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Aqueous Flower Extract of *Mangifera indica*: An Investigation into its *In Vitro* Anti-Diabetic Effects

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Abstract: Type 2 diabetes is the most common form of the disease, affecting 90% of people with diabetes globally. Type 2 diabetes has spread from developed to developing countries. Combining a low-dose oral hypoglycemic medication with a low-dose or even higher-dose of *Mangifera indica* (MI) extract is one approach for treating diabetes mellitus. This combination has various benefits, including controlling blood glucose levels. More adverse effects would occur with an increase in the dosage of the traditional oral hypoglycemic medication. Our study revealed that after 15 days of oral treatment of an aqueous MI extract, rats with alloxan-induced diabetes had noticeably reduced fasting blood glucose levels. Compared to using gliclazide alone, the combination of MI extract with gliclazide considerably lowered the blood glucose level. In this investigation, rats who had developed diabetes due to alloxan were shown to have normal fasting blood glucose levels when MI extract was administered.

Keywords: Anti-diabetic, *Mangifera indica*, Flower extract, *In vitro*, Gliclazide, Type 2 diabetes, Alloxan, Blood glucose, Hypoglycemia

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Introduction

An explanation of diabetes was given over two thousand years ago. It has played an important role in the development of contemporary medicine during the last two centuries. When insulin production is insufficient, either alone or in conjunction with insulin resistance, metabolic abnormalities and inappropriate hyperglycemia manifest as a syndrome. An "iceberg" disease is diabetes (Cardenas *et al.*, 2020). Type 2 diabetes mellitus accounts for 90% of all occurrences worldwide, making it the most common type of diabetes. Regardless of a country's economic status, type 2 diabetes mellitus is a global epidemic. According to projections made by the World Health Organisation (WHO), the number of individuals affected by diabetes is expected to increase from 180 million in 2018 to 300 million in 2025. Predictions made by the World Health Organisation (WHO) indicate that the number of diabetics in India will increase from 19.4 million in 1995 to 57.2 million in 2025. An revised projection puts the number at 80.9 million by 2030. Consistent increases have been observed in the rates since 1970, when the ICMR study indicated a 2.3% urban prevalence and a 1.5% rural prevalence (Nikhal and Mahajan, 2010). While the present prevalence rates in urban Indian people range from 10% to 18%, there is evidence that the prevalence is also increasing in rural populations. An increase in diabetes incidence is being caused by a combination of factors, including a longer life expectancy, a substantial rise in obesity, and an increasingly sedentary lifestyle. Factors such as central obesity, insulin resistance, urbanisation, ethnicity, and inheritance all play a role in this dramatic rise. Worldwide, 1 in 5 persons with diabetes are Indian, and in highly crowded Indian cities like Mumbai, the figure is 1 in 10. Glycemic control through dietary changes, lifestyle modifications, regular exercise, medication (such as oral anti-diabetic drugs), and insulin therapy are the goals of treatment for diabetes mellitus and its complications, including dyslipidemia, hypertension, obesity, coronary heart disease, and neuropathy. Additionally, these complications can

be screened for or managed during treatment (Kumar *et al.*, 2021; Ahire *et al.*, 2023; Najim *et al.*, 2023).

People with diabetes use plants and the bioactive components in them to control their disease. This is especially true in areas where conventional medical therapies are not easily accessible. Several investigations have shown that MI can cause hypoglycemia. MI is a tree that grows naturally in rural and semi-urban parts of India. Globally, it is among the most significant for tropical plant marketing. Its edible fruits have led to its extensive cultivation across Africa, with a focus on the southern areas of Nigeria. People from all around the globe have long relied on MI for its medicinal benefits. These properties can be found in its bark, roots, and leaves. Some of the medical conditions that MI has been found to help with include asthma, coughing, diarrhoea, jaundice, leucorrhoea, pain, and malaria. Researchers in Michigan have detected phenolic components, triterpenes, flavonoids, phytosterol, and polyphenols through phytochemical research. In addition to its many other medical benefits, this species is engineered to decrease inflammation, combat bacteria, strengthen the immune system, shield against oxidative stress, and reduce cholesterol levels (Talele *et al.*, 2021; Salimi *et al.*, 2023; Pathan *et al.*, 2024).

In this study, we used rat models of alloxan-induced diabetes to examine the anti-diabetic effects of MI flower extract both alone and in conjunction with the oral hypoglycemic medication gliclazide.

Materials and Methods

Preparation of Plant Materials and Extractions:

Locally available MI flowers were used in the experiment. The collection of MI flowers was initiated after their identification. The foliage was drained and allowed to dry in the shade. The next step was to use an electric grinder to crush them. The powdered flowers were immersed in water, stirring it every so often as it sat overnight.

Maceration was followed by drying the pulp at a reduced temperature. This inert substance is useful for the experiment because it is an aqueous extract of MI flowers (Fazeli *et al.*, 2020; Sable *et al.*, 2023).

Animals:

The experiment included 36 adult albino rats (both sexes; 200 to 250 g b wt.) with 6 animals in each group. Oral administration of all drugs to the animals was done using a blunted hypodermic needle covered with polythene. For a duration of one week, the animals were housed in a controlled environment that included a temperature range of $25\pm1^{\circ}\text{C}$, a relative humidity level of $60\pm5\%$, and a 12-hour period of darkness after light cycles. Rats were provided with regular pellet food and an endless supply of water (Ahmad *et al.*, 2015; Sable *et al.*, 2023).

Development of type 2 diabetes in rats:

Using alloxan monohydrate, diabetes mellitus was induced. After an overnight fast rats were given intraperitoneally 5% solution of alloxan monohydrate in 0.9% sodium chloride (normal saline). The dosage was 125 mg/kg. After an alloxan injection, the animals were observed closely for the first twenty-four hours to detect hypoglycemia, seizures, aberrant behaviour, or allergic reactions. None of the animals experienced any negative side effects. The induction of diabetes was confirmed by an elevated fasting blood glucose level after the fifth day of alloxan administration. Rats with blood glucose levels above 150 mg/dl were the only ones involved in the study (Keservani *et al.*, 2023; Sable *et al.*, 2023).

Design of experiments aimed at preventing diabetes:

The anti-diabetic trial involved six groups of six diabetic rats. Medications for the alloxan treatment started to be given on day six. Each medication was taken orally once daily, first thing in the morning. We checked blood glucose levels when fasting on days 0, 10, and 15 (Gautam *et al.*, 2015; Keservani *et al.*, 2017).

Blood sample collection and determination of blood glucose:

Glucose levels were estimated by drawing blood from a vein in the rats' tails. Blood glucose levels were determined in all rats after they fasted for one night. The rat tail vein was made more apparent by using xylene, and blood samples were obtained from it. Blood glucose levels were estimated using glucometers and glucose oxidase peroxidase reactive strips (Yadav *et al.*, 2022; Sable *et al.*, 2023).

Results

The The goal of this research was to see how fasting blood glucose levels responded to an aqueous MI flower extract in albino rats that had developed diabetes due to alloxan, either alone or in combination with a standard oral anti-diabetic drug. Six groups of six animals were used for the study, using albino rats weighing 200-250 g each. Each medicine was given orally once day for fifteen days.

Effect of Mangifera indica on alloxan-induced diabetic rats' blood glucose:

Blood glucose levels in alloxan-treated rats peaked on day 5 and remained consistent throughout the trial. The present study showed that fasting blood glucose levels can be dramatically decreased by using an aqueous MI flower extract for 15 days. Using 200 mg/kg MI extract in diabetic rats, the fasting blood glucose levels were 136.0 ± 1.82 on the 10th day and 119 ± 1.91 on the 15th day, respectively as compared to diabetic rats (control) which is 185.2 ± 2.42 and 194.9 ± 3.13 on the 10th and 15th day, respectively (Table 1). On the 10th day, the animals administered 400 mg/kg of MI extract had fasting blood glucose levels of 131.0 ± 1.592 and on the 15th day it was 112.1 ± 1.82 . In comparison, the control group had fasting blood glucose levels of 185.2 ± 2.24 and 194.9 ± 3.13 , respectively on the 10th and 15th day (Table 1). Those administered 200 mg/kg or 400 mg/kg of MI aqueous extract showed a dose-dependent hypoglycemic effect by lowering fasting blood glucose levels, in comparison to the control group.

Table 1: Effect of *Mangifera indica* aqueous extract alone and with gliclazide in alloxan-induced diabetic rats

Blood glucose (mg/dl)	Treatment	0 day	10 th day	15 th day
I	Diabetic rats with gum acacia 5%	188.4± 6.125	185.2± 2.421	194.9 ± 3.135
II	Diabetic rats with MI – 200 mg/kg	179.6± 7.052	136.0 ± 1.826	119.4 ± 1.911
III	Diabetic rats with MI – 400mg/kg	195.8 ± 7.513	131.0 ±1.592	112.1 ± 1.826
IV	Diabetic rats with Gliclazide 2mg/kg	183.2± 4.345	129.3± 1.874	109.2± 1.435
V	Diabetic rats with Gliclazide 4mg/kg	189.3± 6.419	121.7± 2.076	98 ± 1.483
VI	Diabetic rats with Gliclazide 2 mg/kg+ MI – 200 mg/kg	190.8± 7.356	125.0± 2.394	103.1 ± 1.224
F value		0.8201	89.88	186.9
P value		0.752	< 0.0001	< 0.0001

Gliclazide's effect on alloxan-induced diabetic rats' blood glucose:

In rats who developed diabetes due to alloxan, gliclazide significantly decreased fasting blood glucose levels ($p < 0.0001$). On day 10 and day 15, the diabetic control animals' fasting blood glucose levels were 185.2 ± 2.24 and 194.9 ± 3.13 , respectively. In contrast, on day 10 the doses of 2 mg/kg and 4 mg/kg gliclazide produced fasting blood glucose levels of 129.3 ± 1.87 and 121.7 ± 2.07 , respectively. On day 15, the levels were 109.2 ± 1.43 and 98 ± 1.48 , respectively in 2 mg/kg and 4 mg/kg gliclazide treated rats.

Effect of Mangifera indica and Gliclazide on alloxan-induced diabetic rats' blood glucose levels:

Research has demonstrated that the most efficient way to lower glucose levels with Gliclazide is to take a combination of 200 mg/kg of aqueous MI extract and 2 mg/kg of Gliclazide orally for 15 days. On the 10th and 15th day, the fasting blood glucose levels in the combination therapy group were 125.0 ± 2.39 and 103.1 ± 1.22 , respectively. In the 2 mg/kg Gliclazide treated group, the levels on day 10 and day 15 were 129.3 ± 1.87 and 109.2 ± 1.42 , respectively.

Discussion

The worldwide incidence of diabetes mellitus is increasing at an alarming rate hence, there must

be accessible and effective alternatives to conventional medicine. Insulin is a prominent therapeutic agent, however, there are ongoing efforts to produce secretagogues, insulin sensitizers, and synthetic or plant-based insulin alternatives for the treatment of diabetes. Plants and the bioactive components they contain can be a lifesaver for people living with diabetes mellitus in countries where traditional medicines are scarce. Evidence from a number of research supports the hypoglycemic effect of MI (Ybañez-Julca *et al.*, 2020).

In this study, we used albino rats that had developed diabetes due to alloxan to investigate the effects of an aqueous MI extract on fasting blood glucose levels, both when administered alone and in combination with a conventional oral anti-diabetic drug. After delivery, the liver converts alloxan to dialuric acid, which is then concentrated in the islet cells. This acid undergoes a second oxidation reaction with water, this time to alloxan, along with the production of hydrogen peroxide, oxygen gas, and hydrogen radicals. The liver contains enzymes that are capable of scavenging free radicals, including glutathione peroxidase, catalase, and superoxide dismutase (SOD). The low concentration of these enzymes makes islet cells sensitive to free radical cytotoxicity. It has been found that elevating islet

cell SOD activity can mitigate or even eliminate alloxan toxicity (Sable *et al.*, 2023).

Our study revealed that after 15 days of oral treatment of an aqueous MI extract, rats with alloxan-induced diabetes had noticeably reduced fasting blood glucose levels. Combining MI extract with gliclazide resulted in an even greater reduction of blood glucose levels than gliclazide alone (Saleem *et al.*, 2019; Mustapha *et al.*, 2023).

The results of this study are in agreement with those of earlier studies. An ethanol extract of MI flowers was seen to considerably reduce streptozotocin-induced blood sugar levels in both healthy and diabetic rats at 250 mg/kg. In theory, the mechanism of action could entail stimulating the release of insulin by cells. Furthermore, the MI leaf extract showed anti-diabetic effects in rats modelled after streptozotocin-induced diabetes and normoglycemic glucose-induced hyperglycemia (El-Nashar *et al.*, 2024). Glucose, cholesterol, and triglyceride levels were all reduced in rats with alloxan-induced diabetes after 21 days of treatment (Sable *et al.*, 2023). Additionally, levels of biochemical markers of liver damage, including AST, ALP, and ALT, were also found to be lower, indicating that the MI aqueous extract did not have any harmful effects on the liver (Saleem *et al.*, 2019). Recent investigations have shown that a methanolic extract of MI leaves inhibits DPP-IV and increases GLP-1 for type 2 DM (Saleem *et al.*, 2019), suggesting that it could be an interesting candidate for future study into the development of anti-diabetic medications. Human studies utilising type 2 (Nikhal and Dambe, 2010; Mistry *et al.*, 2023).

The necessity of the study was established when patients whose diabetes could not be managed with oral hypoglycemic drugs or in whom these drugs had negative side effects when used in higher dosages. MI flowers, when taken in combination with these drugs, brought glucose levels down to normal. It has been speculated that MI extract has strong antioxidant properties due to its high concentrations of total flavonoids and total phenols. These antioxidant actions may have

mitigated diabetes complications in rats that were alloxan-induced diabetics. It also promotes cell repair and regeneration, increases C peptide levels, and protects cells from oxidative stress. The result is a permanent decrease in the risk of diabetic complications (Sapin *et al.*, 2021; Kumar *et al.*, 2021).

Conclusion

The present study revealed in rats who were made diabetic by alloxan, MI brought their fasting blood glucose levels recovered to normal. The extract reduces fasting blood glucose levels in a dose-dependent manner. Using MI extract in conjunction with gliclazide provided the most effective management of fasting blood glucose levels. The current study concluded that MI extract has hypoglycemic activity, meaning it restores normal fasting blood glucose levels in rats induced with diabetes by alloxan. The chemical compounds responsible for this effect include flavonoids, tannins, steroids, and terpenoids. The aqueous flower extract has a higher concentration of phenols and flavonoids, which have greater antioxidant activity and reduce diabetic complications.

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