



Anti-Dyslipidemia Effect of Ethanol Extract of *Passiflora foetida* on Dextrose Induced Diabetic Rats

Ravi Babu Birudu¹, M. Jagadish Naik^{2*}, Janardhan M³

¹Department of Biotechnology, Acharya Nagarjuna University, Guntur- 522510, A.P, India

²Department of Zoology & Aquaculture, Acharya Nagarjuna University, Guntur- 522510, A.P, India

³Department of Pharmacology, Nimra College of Pharmacy, Jupudi, Vijayawada- 521456, A.P, India

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*Corresponding Author:

E-mail: Jagadish100naik@gmail.com

Mob.: +919948120530

Abstract

Dyslipidemia leads to cardiovascular disease (CVD) and it is determined by elevation of plasma concentration of lipoproteins. Diabetes is a chronic disorder and it is controlled by different allopathic and Ayurvedic formulation. The synthetic drugs include sulfonyl ureas, biguanides, metformin HCl, DPP-4 inhibitors etc. The folk medicine is practiced by local people. The people use herbal medicine to control and treat the various types of diseases. In India, tribal people used different types of medicinal plants to control the diabetes. In present study ethanol extracts of *Passiflora foetida* leaves were evaluated for anti-dyslipidemia activity in dextrose induced diabetic rats. The ethanol extracts of *P. foetida* were administered at the doses of 100 mg/kg body weight, 250 mg/kg body weight and 500 mg/kg body weight to the dextrose induced diabetic rats. The silver nanoparticles were prepared by the reaction of 1 mM silver nitrate and 5% leaf extract of *P. foetida*. The antidyslipidemia activity of ethanol extracts was compared with standard drugs Glipizide, Sitagliptin and Vildagliptin. The standard drugs normally decreased the lipid parameters in diabetic rats. The ethanol extract at the dose of 500 mg/kg body weight showed significant lowering effect on dextrose induced diabetic rats. The total cholesterol, triglycerides, low-density lipoprotein (LDL) and very low density lipoprotein (VLDL) were decreased by ethanol extract and standard drugs. Additionally the ethanol extract reduced the HDL level in treated animals. The silver nanoparticles produce lower effect on lipid profile.

1 Introduction

Diabetes is metabolic disorders and whole world is facing the problem of diabetes. Diabetes severely affect the normal routine life of human^{1,2}. WHO stated that the occurrence of diabetes is enhanced by 35%. Presently 150 million people are effected by diabetes and it is assume to be increased by 300 million at the end of 2025³. It is emerging as one of the leading causes of end stage renal disease, heart attack, non-traumatic amputation, and blindness, increasing the mortality and morbidity burden on the community.

Diabetes is metabolic disorder and is characterized by hyperglycemia, altered lipids, carbohydrates, and proteins metabolism. Diabetes is a metabolism in which a person has high blood sugar, either because the body does not produce enough

insulin, or because cells do not respond to the insulin that is produced. Glucose metabolism disturbances are major factors leading to diabetes^{4,5}. Apart from hyperglycemia, the reactive oxygen species and hyperlipidemia play chief role in occurrence of diabetes^{6,7}. Diabetes produces disturbances in lipid profiles and especially, an increased susceptibility to lipid peroxidation. In the last stages of diabetes, lipid metabolism is affected and seen as hyperlipidemia and hypercholesterolemia which are risk factors in atherosclerosis⁶⁻⁸.

Dyslipidemia is characterized by abnormal level of lipid in blood, including lipoprotein overproduction or deficiency. Consequently, the total cholesterol, LDL, triglycerides, apo B or Lp(a) levels above the 90 percentile or HDL and Apo A levels below the 10 percentile of the general population in Dyslipidemia patient. Several methods have

been used to classify the lipoproteins in respect to their density, physical, and chemical properties. Based on these classifications, different types of lipoproteins, including chylomicrons, IDL1, VLDL2, LDL3, and HDL4, and apolipoproteins (Apo), including Apo A, Apo B, Apo C, and Apo E, have been introduced. Atherosclerosis is a chronic inflammatory disease compelled in large part by hypercholesterolemia and often revealed in myocardial infarction or stroke⁹.

The dyslipidemia leads to CVD and similarly it provokes the coronary heart disease (CHD). It is documented that the mortality of CHD in the developed countries is expected to reach almost 29% and 48% in women and men, respectively in years 1990-2020. However, in developing countries these data has been increased by 120% and 137% in women and men, respectively¹⁰. Hence, there is an urgent need to study the screening of anti-dyslipidemia properties of medicinal plants, which will be helpful in the treatment of diabetes, CVD and CHD.

Passiflora foetida belongs to Passifloraceae, and is an exotic and fast-growing perennial, vine, occurring in west USA and extend to the Asian countries like India. The tribal people uses *P. foetida* for the treatment of various diseases namely diarrhea, asthma, intestinal tract, neurological disorders, throat, headache, ear infections, fever, hysteria and skin diseases. The phytoconstituents presents in *P. foetida* are alkaloids, phenols, glycosides, flavonoids, cyanogenic compounds, passifloricins, polypeptides and alpha-pyrone¹¹⁻¹⁵. The present study was planned to evaluate the ant-dyslipidemia activity of ethanol extract of leaves of *P. foetida* in dextrose induced diabetic rats.

2 Materials and Methods

2.1 Plant material

The fresh leaves of *Passiflora foetida* were collected from the area of botanical garden, Acharya Nagarjuna University, Guntur. The plant material was identified and authenticated by a taxonomist in the University. The collected leaves were dried under shade and then ground into fine powder using laboratory mortar and pestle.

2.2 Preparation of plant extract

The powder (100 gm) of leaves was macerated in solvent containing 70% ethanol and 30% distilled water at room temperature for 72 h. This was then filtered using a filter paper and the filtrate was evaporated to dryness on water bath at 60 °C and dried brown extract was kept in an air tight bottle until used.

2.3 Chemical used

All chemicals and drugs used were obtained commercially and were analytical grade. Dextrose was purchased from National Scientific Laboratory, PVT Ltd, Vijayawada.

2.4 Biosynthesis of Silver Nanoparticles

5% leaves extract, 10 mL of ammonia solution (1 M), and 10 mL of silver nitrate solution (10 mM) were mixed. The solution pH adjusts to the desired value by using sodium hydroxide or phosphoric acid solution and then was diluted until 100 mL with distilled water. The mixture was stirred for 4 h at 45°C. After centrifuging of silver nanoparticles solution for 10 min at 10000 rpm, silver nanoparticles were sedimented at the bottom of the conical tube. The supernatant phase was removed and silver nanoparticles were washed with 10 mL water for three times. After the washing, the residue was transferred to freeze dryer, and finally powder obtained^{16,17}.

2.5 Acute toxicity studies of the plant extract

The index of the acute toxicity was the LD₅₀. In the initial phase, rats were divided into 3 groups of 6 rats each and were treated with *P. foetida* extract at doses of 100 mg, 250 mg, 500 mg and 1000 mg/ kg body weight orally. The animals were observed for 24 h for signs of toxicity including death. Based on the results the next experiment was designed¹⁸.

2.6 Induction of experimental diabetes

Normal healthy male Wistar albino rats, 9-12 weeks old with an average weight of 200-250 gm were procured from the Mahaveer Enterprises, Bagh Amberpet, Hyderabad. They were housed in polypropylene cages and fed with a standard chow diet and water *ad libitum*. The animals were acclimatized to the conditions by maintaining them at a temperature 25±2 °C and relative humidity 55±10 at 12 hour each at dark and light cycle for about 7 days prior to dosing and during the commencement of experiment. All experimental procedures involving animals were conducted in accordance with the guidelines of Committee for the Purpose of Control and Supervision on Experiments on Animals (CPCSEA).

Dextrose was used to induce diabetes mellitus in male albino wistar rats. A freshly prepared dextrose solution was given orally at 6.6 gm/rat/5ml. After 15 days, rats with moderate diabetes having glycosuria and hyperglycemia were selected for the experiment.

2.7 Experimental design

A total of 54 rats were used in the present investigation. The animals were randomly divided into 9 groups and each group contain 6 rats. The group I considered as normal group and no any treatment has given to them. The group II to group IX were administered dextrose, and further group II is considered as diabetic control group. Group III, Group IV and Group V were treated with extract at the dose of 100

mg/kg bw, 250 mg/kg bw and 500 mg/kg bw, respectively. Group VI were treated with glipizide (4 mg/kg bw); Group VII were treated with sitagliptin (0.14 mg/100gm bw); Group VIII were treated with vildagliptin(10 g/kg bw); and Group IX were treated with silver nanoparticles(10 ml/kg bw). All treatments were given once daily for a period of 45 days.

At the end of the treatment, all rats were fasted for 12 hours and sacrificed by cervical decapitation. The blood was collected into heparinized tubes and plasma was separated by centrifugation and used for biochemical analysis.

2.7.1 Estimation of glucose

The collected serum samples of different study group were subjected to the serum glucose level estimation by enzymatic GOD-POD method.

2.7.2 Estimation of biochemical parameters

The biochemical parameters were determined on day 45 after the animals were sacrificed by cervical dislocation. Total cholesterol, triglycerides (TGL), high-density lipoprotein (HDL), low-density lipoprotein (LDL) and very low density lipoprotein (VLDL), were determined by the glucose oxidase method, using an auto-analyzer¹⁹⁻²².

2.8 Statistical analysis

The results are expressed as mean \pm SEM of six independent experiments. Statistical significance between the groups was evaluated by one-way analysis of variance (ANOVA) followed by Dunet's test. A $P < 0.05$ value was considered as statistically significant.

3 Results

The normal rats have the glucose level mean value 134.50 \pm 5.75. The diabetic induced rats have the mean value of 428.67 \pm 25.97 which has significant variance when compared to normal rat mean. Standard glipizide treated group gives the result as 144.00 \pm 12.02 which is very near to the normal value 134.50 \pm 5.75. The low dose of 100 mg of PSF gives the value 275.17 \pm 24.65. Medium dose 250 mg of *P. foetida* extract (PSF) gives the result as 254.00 \pm 21.12 which was also near to the normal and not worked properly. High dose 500 mg of PSF produces value 133.83 \pm 4.02 which is similar to the normal value. Sitagliptin and Vildagliptin treated rats produces result upto 153.00 \pm 6.36 and 144.17 \pm 4.96, respectively. Silver nano particles gives the mean value of 193.33 \pm 15.42. Among these high dose of PSF is works effectively and lower the glucose levels in diet induced diabetic rats. Plant extract high dose 500 mg worked well and lower the glucose levels in diet induced diabetic rats.

The mean of total cholesterol of normal rats were 97.12 \pm 2.15. Diet induced diabetic rats have mean 157.52 \pm 2.35. This value was significant difference when compared to normal mean. Diabetic rats treated with standard drug Glipizide produces 124.27 \pm 2.62 value which was significant difference from diabetic control group. Plant extracts of PSF low, medium and high dose gives the mean values 154.22 \pm 2.90, 134.47 \pm 3.11 and 103.90 \pm 1.45. Among the extract, higher doses produces maximum antidiabetic activity. Diabetic rats treated with sitagliptin and viladagliptin have mean values of 117.10 \pm 2.17 and 114.05 \pm 2.24, respectively. Both mean values were significant differences from diabetic control group. Diabetic rats treated with silver nanoparticles have mean value 107.88 \pm 1.93 which was significant (Table 1). Among these high dose and sitagliptin have effective mean values to reduce the total cholesterol.

Table 1 exhibited triglycerides given the mean values of drugs used for diet induced diabetic rats. Normal means of rats were 132.85 \pm 1.82. Diet induced diabetic rats have mean value of 169.13 \pm 2.75. The triglycerides of control group were significant increased compared to normal group rats. The triglycerides of Glipizide, sitagliptin and vildagliptin treated rats significantly lowered when compared to diabetic rats. The extract treated rat decreases the triglycerides level in rats, while the medium and high doses exhibited significant decrease in triglycerides level. The diabetic rats treated with silver nanoparticles exhibited insignificant decreases in triglycerides level compared to diabetic rats. Among these, high dose is effective to reduce the triglycerides levels.

HDL mean of normal rats were 40.37 \pm 2.39 mg/dl. Diet induced diabetic rats have mean value of 21.60 \pm 2.50. The HDL of control group was significant decreased compared to normal group rats. The HDL of Glipizide, sitagliptin and vildagliptin treated rats significantly enhanced when compared to diabetic rats. The extract treated rat increases the HDL level in rats, while the medium and high doses exhibited significant increases in HDL level. The diabetic rats treated with silver nanoparticles exhibited insignificant increases in HDL level compared to diabetic rats (Table 1). Among these, high dose is effective to increases the HDL levels. The high dose of plant extract works effectively and improves the HDL Cholesterol levels in diet induced diabetic rats.

The LDL mean of normal rats were 30.18 \pm .46 mg/dl. Diet induced diabetic rats have mean value of 63.09 \pm 3.40. The LDL of control group was significant increased compared to normal group rats. The LDL of Glipizide, sitagliptin and vildagliptin treated rats significantly lowered when compared to diabetic rats. The extract treated rat decreases the LDL level in rats, while the medium and high doses exhibited significant decrease in LDL level. The diabetic rats treated with silver nanoparticles exhibited significant decreases in LDL level

compared to diabetic rats (Table 1). Among these, high dose is effective to reduce the LDL levels.

Table 1: Effect of ethanol extract on total cholesterol, triglycerides, HDL, LDL and VLDL levels in dextrose induced diabetic rats

Group	Total cholesterol	Triglycerides	HDL	LDL	VLDL
Normal	97.12±2.15	132.85±1.82	40.37±2.39	30.18±.46	26.57±.36
Diabetic controlled	157.52±2.35 ^a	169.13±2.75 ^a	21.60±2.50 ^a	63.09±3.40 ^a	45.82±.55 ^a
Diabetic + PSF (100 mg/kg)	154.22±2.90	163.55±1.55	27.30±1.20	65.21±3.05	32.71±.31
Diabetic + PSF (250 mg/kg)	134.47±3.11 [†]	159.20±2.42 [†]	36.75±1.67 [†]	48.87±3.09 [†]	31.84±.48
Diabetic + PSF (500 mg/kg)	103.90±1.45 [†]	133.53±1.95 [†]	42.50±1.79 [†]	36.69±1.76 [†]	26.71±.39 [†]
Diabetic + Glipizide (4 mg/kg)	124.27±2.62 [†]	151.17±2.86 [†]	45.17±1.37 [†]	40.86±2.19 [†]	25.23±.57 [†]
Diabetic + Sitagliptin (0.14 mg/100 gm)	117.10±2.17 [†]	151.50±4.68 [†]	42.32±1.60 [†]	44.48±3.46 [†]	26.30±.94 [†]
Diabetic + vildagliptin (10 g/kg)	114.05±2.24 [†]	152.57±1.66 [†]	42.50±4.85 [†]	41.04±5.90 [†]	25.51±.33 [†]
Diabetic + silver nanoparticles (10 ml/kg)	107.88±1.93 [†]	165.88±1.86	33.02±1.78	32.69±3.06 [†]	31.18±.37 [†]

Ethanol extract of *Passiflora foetida* of leaves (PSF), Values are expressed as mean ± SEM (Number of animals, n=6); significantly different at [†]P<0.05 when compared with normal control group

The VLDL mean of normal rats were 26.57±.36 mg/dl. Diet induced diabetic rats have mean value of 45.82±.55. The VLDL of control group was significant increased compared to normal group rats. The VLDL of Glipizide, sitagliptin and vildagliptin treated rats significantly lowered when compared to diabetic rats. The extract treated rat decreases the VLDL level in rats, while the medium and high doses exhibited significant decrease in VLDL level. The diabetic rats treated with silver nanoparticles exhibited significant decreases in VLDL level compared to diabetic rats (Table 1). Among these, high dose is effective to reduce the VLDL levels.

4 Discussions

Globally medicinal plants are used for the remedy of various types of diseases. The present study exhibited a proliferation in the concentration of total cholesterol, triglyceride, low-density lipoprotein cholesterol (LDL) and a decrease in HDL in diabetic rats. This results support the findings of Mitra *et al.* (1995)²³ that who have reported increased plasma cholesterol, triglycerides, LDL and decreased HDL in dextrose-induced hyperglycemia in rats. Daisy *et al.* (2009) had reported insulin deficient associated hypercholesterolemia and hypertriglyceridemia in streptozocin induced diabetes in rats²⁴. Mathe

(1995) reported that hypercholesterolemia in streptozotocin results from increased intestinal absorption and synthesis of cholesterol²⁵. Diabetic-induced hyperlipidemia is attributable to excess mobilization of fat from the adipose due to under utilization of glucose²⁶. The lack of insulin and elevations of the counter-regulatory hormones lead to activation of enzymes (hormonesensitive lipase) that stimulate lipolysis and enhanced release of free fatty acids from adipose tissue²⁷. The fatty acids release from adipose tissues produces energy during mobility, but excess fatty acid stored in liver further converted to triglyceride⁸. The marked hyperlipidemia that characterizes the diabetic state may therefore be regarded as a consequence of unlimited actions of lipolytic hormones on the fat depots¹. Lowering of serum lipid levels through dietary or drugs therapy seems to be associated with a decrease in the risk of vascular disease in diabetes through dietary or drugs therapy seems to be associated with a decrease in the risk of vascular disease in diabetes²⁸. In this study, administration of all doses of the ethanol leaves extract of *P. foetida* significantly reduced serum levels of total cholesterol, triglyceride, low-density lipoprotein and increased serum levels of high-density lipoprotein in dextrose-induced diabetic Wistar rats.

However, significantly decrease on serum lipid profile levels observed on treatment with the ethanolic leaves extract of *P. foetida* may presumably be mediated by a control of lipid metabolism by some of the phytochemicals present in the plant. Many nutritional factors such as saponins and tannins have been reported to contribute to the ability of herbs to improve dyslipidemia. Preliminary phytochemical screening of the extract revealed the presence of saponin among other polyphenolic compounds. This may be responsible for the lipid-lowering effect of *P. foetida* on plasma lipid. Saponins are known antinutritional factors, which lower cholesterol by binding with cholesterol in the intestinal lumen, preventing its absorption and/or by binding with bile acids, causing a reduction in the enterohepatic circulation of bile acids and increase its fecal excretion²⁹. Increased bile acid excretion is offset by enhanced bile acid synthesis from cholesterol in the liver and consequent lowering of the plasma cholesterol. Hence, saponins have been reported to have hypocholesterolic effect. Kumarappen *et al.* (2007) reported that administration of polyphenolic compounds to alloxan-induced diabetic rats reduced hyperlipidemia and attributed this to a reduction in the activity of hepatic HMG-CoA reductase, which is the first committed enzymatic step of cholesterol synthesis. This lowers elevated LDL cholesterol levels, resulting in a substantial reduction in coronary events and deaths from CHD that occurs in diabetics³⁰. Thus, the observed hypolipidemic effect of *P. foetida* can be therefore, linked to the synergistic actions of phytochemicals like saponins and polyphenolic compounds contained in the plant extract. It is reported that the derangement of glucose, fat and protein metabolism during diabetes, results into the development of hyperlipidemia³¹. In this study, all doses of the plant extract used produced a significant beneficial effect on serum lipid profile in dextrose-induced diabetic rats. This beneficial effect on the lipid profile may be secondary to glycemic control. The significantly lowered cholesterol level may have contributed to the observed significant high serum high-density lipoprotein cholesterol in the animals. Significant lowering of total cholesterol and rise in HDL is a very desirable biochemical state for prevention of atherosclerosis and ischaemic conditions. HDL function to remove cholesterol antheroma within arteries and transport it back to the liver for its excretion or reutilization, thus high level of HDL protect against cardiovascular disease (. Therefore, the observed increase in the serum HDL level on administration of various doses of the extract in dextrose-induced diabetic rats, indicates that the extract have HDL boosting effect. Moreover, the stabilization of serum triglyceride and cholesterol levels in rats by the plant extract may be attributed to glucose utilization and hence depressed mobilization of fat. This implies that the plant extract may be useful in reducing the complications of hyperlipidemia and hypercholesterolemia which often coexist in diabetics^{32,33}. The study also revealed that

administration of the extract at various doses significantly lowered the serum LDL in dextrose-induced diabetic Wistar rats.

5 Conclusion

The study also showed that oral administration of all doses of the extract resulted to a significant decrease on the levels of lipid profile in dextrose-induced diabetes mellitus as well as improved hyperlipidemia associated with diabetes. In present study, all doses of *P. foetida* plant extract appeared to be effective and were comparable to the standard drugs (Glipizide, Sitagliptin and Vildagliptin). The result obtained from this work showed that the plant may be useful in the management of secondary complications of diabetes (dyslipidemia) associated with diabetes mellitus.

6 Competing interest

Author claims no competing interests.

7 Author's contributions

The study was conceived, planned, performed and written in the form of manuscript by RBB, MJN and JN. All authors read and approved the final manuscript.

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