Research Article

Pharmacological Evaluation of Antidiabetic Activity of Hydroethanolic Seeds Extract of Peganum Harmala in Streptozotocin Induced Diabetes in Albino Rats

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Abstract:

Using streptozotocin to artificially induce diabetes in rats, this study aimed to assess the potential effects of a hydroalcoholic extract of Peganum harmala on blood sugar levels. For this experiment, five groups of male Wistar albino rats (weighing 200-230 g each) were randomly allocated. Oral administration of two doses of Peganum harmala hydroalcoholic seed extract, along with normal saline, was given to diabetic and control rats. Two hundred and fifty milligrams per kilogram were administered. Blood samples were taken at the end of therapy to determine measures of glucose, triglycerides, total cholesterol, LDL, HDL, Malondialdehyde (MDA), total antioxidant capacity (TCA), ALT, AST, bilirubin, and glycosylated haemoglobin (HbA1C). Compared to normal rats, STZ-induced diabetic rats had substantially different levels of glucose, triglycerides, total cholesterol, LDL-c, MDA, TAC, ALT, AST, GGT, bilirubin, and HbA1C. Rats with diabetes showed a considerable improvement in lipid profile, glucose, bilirubin, AST, GGT, and TAC levels after receiving the extract, but a marked decline in glucose, MDA, ALT, and HbA1C. According to the results of this investigation, hydroalcoholic seed extract of Peganum harmala possesses antidiabetic activity and might be useful in treating diabetes mellitus. Recent studies have demonstrated that P. harmala and its active alkaloids, especially harmine and harmaline, have a wide range of pharmacological and therapeutic actions. Chemical analyses have shown that harmalol, harmaline, and harmine are the principal components of this plant. These are beta-carboline alkaloids. There has been a disproportionate amount of focus on harmine among these naturally occurring alkaloids.

Keywords: Pharmaceutical effects, harmine, harmaline, peganum harmala

Introduction:

Hyperlipidaemia, polyuria, polyphagia, and polydipsia are symptoms of diabetes, a metabolic disease category. Glycosuria and excessive thirst are further symptoms. It happens when insulin levels in the blood drop too low or when the pancreas stops producing enough insulin. Nephropathy, retinopathy, and neuropathy are microvascular consequences of high blood glucose levels; stroke and heart failure are macrovascular consequences. Basically, it's a disease that occurs when insulin is not produced enough. Among these mechanisms, one might be responsible for the onset of diabetes:

1) The pancreas does not produce enough insulin, which might be because of a lack of β-cells or an anomaly in their gluco-receptors.

2) Secondly, the peripheral tissues are not insulin sensitive.

3) Thirdly, a hyperglycaemic chemical mediator (glucagon, etc.) level that is high. Another complication of obesity is insulin resistance.

4) When blood sugar levels are too high, extremely reactive oxygen species are produced. Numerous degenerative diseases, including diabetes mellitus, will result from this.

The epidemic quickly spread around the globe, affecting many communities. Diabetic complications most often manifest as Type II diabetes mellitus3.

Frequent urination, tingling or paralysis in the extremities, excessive thirst, lethargy, weight loss, abnormal hunger, sudden changes in vision (including blurred vision), skin that is too dry, injuries that take longer than expected to heal, and a host of other symptoms are all signs of diabetes mellitus.

Regulation of insulin

Insulin consists of two polypeptide chains, each containing 51 amino acids. The average hourly insulin release from a human pancreas is 1 unit. Metabolically, it is responsible for transporting glucose molecules across cell membranes. Insulin was necessary for glycogen production as well as skeletal muscle. Using glucose as a building block for triglycerides and DNA and protein synthesis. Binding to cells that have insulin receptors is how it works.

Hormones, neurones, and chemical mediators control insulin secretion:

Chemical mediators: When the intracellular Ca2+ level rises, the β-cells of the pancreas begin to secrete insulin from their storage granules. These β-cells contain a glucose detecting detector system that allows glucose to enter the beta cells.

Method and Materials:

The process of collecting plant seeds extract:

Using a mixture of distilled water (30%) and ethanol (70%), 500 grams of powdered peganum harmala seeds were extracted using the

hydroethanolic extraction technique in a soxhlet device at temperatures ranging from 35 to 400 degrees Celsius. After passing it through a Buchner funnel, the mixture will be allowed to dry in a water bath. Extraction yielded X grams. The percentage yield is then determined.

Acute toxicity study

After 24 hours of general observation, the animals in the study did not differ significantly from the control group in terms of any of the following **behavioural** or physical characteristics: trembling, diarrhea, salivation, breathing, impaired food intake, water consumption, postural abnormalities, hair loss, sleep, lethargy, restlessness, eye **colour**, mucous membrane, salivation, skin/fur effects, body weight, injury. This occurred when the plant extract dosage reached 250 mg/kg. Following oral treatment, the **Hydroethanolic** seeds extract of Peganum **Harmala** (HEEPH) exhibited an LD50 value of 1500 mg/kg in rats. Please refer to the tables for the results of the oral administration of plant extract to rats. Orally administered animals showed ataxia and abdominal muscular spasms that lasted for many hours. They were sleepy and unresponsive at the six-hour mark. A correlation existed between the dosage and the intensity of these side effects. Nonetheless, by the twenty-fourth hour, the majority of the survivors had overcome these symptoms.

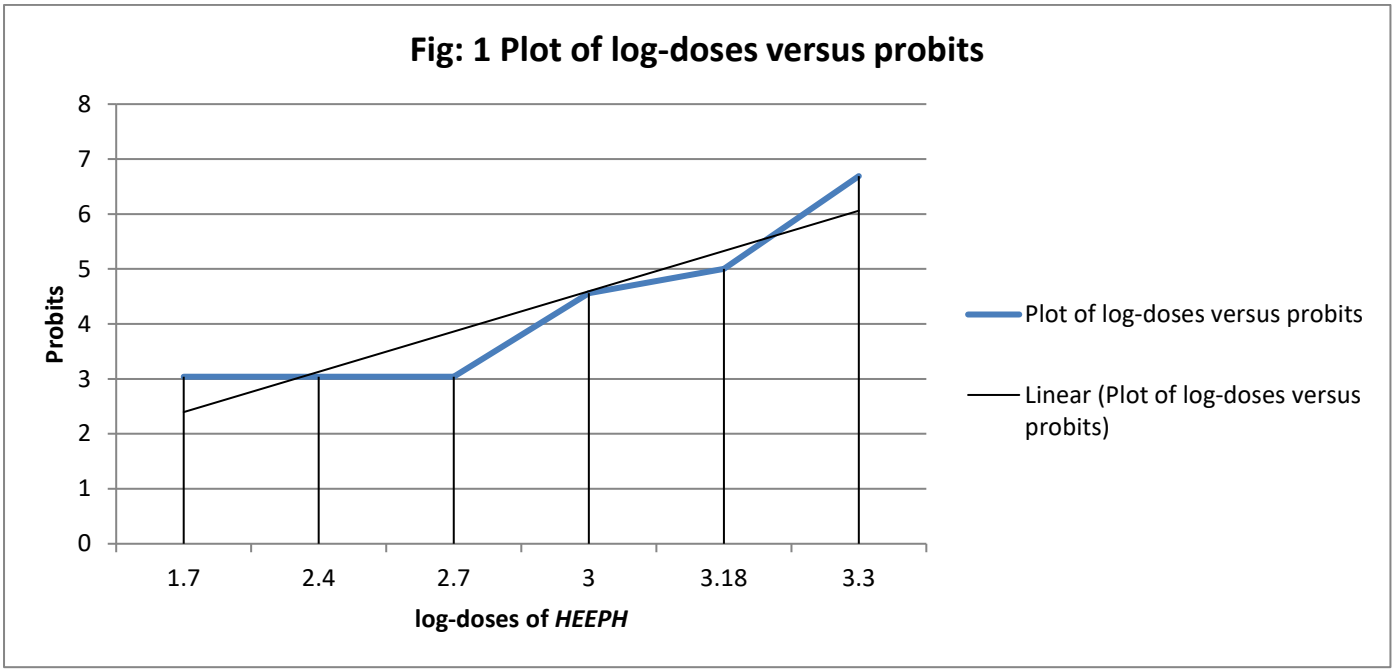
Oral administration of the compound with the LD50 values shown here has an anti-cancer impact that is 10-15 times stronger than dosages of plant extract

Table: 1 Results of the lethal doses of HEEPH for the determination of the LD_{50} after oral administration in rats (n=06).

Group No.	Dose (mg/kg) of HEEPH	Log Dose of HEEPH	No. of Deaths	%Deaths	*Corrected %	Probits
1	50	1.7	0/6	0	4.16	**3.04**
2	250	2.4	0/6	0	4.16	**3.04**
3	500	2.7	0/6	0	4.16	**3.04**
4	1000	3.00	2/6	33.33	33.33	**4.56**
5	1500	3.18	3/6	66.66	66.66	**5.00**
6	**2000**	**3.3**	**6/6**	**100**	**95.83**	**6.69**

*Corrected % Formula: For 0 and 100 % deaths,

For 0% dead: 100(0.25/n), for 100% dead: 100(n-0.25/n)



***Corrected % Formula: For 0 and 100 % deaths,**

For 0% and 100% fatalities, the *corrected % formula is

The equation 100(0.25/n) for 0% dead and 100(n-0.25/n) for 100% dead are equivalent.

Experimental animals were given the selected plant extract orally, and it was shown to be a relatively safe extract. To further evaluate the extract's pharmacological activity, we used doses equal to 1/10 or 1/5 of the LD50, or 250 mg/kg and 500 mg/kg, respectively, since it did not cause any toxic symptoms of mortality in rats up to this dosage level.

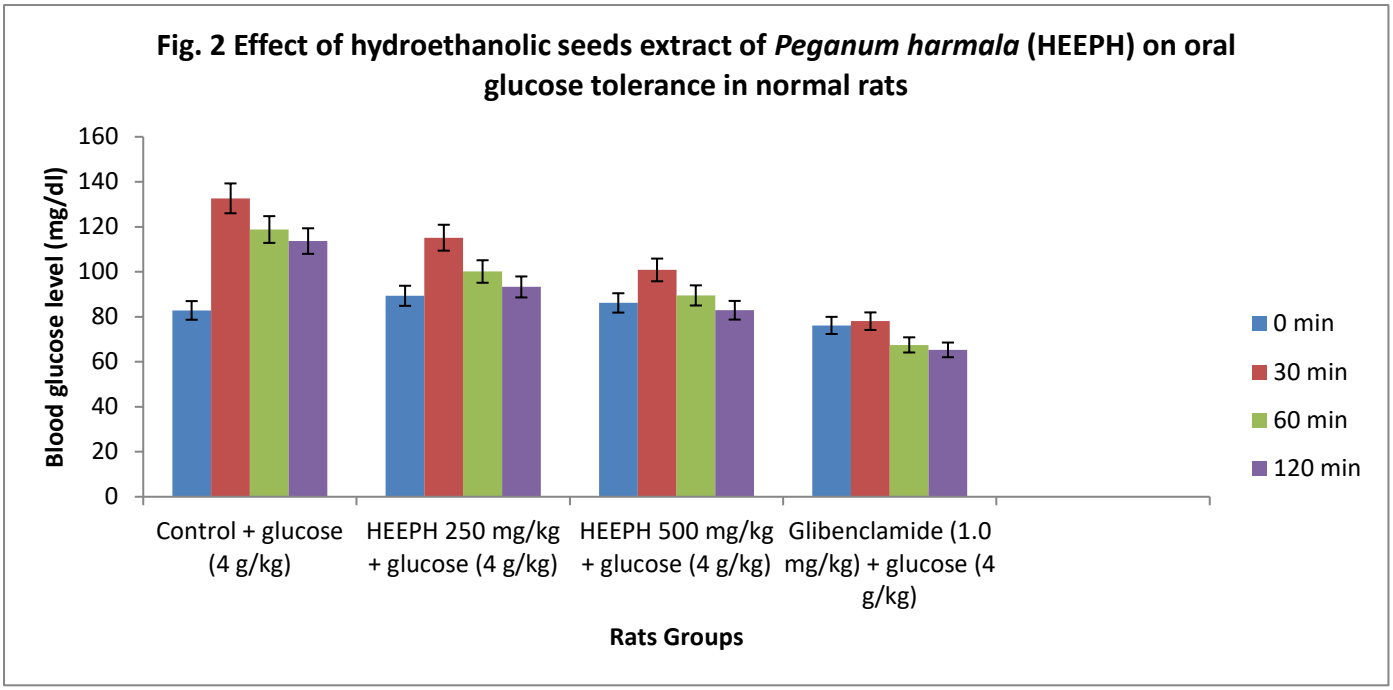
Evaluation of In-vivo antidiabetic activity

Table 2: Effect **of Hydroethanolic seeds extract of *Peganum Harmala* (HEEPH)** on oralglucose tolerance in normal rats

Blood glucose level (mg/dl)				
Time (min)	**Control glucose(4g/g)**	**HEEPH 250 mg/kg + glucose (4 g/kg)**	**HEEPH 500 mg/kg + glucose(4 g/kg)**	**Glibenclamide**(1.0m g/kg)+glucose(4g/kg)
0	82.83±3.60	89.33±1.17	86.16±2.53	**76.16±5.01**
30	132.65±3.94	115.16±2.28	100.83±1.91	**78.05 ±3.31**
60	118.79±4.42	100.13±3.12	89.50±1.33	**67.50±2.93**
120	113.66±2.89	93.27±1.43	82.91±2.56	**65.29±4.05**

Values are mean ± SEM (*n* = 6). P < 0.05, P < 0.01 when compared with control group at corresponding time.

Figure 2: Effect **of Hydroethanolic seeds extract of *Peganum Harmala* (HEEPH)** on oralglucose tolerance in normal rats.



The blood sugar levels of diabetic rats were significantly reduced when either 250 or 500 mg/kg of HEEPH. Diabetes rats given 250 mg/kg HEEPH had a marked improvement in hyperglycaemia compared to the diabetic control group (DC), but their fasting blood glucose (FBG) levels did not return to normal. On the other hand, compared to the NC group, diabetic rats given 500 mg/kg HEEPH exhibited decreased blood sugar levels. There was no significant difference in blood glucose levels between the NC group and the normal rats administered 250 mg/kg of HEEPH, indicating that HEEPH effectively restored glucose homeostasis.

Hypoglycemic effects caused by HEEPH might be due to its ability to promote insulin release from the islets of Langerhans' existing β cells. The plasma glucose lowering activity of glibenclamide, the conventional oral hypoglycemic that has been used for several years to treat diabetes, was investigated by Stephen (2001), Swanston-Flatt et al. (1990), and Shirwaikar et al. (2004) to activate pancreatic β cells.

Measurements of fasting blood glucose:

Both normal and STZ-induced diabetic rats had their fasting blood glucose levels assessed after one day of therapy as well as after seven, fourteen, and twenty-one days of treatment (Tables 4.3 and 4.4 & Figures 4.3 and 4.4). Here, after 21 days of therapy, diabetic rats' blood sugar responses changed significantly. Blood sugar levels in the normal control group (NC) rats were consistently stable throughout the course of the trial.

See Table 4.3 for a comparison of normal and streptozotocin (STZ)-induced diabetic rats' fasting

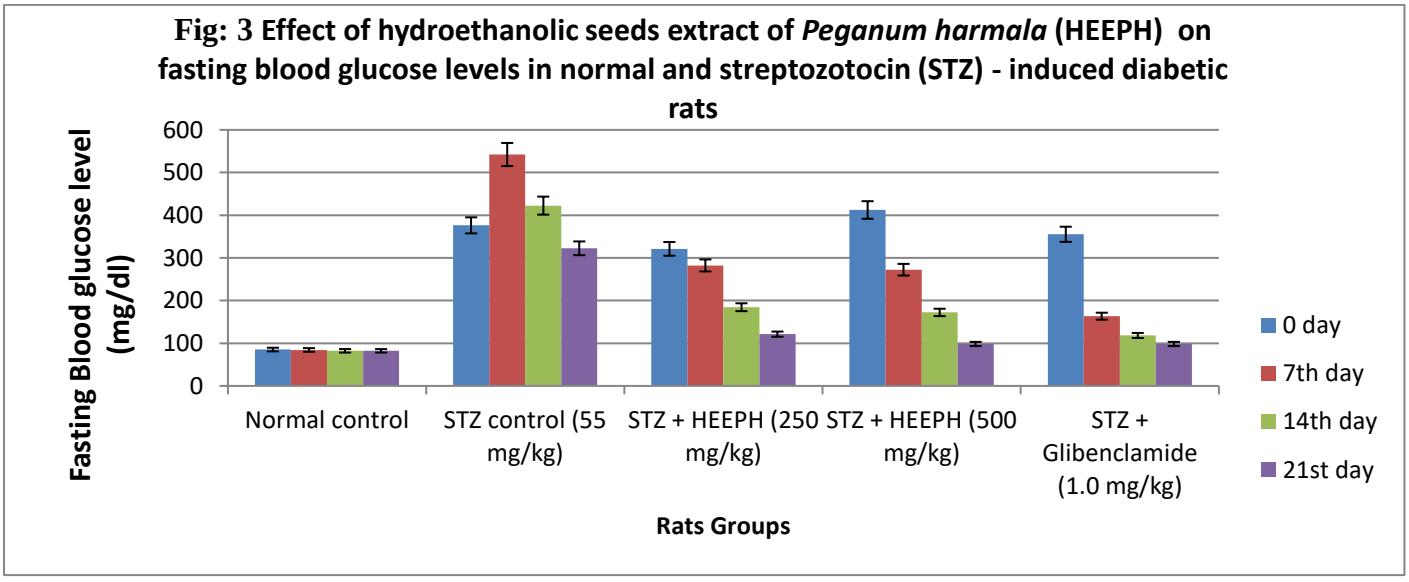
blood glucose levels as a result of Hydroethanolic seed extract of Peganum Harmala (HEEPH).

Table 3: Effect **of Hydroethanolic seeds extract of *Peganum Harmala* (HEEPH)** on fasting blood glucose levels in normal and streptozotocin (STZ) - induced diabetic rats.

Fasting blood glucose level (mg/dl)				
Treatment	**0 day**	**7th day**	**14th day**	**21st day**
Normal control	85.23±3.20	84.26±2.37	82.29±4.22	**82.20±3.29**
STZ control (55 mg/kg)	376.20±4.26	542.20±21.36	422.46±15.39	**322.47±12.44**
STZ + HEEPH (250 mg/kg)	321.13±32.8	282.29±29.49	184.37±26.46	**121.26±6.38**
STZ + HEEPH (500 mg/kg)	412.26±12.3	272.25±25.26	172.22±25.43	**98.26±4.70**
STZ+Glibenclamide (1.0 mg/kg)	355.28±26.1	163.40±21.26	118.20±2.94	**98.25±3.23**

Values are mean ± SEM (n = 6). P < 0.01 when compared with STZ control group; P < 0.01 when compared with normal control group.

Figure 3: Effect **of hydroethanolic seeds extract of *Peganum harmala* (HEEPH)** on fastingblood glucose levels in normal and streptozotocin (STZ) - induced diabetic rats



During the study period, STZ (55 mg/kg, i.p.) caused blood glucose levels to be many times higher than the normal control group (NC), suggesting that hyperglycaemia was stable. The fasting blood glucose (FBG) levels of the normal control group (NC) and the group treated with 250 mg/kg of HEEPH (Group II) were not statistically different. While glibenclamide (1.0 mg/kg) and HEEPH (500 mg/kg) both decreased hyperglycaemia considerably ($P < 0.01$) compared to the diabetic control group (DC), the blood glucose levels of the NC group were nearly normalized by glibenclamide (1.0 mg/kg).

Impact on total body mass

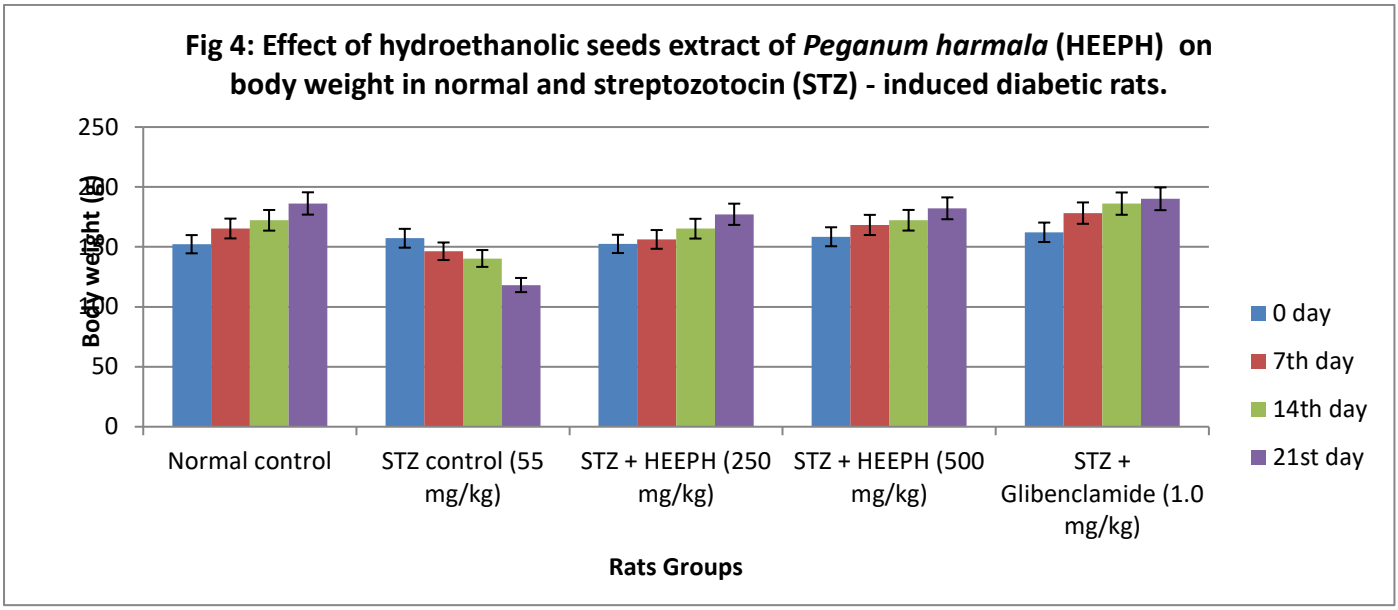
Tables 4.5 and 4.6, as well as Figures 4.5 and 4.6, show the effects of HEEPH on the body weight of both normal and diabetic animals. Diabetic rats demonstrated a significant decrease in body weight over the course of 21 days, in contrast to the normally weight-holding NC animals. The therapy with HEEPH and MEGO dramatically undid the body weight decrease induced by STZ ($P < 0.01$).

Table 4: Effect **of hydroethanolic seeds extract of *Peganum harmala* (HEEPH)** on bodyweight in normal and streptozotocin (STZ) - induced diabetic rats

Body weight (g)				
Treatment	**0 day**	**7th day**	**14th day**	**21st day**
Normal control	152.26±2.36	165.36±2.47	172.20±1.20	**186.27±3.38**
STZ control (55 mg/kg)	157.23±2.27	146.40±1.38	140.37±1.08	**118.20±2.72**
STZ + HEEPH (250 mg/kg)	152.52±2.15	156.26±2.40	165.22±2.56	**177.23±1.74**
STZ + HEEPH (500 mg/kg)	158.47±1.60	168.33±1.67	172.26±2.25	**182.21±1.67**
STZ+Glibenclamide (1.0 mg/kg)	162.20±2.22	178.20± 1.41	186.11±2.28	**190.16±1.23**

Values are mean ± SEM (*n* = 6). P < 0.01 when compared with STZ control group;

Figure 4: Effect **of hydroethanolic seeds extract of *Peganum harmala* (HEEPH)** on bodyweight in normal and streptozotocin (STZ) - induced diabetic rats.



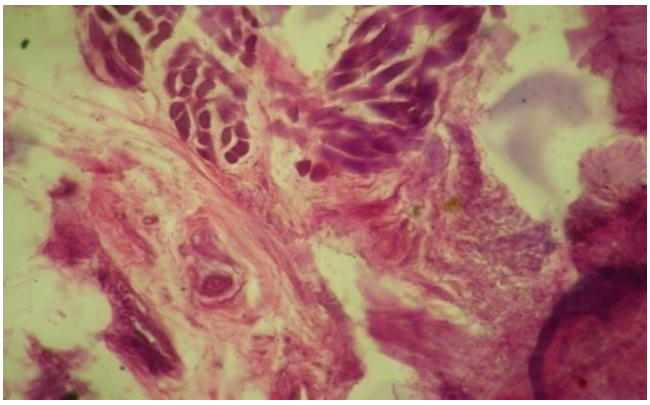
Data are presented as the mean plus or minus the standard error of the mean (n = 6). There was a significant difference ($P < 0.01$) when looking at the STZ control group.

Body weight in normal and streptozotocin (STZ) induced diabetic rats is affected by the hydroethanolic seeds extract of Peganum harmala (HEEPH), as shown in Figure 4.5.

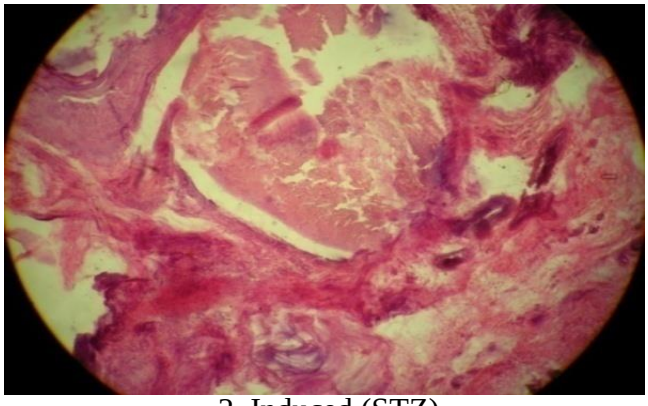
Body weight was significantly improved in diabetic rats treated with HEEPH and MEGO compared to the STZ control group, suggesting that these compounds had a considerable impact in preventing the diabetic rats' weight loss. A lower HbA1C level was seen after oral administration of HEEPH and MEGO. The increased production of HbA1C might explain why diabetic rats have lower levels of total haemoglobin. Adding glucose to the N-terminal of the haemoglobin β chain is the process that makes glycohemoglobin during the life of red blood cells (RBCs) in the circulatory system. This enzyme-free method mimics the cumulative effect of prolonged glucose exposure on haemoglobin

Histopathological examination of Pancreases:

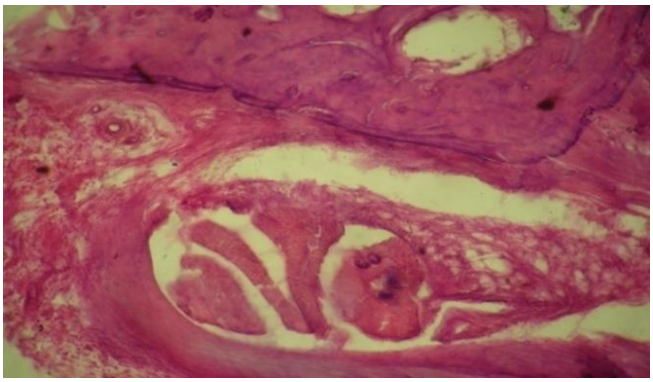
Fig 5: Histopathological examination of pancreas tissue of different groups



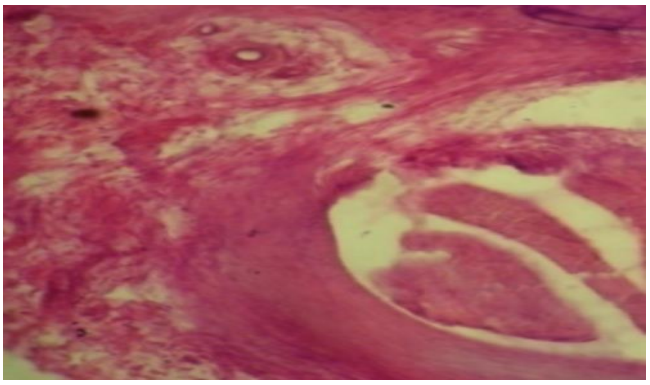
1. Control



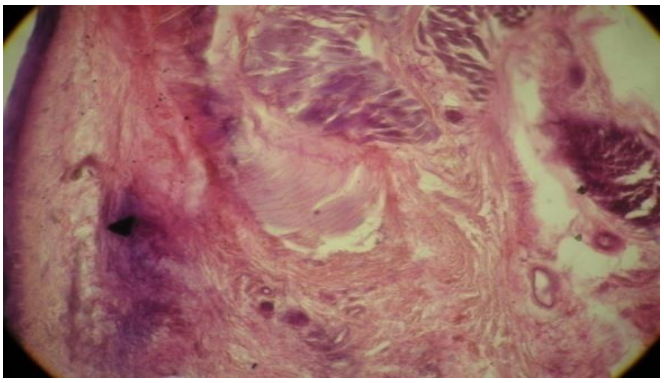
2. Induced (STZ)



3. Test-1



4. Test-2



5. Standard

The embedding process was carried out in paraffin wax using a Leica EG1160 embedding machine and a Leica RM2125RT rotatory microtome, with sections taken at 5 µm intervals. Before being mounted on distyrene plasticizer xylene, the slices were dyed with hematoxylin and eosin. All of the groups had photomicrographs taken using a Leitz Wetzlar light microscope and a digital microscope camera (Scope Photo ® DCM 510 megapixels). The pancreatic islets were evaluated histomorphometrically by measuring their total surface area across all groups (10 islets/group) using transparent gridlines with similar size (1 cm 2 × 1 cm 2) over the islet region. We tallied the number of finished squares (S 1) inside the islet area's perimeter, and we also counted the infinite number of unfinished squares (S 2).

Comparing the pancreas of normal and diabetic Wistar rats treated with streptozotocin (STZ) histopathologically.

(1) Normal Control: Islets exhibiting typical cellular features.

(2) Control of diabetes; a considerable decrease in the quantity and volume of islets.

(3) HEEPH (500 mg/kg body weight)-treated diabetic rats produced by STZ.

(4) Glibenclamide (1.0 mg/kg body weight) was administered to diabetic rats that had been induced by STZ.

Degenerative and necrotic alterations, including smaller islets of Langerhans, were readily apparent in diabetic control rats. Using hematoxylin-eosin's

staining at 40x magnification, we observed that treatments with glibenclamide (1.0 mg/kg body weight) and HEEPH (500 mg/kg body weight) improved the islet volume.

Quantitative Evaluation

The data was analyzed by comparing means and standard errors of the means. A significance level of $P < 0.05$ was deemed significant when using the Student t-test. To compare the mean values between the various groups, one-way analysis of variance was employed. EZ Analyze Version 3.0, an add-in statistical software tool for Microsoft Excel, was utilized for all statistical analysis (Poyton, 2007).

The pancreatic damage caused by a reduction in the number of β-cells was shown by the histological examination of pancreatic tissues. Because STZ produces diabetes mellitus and is highly selective to β-cell toxicity, it is commonly employed in animal research to examine β-cell damage in vivo. The induced rats' pancreas showed signs of necrosis and vacuolization of pancreatic islet β-cells in this study. Nevertheless, according to the histomorphometrical analysis in this work, providing diabetic rats with oral HEEPH improved their pancreatic islet injuries, preserved their surviving β-cells, and may have even stimulated the regeneration of some β-cells in the islets. From a histomorphological standpoint, compared to rats treated with STZ, HEEPH considerably decreased the vacuolization and necrosis of pancreatic islets β-cells. To retain the surviving pancreatic β-cells and increase their synthesis and secretion of insulin to maintain glucose homeostasis, HEEPH may have protected the pancreatic islets from free radicals and hyperglycaemic-mediated oxidative damage. To fortify the antioxidant defence system, several researchers have suggested such a chain of events. This research provides evidence that HEEPH has antidiabetic properties by protecting and repairing the pancreatic β-cells' structural and functional integrity.

Discussion:

In Tables and Figures, we can observe the effects of the hydroethanolic seeds extract of Peganum harmala on rats that have been provided with glucose. The oral glucose tolerance test (OGTT) results provided substantial evidence that HEEPH, HEEPH, and glibenclamide therapy improved glucose tolerance. The groups did not differ significantly with respect to their blood glucose base line (0 min) concentrations. Compared to the NC group at30, 60, and 120 minutes into the oral glucose tolerance test (OGTT), rats given 250 or 500 mg/kg of HEEPH showed a little rise in glucose levels after loading. The blood glucose levels after glucose infusion at 120 minutes are dramatically reduced ($P < 0.01$) by glibenclamide.

At 250 and 500 mg/kg, HEEPH significantly lowered blood sugar levels in diabetic rats. While 250 mg/kg of HEEPH significantly reduced hyperglycaemia compared to the diabetic control group (DC), it failed to restore the fasting blood glucose (FBG) level to that of the normal control group (NC). In contrast, 500 mg/kg of HEEPH

brought the blood sugar levels of the diabetic rats back to the NC level.

Hypoglycemia may also be caused by HEEPH and its ability to promote insulin release from the islets of Langerhans' existing β cells. Stephen (2001), Swanston-Flatt et al. (1990), and Shirwaikar et al. (2004) examined the plasma glucose lowering activity of glibenclamide, the standard oral hypoglycemic that has been used for several years to treat diabetes, in order to activate pancreatic β cells.

Both normal and STZ-induced diabetic rats had their fasting blood glucose levels recorded after one day of therapy as well as after seven, fourteen, and twenty-one days. Tables and figures show that the diabetic rats' blood sugar response changed significantly after the 21st day of treatment. Blood sugar levels in the normal control group (NC) rats were consistently stable throughout the course of the trial.

During the study period, STZ (55 mg/kg, i.p.) caused blood glucose levels to be many times higher than the normal control group (NC), suggesting that hyperglycaemia was stable. When compared to the diabetic control group (DC), hyperglycaemia was considerably reduced ($P < 0.01$) with HEEPH at 250 and 500 mg/kg. The blood glucose levels were lowered to a level near to the normal control group (NC) level due to the considerable ($P < 0.01$) effect of the glibenclamide (1.0 mg/kg).

Conclusion:

As compared to STZ control rats, rats with STZ-induced hyperglycaemia showed a marked improvement in blood glucose management and normalization of serum biochemical profiles, including lipid levels, after receiving HEEPH. Thus, it may be inferred that the plant extract shown remarkable efficacy in treating STZ-induced diabetes in Wistar rats, lending credence to its ethnomedicinal use. It is reasonable to assume that HEEPH will serve as an inspiring alternative medicine option for the efficient control of diabetes based on the determined oral hypoglycemic activity in STZ-induced diabetic rats. In male rats that have been driven to diabetes by streptozotocin, our results suggest that a hydroalcoholic extract of Peganum harmala has antidiabetic and hypolipidemic effects. Nevertheless, it is not yet known which components are responsible for the antidiabetic effect. Hence, more research is required to discern and catalog the components found in the extracts.

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