

***Argyreia nervosa* Mitigates Insulin Resistance in Liver via IR/IRS-1 Mediated Signaling in Streptozotocin-Induced Type-2 Diabetic Rats**

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Abstract

Argyreia nervosa, commonly known as Hawaiian baby woodrose or wooly morning glory, is a plant native to India and is also found in various parts of the world. It is known for its seeds, which have been used traditionally in Ayurvedic and traditional medicine systems for various diseases. The study was aimed at assessing the effect of *Argyreia nervosa* on insulin signaling molecules of the liver in streptozotocin (STZ)-induced experimental type-2 diabetic rats. Healthy adult male Wistar albino rats -150-180 days old weighing 180-200g was used for the study and divided as Group I - Normal rats; Group II – type-2 diabetic rats; Group III -Diabetic rats + *A. nervosa* 500 mg/kg b.wt; Group IV-Normal rats + *A. nervosa* 500 mg/kg b.wt. Fasting blood glucose, and fasting serum insulin were measured by calorimetric methods. Further mRNA expression analysis of insulin receptor (IR) was measured in control and treated animals by quantitative Real Time PCR analysis. *A. nervosa* root extract significantly reduced fasting blood glucose and serum insulin concentrations in STZ-induced rats compared with control. In addition, mRNA expression of IR showed a one-fold increase in the expression which shows that *A. nervosa* is involved in the regulation of insulin signaling in the liver and thereby reduces insulin resistance and type-2 diabetes. Our study concludes that *A. nervosa* root extract has a significant role on insulin signaling molecules thereby it reduces hyperglycemia and hyperinsulinemia via insulin receptor-mediated pathways. Hence, *A. nervosa* may be considered as one of the therapeutic natural antidiabetic drugs.

Keywords: *Argyreia nervosa*, Health and Well-Being, Insulin Signaling, Type-2 Diabetes, Wistar Albino Rats.

Introduction

Infections, diseases, and illnesses have all been effectively treated using plants that contain a variety of secondary metabolites [1]. These days, lifestyle problems and non-communicable diseases are the main causes of suffering, depression, and premature mortality. Metabolic syndrome is distinct from other non-communicable diseases and is a major concern. Diabetes mellitus type II and dyslipidemia are the two main components of this disorder [2]. This latter condition is

characterized by chronic hyperglycemia and abnormalities in protein, lipid, and carbohydrate metabolism brought on by deficiencies in insulin secretion or action, or both [3,4].

The use of herbal medicine and drugs of natural origin are increasing nowadays, because of their low side effects [5]. Medicinal plants have been known for several years and are esteemed all over the world as a rich source of therapeutic agents for the prevention of diseases and other health problems [6,7].

Argyrea nervosa (*A. nervosa*), often known as elephant creeper is a key plant in indigenous systems of healing. It has a big climbing bush with a tomentose woody stem [6]. Indian subcontinent-born *A. nervosa* is primarily found in the Deccan, Karnataka, and east hillsides of the West Ghats at a height of 900 metres. *A. nervosa* roots come in a variety of sizes and densities. The slender roots typically have a diameter of 2-4 mm and have a smooth, brownish appearance. Transverse cuts reveal a thin periderm and cambium that almost exactly sits in the middle of the inner and outer circumferences, dividing the outer phloem from the inner center wood [7-9].

Historically employed in the treatment of gonorrhea and chronic ulcers, this botanical marvel also finds itself adorning gardens as an ornamental plant, thanks to its captivating array of leaves and vibrant flower hues [10]. Not merely a feast for the eyes, its leaves harbor promising potential in the realms of anti-cancer and anti-bacterial properties [11]. Sporting funnel-shaped blooms in shades of violet or lavender, its allure extends beyond aesthetics, boasting a rich composition including β -sitosterol, 1-tricontanol, flavonoids, lipids, and quercetin within its verdant foliage [12]. Delving deeper, its roots emerge as potent agents in the management of obesity, diabetes, tuberculosis, ulcers, and wounds, underscoring its multifaceted therapeutic prowess [13]. Encapsulated within the dried-out flower pods lie seeds of jet black hue, with each pod containing a bounty of three to five such seeds [14]. But the mechanisms underlying the effects of *A. nervosa* has not been proved. Hence, the study was aimed to find out the effect of *A. nervosa* on insulin signaling molecules of the liver in streptozotocin induced experimental diabetic rats. In this study, we have shown possible effects of *A. nervosa* in mitigating insulin resistance in hepatocytes using in vivo experimental study.

Materials and Methods

Chemicals and Reagents

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 was verified at Anna Siddha Hospital in Chennai, Tamil Nadu, using *Argyrea nervosa* root powder obtained.

Extract Preparation

The roots of *Argyrea 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.

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 ($65 \pm 5\%$) and temperature ($21 \pm 2^\circ$) with constant 12 h light and 12 h dark schedule. The standard pellet diet (Lipton India, Mumbai, India) was provided with clean drinking water in *ad libitum*.

Induction of Type-2 Diabetes

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.

Experimental Design

Healthy adult male Wistar albino rats -150-180 days old weighing 180-200g was used for the study and divided as Group I - Normal rats; Group II – type-2 diabetic rats (STZ-induction); Group III -Diabetic rats treated with oral administration of *A. nervosa* 500 mg/kg b.wt; Group IV-Normal rats treated with oral administration of *A. nervosa* 500 mg/kg b.wt. *A. nervosa* was given orally, for 30 days, once in day. After 30 days of treatment, all the animals were anaesthetized, blood was collected and liver from the control and treated animals were dissected out for the assessment of gene expression studies.

Assessment of 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.

Measurement of Fasting Serum Insulin

Serum insulin was assayed using an 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 antibodies to rat insulin was 100%. The intra-assay coefficient of variation was ≤10.0% and the inter-assay coefficient of variation was ≤10.0%. Results were expressed as mIU/ml.

Gene Expression Analysis

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 4°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 by spectrometric method. 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 in the total volume of 45µl except the cDNA was made, mixed intensively and spun down. In individual PCR vials, about 5µl of control DNA for positive control, 5µl of water for negative control and 5µl of template cDNA for samples were taken and a reaction mixture (45 µl) was added. 40 cycles (95°C for 5 min, 95°C for 5 s, 60°C for 20 s and 72°C for 40 s) were set up for the reaction and obtained results were plotted by the PCR machine (Stratagene MX 3000 P, Agilent Technologies, 530 1, Stevens Creek Blvd, Santa Clara CA, 95051) on a graph. Relative quantification was calculated from the melt and amplification curves analysis.⁹ The following primers were used to analyze gene expression analysis. Rat IR Sense primer: 5'- GCC ATC CCG AAA GCG AAG ATC-3',

Anti-sense primer: 5'- TCT GGG TCC TGA TTG CAT-3'; Rat β -actin Sense primer: 5'- AAG TCC CTC ACC CTC CCA AAA G-3' , Anti-sense primer: 5'- AAG CAA TGC TGT CAC CTT CCC-3'.

Statistical Analysis

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

Results

Effect of *A. nervosa* Root Extract on the Fasting Blood Glucose

Fasting blood glucose (FBG) is a crucial parameter in the diagnosis, management, and monitoring of type 2 diabetes mellitus. It serves as a fundamental tool for assessing glycemic control and has several important implications in the context of diabetes care. Regular monitoring of FBG levels helps healthcare providers and individuals evaluate the effectiveness of treatment regimens, including lifestyle modifications and medication therapy. In the present study, STZ treatment showed a significant increase ($p < 0.05$) in the levels of fasting blood glucose compared to control (Fig. 1). However, T2DM rats treated with *A. nervosa* extract hampered hyperglycemia.

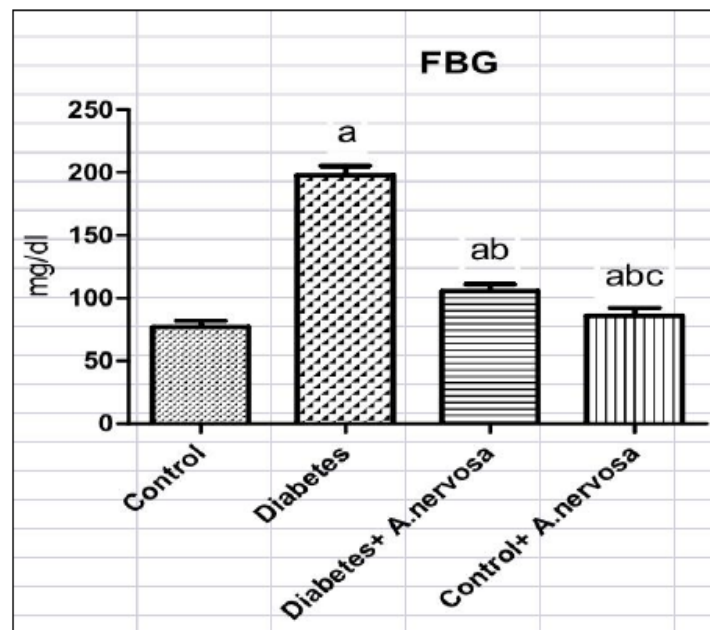


Figure 1. The Effect of *A. nervosa* Root Extract on Fasting Blood Glucose in Control and STZ-Induced Rats.

Effect of *A. nervosa* Root Extract on Serum Insulin Level in Type-2 Diabetic Rats

Serum insulin levels are an important parameter to assess in the context of diabetes and related metabolic conditions. Elevated serum insulin levels, when not accompanied by normal glucose levels, can be indicative of

insulin resistance, a condition where the body's cells do not respond well to insulin. In this study, insulin concentration in STZ treated rats was significantly increased ($p < 0.05$) compared to control rats. However, treatment with plant extract reduced hyperinsulinemia near to that of the normal level suggesting that *A. nervosa* controls diabetic nephropathy (Fig.2).

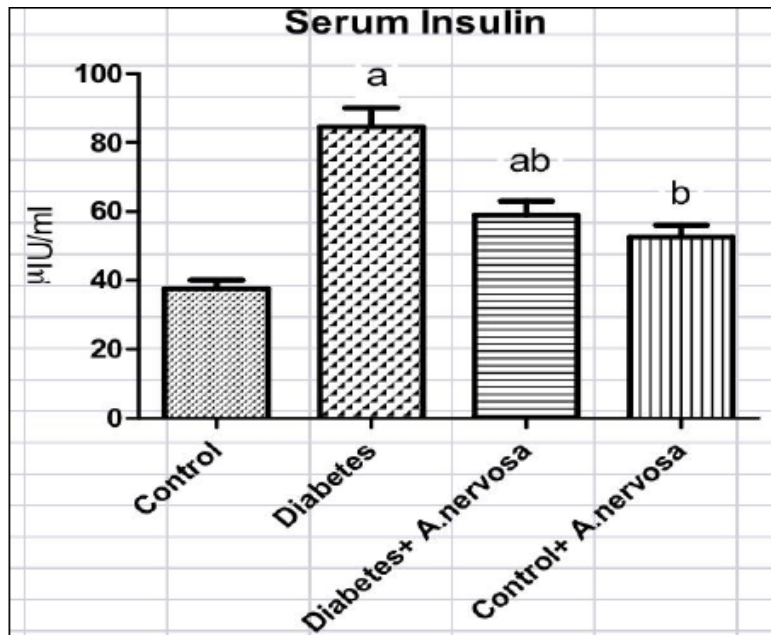


Figure 2. Effect of *A. nervosa* Root Extract on Serum Insulin Levels in Control and Treated Groups. The Numbers are as the Mean ± SEM for Six Rats in Each Group.

Effect of *A. nervosa* Root Extract on Insulin Receptor (IR) mRNA Expression in the Liver of STZ-Induced Type-2 Diabetic rats

The insulin receptor is a critical component of the body's regulation of blood glucose levels and plays a central role in diabetes, particularly in type 2 diabetes and some forms

of monogenic diabetes. Considering this fact, in the present study also, we measured gene level expression of IR mRNA in the control and treated rats. STZ-induced rats caused a severe decrease in the expression of IR compared to control whereas *A. nervosa* root extract improved the expression of IR gene (Fig.3).

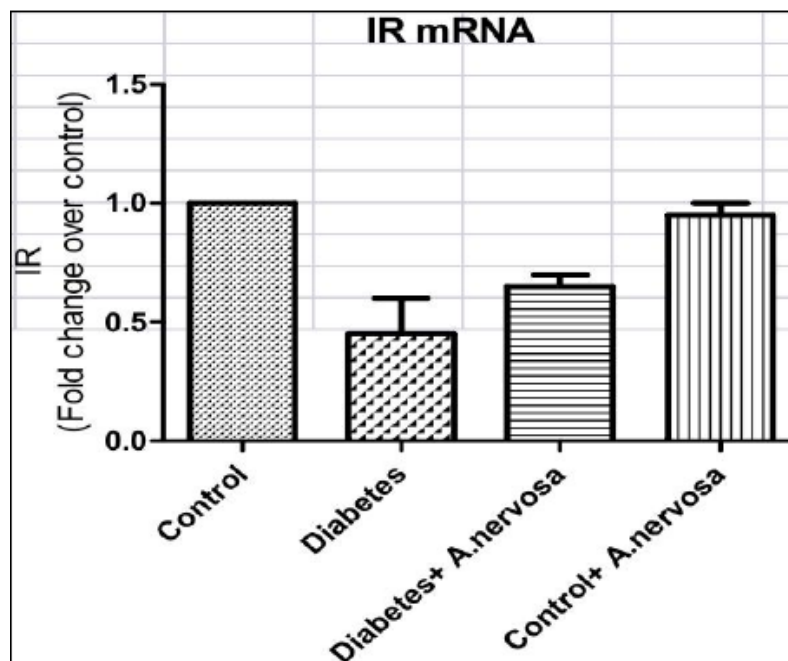


Figure 3. mRNA Expression of Insulin Receptor (IR) in Response to *Argyrea nervosa*.

Discussion

The occurrence of T2DM stems from the inability of the body's cells to effectively metabolize sugar, which can be attributed to either inadequate insulin construction by the pancreas or ineffective utilization of body insulin. The condition is characterized by chronic hyperglycemia and changes in the metabolism of macromolecules resulting from flaws in insulin production and activity [15]. T2DM constitutes the majority of diabetes cases, making up approximately 90%. Preventing and managing T2DM involves adopting a comprehensive approach that emphasizes the promotion of a healthy lifestyle and regular exercise. Obesity can raise the risk of T2DM by causing insulin resistance. Adipocytes that reside in adipose tissue and hypertrophied immune cells define obesity, as a proinflammatory state marked by elevated circulation levels of proinflammatory cytokines [16-18]. The specialized macrophages of the liver, known as Kupffer cells, are responsible for producing chemokines and cytokines. Pro-inflammatory chemicals, which include surplus FFA and proinflammatory cytokines, draw in more macrophages and other immune cells when they are introduced or encountered locally. Elevated reactive oxygen species (ROS) also decrease insulin receptor substrate recruitment, which obstructs the downstream PI3K-AKT cascade from activating. Pro-inflammatory cytokines can cause peripheral target organs to produce acute-phase proteins, insulin resistance, and pancreatic β -cell death. These gradually become pro-inflammatory instead of anti-inflammatory, and it is thought that this association with the cells of peripheral target organs causes insulin resistance [19].

An increasing variety of plants from various countries are recognized to have anti-diabetic qualities, and herbal therapies are widely used as supplements to modern medications to treat diabetes and its aftereffects. More than 1200

plants have hypoglycemia potential, according to ethnopharmacological studies, and in ancient Indian literature, more than 800 herbs with antidiabetic properties are listed [20,21].

FBG is the key parameter for confirmation of the diabetic condition.

Elevated fasting blood glucose levels are indicative of impaired glucose metabolism and may signify the presence of insulin resistance, a condition where cells become less responsive to insulin's signaling. Monitoring fasting blood glucose levels alongside assessing insulin resistance provides valuable insights into an individual's metabolic health and risk of developing type [22- 24].

The figure 1 shows the levels of fasting blood glucose in different groups of rats. An elevated level of fasting blood glucose in diabetic rats was seen in the STZ-diabetic rats whereas the levels of fasting blood glucose is statistically decreased in rats fed with *Argyreia nervosa* root suggesting that *A. nervosa* root has potential antidiabetic properties by reducing hyperglycemia. The primary focus of studies related to *A. nervosa* has been on its psychoactive properties rather than its potential use for diabetes management. Consequently, there are no well-established scientific findings or clinical evidence to support the role of *A. nervosa* in antidiabetic activity. Figure 2 represents the levels of insulin in different groups of rats. We were able to measure an elevated level of insulin in diabetic rats, whereas the levels of insulin are statistically decreased in rats fed with *Argyreia nervosa*.

A condition known as hyperinsulinemia occurs when there are excessive amounts of insulin circulating in the blood compared to the amount of glucose. Contrary to popular belief, hyperinsulinemia can be caused by a wide range of metabolic disorders, including diabetes, hyperglycemia, and non-nutritive carbohydrates in the diet. Although hyperinsulinemia is a common sign of type 2 diabetes mellitus in its early stages, it is not

the root cause of the disorder [8]. Only when pancreatic beta-cell activity is compromised does type 1 diabetes develop. Numerous disorders, including type 2 diabetes mellitus, neonatal hyperinsulinemia, and drug-induced hyperinsulinemia, can cause hyperinsulinemia [9]. It can also manifest in nesidioblastosis, a kind of congenital hyperinsulinemia.

The insulin receptor is a transmembrane protein found on the surface of various cells in the body, including muscle, fat, and liver cells. It acts as a receptor for insulin; a hormone produced by the pancreas and plays a key role in regulating glucose uptake into cells. When insulin binds to its receptor, it initiates a signaling cascade within the cell [25, 26]. This signaling pathway promotes the uptake of glucose from the bloodstream into cells, primarily in muscle and fat tissue, by translocating glucose transporter proteins (GLUT4) to the cell membrane. In the present study, STZ-induction significantly reduced insulin receptor mRNA expression in the liver while *A. nervosa* treatment facilitated the IR mRNA expression at a dose of 500mg suggesting that the plant extracts has a significant role in insulin metabolic signaling in hepatocytes. This may be due to anti-inflammatory potential of *A. nervosa* and its bioactive compounds present in the root extract. In this regard, studies have shown that *A. nervosa* has strong antioxidant, anti-inflammatory, alpha and alpha glucosidase inhibitory activity [27-35]. Our study concludes that *A. nervosa* potentially reduces hyperglycemia and hyperinsulinemia-induced insulin resistance in the liver by facilitating insulin receptor in the liver due the presence of bioactive compounds in root extract.

Conclusion

According to this study, *Argyrea nervosa* does indeed have the ability to treat diabetes by controlling blood sugar levels. It also

controls STZ-induced hyperinsulinemia by regulating the expression of insulin upstream signaling molecules thereby control blood sugar level. Our study concludes that *A. nervosa* root can be used as a therapeutic drug for the treatment of diabetes mellitus.

Conflict of Interest

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

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Author Contribution

A) Lakshana Suresh - contributed in designing the study, execution of the project, statistical analysis, manuscript drafting.

B) Dr. 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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