Argyreia Nervosa Controls Dyslipidemia in STZ-Induced Type 2 Diabetic Rats by Modulating the Expression of Proinflammatory Signaling Molecules in Adult Male Rats

Sujitha A[1], R. Gayathri[2*], J. Selvaraj[3], V. Vishnu Priya[4], Kavitha.S[5]

[1]Saveetha Dental College and Hospitals, Saveetha Institute of Medical and Technical Sciences, Saveetha University, Chennai, India
[2*]Department of Biochemistry, Saveetha Dental college and Hospitals, Saveetha Institute of Medical and Technical Sciences, Saveetha University, Chennai, India
[3]Department of Biochemistry, Saveetha Dental college and Hospitals, Saveetha Institute of Medical and Technical Sciences, Saveetha University, Chennai, India
[4]Department of Biochemistry, Saveetha Dental college and Hospitals, Saveetha Institute of Medical and Technical Sciences, Saveetha University, Chennai, India
[5]Department of Biochemistry, Saveetha Dental college and Hospitals, Saveetha Institute of Medical and Technical Sciences, Saveetha University, Chennai, India

Abstract: **Introduction**: Metabolic syndrome (MetS) includes a series of metabolic abnormalities that leads to diabetes mellitus and cardiovascular diseases, characterized by several metabolic abnormalities including insulin resistance, type 2 diabetes, obesity, hypertension and dyslipidemia. Dyslipidemia is usually associated with uncontrolled diabetes.
Recently, herbal medications have drawn more attention due to their fewer side effects and lower cost. We look at one such excellent plant, Argyreia nervosa, which has been used in Ayurveda for a very long time to treat diabetes and various other illnesses due to its unique properties like hypoglycemic, anti-inflammatory, immunomodulatory, and anticonvulsant properties.
Aim and Objective: To evaluate the anti-dyslipidemic property of Argyreia nervosa in STZ-induced type 2 diabetic rats by modulating the expression of pro-inflammatory signaling molecules in adult male wistar rats.
Materials and Methods: Diabetes was induced in adult male Wistar rats by STZ administration and were divided into groups to study the antidiabetic property of Argyreia nervosa ethanolic extract after its oral administration.
Fasting blood glucose, serum insulin, total cholesterol, leptin mRNA expression and adiponectin mRNA expression were the parameters studied.
Results: Rats treated with Argyreia nervosa ethanolic extract showed significant decrease in fasting blood glucose, serum insulin, total cholesterol and leptin mRNA expression and the values significant with the standard drug Metformin.
Conclusion:Our present findings shows that Argyreia nervosa has the potency to regulate lipid metabolism in adipose tissue and hence act as a very effective drug against diabetes mellitus and dyslipidemia.

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1. INTRODUCTION

A metabolic disorder called dyslipidemia is caused by elevated levels of total cholesterol and is characterized by changes in the levels of the lipoproteins cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), very-low-density lipoprotein cholesterol (VLDL-C), and triglycerides (TGs) in the blood as well as a concurrent decline in the levels of high-density lipoprotein cholesterol (HDL-C). The most common marker for vulnerability to cardiovascular illnesses is dyslipidemia, which is characterized by hypercholesterolemia. Heart failure is caused by a number of factors, including a high-saturated-fat-and-cholesterol diet, age, family history, hypertension, and lifestyle choices. However, coronary heart disease is mostly brought on by high levels of cholesterol, specifically TC, TG, and LDL cholesterol (CHD). (V. Srilatha Goud et al.,2016). Diabetes frequently causes dyslipidemia, and there is compelling evidence that decreasing cholesterol has a positive impact on cardiovascular outcomes even in people with seemingly ordinary lipid profiles.(1) Prior to the onset of biochemical hyperglycemia, type 2 diabetes patients frequently experienced an increased cardiovascular risk for several years. The condition known as metabolic syndrome, which is characterized by obesity, insulin resistance, hypertension, and dyslipidemia, is frequently present during this time.(2)

The root cause of diabetes and other lifestyle disorders like blood pressure is inflammation. The pathogenesis of inflammation may involve two pathways. First, oxidative stress and inflammatory changes are brought on by the consumption of glucose and macronutrients. Thus, chronic overeating and obesity may be pro-inflammatory conditions accompanied by oxidative stress. Second, the elevated levels of TNF-α and IL-6 linked to type 2 diabetes and obesity may impair insulin action by inhibiting insulin signal transduction. This could interfere with insulin's anti-inflammatory effect, which in turn might promote inflammation. (3)

The condition known as insulin resistance, which impairs the function of insulin in adipose tissue, is more closely associated with intra-abdominal fat than with fat in other depots. With an increase in body fat, adiponectin expression declines. Adenosine monophosphate dependent kinase (AMPK), PPAR-α, and maybe other as-yet-unidentified signaling pathways are activated when adiponectin binds to its receptors AdipoR1 and AdipoR2, which mediates the insulin-sensitizing action. Plasma levels of adiponectin are markedly increased by weight loss. In humans, decreased adiponectin has been linked to insulin resistance, dyslipidemia, and atherosclerosis. Leptin is another significant adipokine. Obesity raises circulating leptin levels, which are significantly influenced by subcutaneous fat.(4) While adiponectin levels are downregulated in obesity, leptin levels are directly correlated with adipose tissue mass. Leptin is mostly produced by adipocytes, although it is also made by cardiomyocytes and vascular smooth muscle cells. Cardiovascular conditions including hypertension, congestive heart failure, and myocardial infarction result in higher plasma leptin concentrations.(5). Our team has extensive knowledge and research experience that has translate into high quality publications(6–15))(16–25))

The plant Argyreia nervosa also known as elephant creeper and wooly morning glory grows as undergrowth in semi-deciduous

forests and along the edges of lakes and rivers. Leaves of A. nervosa mainly contain β-sitosterol, 1-triacontanol and quercetin. Traditionally, the plant has been used therapeutically for its wide range of clinical effects such as antiviral, antibacterial, anti-fungal and anti-inflammatory properties.(26)In a previous study, it was found that when STZ-induced diabetic rats were fed with alcoholic extract of A. nervosa, it showed significant anti hyperglycemic effect. In this study we would further evaluate the anti-dyslipidemic property of ethanolic extract of A. nervosa in STZ-induced type 2 diabetic rats by modulating the expression of pro-inflammatory signaling molecules.

2. MATERIALS AND METHODS

Chemicals Used:
The entire chemicals and reagents used in this research were of the molecular and analytical grade acquired from Sigma Chemical Company, and Sisco Research Laboratories (Mumbai, India).

Plant collection
The species will be verified at Anna Siddha Hospital in Chennai, Tamil Nadu, using Argyreia nervosa root powder obtained from a pharmacy.

Extract preparation
The roots of Argyreia nervosa powder were soxhlet extracted with 70% ethanol. The extract was then filtered with Whatman no. 1 filter paper and the solvent evaporated at reduced pressure by using a Rotary evaporator apparatus to get a viscous mass, which was then stored at 4°C until used (27)

Animals
Animals were maintained as per the National Guidelines and Protocols approved by the Institutional Animal Ethics committee (BRULAC/SDCH/SIMATS/IAEC/04-2022/109). Healthy adult male Wistar albino rats of Wistar strain (150–180 days old weighing 180–200 g) were used in this study and maintained in clean polypropylene cages at the Biomedical Research Unit and Lab Animal Center (BRULAC), Saveetha Dental College & Hospitals, Saveetha Institute of Medical & Technical Sciences, Chennai – 600 077, Tamil Nadu, India, under specific humidity (65 ± 5%) and temperature (21 ± 2°) with constant 12 h light and 12 h dark schedule. The standard pelleted diet (Lipton India, Mumbai, India) was provided with clean drinking water in ad libitum.

STZ induction
Diabetes was induced in rats by a single intraperitoneal administration of STZ (55 mg/kg) dissolved in 0.1 M citrate buffer, pH 4.5. 48 hours later, blood samples were collected and glucose levels were estimated to confirm the development of diabetes. The rats that showed hyperglycemia (blood glucose level > 250 mg/dl) were selected for experimental study.

Grouping
Animals were grouped into 3 groups of six animals each and treated oral administration for 15 days.

Group I - Normal rats
Group II- diabetic rats
Group III - diabetic rats + oral administration of argyreia nervosa 500 mg/kg/day
Group IV - normal rats+ oral administration of argyreia nervosa 500 mg/kg/day

Parameters to be studied:

Fasting blood glucose (FBG)
After the overnight fasting, the blood glucose was estimated using On-Call Plus blood glucose test strips (ACON Laboratories Inc., USA). From the rat tail tip, the blood was collected and the results were expressed as mg/dl.

Oral glucose tolerance test (OGTT)
For the oral glucose tolerance test, animals fasted overnight. After giving the oral glucose load (10 ml/kg; 50% w/v) blood glucose level was estimated at various time periods (60, 120, and 180 min) by using

On-Call Plus blood glucose test strips. Before giving a glucose load, the value of blood glucose is considered as 0 min value. Results were marked as mg/dl.

Fasting serum insulin

Serum insulin was assayed using ultrasensitive rat insulin ELISA kit obtained from Crystal Chem Inc (Illinois, USA). The range of detection is 0.1–64 ng/ml. The percentage cross reactivity of insulin antibody to rat insulin was 100%. The intra assay coefficient of variation was ≤10.0% and inter-assay coefficient of variation was
≤10.0%. Results were expressed as mIU/ml.

Total RNA isolation, cDNA conversion and real-time PCR

Using a TRIR kit (Total RNA Isolation Reagent Invitrogen), total RNA was isolated from control and experimental samples. In brief, to 100 mg of fresh tissue, 1 ml of TRIR was added and homogenized. The content was transferred to a microcentrifuge tube instantly and 0.2 ml of chloroform was added, vortexed for 1 min then kept at 4ө C for 5 min. Later, the contents were centrifuged at 12,000 ×g for 15 min at 4°C. The aqueous phase (upper layer) was carefully transferred to a fresh microfuge tube and an equal volume of isopropanol was added, vortexed for 15 S and placed on ice for 10 min. After centrifugation of the content at 12000 ×g for 10 min at 4°C, the supernatant was discarded and RNA pellet was washed with 1 ml of 75% ethanol by the vortex. The isolated RNA was estimated spectrometrically. The RNA concentration was expressed in micrograms (µg). By using the reverse transcriptase kit from Eurogentec (Seraing, Belgium), complementary DNA (cDNA) was synthesized from 2 µg of total RNA as stated in the manufacturer's protocol. To perform real-time PCR, the reaction mixture containing 2x reaction buffer (Takara SyBr green master mix), Forward and reverse primers of the target gene and house-keeping gene, water and β-actin (the primer sequences were listed in Table 1) in total volume of 45 µl expect the cDNA was made, mixed intensively and spun down.

In individual PCR vials, about 5 µl of control DNA for positive control, 5 µl of water for negative control and 5 µl of template cDNA for samples were taken and a reaction mixture (45 µl) were added. 40 cycles (95°C for 5 min, 95°C for 5 s, 60°C for 20 s and 72°C for 40 s) was set up for the reaction and obtained results were plotted by the PCR machine (Stratagene MX 3000 P, Agilent Technologies, 530 l, Stevens Creek Blvd, Santa Clara CA, 95051) on a graph. Relative quantification was calculated from the melt and amplification curves analysis.

Statistical analysis

The data will be analyzed statistically and ONE-WAY- ANOVA will be used followed by Dencan's multiple range test will be used to check statistical significance among groups. The significance will be considered at the levels of $P<0.05$.

Gene name	Primer sequence	Reference
TNF-α	Sense primer: 5´ -GTCGTAGCAAACCACCAAGC-3´ Anti-sense primer: 5´ -CTCCTGGTATGAA ATGGCAAA-3´	(28)
IL-6	Sense primer: 5´ -GTGAGAAGTATGAGAAGTGTGA-3´ Anti-sense primer: 5´ -GCAGGATGAGAATGATCTTTG-3´	(28)
IL 1β	Sense primer: 5′ - CTC AAT GGA CAG AAC ATA AGC C-3′ Anti-sense primer: 5′ -GGT GTG CCG TCT TTC ATC A-3	(29)
Rat β-actin	Sense primer: 5′ - GAC GTT GAC ATC CGT AAA GAC C-3′	(29)

	Anti-sense primer: 5′ - TGC TAG GAG CCA GGG CAG TA-3′	

3. RESULTS AND DISCUSSION

Table 1:

	Control	Diabetes	Diabetes+ A.nervosa	Diabetes+ Metformin
FBG	72	190	100	80
	82	205	111	92
Serum Insulin	35	90	63	56
	40	79	55	49
TC	105	280	169	101
	85	309	153	115
Leptin	102	168	124	106
	111	184	132	115
Adiponectin	9	4	7	8
	12	6	8	9

Figure 1: Fasting Blood Glucose

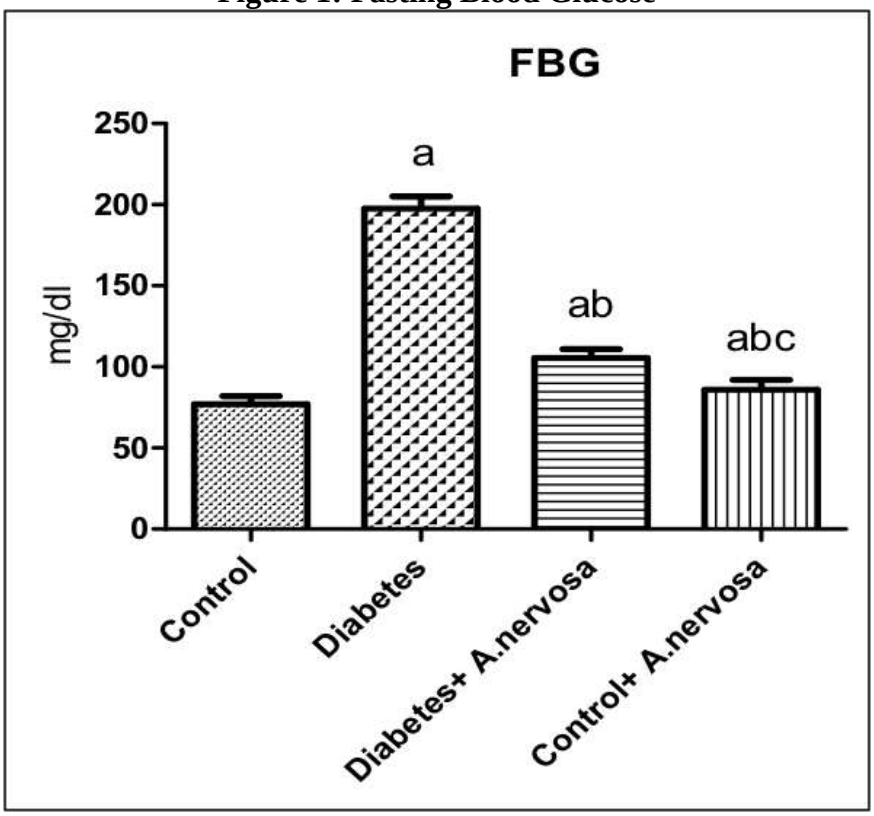


Figure 2: Serum Insulin

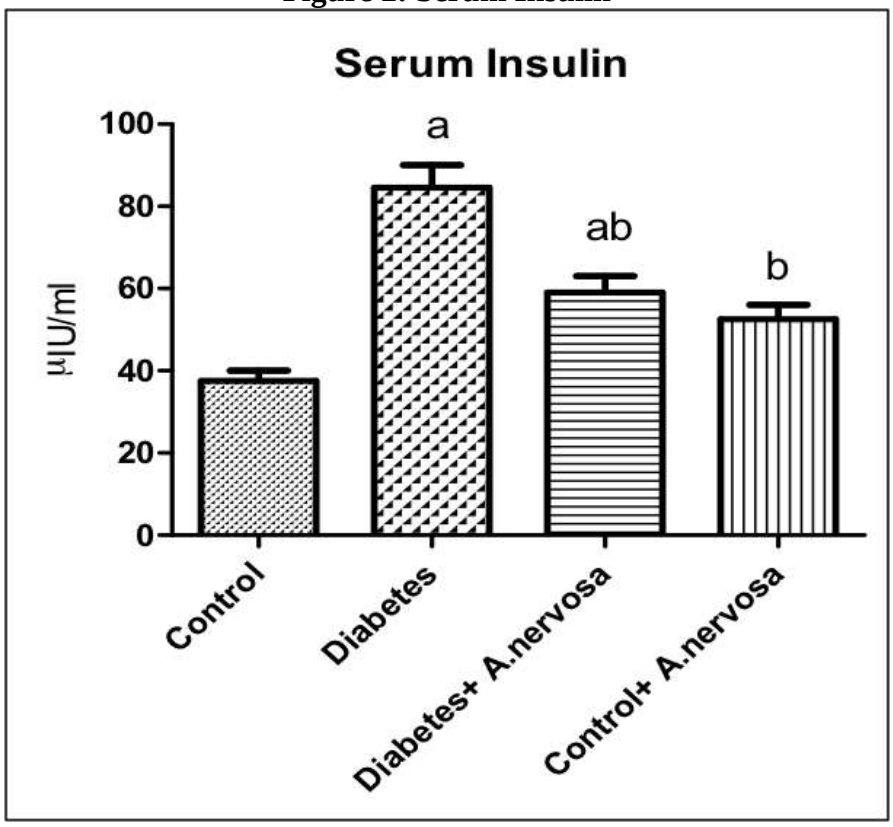


Figure 3: Total Cholesterol

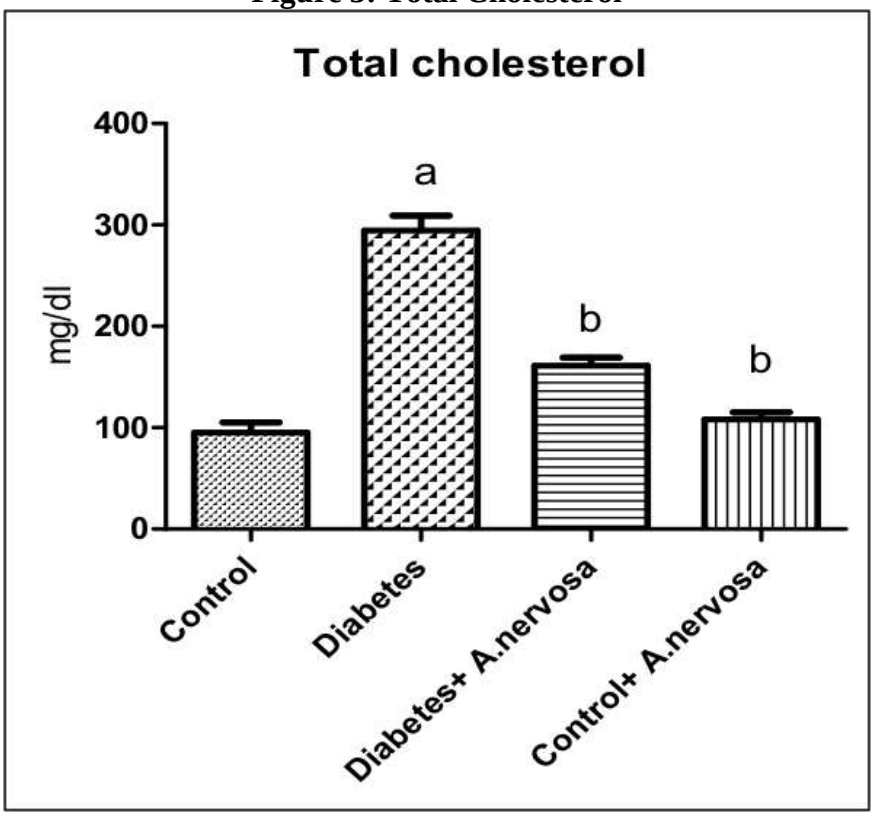


Figure 4: Leptin

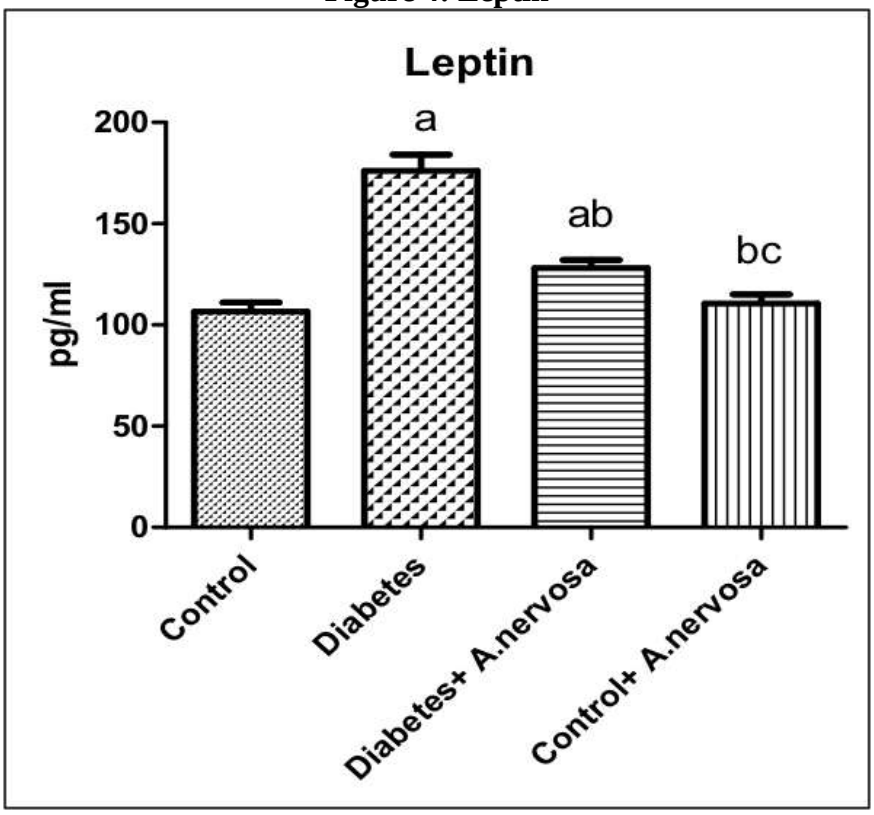
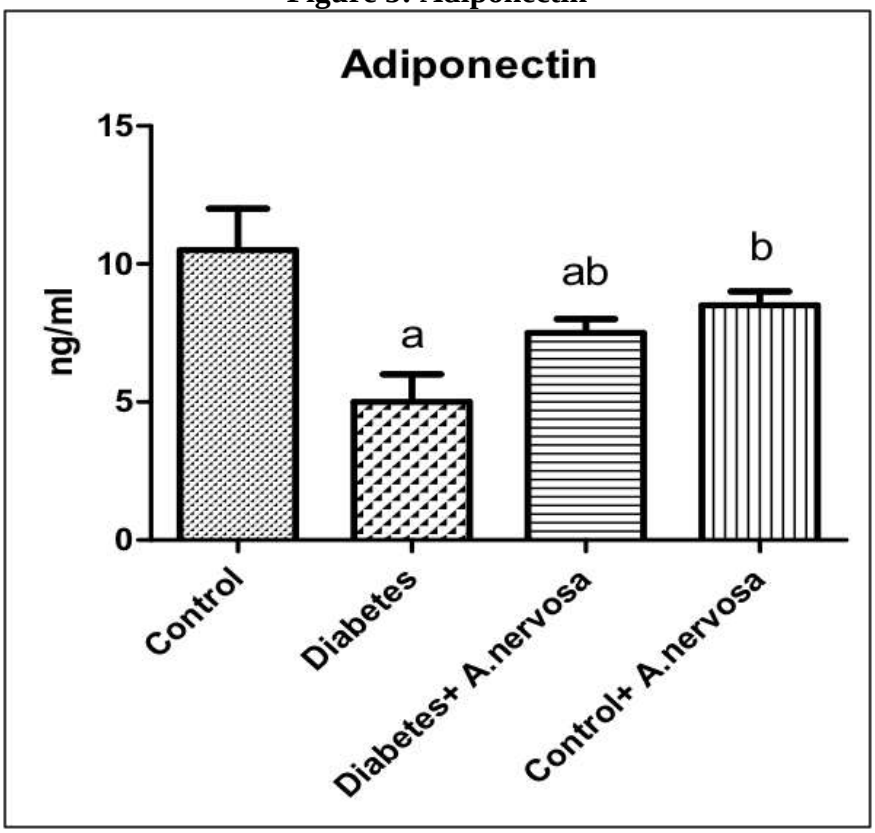


Figure 5: Adiponectin



One of the main risk factors for cardiovascular disease in people with diabetes mellitus is dyslipidemia. High plasma triglyceride level, low HDL cholesterol level, and an increase in the number of small, dense LDL cholesterol particles are the defining characteristics of diabetic dyslipidemia.(30)Despite the fact that there is a huge class of hypolipidemic medications used in the treatment, none of them are now fully effective, completely safe, or side effect-free. In order to correct lipid metabolism and prevent cardiac diseases, efforts are being made to identify safe and efficient treatments.

In this study, we used STZ-induced diabetic rats which also showed hypercholesterolemia which results from increased synthesis and intestinal absorption of cholesterol. (31)In addition to having a significant impact on diabetes, the liver is essential for maintaining lipid and glucose homeostasis. The liver and kidneys produce cholesterol, phospholipids, and triglycerides in addition to taking part in the absorption, oxidation, and metabolism of free fatty acids. Our team has extensive knowledge and research experience that has translate into high quality publications (32), (33), (34), (35), (36,37), (38), (39), (40), (41), (42), (43), (44), (45).

Despite the availability of anti-diabetic medications on the market, treating diabetes with medicinal plants is frequently effective. For the treatment of this illness, herbal remedies and plant substances with low toxicity and no adverse effects are well-known therapeutic choices worldwide.(46) The ethanolic extract of Argyreia nervosa was given as an oral administration for 15 days to the diabetic rats and compared with the diabetic rats treated with the standard drug Metformin. The fasting blood glucose levels were very well controlled by the ethanolic extract as compared to the standard drug (figure 1) similar were the levels of serum insulin (figure 2), total cholesterol (figure 3) and leptin (figure 4) while adiponectin levels (figure 5) were almost equally in par with

the standard drug. Leptin and adiponectin mRNA levels were considerably altered in adipocytes of STZ induced diabetic rats as compared to control rats. However, the A. nervosa treated group significantly restored these mRNA levels near to normal.

4. CONCLUSION

The present study concentrated on examining A. nervosa's anti-dyslipidemic effects in STZ induced diabetic rats. We were promised better outcomes by the results. In comparison to the standard medication, the measured values of fasting blood glucose, serum insulin, total cholesterol, leptin, and adiponectin were significant. When the specific ingredients responsible for the anti-dyslipidemic property are located, separated, and employed for pharmacological purposes, this could ensure superior herbal medications with fewer side effects and cost-effective treatment.

Conflict of Interest :
The authors hereby declare that there is no conflict of interest in this study.

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Author Contribution :
A) SUJITHA A - contributed in designing the study, execution of the project, statistical analysis, manuscript drafting.
B) Dr. J. Selvaraj - contributed in designing the study, execution of the project, statistical analysis, manuscript drafting.
C) Dr.V.Vishnupriya - contributed in study design, guiding the research work, manuscript correction.
D) Dr. Gayathri R - study design, statistical analysis, manuscript proofreading and correction.
E) Dr. Kavitha S - study design, statistical analysis, manuscript proofreading and correction.

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