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Evaluation of glucose lowering potential of *Murraya paniculata* plant on alloxan-induced diabetic mice

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Abstract

Numerous cultures have a history of using herbal remedies to manage diabetes based on the belief that some plants possess antidiabetic properties with limited adverse effects. *Murraya paniculata* plant displays pharmacological properties that combat several ailments such as diabetes, bacterial infections, cancer, diarrhea and anxiety. This study aimed at phytochemical investigation and the evaluation of the blood glucose lowering impact of *M. paniculata* plant extracts on diabetic mice stimulated by alloxan. 85 % methanolic extract of *M. paniculata* was fractionated using petroleum ether, chloroform and ethyl acetate. Various qualitative chemical assays were conducted to categorize different groups of chemicals in the plant extracts. An oral dose of 500 mg/kg of petroleum ether, chloroform and ethyl acetate extracts from the whole plant of *M. paniculata* was given to alloxan-stimulated diabetic mice for 14 days. Blood glucose levels were measured using a glucometer and compared with non-diabetic mice, alloxan-induced diabetic mice without treatment and diabetic mice treated with metformin. The results of the phytochemical analysis detected various secondary metabolites in distinct fractions of the extract. Also, the study found no statistically significant difference in blood glucose levels among the non-diabetic group, the group treated with metformin and those treated with chloroform or ethyl acetate extract, but the group that received petroleum ether extract treatment exhibited a notable difference compared to the other groups in the study. This study concluded that the ethyl acetate and chloroform extracts of *M. paniculata* effectively regulated blood glucose levels in mice with diabetes caused by alloxan.

Keywords

Alloxan; antidiabetic effect; *Murraya paniculata*; fractionation; qualitative phytochemical screening; soxhlet

Introduction

Diabetes mellitus is an intricate metabolic condition defined by consistently elevated blood glucose levels as a result of insufficient insulin production, insulin resistance or a combination of the two (1). Studies have demonstrated that plants and microorganisms have advantageous effects on the health of humans and other animals. Approximately 80 % of the population, as estimated by the World Health Organization, in underdeveloped nations relies on conventional or folk remedies, primarily derived from plants, for

illness prevention and treatment (2). Numerous cultures have a lengthy history of using herbal remedies to manage diabetes based on the belief that some plants and their extracts possess anti-diabetic properties with limited adverse effects (3, 4). *Murraya paniculata* (L.) Jack (Fig. 1), sometimes referred to as orange jessamine, is a member of the Rutaceae family; the plant is a prominent ornamental species in tropical and subtropical regions (5). This plant possesses many applications in traditional medicine for treating many ailments, such as gastrointestinal discomfort, diarrhea, headache, fluid retention, thrombosis and blood stasis (6). The extract of *M. paniculata* contained alkaloids, flavonoids, triterpenoids, phenols, steroids and carbohydrates (7). The plant displays pharmacological properties that combat several ailments, such as diabetes, obesity, bacterial infections, implantation issues, oxidative stress, cancer, diarrhea, depression and anxiety (8). *M. paniculata* leaf extract shows hypoglycemic effects in circumstances of oxidative stress and non-diabetic states. The hypoglycemic effect may be due to increased insulin activity, which can be achieved by either increasing insulin production from the beta cells of the islets of Langerhans in the pancreas or by promoting the release of insulin from its inactive form (9). When *M. paniculata* extract was administered, blood glucose levels were significantly and dose-dependently lowered, as well as levels of cholesterol, triglycerides and lipids in rats with diabetes. The extract of this plant exhibits notable anti-hyperglycemic and antioxidant properties, which can be linked to its historical use as a dietary supplement for managing diabetes (9, 10). Diabetes is a prevalent condition that affects over 463 million individuals worldwide. It remains a significant issue since it is a leading cause of mortality in wealthy nations (11). The recent surge in the global prevalence of diabetes and its numerous related complications has prompted a greater focus on finding effective therapies for this condition from nature, although the process of synthesizing and gathering secondary metabolites from plants is intricate and influenced by various factors (12-14). In this study a range of qualitative chemical assays were performed to classify distinct chemical groups present in the *Murraya paniculata* extracts. Also assessed the ability of different *Murraya paniculata* plant extracts to reduce blood glucose in diabetic mice stimulated with alloxan.

Fig.1. Photo of *Murraya paniculata* (orange jessamine).

Materials and Methods

Plant materials

The whole *Murraya paniculata* plant, cultivated in Iraq, was collected from a farm in Alhilla in April 2023. Dr. Israa Abdel Razzaq Al Majeed, a specialist from the Department of Biology at the College of Sciences, University of Baghdad, investigated and validated the plant. The plant underwent a thorough cleansing process and was then dried in a shaded area for about one month. The material was first crushed manually and then refined with a mechanical grinder. The sample was subsequently weighed and subjected to extraction techniques.

Plant extraction and fractionation

A quantity of 300 g of dried plant powder was soaked in 1500 mL of n-hexane for 3 consecutive days. The solvent was replaced daily to eliminate chlorophyll, waxes and fatty substances. The plant powder, which had been stripped of its fats, was then placed in a thimble for extraction using the hot method with a soxhlet apparatus. In a round flask, 1500 mL of a solvent consisting of 85 % methanol and water was added and connected to the thimble chamber. Boiling chips were added to the round flask and the mixture was heated on a heating mantle for 16 h. The methanolic extract was filtered using filter paper and then evaporated with a rotary evaporator. The active components were isolated from the solution using solvents with different polarities in a separatory funnel, starting with petroleum ether, then chloroform and finally ethyl acetate. The solvents were combined with the crude extract, which had been suspended in 250 mL of distilled water. This process was repeated for three consecutive days, utilizing 250 mL of solvent each day. The combined volumes of each solvent were then concentrated using a rotary evaporator.

Qualitative phytochemical screening

Three fractions of *M. paniculata* extract (petroleum ether, chloroform, ethyl acetate) were subjected to qualitative analysis by using the standard chemical tests for the identification of many active constituents (Table 1).

Animals

10-12 week-old albino male mice weighing 25–30 g were obtained from the animal facility at Al-Nahrain University College of Pharmacy. The mice were kept in polycarbonate cages with wood shavings as bedding and steel wire tops. The mice were kept in the departmental facility at a temperature of 26 ± 1 °C and had unrestricted access to food and drink. We evaluated the body weight of mice weekly using a digital balance to track any changes in each animal throughout the trial.

Ethical approval

The author (s) obtained and kept the documented ethical approval as per the global norms. (Approval number RE-CA4BC482023S, Approval date 4/8/2023-4/8/2024).

Drugs and Chemicals

The compound Alloxan with the CAS number 2244-11-3 was acquired from Sigma-Aldrich. Metformin with the CAS

Table 1. Chemical assays employed for the detection of active components (15).

Constituent	Test
Alkaloids	Mayer's test: Added a few drops of diluted HCl and Mayer's reagent to 2-3 mL of filtrate, then shook the mixture thoroughly. The occurrence of a yellow precipitate indicated the existence of alkaloids. Dragendroff's test: Added diluted HCl and Dragendroff's reagent to 2-3 mL of filtrate, and then stirred the mixture well. Alkaloids were detected through the observation of an orange-brown precipitate.
Flavonoids	Lead Acetate: A solution of lead acetate was added to 2-3 mL of the extract. The occurrence of a yellow precipitate indicated the existence of flavonoids.
Coumarins	2 mL of the extract was mixed with 10 % NaOH and vigorously shaken for 5 min, resulting in the appearance of a yellow colour.
Steroids	Salkowaski test: 2 mL of chloroform and 2 mL of conc. H_2SO_4 were added to 2 mL of the extract. Upon agitation, the chloroform layer of the solution exhibited a red coloration, while the acid layer had a fluorescence that seemed greenish-yellow, indicating the presence of steroids.
Saponins	Frothing/ Foam test: Combine 0.5 mL of the filtrate with 5 mL of distilled water and vigorously shook the mixture. The continued presence of foaming indicated the existence of saponins.
Phenolics and Tannins	$FeCl_3$ test: Added a small amount of 5 % $FeCl_3$ solution into the extract. The emergence of a dark blue-black color signified the existence of tannins.
Anthraquinone Glycosides	Borntrager's test: The extract was diluted with 3 mL of H_2SO_4. Subsequently, the solution was subjected to boiling and filtration. The filtrate was chilled, and an equivalent volume of benzene was added to it. The solution was thoroughly agitated and the organic layer was subsequently isolated. The organic layer was supplemented with an equivalent amount of diluted ammonia solution. The ammonia layer had a pink coloration, indicating the presence of glycosides.
Cardiac Glycosides	Keller-Kiliani test: 1 mL of conc. H_2SO_4, 2 mL of glacial acetic acid and 1 drop of $FeCl_3$ solution were added to the 5 mL of extract. Cardiac glycosides were detected by the formation of a brown ring.
Quinones	The extract was mixed with 2 mL of conc. H_2SO_4 and vigorously shaken for 5 min, resulting in the appearance of a red colour.
Fixed oils	Spot test: Applied a small quantity of extract, which resulted in the formation of a greasy mark that permeated the paper. This occurred because lipids did not adhere to the paper unlike water, thereby established the presence of oils.

number 1115-70-4 was obtained from Supelco Inc.

Induction of diabetes and treatment protocol

Diabetes was induced in 30 male albino mice by intraperitoneally injecting them with a fresh solution of alloxan in physiological saline. The dosage administered was 150 mg/kg body weight. After 4 h, the mice were administered with a 25 % glucose solution orally, ranging from 0.3 to 0.4 mL, to avert fetal hypoglycemia. On the second day, the same procedure was repeated. Mice with fasting blood glucose levels exceeding 200 mg/dL after 72 h were categorized as severe diabetic (1). Another set of 5 mice was given ordinary water and injected with physiological saline to serve as a control group (G1). 30 mice with diabetes induced by alloxan were randomly allocated into five groups. Each group was administered with the medication once daily for two weeks as follows: Group 2 (n = 5, G2) received oral administration of physiological saline, Group 3 (n = 5, G3) received oral administration of 100 mg/kg of metformin , Group 4 (n = 5) was given an oral dosage of 500 mg/kg of the petroleum ether fraction of *M. paniculata* extract, Group 5 (n = 5) was given an oral dosage of 500 mg/kg of the chloroform fraction of *M. paniculata* extract and Group 6 (n = 5) was given an oral dosage of 500 mg/kg of the ethyl acetate fraction *of M. paniculata extract* (Table 2).

Statistical analysis

The data is presented in the form of Mean ± SD. The statistical analysis of the data was done using one-way ANOVA followed by the Tamhane's Tukey post hoc test. The difference between the means is deemed statistically significant at 5 % confidence level.

Results

Phytochemical analysis

The phytochemical analysis identified numerous phytochemicals, such as alkaloids, flavonoids, coumarins, phenols, tannins, steroids and other secondary metabolites (Table 3).

Effect of plant extracts on blood glucose levels in alloxan induced diabetic mice

The results indicated that there was no significant difference in blood glucose levels between the G1 (non-diabetic control mice without any treatment), G3 (metformin

Table 2. Animal group design and dosage details.

Experimental group	Dose
Group 1 (G1)	Non diabetic control mice without any treatment
Group 2 (G2)	Diabetic control mice without any treatment
Group 3 (G3)	Diabetic mice treated with metformin at 100 mg/kg per day for 14 days
Group 4 (G4)	Diabetic mice treated with petroleum ether extract of *M. paniculata* whole plant at 500 mg/kg per day for 14 days
Group 5 (G5)	Diabetic mice treated with chloroform extract of *M. paniculata* whole plant at 500 mg/kg per day for 14 days
Group 6 (G6)	Diabetic mice treated with ethyl acetate extract of *M. paniculata* whole plant at 500 mg/kg per day for 14 days

group), G5 (chloroform group), and G6 (ethyl acetate group) (p-value > 0.05). However, the G4 (petroleum ether group) showed a significant difference compared to G1, G3, G5 and G6 (p-value < 0.05). Additionally, the G2 (alloxan-only group) exhibited a highly significant difference compared to G3, G4, G5 and G6 (p-value < 0.01) (Table 4 and Fig.2)

Table 3. Qualitative phytochemical analysis of several extracts of *Murraya paniculata.*

Constituent	Chemical test	Different extracts of *Murraya paniculata*		
		Petroleum ether	Chloroform	Ethyl acetate
Alkaloids	Mayer's test	-	+	-
	Dragendroff's test	-	+	-
Flavonoids	Lead Acetate test	-	-	+
Coumarins		-	+	+
Steroids	Salkowski test	+	-	-
Saponins	Frothing/ Foam test	+	+	+
Phenolics and Tannins	$FeCl_3$ test	-	+	+
Anthraquinone Glycosides	Borntrager's test	-	-	-
Cardiac Glycosides	Keller-Kiliani test	+	+	+
Quinones		-	+	+
Fixed oils	Spot test	+	-	-

Table 4. Assessment of blood glucose (Mean ± SD; mg/dL) of various groups in the study.

Group	Mean ± SD
G1 (Non diabetic control mice without any treatment)	88.4 ± 2.07
G2 (Diabetic control mice without any treatment)	364 ± 35.23
G3 (Diabetic mice treated with metformin at 100 mg/kg per day for 14 days)	101.2 ± 4.82
G4 (Diabetic mice treated with petroleum ether extract of *M. paniculata* whole plant at 500 mg/kg per day for 14 days)	149.6 ± 18.20
G5 (Diabetic mice treated with chloroform extract of *M. paniculata* whole plant at 500 mg/kg per day for 14 days)	118.4 ± 2.30
G6 (Diabetic mice treated with ethyl acetate extract of *M. paniculata* whole plant at 500 mg/kg per day for 14 days)	91.4 ± 2.07

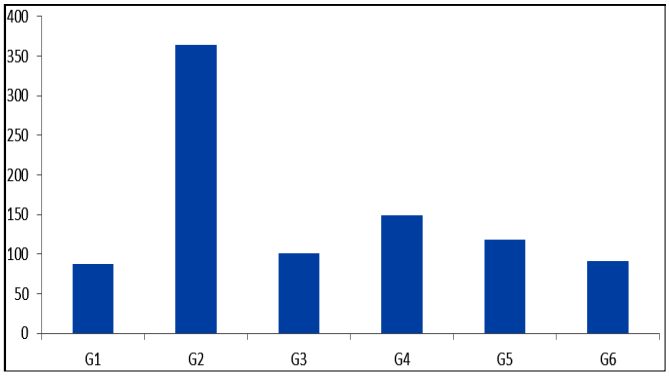

Fig. 2. Displays the mean of blood glucose levels of normal mice without any treatment (**G1**), diabetic mice without any treatment (**G2**), diabetic mice treated with metformin (**G3**) and diabetic mice treated with petroleum ether extract (**G4**), chloroform extract (**G5**) and ethyl acetate extract (**G6**) of *Murraya paniculata* during a 14-day treatment period.

Discussion

Various chemical tests were utilized for the qualitative evaluation of a broad spectrum of secondary metabolites present in the plant extracts (16). From the results, the phytochemical investigation of different solvent extracts of *Murraya paniculata* has identified the presence of diverse secondary metabolites. It was confirmed that the petroleum ether fraction contained steroids, fixed oils and fats, whereas the chloroform fraction showed the occurrence of alkaloids and phenolic compounds. The ethyl acetate fraction exhibited the presence of flavonoids, coumarins, phenols, saponins and other compounds.

Diabetes mellitus, a metabolic illness, presents a substantial health concern worldwide and is acknowledged as a prominent non-communicable disease. This prevalent issue affects the welfare of individuals (17). Medicinal herbs are regarded as an alternative treatment for diabetes mellitus due to their ability to manage glucose levels. Furthermore, numerous plants provide a plentiful supply of bioactive chemicals with powerful pharmacological properties without adverse side effects (18, 19). Alloxan is frequently used to induce type 1 diabetes in animal models (20). In this investigation, the fasting blood glucose level was dramatically increased in normal euglycemic mice following intraperitoneal injection of alloxan. Alloxan has a specific tendency to accumulate in pancreatic beta cells by utilizing the GLUT2 glucose transporter. Inside the cells, thiols such as glutathione, combine with alloxan in a cyclic redox reaction to produce reactive oxygen species (ROS) through its reduction product, dialuric acid. Dialuric acid undergoes autoxidation to produce superoxide radicals and hydrogen peroxide. In the presence of iron, hydroxyl radicals are also generated. Hydroxyl radicals ultimately kill beta cells, which have a limited ability to defend against antioxidants, resulting in a condition known as insulin-dependent alloxan diabetes (21). When orally administered three different extracts of *M. paniculata* (petroleum ether fraction, chloroform fraction, ethyl acetate fraction) with a dose of 500 mg/kg per day in alloxan induced diabetic mice, after 14 days of treatment, the result showed that these three fractions decreased blood glucose levels. However, ethyl acetate and chloroform

extracts significantly decreased blood glucose levels, like the standard drug metformin. Petroleum ether extract could also decrease the blood glucose level with an efficiency less than the other solvent extracts. Oral hypoglycemic medication such as metformin primarily activates AMPK (Adenosine Monophosphate-Activated Protein Kinase) within cells and decreases the rate of gluconeogenesis and glucose output from the liver. Additionally, it decreases the formation of advanced glycation end products and the creation of reactive oxygen species (22). The mechanism through which *M. paniculata* extract induces its hypoglycemic effects may involve augmenting the efficacy of insulin by either enhancing insulin secretion from the beta cells of the islets of Langerhans in the pancreas or promoting the release of insulin from its dormant state (10). Lowered fructosamine and glycated hemoglobin levels were associated with the reduction of blood glucose level caused by the *M. paniculata* extract. It could also alleviate the diabetes-related structural alterations in the kidney, pancreas and liver. *M. paniculata* extract reduces blood glucose levels through multiple mechanisms. It acts similarly to glibenclamide and metformin and its glucose-lowering effect is partly attributed to the inhibition of ATP-sensitive K^+ channels. Thus, the extract showed the potential to use it for the treatment of diabetes mellitus and its related complications (23).

Conclusion

The present investigation concluded that the ethyl acetate and chloroform extract of *M. paniculata* efficiently modulated the blood glucose levels in diabetic mice induced by alloxan, exhibiting similar effects to those of metformin medication. The phytochemical examination of distinct fractions in chloroform and ethyl acetate of the extract of *M. paniculata* detected diverse secondary metabolites. These metabolites could be accountable for the reported antidiabetic effects. Finally, the results of this study also indicated that *M. paniculata* may be a reservoir of many potent hypoglycemic agents. In the future, this study will need to enlarge its sample size, take longer to confirm the impact precisely, and demonstrate any active ingredient in *Murraya paniculata* that is responsible for the effect.

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Authors' contributions

The authors confirm contribution to the paper as follows: study conception and design; data collection; analysis and interpretation of results by Zainab Ali Qasim and Amjed Haseeb Khamees. All authors reviewed the results and approved the final version of the manuscript

Compliance with ethical standards

Conflict of interest: The authors declare no conflict of interest.

Ethical issues: According to international standards, the author(s) received and maintained the documented ethical approval. (Approval number RECA4BC482023S, Approval date 4/8/2023–4/8/2024) from the Baghdad University/College of Pharmacy.

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