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Investigation of *Cyperus Rotundus* Root Extract on Diabetic Complications in Rats with Alloxan-Induced Diabetes

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Abstract

Background and Introduction: *The prevalence of hyperglycemic diseases known collectively as diabetes has reached epidemic proportions in the current century. Diabetics are particularly vulnerable to infections, which can have devastating health consequences. The purpose of this research was to examine the effects of an aqueous extract of Cyperus rotundus roots on diabetic complications in rats with diabetes caused by Alloxan.* ***Martial and Methods:*** *Specifically: Alloxan monohydrate, Borosilicate, and a diagnostic kit. Specifically: a diagnostic kit, a phrase, or a paraphrase. Centrifuge Micropippet, Glucose check monitoring device, electronic digital scales, EDDY's Hot plate analgesometer MK-11, and the Biofuse pico. All chemicals employed were of the AR grade variety, including the alloxan monohydrate, metformin, chloroform, diethyl ether, and ethyl ether.****Results:*** *No deaths or toxicity symptoms were observed in the AECR acute toxicity test in mice, indicating that the extract was well tolerated and the test doses were safe in the animals. The effect of AECR on fasting blood glucose level in alloxan-induced diabetic rats was measured using an auto analyzer glucose kit to determine the compound's antidiabetic activity. The plasma or blood glucose level is measured after an individual has fasted as part of a carbohydrate metabolic test. The hormone glucagon is secreted into the bloodstream during fasting to facilitate the catabolic release of glucose.* ***Conclusion:*** *The results show that in alloxan-induced diabetic rats, the oral administration of an aqueous extract of Cyperus rotundus exhibited neuroprotective, nephroprotective, and hepatoprotective activities by increasing insulin production and decreasing glucogan production and an SGOT snd SGPT level.*

Keywords: *Cyperus rotundus, root extract, diabetic, alloxan-induced diabetes*

1. Introduction

The prevalence of hyperglycemic diseases known collectively as diabetes has reached epidemic proportions in the current century. Diabetics are particularly vulnerable to infections, which can have

devastating health consequences. Vascular and renal damage due to diabetes manifests as hypertension, dyslipidemia, micro-albuminuria, macro-albuminuria, and an increase in glomerular mesangial thickness [1, 2]. Symptoms of diabetes mellitus include an increased appetite, increased thirst, increased urination, blurred eyesight, and a loss of body weight. Hypertonic or non-hypertonic? In its extreme or non-hypertonic state, death may be a complication [3, 4].

About 10% of those with diabetes mellitus have type-1 diabetes, which is caused by the immune system's attack on the beta cells of the pancreas. There appears to be a correlation between the rate of -cell autoimmunity and the prevalence of Type-1 diabetes mellitus. Within communities of people. Diabetes mellitus type 2 is a metabolic condition that manifests in a variety of ways. The most common form of diabetes is type-2 diabetes mellitus, which is characterized by a deficit in insulin secretion and a defect in sensitivity to insulin [5, 6].

The exocrine function of the pancreas is carried out mostly by acinar cells, which produce and discharge digesting enzymes into the duodenum. The endocrine pancreas consists of several tiny nests of cells called the "islets of langerhans," which are dispersed more or less randomly throughout the pancreas and account for only 2% of its weight but secrete several vital hormones straight into the blood stream [7, 8].

The erect perennial glabrous grass-like sedge *Cyperus rotundus L. (Cyperaceae),* commonly known as 'Nagarmotha,' has thin underground stolons that produce ovoid or cylindrical brown edible tubers. It can be found in most temperate regions, including India, Ceylon, and the rest of the world. Oils, alkaloids, glycosides, saponins, flavonoids, tannins, starch, and carbs have all been found in *C. rotundus*, according to various sources. In addition to magnesium, vanadium, chromium, manganese, and cobalt, it is a protein. In traditional Indian medicine, *C. rotundus* rhizomes were used to treat fever, diarrhea, pruritis, pain, vomiting, and a number of blood problems [9, 10].

High levels of glycosuria are typically present when a clinical diagnosis of diabetes is made, along with symptoms such increased thirst and urine volume, recurring infections, and, in severe cases, weight loss, sleepiness, and coma [11]. The purpose of this research was to examine the effects of an aqueous extract of *Cyperus rotundus* roots on diabetic complications in rats with diabetes caused by Alloxan. The purpose of this study is to assess the efficacy of *Cyperus rotundus* aqueous extract (AER) in the treatment of problems associated with type 2 diabetes mellitus in a human model.

2. Materials And Methods

The equipment used in this study includes a Borosilicate Soxhlet extractor, Alloxan monohydrate obtained from Sigma Aldrich in the United States, a Biochemical Analyser-ROBONIK (prietest easylab) from Mumbai, and a ROBONIC diagnostic kit for measuring creatinine, total protein, urea, and uric acid. Additionally, a Centrifuge Biofuse pico from Heraeus, an electronic digital weighing scale from Apex, an EDDY's Hot plate analgesometer MK-111 from Sisco in Thane, Maharashtra, a Glucose check monitoring system from Aspen Diagnostics Ltd in Delhi, India, and a micropipette were utilized.

Drugs and Chemicals

The chemicals utilized in this study were of analytical reagent (AR) grade. These included Alloxan monohydrate (Sigma Aldrich, USA), Metformin (Alembic Pharma), Chloroform (Fisher scientific), Diethyl ether (Fisher scientific), and various other compounds.

Preparation of extract:

Dried roots of *Cyperus rotundus* were gathered and pulverized to obtain powdered plant material. The powdered medication was subsequently subjected to sieving using a no. 44 sieve, and this sieved material was employed for the extraction procedure. Around 100 grams of powder was introduced into a Soxhlet extractor, along with 400 milliliters of water in a ratio of 1:4. The extraction process lasted for a duration of 72 hours. The ultimate output is determined to be 20.2 grams. The extract was subjected to a drying and concentration process at a temperature of 45°C using a water bath. The resulting residue of the extract was then analyzed for the experiment. The extract was diluted in distilled water and administered orally throughout the animal dosing procedure [12].

Experimental animals

The Wister albino rats, weighing between 200-250g, were procured from the central animal house of Sigma Institute of Clinical Research & Administration Pvt. Ltd, located in Hyderabad. The animals were maintained in a controlled environment with a temperature range of 24±2°C and a relative humidity range of 30-70%. The study adhered to a light:dark cycle of 12 hours each. All animals were provided unrestricted access to water and were fed a normal pellet laboratory animal diet. The animals underwent acclimatization to laboratory settings before to the implementation of the experimental process, which was conducted in accordance with the methodology outlined by Zimmerman et al. The study protocol was approved by the Institutional Animal Ethics Committee [13].

Acute oral toxicity study

Acute toxicity evaluations were performed according to OECD-423 recommendations category IV drug. This study used male and female albino mice that were chosen at random. After a 4-hour fast during which they had free access to water, the animals were fed. Cyperus. rotundus root extracts were given orally, with a maximal dose of 2000 mg/kg. Three days of mortality data were collected. A toxic dose was defined as one in which two-thirds or more of the test animals died. If only one mouse out of three died, however, the same dose was given once more to confirm the toxicity. If there was no death toll from the initial procedure, a second round with a larger dose was administered [15].

Qualitative chemical analysis:

Preliminary phytochemical analysis:

Chemical studies were conducted on the aqueous extract derived from the root plant of Cyperus rotundus in order to identify its active ingredients [16].

Tests for carbohydrates and glycosides

A discrete amount of the extract was individually diluted in 4 ml of distilled water and subsequently subjected to filtration. Molisch's test was performed on the filtrate in order to identify the presence of carbohydrates [17].

Tests for phytosterol

The extract was subjected to reflux with a solution of alcoholic potassium hydroxide until full saponification occurred. The solution was subjected to dilution and afterwards underwent extraction using ether. The ether layer underwent evaporation, and afterwards, the resulting residue was subjected to analysis in order to determine the presence of phytosterols [18].

Flavonoids Tests

Aqueous sodium hydroxide solution:

Anthocyanins are responsible for the blue to violet coloration, whereas flavones contribute to the yellow coloration. Flavonones, on the other hand, are responsible for the yellow to orange coloration.

Shinoda’s test

A little amount of the extract was dissolved in alcohol, and afterwards, a piece of magnesium was introduced, followed by the gradual addition of concentrated hydrochloric acid (HCl) while applying heat. The manifestation of the magenta hue indicates the existence of flavonoids.

Experimental induction of Diabetic in rats

Following a 48-hour period of fasting, the animals were administered intraperitoneal (i.p) injections of alloxan monohydrate dissolved in a solution of 0.9% sodium chloride. The control group of rats was administered intraperitoneal injections of a solution containing 0.9% sodium chloride. Blood glucose concentrations were determined using a diagnostic kit within 48 hours after the administration of alloxan. The rats exhibiting serum glucose levels exceeding 250mg/dl were chosen for the current investigation. Following the creation of diabetes in the animal subjects, diabetic rats were randomly assigned to five groups, each consisting of six animals. These groups were categorized as follows: normal, control 0, diabetic animals treated with Metformin, diabetic animals treated with AECR, and

diabetic animals treated with AECR AECR. The initiation of treatment occurs subsequent to the identification of blood glucose levels following alloxan administration. The participants' body weight was recorded on a daily basis, while their serum glucose levels were measured on the 1st, 7th, and 14th day of the study [19].

ESTIMATION OF NOCICEPTION

Test with tail submersion in hot water:

The rat's tail was subjected to immersion in a heated water bath until the occurrence of tail withdrawal or indications of resistance were detected. The abbreviation of the tail withdrawal time is indicative of the presence of hyperalgesia.

Hot plate study

The hyperalgesic reaction observed on the hot-plate is believed to arise from a confluence of both cerebral and peripheral processes. During the experiment, the animals were individually positioned on a hot-plate where the temperature was carefully regulated to 55 ± 1 °C. The measurement of the latency to the initial manifestation of paw licking or hop response as a means to evade the heat was utilized as an indicator of the pain threshold. To prevent any harm to the paw, a time limit of 10 seconds was established as the cutoff point [18, 19].

Measurement of body weight and blood sugar

The portable glucometer was utilized to measure blood glucose levels. In summary, blood samples were collected from the rats using the tail vein rupture technique, and a little amount of blood was applied to the glucometer strip inserted into the glucometer device for the purpose of measuring blood glucose levels. Throughout the experiment, the researchers assessed blood glucose levels and body weights on a weekly basis [20].

Biochemical analysis

Blood was collected from rats on day 14 using a retrobital puncture technique while the animals were under moderate ether anesthesia. The rats had been fasted overnight prior to the blood collection. The fasting blood sugar levels were then assessed. The serum was separated and afterwards subjected to analysis for serum creatinine, serum urea, serum uric acid, as well as the estimation of SGOT and SGPT [21].

Principle of Serum Creatinine

The reaction between picric acid and creatinine in an alkaline environment result in the formation of an orange-colored complex with the alkaline picrate. The intensity of color produced at a wavelength of 520 nm, as measured over a defined duration, exhibits a clear correlation with the concentration of creatinine inside the given sample.

3. Results and Discussion

Acute toxicity Analysis:

The study's findings indicate that the LD50 value for oral toxicity of extracts AECR in mice is greater than 2000 mg/kg b.w. The extracts have been determined to be suitable for prolonged administration without any adverse effects.

Plant extract preliminary phytochemistry:

The percentage yield of the aqueous extract obtained from the root of Cyperus rotundus was determined to be 7.9% (w/w). The initial phytochemical investigation indicated the presence of many phytochemical elements in the plant, including alkaloids, steroids, saponins, tannins, phytosterols, flavonoids, glycosides, and carbohydrates.

In rats with alloxan-induced diabetes, AECR affects BSL:

Table 1 shows how aqueous extract of AECR affected blood glucose levels in alloxan-diabetic rats after repeated oral administration, while table 2 shows how it affected body weight. The serum glucose levels of alloxan diabetic rats were substantially higher than those of non-diabetic rats. Both 200 and 400

mg/kg of AECR significantly decreased blood glucose levels in alloxan-treated diabetic rats compared to the control diabetic group, and this effect was dosage and time dependent. On day 14, we saw the greatest decrease. There was also a noticeable gain in total body mass over time. Diabetic rats had the greatest response to AECR at doses of 200 and 400mg/kg. Metformin 14.25 mg/kg orally twice day for 14 days.

Table 1: In rats with alloxan-induced diabetes, AECR affects blood sugar level

Treated groups	Amount of serum glucose			
Groups	**0th Day**	**1st Day**	**7th Day**	**14th Day**
Normal	90.14±2.14	91.72±3.01	88.44±2.16	88.81±3.16
Control	239.10±6.82	251.57±5.77	269.90±3.87	291.71±2.14
Standard	231.71±4.49	159.29±3.72	100.63±2.81	81.51±3.51
AECR 200 mg/kg	239.20±2.62	189.43±3.06	110.20±2.29	88.56±2.88
AECR 400 mg/kg	249.70±5.41	189.25±3.41	95.89±2.49	81.44±2.10

After 14 days of inducing diabetes complications, the tail flick latency of alloxan-treated rats was significantly shorter than that of the control group in a cold immersion test. After 14 days of therapy with AECR 200 and 400mg/kg, the delayed tail flick response deficit was dramatically improved. Metformin 14, 25 mg/kg orally for 14 days significantly decreased tail flick delay compared to controls.

Table 2: Alloxan-induced hyperglycemia in rats: effect of AECR on tail immersion in cold water allodynia

Treatment Groups	Latency of a tail flick in seconds		
	1st Day	**7th Day**	**14th Day**
Normal	10.19±1.12	6.13±1.49	13.67±1.69
Control	8.49±1.54	3.75±1.39	9.88±1.11
Standard	10.39±1.01	5.87±0.42	14.88±1.13
AECR 200 mg/kg	9.34±1.81	5.76±0.24	14.99±0.51
AECR 400 mg/kg	9.54±1.49	6.29±1.35	14.13±1.53

AECR's effect on tail immersion (hot water) hyperalgesia in rats with alloxan-induced diabetes

Throughout the duration of the trial, no significant alteration in tail flick latency was found in the control group of mice. A progressive decrease in latency was found in the control group of rats starting from the 7th day, reaching its lowest point on the 14th day. This observation suggests the existence of neuropathic pain resulting from diabetes. The group of animals administered with AECR at doses of 200 and 400mg/kg, as well as the group treated with Metformin at a dose of 14.25mg/kg, exhibited a decrease in latency on the 14th day. This decrease was followed by an increase in the duration of pain threshold in the following days, suggesting the lack of pain sensation caused by the immersion of the tail in hot water.

Table 3: AECR's effect on tail immersion allodynia in rats with alloxan-induced diabetes

Treatment group	Tail Flick Latency in Hot Water in Seconds		
	1st Day	**7th Day**	**14th Day**
Normal	7.35±1.41	11.11±1.15	11.41±1.23
Control	4.89±1.21	7.42±1.38	5.82±1.87
Standard	7.81±1.33	11.44±1.78	11.74±1.91
AECR 200 mg/kg	6.74±1.81	10.55±1.79	7.67±1.72
AECR 400 mg/kg	7.11±1.69	13.79±1.96	10.64±1.44

Effect of AECR on rats with diabetes caused by alloxan and thermal hyperalgesia

Diabetic rats have a considerably lower nociceptive threshold compared to their healthy counterparts. The existence of algesia by heat was evidenced by a steady reduction in latency reported for the Control group of animals from day 7 to day 14, when the pain was observed to be at its peak. Protective impact of AECR against hyperalgesia induced in diabetic mice was suggested by the lack of a substantial reduction in pain latency in the drug-treated group of animals. In Table No. 4, we see diabetic rats. According to our findings, the average levels of urea in experimental animals were substantially greater than those in healthy animals. Serum urea levels were dramatically reduced in the Metformin 14.25 mg/kg group compared to the diabetes control group. Urea levels in diabetic rats were significantly reduced after 14 days of treatment with AECR extract at 200 and 400 mg/kg, compared to the control group.

Creatinine

The data revealed that the mean values of creatinine exhibited a statistically significant increase in control rats in comparison to the normal rats. The group that received a dosage of Metformin at a rate of 14.25mg/kg shown a notable decrease in blood creatinine levels in comparison to the control group consisting of individuals with diabetes. The administration of the AECR extract at doses of 200 and 400 mg/kg to diabetic rats over a period of 14 days resulted in a notable reduction in creatinine levels as compared to the control group.

Uric aicd

The data revealed that the mean values of uric acid were considerably elevated in the control rats in comparison to the normal rats. The group that received a dosage of Metformin at a rate of 14.25mg/kg demonstrated a notable decrease in blood uric acid levels in comparison to the diabetic control group. The administration of the AECR extract at doses of 200 and 400 mg/kg to diabetic rats over a period of 14 days resulted in a notable reduction in uric acid levels as compared to the control group.

SGOT

The data revealed that the mean values of SGOT were considerably elevated in the control rats in comparison to the normal rats. The group that received a dosage of Metformin at a rate of 14.25mg per kilogram had a notable decrease in serum SGOT levels in comparison to the control group consisting of individuals with diabetes. The administration of the AECR extract at doses of 200 and 400 mg/kg to diabetic rats over a period of 14 days resulted in a notable reduction in SGOT levels when compared to the control group.

SGPT

The data revealed that the mean values of SGPT were considerably elevated in the control rats in comparison to the normal rats. The group that received a dosage of Metformin at a rate of 14.25mg/kg demonstrated a notable decrease in serum SGPT levels in comparison to the diabetes control group. The administration of the AECR extract at doses of 200 and 400 mg/kg to diabetic rats over a period of 14 days resulted in a notable reduction in SGPT levels when compared to the control group.

Pancreases histopathology

Histopathological alterations were identified in both the control and treatment groups of rats. The pancreas of the control rat exhibited the typical morphology of islet cells. Vacuolization, necrotic alterations, and reduced islet cell population in the pancreas were seen in the rats subjected to alloxan treatment. The rats that were treated with alloxan and orally administered with aqueous extract of Cyperus rotundus at doses of 200 and 400 mg/kg body weight exhibited significant reductions in the extent of necrosis, vacuolization, and islet cell reduction in the pancreas.

The acute toxicity test conducted on mice shown that the administration of AECR did not result in any fatalities or indications of toxicity, even at a dosage of 2000 mg/kg. These findings suggest that the extract was well-tolerated by the animals and that the test levels were deemed safe. The antidiabetic efficacy of AECR was assessed in alloxan-induced diabetic rats by the examination of its impact on fasting blood glucose levels, employing an auto analyzer glucose kit. The fasting blood sugar test is a diagnostic procedure used to assess carbohydrate metabolism by measuring the concentration of glucose

in the plasma or blood following a period of fasting. During periods of fasting, the human body initiates the secretion of the hormone glucagon, which subsequently facilitates the release of glucose into the bloodstream via catabolic mechanisms [19-21].

In individuals without diabetes, the human body typically synthesizes and metabolizes insulin in response to elevated glucose concentrations. However, individuals with diabetes experience a disruption in this physiological process, resulting in sustained hyperglycemia as seen by elevated glucose levels in diagnostic tests. Alloxan, along with streptozotocin, is commonly employed as an agent for inducing diabetes mellitus. Previous studies have demonstrated its detrimental impact on the beta (β) cells of the pancreas. The pancreas serves as the principal organ responsible for detecting an organism's dietary and energetic conditions by monitoring the quantity of glucose in the bloodstream. In the event of increased blood glucose levels, the pancreas secretes insulin. Nevertheless, the induction of diabetes by alloxan is attributed to its capacity to impair the functionality of pancreatic beta cells, which are responsible for the production of insulin. Insufficient availability of beta-cells to adequately produce insulin, leading to the development of insulin-dependent diabetes [22, 23].

There exists a significant correlation between glycemia and the occurrence of diabetic microvascular complications in individuals with both type 1 and type 2 diabetes. The generation of superoxide as a result of oxidative stress in diabetes may potentially contribute to the development of vascular and neurological consequences, including the manifestation of painful neuropathy. In the context of diabetes, the presence of elevated levels of glucose within cells leads to disruptions in the normal flow of blood and an increase in the permeability of blood vessels. Both quantitative and qualitative defects of the extracellular matrix have a role in the irreversible elevation of vascular permeability. Microvascular cell loss is partially attributed to programmed cell death. Hyperglycemia has the potential to reduce the synthesis of trophic substances that are essential for the growth and development of endothelial and neural cells. Collectively, these alterations result in the development of edema, ischemia, and hypoxia-induced neovascularization in the retina, proteinuria, mesangial matrix enlargement, glomerulosclerosis in the kidney, and multifocal axonal degeneration in peripheral nerves [24, 25].

There is evidence to suggest that compromised blood circulation also plays a role in the development of heightened sensitivity to noxious stimuli. The involvement of oxidative stress-induced decrease in perfusion has been postulated to contribute to the development of cardiac autonomic dysfunction and small fiber sensory neuropathy. Alloxan, along with its reduction products, namely dialuric acid, is involved in the establishment of a redox cycle that leads to the generation of superoxide radicals. The radicals undergo a dismutation process resulting in the formation of hydrogen peroxide. Subsequently, the Fenton reaction gives rise to the formation of hydroxyl radicals, which exhibit a high degree of reactivity. The rapid death of Beta cells is caused by the interaction between reactive oxidant species (ROS) and a concomitant significant rise in cytosolic calcium concentration [25]. The implementation of pharmaceutical intervention in the early stages of hyperglycemia-induced cross-linking serves as a preventive measure against the emergence of severe late problems associated with diabetes [26, 27].

Recent research has connected hyperglycemia in the onset and progression of several forms of diabetes complications. Nephropathy is a notable microvascular consequence that has been documented in patients with diabetes. Furthermore, it was observed that uncontrolled diabetic persons exhibited elevated levels of blood urea, uric acid, and creatinine. This rise in concentrations may be attributed to poor renal function caused by heightened blood glucose levels. The findings of our study demonstrated, for the first time, that the average concentrations of these end products in the serum exhibited an increase in untreated diabetic rats. However, following the injection of AECR, there was a considerable drop in these concentrations. Therefore, it is plausible that this extract could enhance renal function, thereby resulting in a decrease in the levels of these end products. According to the findings, persons with diabetes had decreased blood creatinine concentrations, along with elevated levels of serum uric acid and urea, in comparison to individuals without diabetes. Therefore, it is likely that the decrease in urea and creatinine concentrations might be attributed to a decrease in blood glucose levels [28, 29].

Additionally, elevated concentrations of serum uric acid, urea, creatine, SGOT, and SGPT have the potential to serve as indicators of renal and hepatic dysfunction. Therefore, it may be postulated that

the aforementioned extract may have a significant impact on mitigating the likelihood of renal and liver complications. Additionally, it exhibits neuroprotective properties by diminishing both hyperalgesia and allodynia, as well as reducing levels of serum urea, uric acid, creatinine, SGOT, and SGPT. The hyperalgesic response observed in the tail-withdrawal test is commonly ascribed to central mechanisms, while the hyperalgesic response observed on the hot plate is attributed to a combination of both central and peripheral mechanisms. The novel findings observed in this investigation provide evidence of the safety profile of AECR extract [30-32].

4. Conclusion

In alloxan-induced diabetic rats, the results showed that the oral administration of an aqueous extract of Cyperus rotundus exhibited neuroprotective, nephroprotective, and hepatoprotective activities by increasing insulin production, decreasing glucogan production, and lowering an SGOT snd SGPT level. Therefore, the toxic activity of alloxan compound may be mitigated by oral administration of this extract, which may have a good effect on the functional capacities of several rat tissues, especially blood, kidney, liver, and nerves. These results provide further evidence for the effectiveness of this plant in traditional treatments for diabetes mellitus and its consequences. Since Cyperus rotundus is safe for human consumption, it seems like a good candidate for treating diabetes and preventing or delaying the onset of the disease's consequences in humans.

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None

Conflict of Interest

None

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