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RESEARCH ARTICLE

Methanolic Extract of Verbascum Thapsus Ameliorates Hyperglycemia and Hyperlipidemia in Alloxan-Induced Diabetic Albino Mice

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Abstract

Diabetes mellitus is a severe endocrine disorder characterized by high blood glucose levels owing to the complete or relative absence of insulin secretion or action. Presently available medicines for DM have numerous adverse effects. Therefore, it is needed to investigate novel methods to improve DM treatment. Thus plant-based management could be a possible strategy. Therefore, current study was designed to evaluate the anti-diabetic and anti- hyperglycemic activity of the Verbascum thapsus in alloxan induced diabetic mice.Alloxan was injected intraperitonially (150 mg/kg,b.w) to induce diabetes in mice. The mice were divided into five groups (n=10); group 1 (normal control) received normal food and water, group 2 (diabetic control) received normal food and clean water, group 3 (diabetic mice) received 200 mg of the methanolic plant extract), group 4 (diabetic mice) received 400 mg of the methanolic extract) , and group 5 (diabetic mice) received the standard drug, Glibenclamide (10mg) for 28 days. Glucose was measured four times and after 28 days, blood samples were collected to measure the lipid profile.Result shows that methanolic extract of V thapsus significantly (P>0.05) reduced the blood glucose, level, TC, TG, LDL, increase in HDL and body weight at 400mg/kg compared to 200 mg and 10 mg of the standard drug after 28 days of treatment.The results of current study suggested that methanolic extract of V thapsus has potent anti-diabetic activity, with no toxicity.

Keywords: Alloxan, Anti-Diabetic, Diabetes mellitus, hyperglycemia, Glibenclamide, Verbascum thapsus.

1 | INTRODUCTION

Diabetes mellitus is an endocrine disorder characterized by prolonged high glucose levels in blood due to irregular or insufficient insulin secretion (1). The frequency of diabetes is increasing worldwide at an alarming rate. Researchers predict that the frequency of diabetes will increase 64% by 2025, meaning that 53.1million peoples will be affected (2). Diabetes has numerous pathogenic routes, from the autoimmune destruction of pancreatic β-cell resulting in a complete lack of insulin secretion(Type I), to several genetic and environmental (obesity, age etc.) (3).

Attheonset of hyperglycemia patients typically experience increased urination (polyuria), thirstiness (polydipsia), and incessant appetite (polyphagia (4) Retinopathy, nephropathy, and neuropathy (5). Prolonged low levels of glucose (hypoglycemia) abrogate fat, protein and lipid metabolism (5).

The conventional treatments of diabetes mellitus are often costly, unobtainable and have several adversarial (6). For example, the utilization of insulin is often associated with low efficacy, a short shelf life, over-prescription and resistance. Other drugs such as sulfonyl ureas and biguanides have been linked to increased body weight (7). Therefore, there is a need to develop high efficacy, low cost, and easily available medicines for the treatment of DM.

Traditional medicinal practices are gaining substantial recognition from mainstream health administrators, global medicinal investigators, and training organizations. The World Health Organization estimates that more than 80% of people in developing nations use traditional medicines (8), as traditional medicines are relatively inexpensive, safe, effective, and reliable (9).

Herbal remedies contain countless varieties of bioactive elements that are used by researchers for potential medicinal uses (10). For example, Metformin is a highly effectively drug traditionally used for the treatment of DM (1). The World health organization has reported that more than 800 traditional plants use foranti-diabetic properties (1) . Certain plants are confirmed to support the renewal of β-cells and promoting the activation of insulin receptors (11, 12). Ginseng is used in traditional Chinese medicine for the management of diabetes. (1).

Verbascum thapsus is a common plant used in traditional medicine. It is widely distributed in the Himalayas (Asia), Europe and North America (13–15). In Pakistan, it is found in different areas of Khyber Pakhtunkhwa and Kashmir (16, 17). Previously it is used for the treatment of pulmonary diseases (17). The leaf has been used as an expectorant and in the treatment of sore throat, bronchitis, and hemorrhoids (17, 18). The Zuni tribe (western New Mexico) has traditionally used the roots of the plant as covering for rashes and various other skin ailments (19). The flowers of the plant have applications in the production of hair dyes (20).The Current study aims to scientifically evaluate hyperglycemia and hyperlipidemia effects of Verbascum Thapsus extracts in Alloxan-induced diabetic albino mice.

2 | MATERIALS & METHODS

2.1 | Area of study

This study was conducted at the Department of Zoology, Hazara University Mansehra and National Veterinary Laboratory Islamabad, Pakistan.

2.2 | Preparation of extract

The plant materials were collected according to the ethnobotanical guidelines issued by various localities in the district of Mansehra, Khyber Pakhtunkhwa (KPK), Pakistan and stored in the herbarium of the Botany Department at Hazara University, Mansehra, KPK, Pakistan under the voucher specimen No-4984.

Supplementary information The online version of this article (https://doi.org/xx.xxx/xxx.xx) contains supplementary material, which is available to authorized users.

2.3 | Phytochemical Analysis of Verbascum thapsus

The harvested leaves of the plant were dried in a shaded area away from direct sunlight for one week and crushed into a rough powder using an electrical grinder. The powder was soaked in 100% methanol (Sigma Aldrich) for 48 hours followed by incessantly shaking for 24 hours. The plant solution was clarified with novel Whitman paper and vaporize using an evaporator machine (Rota vapor R-3) at 50 °C until a sticky dense liquid was achieved, and processed material was stored in a freezer at 4°C for use.

2.4 | Phytochemical Analysis of Verbascum thapsus

Qualitative pre-liminary phytochemical analysis was performed on the methanolic extract of Verbascum thapsus for presence or absence of different chemical constituents such as alkaloids, tannins, flavonoid, carbohydrates, phenolic compounds and saponins by using standard protocols as described before (21, 22). These chemical constituents were identified by characteristic color change.

2.5 | Acute toxicity testing

Toxicity of the extract was tested according to the protocol described before with some modifications [23].Briefly, mice were kept on fast overnight and then extract were administered at dose of 1000mg/kg. b.w. The mice were kept under observation for 24 hrs. for behavioral and neurological changes. The mice were observed for 14 days for any toxic symptoms. Some guidelines were set that if mortality is observed in 1 or 2 animals then this dose was considered toxic and if no death occurred then this dose was assigned as non-toxic.

2.6 | Experimental animals

Fifty, 8-10-week-old, healthy male mice (BALB/C), weighing 30-40 g were bought from the National Institute of Health (NIH), Islamabad, and acclimatized for one week at the animal house. The mice were provided normal food and water, ad libitum.

2.7 | Standard drug (Glibenclamide)

Standard drug (Glibenclamide) tablets (10 mg) were bought from Sanofi- Aventis Pakistan limited for a positive control in the experiments. The pills were crushed into satisfactory residues and liquefied in refined water to make a solution.

2.8 | Induction of diabetes

For the diabetes induction, the mice were starved and only allowed to drink water. A single dose (150 mg/kg) of Alloxan monohydrate (Sigma Aldrich, USA) was freshly prepared in phosphate buffer saline (PBS) for intra-peritoneal injection. The blood glucose levels of the mice were measured 72 hours after Alloxan injection. Mice that had a fasting blood glucose level above 200 mg/dl were considered diabetic, while mice that had a blood glucose level of less than 200 mg/dl were exclude from the study.

2.9 | Experimental Design

A total of 50 strong male mice were selected for the experiment and separated into five clusters: each set consisting of 10 mice.

2.9.1 | Group I-Normal control

Received normal food and purified water throughout the experiment.

2.9.2 | Group II- Diabetic control

fed normal food and normal water

2.9.3 | Group III – Extract treated

Treated with V thapsus plant extract (200 mg/kg) for 28 days.

2.9.4 | Group IV – Extract treated

Treated with V thapsus extract (400 mg/kg) for 28 days.

2.9.5 | Group V-standard drug treated

Treated with commercially availableMedicine Glibenclamide (10 mg/kg) for 28 days.

2.10 | Bodyweight counting

During the entire experiment period, the body weights of the mice were measured every week and the variations were documented.

2.11 | Blood glucose determination

Blood samples were extracted from the tail of the mice. The blood glucose concentration was measured by Glucometer, using glucose strips (On-Call Extra). Blood glucose concentrations were recorded and expressed in mg/dl.

2.12 | Lipid profile determination

Mice were sacrificed after anesthetized and blood was taken from heart directly via sterile syringe. The plasma was left at standing position at RT for 1hr for blood clothing and then spins down at 5,000 rpm for 15 min, and the supernatant (serum) was used for lipid profiling. The serum concentration of high-density lipoprotein (HDL), low-density lipoprotein (LDL) were measured using a method as described (23). Total cholesterol (TC), and triglycerides (TG) was measured using a method as developed before (24).

2.13 | Statistical Analysis

The data in this study is presented as the mean ± SD of three independent experiments. The SD was calculated using Microsoft Excel and Graph pad prism software (version 5), one-way ANOVA (analysis of variance).

3 | RESULTS

3.1 | Preliminary Phytochemical Screening

In this study the phytochemical screening of V thapsus showed the presence of some secondary metabolites that are summarized in theTable 1.

TABLE 1: Phytochemical Screening of V thapsus

Metabolites	Results
Tannins	++
Saponins	++
Proteins and Amino acids	--
Alkaloids	++
Terpenoids	++
Flavonoids	++
Coumarins	--
Glycosides	++

Notes: ++ = Test Positive; – = Test Negative

3.2 | Acute Toxicity studies

For the determination of safer and non-toxic dose of v thapsus the mice were treated with 1000mg/kg.b.w and kept under observation for behavioral and neurological symptoms. No behavioral and neurological signs and symptoms were observed in all tested mice. No mortalities were observed at 1000mg/kg. b.w drug dose during 14 days of treatment. Hence it was found that V. thapsus is safe and have no toxic effects on mice. Therefore, in current studydifferent dose (200,400/kg. b.w) was selected.

3.3 | Week Wise effect of the Methanolic Extract of V thapsus on Glucose Level in Alloxan Indced Mice

Results shows that mice treated with 400 mg/kg of the V thapsus plant extract show significantly ($P< 0.05$) reduction in fasting blood glucose concentrations compared to the group that were treated with glibenclamide, (10 mg/kg) and 200mg and standard control,. The mice treated with the dose of (200 mg/kg) of extract did not have statistically significant ($P> 0.05$) reductions in blood glucose level Table 2 relative to the standard drug control group.

Alloxan induced diabetic group of mice. Values expressed as Mean ± SD, (n= 10), *$P< 0.05$.

TABLE 2: Effect of V thapsus extracts and glibenclamide on fasting blood glucose levels in

Fasting blood glucose levels (mg/dL) per week					
Treatment groups	Day 1	Day 7	Day 14	Day 21	Day 28
Normal Control	118.8±20.0	90.4±12.2	108.6±14.8	106.5±17.4	109.9±13.0
Diabetic Control	284.7±132.9	335.7±120.0	373.4±102.4	366.5±75.5	372±88.6
V. thapsus extract 200 mg/kg	334.3±104.2	293.4±96.7	239.4±133.7	232.5±153.3*	225.6±118.2*
V.thapsus extract 400 mg/kg	308.6±175.3	187.5±91.3*	178.5±150.6*	172.7±84.0*	164.5±84.8*
Glibenclamide10 mg/kg	297.8±69.0	273.4±58.7	220±75.6*	191.5±54.5*	186.2±64.2*

3.4 | Measurement of mice body weights

A significant increase in body weight was observed in the treated groups, while a significant decrease in body weight was seen in the diabetic control group. The oral administration of V thapsus extract (200, 400 mg/kg) and glibenclamide (10 mg/kg), was found to increase the body weight of the mice, 25.5±4.4 to 31.5±6.7 in the 200 mg/kg treatment group, 26±2.1 to 35±3.3 in the 400 mg/kg treatment group, and 27.5±5.4 to 32.5±5.4 in the glibenclamide (10 mg/kg) treatment group, respectively, relative to the diabetic control group ($P<0.05$). The body weight was measured five times throughout the study using a digital scale. Results show that the increase in body weight treating with the plant extract was likely due to a build-up of protein. Variations in the body weight of the different groups documented in the tables Table 3.

TABLE 3: Result of V. thapsus extracts and glibenclamide on the mice body weight. Values expressed as Mean ±SD, (n= 10), *P< 0.05.

Bodyweight of mice (gm) per week					
Treatment groups	Day 1	Day 7	Day 14	Day 21	Day 28
Normal Control	35±3.3	34.5±2	28.5±1	35±2.4	35±1.6
Diabetic Control	38.5±	36.5±	29±8	24.5±	21.5±2.4
V. thapsus extract 200 mg/kg	25.5±4	26±4.6	29±5.2	31±2.1	31.5±6.7*
V. thapsus extract 400 mg/kg	26±2	27±3	31±2	34.5±	35±3.3*
Glibenclamide 10 mg/kg	27.5±5	28±4.2	29±2.1	31±3.9	32.5±5.4*

3.5 | Measurements of Lipid profile

Lipids play crucial roles in the etiology of DM because the level of cholesterol increases due to alter metabolism of lipids. In the current study, elevated levels of cholesterol were seen in diabetic control mice. Mice treated with extract shows gradually reduction in cholesterol levels. Table 4 showed the effects of glibenclamide and methanolic extracts of V. thapsus on the serum Triglycerides (TG), High Density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C) and total cholesterol (TC). The TG value were significantly ($p<0.05$) higher in diabetic control mice. Diabetic mice had shown significant reduction in TG value treated with different doses (200 mg/kg, 400 mg/kg) of V. thapsus for four weeks. The level of TC and LDL upon the administration of different doses of V. thapsus and Glibenclamide (10mg) were reduced significantly ($p<0.05$) compared to the diabetic group which showed that methanolic extract of V. thapsus were effective in normalizing the level of cholesterols in alloxan induced diabetic mice.

4 | DISCUSSION

Historically, plant-based medicines have been extensively used worldwide for the treatment of diabetes mellitus (25). Presently commonly prescribed

TABLE 4: Effect of Glibenclamide and V. thapsus extract on Lipid profile of Alloxan-induced diabetic mice after four weeks of treatment. Values expressed as Mean ± SD, (n= 10), *P< 0.05.

Lipid profile				
Treatment Groups	(TG)	(HDL)	(LDL)	(TC)
Normal control	73.59±11.64	45±2.5	56.87±4.00	116.83±11.20
Diabetic Control	129.63±21.53	37.35±2.58	98.73±9.5	145.13±7.94
V. thapsus extract 200 mg/kg	121.53±15.01	38.67±3.51	93±2.7	139.77±20.61
V. thapsus extract 400 mg/kg	99.54±14.01*	42.86±2.42*	75.67±3.64*	126.45±15.61*
Glibenclamide dose 10 mg/kg	118.56±15.65	39.32±2.23	88.56±2.43	136.55±16.73

modern anti- diabetic medicines have been associated with numerous side effects (26–28). Therefore, researchers have been trying to develop plants-based medicines for the treatment of diabetes, as they have little side effects, high efficacy and relatively cheap and easily assessable (29).

The current investigation aimed to examine the anti-diabetic effects of a methanolic leaf extract of V thapsus on Alloxan induced diabetic mice. Earlier studies on the plant are its antioxidant activity, effects on the production of body odor, for lung other cutaneous disorders (30–32). The anti-diabetic properties of this plant have not been fully investigated, until now. Our findings revealed that methanolic extracts of V thapsus have strongly antihyperglycemic and anti- hyperlipidemic activities at two different concentrations (200 mg/kg and 400 mg/kg). The anti-diabetic activities were particularly significant (P< 0.05) in mice treated with 400 mg/kg of the plant extract and standard control drug, glibenclamide at (10 mg/kg).

A previous study reported that a methanolic leaf extract of zingiber officinale (300 mg/kg) is effective in reducing blood glucose concentrations in Alloxan induced diabetic rats in six weeks of treatment (33). Although this plant extract appears to be more effective than the results for V Thapsus (400 mg/kg) due to the duration of the treatment.

Similarly another study which showed that the oral administration of an aqueous leaf extract of C. hirsutus (250, 500, 1000 mg/kg) for four weeks was effective at the high concentration (1000 mg/ kg) (P < 0.01) in reducing blood glucose concentrations (34). This result is comparable to our findings even though the effective dose of C. hirsutus (1000 mg/kg) is significantly greater than the effective dose identified for V thapsus (400 mg/kg), suggest that V thapsus is also more effective. Another study regarding the administration of an ethanolic extract of Phyllanthus amarus (400 mg/kg b.w for 7 weeks and three days) also have similar results as in our study [36]. The prolonged management period with P. amarusmay be considered more effective than V. thapsus, however this hypothesis needs to be further verified in the future.

Our study revealed that V thapsus extracts (200 and 400 mg/kg b.w) and Glibenclamide (10 mg/kg) treatments, lead to dose-dependent, significant (P< 0.05) increases in the body weight of diabetic mice in the 28^{th} days of treatment. It has been established in previous studies that the increase in body weight of diabetic mice may be due to the enhanced production of insulin (35). Other similar studies involving Ficus bengalens is and foenumgreacumplant treatments demonstrated similar result in increasing in the body weight of Alloxan induced diabetic rats (36–38).

In a study regarding the oral administration of C. hirsutus aqueous leaf extract (250, 500, 1000 mg/kg; for four weeks) shows (1000 and 500 mg/kg) significant increases in body weight, suggesting that the treatment had a positive influence (34) . The results were like that observed in this study.

Lipids performed a vital role in the causing of diabetes (39). The chief complications of high level of cholesterol are hyper cholesterolemia and hyper triglyceridemia in diabetes (40). In the present investigation, we observed that the leaves extract of V. thapsus declines cholesterol level in the blood at a dose of 400mg and 200mg/kg of b.w).

A study showed that Nigellasativa leaves extract reduced the level of Cholesterol in STZ-induced dia-

betic rats at dose of (350 mg/kg)for three weeks treatment, compared to the diabetic control mice (41). In our present study, diabetic mice treated with V. thapsus extract (200 and 400 mg/kg) for 28 days showed a decrease the level of low-density lipoprotein-cholesterol (LDL), improved high-density lipoprotein (HDL) regularized (TC) and Triacylglycerol (TG) significantly (P>0.05).

The reduced cholesterol levels following V. thapsus extract management may be due to the great competence of definite enzymes like lecithin cholesterol acyl transferase enzymes, which controls blood lipid amount and alter the fatty acid into its accumulated form (triglyceride). Insulin shortage is also accountable for the deposition of cholesterol since insulin inhibits the carriage of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) which is responsible for the deprivation of rich cholesterol LDL elements. (42).

5 | CONCLUSIONS

The antidiabetic activities of a methanolic leaf extract of V thapsus (400 mg/kg) were evaluated in Alloxan induced diabetic mice. The extract was found to be a more effective antihyperglycemic agent than the commercially available and frequently prescribed medicine, glibenclamide (10 mg/kg). The extract effectively reduced the blood glucose concentrations and countered extreme weight loss in diabetic mice. Based on our results and literature review, it can be deduced that the V thapsus extract improves the peripheral consumption of glucose by improving glycolysis in the liver and the ability of the kidney to maintain glucose homeostasis. The extract, like insulin, also likely impedes gluconeogenesis. These properties of the extract may be attributed to the existence of compounds such as iridoid, saponins, flavonoids, glycosides, vitamin C and phenylethanoid, which act individually or in synergy with other compounds to overcome irregular glucose metabolism.

The positive results from this study strongly advocate further biochemical and pharmacological studies so that the bioactive components and their respective mechanisms of action may be ascertained. There is an abundance of natural materials that may potentially be used to manage and treat various human diseases. This study has demonstrated that the V thapsus plant has great implications as a medicine for the treatment of diabetes mellitus.

6 | ETHICAL APPROVAL

All experiments were conducted according to the principles of the Department of Zoology, Hazara University Mansehra and National Veterinary Laboratory Islamabad, Pakistan.

7 | ACKNOWLEDGMENTS

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8 | CONFLICTS OF INTEREST

The authors have no conflicts of interest.

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