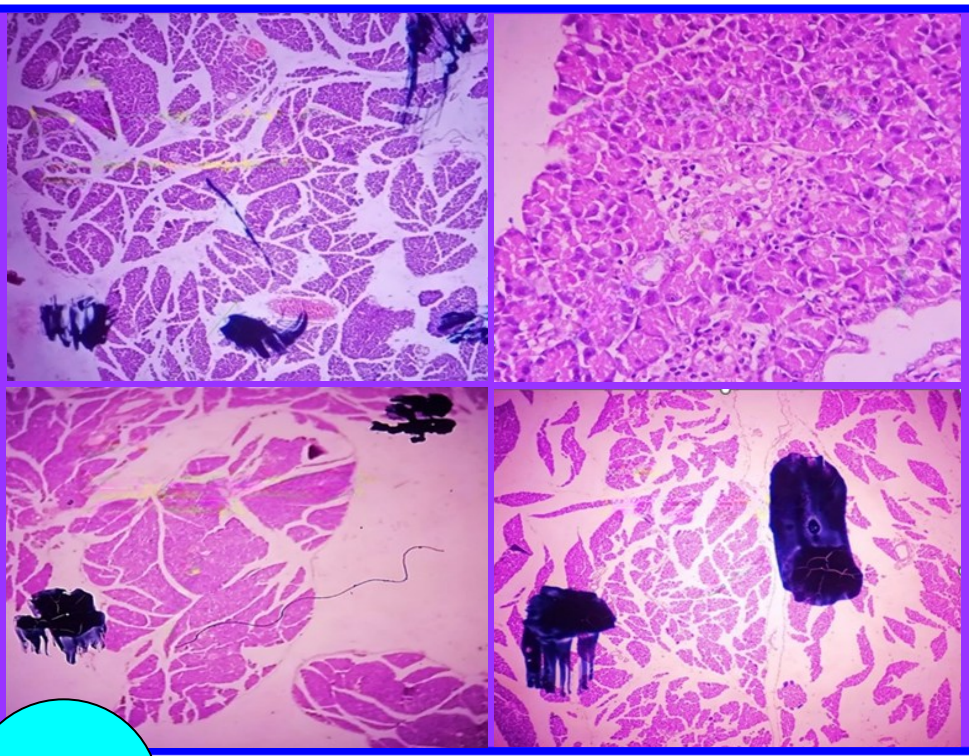

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Hypoglycemic potentials of *Malvaviscus arboreus* leaves against alloxanated albino rats

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Abstract

The study aimed to perform the anti-diabetic potential of leaf extracts of *Malvaviscus arboreus* in an alloxan-treated albino rat model. Various extracts were prepared by ultrasonication-based successive extraction techniques. Six groups of albino rats (n=5 in each group) induced with alloxan received doses of plant extracts (25 mg/kg) or standard (1 mg/kg) for 14 days. Throughout the study, the blood glucose levels decreased. On day 14, *n*-hexane and dichloromethane extracts had mean (± SEM) blood glucose levels of 121.2 ± 2.1 and 91.6 ± 1.3 mg/mL respectively, while the extracts of ethyl acetate and methanol resulted in 119.8 ± 3.6 and 114.6 ± 6.1 mg/mL. The histopathological examination of the pancreas revealed reduced inflammation and congestion in the treated groups. Two-way ANOVA showed the level of significance of extracts of dichloromethane p=0.0002, ethyl acetate p=0.0004, methanol p=0.0058 and *n*-hexane p=0.0003 value. In conclusion, *M. arboreus* extracts show anti-diabetic activity.

Introduction

A metabolic condition, diabetes mellitus, causes excessive blood glucose levels because of problems with insulin secretion, action, or both (Gollapalli et al., 2022). Drugs belonging to classes like dipeptidyl peptidase-4 (DPP-4) inhibitors, biguanides, sulfonylureas, and insulins have been used primarily, but recently, GLP-1 receptor agonist have also been used to treat diabetes mellitus (American Diabetes Association, 2021).

Medicines from natural sources have been used to treat patients with type II diabetes mellitus for a long time because they are safe and less expensive compared to synthetic medicines (Gaikwad et al., 2014). The active component of plant sources is involved in the regeneration of the β cells of the pancreas, the release of insulin, and improving the uptake of glucose. Besides this, the plants that have anti-diabetic activity also have antioxidant activity as well (Prabhakar and Doble, 2011). Multiple diseases may occur if the insulin pathway gets impaired due to the high levels of reactive oxygen species (González et al., 2023). This imbalance causes a wide range of disorders such as cancer, cardiovascular disease, diabetes, aging, liver, and lung diseases (Rajendiran et al., 2018).

Malvaviscus arboreus Cav, a perennial herb, is a medicinal plant that belongs to *Malvaceae* family and is used in the making of herbal dyes, salads, and teas. It is also used to treat various disorders such as fever, diarrhea, tonsillitis, bronchitis, gastritis, dysentery, liver, and kidney diseases (Abdelhafez et al., 2018). The aqueous extract of the leaves of *M. arboreus* has phenols and flavonoids and inhibits the α-amylase and α-glucosidase enzyme activities (Rodríguez-García et al., 2019). This *in vitro* study opened a gateway to further evaluate the hypoglycemic potential of the plant using *in vivo* methodology by focusing on different extracts of different polarities and evaluating the pancreatic

histopathology.

Other members of Malvaceae family, *Abroma augusta,* have been reported to have taraxerol, phenolic compounds, and flavonoids and lower blood glucose levels (Khanra et al., 2015). Similarly, *Malva parviflora* and *Hibiscus sabdariffa* have antioxidant properties and enhance the synthesis of insulin and reduce blood glucose levels (Mohammed et al., 2022) (Mardiah et al., 2014). Another species, *Ceiba pentandra* G is abundant in flavonoids, saponins, resins, terpenoids, glycosides, and tannins, and possesses anti-diabetic activity (Odoh et al., 2016).

Multiple studies have been carried out on different parts of this plant. Red flowers of *M. arboreus* are abundant in flavonoids and phenolic compounds that possess antimicrobial, cytotoxic, anti-inflammatory, and antioxidant potential (Gazwi et al., 2022). The stem of the plant has antifungal activity while the leaves contain antioxidant and antimicrobial activity (Lim, 2014). The anti-diabetic potential was identified by the *in vitro* methodology on the leaves of *M. arboreus* (Rodríguez-García et al., 2019); however, to evaluate the efficacy, more detailed research is required. Therefore, this study uses different extracts to assess the anti-diabetic potential of the leaves of *M. arboreus* using *in vivo* methodology.

Materials and Methods

Chemicals

Alloxan, *n*-hexane, dichloromethane, ethyl acetate, and Tween 20% were purchased from Sigma Aldrich, Germany. Other chemicals such as glibenclamide (Sanofi, France), methanol (VWR Chemicals, North America), DMSO (Duksan Reagents, Korea), and ascorbic acid (Merck, Germany) were used in this study.

Plant material and extraction

The leaves of *M. arboreus* were collected from the Lawrence Garden, Lahore, Pakistan. A taxonomist, Prof. Zaheer-ud-Din Khan (Department of Botany, Government College University Lahore, Pakistan) authenticated the plant. A voucher specimen (GC Herb. Bot. # 3932) was deposited in the herbarium of Government College University Lahore. The collected leaves of plant were dried at room temperature for one week. The dried leaves were crushed into fine powder by a grinding machine. The weight of the leaves was measured at 8 kg. After the procedure was completed, successive extraction was carried out. The extraction sequence was created using an ultrasonic evaporator at four intervals of 10 min, taking into account the polarity of the given solvents, i.e. *n*-hexane, dichloromethane, ethyl acetate, and methanol (Singh et al., 2021). With the use of a rotary evaporator (HEI- VAP series, Heidolph, Germany), all the extracts were dried at a temperature below the solvent's boiling point. The extracts were gathered into storage vials that had been cleaned, tarred, and labeled. They were, then, left to dry in an oven set to 40°C until the solvent evaporated.

In vivo hypoglycemic activity of leaves extracts of *M. arboreus*

Preparation of dosage

The model was created, and the extract dosages were chosen. The normal dose of alloxan ranges from 100-200 mg/kg. The study selected the dosage of 100 mg/kg of alloxan while 25 mg/kg for each extract. The dosage of glibenclamide was 1 mg/kg.

Study design

Healthy albino (both male/female 85-164 g) rats were taken and alloxan (100 mg/kg) was introduced peritoneally, and the study was continued for 14 days. The glucose content of blood samples of all rats was checked (One Touch Ultra, USA) on day 0, day 4, day 7, and day 14. Six groups of rats were introduced. The diabetic control group had no drug, the standard drug had glibenclamide, while extracts of *n*-hexane, dichloromethane, ethyl acetate, and methanol with 25 mg/kg doses were selected. The method was designed to measure the efficacy of the plant in rats. Five rats were introduced in each group and the weight was measured. After measuring the weight of the individual rat, the dose of alloxan was calculated. It was 100 mg/kg. Before administration of the required dose, all rats had remained in a fasting state for 18 hours and the blood glucose level was monitored. Each rat received alloxan through the intraperitoneal route. Normally, alloxan requires 1-2 days to take effect and the experimental subjects may face serious consequences like hypoglycemia. Keeping in view the consequences, dextrose 10% was given to all the subjects as a liquid intake.

Diabetes induction

Fasting blood glucose levels of all the subjects were checked by puncturing the tail vein. The blood glucose level was monitored before and after the administration of alloxan. After analyzing glucose through a glucometer, all the rats had increased glucose levels. Those rats whose blood glucose levels were raised >150 mg/dL were considered diabetic and were ready for administration of solvent extracts. Each model of the rats was given water as liquid intake except for the diabetic control model, which was given dextrose 10% throughout the study.

Dosing with extracts

Out of six groups, one group was used as a control. No drug was administered to the rats present in Group I

until day 14. Four extracts were separated after the separation process. Diabetic rats were selected, and extracts of *n*-hexane, dichloromethane, ethyl acetate, and methanol were administered in their respective groups. Out of six groups, four were given extracts, and dosing was done regularly till day 14. Glibenclamide was administered in one group, and dosing was done on a regular basis. All the extracts were administered through an oral route through a dossier. The rats were housed in cages at a standard temperature in PUCP animal house.

Collection of organs

After 14 days, animals were sacrificed, and the pancreas was separated. For histopathological examination, the pancreas was kept in a 10%formalin solution (Abdul-Hamid and Moustafa, 2013).

The pancreatic tissue was grossly examined and processed in the fixation process to maintain the cellular component and prevent its degradation. The sample was cut and placed into the cassette and numbered individually. These cassettes were kept in formalin 10%. Further processing was done by an automatic machine which replaced the water from tissue with molten paraffin wax. The embedding of the the tissue involved both hot and cold methods where the hot surface of the machine kept the wax as a liquid to manipulate the sample into the mold. The mold was then filled with the liquid paraffin wax and the entire block was rapidly cooled. A microtome was used to cut the thin sections of the tissue. These sections were floated out of the water bath and warm water made sure to maintain the smooth sections of the tissue. These sections were placed on a glass slide. The tissue section on the slide was stained with hematoxylin and eosin. Finally, a thin glass slide was placed over the tissue section for protection and microscopic analysis (Slaoui & Fiette, 2011).

Statistical analysis

To evaluate the level of significance, several tests were applied to the control group and other groups using two-way *ANOVA* through GraphPad Prism (version 8). Mean and standard error were evaluated using SPSS.

Results

Fasting blood glucose levels

Alloxan was administered and the fasting glucose level of all the groups was checked on day 0 (Table I). It was seen that all the values were increased. During the study, a few rats faced severe hypoglycemia, but immediate administration of oral dextrose helped to overcome the severity of the condition. Blood glucose level was monitored on day 4, which showed a significant antihyperglycemic effect of glibenclamide (standard) in comparison to all the other extracts. On day 14, all the extracts showed a significant hypoglycemic effect with the mean (± SEM) blood glucose levels for dichloromethane and ethyl acetate extracts being 91.6 ± 1.3 and 119.8 ± 3.6 mg/mL. While the mean (± SEM) blood glucose levels for *n*-hexane and methanol extracts were 121.2 ± 2.1 and 114.6 ± 6.1 mg/mL, respectively.

The blood glucose level monitoring continued until day 14, and all the extracts showed an antihyperglycemic effect. When two-way ANOVA was applied in comparison of extracts with the diabetic control group, the dichloromethane extract had a significant value of p=0.0002. Ethyl acetate had a significant value of p=0.0004, whereas methanol had a significant value of p=0.0058 and *n*-hexane had a p=0.0003 value.

Histopathological evaluation of pancreas

Histological examination of all the extracts was analyzed, showing no malignancy. The diabetic control group specimen revealed disturbing architecture of pancreatic morphology with severe congestion and mild inflammation. The lobules were formed, which were separated by intralobular and interlobular connective tissue. The drug control group specimen showed mild congestion and inflammation. Intralobular and interlobular connective tissue septa

Table I

Effects of leaf extracts of *M. arboreus* on fasting blood glucose level

	Fasting blood glucose level (mg/dL)			
Extracts	Day 0	Day 4	Day 7	Day 14
Diabetic control	335.0 ± 8.6	281.0 ± 8.1	268.0 ± 8.1	218.4 ± 6.5
Glibenclamide	330.1 ± 6.8	114.5 ± 5.6[a]	102.6 ± 7.0[a]	86.5 ± 3.3[b]
n-Hexane	314.2 ± 3.3	203.0 ± 5.4[a]	133.2 ± 2.6[b]	121.2 ± 2.1[b]
Dichloromethane	299.8 ± 6.1	332.0 ± 9.2	107.8 ± 3.9[b]	91.6 ± 1.3[b]
Ethyl acetate	351.0 ± 8.6	388.6 ± 4.2[a]	136.4 ± 5.7[b]	119.8 ± 3.6[b]
Methanol	318.0 ± 8.0	318.0 ± 8.3	127.8 ± 7.5[a]	114.6 ± 6.1[a]

Data are mean ± SEM; n=5; [a]p<0.01; [b]p<0.01 when compared with diabetic control

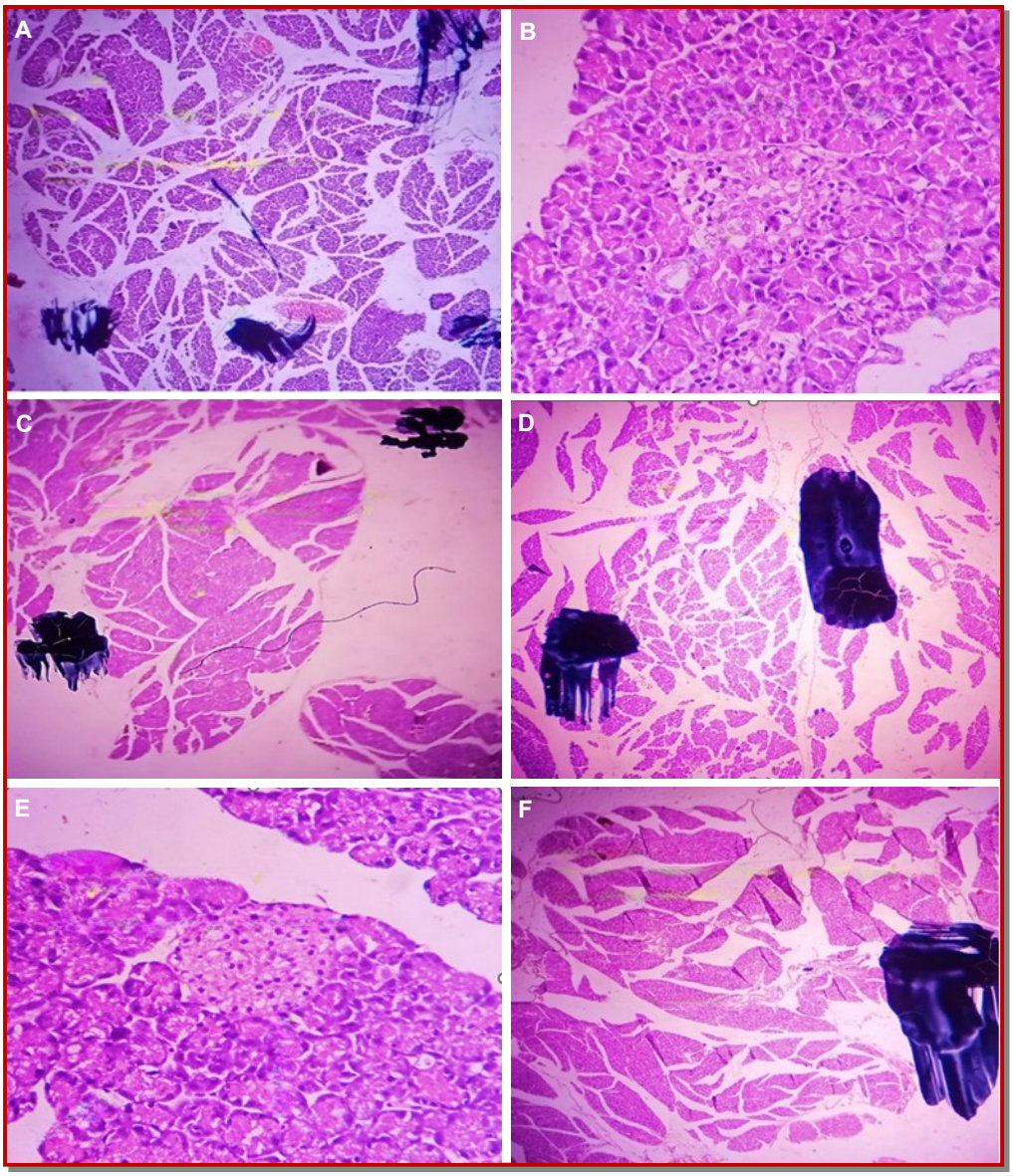

Figure 1: Effects of *M. arboreus* leaf extracts on histopathological changes of pancreas in albino rats in diabetic control (A), drug control (B), *n*-hexane (C), dichloromethane (D), ethyl acetate (E), methanol (F)

separation was visible. *n*-Hexane extract specimen showed division by intralobular and interlobular connective tissue septa in pancreatic lobules. The specimen showed mild congestion and no inflammation. Dichloromethane extract revealed disturbed pancreatic morphology. The acinar cells were swollen, and small vacuoles were observed in all acinar cells. Interlobular congestion was also visible, but there was no inflammation. The ethyl acetate extract specimen also revealed loss or disturbed architecture of pancreatic tissue. The focal area showed interlobular ducts lined by flattened epithelium and mild congestion. Rest areas showed pancreatic lobules separated by intact connective tissue septa. No inflammation was seen. Methanolic extract specimen revealed disturbed architecture or morphology of pancreatic tissue having intermixed pancreatic lobules with moderate congestion and mild inflammation. (Figure 1).

Discussion

The results highlighted the hypoglycemic potential of *Malvaviscus arboreus* leaf extracts in alloxan-induced albino rats. The anti-hyperglycemic effect may be due to increased insulin production or β-cell protection. It was studied that oxidative stress plays a major role in impairing the insulin signaling pathway (González et al., 2023). *M. arboreus* leaves have antioxidant properties (Fahim et al., 2021), which may reduce oxidative stress and improve pancreatic function (Prabhakar and Doble,

2011).

In the current study, *n*-hexane, dichloromethane, ethyl acetate, and methanolic extracts were given for 14 days to alloxan-induced diabetic rats, that showed a decrease in blood glucose levels throughout the study. The maximum hypoglycemic effect was found in dichloromethane and ethyl acetate extracts in comparison with the diabetic control group, as it was observed similarly with *Setaria megaphylla* for the treatment of diabetes induced by alloxan (Okokon et al., 2022).

The anti-diabetic effect may occur due to the oxidation of essential SH groups in β-cells (Sen and Bhattacharya, 1952).

The observed greater anti-diabetic activity of the *n*-hexane extract of *M. arboreus* leaves could be due to the presence of certain bioactive components like flavonoids and non-polar lipophilic compounds such as fatty acids, vitamins, sesquiterpenes, triterpenes, and diterpene as studied previously (Rodríguez-Morales et al., 2021), which may effectively manage postprandial hyperglycemia by inhibiting intestinal α-amylase and α -glucosidase activity (De et al., 2013).

In contrast, the methanolic extract of *M. arboreus* leaves contains several polar bioactive components such as flavonoids, tannins, coumarins, saponins, glycosides, phenols, terpenoids, steroids, anthocyanins, and alkaloids which can reduce oxidative stress. Additionally, the polar flavonoids in the extract have more potential towards anti-inflammatory, antimicrobial, and free radical scavenging activities rather than direct enzyme inhibition. Methanolic extraction of *M. arboreus* leaves showed more scavenging activity due to the presence of phenols (Yeasmin et al., 2014). The hydroxyl groups present in the flavonoids are crucial to exhibit both antioxidant and anti-diabetic activity. Moreover, triterpenes inhibit the polyol pathway during hyperglycemia, resulting in the decrease in the formation of sorbitol and fructose (Sarian et al., 2017; Yin, 2015).

Successive extraction was carried out by dichloromethane on leaves of *M. arboreus* while flowers of *M. arboreus,* yielded flavonoids and phenolic compounds responsible for antioxidants, anti-infective, and hypoglycemic properties (Abdelhafez et al., 2020; Lin and Zhang, 2023). The extraction of *M. arboreus* leaves with ethyl acetate showed a hypoglycemic effect. This effect may occur due to the increase in insulin secretions or by stimulating the uptake of glucose, likely due to the presence of flavonoids and phenolic acids. These active components were also involved in antioxidant properties (Abdelhafez et al., 2018; Olaokun et al., 2016).

Pancreatic histological examination revealed less tissue damage and more preserved pancreatic structure in *n*-hexane extract in comparison to methanolic extract. There was a qualitative decrease in the islets of Langerhans region, which may be due to the presence of flavonoids, terpenoids, and steroids in *n*-hexane extract (De et al., 2012). However, extracts of dichloromethane and ethyl acetate showed disturbed morphology but with a prominent hypoglycemic effect. Both the extracts showed mild congestion. The dichloromethane extract specimen showed small vacuoles, while the ethyl acetate extract showed flattened epithelium. These damages may be reversed if the doses of extract are increased, as discussed in previous studies (Ahmed et al., 2014; Izu et al., 2024).

The overall findings evaluated that the leaves of *Malvaviscus arboreus* possess anti-diabetic activity. The diabetogenic potential could be reversed in alloxan-induced rats due to the inclusion of multiple active compounds found in various extracts (Kannan et al., 2018).

The study is preliminary and focuses on evaluating the hypoglycemic activity of several extracts through *in vivo* method; however it limits the characterization of bioactive components required to evaluate the exact mechanism involved in hypoglycemic activity, which could be further explored through Thin Layer Chromatography.

Conclusion

Dichloromethane and ethyl acetate extracts of *M. arboreus* leaf show a greater anti-diabetic effects than *n*-hexane and methanolic extracts. The histopathological examination of the pancreas indicated the potential to preserve the morphology, which also supported the evidence to reverse the damage induced by diabetes.

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Ethical Issue

The protocol was approved by Punjab University Institutional Ethics Review Board (Diary No. 758).

Conflict of Interest

The authors declare no conflict of interest.

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