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Research Article
Evaluation of Antidiabetic Effects of Saponins Extracted from Methanol Leaf Extract of *Commiphora kerstingii* Engl.

Yerima Musa and Yusuf Ibrahim Alkali

Department of Pharmacology and Toxicology, Usmanu Danfodiyo University, Sokoto, Nigeria

Abstract

Background and Objective: About 80% of population of developing countries relies exclusively on plants to meet their health care needs, according to World Health Organization. This study aimed to further investigate the hypoglycemic activity of saponins extracted from the leaf of *Commiphora kerstingii*. **Materials and Methods:** Hyperglycaemia was induced by single intraperitoneal injection of alloxan and high dose fructose administration. Acute oral LD_{50} of the fraction in rats was conducted according to the method described by Lorke. **Results:** The oral LD_{50} of the extract was found to be 1,352 mg kg^{-1}. The extract lowered the Blood Glucose Level (BGL) in the 3 doses used (100, 200 and 400 mg kg^{-1}) and was significant at $p<0.02$ for the 400 mg kg^{-1} dose after the 8th, 16th and 24th h. The saponin-rich portion of the methanol leaf extract of *Commiphora kerstingii* Engl. significantly lowered elevated BGL in the experimental animal models. **Conclusion:** The saponin extracted from the methanol leaf extract of *Commiphora kerstingii* showed antidiabetic activity in the experimental models employed at the doses used.

Key words: Alloxan, fructose, hyperglycemia, metformin, *Commiphora kerstingii*

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Corresponding Author: Yerima Musa, Department of Pharmacology and Toxicology, Usmanu Danfodiyo University, Sokoto, Nigeria Tel: +2348035960302

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Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

About 80% of population of developing countries relies exclusively on plants to meet their health care needs, according to World Health Organization. Biologically active substances derived from plants have served as templates for the synthesis of Pharmaceuticals[1].

World Health Organization defined diabetes mellitus as "a metabolic disorder of multiple etiologies, characterized by chronic hyperglycemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action or both". The effects of diabetes mellitus include long-term damage, dysfunction and failure of various organs[2]. Therefore, the metabolic aberration of diabetes results from insufficient insulin action, due to deficient insulin secretion or insensitivity to its action or a combination of both[2,3].

In developing countries adherence to therapies is very low, resulting in poor health outcomes at an expensive cost for society, governments and families[4]. If not successfully managed, diabetes along with other chronic diseases will become the most expensive problem faced by the health care systems. Several herbal preparations have been studied in the search for an effective management of diabetes mellitus and most of them have therapeutic claims[5].

Commiphora kerstingii is a tree of 10 m high that grows in savanna from Togo to Nigeria and on to Central African Republic and it belongs to the family Burseraceae. The wood is soft and it is used to make saddle and is sometimes hollowed out to make quivers in the Yola area of northern Nigeria. The bark is sometimes used as an antidote to arrow-poison. Fulani herdsmen feed the leaves to goats and in a superstitious token lay sticks of the plant across graves, perhaps in the same sense of conferring protection[6].

The WHO has recommended and encouraged the use of alternative therapy especially in countries where access to the conventional treatment of diabetes is not adequate. The World Health Organization also approved the use of plant-based drugs for different ailments including diabetes mellitus[7]. Also in 2002, WHO Expert Committee on diabetes mellitus recommended an urgent and further evaluation of the folkloric methods of managing the disease[8]. In response to this recommendation, several medicinal plants are currently being investigated for their hypoglycemic efficacies and one of such plants is *Commiphora kerstingii.* Use of medicinal plants including the leaves of *Commiphora kerstingii* for the local management of diabetes mellitus is still low. Therefore, this study further investigated the hypoglycemic activity of the saponins extracted from methanol leaf extract of *Commiphora kerstingii*.

MATERIALS AND METHODS

Plant collection: The fresh leaves of *Commiphora kerstingii* were collected in June, 2017 from Samaru, Zaria, Nigeria. The plant was authenticated at the Herbarium, Department of Biological Sciences, Ahmadu Bello University (ABU) Zaria, Nigeria. A voucher specimen number of 006 was deposited at the herbarium for future reference.

The leaves were cleaned and air dried under shade for 26 days. It was then pulverized using a pestle and mortar and then sieved to obtain the fine powder. The powder was weighed and kept in an air tight container.

Male and female wistar albino rats (weighing 150-200 g) obtained from the Department of Pharmacology and Therapeutics, Ahmadu Bello University, Zaria were used. The rats were housed in polypropylene cages at room temperature and maintained on standard laboratory animal feed obtained from the department and water *ad libitum*, throughout the study. These studies were carried out in Ahmadu Bello University in accordance with the rules governing the use of laboratory animals as accepted internationally.

Preparation of the plant extract: About 100 g of the powdered leaves was macerated with 500 mL methanol for 72 h with occasional shaking. The extract was concentrated *in vacuo* and subsequently referred to as methanolic leaf extract of *Commiphora kerstingii* (CKMLE).

Saponin-rich fraction: The method described by Woo *et al.*[9] was followed. The method involves defatting initially with petroleum ether followed by extraction with hydroalcoholic solution. Polar compounds were further removed by dissolving the hydroalcoholic extract in diethylether solution with subsequent addition of water. Butanol was added to the water residue and the mixture shaken vigorously. The two distinct layers were then separated and 1% potassium hydroxide (KOH) solution was added to the butanol residue (contained the saponin-rich portion) and gently shaken.

Acute toxicity studies: The oral median lethal dose (LD_{50}) of the extract in rats was conducted according to the method of Lorke[10] with modifications. The method was divided into two phases. In the initial phase, 3 groups of three rats each were treated with the extract at doses of 10, 100 and 1000 mg kg^{-1} b.wt., orally and the rats were observed for clinical signs and symptoms of toxicity within 24 h and death within 72 h. In the second phase, 4 groups each containing one fresh rat was administered with three more specific doses of the extract based on the result of the initial phase. The animals were also observed for clinical signs and symptoms

of toxic effects and mortality for 14 days. The LD_{50} value was determined by calculating the geometric mean of the lowest dose that caused death and the highest dose for which the animal survived (0/1 and 1/1).

Alloxan-induced hyperglycemia: Hyperglycemia was induced by a single intraperitoneal injection of 150 mg kg^{-1} body weight of alloxan to 12 h fasted rats[11,12]. About 6 h after the alloxan administration, the rats were maintained on 5% glucose solution for the next 24 h to prevent hypoglycemia that may result from acute massive pancreatic release of insulin[13]. About 72 h after drug administration, the rats were examined for hyperglycemia by cutting the tail tip and using a one touch glucometer with compatible strips. Animals with fasting blood glucose of 180 mg dL^{-1} and less than 550 mg dL^{-1} were used in the study. Blood samples for blood glucose determination were collected from the tail at intervals of 0, 1, 4, 8, 16 and 24 h. Determination of blood glucose level was done by the glucose-oxidase principle using the one touch Basic[14]:

Group I : Received normal saline orally
Group II : Received 100 mg kg^{-1} b.wt., of saponin-rich fraction of methanol leaf extract of *C. kerstingii* orally
Group III : Received 200 mg kg^{-1} b.wt., of saponin-rich fraction of methanol leaf extract of *C. kerstingii* orally
Group IV : Received 400 mg kg^{-1} b.wt., of saponin-rich fraction of methanol leaf extract of *C. kerstingii* orally
Group V : Received metformin 250 mg kg^{-1} b.wt., orally[15,16]

Fructose-induced insulin resistance model: For this model, the method of Dai and McNeill[17] and Vikrant *et al.*[18] was adopted. The animals were divided into six groups of six rats each:

Group I : Received 10% w/v fructose solution *ad libitum* and 100 mg kg^{-1} b.wt., saponin-rich fraction of methanol leaf extract of *C. kerstingii* orally daily for 28 days
Group II : Administered 10% w/v fructose solution *ad libitum* and 200 mg kg^{-1} b.wt., of saponin-rich fraction of methanol leaf extract of *C. kerstingii* orally daily for 28 days
Group III : Received 10% w/v fructose solution *ad libitum* and 400 mg kg^{-1} b.wt., of saponin-rich fraction of methanol leaf extract of *C. kerstingii* orally daily for 28 days
Group IV : Fructose-fed with 10% w/v fructose solution *ad libitum* in their drinker for 28 days only
Group V : Received normal saline only
Group VI : Received 10% w/v fructose solution *ad libitum* and metformin 250 mg kg^{-1}

All rats were fasted for half an hour prior to extract administration every day.

Statistical analysis: Results were expressed as Mean±SEM. Statistical analysis was performed by one-way analysis of variance (ANOVA). Student's t-test at 95% level of significance was used to assess significant difference between the control and treated group. The results are presented in tables and charts.

RESULTS

The extract lowered the blood glucose level in the three doses used (100, 200 and 400 mg kg^{-1}). However, the reduction was only significant ($p<0.02$) with the 200 mg kg^{-1} dose after 24 h. The 100 and 200 mg kg^{-1} doses also lowered the blood glucose level from the 8th to the 24th h however; the reduction noticed was only slight, not significant when compared to the normal saline group (Table 1).

Table 1: Effect of saponin-rich fraction extracted from the leaf extract of *C. kerstingii* on blood glucose levels of alloxan induced hyperglycaemia

	Mean BGL (mg dL^{-1})				
	Post-treatment time (h)				
Groups	0	1	8	16	24
N/saline	492±27	491±19	496±14	496±26	498±22
SF 400 mg kg^{-1}	453±34	375±18	283±25**	280±28**	358±13**
SF 200 mg kg^{-1}	480±45	393±25	385±29	348±16	263±28**
SF 100 mg kg^{-1}	467±31	399±24	375±18	368±31	363±24
MFN 250 mg kg^{-1}	431±27	279±27**	299±36**	286±28**	277±29**

n = 6, **Significant at $p<0.02$ vs. normal saline. Student's t-test, SF: Saponin fraction, MFN: Metformin

Table 2: Effect of saponin-rich fraction extracted from the methanol leaf extract of *C. kerstingii* on blood glucose level of fructose induced insulin resistance in wistar rats after 10 and 20 days

	Mean blood glucose level (mg dL^{-1})	
Groups	10 days	20 days
Normal saline	92±0.9	94±0.6
SF 400 mg kg^{-1}+fructose	112±0.9*	94±1.0*
SF 200 mg kg^{-1}+fructose	126±1.7	118±1.3*
SF 100 mg kg^{-1}+fructose	112±1.3*	104±1.5*
Fructose only	188±2.5	184±2.3
MFN 250 mg kg^{-1}+fructose	82±2.2**	93±2.0*

n = 6, *Significant at p<0.05 vs. fructose only group. Student's t-test, **Significant at p<0.02 vs. fructose only group, SF: Saponin fraction, MFN: Metformin

All doses of the saponin-rich fraction used lowered the BGL on the 10th and 20th days, but it was significantly lowered on both days at 400 and 100 mg kg^{-1} doses. However, the 200 mg kg^{-1} dose only lowered the BGL significantly on the 20th day (Table 2).

DISCUSSION

The leaf extract of *Commiphora kerstingii* Engl. has been reported to have blood glucose lowering activity in hyperglycemic animals[19,20]. In the present study, the oral median lethal dose of the fraction was calculated to be 1,352 mg kg^{-1}. According to the scale proposed by Lorke[10], LD_{50} values greater than 1000 mg kg^{-1} are considered safe.

In the present study, alloxan caused a significant increase in blood glucose concentration when compared to normal animals. It can be suggested that *C. kerstingii* lowers the elevated glucose level by increasing peripheral glucose uptake. This is supported by the fact that in this experiment metformin also lowered glucose level meaning that there is still likely some residual function of the β-cells. High fructose intake over a long period has been shown to lead to rapid stimulation of lipogenesis and triglyceride accumulation, resulting in reduced insulin sensitivity and hepatic insulin resistance or glucose tolerance[21-23].

The saponin-rich fraction reduced the elevated level of BGL in both the alloxan and fructose-induced hyperglycemia at all the doses used. However, BGL was only significantly ($p<0.05$) lowered after 8 and 16 h for 400 mg kg^{-1} dose and after 24 h for the 200 mg kg^{-1} dose. Shane-McWhoeter in 2001 reported that extracts with high triterpenoid saponin content mediate their hypoglycemic effect through inhibition of intestinal glucose uptake, increase hepatic glucose deposition and enhanced hyperinsulinemia[24]. Saponins have been reported to cause a reduction in glucose concentration seen in both the alloxan and fructose induced hyperglycemia which could be due to the presence of triterpenoid. Other studies further showed that saponin was used to decrease experimental hyperglycemia induced by adrenaline, glucose and alloxan[25,26]. Abdel-Hassan *et al.*[27] reported that saponin components have been used to reduce glycemia induced by alloxan in rabbits and suggested that saponin glycoside components could be responsible for the observed hypoglycemic effect.

Tao and colleagues also used saponins from *Entada phaseoloides* (L.) to reduce both hyperglycemia and hyperlipidemia in type 2 diabetic rats[28]. On the basis of these findings, it can be recommended that the saponin can be used as antidiabetic agent. However, the mechanism of antidiabetic activity should be further investigated.

CONCLUSION

The saponin extracted from the methanol leaf extract of *Commiphora kerstingii* showed antidiabetic activity in the experimental models employed at the doses used. This justifies its use in the management of diabetes and further supports earlier reports on the use of the leaf in hypoglycemic studies.

SIGNIFICANCE STATEMENT

This study discovered that saponins extracted from the leaves of *Commiphora kerstingii* can be beneficial for the management of diabetes. This study showed the efficacy of the saponins from this plant, it also could serve as a new lead for drug development.

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