after glucose loading during OGTT seen in HC group rats, indicating that the ability of insulin to stimulate glucose disposal is markedly impaired in peripheral tissues.

In rats treated with hydroalcoholic extract orally, 30 min before the oral glucose load, there was a reduction of serum glucose level. The reduction caused at 250 mg kg<sup>-1</sup> of extract was higher than that of 500 mg kg<sup>-1</sup>.

The maximal percentages of reduction that occurred after 60 min of hydroalcoholic extract (250 mg kg<sup>-1</sup>) were 19% compared to hyperlipidemic control rats. This revealed that the *P. alba* roots hydroalcoholic extract has the capacity to lower blood glucose levels.

Our study suggests that the hypoglycemic activity of *Plumeria alba* is not related to the insulin secretion and that post prandial glucose reduction is probably effected without any extra load on pancreatic cells and/or stimulation of glucose uptake by peripheral tissues. Hence, the hypoglycemic effect may be probably brought by an extra pancreatic mechanism. There are medicinal plants which are known to exert antidiabetic activity without the stimulation of insulin secretion (Hannan *et al.*, 2003; Maghrani *et al.*, 2003). The marked increase in serum triglycerides and cholesterol observed in hyperlipidemic control is in agreement with the findings of Aziz *et al.* (2013). The most common lipid abnormalities in diabetes are hypertriglyceridemia and hypercholesterolemia (Khan *et al.*, 1995). Hypertriglyceridemia is also associated with metabolic consequences of hyperinsulinemia, insulin resistance and insulin intolerance (Gingsberg, 1994). In our study, administrations of the extract reduced total triglycerides and cholesterol. The observed hypolipidemic effect may be because by decreased cholesterogenesis and fatty acid synthesis. Significant lowering of total cholesterol and raise in HDL cholesterol is a very desirable biochemical state for prevention of atherosclerosis and ischemic conditions (Luc and Fruchart, 1991). Various studies on medicinal plants have reported a similar lipid lowering activity (Jouad *et al.*, 2003; Okpuzor *et al.*, 2009; Aziz *et al.*, 2013; Zhang *et al.*, 2013). The characteristic loss of body weight to increased muscle wasting in diabetes (Swanston-Flat *et al.*, 1990). Previous phytochemical studies reported that *Plumeria alba* contains a copious amount of alkaloids and flavonoids. Certain



phytocomponents, particularly flavonoids, have been reported to lower serum lipids by inhibiting the activity of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase and up-regulating the hepatic expression of peroxisome proliferators- $\alpha$  and  $\gamma$  (Sharma *et al.*, 2008). Thus, the presence of other hypolipidemic phytocomponents like alkaloids and flavonoids in *Plumeria alba* (Zaheer *et al.*, 2010) could account for the observed bioactivity. The atherogenic index is strong and reliable indicator of whether or not cholesterol is deposited into tissues or metabolized and excreted (Hertog *et al.*, 1993). In this present study, results showed that treatment with *Plumeria alba* caused profound reductions in the atherogenic index in experimental hyperlipidemic rats and this suggest that *P. alba* possesses cardioprotective potential. The *Plumeria alba* hydroalcoholic extract treated animals showed a weight loss in our studies which may be directly due to the lipid lowering activity of the extract or indirectly to the influence on various lipid regulation systems.

The results show that the extract had an antioxidant effect nearby that of quercetin. There is a widespread understanding that hyperglycemia and hyperlipidemia create excess reactive oxygen species which are probably involved in some of complications of diabetes (Reddy *et al.*, 2009). The antioxidant activities of *Plumeria alba* can be then useful in the treatment of diabetes.

## CONCLUSION

The results of this study indicate that *Plumeria alba* extract at 250 mg kg<sup>-1</sup> is more active than 500 mg kg<sup>-1</sup>; this suggest that the efficacious dose can be 250 mg kg<sup>-1</sup>. In conclusion, the results of this study showed that *Plumeria alba* have potentials therapeutic effects in the treatment of obesity, hyperlipidemia and in the prevention of atherogenic cardiovascular diseases. These effects may be mediated via inhibition of intestinal lipid uptake and novo triglyceride and cholesterol biosyntheses. Further studies aimed to isolated and characterizing the antidiabetic, anti-obesity and antihyperlipidemic phytoprinciples of *Plumeria. alba* extract.

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