

Evaluation of Antidiabetic and Antioxidant Potential of Hydromethanolic Seed Extract of *Datura stramonium* Linn (Solanaceae)

This article was published in the following Dove Press journal:
Journal of Experimental Pharmacology

Bamlaku Cherie Melaku
Gedefaw Getnet Amare 

Department of Pharmacy, College of
Medicine and Health Sciences, Wollo
University, Dessie, Ethiopia

Background: Nature has gifted a variety of phytochemicals having a potential effect against diabetes mellitus. *Datura stramonium* has been used as a remedy for the treatment of diabetes mellitus. The study aimed to determine the in vivo antidiabetic potential of hydromethanolic seed extract of the plant.

Methods: Dried seeds of *Datura stramonium* were macerated in hydromethanol. Three doses (100, 200, and 400 mg/kg) of the seed extract were given orally to normoglycemic, glucose-loaded, and Streptozocin-induced diabetic mice. Diphenyl-1-picrylhydrazine (DPPH) assay was employed to determine antioxidant activity of the seed extract.

Results: All doses of hydromethanolic seed extract of *D. stramonium* were devoid of any significant hypoglycemic effect in normoglycemic mice compared to the negative control group. Acute glucose reduction was significant ($P < 0.05$ at 100, $P < 0.01$ at 200 and 400 mg/kg) with respect to negative control in oral glucose-loaded mice. All doses of seed extract significantly ($P < 0.01$) reduced blood glucose level on weeks 1 and 2 in STZ-induced daily-treated diabetic mice. The seed extract at the doses of 200 and 400 mg/kg significantly ($P < 0.05$) improved the body weight of diabetic mice on weeks 1 and 2. A low (100 mg/kg) dose of the seed extract delayed and significantly ($P < 0.05$) increased body weight of mice on week 2 compared to negative control. The finding showed that the antioxidant activity of the hydromethanolic seed extract was concentration dependent and comparable with ascorbic acid. IC50 of the seed extract and ascorbic acid was found to be 11.95 and 5.07 mg/mL, respectively.

Conclusion: The findings of the study showed that hydromethanolic seed extract of *Datura stramonium* endowed significant antihyperglycemic and antioxidant activity.

Keywords: diabetes, Streptozotocin, *Datura stramonium*, antioxidant, mice

Background

Diabetes mellitus has emerged as a global life-threatening metabolic disorder characterized by hyperglycemia due to impaired insulin secretion or action.^{1,4} Insulin resistance causes the development of life-threatening complications including hypertension, dyslipidemia, and atherosclerosis.⁵ The prevalence and burden of diabetes mellitus is very high in the world. In 2017, 425 million people live with diabetes and this number will increase to 629 million in 2045. Among all types of diabetes mellitus, type 2 diabetes contributes greater than 90%.⁶ Glucose homeostasis is maintained through phosphatidylinositol 3-kinase (PI3K), adenosine monophosphate kinase (AMPK), and peroxisome proliferator-activated receptor- γ (PPAR- γ) signal

Correspondence: Gedefaw Getnet Amare
Wollo University, Dessie 1145, Ethiopia
Tel +25 191 1737428
Email gedefawg39@gmail.com

transduction pathways. Phytochemicals play a vital role in glycemic control through modulating of PI3K, AMPK, and PPAR- γ signal transduction pathways.^{7,9}

Nature has gifted a variety of vital phytochemicals having a potential effect against diabetes mellitus. A modern antidiabetic drug (metformin) has been isolated from medicinal plants.^{10,11} In recent years, many plant species have shown promising effects against diabetes mellitus. For instance, Catechol glycoside esters, isolated from the leaves of *Dodecadenia grandiflora* and protodioscin isolated from the seed of fenugreek showed a very good effects on blood glucose level.^{9,12} *Moringa stenopetala* and *Aloe Vera* offer useful and promising evidence for the development of plant-based antidiabetic drugs.^{13,15}

Datura stramonium is belonging to the genus *Datura* and family Solanaceae. Even though *D. stramonium* originates in America, nowadays the plant is widely distributed throughout the world, including Ethiopia. The plant is a widespread annual plant and grows to 1.2 m high. The root of the plant is long, thick, fibrous, white, and the stem is stout, erect, leafy, smooth, and pale yellow-green (Figure 1).^{16,17}

The seeds of *Datura stramonium* contain amino acids (alanine, glutamate, phenylalanine, and tyrosine) along with numerous other phytochemicals, for instance, alkaloidal drugs including scopolamine, atropine, and hyoscyamine.^{18,21}

Various studies showed that *Datura stramonium* endowed antiepileptic, anti-obesity, anti-microbial, anti-



Figure 1 Picture of *Datura stramonium*.

viral, anticholinergic, and bronchodilator activities.^{18,20,22,23}

Hydromethanolic, the root extract, endowed significant anti-diabetic and antidyslipidemic activity in mice.²⁴ In another study, methanolic, the seed extract of *D. stramonium*, revealed higher (94.56%) α -amylase inhibitory activity, despite a lack of in vivo investigation.²⁵ The plant has been used as a remedy for the treatment of diabetes mellitus and others diseases.²⁶ These pertain to determine the antidiabetic potential of hydromethanolic seed extract of *Datura stramonium* in STZ-induced type 1 diabetic model.

Methods

Drugs, Chemicals, and Instruments

Streptozotocin (Sigma Aldrich, Germany), glibenclamide (Julphar Pharmaceuticals), 80% methanol, FeCl₃ (MA, USA), NaOH (India), HCl (Supperetek Chemical), 40% glucose solution (Shandong, China), Lyophilizer, i-QARE DS-W[®] blood glucose meter, and test strips (Alliance International, New Taipei City, Taiwan), scissors, mask, animal cages, insulin syringe with needle, oven, and desiccators were used in this experimental study.

Plant Material Collection

The seeds of *D. stramonium* were collected from Wollo in October 2019. Plant identification was carried out and the specimen of the plant material was deposited in Wollo University with the specimen voucher number GG-004/2019.

Preparation of Plant Extract

The seeds were washed with distilled water, dried under shade, and then dried seeds were reduced into coarse powder by using an electric mill. The coarse powder of the seed (200 g) was maceration in hydromethanol. After 72 hours, filtration was carried out by using white cotton gauze and Whatman filter paper No.1. The marc was re-macerated twice in hydromethanol for 72 hours and then filtered again. The filtrates were collected and concentrated using a rotary evaporator under reduced pressure at 40°C. Methanol was evaporated in an oven at 40°C and the water was removed by using a lyophilizer. The dried seed extract was kept in a clean and dry vial, then stored in a desiccator until used for the experiment.

Experimental Animals

The mice were obtained from Wollo University pharmacology department and were handled in a 12 hour light-dark cycle with pellet diet and water *ad libitum*. Healthy

male Swiss albino mice with body weight of 20–35 g and age of 8–12 weeks were used in the experimental study and healthy female mice with the same weight and age were used for an acute oral toxicity study. This study was carried out based on the guide for the care and use of laboratory animals.²⁷

Phytochemical Analysis of Seed Extract of *D. stramonium*

Qualitative preliminary screening was carried out in the seed extract to determine the presence of flavonoids, alkaloids, tannins, steroids, phenols, saponins, glycosides, and anthraquinones according to the standard methods.^{28,29}

Test for Flavonoids (Lead Acetate Test)

Ten milligrams of the seed extract was measured and a few drops of 10% lead acetate solution was added. The appearance of yellow color precipitate indicates the presence of flavonoids.

Test for Alkaloids (Wagner's Test)

Ten milligrams of hydromethanolic seed extract was dissolved in distilled water. Three drops of Wagner's reagent were then added to the mixture; formation of a reddish brown color indicates a positive result for the presence of terpenoids.

Test for Tannins (Lead Acetate Test)

About 0.05 g of seed extract was dissolved in 1 mL distilled water and then 0.5 mL of 1% lead acetate solution was added. The appearance of yellowish color precipitate on the mixture confirmed a positive result for the presence of tannins.

Test for Phenols (Ferric Chloride Test)

Ten milligrams of seed extract was dissolved in 1 mL distilled water. Then, 0.5 mL of 5% ferric chloride was added and the formation of black color indicated the presence of phenols.

Test for Steroids

About 0.5 g seed extract was dissolved in 0.5 mL dichloromethane to produce a dilute solution, and 0.5 mL of acetic anhydride was added, followed by three drops of concentrated sulphuric acid. The appearance of a blue-green color on the mixture confirmed the presence of steroids.

Test for Saponins (Foam Test)

About 0.3 g of the seed extract was dissolved in 20 mL of distilled water. The formation of 3 cm persistent foam on

vigorous shaking observed for 30 minutes indicates a positive result for the presence of saponins.

Test for Glycosides (Glycoside Test)

About 1 g of seed extract was dissolved in 1 mL of distilled water and then three drops of 20% sodium hydroxide solution was added. The formation of yellowish color confirmed a positive result for the presence of glycosides.

Test for Anthraquinones (Borntragers Test)

About 0.5 g seed extract was taken into a dry test tube and 5 mL of chloroform was added and shaken for 5 minutes. The extract was filtered and the filtrate was shaken with an equal volume of 10% ammonia solution. A pink violet in the lower layer indicates the presence of anthraquinones.

Toxicity Study

An acute oral toxicity study was conducted according to OECD guideline 425.³⁰ One healthy female mouse was fasted for 3–4 hours and then body weight was measured. The seed extract at the dose of 2,000 mg/kg was given orally to the mouse and strictly observed for 24 hours of physical and behavioral changes, giving special attention to the first 4 hours. Based on the result, another four mice were fasted for 3–4 hours and fasted body weight was measured. The seed extract at the dose of 2,000 mg/kg was given to each mouse and they were observed in the same manner to determine physical and behavioral changes of mice. Follow-up was continued for 2 weeks for any physical and behavioral changes of the mice before initiation of the experiment.

In vitro Antioxidant Activity of Hydromethanolic Seed Extract of *D. stramonium*

Antioxidant activity of the seed extract was evaluated in 2, 2-diphenyl-1-picrylhydrazyl method.³¹ Diphenyl-1-picrylhydrazine (DPPH) solution (3.9 mL) (4 mg DPPH/100 mL methanol) was mixed with a 0.1 mL methanolic solution (5–80 mg/mL) of seed extract and incubated in the dark for half an hour. Ascorbic acid was used as a standard antioxidant. After half an hour, the absorbance of the mixture and the control were read at 517 nm by using a UV spectrophotometer. The test was done in triplicate and the percentage of inhibition was calculated as:

$$\% \text{ free radical scavenging} = \frac{\text{Abs Control} - \text{Abs Sample}}{\text{Abs Control}} \times 100$$

where AbsControl was the absorbance without sample, AbsSamples was the absorbance of the sample latex or ascorbic acid.

Induction of Diabetes

Streptozocin (STZ) was dissolved in 0.1 M fresh cold citrate buffer (pH 4.5). Type 1 diabetes was induced by injection (i.p.) of Streptozocin solution at the single dose of 150 mg/kg.^{32,34} After 30 minutes, pallet diet was allowed to the mice and after 6 hours of STZ injection, glucose solution (5%) was given to each mouse for 1 day to prevent hypoglycemic shock. After 72 hours of STZ injection, a fasting blood glucose level in each mouse >200 mg/dL was considered diabetic and used in the study.^{35,37}

Evaluation of Hypoglycemic Effect of the Seed Extract in Normoglycemic Mice

Normoglycemic mice were fasted overnight (16 hours) and randomly assigned into five groups (n=6). Group I (negative control) was treated with 10 mL/kg distilled water and Group II (positive control) was treated with 5 mg/kg glibenclamide, Groups III, IV, and V were treated with 100, 200, and 400 mg/kg seed extract, respectively. Tail vein blood glucose of each mouse was measured at 0 (before treatment) and at 1, 2, 4, and 6 hours post-treatment.³⁶

Glucose Tolerance Test (OGTT)

To evaluate acute glucose lowering potential hydromethanolic seed extract of *D. stramonium*, OGTT was employed on 16 hour fasted mice.^{24,38} Normoglycemic overnight fasted mice were randomly assigned into five groups (n=6). Group I and II (negative and positive control) were treated with 10 mL/kg distilled water and 5 mg/kg glibenclamide, respectively; Group III, IV, and V were treated with 80% methanolic seed extract at the dose of 100, 200, and 400 mg/kg, respectively. After 30 minutes, 40% glucose solution was administered at the dose of 2 g/kg to each mouse.^{34,39} Tail vein blood glucose of each mouse was measured before glucose loading and then at 30, 60, and 120 minutes post-glucose loading.^{37,40,41}

The Effect of Hydromethanolic Seed Extract on Blood Glucose Level and Body Weight in STZ-Induced Diabetic Mice

Overnight (16 hour) fasted diabetic mice were randomly grouped into six groups (n=6). Group I was treated with 10 mL/kg distilled water; Group II (diabetic positive control)

was treated with 5 mg/kg glibenclamide; Groups III, IV, and V (diabetic test groups) were treated with 80% methanolic seed extract at the dose of 100, 200, and 400 mg/kg every day for 2 weeks, respectively. Fasting blood glucose level and body weight of each mouse was measured on day 1 (After 3-day STZ injection). On weeks 1 and 2, overnight fasting mice were given vehicle, glibenclamide and seed extract in respect to their grouping and then, after 2 hours, blood glucose level and body weight of the mice were measured.^{13,39}

Statistical Analysis

The data was expressed as mean±standard error of the mean. Means of all parameters among groups and within a group were compared using one-way ANOVA followed by Tuckey's post-hoc multiple comparison test. *P*-values<0.05 were considered statistically significant and SPSS Version 23 Software was used for analysis.

Results

Acute Oral Toxicity Test

Sign of toxicity and mortality associated with 2,000 mg/kg loading hydromethanol seed extract of *D. stramonium* not recorded in female mice within 2 weeks observation. Therefore, LD50 of hydromethanolic seed extract is >2,000 mg/kg.

Phytochemical Screening of Hydromethanolic Seed Extract of *D. stramonium*

Qualitative preliminary phytochemical study showed that hydromethanolic seed extract contained secondary metabolites (Table 1).

Antioxidant Activity of the Seed Extract of *D. stramonium*

The finding of the study showed that free radical-scavenging activity of the seed extract was concentration dependent and comparable to ascorbic acid. IC50 of the seed extract and ascorbic acid in the assay was found to be 11.95 and 5.07 mg/mL, respectively (Table 2).

Effect of Hydromethanolic Seed Extract of *D. stramonium* in Normoglycemic Mice

All doses of hydromethanolic seed extract of *D. stramonium* were devoid of a significant hypoglycemic effect at all time points in normoglycemic mice compared to negative

Table 1 Phytochemical Screening of 80% Methanolic Seed Extract of *D. stramonium*

Phytoconstituents	Result
Flavonoids	+
Phenols	+
Tannins	+
Saponins	+
Alkaloids	+
Terpenoids	+
Glycosides	+
Steroids	+
Anthraquinones	-

Notes: +, present; -, absent.

Table 2 Percentage of Free Radical-Scavenging Activity of the Seed Extract of *D. stramonium*

Concentration (mg/mL)	% of DPPH Inhibition		IC50	
	AA	SE	AA	SE
5	28.22±0.21	6.67±0.71	4.97	11.95
10	45.66±0.42	14.14±0.53		
20	66.81±0.42	21.01±0.41		
40	80.26±0.45	28.01±0.31		
80	92.53±0.54	40.54±0.27		

Note: Values of % inhibition of DPPH free radical is described as mean±standard error of the mean.

Abbreviations: AA, ascorbic acid; DPPH, 2,2-diphenyl-1-picrylhydrazine; IC, inhibitory concentration; SE, seed extract.

control. The standard drug (5 mg/kg glibenclamide) showed a significant ($P<0.001$) hypoglycemic effect at 2, 4, and 6 hours with respect to negative control (Table 3).

Effect of Hydromethanolic Seed Extract of *D. stramonium* on Blood Glucose Level in Oral Glucose-Loaded Mice

There was no significant variation in fasting blood glucose level of the mice before oral glucose administration and at 30 minutes in all groups (Figure 2). Maximum blood glucose

level was measured after 30 minutes of glucose administration. Glucose reduction of the seed extract was significant ($P<0.05$ at 100, $P<0.01$ at 200 and 400 mg/kg) after 60 and 120 minutes glucose administration compared to the negative control. Glucose reduction of 100 mg/kg dose was significantly ($P<0.05$) lower than 5 mg/kg glibenclamide ($P<0.001$).

Antihyperglycemic Effects of Hydromethanolic Seed Extract of *D. stramonium* in Diabetic Mice

After induction of diabetes, the blood glucose level of daily-treated diabetic mice was measured every week. The seed extract at the doses of 100, 200, and 400 mg/kg significantly ($P<0.01$) reduced the glucose level at week 1 and 2 compared to the diabetic control group (Table 4). Glucose reduction of glibenclamide was significant ($P<0.001$) at week 1 and 2 compared to the diabetic control group. There was no significant BGL variation among seed extract and standard drug in the STZ-induced model.

Effect of Hydromethanolic Seed Extract of *D. stramonium* on Body Weight of Diabetic Mice

The seed extract at the doses of 200 and 400 mg/kg significantly ($P<0.05$) increased the BW of diabetic mice at week 1 and 2 compared to diabetic control (Table 5). The effect of the 100 mg/kg dose was delayed and significantly ($P<0.05$) improved BW at week 2 compared to the negative control group. In addition, glibenclamide significantly ($P<0.01$) improved the body weight of diabetic mice at week 1 and 2 with respect to negative control group.

Discussion

Blood glucose reduction potential of hydromethanolic seed extract of *D. stramonium* was evaluated in normoglycemic,

Table 3 Effect of Hydromethanolic Seed Extract of *D. stramonium* in Normoglycemic Mice

Fasting BGL (mg/dL)					
Groups	0 hour	1 hour	2 hours	4 hours	6 hours
10 mL/kg NC	90.46±0.31	88.29±0.75	80.52±0.68	75.82±1.71	75.06±2.03
5 mg/kg GB	89.28±1.02	72.82±0.91	66.79±1.06 ^{a,*,b,*}	60.39±2.29 ^{a,*,b,*}	56.45±2.09 ^{a,*,b,*}
100 mg/kg SE	90.53±1.75	87.21±0.42	79.58±0.74 ^{c,*}	74.83±1.73 ^{c,*}	74.09±0.39 ^{c,*}
200 mg/kg SE	89.53±0.45	86.45±1.90	77.88±1.30	73.97±1.17	73.56±2.03
400 mg/kg SE	90.06±1.64	85.51±0.46	77.62±1.29	72.88±1.25	72.11±2.69

Notes: Each data describes as mean±standard error of the mean, n=6; ^acompared to negative control; ^bto 100 mg/kg; ^cto 5 mg/kg GB; * $P<0.05$; ** $P<0.001$.

Abbreviations: BGL, blood glucose level; GB, glibenclamide; NC, negative control; SE, seed extract.

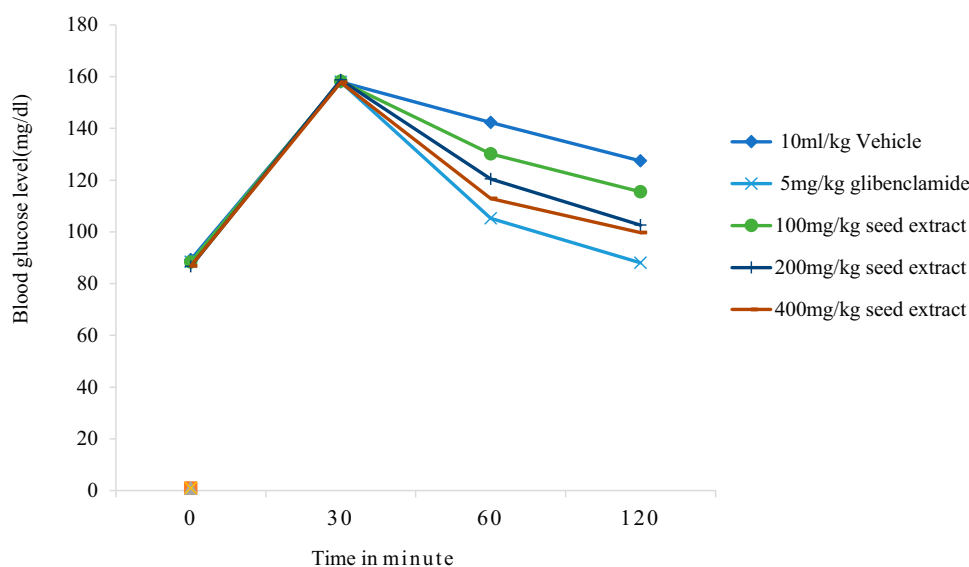


Figure 2 Effect of 80% methanolic seed extract of *D. stramonium* on blood glucose level of oral glucose-loaded mice.

glucose-loaded, and Streptozocin-induced diabetic mice. The normoglycemic model was used to determine the hypoglycemic effect of the seed extract and acute postprandial glucose reduction of the plant was assessed in the oral glucose tolerance test.^{13,36,42} Cumulative blood glucose reduction ability of the plant was evaluated in every day-treated Streptozocin-induced diabetic mice.³⁸ Hydromethanol (80% methanol) was selected as the solvent of the extraction since a wide variety of polar and moderately polar phytochemicals were extracted in hydromethanol.^{24,36,43}

Diphenyl-1-picrylhydrazine (DPPH) is a stable free radical widely employed to determine the antioxidant capacity of natural products.⁴⁴ In the present finding, hydromethanolic seed extract showed concentration dependent antioxidant activity. IC₅₀ of the seed extract was found to be 11.95 mg/mL, which is comparable with the IC₅₀ of

ascorbic acid (5.07 mg/mL). The finding is in line with the concentration dependent antioxidant activity of root extract of the plant.²⁴ Plant derived supplement prevents the devastating effect of oxidative stress (ROS) in chronic diseases like diabetes mellitu⁴⁵ and the study plant might offer health benefits through its antioxidant property.

Normoglycemic models offer a clue to predict the mechanism of action of natural remedies and detect hyperglycemic agents.^{32,36} In the current study, all doses of hydromethanolic seed extract did not show significant hypoglycemia at all time points compared to the negative control group. Blood glucose reduction of standard drug (5 mg/kg glibenclamide) was significant ($P<0.01$) at 2, 4, and 6 hours in normoglycemic mice. Therefore, the mechanism of action in glucose lowering activity of hydromethanolic seed extract of *D. stramonium* and glibenclamide might not be the same. Similar to this finding,

Table 4 Antihyperglycemic Effects of 80% Methanolic Seed Extract of *D. stramonium* in Diabetic Mice

Group	Fasting BGL (mg/dL)		
	Day 0	Day 7	Day 14
10 mL/kg NC	254.62±1.05	266.00±1.73	268.94±0.49
5 mg/kg GB	255.46±0.34	243.22±0.42 ^{a,**}	240.18±1.63 ^{a,**}
100 mg/kg SE	256.06±1.27	255.06±0.57 ^{a,*}	250.22±0.29 ^{a,*}
200 mg/kg SE	255.44±0.88	249.17±1.06 ^{a,*}	248.55±1.06 ^{a,*}
400 mg/kg SE	255.89±0.92	246.45±0.51 ^{a,*}	247.17±0.25 ^{a,*}

Notes: Each data described as mean±standard error of the mean, n=6; ^acompared to negative control; ^{*}P<0.01; ^{**}P<0.001.

Abbreviations: BGL, blood glucose level; GB, glibenclamide; NC, negative control; SE, seed extract.

Table 5 Effect of 80% Methanolic Seed Extract of *D. stramonium* on Body Weight of Diabetic Mice

Groups	Body Weight (g)		
	Day 0	Day 7	Day 14
10 mL/kg NC	22.89±0.69	22.84±0.51	23.08±0.64
5 mg/kg GB	23.43±0.33	27.59±0.31 ^{a,**}	28.26±0.46 ^{a,**}
100 mg/kg SE	22.59±0.55	24.59±0.64 ^{a,*}	25.48±0.49 ^{a,*}
200 mg/kg SE	23.87±0.23	26.34±0.53 ^{a,*}	25.91±0.61 ^{a,*}
400 mg/kg SE	24.27±0.63	27.21±0.39 ^{a,*}	26.72±0.34 ^{a,*}

Notes: Each data described as mean±standard error of the mean, n=6; ^acompared to negative control; ^{*}P<0.05; ^{**}P<0.01.

Abbreviations: GB, glibenclamide; NC, negative control; SE, seed extract.

hydromethanolic seed extract of *Calpurnia aurea* and root extract of the plant devoid significant hypoglycemic activity in normoglycemic mice.^{24,46}

Glucose tolerance test (OGTT) was employed in the current study to determine acute blood glucose reduction potential of hydromethanolic seed extract of *D. stramonium*. The result showed that the glucose level was significantly ($P < 0.05$ at 100 mg/kg, $P < 0.01$ at 200 mg/kg and 400mg/kg) reduced after 60 and 120 minutes oral glucose loaded compared to the negative control group. Glucose reduction effect was found to be dose dependent in the glucose tolerance test. Blood glucose reduction of 100 mg/kg dose was significantly ($P < 0.05$) lower than 5 mg/kg glibenclamide ($P < 0.001$, after 60 and 120 minutes). Similar to this finding, hydromethanolic seed extract of *Calpurnia aurea* and root extract of the plant revealed a significant glucose reduction in oral glucose-loaded mice.^{24,46}

Streptozocin is a widely used diabetogenic agent to induce experimental diabetes in rodent models. A single dose of Streptozocin at 150 mg/kg induced type I diabetes through destroying pancreas β cells by DNA methylation and free radical generation.^{33,47,48} In the STZ-induced diabetic model, the blood glucose level of daily-treated diabetic mice was measured every week. The result of the study showed that blood glucose level was significantly ($P < 0.01$) changed at the dose of 100, 200, and 400 mg/kg hydromethanolic seed extract on week 1 and 2 compared to negative control. This showed that the plant endowed antidiabetic activity and in line with hydromethanolic seed extract of *Calpurnia aurea* and root extract of the plant,^{24,46} in a streptozotocin-induced diabetic model. In another study, the seed extract of *Datura metel* in the genus *Datura* showed significant blood glucose lowering activity.⁴⁹

At the same time, there was significant improvement of body weight in seed extract and standard drug-treated groups in respect to negative control in STZ-induced diabetic mice. Body weight of the mice treated with all doses of hydromethanolic seed extract of *D. stramonium* significantly improved at week 1 and 2. This implies that hydromethanolic seed extract of the study plant prevention of hyperglycemia induced muscle wastage.

Preliminary phytochemical analysis of hydromethanolic seed extract of *D. stramonium* showed the present of secondary metabolites (flavonoids, glycosides, alkaloids, terpenoids, and others) which revealed antihyperglycemic and antioxidant activities in different plants extracts through various mechanisms of action.^{13,45} Alkaloids,

flavonoids, terpenoids, phenols, and glycosides have been presented in *Datura metel*, *Moringa stenopetala*, *Calpurnia aurea*, and other plant extracts,^{13,24,42,45} that endowed potential antidiabetic and antioxidant activities. Therefore, the antihyperglycemic activity of hydromethanolic seed extract of *D. stramonium* was possibly due to a single or synergetic action of these secondary metabolites.

Conclusion

The finding of the study showed that hydromethanolic seed extract of *Datura stramonium* endowed significant antihyperglycemic and antioxidant activities. Further investigation will require for bioassay guided fractionation, isolation, and characterization of active compound (s) that possess antidiabetic activity of the plant.

Abbreviations

OECD, Organization for Economic Cooperation and Development; STZ, Streptozocin; BGL, blood glucose level; BW, body weight.

Data Sharing Statement

All the datasets used/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics Approval

The study was conducted according to OECD Guidelines and the Guide for the Care and Use of Laboratory Animals. Ethical approved was obtained from the ethical review committee of School of Pharmacy, College of Medicine and Health Sciences, Wollo University.

Acknowledgments

We would like to acknowledge Wollo University for providing the necessary facilities in this study.

Funding

Not applicable.

Disclosure

The authors declared that they do not have any conflict of interest.

References

1. Skyler JS, Bakris GL, Bonifacio E, et al. Differentiation of diabetes by pathophysiology, natural history, and prognosis. *Diabetes*. 2017;66(2):241–255. doi:10.2337/db16-0806

2. Alberti KGMM, Zimmet P. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus. Provisional report of a WHO consultation. *Diabet Med.* 1998;15(7):539–553. doi:10.1002/(SICI)1096-9136(199807)15:7<539::AID-DIA668>3.0.CO;2-S
3. Schofield JD, Liu Y, Rao-Balakrishna P, Malik RA, Soran H. Diabetes dyslipidemia. *Diabetes Ther.* 2016;7(2):203–219. doi:10.1007/s13300-016-0167-x
4. Vijayaraghavan K. Treatment of dyslipidemia in patients with type 2 diabetes. *Lipids Health Dis.* 2010;9(1):144. doi:10.1186/1476-511X-9-144
5. Ormazabal V, Nair S, Elfeky O, et al. Association between insulin resistance and the development of cardiovascular disease. *Cardiovasc. Diabetol.* 2018;17:122.
6. International Diabetes Federation. *IDF Diabetes Atlas*. 8th ed. Belgium: Brussels; 2017.
7. Sharma BR, Kim H, Rhyu D. Caulerpa lentillifera extract ameliorates insulin resistance and regulates glucose metabolism in C57BL/KsJ-db/db mice via PI3K/AKT signaling pathway in myocytes. *J Transl Med.* 2015;13:62. doi:10.1186/s12967-015-0412-5
8. Janda E, Lascala A, Martino C, et al. Molecular mechanisms of lipid- and glucose-lowering activities of bergamot flavonoids. *Pharma Nutrition.* 2016;4:S8–S18. doi:10.1016/j.phanu.2016.05.001
9. Hung HY, Qian K, Morris-Natschke SL, Hsu CS, Lee KH. Recent discovery of plant-derived anti-diabetic natural products. *Nat Prod Rep.* 2012;29(5):580–606.
10. D A, Geleta G, Bacha K, Abdissa N. Phytochemical investigation of Aloe pulcherrima roots and evaluation for its antibacterial and antiplasmodial activities. *PLoS One.* 2018;12(3):e0173882.
11. Yousef F, Yousef N, Mansour O, Herbali J. Metformin: a unique herbal origin medication. *Glob J Med Res.* 2017.
12. Goel PK. Novel antidiabetic furostanolic saponin rich (fsr) fraction from fenugreek seeds. *Google Patents.* 2012.
13. Toma A, Makonnen E, Mekonnen Y, Debella A, Adisakwattana S. Antidiabetic activities of aqueous ethanol and n-butanol fraction of Moringa stenopetala leaves in streptozotocin-induced diabetic rats. *BMC Complement Altern Med.* 2015;15(1):242. doi:10.1186/s12906-015-0779-0
14. Abo-Youssef AM, Messiha BA. Beneficial effects of Aloe vera in treatment of diabetes: comparative in vivo and in vitro studies. *Bull Fac Pharm Cairo Univ.* 2013;51(1):7–11. doi:10.1016/j.bfopcu.2012.03.002
15. HF H, Hajiaghache R, Dabaghian FH. Anti-hyperglycemic and anti-hypercholesterolemic effects of Aloe vera leaf gel in hyperlipidemic type 2 diabetic patients: a randomized double-blind placebo-controlled clinical trial. *Planta Med.* 2012;78(04):311–316. doi:10.1055/s-0031-1280474
16. Samuels J. Biodiversity of food species of the Solanaceae family: a preliminary taxonomic inventory of subfamily Solanoideae. *Resources.* 2015;4(2):277–322. doi:10.3390/resources4020277
17. Gebhardt C. The historical role of species from the Solanaceae plant family in genetic research. *Theor Appl Genet.* 2016;129(12):2281–2294. doi:10.1007/s00122-016-2804-1
18. Al-Snafi AE. Medical importance of Datura fastuosa (syn: Datura metel) and Datura stramonium-A review. *IOSR J Pharm.* 2017;7(2):43–58. doi:10.9790/3013-0702014358
19. Soni P, Siddiqui AA, Dwivedi J, Soni V. Pharmacological properties of Datura stramonium L. as a potential medicinal tree: an overview. *Asian Pac J Trop Biomed.* 2012;2(12):1002–1008. doi:10.1016/S2221-1691(13)60014-3
20. Miraj S. Datura stramonium: an updated review. *Der Pharma Chemica.* 2016;8(17):253–257.
21. Lewis O, Nieman E, Munz A. Origin of amino acids in Datura stramonium seeds. *Ann Bot.* 1970;34(4):843–848. doi:10.1093/oxfordjournals.aob.a084415
22. Rashid S, Ahmad M, Zafar M, et al. Ethnopharmacological evaluation and antioxidant activity of some important herbs used in traditional medicines. *J Tradit Chin Med.* 2016;36(5):689–694. doi:10.1016/S0254-6272(16)30091-7
23. Baynesagne S, Berhane N, Sendeku W, Ai L. Antibacterial activity of Datura stramonium against standard and clinical isolate pathogenic microorganisms. *J Med Plants Res.* 2017;11(31):501–506. doi:10.5897/JMPR2017.6381
24. Belayneh M, Birhanu Z, Birru M, Getenet G. Evaluation of in vivo antidiabetic, antidyslipidemic and in vitro antioxidant activities of hydromethanolic root extract of Datura stramonium L. (Solanaceae). *J Exp Pharmacol.* 2019;11:29–38. doi:10.2147/JEP.S192264
25. Mehrabadi M, Saadati F, Mahmudvand M. α -Amylase activity of stored products insects and its inhibition by medicinal plant extracts. *J Agr Sci Tech.* 2011;13:1173–1182.
26. Meresa A, Gemechu W, Basha H, et al. Herbal medicines for the management of diabetic mellitus in Ethiopia and Eritria including their phytochemical constituents. *Am J Adv Drug Deliv.* 2017;5(1):40–58. doi:10.21767/2321-547X.1000011
27. Janet CG, Joseph T, Bielitzki L, Ann C. *Guide for the Care and Use of Laboratory Animals*. Eighth ed. Washington, DC: Institute of Laboratory Animal Resources, National Research Council; 2010:248.
28. Pandey A, Tripathi S. Concept of standardization, extraction and pre phytochemical screening strategies for herbal drug. *J Pharmacogn Phytochem.* 2014;2(5).
29. Tiwari P, Kumar B, Kaur M, Kaur G, Kaur H. Phytochemical screening and extraction: a review. *Int Pharm Sci.* 2011;1(1):98–106.
30. OECD/OCDE. OECD guideline for the testing of chemicals: acute oral toxicity; up-and-down procedure (UDP). No 425. OECD; 2008.
31. MacDonald-Wicks LK, Wood LG, Garg ML. Methodology for the determination of biological antioxidant capacity in vitro: a review. *J Sci Food Agric.* 2006;86(13):2046–2056. doi:10.1002/jsfa.2603
32. Etuk E. Animal models for studying diabetes mellitus. *ABJNA.* 2010;1(2):130–134.
33. MMPC. Streptozotocin-induced type 1 diabetes model. *Mouse Metabolic Phenotyping Centers protocols.* 2013.
34. Sulyman A, Akolade J, Sabiu S, Aladodo R, Muritala H. Antidiabetic potentials of ethanolic extract of Aristolochia ringens (Vahl.) roots. *J Ethnopharmacol.* 2016;182:122–128. doi:10.1016/j.jep.2016.02.002
35. Baquer NZ, Kumar P, Taha A, Kale R, Cowsik S, McLean P. Metabolic and molecular action of Trigonella foenum-graecum (fenugreek) and trace metals in experimental diabetic tissues. *J Biosci.* 2011;36(2):383–396. doi:10.1007/s12038-011-9042-0
36. Tamiru W, Engidawork E, Asres K. Evaluation of the effects of 80% methanolic leaf extract of Caylusea abyssinica (fresen.) fisch. & Mey. on glucose handling in normal, glucose loaded and diabetic rodents. *BMC Complement Altern Med.* 2012;12(1):151. doi:10.1186/1472-6882-12-151
37. Demoz MS, Gachoki KP, Mungai KJ, Negusse BG. Evaluation of the anti-diabetic potential of the methanol extracts of aloe camperi, meriandra dianthera and a polyherb. *J Diabetes Mellit.* 2015;5(04):267. doi:10.4236/jdm.2015.54033
38. Zhang Y, Feng F, Chen T, et al. Antidiabetic and antihyperlipidemic activities of Forsythia suspensa (Thunb.) Vahl (fruit) in streptozotocin-induced diabetes mice. *J Ethnopharmacol.* 2016;192(2562):56–263. doi:10.1016/j.jep.2016.07.002
39. Sharma S, Choudhary M, Bhardwaj S, Choudhary N, Rana AC. Hypoglycemic potential of alcoholic root extract of Cassia occidentalis Linn. in streptozotocin induced diabetes in albino mice. *Bull Fac Pharm Cairo Univ.* 2014;52(2):211–217. doi:10.1016/j.bfopcu.2014.09.003
40. Rajurkar B. Phyto-pharmacological investigations of Clerodendrum infortunatum Gartn. *Int Res J Pharm.* 2011;2:130–132.
41. Tesfaye A, Makonnen E, Gedamu S. Hypoglycemic and antihyperglycemic activity of aqueous extract of Justicia Schimperiana leaves in normal and streptozotocin-induced diabetic mice. *Int. J Pharm Sci Res.* 2016;7(02):110–113.

42. Hammeso W, Emiru Y, Ayalew G, Kahaliw W. Antidiabetic and antihyperlipidemic activities of the leaf latex extract of *Aloe megalantha baker* (Aloaceae) in streptozotocin-induced diabetic model. *Evid Based Complement Alternat Med.* 2019;2019:1–9. doi:10.1155/2019/8263786
43. Otsuka H. Purification by solvent extraction using partition coefficient. In: Sarker D, Latif Z, Gray A, editors. *Methods in Biotechnology Natural Products Isolation*. Human Press; 2006:269–273.
44. Moon J-K, Shibamoto T. Antioxidant assays for plant and food components. *J Agric Food Chem.* 2009;57(5):1655–1666. doi:10.1021/jf803537k
45. Misbah H, Aziz AA, Aminudin N. Antidiabetic and antioxidant properties of *Ficus deltoidea* fruit extracts and fractions. *BMC Complement Alternat Med.* 2013;13:118. doi:10.1186/1472-6882-13-118
46. Belayneh Y, Birru EM, Ambikar D. Evaluation of hypoglycemic, antihyperglycemic and antihyperlipidemic activities of 80% methanolic seed extract of *Calpurnia aurea* (Ait.) Benth (Fabaceae) in mice. *J Exp Pharmacol.* 2019;11:73. doi:10.2147/JEP.S212206
47. Deeds M, Anderson J, Armstrong A, et al. Single dose streptozotocin-induced diabetes: considerations for study design in islet transplantation models. *Lab Anim.* 2011;45(3):131–140. doi:10.1258/la.2010.010090
48. Šoltésová D, Herichová I. On the mechanisms of diabetogenic effects of alloxan and streptozotocin. *Diabetol Metab Endocrinologie.* 2011;14:130–138.
49. Krishna Murthy B, Nammi S, Kota MK, Krishna Rao RV. Evaluation of hypoglycemic and antihyperglycemic effects of *Datura metel* (Linn.) seeds in normal and alloxan-induced diabetic rats. *J Ethnopharmacol.* 2004;91(1):95–98. doi:10.1016/j.jep.2003.12.010

Journal of Experimental Pharmacology

Dovepress

Publish your work in this journal

The Journal of Experimental Pharmacology is an international, peer-reviewed, open access journal publishing original research, reports, reviews and commentaries on all areas of laboratory and experimental pharmacology. The manuscript management system is completely

online and includes a very quick and fair peer-review system. Visit <http://www.dovepress.com/testimonials.php> to read real quotes from published authors.

Submit your manuscript here: <https://www.dovepress.com/journal-of-experimental-pharmacology-journal>