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Original Research Paper Pharmacology

EVALUATION OF ANTI-DIABETIC ACTIVITY OF ROOT EXTRACT OF CURCUMA CASSIA ROXB IN DIABETIC RATS

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ABSTRACT To investigate the effect of anti-diabetic uses of root extract of Curcuma cassia Roxb on streptozotocin-induced diabetes rats. Diabetic rats were treated with a 200 mg/kg.p.o dose of ethanolic and aqueous extracts for 21 days. The blood glucose levels were monitored at specific intervals using a Glucose tolerance test. The blood samples were collected from overnight fasted diabetic rats on day 22 to estimate the blood glucose level using streptazotocin induced diabetic in rats. The body weight, serum lipid profile and activities of liver and kidney enzymes were measured. The ethanolic and aqueous extracts of Curcuma cassia Roxb at 200 mg/kg.bw.p.o. showed significantly lowered ($P < 0.01$) blood glucose levels in diabetic rats, whereas on 21 days treatment of diabetic rats with ethanolic extract 200 mg/kg showed highly significant ($P < 0.001$) antihyperglycemic effect. The body weight and serum parameters were significantly improved in all drug treated groups compared with the control group. The present study investigated that have therapeutic effect of Curcuma cassia Roxb on diabetes due to its medicinally important bioactive compounds in depicts that it has Curcuma cassia Roxb as great potential for becoming a future drug for the treatment of diabetic patients.

KEYWORDS : Curcuma cassia Roxb, Streptozotocin, Blood glucose levels, Diabetic

INTRODUCTION:

Diabetes Mellitus is a group of metabolic disorder characterized by inadequate production or utilization of insulin and resulting in excessive amounts of glucose in the blood with disturbances in carbohydrates, protein and fat metabolism resulting from insulin deficiency impaired the effectiveness of insulin's action, or to a combination of both[1]. Diabetes mellitus worldwide has shown an alarming upsurge, ranking it as the fourth or fifth leading cause of death in the world. It is associated with serious complications including coronary artery and peripheral vascular disease, stroke, diabetic neuropathy, amputations, renal failure and blindness[1,2]. The current rapid global rise in diabetes rate is attributed to rapid rise in unhealthy lifestyles, urbanization and aging[3]. Global estimate of the number of diabetics within the past three decades showed an increase from 153 million in 1980 to 347 million in 2008. Currently the prevalence of diabetes is estimated at 382 million people in 2013 and is expected to rise to 592 million by the year 2035. With this high prevalence, the highest mortality due to diabetic mellitus occurs in low and middle income countries[3]. India leads the way with its largest number of diabetic subjects in the world. It has been estimated the number of diabetes in India is expected to increase 57.2 million by the year 2025. Clinical studies on different species of animals have shown that consuming less food reduces the risk of diabetes and heart disease[4].

Similarly the current treatment for diabetic patients are available such as Insulin, sulfonylurea's and biguanides thiazolidinediones and alphaglucosidase However, all these treatments have limited efficacy and have been reported to be associated with undesirable side effects[5]. In order to overcome the side effects associated with diabetes, interest has been shifted to use of other alternative medicine[7]. Hence, search for a drug with low cost, more potential and without adverse side effects is being pursued in several laboratories around the world are the keystone of diabetes treatment [5,7]. World Health Organization (WHO) has recommended the traditional plant treatments for diabetes warrant further evaluation[6]. Moreover, today it is necessary to provide scientific proof as to whether it is justified to use a plant or its active principles for treatment. Traditional medicines and extracts from medicinal plants have been extensively used as alternative medicine for better control and management of diabetes mellitus. Medicinal plants have continued to be a powerful source for new drugs, now contributing about 90% of the newly discovered pharmaceuticals[8].

The genus *Curcuma cassia* is a well-known specie of India. It is also called Haldi and more than 200 species and subspecies of it is found all across the world. One of which is *Curcuma caesia* Family: *Zingiberaceae.* It is also known as "Kali Haldi Traditionally the plant has been used as Piles, leprosy, asthma, cancer, wound, impotency, fertility, tooch ache, vomiting, cough dycentry, antioxidant antidiabetic, fever, worm infection, epilepsy and rheumatoid arthritis[9] . The *C. cassia Roxb* contains several reported biologically active constituents camphor, ar-turmerone,(*Z*)-ocimene, ar-curcumene, 1, 8-cineole, elemene, borneol, bornyl acetate and curcumene as the major constituents *C. caecia* has medicinal value due the presence of natural constituents. The majority of their activity is due to bioactive compound viz alkaloids, steroids, phenolics, and tannins[9,10].

Root of the *C. cassia Roxb* have been explored for antifungal, smooth muscle relaxant, anti-asthmatic, antioxidant, analgesic, anticonvulsant and muscle relaxant effects, anxiolytic and CNS depressant activity, anti-bacterial and anti-ulcer activities[10].

Therefore the objective of this study was to investigate the effect of ethanolic and aqueous extracts on diabetic rats. Hence this study was shown the antidiabetic effect of ethanolic and aqueous extracts. Both extracts showed the significant effect on diabetic rats. However, The ethanolic extract showed the greater antidiabetic effect on STZ induced diabetic in rats as compared to aqueous extract. It may be effective for the management of diabetes patient for future aspect.

MATERIALS & METHODS:

MATERIALS:

Collection and authentication:

The matured roots of *C. cassia Roxb* were collected from Bhopal, M.P, India in December-January 2014. The roots were identified by Dr. Zia Ulttaran Professor and head Department of Botany Saifia Science College Bhopal-462001, India. (Specification no 495/Bot/Saifia/14).

Drugs and chemicals:

Streptozotocin (STZ) from SISCO Research Laboratory, Mumbai, India; Glibenclamide from Hoechst, Mumbai, India. All the other reagents were used of analytical A grade which were obtained commercially[11].

Methods:

Drying and Size reduction of Plant Material:

The collected rhizomes were shade dried and subjected for size reduction to get coarse powder using dry a grinder and passed through sieve number 40. The course powder was packed in to airtight container and store in cool and dry place for further study.

Preparation of extracts:

The powder was divided into two equal parts and cold macerated with ethanol and Purified water overly for 7 days at room temperature with occasional stirring. 2% ethanol has been added in purified water for prevention of microbial growth. The ethanol and aqueous containers were closed with a cap and aluminium foil to prevent evaporation and exposure to contamination. After 7 days, the contents were filtered by vacuum filtration and the filtrate was evaporated by rotary vacuum evaporator[12]. The ethanolic extract and aqueous extracts concentrate were collected and stored in airtight containers in refrigerator below 10 ^{0}C.

Experimental animals:

Wistar rats of either sex, aged 90 days, and weighing 160-250 g, were obtained from the central animal house of SIRT-Pharmacy, Bhopal, M.P. reared on the premises of the Institute under illumination at night and early morning, with feed and drinking water provided *ad libitum*. The experimental protocol was cleared from the Institutional Animal Ethics Committee with resolution No.SIRT/IAEC/2014/05 Bhopal, M.P. before conducting the experiments. All the protocols and the experiments were conducted in strict compliance with the ethical principles and guidelines provided by the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA).

Acute toxicity:

The acute oral toxicity study was conducted as per guidelines on acute oral toxicity test 425 according to the Organisation for Economic Cooperation and Development. A limit dose of 2000 mg/kg .b.w.p.o was used for rat. The signs of toxic effects and mortality were observed 4 h after administration, then for the next 48 h. The body weight was recorded for uninterrupted 14 days. Since the extracts were found safe up to the dose level of 2000 mg/kg body weight, 1/10 dose 200 mg/kg.b.w has been selected of both extracts for screening the antidiabetic activity[13].

Induction of diabetes:

Diabetes was induced by intraperitoneal injection of 60 mg/kg body weight of rats. The streptozotocin (STZ) (Sigma, St Louis, MO, USA) was dissolved in freshly prepared citrate buffer. Fasting blood sugar was measured after 72 h of each rat. Diabetes mellitus was induced in overnight fasted rats by a single intraperitoneal injection of streptozotocin (60 mg/kg body weight). After 3 days, fasting blood glucose levels was measured and the animals showing blood glucose level 225 mg/dl were used for the present investigation. Rats with fasting blood sugar level 200 mg/dL were considered as diabetic[3,14].

Oral glucose tolerance test with extracts in diabetic rats:

Thirty rats were selected and divided into 5 groups of six rats each. **In Group 1,** normal rats were treated with normal saline and used as the negative control. **In Group 2,** diabetic control rats were treated with normal saline water + STZ. **In Group 3,** diabetic rats were given standard drug glibenclamide (5 mg/kg .b.w.i.p). + STZ **Groups 4,** served as diabetic rats given ethanolic extract 200 mg/kg.b.w.p.o.+ STZ. **Group-5,** aqueous extracts at a dose of 200 mg/kg.b.w.p.o.+STZ respectively.

Glucose Tolerance Test:

All the diabetic rats were fasted overnight (14h) before the oral glucose tolerance test was done. Thirty minutes following the extracts or glibenclamide treatment, each rat was given an oral glucose load of 3 g/kg body weight. Blood samples were withdrawn from retro-orbital site at intervals of 30, 60, 90 and 120 min after glucose administration[15].

Experimental protocol for 21 days treatments:

The rats were divided into five groups (n = 6). Except **Group-I** which served as normal non diabetic control all other groups were comprised of diabetic rats. **Group-II** served as diabetic (STZ) control. **Group-III** received the reference drug glibenclamide (5 mg/kg b.w.p.o.) daily for 21 days. **Groups-IV** received Ethanolic extract200 mg/kg b.w., p.o. and **Group-**V received aqueous extracts at the dose of 200 mg/kg b.w., p.o. respectively. Fasting blood glucose (FBG) level and body weight of each rat was measured on 0, 7th, 14th and 21 day by using a single pan weighing balance and blood glucose was measured by one touch glucometer[15,16].

Collection of blood samples and estimation of biochemical parameters:

At the end of the experimental period, day 21, the animals were fasted an overnight and the rats were sacrificed by cervical decapitation and fasting blood samples were collected in EDTA tubes. For serum samples, blood was allowed to coagulate, followed by centrifugation at 3000 r/min for 15 min at 4 °C to separate serum. Sera were divided into aliquots and stored at -80°C for biochemical parameters viz. serum glutamate oxaloacetate transaminase (SGOT), serum glutamate pyruvate transaminase (SGPT), serum alkaline phosphatase (SALP), total proteins and cholesterol were estimated by using commercially available reagent kits (Span Diagnostic Ltd., Surat, India). Serum total protein was estimated according to the reported method[17].

Statistical Analysis:

The experimental data were expressed as mean ± standard error of mean (SEM). Statistical significance was analyzed by one-way analysis of variance (ANOVA) followed by Dunnett's post hoc test of significance. P values of < 0.001 were considered as statistically significant.

RESULTS AND DISCUSSION:

Acute toxicity study:

Ethanolic and aqueous extracts were safe up to a dose of 2000 mg/kg.b.w.p.o. The Behavior of the animals was observed for the first 4h then at an interval of every 4 h during the next 48 h, the extracts did not produce significant changes in the behavior of the animals or mortality.

Effect of ethanolic and aqueous extract of *C. cassia Roxb* on oral glucose tolerance in diabetic rats:

Streptozotocin (STZ) is an antibiotic obtained from Streptomyces achromogenes. STZ enters the pancreatic cells via a glucose transporter-GLUT2 and causes alkylation of deoxyribonucleic acid (DNA) leading to pancreatic damage. Its toxicity depends upon the potent alkylation properties combined with the synergistic action of nitric oxide and reactive oxygen species that continue to DNA fragmentation. As a result of STZ action, streptozotocin pancreatic cells are destroyed by necrosis. STZ is not only damaging to the pancreatic cells, but also to hepatocytes, nephrons and cardiomyocytes[18-19].

Oral glucose tolerance test showed that increase the blood glucose level from 30 minute interval to 120 minutes in the control group when compared with a minute group. All drugs treated groups showed significant reduction in blood glucose level from a 30 minute to 120 minute interval compared with a 0 minute of each group. **Table-I.**

The present study was aimed to anti diabetic effect of long treatment with ethanolic and aqueous extracts of ***C. cassia* Roxb** on STZ-induced diabetic rats. Hyperglycemia was observed on the 7th day in STZ-induced diabetic rats. In control group blood glucose level significantly increased on 0 days to 21 days compared with normal group. Treatment with ethanolic and aqueous extracts in STZ-induced diabetic rats started reducing the significantly fasting blood glucose levels after 7th days onward and made them completely normoglycemic after 21 days. The antidiabetic effect of

ethanolic and aqueous extracts of *C. cassia Roxb* revealed the presence of alkaloids, glycosides, steroids, flavonoids, saponins, tannin, phenol, resins, carbohydrates, protein, fixed oils. It also contains camphor, ar-turmerone, (*Z*)-ocimene, ar-curcumene, 1, 8-cineole, elemene, borneol, bornyl acetate and curcumene are the major constituents. In the present study both extracts on 21 days continuous treatment to STZ-induced diabetic rats showed prominent reduction and normalization of elevated blood sugar levels i.e. antidiabetic effect, compared with control rats. The ethanolic extract was more effective than aqueous extract. Therefore, this result indicates that ethanolic extracts of is possessed remarkably effective antidiabetic potential against streptozotocin induced diabetes in Wistar rats **Table: 3**

Induction of diabetes with STZ had been associated with a characteristic loss of body weight, which is due to increased muscle wasting and loss of tissue proteins. Diabetic rats treated with the ethanolic and aqueous extract showed significant improvement in body weight on days 14 to 21 days as compared to the STZ induced diabetic in the control group. **Table-3**

Effect of ethanolic and aqueous extracts of *C. Cassia Roxb* on biochemical parameters

It has been well established that elevated levels of SGOT, SGPT and SALP are indicative of cellular leakage and loss of functional integrity of the hepatic cell membranes implying hepatocellular damage[20]. Serum total proteins on the other hand are related to the function of the hepatic cells, revealing the functional status of the hepatic cell. Elevated serum cholesterol levels in STZ challenged rats indicated impaired fat metabolism. Altered serum biochemical parameters in STZ-induced rats were reported elsewhere[21].

In the present study the effect of both extracts on hepatic and renal markers was analyzed on the 21 days. The SGPT, SGOT, ALP and cholesterol level are significant ($p<0.001$) increased and significant ($p<0.001$) decrease the total protein level in the diabetic control group compared with normal group. Glibenclamide 5mg/kgb.w. and extracts treated groups at a dose of 200 mg/kg showed significant *p<0.01* reduction in SGPT, SGOT, ALP and cholesterol compared with the diabetic control group (Table 4). The levels of Total protein showed significantly imporved in the treated groups of extracts as compared with the diabetic control.

The findings of the present study are encouraging enough to warrant further studies on this plant in pursuit of a new oral hypoglycemic agent. The ethanolic extract 200 mg/kg.b.w of *C. cassia Roxb* was found to be comparable to that the effect exerted by the reference drug, glibenclamide at the dose of 5 mg/kg.b.w.

Table no 1 Effect of rhizome extract of *C. cassia Roxb* on blood glucose level

Treatment Group Dose (mg/kg)	Blood Glucose level				
	0 min	30 min	60 min	90 min	120 min
Control group Normal saline+ STZ (60mg/kg)	84.1± 1.22	110.5± 4.33	121 ± 2.17	131 ± 0.78	141 ± 3.47
Standard Group Glibinclamide (5mg/kg)+ STZ (60mg/kg)	82.1 ± 1.28	78.03 ± 3.64	73± 1.87**	66.8 ± 3.18**	64.2± 3.19**
Test Group-I 200 mg/kg alcoholic extract STZ (60mg/kg)	87.9 ± 2.19	81.02 ± 2.13	73.6 ± 2.11**	65. ± 3.68**	63.7 ± 2.13**
Test Group-II 200 mg/kg aqueous extract +STZ (60mg/kg)	85.8 ± 1.47	85.8 ± 1.76	81.5 ± 0.78**	77.1 ± 1.56**	73.1 ± 1.03**

The values are expressed as mean ± SEM (N=06), Control group compared with normal group and drug treated group compared with a control group P value less then* *P<0.001, *P<0.01, considered as significant.

Table no 2 : Effect of root extracts of *C. cassia Roxb* on blood glucose level on streptozotocin induced diabetic rats

Treatment Group Dose (mg/kg)	Blood Glucose level			
	0 Day	7th Day	14th Day	21th day
Normal Group 5 ml/kg saline	76.85 ±2.	76.85± 2.	76.85±2.	76.85±2.1
Control group Normal saline+ STZ (60mg/kg)	275.52 ±8.9*	279.89 ±9.8*	287.71± 10.3*	291.69±8. 8*
Standard Group Glibinclamide (5mg/kg)+ STZ	269.49 ±12.3	94.41± 2.6**	84.67±1. 6**	71.89±2.3 **
Test Group-I 200 mg/kg alcoholic extract +STZ (60mg/kg)	264.74 ±15.8	89.54± 4.3**	82.56±2. 9**	78.61±2.5 **
Test Group-II 200 mg/kg aqueous extract +STZ (60mg/kg)	271.41 ±13.7	118.63 ±8.1**	93.38±1. 9**	89.77±2.4 **

The values are expressed as mean ±SEM (N=06), Control group compared with normal group Drug treated group compared with a control group P value less then* *P<0.001, *P<0.01, considered as significant.

Table no 3: Effect of root extracts of *C. cassia* Roxb on body weight

Treatment Groups Dose (mg/kg)	Body weight			
	0 Days	7th day	14th day	21th day
Normal group 5 ml/kg saline	175.00± 7.86	178.±11. 21	189.2± 4.97	193± 3.49
Control group Normal saline+ STZ (60mg/kg)	167.4± 8.48	151.2± 8.94	139.2±7. 63**	129.3±7. 85**
Standard Group Glibinclamide (5mg/kg)+ STZ (60mg/kg)	172.8± 3.26	183.4± 2.40	187.8±2. 55**	191±2.42 **
Test Group-I 200 mg/kg alcoholic extract STZ (60mg/kg)	168.9± 5.82	175.6± 10.21	177.9± 5.99**	180± 6.03**
Test Group-II 200 mg/kg aqueous extract +STZ (60mg/kg)	166.7± 4.04	171.1± 9.66	174± 5.13**	177.6±5. 45**

The values are expressed as mean ±SEM (N=06), Drug treated group compared with a control group P value less then* *P<0.001, *P<0.01, considered as significant.

Table 4: Effect of rhizome extracts of *C. cassia* Roxb on biochemical parameters

Treatment Group Dose (mg/kg)	Biochemical Profile				
	SGOT	SGPT	Total Protein (g/dl)	ALP (IU/L)	Cholesterol (mg/dl)
Normal Group 5 ml/kg saline	22.34± 5.1	24.57± 3.6	7.14±1. 2	167.6± 12.4	149.81 ±8.7
Control group Normal saline+ STZ (60mg/kg)	39.3±5. 6*.	42.7±4. 8* **	4.31±0. 6* **	241.5± 13.2*	217.2± 14.1*
Standard Group Glibinclamide (5mg/kg)+ STZ (60mg/kg)	22.54± 2.9**	24.8±3. 9**	6.9±3.4 **	184.8± 8.7**	163.83 ±10.8**
Test Group-I 200 mg/kg alcoholic extract STZ (60mg/kg)	23.7±3. 9**	26.8±5. 9**	6.85±3. 3**	189.5± 12.9**	179.52 ±9.8**
Test Group-II 200 mg/kg aqueous extract +STZ (60mg/kg)	29.4±4. 8**	28.9±3. 8**	6.12±2. 5**	214.5± 14.1**	189.7± 12.2**

CONCLUSION:

The Root of ethanolic and aqueous extracts of *Curcuma Cassia Roxb*

may be consumed to reduce the sugar level in the blood and thereby help to treat the diabetic diseases without any risk of toxicity. The ethanolic extract is highly potent as compared to aqueous extract.

CONFLICT OF INTEREST:

We certify that this manuscript is not under any conflict of interest.

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