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A COMPARATIVE STUDY ON THE HYPOGLYCAEMIC EFFECT OF *Pterocarpus Marsupium* SEED EXTRACT IN ALLOXAN INDUCED AND GABAPENTIN INDUCED DIABETES IN EPILEPTIC RATS

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ABSTRACT

AIM: Diabetes mellitus is a metabolic disorder, which is affecting the population of the developed and developing countries. Diabetes contains a number of chronic complications like nephropathy, neuropathy, retinopathy and cardiovascular diseases. *Pterocarpus marsupium* is a medicinal plant used in Ayurvedic system of medicine to control blood sugar. The aim of the study is to evaluate the antidiabetic activity of *Pterocarpus marsupium* seed extract on alloxan induced diabetes and compare the results with gabapentin induced diabetes in epileptic rats. MATERIALS AND METHODS: The present work was designed to evaluate the anti hyperglycemic activity of *Pterocarpus marsupium* seed extract (100mg/kg and 200mg/kg) on alloxan induced diabetes and gabapentin induced diabetes in epileptic rats. Blood glucose level, serum triglycerides, total cholesterol, HDL cholesterol and LDL cholesterol were evaluated in alloxan and gabapentin induced diabetic rats. The results of the test drug were compared with the standard drug. RESULT: Rats treated with ethanolic seed extract of *Pterocarpus marsupium* at 100mg/kg and 200 mg/kg had significantly reduced the blood glucose level. The fall in blood sugar level produced by *Pterocarpus marsupium* was more effective in gabapentin induced diabetes compared to the standard drug. *Pterocarpus marsupium* shows significant decrease in triglycerides levels, serum cholesterol levels, LDL levels and increased HDL levels, total protein levels in both alloxan induced and gabapentin induced diabetic models compared to the disease control group. CONCLUSION: In conclusion, the ethanolic seed extract of *Pterocarpus marsupium* has potential hypoglycaemic action and hypolipidaemic action in alloxan induced and gabapentin induced diabetic rats and more effective in reducing blood sugar level in gabapentin induced diabetes in epileptic rats compared to the standard drug.

Keywords: *Pterocarpus marsupium*, Diabetes mellitus, Alloxan, Gabapentin, Metformin.

INTRODUCTION

Diabetes mellitus (DM) is a chronic disease caused by inherited and/or acquired deficiency in production of insulin by the pancreas, or by the ineffectiveness of the insulin produced. Such a deficiency results in increased concentrations of glucose in the blood, which in turn damage many of the body's systems, in particular the blood vessels, nerves, kidneys, liver, eyes and heart [1]. Besides hyperglycemia, several other factors including dislipidemia or hyperlipidemia are involved in the development of micro and macrovascular complications of diabetes that are the major causes of morbidity and death [2].

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Reasons for this rise include increase in sedentary lifestyle, consumption of energy-rich diet, obesity, higher life span, etc.

The heartwood of *Pterocarpus marsupium* is used in the treatment of inflammation and reported to have medicinal importance in the management of diabetes since long [3]. It is also known as the Indian kino tree or Malabar kino tree. The bark contains l-epicatechin. The heartwood yields liquiritigenin, isoliquiritigenin, alkaloid (0.017%), and resin (0.9%) [4]. Ethyl acetate extract of powdered dried heartwood of P. marsupium revealed the presence of following constituents: (-) epicatechin (a flavonoid), pterosupin (a dihydrochalcone), marsupin (a benzofuranone), pterostilbene, liquiritigenin (a stilbene), isoliquiritigenin, (2S)-7-hydroxyflavanone, 7, 4'-dihydroxyflavone, p-hydroxybenzaldehyde, (2R)- 3 -(p-hydroxyphenyl)-lactic acid, and pm-33 [5].

The flavonoids and phenolic contents present in the tree viz., marsupin, pterosupin, and liquiritegenin are reported to have antihyperglycemic and antihyperlipidemic activities [6,7,3]. *Pterocarpus marsupium* extracts may serve as a potential source of natural antioxidant as well as for the treatment of diabetes [8-10].

The ethanolic extract of P. marsupium at 100 mg/kg bw when given to STZ-induced diabetic rats for 10 consecutive days declined blood glucose, improved OGTT and increased their serum insulin levels. The ethanolic extract of P. marsupium also showed marked antidyslipidemic effects on high fat diet fed Syrian golden hamsters [11]. Flavonoid (epicatechin) fraction from P. marsupium had shown to cause pancreatic β-cell regeneration [12]. The other mechanism of P. marsupium for hypoglycaemia may be increase release of insulin from β-cells [13] prevent insulin resistance [14] and hindering the absorption of glucose from intestine [15]. Administration of EtOAc extract for 14 consecutive days produced a significant reduction of serum triglyceride, total cholesterol, and LDL- and VLDL-cholesterol levels without any significant effect on the level of HDL-cholesterol [16].

Pterocarpus marsupium has also been documented to help in regeneration of pancreatic β-cells [17,18]. The active antidiabetic ingredients in the aqueous extract has been identified as (-) epicatechin, a benzopyran which on administration to alloxan-induced diabetic rats increased insulin secretion and number of islets in the pancreas. Insulin likes activity of (-) epicatechin has been reported (Chakravarthy BK et al., 1982). Heartwood of *Pterocarpus marsupium* has also been tested clinically and found effective in non insulin dependent diabetes mellitus patients (Type 2DM) [19].

The purpose of this experimental study is to investigate the antidiabetic activity of *Pterocarpus marsupium* seed extract on alloxan induced diabetes and compare the results with gabapentin induced diabetes in epileptic rats. The anti-diabetic activity was evaluated by measuring the blood glucose levels, lipid profile and histopathological examination.

MATERIALS AND METHODS

Animals

Male wistar albino rats weighing 200 – 250 gm were used in the study. They were housed and maintained under standard condition in the central animal house. The rats were kept in clean, clear polypropylene cages in groups of three in each cage and maintained at 10 hours of light and 14 hours dark cycle. They were maintained under standard environmental conditions and fed with standard pellet diet (Laboratory animal feeds) and water *ad libitum*.

Extraction of *Pterocarpus marsupium*

The seeds are collected, washed, shade dried, coarsely powdered and then passed through 40 mesh sieves. The coarsely powdered materials were subjected to successive extraction with petroleum ether, ethyl acetate, and ethanol for 72 hrs. The extract solutions obtained were collected separately and the collected extract was concentrated under reduced pressure (< 45ºC) using a vacuum pump for complete removal of the solvent. Pure organic part of the sample thus prepared and was stored at 4-5 ºC until used. The yield of ethanolic extract was collected and weighed.

Diabetes induced by alloxan

After overnight fasting, experimental diabetes was induced by single intra-peritoneal injection of alloxon (150mg/kg) in rats. The alloxon was freshly prepared by dissolving 150 mg of alloxon in normal saline solution. The animals were allowed to drink 20% glucose solution to overcome the drug induced hypoglycemia. 48 hours after injection of alloxon, fasting plasma blood glucose was estimated. Animals with plasma glucose levels of >250mg/dl were selected for anti diabetic activity. Then the rats were divided into 5 groups consisting of six rats in each group, the animals were treated for 21 days.

Diabetes induced by gabapentin in epileptic rats

After overnight fasting, experimental diabetes was induced by single intra-peritoneal injection of gabapentin (150mg/kg) in rats. The gabapentin was freshly prepared by dissolving 150 mg of gabapentin in normal saline solution. The animals were allowed to drink 20% glucose solution to overcome the drug induced hypoglycemia. 48 hours after injection of gabapentin, fasting plasma blood glucose was estimated. Animals with plasma glucose levels of >250mg/dl were selected for anti diabetic activity.

Experimental design

The study was carried out after obtaining approval by the Institutional Animals Ethics Committee

(IAEC). Sixty rats were used in this study. They were divided into ten groups of six animals each. The vehicle/drug was administered for a period 21 days from the day of induction of diabetes. Drug/vehicle was administered orally (p.o) under aseptic conditions.

The treatment schedule for alloxan induced diabetic rats:

Group I- Normal control group, normal rats were administered with normal saline (10ml/kg) and no drug treatment. Group II – Disease Control group, diabetic rats were administered with normal saline (10ml/kg) and no drug treatment. Experimental diabetes was induced by single intra-peritoneal injection of alloxan (150mg/kg). Group - III – Diabetic rats were administered with standard drug metformin (150mg/kg, p.o). Group – IV – Diabetic rats were administered with *Pterocarpus marsupium* (100mg/kg, p.o). Group V - Diabetic rats were administered with *Pterocarpus marsupium* (200mg/kg, p.o). Drug/Vehicle was administered to the rats for 21 days.

The treatment schedule for gabapentin induced diabetes in epileptic rats:

Group I- Normal control group, normal rats were administered with normal saline (10ml/kg) and no drug treatment. Group II – Disease Control group, diabetic rats were administered with normal saline (10ml/kg) and no drug treatment. Experimental diabetes was induced by single intra-peritoneal injection of gabapentin (150mg/kg). Group - III – Diabetic rats were administered with standard drug metformin (150mg/kg, p.o). Group – IV – Diabetic rats were administered with *Pterocarpus marsupium* (100mg/kg, p.o). Group V - Diabetic rats were administered with *Pterocarpus marsupium* (200mg/kg, p.o). Drug/Vehicle was administered to the rats for 21 days.

Collection of blood

The blood samples were collected on 1st, 7th, 14th and 21st day from tail and retro-orbital venous plexus of rats by giving anesthesia using a glass capillary tube after a fast of 12 hrs and the blood was centrifuged to get serum. The serum was used for biochemical estimation of blood glucose, triglycerides, serum cholesterol, HDL-cholesterol, LDL- cholesterol, total proteins. Blood glucose levels were estimated by using Glucose oxidase-peroxidase (GOD-POD) kit. On 21st day all the animals were sacrified after collection of blood samples and the pancreas was collected. The isolated pancreas were used for study the anti-oxidant parameters.

Estimation of blood glucose

Blood glucose was estimated by using glucose kit obtained from Span Diagnostics using Glucose oxidase-peroxidase (GOD-POD) method. Glucose oxidase (GOD) oxidizes glucose to glucoronic acid and H_2O_2. In presence of enzyme peroxidase, released H_2O_2 is combined with phenol and 4-aminoantipyrine (4-AAP) and forms coloured quinoneimine dye. By using colorimeter Absorbance of dye is measured at 505 nm by and is directly proportional to glucose concentration in the sample [20].

Estimation of triglycerides (GPO-POD method)

Triglycerides were estimated by using the kit obtained from Span Diagnostics. Triglycerides were hydrolysed by lipoprotein lipase (LPL) to produce glycerol and free fatty acid (FFA). In presence of glycerol kinase (GK), adenosine triphosphate (ATP) phosporylates glycerol to produce glycerol-3-phosphate and adenosine diphosphate (ADP). Glycerol 3-phosphate is further oxidized by glycerol 3-phosphate oxidase (GPO) to produce dihydroxy acetone phosphate (DAP) and H_2O_2. In presence of peroxidase (POD), hydrogen peroxide couples with 4-amino antipyrine (4-AAP) and 4-Chloro phenol to produce red quinoneimine dye. Absorbance of coloured dye is measured at 505 nm and is proportional to triglycerides concentration in the sample [21].

Estimation of Total cholesterol (Chod-Pod/ Phosphotungstate Method)

Pipette the samples and the reagent into 3 test tubes labelled blank (B), standard (S), and Total cholesterol (Tc). Mix well and incubate for 5 min at 37°C or 10 min at room temperature. Read the absorbance of standard (S), total cholesterol (Tc) against blank at 505 nm. Absorbance of Quinoneimine was measured at 505 nm which is proportional to cholesterol concentration. Total cholesterol (in mg/dl) = (Abs. of Test / Abs. of Standard) X 200. Cholesterol concentration = Concentration (mg/dl) X 0.0259 [21].

Estimation of HDL

Pipette out serum/plasma 0.2 ml and precipitating reagent 0.3 ml into the centrifuge tube. Mix well and allow standing at room temperature for 5 min. Centrifuge at 3000 rpm for 10 min to get a clear supernatant. If supernatant is not clear (high TGL level) dilute the sample 1:1 normal saline and multiply the result with 2. Pipette into 3 test tubes labelled blank (B), standard (S), HDL cholesterol (TH). Mix well and incubate for 5 min at 37°C or 10 min at room temperature. Read the absorbance of standard (S), HDL cholesterol (TH) against blank at 505 nm. HDL cholesterol was calculated using the formula. HDL Cholesterol (mg/dl) = Absorbance of test/ Absorbance of standard X 50.

Estimation of Total protein: (Biuret Method)

Proteins bind with copper ions in the alkaline medium of biuret reagent and reduce a purple colored complex, whose absorbance is proportional to the protein concentration. Pipette out the samples and reagents into clean dry test tubes labelled blank (B), standard (S) and

test (T). Mix well and incubate at 37°C for 10 min. Measure the absorbance of standard (S) and test (T) against blank (B) on a spectrophotometer at 555 nm. Total protein (gm %) = Absorbance of test / Absorbance of standard X 6.5 [22].

Histopathology Studies

Light microscopy: The pancreas were removed, washed immediately with saline and then fixed in 10% buffered formalin. The Pancreas stored in 10% buffered formalin, were embedded in paraffin, sections cut at 5µm and stained with hematoxylin and eosin. The hematoxylin and eosin stained sections were then examined under a light microscope for histological changes.

Statistical Analysis

The mean values ± SEM will be calculated for each parameter. Data analysis was carried out using one-way analysis of variance (ANOVA) followed by Dennett's multiple comparison tests by using Graph pad prism version 5.01.

RESULTS

When the rats were sacrificed, the abdominal cavity was examined macroscopically before and after removing the pancreas for any abnormality. It was observed that there was no visible abnormality seen in pancreas and other visceras in the abdominal cavity in both alloxan group and gabapentin group.

Histopathological Reports of drug induced diabetic rats

In the histopathological studies, the normal control groups of rats showed normal islets of langerhans, acinar cells and β cells. In disease control group, degenaration and necrosis of pancreatic cells; extensive damage to the islets of langerhans and damage of intralobular ducts were observed. Rats treated with standard drug metformin showed normal pancreatic β cells, normal islets of langerhans. Rats treated with seed extract of *Pterocarpus marsupium* showed the regeneration of pancreatic β cells with normal islets cells, normal acinar cells and normal intra lobular ducts.

Effect of *P. marsupium* on blood sugar level of alloxan group

Rats treated with *Pterocarpus marsupium* 100mg/kg and 200mg/kg has significantly reduced blood sugar compared to disease control group on 1st day, 7th day, 14th day, 21st day in alloxan induced diabetic rats. The fall in blood sugar level in rats treated with *Pterocarpus marsupium* 100mg/kg (132.4±1.05) and 200 mg/kg (124.6±1.66) was comparable to the results produced by the standard drug metformin (128.6±1.46) on day 21 (Table-1).

Effect of *P. marsupium* on blood sugar level of gabapentin group

Rats treated with *Pterocarpus marsupium* 100mg/kg and 200mg/kg has significantly reduced blood sugar compared to disease control group on 1st day, 7th day, 14th day, 21st day in gabapentin induced diabetes in epileptic rats. The fall in blood sugar level in rats treated with *Pterocarpus marsupium* 100mg/kg (104.4±1.05) and 200 mg/kg (101.6±1.87) was comparable to the results produced by the standard drug metformin (120.7±0.54) on day 21 (Table-2).

Effect of *P. marsupium* on lipid profile and total protein of alloxan group

Rats treated with alloxan showed a significant increase in the triglycerides levels compared to control group. Standard drug metformin improved the increased cholesterol levels comparable to the control group. Rats treated with *Pterocarpus marsupium* 100mg/kg and 200mg/kg significantly decreased triglycerides levels, serum cholesterol levels, LDL levels and increased HDL levels, total protein levels compared to the disease control group. The improvement in lipid profile was comparable to the standard drug metformin (Table 3).

Effect of *P. marsupium* on lipid profile and total protein of gabapentin group

Rats treated with gabapentin showed a significant increase in the triglycerides levels compared to control group. Standard drug metformin improved the cholesterol levels comparable to the control group. Rats treated with *Pterocarpus marsupium* significantly decreased triglycerides levels, serum cholesterol levels, LDL levels and increased HDL levels, total protein levels compared to the disease control group. The improvement in lipid profile was comparable and slightly higher than the standard drug metformin (Table 4).

Table 1: Effect of extract of *Pterocarpus marsupium* seeds on plasma glucose levels in alloxan induced diabetic rats

Group	Glucose levels (mg/dl) 1stday	Glucose levels(mg/dl) 7th day	Glucose levels(mg/dl) 14th day	Glucose levels(mg/dl) 21stday
Normal control	108.21±0.75	114.1±1.52	110.3±0.89	106.9±1.54
Disease control	284.6±1.39	276.7±1.43	290.4±1.28	288.7±0.58
Standard (Metformin)	164.1±0.25*	153.1±0.50*	138.3±0.68*	128.6±1.46*
P. marsupium (100mg/kg)	211.3±1.52*	214.4±0.4*	164.8±1.83*	132.4±1.05*
P. marsupium (200mg/kg)	186.1±0.19*	203.8±1.58*	153.4±1.57*	124.6±1.66*

Values are expressed as mean ± SEM, Oneway ANOVA followed by Dunnet's test. *P<0.001 when compared with disease control group

Table 2: Effect of extract of *Pterocarpus marsupium* seeds on plasma glucose levels in Gabapentin induced diabetic rats:

Group	Glucose levels (mg/dl) 1stday	Glucose levels(mg/dl) 7th day	Glucose levels(mg/dl) 14th day	Glucose levels(mg/dl) 21stday
Normal control	113.4±0.68	120.1±1.02	105.1±1.02	110.1±1.02
Disease control	289.5±1.70	293.7±0.34	274.4±0.68	288.7±0.85
Standard (Metformin)	161.1±0.51*	141.1±0.51*	126.8±1.36*	120.7±0.54*
P. marsupium (100mg/kg)	215.4±1.43*	161.4±0.74*	118.8±1.83*	104.4±1.05*
P. marsupium (200mg/kg)	198.1±0.91*	152.8±1.4*	111.4±1.75*	101.6±1.87*

Values are expressed as mean ± SEM, Oneway ANOVA followed by Dunnet's test. *P<0.001 when compared with disease control group

Table 3: Effect of extract of *Pterocarpus marsupium* seeds on biochemical parameters in serum of alloxan induced diabetic rats:

Groups	TG (mg/dl)	Cholesterol	HDL	LDL	Total protein
Normal control	85.23±3.54	125.15±3.52	52.16±2.66	68.40±2.66	6.25±1.22
Disease control	186.25±4.01	264.25±4.71	32.52±2.68	174.1±2.02	3.17±0.15
Standard (Metformin)	98.48±3.58**	142.1±2.52**	54.27±1.54**	75.05±2.58**	6.53±2.17**
P. marsupium (100mg/kg)	145.23±4.36*	164.3±3.08**	41.24±3.02*	98.35±4.42**	7.82±0.30**
P. marsupium (200mg/kg)	115.52±3.42**	136.26±4.10**	48.45±3.45**	75.23±2.05**	8.54±1.21**

Values are expressed as mean ± SEM, Oneway ANOVA followed by Dunnet's test. *P<0.05, and **P<0.001 when compared with disease control group

Table 4: Effect of extract of *Pterocarpus marsupium* seeds on biochemical parameters in serum of gabapentin induced diabetic rats:

Groups	TG	Cholesterol	HDL	LDL	Total protein
Normal control	79.47±1.95	131.1±1.02	55.83±0.78	71.04±0.88	6.97±0.03
Disease control	169.15±1.23	247.5±0.51	36.41±0.68	188.13±0.68	3.79±0.11
Standard (Metformin)	105.48±0.98*	153.1±1.02**	48.32±0.71*	92.51±0.33**	5.74±0.08**
P. marsupium (100mg/kg)	91.83±1.36**	136.4±1.98**	48.12±1.02*	84.53±0.42**	6.63±0.30**
P. marsupium (200mg/kg)	83.35±1.41**	127.6±1.19**	52.36±1.44**	79.53±1.00**	7.84±0.11**

Values are expressed as mean ± SEM, Oneway ANOVA followed by Dunnet's test. *P<0.05, and **P<0.001 when compared with disease control group

Fig. 1. Plasma glucose levels in alloxan induced diabetic rats

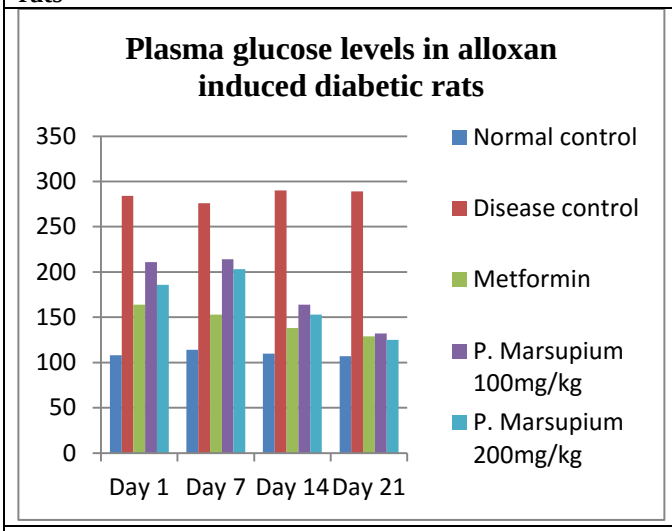


Fig. 2. Plasma glucose levels in gabapentin induced diabetic rats

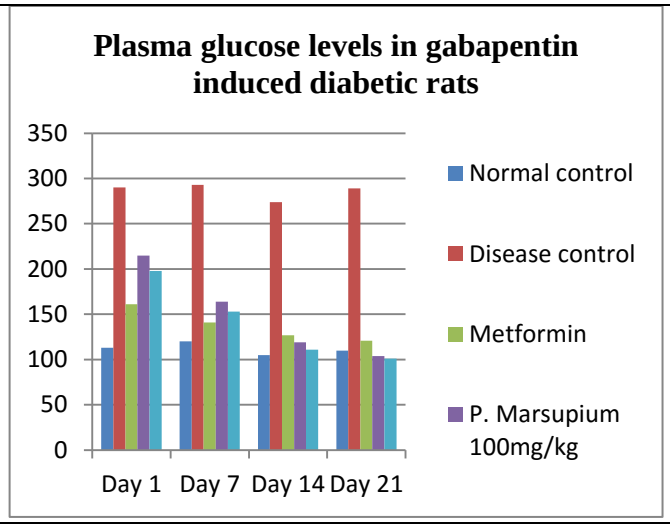


Fig. 3. Biochemical parameters in alloxan induced diabetic rats

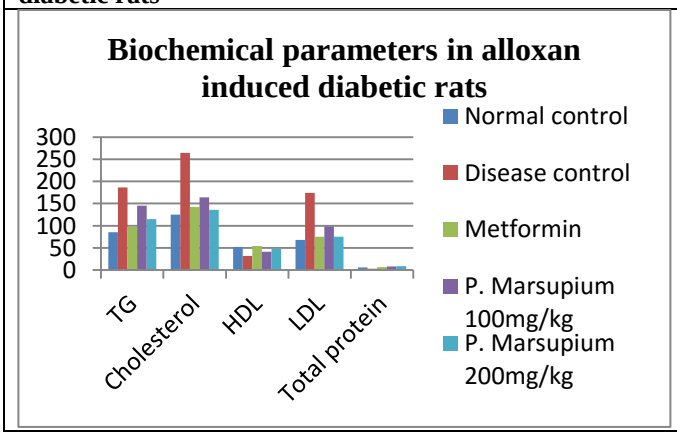
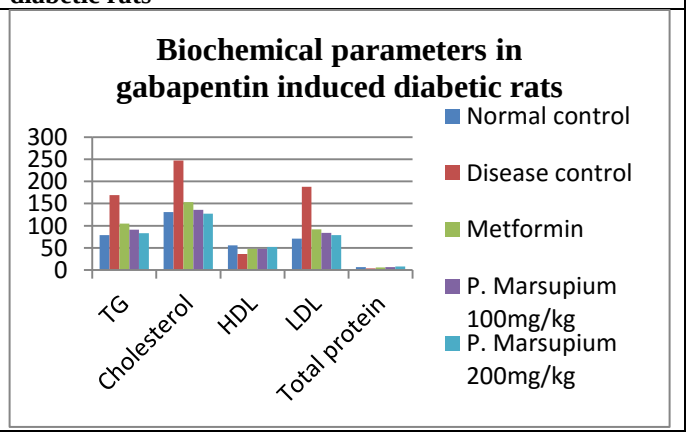


Fig. 4. Biochemical parameters in gabapentin induced diabetic rats



DISCUSSION AND CONCLUSION

Diabetes mellitus is the one of the major metabolic disorder which affecting the three fourth of the world's population. According to WHO projections, the prevalence of diabetes is likely to increase by 35%. Statistical projection about India suggests that the number of diabetics will rise from 15 million in 1995 to 57 million in the year 2025, the highest number of diabetics in the world [23]. According to International Diabetes Federation, 387 million people worldwide have diabetes and it is projected to reach 592 million by 2035 [24]. Diabetes can cause micro and macro vascular complications like renal failure, coronary artery disorders cerebrovascular disease, neurological complications, blindness, obesity, and hyperglycemia.

As a strong oxidant, alloxan is widely used in experimental animals to induce insulin-dependent diabetes (type 1). It works by increasing generation of reactive oxygen species from metabolic reactions in the body, together with massive increase of cytosolic calcium concentration, and it can rapidly cause destruction of pancreatic β-cells [25]. Gabpentin is used in the treatment of epileptic seizures. Administration of gabapentin significantly increases the glucose levels when compared to normal control group, which account for cytotoxic action of gabapentin. Metformin was taken as standard.

Histopathological examination shows that the pancreas of normal control group of rats showed normal islets of langerhans, acinar cells and β cells. In experimental diabetes induced by alloxan and gabapentin there is degenaration and necrosis of pancreatic cells, extensive damage to the islets of langerhans and damage of intralobular ducts. *Pterocarpus marsupium* seed extract at low dose (100 mg/kg) and high dose (200 mg/kg) shows regeneration of pancreatic β cells with normal islets cells, acinar cells and intra lobular ducts. Metformin treated diabetic rats also shows normal pancreatic β cells, islets of langerhans. *Pterocarpus marsupium* improved the pancreatic function of experimental diabetes.

The present study was designed to evaluate the Hypoglycemic and Hypolipidemic activity of seed extract of *Pterocarpus marsupium* in alloxon and gabapantine drug induced diabetes and compare the effect of *Pterocarpus marsupium* on these two models. The seed extract of *Pterocarpus marsupium* in lower dose (100mg/kg), higher dose (200mg/kg) were taken. The glycemic statuses of the control and test groups of rats were compared with the normal group to assess the antidiabetic activity. Drug induced diabetes was protected by the standard drug metformin. The test drugs show decrease in levels of glucose when compare to disease control group.

Pterocarpus marsupium decreased the blood sugar level of experimental diabetes compared to disease control group. The test drug in high dose i.e, 200 mg/kg reduced the blood sugar level slightly more than the low dose, 100 mg/kg in both alloxan induced and gabapentin induced diabetes. In gabapentin induced diabetes in epileptic rats, the lowering of blood sugar by *Pterocarpus marsupium* at 100 mg/kg and 200 mg/kg was slightly more than the standard drug metformin. This shows that *Pterocarpus marsupium* seed extract is better than the standard drug in controlling blood sugar level in gabapentin induced diabetes in epileptic rats.

The test drug shows significant decrease in serum total cholesterol level, triglycerides and LDL level when compared to the disease control group. HDL and total protein levels were also significantly increased with the test drug when compare to disease control group. Test drug at both low dose (100 mg/kg) and high dose (200mg/kg) showed significant reduction of TG, total cholesterol, LDL levels in both alloxan induced and gabapentin induced diabetes models. The improvement in bloog sugar level and lipid profile is probably due to the antioxidant activity and insulin like action of alkaloids and flavonoids present in the seed extract.

In conclusion, *Pterocarpus marsupium* ethanolic seed extract at 100mg/kg and 200 mg/kg has significantly reduced the blood glucose level on all the days of blood sampling in both alloxan induced and gabapentin induced diabetes in epileptic rats. The improvement in blood sugar level was more significant in gabapentin induced diabetes compared to alloxan induced experimental diabetes. *Pterocarpus marsupium* at low dose and high dose has also significantly reduced the total cholesterol, triglycerides and LDL levels and increased the HDL level compared to disease control group of rats. There was no difference between the alloxan and gabapentin induced diabetes in terms of lipid profile. In the present study the ethanolic seed extract of *Pterocarpus marsupium* has potential hypoglycaemic action and hypolipidaemic action in alloxan induced and gabapentin induced diabetic rats and more effective in reducing blood sugar level in gabapentin induced diabetes in epileptic rats compared to the standard drug.

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