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ANTIDIABETIC, HYPOLIPIDEMIC AND PHYTOCHEMICAL ANALYSIS OF PEGANUM HARMALA ETHANOL EXTRACT IN ANIMAL MODEL

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Abstract

Aims: The study was designed to determine *Peganum harmala* seeds effects on Streptozotocin induced Diabetes, Obesity and triglycerides levels in Swiss Albino Mice**.**

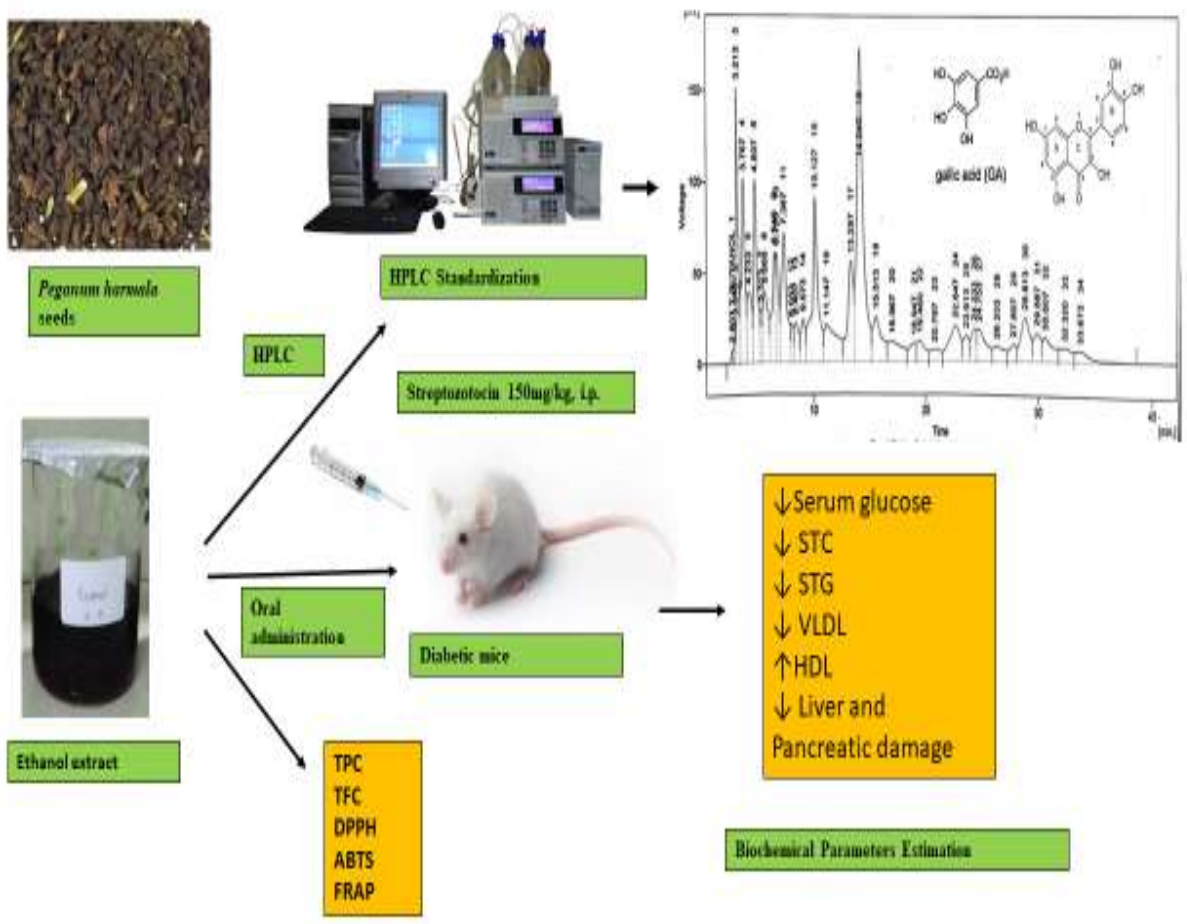
Material and Methods: The antidiabetic activity was assessed on three different models normoglycemic, oral glucose tolerated mice and Streptozotocin induced diabetic mice. The antioxidant analysis was done by ABTS, FRAP, DPPH and phytochemical estimation was carried out by HPLC, TPC (Total phenolic contents), TFC (Total flavonoids contents).

Results: The ethanol extract of *Peganum harmala* seed extract (EEPHS) showed significant ($p>0.001$) hypoglycemic activity in all the three models. Similarly, significant $p>0.05$ concentration dependent antioxidant potential was seen by all three methods. The extract showed considerable range of TPC and TFC. The HPLC analysis showed the presence of potentially active compound such as quercetin, gallic acid, Sinapic acid vanillic acid, Ferulic acid, chlorogenic acid, Syringic acid, Cinnamic acid.

Conclusion: *Peganum harmala* seeds extract showed Significant anti-hyperglycemic activity and anti-hyperlipidemic activity.

Key words: *Peganum harmala*, ethanol extract, antioxidant, diabetes mellitus, medicinal plants, antihyperlipidemic

Graphical abstract:



Introduction

Diabetes mellitus (DM) is rapidly rising worldwide disease, and (I.D.F., 2018) reported approximately 425 diabetics in 2017 and in 2045 this figure will be rise to 35.35%. Diabetes mellitus is long-lasting metabolic disease characterized by disturb protein, carbohydrate and fatty acid metabolism. Among the two prevalent types of diabetes mellitus, type two diabetes (T2D) is the most widespread, contributing to over 90% of the morbidity and mortality associated with diabetes (I.D.F., 2018). It arises from the cells' inability to effectively utilized insulin produced by the pancreatic β-cells. Pancreatic beta cells resist insulin resulting in the elevation of blood glucose level [1]. Continuous raised blood glucose levels, a characteristic feature of type 2 diabetes (T2D), is identified as the primary hallmark. This chronic hyperglycemia stimulates free radicals' formation. Continuous free radicals' formation results in a redox imbalance, causing a simultaneous decreases the body's natural antioxidant defenses and ultimately leading to oxidative stress. Oxidative stress is recognized as the key initiator of macro and micro-vascular problems associated with type 2 diabetes such as retinopathy, microangiopathy, nephropathy and death [2]. Currently, there are numerous antidiabetic drugs available in the market to treat hyperglycemia. Theses medication primary work to enhance insulin sensitivity, optimizing insulin performance, increasing insulin secretion and prompting glucose uptake. However, antidiabetic drugs like metformin and sulfonylureas are associated with various side effects. For instance, metformin has been linked to issues such as lactic acidosis and diarrhea, while sulfonylureas causes weight gain,, hepatic dysfunction, hypothyroidism and tachycardia [3, 4]. Plants have consistently been regarded as among the most dependable reservoirs of therapeutic agents for treating various ailments, and many synthetic drugs are either directly or

indirectly derived from them. According to recent research, plants and their derivatives can possess potent antidiabetic properties [5]. Medicinal plants, renowned for their antidiabetic effects achieved by inhibiting enzymes and exhibiting free radical scavenging properties, are emerging as promising strategies for the diabetes management and its associated complications [4]. The medicinal plants in discovering the potential antidiabetic activities have grown, drawing attention as reservoirs of bioactive compounds and antioxidants. The protective role of antioxidant properties of medicinal plants is vital for the restoration of β-cell function in diabetes mellitus. Since free radicals are known to cause damage and alterations to cells, oxidative stress plays a key role in the development of diabetes mellitus and its complications. Thus medicinal plants with antioxidant capabilities hold significant importance in managing diabetes mellitus and its associated challenges by neutralizing free radicals. [6]. On the other hand, there has been significant attention given to natural products as reservoirs of bioactive compounds known for their anti-hyperlipidemic properties. Maintaining a well-balanced lipid profile is essential to mitigate the risk of heart disease and atherosclerosis linked to diabetes, halting from diabetic dyslipidemia [7, 8]. *Peganum harmala* L. also commonly known as harmal belongs to Zygophyllaceae family is a well fame medicinal plant. The various parts of the plants have been used for therapeutic purpose including root, stem, bark and seeds. Recent years of research reported its number of pharmacological properties and bioactive alkaloids harmaline and harmine. Studies on phytochemistry of the plant show the presence of; beta-carboline alkaloids including harmalol, harmine and harmaline. Harmine is widely studied alkaloid [9]. The study was designed to determine *Peganum harmala* seeds effects on Streptozotocin induced Diabetes, Obesity and triglycerides levels in Swiss Albino Mice**.**

Methodology

Collection and Identification of Plant Sample

The *Peganum harmala* seeds were purchased from Faisalabad local market and authenticated and identified from the expert of Botany department of, GCUF; voucher number of sample plant was GMB-246/22 and deposited in the herbarium of botany department GCUF.

Plant extract preparation

The seeds were weighed and washed with water and then dried at room temperature. 500 grams of seeds were ground in electric grinder. The powder of the seeds was macerated in 100% ethanol in a 5-liter glass beaker for 7 days period with occasional stirring and shaking. After seven days the macerated material was filtered with Whatman no. 8 filter paper. The solvent was evaporated by rotary evaporator at forty degrees centigrade. The percentage yield was 19.34%

Determination of Antioxidant capacity of *Peganum harmala* Seed Extract

Antioxidant capacity of *Peganum harmala* seed extracts were determined by DPPH (2, 2'-diphenyl-2- picrylhydrazyl) radical scavenging assay, FRAP ferric reducing antioxidant potential (FRAP) assay and ABTS (2,2'-Azinobis (3-Ethylbenzothiazoline-6-Sulphonic Acid) method. Antioxidant activity by DPPH assay was evaluated by the described by [10]. Ascorbic acid used as reference. 2mL of ethanol extract at different concentration mixed with 1ml of DPPH solution. The mixture was incubated for 30 min at room temperature in the dark. Control was prepared by mixing 1ml DPPH solution in double distilled water. Spectrophotometer was used to measure the absorbance 517nm. The reduced absorbance of mixture showed the higher DPPH activity. The sample reading was calculated in triplicate.

The ferric reducing antioxidant potential was performed by the method described by [11]. 2ml of 1ml of FRAP reagent was mixed in 3mL of ethanol extract at different concentration. The mixture was incubated for 30 min at room temperature in the dark. The absorbance was measured by using spectrophotometer at 593 nm. Increased absorbance showed the higher reducing activity. Ascorbic acid used as reference drug. Standard curve was prepared and Results were expressed in mg of ascorbic acid equivalents (AAE)/mL of extract.

[12] method was used to determine the ABTS (2,2'-Azinobis (3-Ethylbenzothiazoline-6-Sulphonic Acid) antioxidant activity of EEPHS. 3ml ABTS reagent was mixed with 2 mL of the ethanol extracts at different concentrations. The mixture was incubated for 10 min at room temperature in the dark. The control was prepared by mixing 2.0 mL of ABTS solution with 1 mL of double distilled water. The spectrophotometer was used to measure the absorbance against a blank at 734 nm. BHT (Merck, Germany) was used as the standard. Samples were prepared and measured in triplicates.

Total Phenolic and Flavonoids contents determination

Total phenol content of the *Peganum harmala* seed extract was assessed via Folin Ciocalteu method described by [13]. The freshly prepared gallic acid reagent in series of concentrations was used to create standard curve (y=0.01017x + 0.004810). Total phenol content was expressed as equivalent (μg)/g of dry weight.

Total flavonoids contents were estimated by aluminium chloride method described by [13]. The quantitative analysis of flavonoids contents was calculated from calibration curve. The equation for calibration curve was (y= 0.0074x- 0.0182). The results were expressed as quercetin equivalent (μg)/g of the dry weight.

Antidiabetic activity

Experimental animals

The study utilized Swiss albino mice weighing between 25-30 grams. These mice were accommodated in a regulated environment maintaining a temperature of (24 ± 2°C), humidity levels at (60 ± 1%), and a light-dark cycle of 12 hours each. Throughout the study, the mice had unrestricted access to standard pellet food and water. To ensure acclimatization, the animals were introduced to the study conditions one week prior to the commencement of the research.

Induction of Diabetes

Swiss albino mice of both genders were employed in the research. The mice underwent an overnight fasting period. To induce diabetes in the mice that had fasted overnight, a streptozotocin was administered at a dosage of 150 mg/kg body weight. Following the injection, all animals were granted ad libitum access to food. The mice were allowed a one-week acclimatization period. Fasting blood glucose levels were measured with a glucometer after seven days from the streptozotocin injection, and only animals exhibiting blood glucose levels exceeding 250 mg/dl were chosen for inclusion in the study.

Grouping and Dosing of Animal

Hypoglycemic Test on Normal Mice

Following a six-hour fasting period, the animals were selected randomly and distributed into four groups, each comprising six animals (n=6). Group I served as the standard control and received glibenclamide 5mg/kg dose. Group II, received distilled water and named normal control. Groups III received *Peganum harmala* seed extract at doses of 200 mg/kg and Group IV received 400 mg/kg. Both the plant extract and glibenclamide dissolved in 5% DMSO solution. A single dose of 10 ml/kg was administered through oral gavage.

Oral Glucose Tolerance Test (OGTT) in Mice

Following a six-hour fasting period with unrestricted access to water, the animals were selected randomly and divided into four groups, each comprising six animals (n=6). Group I received the standard drug glibenclamide at 5mg/kg dose. Group II, received distilled water and named the normal control. Groups III received *Peganum harmala* seed extract at doses of 200 mg/kg and Group IV received 400 mg/kg. Both EEPHS and glibenclamide dissolved in 5% DMSO solution, and a single dose was orally administered to all animals. After a 30-minute interval, glucose solution at a dose of

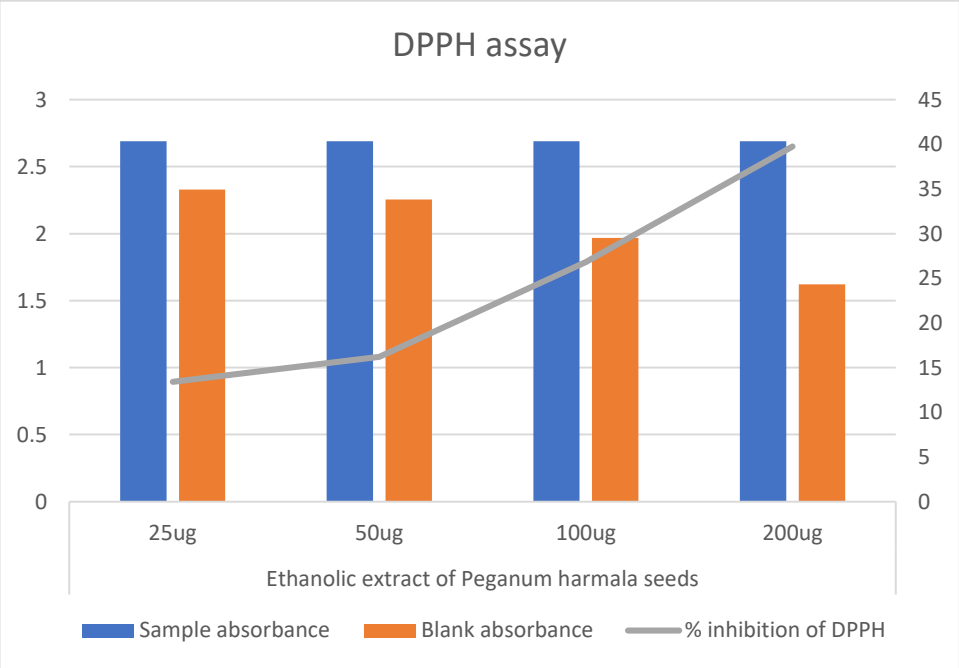
2g/kg was given to all animals. Blood samples were collected from each mouse, and baseline blood glucose levels were measured at 0 minutes. Subsequent measurements were taken at 30, 60, and 120 minutes after the administration of glucose.

Antihyperglycemic activity of *Peganum harmala* ethanol extract in STZ-induced diabetic mice
In this study design 60 mice were used. All the 60 mice were divided into five groups. Group 1 untreated diabetic mice, Group II received normal saline and was named normal control; Group III treated with Glibenclamide 200mg/kg and named standard control; Group IV treated with 400mg/kg EEPHS and Group IV treated with 200mg/kg EEPHS. EEPHS and glibenclamide administered once daily for 15 days. All groups received their respective treatments in a volume of 10 mL/kg daily for 15 days through oral gavage. By using electronic weight machine body weight measured.

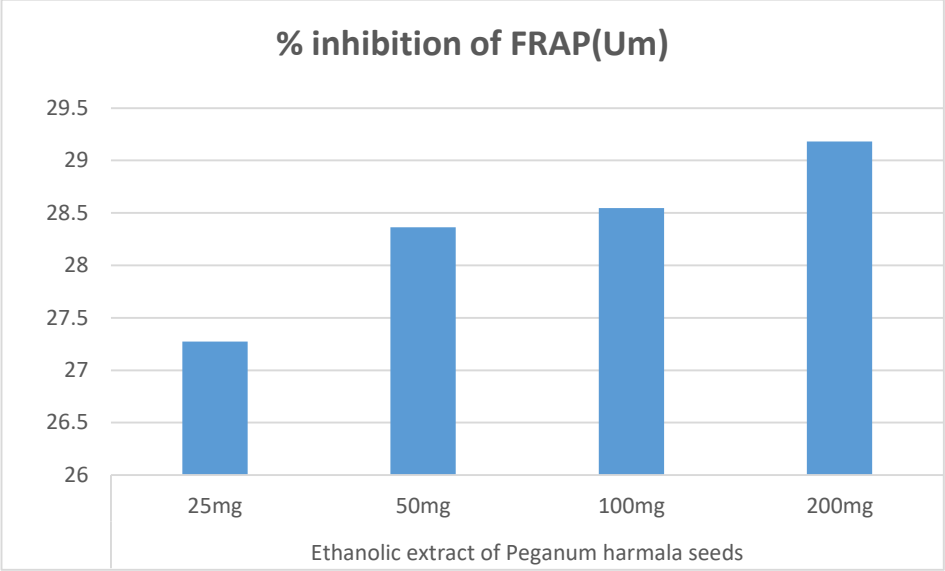
Blood sampling and biochemical parameters determination
On 0, 7 and 15th day of the study blood sample collected from the tail vein. Blood glucose level was measured by glucometer. HDL, STG, STC and VLDL was measured**.**

Statistical analysis:
Data were expressed as mean ± SEM. One-way ANOVA followed by post hoc test was applied on the data for statistical analysis.

Results
Antioxidant Potential
DPPH assay
Peganum harmala showed DPPH activity in concentration dependent. The extract showed scavenging activity in the order of 200 µg>100 µg>50 µg> 25 µg i.e. (35.46±0.133%)> (16.188±0.22%), > (12.44±0.33%), > (8.43±3.33%) respectively as in Figure 1.

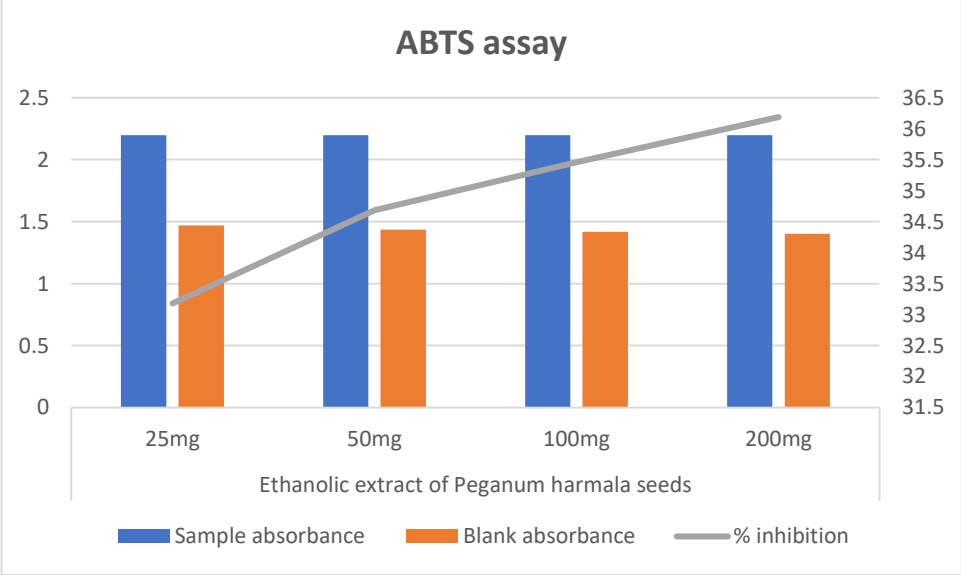


FRAP assay
The *Peganum harmala* seed extract showed ferric ion reducing activities in the order of 200 µg>100 µg>50 µg> 25 µg i.e. 30.33>29.454>, 27.246 >, 24.433 µmol TE/g respectively Figure 2.



ABTS assay

The order of reducing ABTS radical scavenging activity at 200mg> 100mg> 50mg>25mg were 37.166±2.33, 36.35±3.44, 33.58±2.55, 31.16±1.66 respectively Figure 3.



Total Flavonoid and Phenolic Contents

The total flavonoids contents were in range of 25mg (375.31±0.31mg QE/g), 50mg (231.5±0.29mg QE/g), 100mg (208.7±0.37mg QE/g), 200mg (144.3±0.67 mg QE/g). Similarly, phenolic contents were in range of 25mg (712.4±0.29mg GAE/g), 50mg (706.7±0.66mg GAE/g), 100mg (445.7±0.39mg GAE/g), 200mg (288.4±0.29mg GAE/g).

Table 1: Concentration range of TPC and TFC in EEPHS

Plant extract	Concentration	MgGaE/g	µg catechin equivalent per Ml
EEPHS	25mg	375.31±0.31	712.4±0.29
	50mg	231.5±0.29	706.7±0.66
	100mg	208.7±0.37	445.7±0.39
	200mg	144.3±0.67	288.4±0.29

The values are expressed as Mean ±SEM.

HPLC-MS screening of Seed extract

Compound displayed on HPLC analysis were, Quercetin (3,4′-O-diglucoside), Gallic acid (3, 4, 5-trihydroxybenzoic acid), vanillic acid (monohydroxybenzoic acid), chlorogenic acid **(**tetrahydroxy-cyclohexane carboxylic acid), synergic acid (dimethoxybenzene), ferulic acid (hydroxycinnamic acid), cinnamic acid mono-carboxylic acid C6H5-CH=CH-COOH and sinapic acid (4-Hydroxy-3,5-dimethoxycinnamic acid). Results described as in parts per million (ppm).

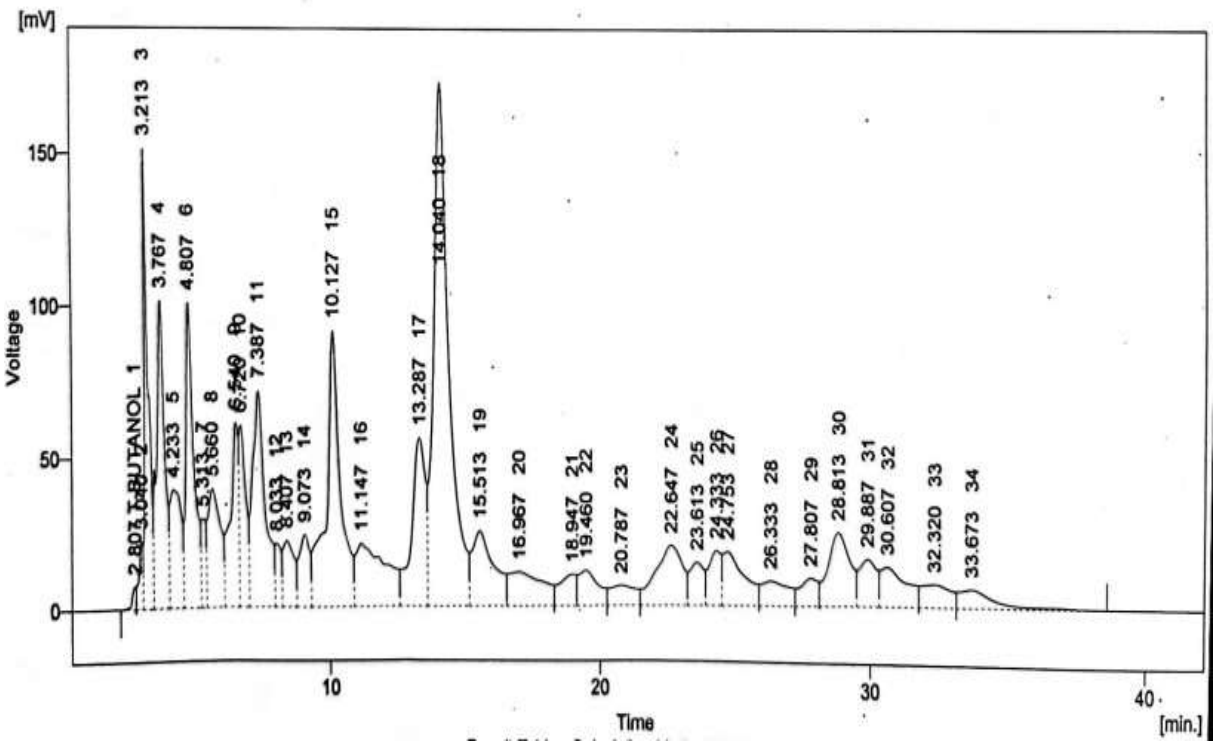


Figure 4 HPLC Chromatogram of the *Peganum harmala* ethanol extract

Table 2 Compound identified in EEPHS by HPLC-analysis

Sr. No	**Compound**	**Retention time (Min)**	**Quantity in µg/g Extract**	**Absorbance**
1.	Sinapic acid	26.33 min	7.5497 ppm	280nm
2.	Cinnamic acid	24.753 min	35.4156 ppm	
3.	Ferulic acid	22.647 min	101.0458 ppm	
4.	Syringic acid	16.967 min	25.2823 ppm	
5.	Chlorogenic acid	15.513 min	110.740 ppm	
6.	Vanillic acid	13.287 min	122.6160 ppm	
7.	Galic acid	4.807 min	74.8542 ppm	
8.	Quercetin	3.040 min	12.2127 ppm	

Effects of EEPHS in normoglycemic mice.

In normoglycemic mice hypoglycemic activity of *Peganum harmala* extract was evaluated. The result showed dose dependent hypoglycemic activity. The extract dose 400mg/kg showed significant ($p>0.001$) hypoglycemic activity in comparison with normal control.

Table 3 Hypoglycemic activity at different time interval

Groups	**0 hr**	**1 hr**	**2 hr**	**4hr**	**6 hr**
Normal Control	121.34±0.33	121.44±1.34	120.33±0.44	119.21±1.33	121.33±2.11
EEPHS 400mg/kg	118.21±1.22	120.33±2.34	117.31±0.67	114.33±2.11	114.33±0.87*
EEPHS 200mg/kg	124.2±2.44	121.21±1.32	120.23±0.56	119.32±1.44	119.66±098
GLC 5mg/kg	120.21±0.76	121.33±1.00	120.33±0.33	119.31±0.22	119.66±034*

Values expressed as Mean and standard error of mean

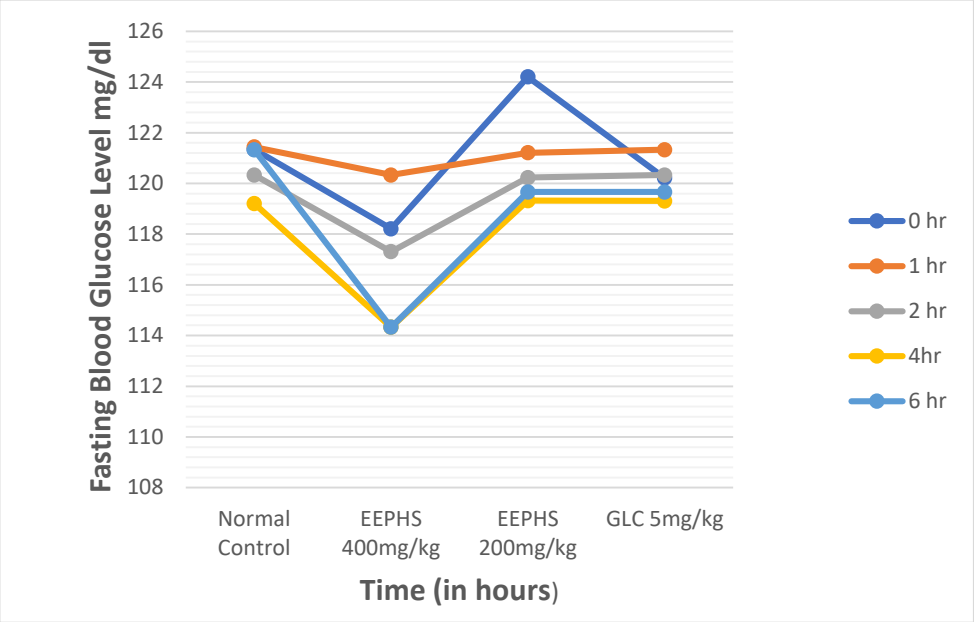


Figure 5 Figure showed extract effects on blood glucose level at different time interval

Effect of EEPHS on Oral Glucose Tolerated Mice

In glucose tolerated mice EEPHS showed significant ($p>0.001$) dose dependent hypoglycemic activity. The extract dose 400mg/kg showed significant hypoglycemia in comparison to normal control.

Table 4 Hypoglycemic activity in Mice undergoing oral glucose tolerance

Group	Base line	30min	60min	120min
Standard Control	123.21±1.22	181.34±0.23	154.21±1.67	143.33±0.66
Normal Control	121.33±1.34	188.22±0.33	180.34±1.34	179.31±0.41
EEPHS 200mg/kg	122.83±1.56	186.33±0.44	178.45±0.91	177.23±0.33
EEPHS 400mg/kg	123.66±1.11	184.33±0.67	169.44±0.56	158.99±0.22

Values are shown in Mean ±SEM. N=6 *p<0.05, **p<0.001, ***p<0.0001

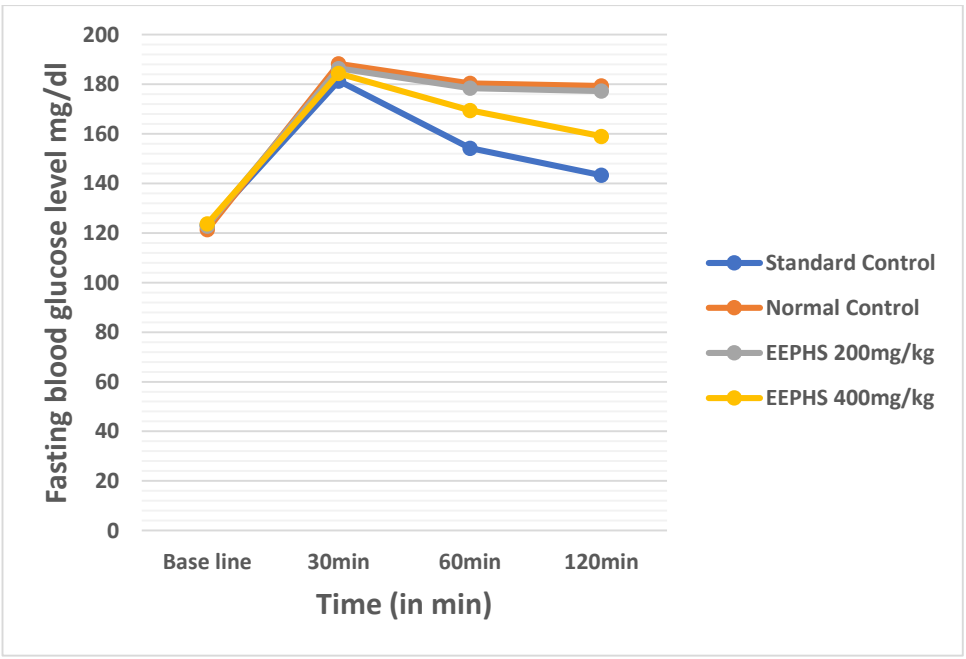


Figure 6

Antihyperglycemic activity in STZ-induced diabetic mice

The hypoglycemic activity of EEPHS was evaluated in diabetic mice. All grouped mice showed considerable increase in blood glucose level at 0 day. The extract group 400mg/kg showed significant ($p>0.01$) fall in blood glucose level on 7th day (268.44±2.33) and further fall occurs on day 15th (230.44±3.44). The result showed comparable effects with standard control.

Table 5 Antihyperglycemic activity in STZ-induced diabetic mice

Group	0 Day	7th Day	15th Day
Diabetic Control	275.33±0.34	293.66±0.11	290.44±0.33
Standard Control	273.22±0.21	244.33±0.44	143.55±0.66
Normal Control	121.3±0.12	120.331±0.22	121.66±0.53
EEPHS 200mg/kg	277.37±0.64	268.44±0.42	230.44±0.26
EEPHS 400mg/kg	276.45±0.266	267.55±0.22	158.66±0.99

Values are expressed as Mean ±SEM. N=6 *p<0.05, **p<0.001, ***p<0.0001

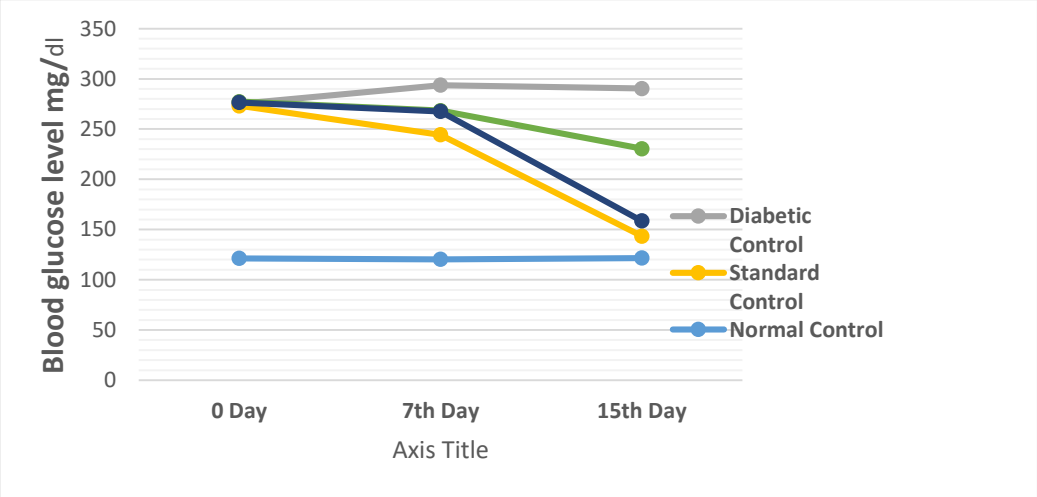


Figure 7 Effect of Extract on blood glucose level on different days

Effect of extract on Obese diabetic mice

The impact of the ethanolic extract of *Peganum harmala* seeds on the body weight of STZ-induced diabetic mice is detailed in Table 6. The diabetic control group experienced notable body weight loss on the 7th and 14th days compared to normal mice. The findings indicated that the doses of EEPHS at 200 mg/kg ($P < 0.05$ on the 7th day) and 400 mg/kg ($P < 0.01$ on the 7th and 14th days) significantly improved body weight compared to the diabetic control. Similarly, diabetic groups on standard drug also exhibited increased body weight ($P < 0.001$). However, when compared to the normal control, the body weight of both the standard control and EEPHS groups remained lower than that of the normal control.

Table 6 Effect on Obese Diabetic mice

Group	Before induction of Diabetes	Base line	Fasting Blood Glucose Level	
			7th Day	15th Day
Diabetic Control	40.11±1.22	39.34±2.11	40.44±6.77	39.88±3.44
Standard Control	39.22±2.34	33.12±0.22**	31.21±0.61	31.23±0.21
Normal Control	39.00±1.34	29.33±2.33	26.21±2.88	25.88±2.11
EEPHS 200mg/kg	38.45±2.33	31.44±4.55***	33.88±1.99*	32.33±3.11*
EEPHS 400mg/kg	39.31±2.11	31.23±1.66***	32.11±4.11**	30.11±2.66***

Values expressed in Mean ±SEM.

Effect on serum Triglycerides levels

A remarkable ($P < 0.01$) rise in serum TG, TC, LDL, and VLDL cholesterol levels occurred after diabetes induction, accompanied by a significant fall in ($P < 0.001$) in HDL cholesterol levels (Table 7). In comparison with the EEPHS 200mg/kg dose, EEPHS 400 mg/kg demonstrated a significant decrease in serum triglycerides level. while exhibiting an increase in serum HDL-c levels ($P < 0.05$) compared to the diabetic control. Similarly, the standard control group exhibited a significant decrease in serum levels of TG, TC, LDL-c, and VLDL-c, along with an elevation in HDL cholesterol levels.

Table 7 Anti-hyperlipidemic activity in diabetic mice.

Group	STC	STG	VLDL	HDL
Diabetic Control	182.33±0.67	162.47±0.22	36.34±0.21	32.55±0.51
Standard Control	170.45±0.41	143.21±0.11	23.12±0.33	43.33±0.16
Normal Control	102.33±0.23	95.31±0.21	11.31±0.12	56.34±0.24
EEPHS 200mg/kg	173.66±0.76	152.87±0.31	38.33±0.22	34.56±0.12
EEPHS400mg/kg	171.55±0.31	146.45±0.22	27.66±0.33	38.66±0.16

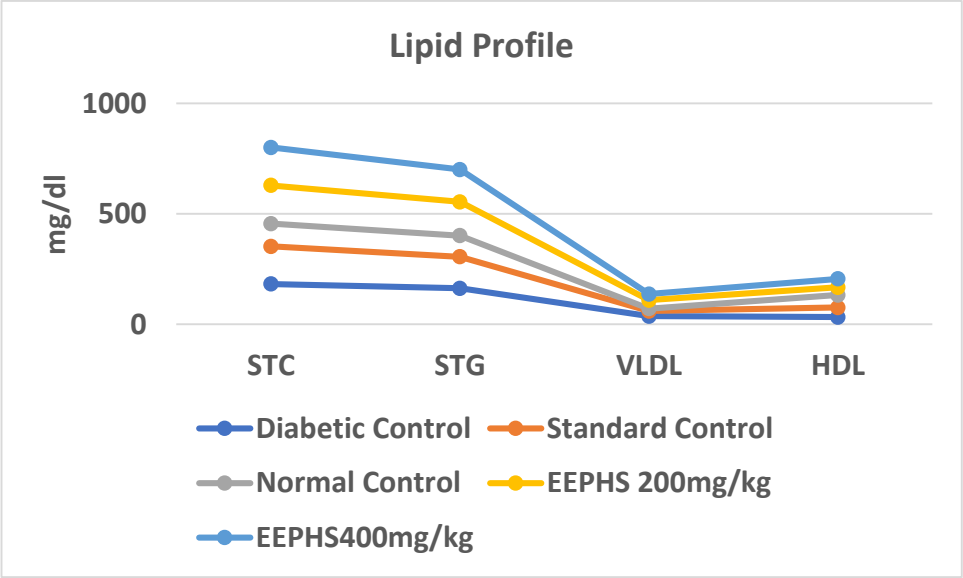


Figure 8 Lipid Profile of different groups

Discussion

Despite the availability of conventional antidiabetic medications, plant derived preparations and extracts hold significant importance within the ethnobotany community because of less side effects than synthetic drugs [14]. The scientific community has shown growing interest in herbal products due to economic and pharmacological advantage [15]. Medicinal plants have gained considerable attention owing to the presence of essential bioactive compounds like flavonoids and phenolics, which demonstrate potent antioxidant properties. The objective of the present research was to evaluate the antidiabetic, anti-hyperlipidemic, antioxidant and potential of *Peganum harmala* seeds as native medicinal plant. This plant has been previously studied for its potential antidiabetic effects, with varying doses and models employed. Previous studies have shown that the plant has hypoglycemic effect on normal rats [16] [17]. According to this source, the plant collected for this study had different geographical area, so active ingredients may also be different and this might cause different results.

In current research work, *Peganum harmala* extract showed significant antioxidant potential. The anti-oxidant activity may be due to polyphenols presence. HPLC-UV fingerprints of EEPHS also confirmed phenolic acid and flavonoid compounds; Quercetin (3,4′-O-diglucoside), Gallic acid (3, 4, 5-trihydroxybenzoic acid), vanillic acid (monohydroxybenzoic acid), chlorogenic acid **(**tetrahydroxy-

cyclohexane carboxylic acid), synergic acid (dimethoxybenzene), ferulic acid (hydroxycinnamic acid), cinnamic acid mono-carboxylic acid C6H5-CH=CH-COOH and sinapic acid (4-Hydroxy-3,5-dimethoxycinnamic acid). In the present study, the antidiabetic activity of extract was evaluated in diabetic and normoglycemic mice. The extract sample significantly reduced blood glucose level in all three models. Quercetin is the abundantly found dietary nutrient. Quercetin involved glucose homeostasis; insulin secreting and sensitizing; glucose uptake in peripheral tissues; the intestinal glucose absorption inhibition [18]. Quercetin produce antidiabetic effects by lowering lipid peroxidation, decreasing absorption of glucose by GLUT2, and inhibition of phosphoinositide 3-kinases which is insulin dependent [19]. Many active phytoconstituents are reported in the *Peganum harmala*. One of the therapeutic bioactive compounds is harmine. Harmine is an alkaloid and its anti-diabetic effect has been investigated [20]. A study on the harmine showed that it involves in the regulation of certain pathways which are the main regulators of the synthesis of adipose tissues. [21]. Another compound display on HPLC was gallic acid (3,4,5-trihydroxybenzoic acid), low molecular weight tri-phenolic compound [22]. Several studies reported the antidiabetic effects of gallic acid. It increases GLUT4 translocation and cellular glucose absorption prevents cardiac dysfunction happens due to diabetes [23]. Presence of active compounds in extract might involve in the antidiabetic effect of *Peganum harmala* seeds extract.

Streptozotocin (STZ) stands out as the predominant and extensively employed chemical model for inducing experimental diabetes. It surpasses alloxan as a diabetogenic agent due to its broader effectiveness across different species. The diabetic effects of STZ are due to DNA alkylating properties of its methyl nitrosourea component. Additionally, its secondary mechanisms include nitric oxide release from nitroso group and reactive oxygen species generation [21] [20].

The streptozotocin induced diabetes mellitus (DM) is related to reduce in body weight, possibly attributed to cellular incapacity for glucose utilization, adipose tissue lipolysis, and protein degradation, resulting in skeletal muscle wasting. Likewise, in the current investigation, the diabetic control groups experienced a substantial percentage of weight reduction induced by STZ. However, the extract, administered at both dose levels, mitigated this weight loss as compare to diabetic control group, although observed outcome did not reach statistical significance. As body weight associated with healthiness, effectiveness of extract on body weight variation in diabetic mice was examined. During the study duration, body weight of mice in the normal control group showed a steady increase. Conversely, prolonged treatment duration led to a substantial decrease in body weight of treated diabetic mice. A substantial ($p < 0.001$) reduction in body weight was noted STZ-induced hyperglycemic mice. The decline diabetic mice body weight is attributed to protein break down, dehydration and muscle atrophy, as carbohydrates are lacking as an energy source, and fat catabolism becomes prominent. The data revealed that following a 14-day treatment period, mice treated with GLC (5mg/kg) and all doses of the extract exhibited a significant increase in weight compared to the diabetes control group and their baseline body weight. The extract's ability to alleviate hyperglycemia associated to its positive impact on reducing body weight. The extract's efficacy in reducing hyperglycemia might be associated with its favorable influence on weight loss. Phytochemical components of *Peganum harmala* are believed to contribute to weight gain by reducing the production of free radicals caused by hyperglycemia shown by current investigation. The extract is thought to enhance glucose utilization, thereby preventing atrophy of muscles and sparing protein catabolism in diabetic mice treated with the extract [24] The present study identified a reliable and positive correlation between elevated blood sugar levels (hyperglycemia) and increased lipid levels (hyperlipidemia). The presence of hyperlipidemia heightens the vulnerability of individuals with diabetes to cardiovascular diseases. This condition is seen as a complication of diabetes mellitus, attributed to the augmented breakdown of lipids and free fatty acids from peripheral deposits in the absence of insulin. This elucidates the reason untreated diabetic mice exhibit elevated levels of LDL, STG, STC but low HDL levels. Raised glucose level is also correlated with an upsurge in lipid profile components such as STG, STC, and LDL, coupled with a decline in HDL levels. Diabetic control mice induced by STZ displayed marked increase in STC, STG, and LDL content, along with a

decrease in HDL, as anticipated. As indicated in the table, the repeated administration of EEPHS over 14 days led to a dose-dependent reduction in STC, STG, and LDL levels, while concurrently increasing HDL content. Nevertheless, it remains unclear whether the extract exerted a direct influence on lipid metabolism or if the observed anti-hyperlipidemic effect was solely a result of diminished hyperglycemia. In mice induced with STZ-induced diabetes, the ethanolic extract from Peganum harmala seeds exhibited a significant decrease in blood glucose levels (BGL) and reductions in STC, STG, and LDL, coupled with an increase in HDL levels.

Conclusion

The result of the present study revealed that ethanol extract of *Peganum harmala* seeds exhibit the potential of lowering blood glucose level in all the three models of animals and also improve the hyperlipidemia in animals. The extract contains the considerable total phenolic contents and total flavonoids contents and also have the strong potential of anti-oxidant activity. However, Further studies are requiring to isolate the phytoconstituent responsible for the antidiabetic and antihyperlipidemic activity

Competing Interests

The authors declare that they have no competing interests.

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