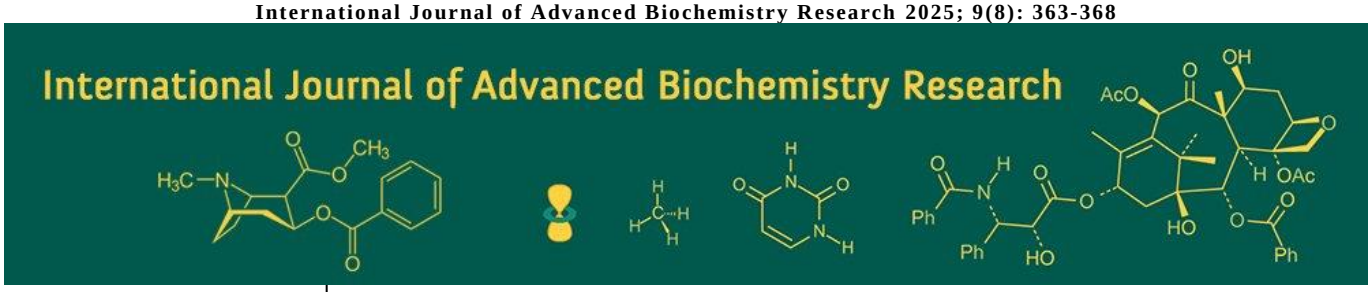

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Hypoglycemic and hypolipidemic effect of *Ficus benghalensis* Linn bark laticiferous sap in alloxan induced diabetes mellitus in rats

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Abstract
The antidiabetic effects of aqueous seed extract of *Ficus benghalensis* Linn laticiferous bark extract was examined and evaluated in diabetes mellitus induced albino wistar rats using alloxan monohydrate, which was also compared with hypoglycemic and hypolipidemic effects of glibenclamide. The selected standard drug is generally used in diabetes mellitus treatment. It is available in tablets for humans as well as canines. These selected drug was studied systematically, analyzed and compared with *Ficus benghalensis* plant extract. For induction of diabetes, male albino wistar rats of average weight about 120 gm were intraperitoneally administered with alloxan monohydrate, a crystal pink powder, dissolved in cold NS, at the dose rate of 120 mg/kg BW. Alloxan was used in all rats except negative control group. Diabetes induction was confirmed by evaluating the blood glucose levels. The blood glucose level of selected rats for this study was about 160 mg/dL. Rats of Group I served as normal control and rats of Group II served as hyperglycemic control. Group III rats were given Glibenclamide in 1 ml of aqueous solution at a dose rate of 10 mg/kg BW p.o.; Group IV rats were orally administered *Ficus benghalensis* Linn laticiferous sap at the dose rate of 0.25 g/kg BW, given in 1ml of diluted aqueous dilution. Group V was orally given *Ficus benghalensis* Linn laticiferous sap at the dose rate of 0.50 g/kg BW diluted in 1ml aqueous solution. Group VI was orally given *Ficus benghalensis* Linn laticiferous sap at the dose rate of 0.75 g/kg BW diluted in 1ml aqueous solution. Alloxan induced diabetic rats of Group II showed increase in the levels of total cholesterol, serum triglycerides, serum creatinine, blood urea nitrogen and blood glucose till the end of this study. Group III were treated with standard drug Glibenclamide at a dose 10 mg/kg BW significantly reduced the elevated blood glucose level, total cholesterol, serum triglycerides, serum creatinine; while blood urea nitrogen (BUN) level was restored to near the normal range. In group IV, administration of *Ficus benghalensis* Linn laticifarous sap at a dose 0.25 g/kg BW significantly reduced the elevated blood glucose level, total cholesterol, serum triglycerides, serum creatinine and serum blood urea nitrogen (BUN) level. In group V, *Ficus benghalensis* Linn laticifarous sap administration at a dose 0.50 g/kg BW significantly reduced the elevated blood glucose level, total cholesterol, serum triglycerides, serum creatinine and serum blood urea nitrogen (BUN) was restored near to the normal range. In group VI *Ficus benghalensis* Linn laticifarous sap administration at a dose 0.75 g/kg BW significantly reduced the elevated blood glucose level, total cholesterol, serum triglycerides, serum creatinine and serum blood urea nitrogen (BUN) was restored near to the normal range. Results showed that *Ficus benghalensis* Linn laticifarous sap showed both hypoglycemic and hypolipidemic effect. There is further scope in study for the advancement of the drug discovery for the treatment of diabetes mellitus using its other parts and qualitative analysis of its phytochemical constituents.

Keywords: Antidiabetic, hypoglycemic, hypolipidemic, *Ficus benghalensis*, alloxan-induced diabetes

Introduction
Diabetes mellitus, is a deadly metabolic disorder of multiple aetiology like lifestyle habits with less physical work, stress, by genetic link from ancestors or beta cell damage due to some environmental toxicants like arsenic and dioxins etc is characterized by chronic hyperglycaemia with disturbance of normal carbohydrate fat and protein metabolism which results in defect in insulin proper secretion, insulin action after the absorption in the normal cell of the various tissue of the body or both may also be the reason based on the aetiology.
Most diabetic canines suffer from diabetes with insulin deficiency, with the underlying cause of an inflammatory process in the exocrine or endocrine tissue. Autoimmunity is suspected in some instances of self-apoptosis of the beta cells, being one of the main causes of

pancreatic β-cell loss or death of the β-cell. Pancreatitis due to some infections, which may be diagnosed concurrently with diabetes in some cases, results in variation or loss of Islet cell of Lagerhans architecture. Canine islets cell of Langerhans have an average of 78% β-Cell producing unit of insulin production, 11% α-cells producing unit for glucagon production (Glucagon is a peptide hormone), ≤ 11% δ-cells or D cells to secrete the hormone somatostatin , while in humans the islets have β-cell 50%, α-cell 40%, δ-cell 10%. The research findings in canines is in contrast with pathological findings, in which insulitis is a distinguishing feature. Insulitis is known to affect, through the presence of a lymphocytic infiltrate, the periphery (peri-insulitis) or the interior of the islet cells of the langerhan (intrainsulitis) in pancreas. Treatment with oral hypoglycemic agent such as Sulphonylurea are often associated with side effects such as desensitization of β-cell, GIT disturbances, skin reaction and rise in hepatic enzyme levels. Treatment with Sulphonylurea and biguanides is associated with side effect, Chronic treatment with sulphonyl urea may desensitize the β cells of the pancreas and high concentrations of sulphonylurea may inhibit insulin biosynthesis *in vitro* and perhaps also *in vivo*. So as alternative therapy, plants may be considered to serve the purpose in patients.

Various medicinal plants have been tested for antidiabetic effects in laboratory animals. Vat vriksha has many medicinal values that can be obtained from stem bark and fruits, also having antidiabetic property. is commonly known as Bargad, belonging to the family Moraceae shows hypolypidemic activity, antioxidant activity etc. The compound isolated form *Ficus benghalensis* Linn was 3'-5-dimethyl-ether of leucocyanidin-3, 0-p-0-D galactosulcellobioside.

Biochemical change associated with diabetes mellitus

An inability to regulate blood glucose is a hallmark trait of diabetes mellitus. The triphasic blood glucose curve in alloxan-diabetic rabbits was documented by Bailey and Bailey (1943) [16]. The phases were marked with early hyperglycemia lasting 2-3 hours.; 6-12 hours long hyperglycemia and ultimately chronic hyperglycemia. In addition to the observations of Bailey and Bailey (1943) [16], Shiplay and Beyer (1947) [2] noted a small initial decrease in blood glucose levels at 15 to 30 minutes and designated the additional curve as tetraphasic. A typical characteristic of hyperglycemia is both clinical (Taylor and Agius, 1988) [3] and experimental diabetes mellitus (Rerup, 1970) [4]. Tomlinson *et al.* (1985) [5] reported that diabetic rat's blood glucose level was 3 to 4 times higher than those of normal rats.

Materials and Methods

White male albino rats of wistar strain weighing about 120-160 g procured and were housed in well ventilated, solid bottom polypropylene cage at normal room temperature. All animals received laboratory pellet feed and water was provided ad libitum. Animals were acclimatized to the laboratory conditions in laboratory animal facility of the Veterinary Pharmacology Department, College of Veterinary Science and Animal Husbandry OUAT, Bhubaneswar, Odisha for 1 week before being used for the experiment. The experimental protocols were accepted by the committee for institutional animal ethics (IAEC).

Chemicals and Drugs

Alloxan monohydrochloride: (SRL laboratories Pvt. Ltd.). Normal saline: (Claris life science Ltd., Ahmedabad) 20% Dextrose normal saline: (Parentral drug limited, Indore). Glucose Solution: 5 g glucose (SD fine chemicals) dissolved in 100 ml of distilled water Rat bleeding capillaries: (Pearls agencies, Hyderabad) Agappe diagnostics LTD. Creatinine serum analysis kit: Ernakulum, Kerala, Biosystem biochemicals cholesterol kit: Irungattukottai, TN. Glibenclamide (Daonil®): Snofi India limited, Ankleshwar, Controle D glucometer strips and digital meter. Ketamin hydrochloride (Aniket®): Neon pharmaceuticals. Tryglycerides Serum Kit: Coral clinical systems, Blood urea nitrogen serum analysis kit: Coral clinical systems, Swent feeding needle set: Jamnagar, GJ, *Ficus bengalensis* Linn Laticiferous sap from campus around lab.BBSR.

Experimental Design

Blood was collected from all the animals and blood glucose concentration was estimated to rule out spontaneous diabetes. Animals which showed a mean blood sugar level of about 60 to 80 mg/dL were selected for the study. From these animals 30 wistar albino rats with a prior fasting of 18 h, were injected with alloxan monohydrochloride (120 mg/kg *i.p* in NS), while 6 animals were injected with normal saline which were used as negative control of group I. To avoid fatal hypoglycemia due to initial massive pancreatic insulin release, animals were given 20% glucose (D20) solution orally (ad lib, in feeder bottles) after 6h of alloxan injection. The rats were then kept for the next 24 h on 5% glucose (D5) solution in drinker bottles in their cages to prevent hypoglycemia. After 72 h, alloxan treated rats with a mean blood glucose level above 170 mg/dL or above were selected for the study and were divided into five groups of 6 animals each. Group I served as normal control group to which there was no induction of diabetes mellitus, Group II as hyperglycemic positive control to which no other medication was given except NS i.p after induction of diabetes by alloxan monohydrate. Rats of group III were given glibenclamide (Daonil®) at dose rate of 10 mg/kg BW p.o by intra gastric needle in 1mL of aqueous solution. Rats of group IV, V and VI were given aqueous diluted *Ficus benghalensis* Linn Laticiferous sap orally as 1mL aqueous solution, as a single dose (g/kg, BW) for 28 days @ 0.25, 0.50, and 0.75, or standardized dose administration by the use of micropipette at 30 µl, 60 µl and 90 µl respectively.

Group I: Normal control: Rats of this group were fed on basal diet without any treatment

Group II: Diabetic control: Rats of this group were induced diabetic models and were served in diabetic control throughout the experiment without the therapy

Group III: Diabetic models of rats with standard drug glibenclamide. Rats of this group orally gavaged with 10 mg/kg BW of glibenclamide (Daonil)

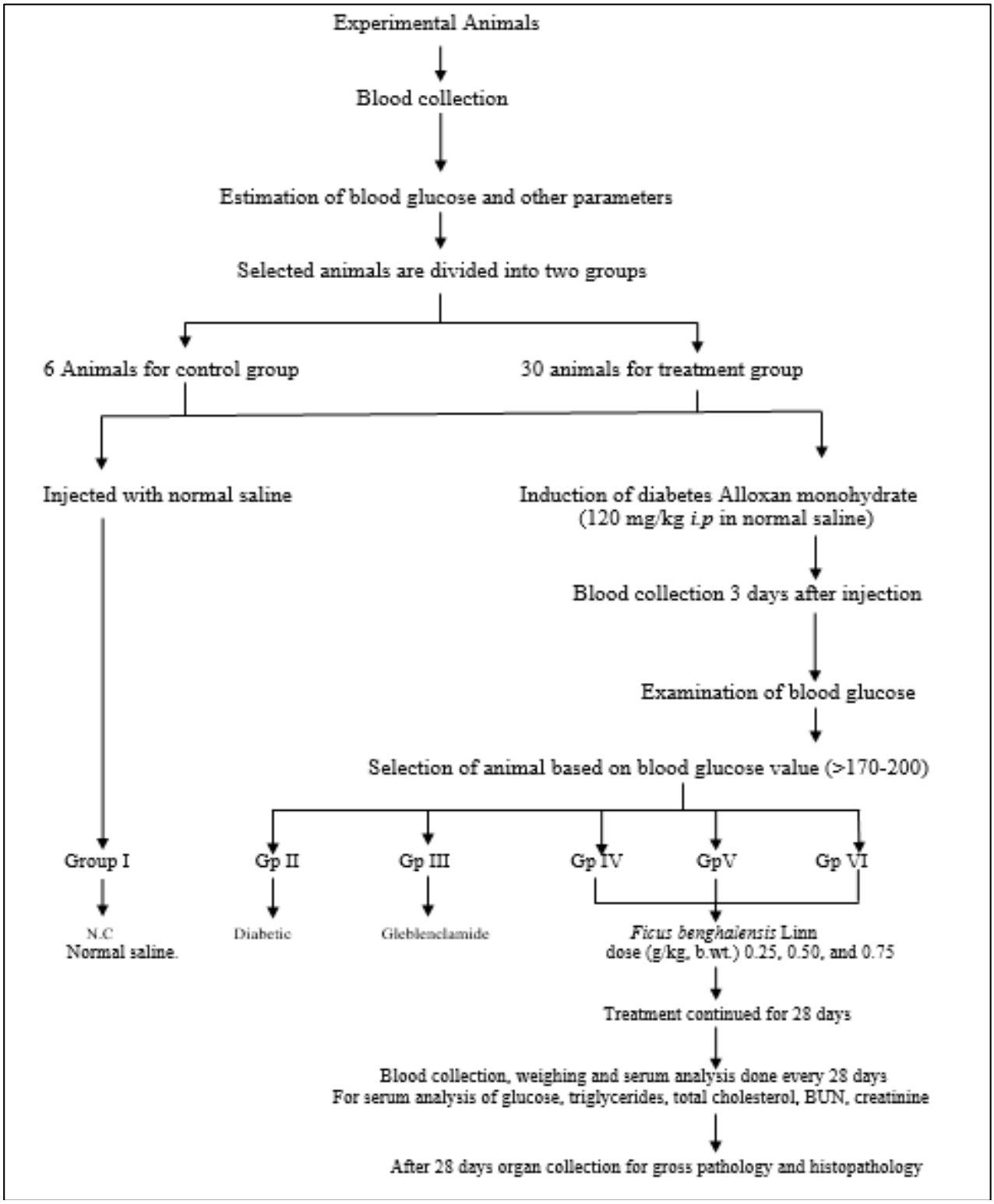
Group IV: Were given aqueous diluted *Ficus benghalensis* Linn laticiferous sap orally as 1mL aqueous solution as a

single dose (g/kg, BW) for 28 days @ 0.25 or standardized dose administration by the use of micropipette at 30 µl,

Group V: Were given aqueous diluted *Ficus benghalensis* Linn Laticiferous sap orally as 1mL aqueous solution as a single dose (g/kg, BW) for 28 days @ 0.50, or standardized dose administration by the use of micropipette at 60 µl.

Group VI: Were given aqueous diluted *Ficus benghalensis* Linn laticiferous sap orally as 1mL aqueous solution as a single dose (g/kg, BW) for 28 days @ 0.75, or standardized dose administration by the use of micropipette at 90 µl.

Schematic representation of the experiment protocol



Serum biochemical estimations

Blood was collected under light ether anesthesia by using heparinized capillary tube. Approximately 1.0 mL of blood was collected from tail vein into heparinized eppendorf tubes. Immediately after blood collection the samples were centrifuged in micro centrifuge machine (Hetitech-Microcentrifuge) at 3000 rpm for 15 minutes at 15 °C. The clear supernatant plasma was separated for estimation of glucose, total cholesterol, triglycerides, serum creatinine, blood urea nitrogen using diagnostic kits.

Statistical analysis
The data was subjected to two way ANOVA as per the methods described by Snedecor and Cochran (1994) [17]. $p<0.01$ was considered as significant.

Results
Results of the trial conducted to evaluate the efficacy of of *Ficus benghalensis* Linn bark extract in alloxan-induced diabetic wistar albino rats compared to conventional drugs on the market such as glibenclamide described below.

Glucose concentration
Plasma glucose concentration in groups IV, V, VI treated with *Ficus benghalensis* Linn bark laticiferous sap at 0.25, 0.50 and 0.75 g/kg.BW respectively showed a significant ($p<0.01$) decrease when compared to diabetic control group starting from the day 7 itself. The trend continued in a similar manner till day 14, 21 and at 28 also. Since there was no published reports on hypoglycaemic property of *Ficus benghalensis* Linn bark laticiferous sap, it was not possible to compare the results of the present study with previous works, but the decrease in plasma glucose concentration of rats in the present study was in accordance with the earlier study conducted on *Ficus relegiosa* Linn, a plant which belongs to the same family Moraceae (Pandit *et al.* 2010) [6].

Table 1: Mean plasma glucose concentrations in mg/dl

Group	B. value	0 day	7 day	14day	21day	28day
G1	58	62	68	69	70	72
G2	60	274	270	269	250	240
G3	56	269	221	190	180	98
G4	61	264	252	230	180	130
G5	59	261	221	210	160	121
G6	62	254	208	191	154	104

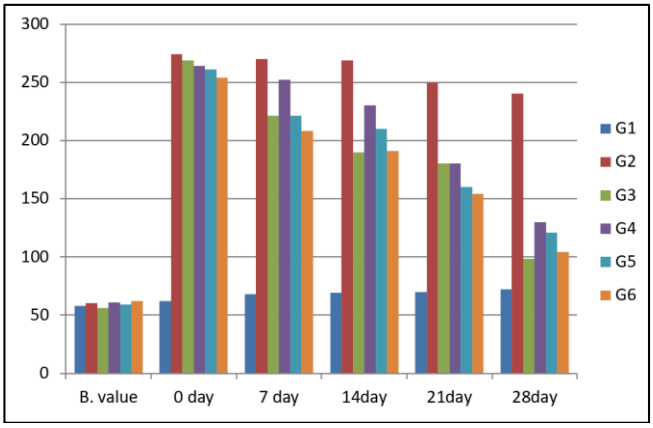


Fig 1: Mean plasma glucose concentration in mg/dl comparison group wise

The exact mechanism by which glucose concentration was controlled could not be traced out yet. The probable mechanism of hypoglycemic action of *Ficus benghalensis* Linn bark laticiferous sap can be attributed by the phytochemicals. The bark contains leuco anthocyanins, leaves contain quercetin-3-galactoside, rutin and β-sitosterol. The other possible mechanism for hypoglycemic action is by increasing peripheral use of glucose. *Ficus benghalensis* Laticiferous sap is effective in controlling diabetes by increasing pancreatic β-cell capacity, or stimulation in the residual pancreatic β-cells to secrete insulin in a manner similar to that of glibenclamide or due to the antidiabetic action by insulin raising effect of stem bark containing flavonoids 3', 5-dimethylether of leucocyanidin-3-0-P-D14. In diabetic controle group lipid profile revealed a significant ($p<0.01$) increase in total cholesterol, triglycerides while the HDL cholesterol showed marked reduction (Bopanna *et al*., 1997, Lino *et al.*, 2004) [7].

Total Cholesterol
A significant ($p<0.01$) increase in plasma cholesterol concentration was observed in alloxan induced diabetic rats. This rise in plasma cholesterol levels was in accordance with the suggestion of Bopanna *et al.* (1997)) [7]. Total cholesterol concentration of the group treated with *ficus benghalinsis* Linn laticiferous sap, In comparison with diabetic control on day 7, aqueous extract showed a significant ($p<0.01$) decrease in total cholesterol and this decrease continued until subsequent observations on day 14, day 21 and day 28 in a dose-dependent manner. (Grundy SM.., et al 1977) [8].

Table 2: Mean plasma total cholesterol concentrations in mg/dl in rats.

Group	B.value	0 day	7 day	14day	21day	28day
G1	73	73	75	72	76	74
G2	74	120	136	132	138	140
G3	72	108	104	98	95	92
G4	72	106	103	98	94	90
G5	73	105	100	98	93	89
G6	72	107	99	90	89	88

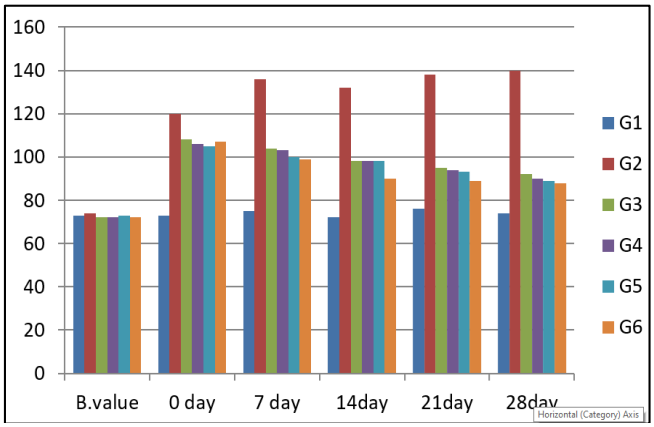


Fig 2: Mean plasma total cholesterol concentration in mg/dl in rats comparison group wise

Triglycerides
In NIDDM the triacylglycerolemia may be due to increased production of triacylglycerol by the liver. The *ficus benghalinsis* treated groups of rats showed significant decrease in plasma concentration of triglycerides on day 0, 7, 14 and 28 days. Fatty acid esterification in the liver results in the formation of triacylglycerol, which can be obtained from dietary carbohydrates, amino acids and reserves of stored adipose tissue. Triacylglycerol is stored inside the cell or can be combined with apoproteins released in the circulating form of VLDL. With increased fatty acid concentration due to diabetic conditions, the fatty acid esterification process can be increased; this results in the presence of nonsaturable fat in the circulation, whereas the presence of apoproteins or other lipoprotein particles may limit the VLDL concentration. Whenever VLDL saturation is achieved, the deposition of triacylglycerol begins in the

liver. VLDL is usually associated with raised plasma triacylglycerol, but it also increases other lipoproteins such as LDL and HDL levels.

The probable action of the laticiferous sap of the aqueous *Ficus benghalensis* Linn bark may be due to the regeneration of the pancreatic β-cells, which may by due to the available active phytochemicals like sterols, flavanoids, phenol, tannins, and saponins.

Table 3: Mean plasma concentration of serum triglycerides (mg/dl) in rats.

Group	B.value	0 day	7 day	14day	21day	28day
G1	42	46	45	46	43	44
G2	44	97	104	114	126	120
G3	42	76	66	65	62	60
G4	42	78	74	72	71	70
G5	44	76	74	70	69	67
G6	44	75	73	71	69	66

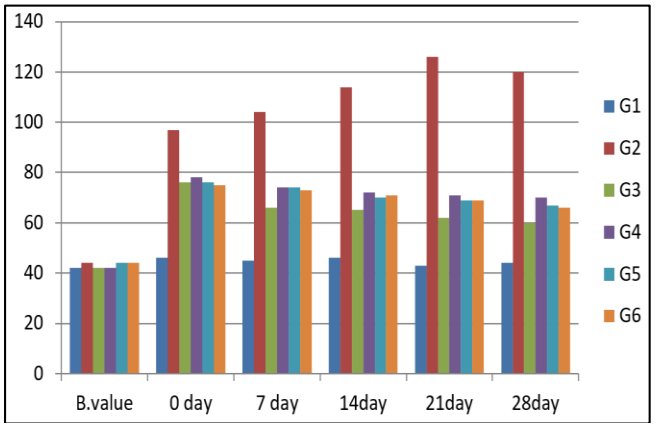


Fig 3: Mean plasma concentration of serum Triglycerides in rats comparison group wise

Discussion

Diabetes mellitus disease is a multifactorial disease that can be induced by different etiologies of the endocrine system. It is a global disease and its incidence is rapidly increasing in most parts of the world, but it is not infectious. People suffering from diabetes are unable to produce natural insulin in the body or use it properly, so they have a high blood glucose level. Diabetes, due to the high incidence, morbidity and mortality, it is becoming the third most notorious 'killer' of mankind after oncological and coronary heart disease (Li *et al.*, 2004) [9].

Alloxan, selectively destructs pancreatic β cells which results in decrease in insulin secretion (Yamamoto *et al.*, 1981) [10]. Further, alloxan has been reported to increase oxidative stress, which is considered to be a possible diabetogenic action mechanism. (Szkudelski, 2001) [11]. The administration of alloxan induced a pronounced increase in blood glucose levels. Blood glucose levels have increased drastically during diabetes due to decreased use of glucose by different tissues, which is a typical condition of insulinopenia. The raised blood glucose levels observed in hyperglycemic rats were almost normalized after selected plant extract treatments, which may be due to stimulation of the use of peripheral tissue glucose and the insulinogenic effects of phytoconstituents on plant material. A variety of plants have previously been observed to show glycemic control through insulin release by stimulating pancreatic effects. (Sharma *et al.*, 2003) [12]. Further, the prepared plant extracts administration to alloxan treated animals reversed the loss in body weight. A direct consequence of pancreatic insulin release seems to be due to the capacity of plant extracts to restore body weight loss. Insulin deficiency and high blood glucose are known to cause biased protein metabolism in diabetic conditions, resulting in the development of a negative nitrogen balance. This, in turn, leads to increased levels of creatinine and urea. (Asayama *et al.*, 1984) [13]

Glibenclamide administration sometimes unable to reduce glucose levels to normal levels, although there has been a significant (p<0.01) decrease in blood glucose levels compared to diabetic control levels. The glucose-independent mode of action of sulphonylyureas means that, irrespective of the circulating regular concentrations of glucose, they continue to exert their effects. They induce insulin release by beta cells by lowering action of ATP-dependent potassium channels. These channels, in addition to pancreatic beta cells, are present in different body tissues, including cardiomyocytes. (SUR 2 isoform). Modern Sulphonylureas act primarily on SUR 1 isoforms, such as glimepride.

The exact mechanism by which glucose concentration was controlled could not be traced out yet. The probable mechanism of hypoglycemic action of *Ficus benghalensis* Linn bark laticiferous sap can be attributed by the phytochemicals. The bark contains leuco anthocyanins, leaves contain quercetin-3-galactoside, rutin and β-sitosterol. The other possible mechanism for hypoglycemic action is by increasing peripheral use of glucose. *Ficus benghalensis* Laticiferous sap is effective in controlling diabetes by increasing pancreatic β-cell capacity, or stimulation in the residual pancreatic β-cells to secrete insulin in a manner similar to that of glibenclamide or due to the antidiabetic action by insulin raising effect of stem bark containing flavonoids 3', 5-dimethylether of leucocyanidin-3-0-P-D14. In diabetic controle group lipid profile revealed a significant (p<0.01) increase in total cholesterol, triglycerides while the HDL cholesterol showed marked reduction (Bopanna *et al*., 1997) [7]. The probable action of the laticiferous sap of the aqueous *Ficus bengalensis* Linn bark may be due to the regeneration of the pancreatic β-cells, which may by due to the available active phytochemicals like sterols, flavanoids, phenol, tannins, and saponins.

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