Research Article

Antidiabetic and Antihyperlipidemic Effects of Bacopa Monnieri Leaf Extract in High-Fat Diet and Streptozotocin-Induced Diabetic Rats

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Abstract

Bacopa monnieri (L.) Wettst., commonly known as Brahmi, is a creeping perennial herb of the family Scrophulariaceae widely used in Ayurvedic medicine. The present study aimed to investigate the antidiabetic and antihyperlipidemic potential of Bacopa monnieri leaf extracts in high-fat diet and streptozotocin (STZ)-induced diabetic rats. Administration of the ethanolic extract (300 mg/kg) significantly reduced fasting blood glucose, total cholesterol, triglycerides, low-density lipoprotein (LDL), very-low-density lipoprotein (VLDL), serum alanine aminotransferase (ALT), and aspartate aminotransferase (AST) levels, while high-density lipoprotein (HDL) levels were significantly increased. Histopathological examination of pancreatic tissue revealed regeneration and increased size and number of β-cells in the islets of Langerhans. Acute toxicity studies confirmed the safety of the extract up to 2000 mg/kg. These findings demonstrate that the ethanolic extract of Bacopa monnieri leaves possesses significant hypoglycemic and hypolipidemic activity, supporting its traditional use in the management of diabetes mellitus and highlighting its potential as a natural antioxidant source.

Keywords: Bacopa monnieri, diabetes mellitus, antihyperglycemic, antihyperlipidemic, streptozotocin, antioxidants.

Introduction

Diabetes mellitus is a chronic and non-communicable leading public health problem. Diabetes mellitus is a metabolic disorder of carbohydrate due to insulin deficiency resulting from dysfunction of pancreatic beta cells. Over the past decade, diabetes prevalence has risen faster in low- and middle-income countries compared to high-income countries. One of the risk factors being the overweight with possible complications include heart attack, stroke, kidney failure, leg amputation, vision loss, and nerve damage. In addition, during pregnancy, poorly controlled diabetes increases the risk of fetal death and other complications [1-3].

Medicinal plants play an important role in both preventive and curative medicinal preparations for human beings. Herbal medicines are the only affordable source of healthcare, especially for the poorest patients. Furthermore, herbal medicines are gaining popularity both in developing and developed countries due to their safety, efficacy, quality, very low adverse effects, and easy availability. Some of the currently available drugs such as aspirin, digitalis, quinine (anti-malarial), vincristine, and vinblastine (anti-cancerous) were derived from the plant sources. Plant-derived phytochemicals have beneficial effect against diabetes, microorganism, inflammation, cardiovascular diseases, blood disorders, cerebral disorders, immune system, oxidative stress, reproductive disorder, and cancer chemotherapy [4-6]. According to the World Health Organization (WHO), more than 21,000 plants are used for medicinal purposes in the world. Despite the introduction of many new antidiabetic drugs from natural and synthetic sources, diabetes and its secondary complications continue to be a major medical problem. Many indigenous medicinal plants have been found to be useful to successfully manage diabetes. One of the great advantages of medicinal plants is that these are readily available and have very low adverse effects. Even though plant sources are potential antidiabetic drugs, they have not gained sufficient momentum among the scientific community. In recent times, it is understood that a proper nutritional regulation with appropriate herbs in our diet shall help to reduce the incidence of diabetes [7-8].

Hyperlipidemia is a characteristics feature of drug-induced (alloxan or streptozotocin) diabetes in rats and rabbits as well as in poorly controlled diabetes in humans. Coronary heart disease (CHD) is the cause of about 50% of all deaths in the United States. The incidence of Coronary heart disease is correlated with elevated levels of LDL cholesterol and triglycerols and with low levels of HDL cholesterol. Hyperlipidemias can also results from genetic defects in lipoprotein metabolism or by a combination of genetic and lifestyle factors [9]. Dislipidemia and hyperhomocysteinemia are important factors associated with the early onset of atherosclerosis. Multiple mechanisms contribute to arterial disease (e.g. atherogenesis) in patients with type 2 diabetes. A high burden of abdominal fat presents the liver with elevated levels of free fatty acids through the portal circulation. This excess of

free fatty acids will drive the overproduction of TG-rich lipoprotein particles, including VLDL-CH, LDL-CH, A reciprocal decrease in HDL accompanies hypertriglyceridemia characteristic of the type 2 diabetic state [10-12].
Bacopa monnieri Linn. commonly called as Brahmi belongs to the family Scrophulariaceae. It is a traditional Indian medicinal plant known for a variety of neuropharmacolgical properties in Ayurveda. The present study was undertaken to explore the anti-diabetic and anti-oxidant effect of selected medicinal plants. The objective of proposed study is to find out a medicinal plant source, which has not been explored, for the treatment of diabetes and its complications. The current work investigated B. monnieri leaves extract for antioxidant and antidiabetic effects using a high-fat diet and streptozotocin-induced diabetic rats.

Materials and Methods

Plant Material Collection and Authentication
Fresh leaves of Bacopa monnieri were collected from the Bhopal region, Madhya Pradesh, India, and authenticated by a Dr Prabhukumar K M, CSIR National Botanical Research Institute, Lucknow. The collected leaves were washed thoroughly to remove adhering impurities and shade-dried at room temperature for approximately one week. The dried plant material was coarsely powdered using a mechanical grinder and stored in airtight containers until further use.
Preparation of Plant Extract
The powdered plant material (200 g) was first defatted using petroleum ether. The defatted marc was subjected to cold maceration with 500 mL of solvents of increasing polarity in separate conical flasks. The flasks were sealed with cotton plugs and kept on a rotary shaker at 120 rpm for 24 hours. The extracts were filtered and concentrated to dryness using a water bath maintained at 105°C. The percentage yield of each extract was calculated based on the initial weight of the powdered plant material.
Phytochemical Screening
Preliminary phytochemical screening of the crude extracts was carried out using standard qualitative methods to detect the presence of major phytoconstituents such as flavonoids, alkaloids, glycosides, saponins, tannins, steroids, and triterpenoids.
Experimental Animals
Healthy Wistar albino rats of either sex weighing 180–200 g were used for the study. Animals were housed in polypropylene cages under standard laboratory conditions (temperature 25 ± 2°C, relative humidity 50 ± 5%, and 12-hour light/dark cycle). Rats were provided with standard pellet diet and water ad libitum. All experimental procedures were conducted according to CPCSEA guidelines and were approved by the Institutional Animal Ethics Committee by Patel college of pharmacy, Madhyanchal professional university ,Bhopal, M.P.(1698/PO/Re/S/13/CPCSEA).
Acute Oral Toxicity Study
The acute toxicity study of Bacopa monnieri leaf extracts was performed to evaluate safety following a single oral administration. Rats were administered extracts at doses of 10, 100, 500, and 2000 mg/kg and observed for 14 days for mortality, behavioral changes, and autonomic responses. Body weight was recorded periodically. No mortality or visible signs of toxicity were observed up to a dose of 2000 mg/kg, indicating the safety of the extract.
Induction of Experimental Diabetes
Animals were divided into dietary groups and fed either a normal pellet diet (NPD) or a high-fat diet (HFD) for eight weeks. After the feeding period, diabetes was induced in HFD-fed rats by a single intraperitoneal injection of streptozotocin (STZ) at a dose of 40 mg/kg prepared in 0.1 M sodium citrate buffer. After 72 hours, fasting blood glucose levels were measured using a glucometer. Rats with fasting blood glucose levels greater than 200 mg/dL were considered diabetic and selected for further study.

Table 1: Experimental design for anti-diabetic study

S No.	Group	Treatment
1	Normal Control	Normal saline

2	Diabetic Control	STZ + Normal saline
3	Standard treated	STZ + Metformin 400 mg/kg
4	EABM 150	STZ + Ethyl acetate extract of B. monnieri (EABM**)** 150 mg/kg
5	EABM 300	STZ + Ethyl acetate extract of B. monnieri (EABM**)** 300 mg/kg
6	EOBM 150	STZ + Ethanol extract B. monnieri (EOBM**)** 150 mg/kg.
7	EOBM 300	STZ + Ethanol extract B. monnieri (EOBM**)** 300 mg/kg

The body mass index (BMI) was determined. The electronic precision balance was used to obtain the weights of animals for six weeks. Rats with a BMI of 310 kg/m2 and above were considered obese and used for the diabetic studies

Evaluation of Antidiabetic activity

All the groups received their treatment by oral route once a day. In addition, the blood glucose level, body weight, food and water intake were measured periodically throughout the treatment period. Extract solutions were prepared by dissolving 5 g of extract in 100ml of distilled water (50mg/ml of extract). Metformin was used as a standard antidiabetic drug in STZ-induced diabetes to compare the antidiabetic properties of a variety of hypoglycemic compounds. A standard dug solution was prepared by Metformin b.w. suspended in 100 ml distilled water. Antidiabetic study of plant extract was conducted by taking albino rats of wistar strain.

Overnight fasted animals were divided into groups to determine the antidiabetic activity of Bacopa monnieri extracts. The experimental rats were divided into groups consisting of six rats per group. The extract, metformin, and normal saline were orally administered once every day for eight weeks. On 0, 7th, 14th, 21stand 28th day of extract administration, the fasting glucose levels were determined. During the experimental tenure, weights of rats were taken daily and mean change was calculated. Blood samples were collected by tail prick method. Body weights and fasting blood glucose levels were measured on a weekly basis. At termination, the rats were fasted overnight and sacrificed by cervical dislocation.

Body weight assessment

The body weight of the normal rats before and after completion of experiment remained unchanged, but a significant reduction in body weight of STZ-induced diabetic rats was noted and maximum reduction was observed on 28th day.

Estimation of insulin level

After 28th day of treatment blood samples were withdrawn by in order to examine the insulin levels. Serum insulin was measured using a Glazyme Insulin-eia test. Insulin was estimated in plasma samples by radioimmunoassay kit (Estradiol RIA Kits,) according to method of Kahnand Roth, 2004. The radioimmunoassay method is based upon the competition of unlabeled insulin in the standard or samples and radio iodinated (125I) insulin for the limited binding sites on a specific antibody. At the end of incubation, antibody bound and free insulin is separated by the second antibody and poly ethyleneglycol (PEG) aided separation method. Insulin concentration of samples is quantitated by measuring the radio activity associated with the bound fraction of sample and standards. The decrease in serum insulin level indicates hyperglycemia in STZ-induced diabetic rats. The STZ-induced diabetic rats exhibited maximum decrease in serum insulin levels on 28th day.

Estimation of biochemical parameters

The animals were sacrificed by cervical dislocation on 28th day for determining various biochemical parameters. Various biochemical parameters like glycosylated hemoglobin, total cholesterol, triglycerides, high-density lipoprotein (HDL) and low-density lipoprotein (LDL). The kit used was kits of Triglycerides and Cholesterol (Minias Globe Diagnostic kit). Semi auto-analyzer was used for the analysis of sample. Theplasma profile for metabolic parameters like triglycerides and total cholesterol in theplasma was estimated in all the experimental groups. These

estimations done by usingcommercially available biochemical kits procured from Accurex, Biomedical(Mumbai, India)

Estimation of glycosylated hemoglobin (HbA1c)

Plasma 0.5ml was separated and cells were washed twice (0.154 M saline) and stored at –200ºC. Oxalic acid (1 ml, 0.3 M) was added to an aliquot (2 ml) of adjusted hemolysate, mixed, and placed immediately in a boiling water bath at 100ºC for exactly 60 min. Evaporation was minimized by placing glass marbles on each test tube. After incubation samples were cooled in cold water for 2min and deproteinization carried out by the addition of1 mlof 40%w/v TCA (Trichloroacetic acid). The tubes were vortexed (30 sec) and then centrifuged (1500 g x 15 min). Thiobarbituric acid (0.5ml, 0.05 M) was added to the clear supernatant (2 ml), mixed, and incubated at 40ºC for60 min. The color developed was noted at 443 nm. Incubated in each assay were a blank using distilled water instead of hemolysate, aqueous standards of 5-HMF (0.01 mM/L - 0.05 mM/L), aqueous standards of fructose (1mM/L - 4 mM/L).

Results and Discussion

Phytochemical screening

Phytochemical analyses of the crude extract of Bacopa monnieri revealed the presence of flavonoid, steroid, glycoside, saponin, tannins, and triterpinoid.

Antidiabetic activity

Ethyl acetate and ethanol extract of plants were found to contain more phytochemicals than petroleum ether and chloroform extract. Ethyl acetate and ethanol extract of plant were found to possess antioxidant activity. Hence Ethyl acetate and ethanol extract of plants were selected for further in vivo antidiabetic activity.

Acute Toxicity Studies

Acute toxicity study of Bacopa monnieri leaves extract on mice was to assess the toxicological profile of the test drug when given intraperitoneally single dose to the test system and monitor the vital signs for 14 days. This study will provide information on the possible health hazards likely to arise from single oral exposure of the extracts of the plant. Plants extracts administered in the dose of 100mg/kg, 500mg/kg and 2000 mg/kg and observed for 14 days. Animals were observed for autonomic or behavioural response during this period. The body weight was also observed. Mortality was observed up to 14 days. In acute oral toxicity study, extracts at the dose of 2000 mg/kg neither showed visible signs of toxicity nor mortality during the study and observations and measurements did not indicate any evidences of substance-related toxicity.

Induction of diabetes

Two dietary regimens were followed: Group 1 was the control group, administered the Normal Pellet Diet (NPD), and the other nine groups were fed a high-fat diet. The animals were fed for eight (8) weeks, and their body weights were taken every week

The body mass index (BMI) was determined. The electronic precision balance was used to obtain the weights of animals for six weeks. Rats with a BMI of 310 kg/m2 and above were considered obese and used for the diabetic studies

Group 1 (also known as the Non-Diabetic Control Group) had regular rat feed for the experiment. The remaining animals, Group 2 to Group 6, were subjected to an eight-week high-fat diet under After that, they received a single intraperitoneal dosage of 40 mg/kg streptozotocin, diluted in 0.1 M sodium citrate buffer, to induce diabetes. At about 72 hours after induction, the rat's tail was wiped. Then, the tip was snipped off to obtain a drop of blood, which was used to evaluate the animals' fasting blood glucose levels using an Acuchek Glucometer. Animals with more than 200 mg/dL were selected and randomly assigned to groups based on their body weight and blood glucose levels. They were distributed into the following groups n=6:, Normal control, diabetic control, Standard (400 mg/kg metformin) and group 4 to 7 plant extract treated. The diabetic control group was fed a regular diet and left untreated. For 21 days, the metformin and the extract were dissolved in water, and fresh preparations were made daily. The animals were free to feed on their regular diet throughout the treatment. During the 21-day treatment period, the feed intake, water intake, urine output, body weight, and faecal output were recorded every day simultaneously.

Effect of Bacopa monnieri on the blood glucose levels in diabetic rats

Overnight fasted animals were divided into groups to determine the antidiabetic effect of Bacopa monnieri on the blood glucose levels in high fat and STZ induce diabetic rats. The experimental rats were divided into groups

consisting of six rats per group. The extract, metformin, and normal saline were orally administered once every day for eight weeks. On 0, 7th, 14th, 21stand 28th day of extract administration, the fasting glucose levels were determined. During the experimental tenure, weights of rats were taken daily and mean change was calculated. Blood samples were collected by tail prick method. Body weights and fasting blood glucose levels were measured on a weekly basis. At termination, the rats were fasted overnight and sacrificed by cervical dislocation.

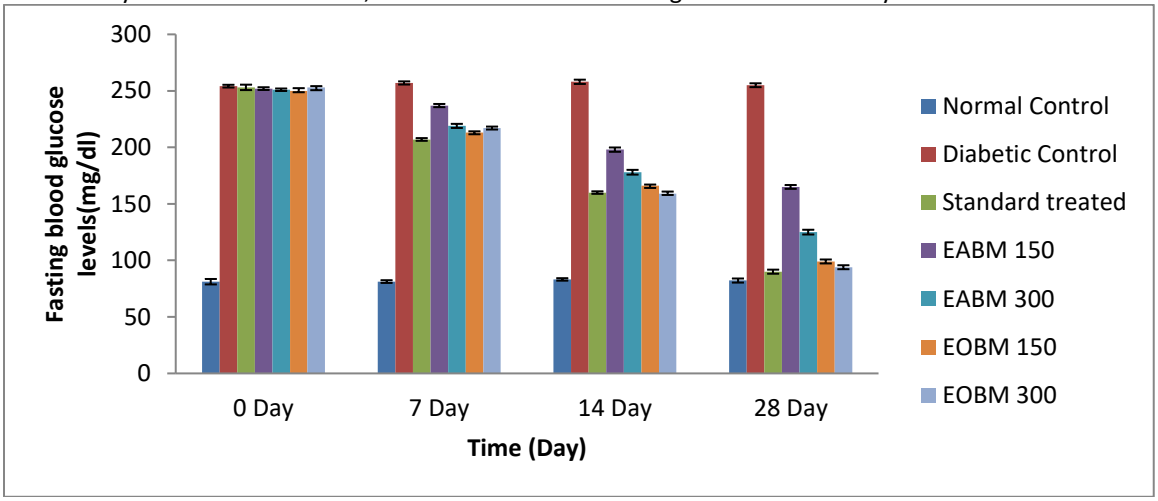

Figure 1: Effect of Bacopa monnieri on the blood glucose levels in diabetic rats Body weight assessment

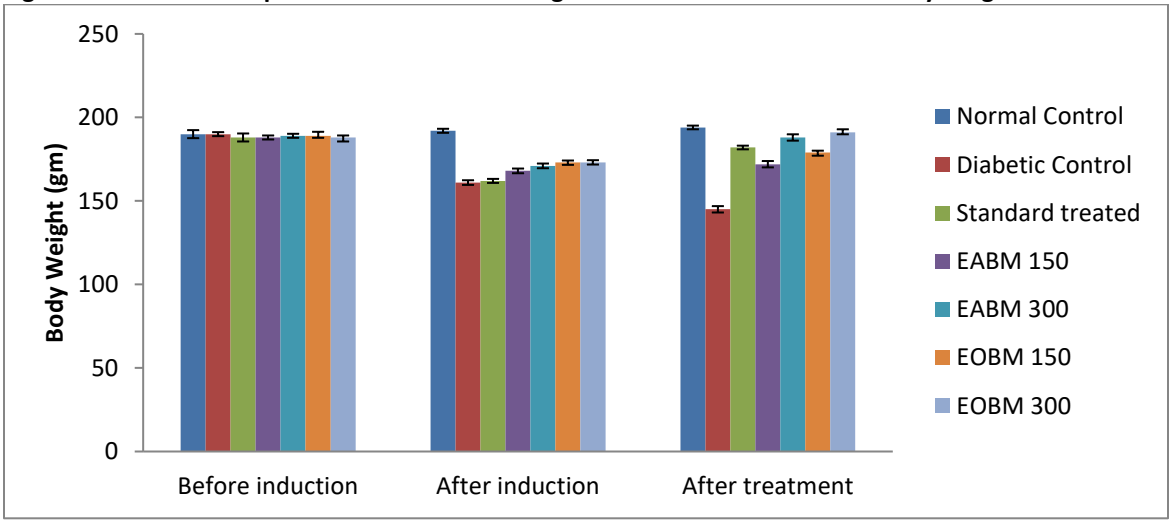

Figure 2: Effect of Bacopa monnieri extracts in change on body weight of animals

The body weight of the normal rats before and after completion of experiment remained unchanged, but a significant reduction in body weight of STZ-induced diabetic rats was noted and maximum reduction was observed on 28th day. The EABM and EOBM and Metformin treated rat showed no significant reduction in body weight on 28th day. Very little variations in body weight were observed in rats treated with ethanol extract and Metformin.

Estimation of glycosylated hemoglobin (HbA1c)

Glycosylated hemoglobin, also known as hemoglobin A1c (HbA1c), is a measure of the average amount of glucose that has attached to your red blood cells over the past two to three months. A blood test for HbA1c is used to screen for and diagnose prediabetes and diabetes, as well as to monitor how well a person's blood sugar levels are being managed with treatment.

When blood glucose levels are high, glucose molecules attach to the hemoglobin in red blood cells. Because red blood cells live for about 120 days (2 to 3 months), the HbA1c level reflects the average blood glucose level over that period. The test measures the percentage of hemoglobin that has been glycosylated. A higher percentage means a higher average blood sugar level over the past few months. There was a remarkable increase in glycosylated hemoglobin in diabetic control animals compared to normal control animals. Their were maximum increased in

HbA1c in diabetic control animals. Treatment with EABM (300 mg/kg) showed HbA1c level 7.65±0.19. Animals treated with ethanol extract of Bacopa monnieri (150 mg/kg, 300 mg/kg) exhibited improvement in Glycosylated hemoglobin level compared to standard treated group.

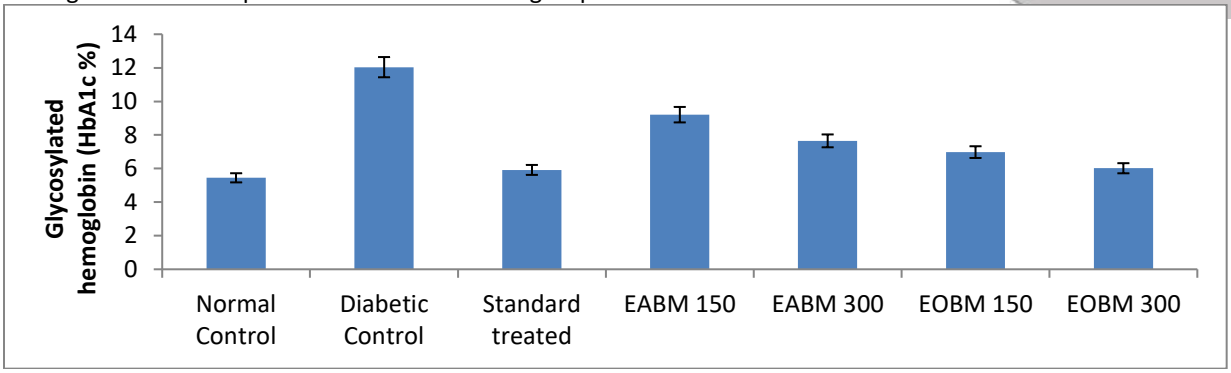

Figure 3: **Effect of Bacopa monnieri extracts on glycosylated hemoglobin levels in animals Lipid profile**

Diabetes is closely linked to a specific lipid profile known as diabetic dyslipidemia, characterized by high triglycerides, low "good" HDL cholesterol, and often high "bad" LDL cholesterol, all of which significantly increase the risk for cardiovascular disease. Poor glycemic control exacerbates these lipid abnormalities.

Carbohydrate and lipid metabolism are closely linked. When there is a disorder in one, it affects the other, leading to lipid metabolism disorders in diabetes. Poor glycemic control: In both Type 1 and Type 2 diabetes, poor blood sugar control specifically increases levels of triglycerides and VLDL (very-low-density lipoprotein) while decreasing HDL-C. Associated conditions: Many people with Type 2 diabetes also have conditions like obesity and insulin resistance, which are they associated with the same lipid abnormalities seen in diabetic dyslipidemia. Having high levels of triglycerides can be a risk factor for developing diabetes. Elevated triglyceride levels over time an also increase the risk for heart disease, heart attacks, and strokes. People with diabetes should get their cholesterol tested yearly to make sure levels are in the right range.

Insulin resistance increases the liver's production of large, triglyceride-rich VLDL particles. Poor glycemic control also raises VLDL levels. Diabetes often results in a higher proportion of small, dense LDL particles, which are considered more atherogenic (plaque-forming). Mild elevations in total LDL may also occur, especially in inadequately controlled diabetes. Diabetes is associated with lower levels of "good" HDL cholesterol. In addition, the HDL particles themselves may be dysfunctional and less effective at removing cholesterol from the body.

The plasma triglyceride and total cholesterol levels were seen to be surprisingly increased in diabetic control animals compared with normal control animals. The administration of ethanol extract at different doses (150 mg/kg and 300 mg/kg) significantly lowered the levels of cholesterol, triglycerides and LDL in diabetic rats when compared with the diabetic control group. Consequently, the HDL significantly increased in groups treated with extracts and standard in comparison to diabetic control group.

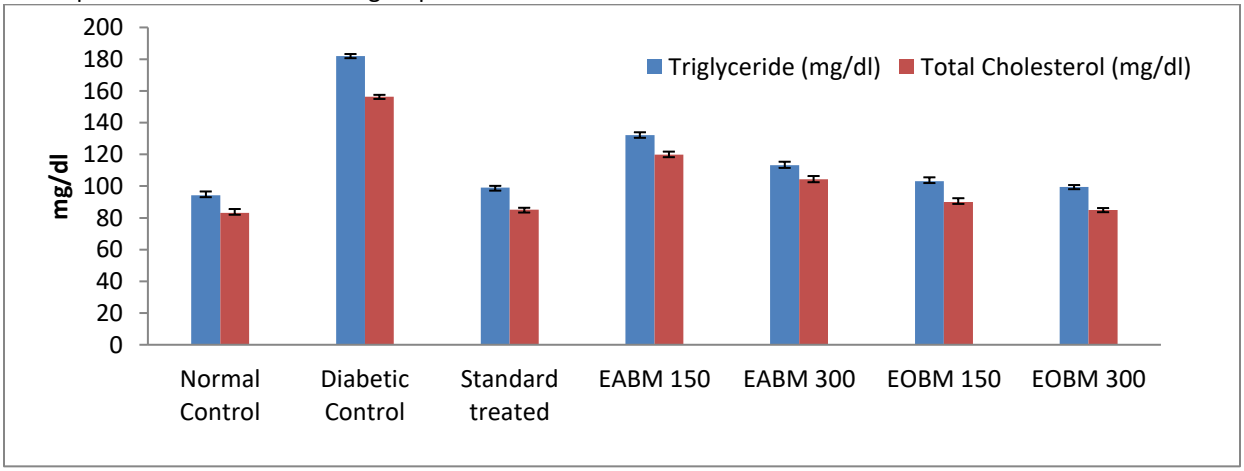

Figure 4: Effect of Bacopa monnieri extracts on Triglyceride and Total Cholesterol

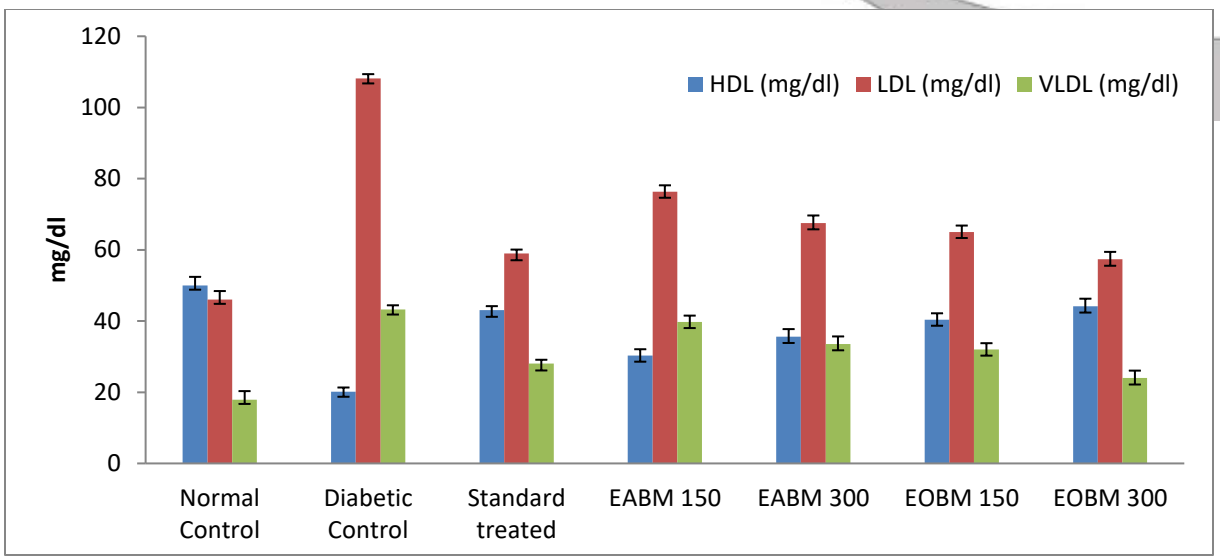

Figure 5: Effect of Bacopa monnieri extracts on HDL, LDL and VLDL

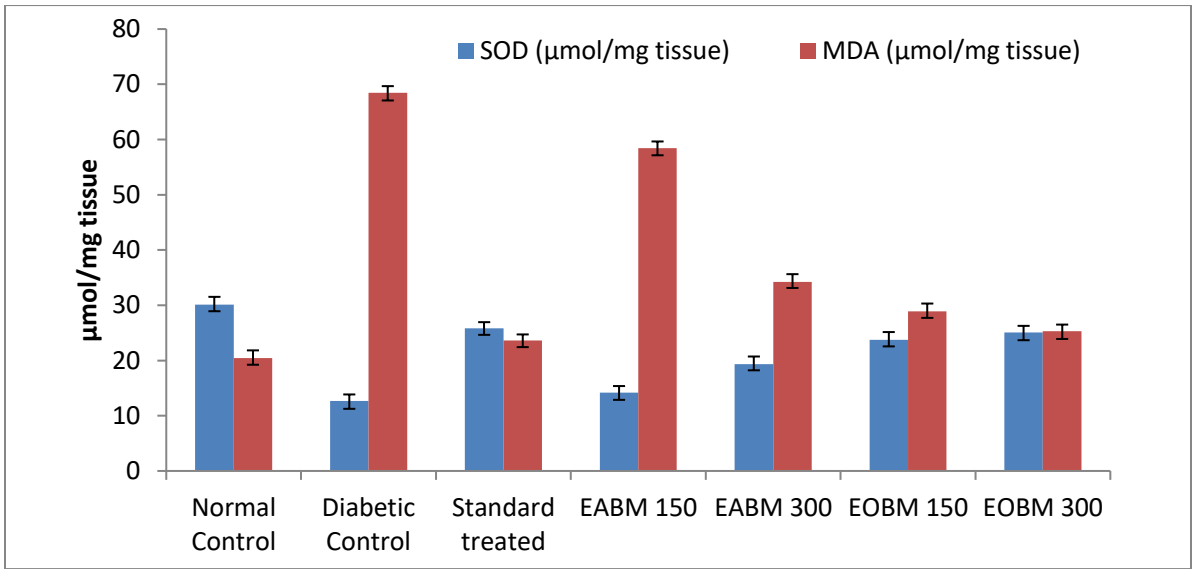

Figure 6: Effect of Bacopa monnieri extracts on anti-oxidant enzyme (SOD and MDA)

Treatment with Bacopa monnieri extracts made dose dependent improvement of damaged histological features. In treatment groups, there was no evidence of pancreatic beta cell degeneration watched. Similar kind of clear and normal histological discoveries were seen on standard antidiabetic drug metformin treated animals. The number of pancreatic beta cells and the average size of beta cell and pancreatic cells area were extremely decreased in STZ animals contrasted to nondiabetic control pancreas. Treatment with Bacopa monnieri ethanol extracts showed progressive and dose dependent improvement in the pancreatic beta cell number and beta cell sizes. This combination of a high-fat diet and STZ creates a robust and reproducible model of type 2 diabetes in rodents that mimics many aspects of the human disease, making it a useful tool for studying diabetes progression and testing potential antidiabetic therapies.

Conclusion

Hyperglycemia and hyperlipidemia are the main causes of oxidative stress in type 2 diabetes. Reactive oxygen species (ROS) formed in this process triggers tissue damage and has been shown to affect the two major mechanisms failing during diabetes: insulin resistance and insulin secretion. In diabetes, tissue damage is considered to be

mediated by free radicals by attacking membranes through peroxidation of unsaturated fatty acids which lead to extensive membrane damage and dysfunction. Decreased lipid peroxidation and improved antioxidant condition could be one of the mechanisms to prevent complications of diabetes. The available drugs for diabetes, insulin or oral hypoglycemic agents have one or more side effects and search for new antidiabetic drugs with minimal or no side effects from medicinal plants is a challenging for us. The present study was undertaken to investigate the antidiabetic and antioxidant activity of Bacopa monnieri leaves. Phytochemical screening showed the presence of steroids, triterpenoids, flavonoids, glycosides, saponins, and tannins that were contribute to biological activity. The present study was undertaken to investigate the antidiabetic activity of Bacopa monnieri leaves. These results indicated that Bacopa monnieri leaves possess strong anti-diabetic potential in high fat streptozotocin induce support traditional medicinal use for the treatment of diabetes mellitus and good source for natural antioxidants. Blood glucose, total cholesterol, triglycerides, low-density lipoproteins, very low-density lipoproteins, serum alanine aminotransferase, and aspartate aminotransferase were significantly reduced, whereas high-density lipoproteins were significantly increased in Bacopa monnieri leaves (300 mg/kg)-treated rats. Histopathological study of the pancreas showed an increase in number, size, and regeneration of β-cell of islets of Langerhans. Ethanolic extract of Bacopa monnieri leaves showed hypoglycemic and hypolipidemic activity in high fat streptozocin-induced diabetic rats. These results indicated that Bacopa monnieri leaves possess strong anti-diabetic and antioxidant potentials and support traditional medicinal use for the treatment of diabetes mellitus and good source for natural antioxidants.

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