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Evaluation of the Anti-Diabetic Effects and Toxicity of an Ethanolic Extract of *Polialthia longifolia* Roots

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Abstract: Diabetes, commonly known as diabetic millets, is a metabolic condition characterized by elevated blood sugar levels. This syndrome is typically attributed to a mix of genetic and environmental factors. Diabetes is characterized as a state of insufficient nutrient utilization despite an abundance of available resources. The reason for the inability of cells to ingest glucose despite its high concentration in the body is attributed to osmotic differences. Insulin, a hormone synthesized within the pancreas, facilitates the uptake of glucose by bodily cells, hence facilitating its conversion into usable energy. When the body's cells are unable to effectively absorb glucose, it results in the accumulation of glucose in the bloodstream. This can lead to acute metabolic issues such as ketoacidosis, as well as contribute to the development of chronic microvascular difficulties over time.

Keywords: Toxicity, Glibinclamide, *Polialthia longifolia* roots, Antibiotic, Diabetes

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Introduction

Medicinal plants hold a substantial significance in the lives of individuals. There exists a significant correlation between herbs and humans. Currently,

medicinal plants are of great significance in scientific advancements and possess substantial untapped potential. This is particularly relevant as

around eighty per cent of the population in poor nations relies on plant resources for their basic healthcare needs (Expert Committee, 1997). The utilization of medicinal plants as a form of traditional medicine is prevalent in underdeveloped nations. Medicinal plants encompass a diverse array of phytochemicals that possess therapeutic potential in addressing both chronic and infectious disorders hence, holding promise for future disease management (Beverley and Eschwege, 2003; Lindberg *et al.*, 2004).

Herbs and humans share a mutually beneficial interaction. The utilization of plants for the mitigation and control of diseases has been recognized since the inception of human civilization. In contemporary times, medicinal plants continue to have significant importance, notwithstanding the remarkable advancements in scientific research (Bell *et al.*, 1980). These plants possess a wealth of untapped potential, as evidenced by the fact that about 80 per cent of individuals residing in poor nations rely on plant resources as their major means of healthcare. Plant-based therapy has been employed as an integral element within traditional medical systems and has also served as a primary source of inspiration for numerous prominent pharmaceutical medications utilized in the prevention and treatment of diverse ailments (Hallas-Moller *et al.*, 1952; Laurence *et al.*, 2010).

Polyalthia longifolia, belonging to the Order Magnoliales and the Family Annonaceae, is a notable plant that is frequently employed as a decorative street tree owing to its efficacy in mitigating noise pollution. *Polyalthia longifolia*, commonly referred to as fake Ashoka, Buddha Tree, Green champa, Indian mast tree, and Indian Fire tree, is a plant species with multiple names (Heise *et al.*, 1998; Surana *et al.*, 2021). The specimen demonstrates a symmetrical pyramidal growth pattern, characterized by slender, drooping branches that create a weeping effect. The leaves are elongated and lanceolate in shape, with wavy edges. The tree has been documented to reach a height above 30 feet. Herbal remedies

have been employed in traditional medicine for the treatment of duodenal ulcers (Jarouliya *et al.*, 2015).

The utilization of this plant in the traditional medical framework has been documented for its therapeutic properties in addressing many ailments such as fever, skin disorders, diabetes, hypertension, and helminthiasis. Several biologically active chemicals have been extracted from the plant (Weyer *et al.*, 1997). The plant's leaves possess a distinct perfume and are commonly employed for decorative purposes. Conversely, the bark of the plant is utilized in traditional medicine inside India to address pyrexia and various bleeding diseases. From an ethnomedical perspective, *Polyalthia longifolia* is a multifunctional botanical species that exhibits a wide range of therapeutic applications, including the treatment of rheumatism, menorrhagia, scorpion sting, diabetes, skin illness, hypertension, helminthiasis, and digestive system disorders (Aguilar-Bryan *et al.*, 1995; Ahmad *et al.*, 2016).

The primary focus and purpose of this study encompassed the examination of the antidiabetic activity and toxicity of the ethanolic extract derived from the roots of *Polyalthia longifolia*.

Materials and Methods

P. longifolia was obtained from the research institute. The fresh samples were meticulously cleansed and subjected to many rinses with fresh water in order to separate mud particles adhering to the plant components. The plant roots that were gathered were fragmented into small pieces measuring around 2-3 inches in size and subjected to mechanical grinding to produce a powdered form.

Extraction of the roots:

The crude powder, weighing 600 g was subjected to extraction using a continuous hot percolation method with 3.5 liters of ethanol. This extraction process was carried out using a Soxhlet apparatus. This activity has the potential to be sustained for a duration of up to 20 h. Once the filtration process has been completed, the resulting residue was

subsequently retained within the desiccator (Keservani *et al.*, 2015; Buddhakala *et al.*, 2020).

Acute Toxicity Study and study conditions:

Female adult Wistar rats aged 8-12 weeks were chosen for the study. Animals that had not previously given birth and were not now pregnant were sourced from the centralized animal housing facility. These animals were allowed a one-week period for acclimatization before being subjected to dosing. According to the OECD Guideline-420, the temperature within the animal housing facility is regulated to be at $22^{\circ}\text{C} \pm 3^{\circ}\text{C}$. The animal room is ideally kept at a relative humidity ranging from 50% to 60%, with a preference for not exceeding 70%. The experimental condition has a light-dark cycle with a duration of 12 h of light followed by 12 h of darkness. The cages utilized in this study are constructed from polypropylene material and include solid bottoms and walls. The lids consist of a stainless steel grill that has the capacity to securely contain both food and water. The laboratory animals were provided with *ad libitum* access to sterile feed and water on a daily basis. The feed utilized in this study was a chow diet with a brown coloration (Finkel *et al.*, 2010; Tiwari *et al.*, 2021).

Test Sample administration:

Animals were subjected to a period of fasting before administration of substances (specifically, food is withheld overnight while water is still provided). Following this, the animals were weighed and the test drug was delivered. The rats that were in a healthy state were selected and subsequently separated into four distinct groups. Subsequently, the petroleum ether extract was solubilized in a solution containing 0.6% sodium carboxyl methyl cellulose in equal proportions. The experimental compound is introduced into the subject's system through a solitary administration via oral gavages, employing a stainless steel feeding needle that is curved and has a ball tip (Finkel *et al.*, 2015; Rajesh and Mehta, 2013; Aher *et al.*, 2023).

Sub-Acute of test Sample:

Both male and female rats were chosen and underwent a 5-day acclimatization period before the commencement of the investigation. The female individuals exhibit nulliparity and are not currently gestating. At the initiation of the study, the weight fluctuation seen in the animals utilized was limited and did not surpass $\pm 20\%$ of the average weight for each gender. A preliminary repeated dose oral research was undertaken in preparation for a long-term investigation. It was preferred that animals from the same strain and source were utilized in both studies (Peter Natesan, 2005; Ahirrao *et al.*, 2023).

Study Conditions:

The temperature within the experimental animal room was regulated at 22°C . The relative humidity ranged from 50% to 60%, while the lighting cycle consisted of 12 h of light followed by 12 h of darkness. The animals were provided with a typical laboratory meal and had access to an unrestricted amount of drinking water for the purpose of feeding. The animals were grouped together in tiny cohorts of the same sex. A random assignment was conducted to allocate healthy young adult animals into control and treatment groups. The cages were strategically arranged to minimize potential consequences resulting from the arrangement of the cages. The animals were individually identified and housed in separate cages for a period of five days prior to the commencement of the investigation, in order to facilitate their adjustment to the laboratory environment (Annan *et al.*, 2013).

Test Sample administration:

The administration of leaf extracts was conducted via oral gavages. A total of ten animals were utilized for each dose level of the respective extracts. The experiment included three experimental groups and one control group for each extract. The selection of the maximum dosage level was intended to induce toxic effects without causing mortality or significant distress. Subsequently, a series of decreasing dosage levels

Table 1: Phytochemical screening of *P. longifolia* root

S. No.	Characteristics	Status
1	Glycosides	Present
2	Flavonoids	Present
3	Saponins	Present
4	Volatile oil	Present
5	Tannins	Present
6	Carbohydrates	Present
7	Alkaloids	Present

Table 2: EPLR Impact on Motor Coordination Evaluation

Group	Control	Low dose	Medium dose	High dose
Male	11.33±0.11	13.66±0.88	12.22±0.77	13.02±0.98
Female	11.6±0.43	13.2±0.79	12.33±0.89	11.92±0.77

were chosen in order to illustrate the relationship between dosage and response, as well as to identify any potential detrimental effects that were not noticed at the lowest dosage level. The animals were administered the test chemical on a daily basis for a duration of 28 days, with a frequency of 7 days per week (Malairajan *et al.*, 2008).

Antidiabetic Activity study:

A total of six adult albino rats, with a weight range of 250-300 g, were selected as subjects for the induction of diabetes. The animals were administered an intravenous injection of Streptozotocin at a dosage of 55 mg/kg of body weight. The administration of Streptozotocin results in the rapid onset of diabetes mellitus within a span of three days, primarily by the destruction of pancreatic beta cells. Diabetic animals and a non-diabetic control group were individually housed in metabolic cages, ensuring distinct and controlled conditions for food and metabolism. The concentration of glucose in the bloodstream of rats with diabetes was found to be higher than that of the non-diabetic control group. Food consumption was quantified in grams (g), water consumption was quantified in milliliters (ml), and urine volume was quantified in milliliters (ml) on a daily basis. Additionally, every

2-4 weeks over a span of 80 days, the levels of C-peptide, insulin, and glucose in blood serum were measured. This allowed for the confirmation of chemical diabetes in rats that were injected with Streptozotocin. Diabetes was confirmed 48 h following the injection of streptozotocin. Blood samples were obtained via retro orbital puncture, and plasma glucose levels were assessed using the enzymatic GOD POD diagnostic kit method. This study involved the selection and utilization of rats with fasting plasma glucose levels exceeding 250 mg/dl (Chanda *et al.*, 2011; Ahirrao *et al.*, 2022).

Results

Extraction of the roots:

An equivalent quantity of the measured powder was combined and introduced into the Soxhlet apparatus utilizing ethanol. Once the filtration process has been completed, the resulting residue is carefully preserved in the desiccator.

Preliminary Phytochemical Screening:

The ethanolic extract of *P. longifolia* root (EPLR) extracts underwent numerous chemical tests using conventional methods to identify the different ingredients. The outcome of this phytochemical investigation is presented in Table 1.

Table 3: EPLR oral glucose tolerance test

Group	Blood glucose levels (mg/dl)					
	0 min	30 min	1 st h	2 nd h	3 rd h	8 th h
Control	85.6±1.23	120.2 ± 1.52	160.90±12.58	138±1.085	110.01±6.72	92.4 ±1.304
Glibenglamide	88.1 ±9.23	71.4 ± 9.23	85.1 ±11.36	82.5 ±12.65	80.3 ±8.258	80.2±7.65
EPLR	85.21±2.08	111.2±3.1	142.31±7.62	129.11±6.61	130.13±5.65	124.11±6.2
EPLR 200 mg/kg	86.5 ±6.65	81.7 ±7.23	82.4 ±2.32	91.3±4.357	81.2±2.62	3.2± 3.32
EPLR 400 mg / kg	87.6±1.33	80.1±0.31	78.14±2.01	78.1±1.6	80.6±3.1	81.2±3.3

Toxicity Study:

The acute toxicity experiments conducted on albino rats revealed no instances of mortality when administered a dose of 2000 mg/kg over a 14-day period. During the course of the study, no significant observations were made regarding the rats. This analysis aids in the prediction that the substance under consideration does not exhibit any form of toxicity and can be deemed entirely harmless. For the subsequent investigation, doses of 200 mg/kg body weight and 1000 mg/kg were chosen.

Sub-Acute toxicity:

Functional observations are crucial for evaluating the neurotoxic effects when assessing the toxic effects of intracellular fluid extract (ICFE). The functional observational battery (FOB) is a noninvasive methodology specifically developed to identify significant functional impairments in animals caused by chemical exposure, as well as to provide a more precise quantification of neurotoxic effects observed in previous investigations. The purpose of this battery of tests is not to offer an extensive assessment of neurotoxicity. This tool is intended to be utilized in conjunction with neuropathologic examination and/or general toxicity testing. In order to comprehensively evaluate the neurotoxicity of a medicine, it is imperative to incorporate other functional assessments.

Antidiabetic Activity:

In the oral glucose tolerance test (OGTT), the administration of the EPLR extract at a dosage of

200 mg/kg resulted in a statistically significant reduction in blood glucose levels seen 30 min after the administration of glucose. The medicine Glibenclamide showed consistent action over all studied time intervals (Table 3).

The body weight of the normal control group exhibited a progressive increase, but the diabetes control group consistently showed weight loss. The group of individuals with diabetes who received treatment had a significant increase of 6.25% and 8.24% in comparison to the diabetic control group, bringing their values closer to the normal range.

Discussion

Qualitative research refers to a methodological approach that focuses on understanding and interpreting social phenomena. A phytochemical screening and ethno botanical survey were conducted on the root extracts of *Polyalthia longifolia*, revealing the presence of specific phytoconstituents such as alkaloids, tannins, polysaccharides, glycosides, terpenoids, and a substantial quantity of volatile oils. The anti-diabetic efficacy of phytochemical components, including glycosides, tannins, triterpenoids, flavonoids, and alkaloids, has been observed (Rupal *et al.*, 2011; Kankate *et al.*, 2023).

In order to assess the safety characteristics of the EPLR, an acute toxicity study was conducted. The results of this investigation confirmed the absence of any toxic effects or death at the higher dosage level of 2000 mg/kg. According to the OECD rules of 1996, the EPLR can be categorized

as a safe medicine based on the Global Harmonized Classification System. In the context of toxicity research, a dosage of 200 mg/kg is typically administered as an extract. For sub-acute toxicity studies, an intermediate dosage of 500 mg/kg (equivalent to the initial dosage multiplied by 2.5) and a higher dosage of 1000 mg/kg (equivalent to the initial dosage multiplied by 5) are commonly employed (Muhammad *et al.*, 2012; Keservani *et al.*, 2017; Ahire *et al.*, 2020).

A sub-acute toxicity study was conducted, and the findings indicated that the EPLR substances have a non-toxic character. Furthermore, it is worth noting that all animals in both the control group and the treatment groups, up to a dosage of 1000 mg/kg, exhibited survival throughout the entire 28-day dosing period. The animals in all the groups that received treatment demonstrated similar increases in body weight as the control group during the whole duration of the dosing period.

The administration of streptozotocin is expected to result in a substantial elevation in serum glucose levels as compared to the control group. The treatment of ERLR as well as glibenclamide exhibited considerable efficacy in reversing the elevated serum glucose concentration in rats caused with Streptozotocin. Diabetes mellitus (DM) is an endocrine condition characterized by poor glucose metabolism resulting from the complete loss of insulin due to the destruction of pancreatic beta cells or inadequate release of insulin from beta cells in the pancreas. The primary process responsible for hyperglycemia involves an excessive accumulation of glucose in the bloodstream, along with a reduced use of glucose by the body's tissues. The current study aimed to investigate the potential impact of EPLR extract on antihyperglycemic action in albino rats with STZ-induced diabetes (Bose *et al.*, 2010).

Streptozotocin, a beta cytotoxic compound, has been observed to induce diabetes in various animal species, including rats. This induction occurs through the selective impairment of the

insulin-secreting beta cells in the pancreas. Intraperitoneal injection of streptozotocin leads to the fragmentation of beta cell DNA, which triggers the activation of poly (ADP ribose) and subsequent damage to DNA. Ultimately, this process results in the destruction of beta cells, as evidenced by the clinical manifestation of hyperglycemia. The action of glibenclamide is dose-dependent, since higher doses of the medication have been observed to result in a more fast normalization of blood glucose levels. This effect is attributed to the insulin-releasing properties of glibenclamide (Dasari *et al.*, 2011).

In the current investigation, increased body weight were observed in the diabetic rats treated with EPLR, in comparison to the normal control rats. This finding suggests that EPLR exhibits an anabolic effect on body weight in diabetic rats. Both hyperglycemia and insulin resistance play significant roles in the development of macrovascular problems. Diabetes mellitus is characterized by impaired glucose uptake and metabolism. Hyperglycemia observed in individuals with diabetes has the potential to impede the process of tissue healing inside the macrovascular beds (Pal *et al.*, 2011). The current investigation of the group treated with EPLR demonstrates hypoglycemic activity, hence confirming the existence of anti-diabetic properties. Sulfonylureas, such as glibenclamide, are frequently employed as a reference medication in diabetes models produced by streptozotocin (STZ) to assess the effectiveness of antihyperglycemic agents. The study revealed a notable increase in blood glucose levels within the diabetes control group as compared to the group of normal animals. The group that received treatment demonstrated a noteworthy decrease in fasting plasma glucose levels in comparison to the group of individuals with diabetes who did not get treatment. The basic cause of hyperglycemia in diabetes mellitus is the increased synthesis of glucose through hepatic glycogenolysis and gluconeogenesis (Sharma *et al.*, 2011).

Conclusion

The current study examined the impact of the ethanol extract of EPLR on albino rats with Streptozotocin-induced diabetes. The phytochemical analysis conducted in this study revealed the presence of tannins, carbohydrates, flavonoids, and reducing sugars, which have been identified as the active components responsible for the anti-diabetic properties. The mice were administered STZ intraperitoneally, following which the diabetic animals received oral treatment with EPLR for a duration of 28 days. The results of the present study indicate that the examination of EPLR as protective agents against Streptozotocin-induced toxicity holds promise. Clinical assessments of the EPLR hold promise in elucidating the underlying mechanisms responsible for its protective properties. These intriguing findings warrant further investigation and exploration in the realm of scientific research.

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