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Pharmacology and Pharmacotherapeutics OPEN ACCESS JOURNAL

DOI: https://dx.doi.org/10.17352/ojpp

Research Article

To evaluate the anti-diabetic effects of *Salvia cabulica* ethanolic extract on alloxan-induced diabetic rabbits

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Received: 06 July, 2022
Accepted: 18 July, 2022
Published: 19 July, 2022

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Keywords: Allaxone monohydrate; Balochistan; Diabetes mellitus; Hypoglycemic; Rabbits; *Salvia cabulica*

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Abstract

Objective: This study aimed to investigate the hypoglycemic effects of *Salvia cabulica* ethanolic extract on alloxan-induced diabetic rabbits.

Method: During the plant's extraction, the dried plant was soaked in ethanol for 14 days at room temperature and filtered. The dark green gummy filtrate was obtained by using a rotary evaporator at 40°C. Rabbits with fasting glucose levels of more than 250 mg/dL were considered diabetic. These rabbits were treated with aqueous plant extract in different doses (250 mg and 500 mg) respectively.

Results: The fasting blood glucose level (BGL) mean was 293 ± 25.65 in diabetic control group D-I compared to the normal control group A 99 ± 6.16 after the 48 hours of diabetes induction. The fasting blood glucose level (BGL) in group D-II was 192 ± 17.06, group D-III 93.515.95and group D-IV was 89.33 ± 7.79.

There was a significant decrease in blood glucose among the group III and IV treated with plant extract at 250 mg/kg and 500 mg/kg, respectively

Conclusion: The plant *Salvia cabulica* has potential hypoglycemic activity. Therefore, the medicinal plant can be used as a folklore herbal drug in the treatment of diabetes locally.

Introduction

Diabetes is a chronic metabolic syndrome marked by high blood glucose levels (BGL), which can cause catastrophic damage to the heart, blood vessels, eyes, kidneys, and nervous system over time. Type 1 diabetes, or insulin-dependent diabetes, is a chronic disease in which the pancreas cannot synthesize enough insulin. Type 2 diabetes, which affects mostly adults and arises when the cells develop insulin resistance or do not produce enough of it, is the most common. Type 2 diabetes has become much more common worldwide during the last three decades [1].

According to IDF Diabetes Atlas 2021, Diabetes prevalence among adults aged 20 to 79 was expected to be 10.5% (536.6 million) in 2021, rising to 12.2% (783.2 million) in 2045. Male and females had similar rates of diabetes, with those aged 75 - 80 years having the high rates. Prevalence was expected to be higher in urban (12.1%) than rural (8.3%) areas in 2021 and in high-income countries (11%) than in low-income countries (5.5%). Between 2021 and 2045, middle-income nations are anticipated to have the highest relative growth in diabetes prevalence (21.1%), followed by high-income (12.2%) and low-income (11.9%) countries. In 2021, global diabetes-related health expenses were forecast to be USD 966 billion; by 2045, they are expected to be USD 1054 billion [2].

Citation: Ghaffar A, Marvi, Younis M, Wahid A, Muhammad S, et al. (2022) To evaluate the anti-diabetic effects of *Salvia cabulica* ethanolic extract on alloxan-induced diabetic rabbits. Open J Pharmacol Pharmacother 7(1): 007-012. DOI: https://dx.doi.org/10.17352/ojpp.000020

In a meta-analysis study conducted on the prevalence of diabetes in Pakistan comprising 635 studies, the prevalence of diabetes in Pakistan was found to be 14.62 % [3]. The prevalence rate of diabetes is high in females (51.2%) than in males (48.8%). The findings revealed substantial variations between age groups (p - value 0.0001). The age group 41 - 60 years old had the highest percentage of patients (44.3%), while the age group 10 - 20 had the lowest percentage of patients (10.1%) (5.2 percent) [4].

In treating diabetes, nonpharmacological therapies such as a good diet, frequent physical activity, and weight loss are critical [5]. Pharmacologically, for treating diabetes, Insulin preparation, sulfonylureas, glinides, biguanides, thiazolidinedione, -glucosidase inhibitors, dipeptidyl peptidase-IV inhibitors, sodium-glucose transporter-2 (SGLT-2) inhibitors, and sodium-glucose transporter-3 (SGLT-3) inhibitors are all examples of pharmacological therapy used to treat diabetes [6]. Before the development of insulin therapy in 1921, medicinal plants were utilized to treat diabetes mellitus [5].

Herbal medications have attracted health practitioners and patients to use them for the treatment of diabetes due to their fewer side effects and low cost. Furthermore, plant-based hypoglycemic medications are gaining popularity around the world. For the treatment of DM, humans have used folkloric medicine derived from plants since ancient times [7].

According to the most recent data on traditional applications of medicinal plants in the Kalat and Khuzdar districts of the province of Balochistan, Pakistan, 61 species belonging to 56 genera and 34 families have historically been utilized by local people to treat a variety of ailments. Family Lamiaceae has the most species of medicinal plants (9 species), followed by families Asteraceae (7 species), Solanaceae, Papilionaceae (Leguminosae), and Zygophyllaceae (3 species) [8].

Salvia is one of the largest genera in the Lamiaceae (Labiatae) family, *Salvia* has 900 species and is extensively dispersed worldwide, including in America, Europe, and Asia. *Salvia* species have long been used in traditional medicine for various purposes. Due to its documented pharmacology and therapeutic activity in various Asian and Middle Eastern nations, particularly China and India, some studies suggest that sage species can be considered for drug development. Salvia species may potentially offer unique natural remedies for the relief or cure of many prominent and life-threatening disorders, including diabetes, depression, dementia, obesity, heart disease, lupus, and cancer, in addition to treating minor common illnesses [9].

Medicinal plants have considerable importance in the local community of Balochistan for their local uses for the prevention and cure of ailments. The geographically southwest region of Balochistan is replete with herbal medicinal plants. Folk use of naturally occurring plants is declining due to poor scientific studies and awareness, safe and effective uses, and toxicity. Therefore, the present study was designed to assess the potential of *Salvia cabulica* for antidiabetics.

Materials and methods

Chemicals and equipment

The chemicals used in the current experimental study were of standard. Alloxan monohydrate (98%) Lot No.8CBT8818 was obtained from Sigma Aldrich pharmaceuticals. Glimepiride (Amaryl, Sanofi Aventis) tablets were purchased from the local market. The Department of Pharmacology, FP&HS, University of Balochistan, Quetta provided ethanol, de-ionized water, and other chemical reagents. Glucometer (Medisign MM800 Auto) and strips with Lot No AUF03Z2C1 were purchased locally (Shanghai International Holding corp. GmbH Europe). Rotary evaporator (RE200, UK), glass wares, and all other equipment were provided by the Department of Pharmacology, FP&HS, University of Balochistan Quetta.

Plant material

The *Salvia cabulica* plant was collected from the hilly areas of Mangocher district Kalat of Balochistan, Pakistan. The whole plant was comprised of leaves, stems, and bark. Department of Pharmacognosy identified the plant, FP&HS, University of Balochistan Quetta, and the plant specimen was submitted to the department for future reference.

Taxon id no. 250090579 according to the flora of Pakistan.

Preparation of *salvia cabulica* plant extract

For the preparation of ethanol extract, the collected plant sample was washed with tap water and air-dried for three weeks. Then the dried plant material was minced and homogenized thoroughly. For the extraction process, the weighed quantity of dry plant was soaked in ethanol for 14 days at room temperature and filtered. The dark green gummy filtrate was obtained by using the rotary evaporator at 40°C. [10].

Animals

Albino rabbits weighing 800g–2000g were arranged from CASVAB and fed with a normal diet and water. The animals were kept for a 7-day acclimatization period in the animal house, Department of Pharmacology, University of Balochistan, Quetta.

Experimental design

The present study was an experimental study conducted on albino rabbits. A total of thirty rabbits were used and divided into five groups, each comprising 6 rabbits. Group A was considered the control group that received a normal diet and water, while the other four groups were diabetic as Group D-I, Group D-II, Group D-III, and Group D-IV administered allaxone monohydrate at a single dose of 100 mg/kg/BW intravenously. Group D-II and D-III were treated with extract of *Salvia cabulica* at the dose of 250 and 500 mg/kg/BW, respectively, and Group D-IV with glimepiride at the dose of 40 mcg/kg [11] Figure 1.

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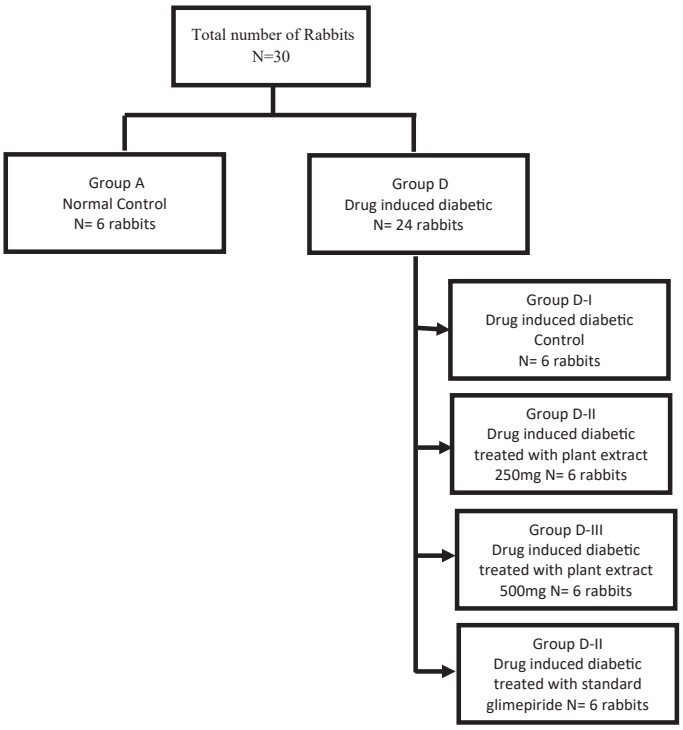

Figure 1: Flow chart of study groups.

Induction of diabetes in albino rabbits

All albino rabbits were housed in a clean cage at 25°C ± 1 and 54 ± 5% humidity, with a twelve-hour light-dark cycle. Animals were provided lab food and water. All rabbits were divided equally into experimental and control groups. After one week of acclimatization, all rabbits were fasting for 12-hrs. Diabetes was induced by injecting freshly prepared alloxan monohydrate (98%) in distilled water with an injection of 100 mg/kg (I.V) in the experimental groups. After 48 hours of injection, fasting blood glucose was measured. The rabbits with fasting BGL higher than 250 mg/dl were considered diabetic and used for the study [12].

Statistical analysis

The mean ± S.D values analyzed for the data obtained in the present investigation were calculated for each group. The data were analyzed by one-way analysis of variance (ANOVA) by unpaired student t-test. A value of $p < 0.05$ was considered significant.

Results

Oral toxicity test

In oral toxicity test, plant extract was given in four different doses i-e 500 mg/kg, 1000 mg/ kg, 1500 mg/kg, and 2000 mg/kg to the designed group of normal rabbits. All the extracts treated rabbits did not show any sign of toxicity during the study period. No mortality and coma were observed for up to one week. Plant extract-treated rabbits had normal food and water consumption compared to the control. Results indicated that the plant extract was harmless to a dose level of 2000 mg/kg. Results for oral toxicity are shown in Table 1.

Assessment of the hypoglycemic effect of salvia cabulica extract

In this experiment, 48 hours after inducing diabetes, the mean + standard deviation of fasting BGL had significantly increased in drug-induced diabetic group D up to 293 ± 25.65 compared to the normal control group A 99 ± 6.16. Oral administration of plant extracts 250 mg to group D-II, 500 mg to Group D-III, and 40mcg of standard drug glimepiride to group D-IV significantly decreased the fasting BGL to 122.33 ± 15.88, 105.6 ± 6.28, and 118 ± 7.43, respectively. The results demonstrated that orally administered plant extract with a high dose of 500 mg/kg significantly reduced the fasting BGL as shown in Table 2 and Figure 2.

Effects on blood urea, creatinine, and uric acid

The results of this study found no significant change in serum urea, serum creatinine, and uric acid throughout the experiment as shown in Table 3. *Salvia cabulica* extract had no toxic effects on renal functions and muscular systems in test animals. According to Jones "mean normal value of serum urea in rabbits is 42-80 ml/100ml " [13]. Mean normal value of serum uric acid in rabbits is 0.42 mg/dL as reported by Özkan Ö, Pekkaya S. [14].

Discussion

Our result for the oral toxicity test indicated that the extract of *salvia cabulica* was harmless up to a dose of 2000 mg/kg, consistent with another study conducted in Pakistan. The author reported that *salvia cabulica* extract up to a dose of 2000 mg/kg was safe for in-vivo use in rodents [15]. Furthermore, the result of the present study shows no significant changes in blood urea, uric acid, and creatinine level before and after the experiment. Hence salvia cabulica has no toxic effect on the renal system and muscular system and slight weight loss were observed in the experimental animals [16].

The finding of the current study of salvia *cabulica* extract in diabetic rabbits resulted in a significantly decreased concentration of BGL. The *salvia cabulica* extract had shown a highly marked reduction of fasting BGL at a dose of 500g/kg when orally administered to diabetic rabbits. Similar findings were reported in a study conducted by Zarei, et al. which found that plant extract had markedly declined the blood glucose in alloxan-induced diabetic rabbits when administered via the

Table 1: Oral toxicity test of salvia cabulica extract in rabbits.

Group	Dose of extracts	Behavioral changes	Diarrhea	Coma	Mortality	Survival
I	N/S 5ml/kg	-	-	-	-	All
II	Plant extract 500mg/kg	-	-	-	-	All
III	Plant extract 1000mg/kg	-	-	-	-	All
IV	Plant extract 1500mg/kg	-	-	-	-	All
V	Plant extract 2000mg/kg	-	-	-	-	75%

N/S; Normal Saline; Kg; Kilo Gram; mg; milli gram

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Table 2: Comparison of fasting blood glucose levels in different groups using different doses of ethanol extract of salvia cabulica and standard.

BGL at a time interval	Group A Control/ Normal	Group D-I Diabetic Control	Group D-II extract treated at 250mg	Group D-III Drug treated 500mg	Group D-IV standard drug treated
0 hours	104±5.43	113±8.45	122.33±15.88	105.6±6.28	118±7.43
48hours	99±6.16	293±25.65*	276±35.09	282.83±21.67	275.83±35.09
7days	101.17±9.81	294±19.15*	263±27.92	262.5±27.79	262.5±27.99
14 days	106.3±6.5	305±16.68*	216±28.09**	116.17±28.09***	104±4.90$^{\lambda}$
21 days	109.17±11.20	304.83±9.83*	192±17.06**	93.515.95***	89.33±7.79$^{\lambda}$

Significant *p* - value = <0.05
* *p* - value is significant between normal and diabetic control
** *p* - value is significant between diabetic control and extracts treated with 250mg
*** *p* - value is significant between diabetic control and extracts treated with 500mg
λ *p* - value is significant between diabetic control and standard drug treated

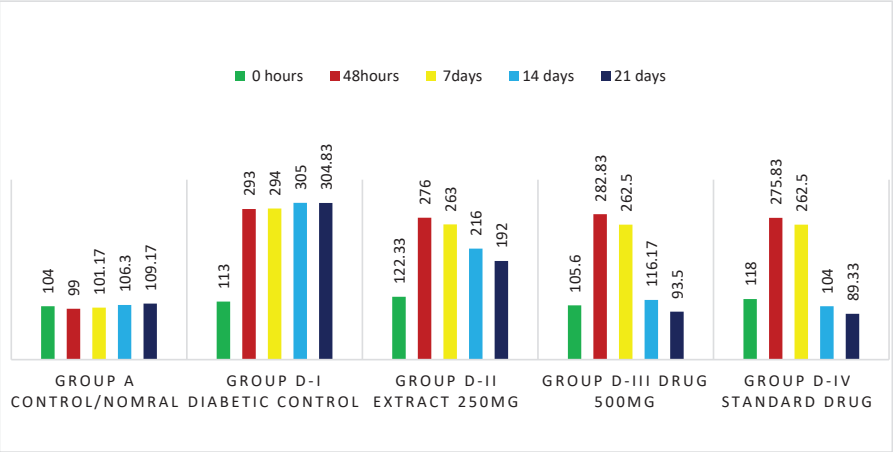

Figure 2: Blood glucose level in different groups using different doses of ethanol extract of *salvia cabulica* and standard glimepiride.

Table 3: Effects of *Salvia cabulica* extract on blood uric acid, creatinine and urea in diabetic and control rabbits.

Groups	Uric acid(mg/dL)		Creatinine(mg/dL)		Urea(mg/cm^2)	
	Before experiment	After experiment	Before experiment	After experiment	Before experiment	after experiment
Normal control	0.29 ± 0.11	0.33 ± 0.16	1.13 ± 0.31	1.0 ± 0.28	77.33 ± 5.27	78.67 ± 7.99
Diabetic control	0.41 ± 0.31	0.78 ± 0.11*	1.32 ± 0.33	1.4 ± 0.31	78.67 ± 5.0	83.00 ± 5.01
Diabetic rabbits treated with Plant extract 250mg/kg	0.32 ± 0.16	0.27 ± 0.05	1.02 ± 0.32	0.95 ± 0.33	73.33 ± 5.95	71.17 ± 6.73
Diabetic rabbits treated with Plant extract 500mg/kg	0.24 ± 0.06	0.20 ± 0.05	0.96 ± 0.35	0.78 ± 0.20	72.83 ± 7.62	70.17 ± 5.49
Diabetic rabbits treated with Standard drug	0.30 ± 0.09	0.25 ± 0.7	0.88 ± 0.22	0.83 ± 0.61	75.00 ± 6.16	73.33 ± 6.34

oral route [10]. another study conducted by Nyingi Wambua & Mburu, 2021 [17] found that *Salvia hispanica L.* (Chia) seeds are packed with nutrients that help prevent diseases like diabetes, hypertension, cancer, obesity, and heart disease. *Salvia hispanica L.* seeds provide essential health benefits since they include omega-6 and omega-3 fatty acids and other active substances [17]. Similarly, a study was conducted on the impact of *Salvia Spinosa L.* on mitochondrial activity and its ability to protect people with diabetes. The result of this study depicts that *Salvia Spinosa* significantly decreased creatinine and blood urea levels while also bringing the kidney weight/body weight back to normal position. In histological investigations, Salvia. Spinosa extract reduced the frequency of glomerular and tubular degenerative alterations [18]. Accordingly, a study was conducted on another specie of *Salvia* (*Salvia Officinalis L.*) on mice for antidiabetic effect. The results of this study indicate that hot extract of *salvia Officinalis* has decreased blood glucose levels [19]. With reference to another study conducted on human diabetic patients for investigating the hypoglycemic effect of *Salvia officinalis* on blood glucose, lipid profile, glycosylated hemoglobin (HbA1c), liver, and kidney function tests. Results indicated that *Salvia officinalis* significantly reduced cholesterol and 2-hour postprandial (2hpp) glucose levels in diabetic patients [20].

Iranian *salvia* has historically been used as a sedative, anxiolytic, hypnotic, analgesic, digestive aid, antibacterial, pain reliever, and antidiabetic. Antidiabetic, antioxidant, antibacterial, cytotoxic, and anti-inflammatory effects are among the most significant pharmacological actions. The indigenous species that are most interesting for human

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health are those that can treat a wide range of illnesses [21]. In another study conducted on *Salvia syriaca*, the results showed its antidiabetic, anti- Alzheimer's, and antioxidant properties [22]. The phytochemical composition of the plant's methanolic extract and essential oil was determined using reverse-phase high-performance liquid chromatography diode array detector techniques and gas chromatography-mass spectrometry. Cytotoxic solid, antioxidant, α-amylase, and α -glucosidase inhibitory properties were displayed by *S. Syriaca* essential oil. The main constituents of essential oil, according to a gas chromatography-mass spectrometry investigation, are spathulenol (87.4%), isospathulenol (7.6%), and bornyl acetate (2.7%). According to a high-performance liquid chromatography examination, the most prevalent phenolic components are rutin, quercetin, apigenin, rosmarinic acid, and ferulic acid. S. Syriaca may provide a valuable source of bioactive natural chemicals for pharmacological, medicinal, and functional food applications .similarly, our study results depict glucose lowing effects and similarity of geographical distribution and phytochemical as per mention in the mention above study [22].

Conclusion

The current study investigates the effect of medicinally important plant *salvia cabulica* extract as an antidiabetic agent and safety up to 2000gm/kg bodyweight in alloxan-induced rabbits. The results show that plant extract has no toxic effects on the kidney and muscular system as no significant changes were observed in the results. Herbal medicines have an excellent potential to reduce diabetes in alloxan-induced rabbits. *salvia cabulica* plant extract controls diabetes in alloxan-induced diabetic rabbits at 250 mg/kg and 500 mg/kg respectively as compared to diabetic control. The fasting BGL reduced significantly in rabbits when administered orally at the dose of 500 mg/kg daily for the period of one month and slight body weight gain was observed at the end of the experiment. Therefore, the medicinal plant can be used as a folklore herbal drug in the treatment of various diseases especially diabetes locally.

Recommendation

Future research may be conducted on the exact mechanism of *Salvia Cabulica's* impact on blood glucose reduction in diabetic rabbits and patients. Further scientific studies are required to ensure the folklore use of medicinally important plants of Balochistan.

Ethical approval

Ethical approval was taken from the ethical committee of research and animal Department of Pharmacology, FP&HS, university of Baluchistan, Quetta.

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