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Research Article

Evaluation of Antidiabetic and Antioxidant Potential of Hydromethanolic Seed Extract of *Datura Stramonium* in Mice

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ABSTRACT

Background: *Datura stramonium* Linn is one of the folkloric medicines in Ethiopia and demonstrated in vitro antidiabetic activity. Thus, the current study was carried out to evaluate antidiabetic activity of hydromethanolic seed extract in mice.

Methods: The seed of *Datura stramonium* was extract by using hydromethanol. The effect of the seed extract on blood glucose level was assessed after oral administration of 100, 200 and 400 mg/kg doses in normal, oral glucose loaded and Streptozocin-induced diabetic mice.

Antioxidant capacity of seed extract was evaluated by using a 2, 2-diphenyl-1-picrylhydrazyl assay.

Results: Hypoglycemic effect of all doses of seed extract was insignificant ($p>0.05$) in normoglycemic model but glucose reduction was significant ($p<0.05$ at 100 mg/kg, $p<0.01$ at 200 mg/kg and 400 mg/kg) with respect to negative control in oral glucose loaded mice. All doses of seed extract significantly ($p<0.0l$) reduced blood glucose level on day 7 and 14 in STZ induced daily treated diabetic mice compared to the negative control. At the same time, 200 and 400 mg/kg doses of seed extract significantly ($p<0.05$) improved body weight of diabetic mice on day 7 and 14 but 100 mg/kg dose was delayed and significantly ($p<0.05$) increased body weight of mice on day 14 compared to the vehicle. The finding showed that antioxidant capacity of the seed extract was concentration dependent and comparable with ascorbic acid. IC50 of the seed extract and ascorbic was found to be 11.95 and 5.07 mg/mL, respectively.

Conclusion: The finding of the study showed that hydromethanolic seed extract of *Datura stramonium* Linn endowed significant antihyperglycemic and scavenging of free radicals.

Keywords: Diabetes, Streptozotocin, Datura stramonium, antioxidant, Mice

Abbreviations: GLUT2: Glucose transporter 2; GLUS-4: Glucose transporter 4; OECD: Organization for Economic Cooperation and Development; STZ: Streptozocin; BGL: Blood glucose level; BW: Body weight

INTRODUCTION

Diabetes mellitus is chronic metabolic disorder characterized by hyperglycemia due to impaired insulin secretion or action or both. Uncontrol hyperglycemia cause suffering of the patients with life threatening complications (retinopathy, nephropathy, and peripheral neuropathy and acquired cardiovascular diseases)[1-5]. The prevalence and the burden of diabetes mellitus is very high in the world. In 2017, 425 million people (aged 20–79 years) live with diabetes and this number will rise to 629 million in 2045 globally [6]. The management of diabetes mellitus is challenging due to deleterious effects and limited efficacy of currently available antidiabetic drugs [7-9]. Medicinal plants with documented traditional uses are source of noble antidiabetic drugs and metformin (N, N dimethyl biguanide) is preferable antidiabetic drug derived from useful medicinal plant, Galega officinalis [10,11]. More than 800 plants have been used in the treatment of diabetes [12]. In recent years, catechol glycoside esters, isolated from the leaves of *Dodecadenia grandiflora* showed comparable antidiabetic effect with metformin and protodioscin isolated from seed of fenugreek demonstrated significant blood glucose lowering effect in rats and human [12,13].

Datura stramonium Linn (Astenagra in Amharic). is one of the well-known medicinal plant that belonging to the genus Datura and the family Solanaceae and originates in Americas. But now a day the plant founds around the world, including the warmer regions

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of North, Central and South America, Europe, Asia, and Africa and distributed throughout the Ethiopia [14,15]. The plant is a widespread annual plant and grows to 1.2 m high and the root is long, thick, fibrous, white and the stem is stout, erect, leafy, smooth, and pale yellow-green (Figure 1). The stem forks off repeatedly into branches and each fork forms a leaf and a single, erect flower. Alanine, glutamate, phenylalanine, tyrosine (amino acids) and antimuscarinic drugs such as scopolamine, atropine and hyoscyamine were isolated from seeds of *Datura stramonium* [16-19].

Datura stramonium Linn used to treat diabetes mellitus, asthma, gastrointestinal problems, wounds, inflammation and tumors traditionally [16,20,21]. Experimental studies revealed that *Datura stramonium* possesses antiepileptic, anti-obesity, anti-microbial, anti-viral, anticholinergic and bronchodilator activities [16,18,21,22]. The leaf and root extracts of *Datura stramonium* exhibited free radical scavenging and anti-inflammatory activities [21,23]. Hydromethanolic root extract of the plant demonstrated significant *in vivo* antidiabetic and antidyslipidemic activity [24-26]. More importantly, the seed extract of *Datura stramonium* demonstrated strong *in vitro* α-glycosidase and α-amylase inhibitory effect despite lack *in vivo* investigated for its potential antidiabetic activity. These call initiation to evaluate antidiabetic activities of hydromethanolic seed extract of *Datura stramonium in vivo.*

METHODS

Drugs, chemicals and instruments

The following drugs, chemicals and equipments were used in this experimental study.

Drugs: Streptozotocin (Sigma Aldrich, Germany), glibeclamide, (Julphar Pharmaceuticals),

Chemicals: 80% methanol, $FeCl_3$ (MA, USA), NaOH (India), HCl (Suppertek Chemical), 40% glucose solution (Shandong, China),

Equipments: 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, desiccators.

Figure 1: Photograph of *Datura stramonium* Linn.

Plant materials collection

The seeds of *Datura stramonium Linn* were collected from the Wollo in October, 2019. Plant identification was carried out and the specimen of the plant material was deposited in the herbarium of biology department for future reference in Wollo University with a voucher number GG-004/2019.

Preparation of crude extract

The Seeds were wash with distilled water, dried under shade and then dried seeds were reduced into coarse powder by using electric mill. About 200 gram coarse powder of the seed was maceration in hydromethanol for seventy-two hrs. Hydromethanol with dissolved plant material was filtered by Whatman filter paper No.1. The marc was re-macerated two times in 80% methanol for seventy-two hours and the filtrates were concentrated by using rotary evaporator and dried in an oven at 40°C and lyophilizer was used to remove water with 24 hr.

Finally, collected seed extract was kept by using vial and stored in desiccator until used for the experiment.

Experimental animals

The mice were obtained from animal house of pharmacology department, Wollo university and were kept in 12 hrs light 12 hrs dark cycle with pellet diet and water *ad libitum.* Healthy male Swiss albino mice with body weight of 20 gram-35 gram 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 acute oral toxicity study. This study was carried out based on the guide for the care and use of laboratory animals [27].

Phytomolecules evaluation of leaf extract of *D. stramonium*

Qualitative preliminary screening was performed for seed extract by using standard reagent and procedures [28,29].

Toxicity study

Acute oral toxicity study was conducted according to OECD guideline 425 [30]. One healthy female mouse was fasted for 3-4 hr and then, body weight was measured. Then, 2000 mg/kg 80% methanolic seed extract was loaded orally to the fasted mouse and then, the mouse was strictly observed for 24 hr of physical and behavioral changes, given special attention to the first four hr. Based on the result from the first mouse, other four mice were fasted for 3-4 hr and fasted body weight was measured. 2000 mg/kg of 80% methanolic seed extract was loaded orally to each fasted mouse and were observed for 24 hr to determine physical and behavioral changes of mice. The follow up was continued for fourteen days for any physical and behavioral changes of the mice before initiation of the experiment.

In vitro antioxidant activity of the hydromethanolic seed extract of *D. stramonium*

Antioxidant capacity of the seed extract was evaluated in 2, 2-diphenyl-1-picrylhydrazyl method [30]. 3.9 ml of solution of DPPH (4 mg DPPH/100 ml methanol) was mixed with a 0.1 ml methanolic solution of different concentrations (5, 10, 20, 40, and 80 mg/mL) extract and incubated in the dark for half hour.

Ascorbic acid used as standard antioxidant. After half hour, the absorbance of the mixture and the control at 517 nm were read by using a UV spectrophotometer. The test was done in triplicate and the percent of scavenging of inhibition of was calculated as:

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

Where Abs Control was the absorbance without sample, Abs samples was the absorbance of sample latex or ascorbic acid.

Streptozocin induced experimental diabetes

Streptozocin (STZ) was dissolved in 0.1 M fresh cold citrate buffer (pH 4.5). Experimental diabetes was induced on overnight fasted (16 hr.) mice by i.p. injection of fresh solution of Streptozocin at the dose of 150 mg/kg [31-33]. After thirty minutes of Streptozocin injection, free access to food was allowed to the animals. For the next 24 hr after STZ injection, excessive insulin release from partially raptured pancreatic beta cells leads to hypoglycemic shock and death. To prevent this, after six hours of STZ injection, 5% glucose solution was given to each mouse for one day. After three days of STZ administration, fasting blood glucose level (BGL) of the mice >200 mg/dl were diabetic and recruited in the study [34-36].

Measurement of blood glucose level

Fasted blood glucose level of each mouse was measured in triplicate via a glucometer and strip by cutting the tail and the average value was taken.

Evaluation of hypoglycemic effect of seed extract in normoglycemic mice

The normal male mice were fasted overnight (16 hr) and d randomly grouped into five groups (n=6). Group I (negative control) was treated with 10 ml/kg distilled water and Group II (positive control) was treated 5 mg/kg glibeclamide, Group III, IV and V were treated with 100 mg/kg, 200 mg/kg and 400 mg/kg seed extract, respectively. Fasted BGL of each mouse was measured at 0 hour (before treatment) and at 1, 2, 4 and 6 hr post treatment.

Evaluation of the effect of seed extract on blood glucose level in oral glucose loaded mice

Sixteen hours (16 hr) fasted male mice were used to evaluate antihyperglycemic effect of the extract after oral glucose administration [37-42]. Normoglycemic overnight fasted mice were randomly grouped into 5 (n=6). Group I and II (negative and positive control) were treated with 10 ml/kg distilled water and 5 mg/kg glibeclamide, respectively; Group III, IV and V were treated with 80% methanolic seed extract at the dose of 100 mg/kg, 200 mg/kg and 400 mg/kg, respectively. Then, after thirty minutes, oral 2 g/kg of 40% glucose solution was administered to each mouse [33,40]. BGL of the mice were measured just before glucose administering and then at 0.5 hr, 1 hr and 2 hr after glucose administering [36,43,44].

Evaluation of the effect of seed extract on blood glucose level and body weight in STZ induced diabetic mice

Overnight (16 hr) fasted STZ induced diabetic mice were randomly grouped into 6 (n=6). Group I was treated with 10 ml/kg distilled water; Group II (diabetic positive control) was treated with 5 mg/kg glibeclamide; Group III, IV and IV (diabetic test groups) were treated with 80% methanolic seed extract at the dose of 100 mg/kg, 200 mg/kg and 400 mg/kg once daily for 14 days, respectively. After three days of STZ injection, fasting BGL and body weight of each mouse was measured. Then, fasting BGL and weight of daily treated each normal and diabetic mouse was measured two hours after treatment on day 7 and 14 [40,45].

Statistical analysis

Data with a group and b/n the groups were compared by 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 statistical analysis.

RESULTS

Acute oral toxicity test

Sign of toxicity and mortality associated with 2000 mg/kg loading hydromethanol seed extract of *D. stramonium* not exhibited on fasted female mice. Therefore, LD50 of hydromethanolic leaf extract is >2000 mg/kg. The three doses (100 mg/kg, 200 mg/kg and 400 mg/kg) of the leaf extract were determined based on acute toxicity result for experimental studies.

Phytochemical screening of hydromethanolic seed extract of *D. stramonium*

Qualitative preliminary phytochemical study showed that hydromethanolic seed extract contained saponins, alkaloids, flavonoids, phenols, tannins, terpenoids, glycosides and steroids (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* was produced insignificant ($p>0.05$) hypoglycemic effect at all time points but standard drug (5 mg/kg glibeclamide) showed significant ($p<0.001$) hypoglycemic effect at 2, 4 and 6 hr with respect to 100 mg/kg dose and negative control (Table 3).

Table 1: Phytochemical screening of 80% methanolic seed extract of *D. stramonium*.

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

Key: +: 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		
10	45.66 ± 0.42	14.14 ± 0.53	4.97	11.95
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. DPPH-2,2-diphenyl-1-picrylhydrazine, AA-Ascorbic acid; SE-seed extract, IC-Inhibitory concertation

Table 3: Effect of hydromethanolic seed extract of *D. stramonium* in normoglycemic mice.

Groups	Fasting BGL (mg/dl)				
	0hr	1hr	2hr	4hr	6hr
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^{a3b2}	60.39 ± 2.29^{a2b1}	56.45 ± 2.09^{a2b1}
100 mg/kg SE	90.53 ± 1.75	87.21 ± 0.42	79.58 ± 0.74^{c1}	74.83 ± 1.73^{c1}	74.09 ± 0.39^{c1}
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

Key: Each data describes as mean ± standard error of the mean, n=6, [a]compared to negative control; [b]to 100 mg/kg, [c]to 5 mg/kg GB, [1] $P<0.05$; [2] $P<0.001$. BGL-blood glucose level; NC-negative control; GB-glibeclamide; SE-seed extract

Effect of hydromethanolic seed extract of *D. stramonium* on blood glucose level of oral glucose loaded mice

There was no significant variation in fasting blood glucose level the mice before oral glucose administration in all groups (Figure 2). The maximum blood glucose level was measured thirty minutes after oral glucose administration in all groups. BGL reduction of the seed extract was significantly ($p<0.05$ at 100 mg/kg, ($p<0.01$, at 200 mg/kg and 400 mg/kg) after 60 and 120 minutes oral glucose administration compared to the negative control. Blood glucose level reduction of 100 mg.kg dose was significantly ($p<0.05$) lower than 5 mg/kg dose glibeclamide ($p<0.001$, after 60 and 120 minutes).

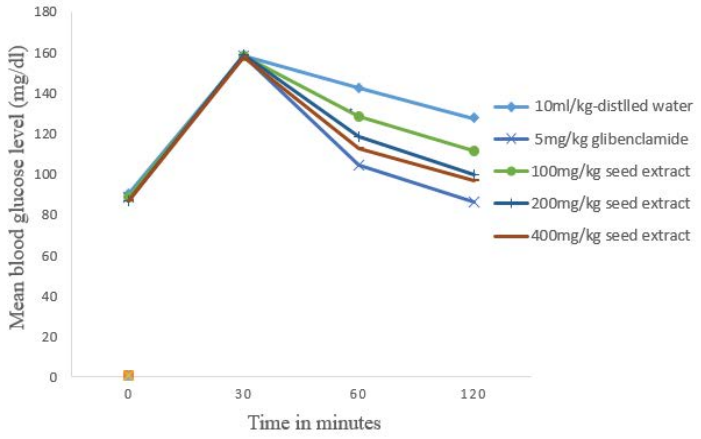

Figure 2: Effect of hydromethanolic seed extract of *D. stramonium* on blood glucose level of oral glucose loaded mice.

Antihyperglycemic effects of hydromethanolic seed extract of *D. stramonium* in diabetic mice

After induction of diabetes, fasted blood glucose levels of daily treated diabetic mice were measured once weekly. The seed extract at the doses of 100 mg/kg, 200 mg/kg and 400 mg/kg significantly ($p<0.0l$) reduced fasted BGL on day seven and fourteen of daily treated diabetic mice compared to the control (Table 4). Antihyperglycemic effect of glibeclamide was significant ($p<0.001$) on day seven and fourteen compared to the diabetic control. There was no significant BGL variation among seed extract and standard drug in STZ induced model.

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^{a2}	240.18 ± 1.63^{a2}
100 mg/kg SE	256.06±1.27	255.06±0.57^{a1}	250.22 ± 0.29^{a1}
200 mg/kg SE	255.44±0.88	249.17±1.06^{a1}	248.55 ± 1.06^{a1}
400 mg/kg SE	255.89±0.92	246.45±0.51^{a1}	247.17 ± 0.25^{a1}

Key: Each data describes as mean ± standard error of the mean, n=6, [a]compared to negative control; [1]$P<0.01$; [2]$P<0.001$; BGL-blood glucose level; NC-negative control; GB-glibeclamide; SE-seed extract

Effect of hydromethanolic seed extract of *D. stramonium* on body weight of diabetic mice

The seed extract at the doses of 200 mg/kg and 400 mg/kg significantly ($p<0.05$) increased BW of diabetic mice on day 7 and 14 compared to diabetic control (Table 5). Body weight improvement of 100 mg/kg dose was delayed and significantly ($p<0.05$) day 14 compared to the negative control. In addition, glibeclamide significantly ($p<0.01$) improved body weight of diabetic mice on day 7 and 14 with respect to negative control.

DISCUSSION

Datura stramonium has been used in Ethiopian folklore medicine and demonstrated *in vitro* blood glucose reduction activity by inhibiting α-glucosidase and α-amylase without *in vivo* test. Therefore, *in*

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[a2]	27.59 ± 0.31[a2]	28.26 ± 0.46[a2]
100 mg/kg SE	22.59 ± 0.55[a]	24.59 ± 0.64[a1]	25.48 ± 0.49[a1]
200 mg/kg SE	23.87 ± 0.23[a]	26.34 ± 0.53[a1]	25.91 ± 0.61[a1]
400 mg/kg SE	24.27 ± 0.63[a]	27.21 ± 0.39[a1]	26.72 ± 0.34[a1]

Key: Each data describes as mean ± standard error of the mean, n=6, [a]compared to negative control; [1] $P<0.05$; [2] $P<0.01$; BGL-blood glucose level; NC-negative control; GB-glibeclamide; SE-seed extract

vivo blood glucose lowering activity of hydromethanolic seed extract of *D. stramonium* was experimentally evaluated by using normoglycemic, oral glucose loaded and Streptozocin induced diabetic in mice. Hydromethanol (80% methanol) was selected as solvent of the extraction since a wide verity of polar and moderately polar phytomolecules extracted in hydromethanol [26,35,46].

The finding of this study showed that all doses of hydromethanolic seed extract were devoid significant hypoglycemic effect at all time points compared to negative control but glucose reduction of standard drug (5 mg/kg glibeclamide) was significant ($p<0.01$) at 2, 4, and 6 hr. Thus, mechanism of action of glucose lowering activity of seed extract and glibeclamide might not be the same. Similar to this finding, hydromethanolic seed extract of *Calpurnia aurea* [47] and root extract of *D. stramonium* [26] devoid significant hypoglycemic activity. In contrast, hydromethanolic leaf extract of *Caylusea abyssinica*, [35] leaf latex of *Aloe vera* [48] and *Aloe megalacantha* [49] demonstrated significant blood glucose lowering activity in normoglycemic model.

In glucose tolerance test, blood glucose reduction of the hydromethanolic seed extract was significantly ($p<0.05$ at 100 mg/kg, ($p<0.01$, at 200 mg/kg and 400 mg/kg) after 60 and 120 minutes oral glucose administration compared to the negative control. Blood glucose reduction of 100 mg/kg dose was significantly ($p<0.05$) lower than 5 mg/kg dose glibeclamide ($p<0.001$, after 60- and 120-minutes). Similar to this finding hydromethanolic seed extract of *Calpurnia aurea*, [47] leaf extract of *Caylusea abyssinica*, [35] root extract of *D. stramonium*, [26] leaf extract of *M. stenopetala* [45] and *Aloe megalacantha* [49] have been demonstrated a significant glucose reduction in oral glucose loaded mice.

In STZ induced diabetic mice treated with 100 mg/kg, 200 mg/kg and 400 mg/kg doses of the hydromethanolic seed extract showed significant ($p<0.01$) glucose level reduction on day 7 and 14 with respect to diabetic control. This showed that the plant endowed antidiabetic activity and in line with administration of the same dose hydromethanolic seed extract of *Calpurnia aurea*, [47] root extract of *D. stramonium*, [26] leaf extract of *M. stenopetala*, [45] leaf latex of *Aloe megalacantha* [49] in streptozotocin-induced diabetic model.2 In another study, administration of leaf extract of *A. vera* at doses of 200 and 400 mg/kg showed comparable glucose reduction with 50 mg/kg metformin [50]. Seed extract of *Datura metel* in the genus *Datura*, has been showed to have significant blood glucose lowering activity [51].

At the same time, there was significant improvement of body weight in seed extract and standard drug treated groups in respect to diabetic control. Body weight of the mice treated with all doses of the hydromethanolic seed extract significantly improved on day 7 and 14. Similar to this finding, many plant extracts possess beneficial effect in the prevention of hyperglycemia induced muscle wastage [52-54] and similar result was observed in this study.

Antioxidant capacity hydromethanolic seed extract of *Stramonium* was determined in 2,2-diphenyl-1-picrylhydrazine (DPPH) [55]. Free radical scavenging property of seed extract was concentration dependent and comparable with standard antioxidant (ascorbic acid). Similar finding reported that strong antioxidant activity of leaf latex and isolated compound of *Aloe schelpei*,[56] and leaf latex of *Aloe megalacantha* [49] in 2, 2-diphenyl-1-picrylhydrazyl (DPPH) assay. Plant derived supplement prevent devastating effect of oxidative stress (ROS) in chronic disease like DM and *Datura stramonium* might offer health benefit through antioxidant property in chronic diseases.

Phytomolecules have been demonstrated blood glucose lowering activity through different mechanisms. They increase glucose up take by augmenting insulin action [57] and increase GLUT 2 expression and promoting translocation GLUS-4 by flavonoids, [58] increase insulin secretion, [59] reduced carbohydrate digestion and absorption by inhibiting α-glucosidase and α-amylase, [45,58,60,61] augment β-cells proliferation and regeneration [45,59] preventing pancreatic β-cells dysfunction through free radical scavenging action by tannins and phenols like flavonoids [62-64] or by any other unknown mechanisms**.** In the present finding, the preliminary phytochemical analysis of the hydromethanolic seed extract of *D. stramonium* has phenolic compounds, anthraquinones, glycosides, saponins, terpenoids, tannins and flavonoids. Therefore, the antidiabetic of the hydromethanolic seed extract could elicit a single or synergetic action of these metabolites.

CONCLUSION

The finding of the study showed that hydromethanolic seed extract of *Datura stramonium* endowed significant blood glucose lowering and antioxidant activity. Further studies are required for bioassay guided fractionation, isolation and characterization of active compound (s) that possess glucose lowering activity.

DECLARATIONS

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.

AVAILABILITY OF DATA AND MATERIALS

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

COMPETING INTERESTS

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

FUNDING

Not applicable

AUTHORS' CONTRIBUTIONS

BC and GG have contributed to conception, design, analysis

and interpretation of data, drafting the article and revising the manuscript and gave final approval for publication.

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