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Exploration of Antidiabetic and Hypolipidemic Activity of Roots of *Croton Zambesicus*

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Abstract: The aim of this study was to investigate the potential antidiabetic and hypolipidaemic effects of aqueous and ethanolic extracts of roots of *Croton zambesicus* in alloxan induced diabetic models to ascertain its pharmacological applicability. The roots of *Croton zambesicus* were collected, dried and extracted. The phytochemical screening as well as Median Lethal Dose determination (LD_{50}) was done. The ethanolic extract of the roots was prepared using soxhelation technique while the aqueous extract was prepared using maceration technique. The pharmacological effects of the two extracts were monitored on the blood glucose level and the lipidprofile for a period of 28 days on the alloxan induced diabetic rats and their effect was evaluated. The ethanolic (100 mg kg^{-1}) and aqueous (100 mg kg^{-1}) extracts caused a significant ($p<0.05$) reduction in the blood glucose levels and the lipid profiles of the alloxan induced diabetic rats. However the ethanolic extract was found to be more potent than aqueous extract in the blood glucose and lipid lowering effects in the rats. The activity of the extracts was compared with the reference drug, glibenclamide (0.5 mg kg^{-1}). Treatment with *C. zambesicus* showed considerable lowering in the blood glucose, serum total cholesterol, triglycerides, LDL cholesterol, VLDL cholesterol and an increase in HDL cholesterol in the alloxan treated diabetic rats. The results of this study suggest that the roots of *Croton zambesicus* possess antidiabetic and hypolipidaemic activities in the treated diabetic models.

Keywords: Antidiabetic Activity, Hypoglycemic Activity, Hypolipidemic Activity, Croton Zambesicus, Alloxan, Glibenclamide

Introduction

Diabetes mellitus, a metabolic syndrome characterized by hyperglycemia resulting from dysfunction in insulin secretion, insulin action causes impaired metabolism of glucose, lipids and proteins (Scheen, 1997). The chronic hyperglycemia is associated with damage, dysfunction and failure of various organs (Lyra *et al*., 2006). In diabetic rats, the utilization of impaired carbohydrate causes to accelerated lipolysis, resulting in hyperlipidemia (Morel and Chisolm, 1989; Granner *et al*., 1996). Despite the presence of known antidiabetic medicines in the market, diabetes and the related complications continue to be a major medical problem. Recently, some medicinal plants have been reported to be useful in diabetes worldwide and have been used empirically as antidiabetic and antihyperlipidaemic remedies (Mitra *et al*., 1996; Shukla *et al*., 2000; Bhattaram *et al*., 2002; Mahomed and Ojewole, 2003; Hou *et al*., 2005; Huang *et al*., 2005). Diabetes mellitus is responsible for the cause of hyperlipidemia through various metabolic derangements. Among several metabolic derangements, insulin deficiency is known to stimulate lipolysis in the adipose tissues and gives rise to hyperlipidemia and fatty liver (Hardman and Limberd, 2001). More than 400 plant species have been found to possess hypoglycemic activity which are available in the literatures (Oliver-Bever, 1986; Rai, 1995); however, searching for novel antidiabetic drugs from a natural source is still concern and advantageous because they contain substances which leave alternative and safe effect on subjects with diabetes mellitus. Most of plants has glycosides, alkaloids, terpenoids, flavonoids, carotenoids, etc., which are frequently implicated as having antidiabetic effect and *C. zambesicus* is among one of them (Loew and Kaszkin, 2002).

Croton zambesicus Muell Arg. (Euphorbiaceace) (syn*C. Amabilis* Muell. Arg. *C. gratissimus* Burch) is an ornamental tree grown in villages and towns of Nigeria. It is a Guineo-congolese species widely spread in tropical Africa. Ethnobotanically, the leaf decoction is used in Benin as anti-hypertensive agent and anti-microbial (urinary infections) (Adjanohoun *et al*., 1989) and in parts of Nigeria as antidiabetic and malarial treatment (Okokon *et al*., 2005; 2006). The roots have been used as antimalarial, febrifuge and antidiabetic by the Ibibios of Niger Delta region of Nigeria (Okokon and Nwafor, 2009). The root has also been used in Sudan for menstrual pain and as aperients (Okokon and Nwafor, 2010). Thus proving a versatile class of drug of natural origin. The drug Glibenclamide works by binding to and inhibiting the ATP-sensitive potassium channels (K_{ATP}) inhibitory regulatory Subunit Sulfonylurea Receptor 1 (SUR1) in Pancreatic Beta Cell (Serrano-Martín *et al*., 2006).

Materials and Methods

Materials

Roots of *Croton zambesicus* growing in natural habitat in Panipat, Haryana, India, were collected in January, 2012 and identified and approved by Dr. Prakash Kumar, Botanist, Assistant Professor, M.M. College, Bhagalpur, T.M. University, Bhagalpur (India). Voucher specimen of the plant has been submitted in the institute for future reference purpose.

Preparation of the Root Extract

Dried and coarsely (500 g) powdered roots of *Croton zambesicus* were extracted with 90% (v/v) ethanol in soxhlet apparatus for 36 h; aqueous extract was prepared by using maceration technique. The filtrate was filtered and concentrated on water bath using petridish. The temperature was maintained to 55°C. Finally the powdered extract was dried and weighed.

The Preliminary Phytochemical Analysis

The preliminary phytochemical studies were performed for testing the presence of different phytochemicals in ethanolic extract and aqueous extract (Harbone, 1988; Mohammed, 1994; Agrawal, 2000; Divakar, 2003).

Toxicity Studies

The animals were divided into six groups separately and were treated orally with aqueous and ethanolic extracts of *Croton zambesicus*at 100, 200 and 400 mg kg^{-1}, body weight doses. The animals were observed for 1 h daily continuously for 14 days. The parameters observed were grooming, hyperactivity, sedation, loss of righting reflex, respiratory rate and convulsion (Ghosh, 1994).

Animals

Wistar albino rats of either sex weighing between 180 and 200 gm were obtained from Nitin Biologicals, New Delhi. The study was approved by the Institutional Ethics Committee for animal experimentation (PDM/IAEC/11/11/11), Safidon, India and all the procedures on animals were carried out as per CPCSEA guidelines, India. These animals were used for the anti-diabetic activity studies. The animals were stabilized for 1 week. They were maintained in standard conditions at room temperature, 60±5% relative humidity and 12 h. light dark cycle. They were consistently given standard pellet diet and water *ad libitum* throughout the course of the study.

Induction of Diabetes

Alloxan monohydrate (Sigma Chemical, St. Louis, MO) was injected intraperitoneally at a dose of 200 mg kg^{-1} Body Weight (BW). The induction of alloxan-induced diabetes was confirmed by measuring the blood glucose level. Rats with glucose levels above 180 to 200 mg dL^{-1} were subjected for further evaluation with a glucose challenge and a standardized oral glucose tolerance test to confirm diabetes mellitus (Tanquilut *et al*., 2009). The drug preparations were fed orally by oral feeding needle to rats of respective groups once daily for 28 days.

Grouping of Animals

The animals were divided into 5 groups each containing 6 animals as per statistical analysis. The groups were as follows:

Group 1: Normal control group
Group 2: Diabetic control group
Group 3: Diabetic rats treated with aqueous extract of *Croton zambesicus* (100 mg kg^{-1})
Group 4: Diabetic rats treated with ethanolic extract of *Croton zambesicus* (100 mg kg^{-1})
Group 5: Diabetic rats treated with Glibenclamide (0.5 mg kg^{-1} p.o)

Experimental Procedure

Albinos Wistar rats initially weighing more than 150 gm were used for the experiments. Prior to dietary manipulation, all rats were fed standard pellet rodent diet and water *ad libitum*. After acclimatization, the rats were divided into five groups having six animals each. Total duration of study was 28 days and the animals used were rendered diabetic by injecting Alloxan through intra-peritoneal (i.p.) route of administration at the dose of 200 mg kg^{-1} body weight. Animals having blood glucose level more than 300 mg dL^{-1} were excluded as per the standard protocol. During the period of study and at the end of the treatment period, blood samples were collected by retro-orbital vein of rat for biological estimations on 7, 14th, 21st and 28th day of experiment,

after every 16 h fasting. The above treatments were given for a period of 28 days both in diabetic and non-diabetic animals.

Procedure for Blood Glucose Monitoring

Blood was taken from the retro-orbital vein of the rats. Blood glucose estimation was carried out using laboratory investigations as per standard guidelines. Effects of various extracts on blood glucose level in diabetic and nondiabetic rats were evaluated and are shown in Tables.

Biochemical Parameters

Triglycerides, total cholesterol, HDL-cholesterol, LDL-cholesterol and VLDL -cholesterol were estimated from the serum by using standard testing kits (Lopes-Virella *et al*., 1977; Lowry *et al*., 1951; McGowan *et al*., 1983).

Body Weight Measurement

Body weight was measured totally ten times during the course of study period (i.e., on before Alloxan induction), using a digital weighing scale.

Statistical Analysis

All the data are presented as mean ± SEM. The differences between group were evaluated by one-way Analysis of Variance (ANOVA) followed by the Dunnette multiple comparisons test's <0.01 was considered to be significant.

Result

Phytochemical Screening

Phytochemical screening of both the plant extracts revealed that the presence of alkaloids, flavanoids, phytosterols, carbohydrates and saponins.

Toxicity Studies

In performing preliminary test for pharmacological activity in rats, ethanolic and aqueous extract did not produce any significant changes in the behavioral or neurological responses upto5000 mg kg^{-1} body weight. Acute toxicity studies revealed the non-toxic nature of the ethanolic and aqueous extracts of *Croton zambesicus.* The result obtained from the LD_{50} study indicates that ethanolic and aqueous extract of *Croton zambesicus* is safer to use in animals even at a dose of 100 mg kg^{-1} p.o. respectively (Okokon *et al*., 2010).

Antidiabetic Effects

Effect of ethanolic and aqueous extracts of *Croton zambesicus* on serum glucose levels in diabetic rats are depicted in Table 1. In animals treated with alloxan (200 mg kg^{-1} i.p) (Group II), a significant increase in serum glucose level was observed on 7th, 14th, 21st and 28th day when compared with normal rats (Group I). Group V received Glibenclamide (0.5 mg kg^{-1} p.o.), showed decrease in serum glucose level when compared with diabetic control rats (Group II). After the oral administration of aqueous extract (Group III) and ethanolic extract (Group lV) of *Croton zambesicus* in diabetic control rats, a significant reduction in blood glucose level was observed on the 7th, 14th, 21st and 28th day when compared with diabetic control rats.

Hypolipidaemic Activity

The lipid profiles in control and experimental rats are depicted in Table 2. The diabetic control rats (Group II) showed significant increase in serum triglycerides, total cholesterol, Very Low Density Lipoproteins (VLDL), Low Density Lipoproteins (LDL) and decrease in High Density Lipoproteins (HDL) when compared with normal (Group I). Standard Glibenclamide (Group V) reduced triglycerides, total cholesterol, Very Low Density Lipoproteins (VLDL), Low Density Lipoproteins (LDL) and increased High Density Lipoproteins (HDL) when compared with normal (Group I). The ethanolic and aqueous extract showed significant reduction ($p<0.05$) in total cholesterol, LDL, VLDL, triglycerides and significant increase ($p<0.05$) in HDL when compared with diabetic control group (Group II). All these effects were observed on day 7th 14th, 21st and 28th day of experiment. The present experimental result indicated that ethanolic and aqueous extracts exhibited potent hypolipidemic activities in alloxan induced diabetic rats.

Table 1. Anti-hyperglycemic activity of extracts of Croton zambesicus on alloxan induced rats

Groups treatment/dose	0th day (mg mL^{-1})	7th day (mg mL^{-1})	14th day (mg mL^{-1})	21st day (mg mL^{-1})	28th day (mg mL^{-1})
Normal control	62.40 ±5.45	96.70 ±5.56	85.80 ±4.45	79.75 ±5.79	70.67 ±5.43
Diabetic control	224.70 ±15.52	214.5 ±10.60	211.33 ±20.30	208.16 ±17.38	201.00 ±16.32
Glibenclamide (0.5 mg kg^{-1})	232.33 ±13.9***	184.83 ±12.8***	129.83 ±19.20 ***	94.50 ±5.46 ***	91.1 ±12.21***
Aqueous extract (100 mg kg^{-1})	230.13 ±1.23***	185.12 ±10.23***	128.11 ±1.23***	95.34 ±1.45***	90.12 ±1.67***
Ethanolic extract (100 mg kg^{-1})	237.0 ±15.0***	190.16 ±16.14***	132.66 ±11.01 ***	98.83 ±10.55 ***	91.34 ±10.23***

The values are mean ± SEM, n = 6 of blood glucose level. When compared with diabetic control, ***$p<0.05$ (One way ANOVA followed by Dunnett's, multiple comparison tests)

Table 2. Antihyperlipidemic activity of extracts of Croton zambesicus on alloxan induced diabetic rats

Groups treatment/dose	TC	TG	HDL-C	LDL-C	VLDL-C
Normal control	80.50	69.33	39.83	42.00	19.83
	±1.35	±0.75	±0.69	±2.79	±0.75
Diabetic control	135.83	139.00	25.67	89.50	29.34
	±1.97	±1.68	±1.15	±2.29	±1.67
Glibenclamide	98.57	88.50	37.23	59.23	23.67
(0.5 mg kg^{-1})	±3.73**	±2.17***	±5.52***	±1.49***	±0.77***
Aqueous extract	96.99	85.34	38.76	58.85	22.23
(100 mg kg^{-1})	±1.23***	±1.89***	±2.43***	±3.54***	±1.23***
Ethanolic extract	99.19	89.00	39.57	58.13	24.93
(100 mg kg^{-1})	±2.26**	±2.69***	±1.33***	±1.62***	±0.37***

The values are mean ± SEM n = 6, when compared with diabetic control, *** = $p<0.05$, (One way ANOVA followed by Dunnett's, multiple comparison tests). Total Cholesterol (TC), Total Glyceride, (TG) HDL-C: High Density Lipoprotein C, LDL-C: Low Density Lipoprotein -C, VLDL-C: Very Low Density Lipoprotein C

Discussion

Diabetes mellitus is the leading causes of death, illness and economic loss all over the world. Insulin-dependent (Type I, IDDM) diabetes is characterized by juvenile onset and by absolute insulin deficiency. Non-insulin-dependent (Type II, NIDDM) diabetes is characterized as mature onset, by varying basal insulin levels and a frequent association of obesity. The diabetes in the animal model was induced with Alloxan and is the model for Type II diabetes in human model. Although a broad category of drugs and medicines are available in the modern allopathic system of medicine as well as in traditional systems of treatment and many of them are quite effective but most of them does not have a satisfactory safety profile and this safety becomes a matter of great concern especially when the drugs or treatment is meant for administration over a long period of time along with high frequency of in case of diabetes mellitus and related conditions. Thus the one option of treatment left is to rely upon the herbal system of medicine because of the fact of having minimum incidence of adverse effects on the patients which is already established universally.

We evaluated the antidiabetic and hypolipidaemic effect of the aqueous and ethanolic extracts of *Croton zambesicus* in the alloxan induced diabetic rats for a period of 28 days. After the alloxan induction we observed the increased blood glucose level accompanied by increase in total Cholesterol, Triglycerides, LDL, VLDL and decrease in HDL cholesterol above the normal limits in alloxan induced diabetic rats when compared to normal group of animals. Oral administration of aqueous and ethanolic extract of *Croton zambesicus* normalized the elevated levels of blood glucose, showing the potent antidiabetic and hypolipidaemic effect of the plant extracts, indicating the role of potent phytochemicals, producing the desired effects in diabetic rats. Similar results were found in the study conducted by Jude *et al*. (2011) which showed the potential antidiabetic and hypolipidaemic effects of the ethanolic extracts of the roots of plants (Jude *et al*., 2011). The study showed better antidiabetic as well as hypolipidemic effect in aqueous as well as ethanolic extract which shows it may be better antidiabetic with antibacterial effect. However the present study revealed the potential effects of the aqueous as well as the ethanolic extracts, which is quite significant. The antidiabetic effect can be attributed to the presence of polysaccharides (Tomoda *et al*., 1985), terpenes and tannins (Reher *et al*., 1991), steroids (Ivorra *et al*., 1984) and alkaloids (Karawya and Wahab, 1984).

In recent years, considerable interest has been directed to the investigation of plasma lipids and lipoproteins involvement in diabetes mellitus due to the already established fact that abnormal lipid level leads to the development of coronary artery disease in diabetic patients (Sarti and Gallagher, 2006). Reduced insulin secretion and defect in insulin function results in enhanced metabolism of lipids from adipose tissue to the plasma. Impairment in insulin sensitivity due to high concentration of lipids in the cells is responsible for the elevated cardiovascular risk in diabetes mellitus (EL-Hazmi and Warsy, 1999). Thus, the altered lipid and lipoprotein pattern observed in diabetic rats could be due to defect in insulin secretion and/or action. Accumulation of cholesterol and phospholipids in liver due to elevated plasma free fatty acids has been reported in diabetic rats.

In the present study, aqueous and ethanolic extract of *Croton zambesicus* had significantly decreased Total Cholesterol, Triglycerides, VLDL and LDL with increase in HDL cholesterol levels along with the beneficial protective function over the heart of induced diabetic models compared to the diabetic control group (Frayn, 2002). Numerous studies have been done in the past involving and concluding the antidiabetic and hypolipidaemic effects of ethanolic extract of the roots. But the importance and significance of this study lies in revealing the antidiabetic and hypolipidaemic of the ethanolic extract as well aqueous extract of the roots and the results of the two of them were found to be more or less potential and significant. Ethanolic extract shows better antidiabetic activity due to its antibacterial effect.

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Author's Contributions

Prakash Kumar: Contributed in concept design and wrote manuscript

Rahul Kumar: Data collection.

Manoj Kumar Rastogi: Statistical analysis.

Krishna Murti: Designed the protocol and final Approval of manuscript.

Ethics

The research was approved by animal ethics committee of PDM School of Pharmacy, Safidon, India (PDM/IAEC/11/11/11).

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