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Influence of *Aconitum heterophyllum* Wall. ex Royle root extract on Plasma and Tissue glycoprotein components in streptozotocin induced diabetic rats.

***Tanveer Ahmad Rah, S.Hemalatha, C.Elachezhiyan**

Department of Zoology (UGC-SAP Sponsored), Faculty of Science, Annamalai University, Annamalai nagar, Tamilnadu, India-608002
*Corresponding author: *rahtanveer786@gmail.com*

Abstract

Objective: The present study was intended to evaluate the role of the local medicinal plant, *Aconitum heterophyllum* on glycoprotein components in streptozotocin-induced diabetic rats **Methods:** Diabetes was induced in male albino Wistar rats by a single intraperitoneal injection of streptozotocin (40 mg/kg b.w). The extract of *Aconitum heterophyllum* was administered orally at a dose of (200 mg/kg b.w) for 28 days. The effect of extract *Aconitum heterophyllum* was studied on plasma, liver and kidney tissues. **Results:** There was a significant increase in the levels of the plasma glycoproteins and also a significant decrease in the level of sialic acid and elevated levels of hexose, hexosamine and fucose in the liver and kidney of diabetic rats**.** Streptozotocin injection (40 mg/kg body weight) caused massive elevation of glycoprotein components such as hexose, hexosamine, sialic acid and fucose in plasma and tissues of diabetic control and experimental animals. Oral administration *Aconitum heterophyllum* root extract (200 mg/kg body weight) for 28 days significantly reverted the hexose, hexosamine, sialic acid and fucose levels to the near normal values. **Conclusion:** These results suggest a normalizing effect of *Aconitum heterophyllum* on glycoprotein components in STZ diabetic rats.

Keywords: Streptozotocin, Glycoproteins, Diabetes mellitus, *Aconitum heterophyllum*, plasma, liver and kidney tissues.

Introduction

Diabetes mellitus (DM) is the worldwide problem leading micro vascular and macro vascular complications (Umar *et al*., 2010). The number of people suffering from the disease worldwide is increasing at an alarming rate with a projected 366 million peoples likely to be diabetic by the year 2030 as against 191 million peoples are expected in 2000 (Wild *et al*., 2000). A number of studies highlights that alterations in glucose metabolism leads to hyperglycemia-induced Cell damage by four key metabolic pathways, viz., increased polyol pathway flux, increased glycation of proteins (enzymatic or no enzymatic), increased hexosamine pathway flux and activation of protein kinase C (PKC)-isoforms (Rolo and Palmeira, 2006). Among the above stated possibilities, glycosylation of proteins has been the prime subject of much interest.

Glycoproteins can be simply defined as proteins that have carbohydrate moiety covalently attached to their peptide portion. They have multiple and complex functions and are found as enzymes, hormones, blood group substances and as constituents of extra cellular membrane. The majority of human proteins are co- or post-transnationally modified by mono- or oligosaccharides. The glycoprotein saccharides add physiochemical properties, influencing protein conformation or increasing stability against proteolytic activity. With their exclusive structural diversity and complexity, carbohydrates attached on proteins or lipids are involved in numerous cell-surface binding events, such as cell growth and differentiation, cell proliferation, cell adhesion, binding of pathogens, fertilization and immune responses (Lis, H; Sharon, N. Eur., 1993; Dwek, R. A., 1996*)*. It is well documented

that the oligosaccharide moieties of glycoproteins, hexose, hexosamine, fucose and sialic acid, have a significant role in protein stability, function and turnover (Wiese *et al*., 1997). During diabetes, use of glucose by insulin independent pathways directs to the synthesis of glycoprotein which may be a predictor of angiopathic complications (Wiese *et al*., 1997). Several workers have suggested that increased levels of glycoproteins in plasma, liver and kidney tissues in the diabetic condition could be an outcome of impaired carbohydrate metabolism. Insulin deficiency and high levels of plasma glucose in the diabetic condition may cause an increased synthesis of glycoproteins. This increase in plasma glycoproteins has been associated with the harshness and duration of diabetes. At the cell surface or inside the cells, the glycoprotein components such as fucose and sialic acid form specific structures, called glycanic chains covalently linked to lipids or proteins. An augment in the biosynthesis or decline in the metabolism of glycoproteins could be related to the deposition of these materials in the basal membrane of pancreatic cells. Variations in glycoproteins level lead to the pathogenesis of diabetes mellitus. Many studies prove the involvement of glycoproteins in diabetic complications (Sundaram *et al*., 2012). Derangement in the metabolism of hexose, hexosamine, fucose and sialic acid has been observed in naturally occurring and in experimental diabetes. Various studies have suggested that alteration in glycoprotein components could be a result of impaired carbohydrate metabolism (Sankaranarayanan, 2011 and Senthilkumar, 2008).

There are many plants and their products (active, natural principles and crude extracts) that have been mentioned or used in the Indian traditional system of medicine and have shown experimental or clinical anti-diabetic activity (Andrew. 2004). Among the major photochemical constituents of plants credited with hypoglycemic action are glycosides, alkaloids, glycans, triterpenes, mucilages, polysaccharides, oils, vitamins, saponins, glycoproteins, peptides, amino acids and proteins (Satyavati *et al*.,1989). *Aconitum heterophyllum*, locally called as Atis, is an important medicinal herb in the North-Western and Eastern Himalayas of India. It is a biennial herb found between 2400 and 3600 m altitude above the mean sea level. It has been listed as a 'critically endangered species' by the International Union for Conservation of Nature and Natural Resources (CAMP, 2003; Nautiyal *et al*., 2002; IUCN, 1993). The aqueous extract of root is used for the treatment of chronic fever and cold. The plant is used as an active ingredient in the herbal formulation *Diarex Vet* with other important medicinal plants for the treatment of indigestion, flatulence and diarrhea (Mitra *et al*., 2001). The paste of *A. heterohyllum* dried tubers mixed with water and sugar is taken orally to treat body ache. It is also used as an aphrodisiac and tonic (Semwal *et al*., 2009). KutajghanVati is a classical Ayurvedic anti-dysentery lozenge prepared from *A. heterophyllum* and other medicinal plants (Lather *et al*., 2010). Recent studies have shown that its roots are used for curing arthritis (Subramoniam *et al*., 2013) as well as in the preparation of Caspa Drops – a polyherbal formulation for improving digestion and preventing abdominal distension (Sojitra *et al*., 2013). To our knowledge, so for no other biochemical investigations has been carried out on the effect of *Aconitum heterophyllum* extract in plasma and tissue proteins of experimental diabetic rats. In this view, the present investigation is carried out to study the effect of *Aconitum heterophyllum* extract on plasma and tissue glycoproteins in STZ- induced diabetic rats.

Materials and Methods

Collection of plant material

The plant *Aconitum heterophyllum* (AHE) subtrean parts were collected from Gurez and Uri, from districts of Bandipora and Baramulla of Jammu and Kashmir state in the months of January and Feberary, 2014. The plant was identified and Authenticated at the Annamalai University, Department of Botany by the taxonomist, Dr. D.Kumarasamy. The Voucher specimen (No-AU4381C) is preserved at the above mentioned department's herbarium for future use.

Preparation of plant extracts

The subtrean part (roots) of *Aconitum heterophyllum* were air dried at room temperature (at 25˚C; 60% relative humidity) until a moisture content of 10–12% (fresh weight basis) was attained. The dried roots were crushed to powder and subsequently extracted using methanol (1:10, w/v) at ambient temperatures between (35 to 60˚C). The extraction was repeated until the solvent becomes yellowish in colour, the extract was filtered through Whatman No 1 filter paper in rotavoparator followed by lyophilisation. The lyophilized extract was stored at 20˚C until further use for biochemical parameters

Chemicals

Streptozotocin was purchased from Sigma-Aldrich (St. Louis, MO, USA). All other chemicals used in this study were of analytical grade obtained from Merck and Hi-media, (Mumbai, India.).

Experimental Animals

Adult Male albino Wistar rats (9 weeks old;180-200 g) were obtained from central Animal House, Department of Experimental Medicine, Raja Muthiah Medical College and Hospital, Annamalai University, and maintained at constant temperature (25±1˚C) on a 12 h light/12 h dark cycle with feeds (Pranav agro industries Ltd, Pune, Maharashtra, India) and water were provided at libitum.The experimental protocol was approved by the Animal Ethics Committee of Rajah Muthaih Medical college and Hospital (RegNo.160/1990/CPCSEA, proposal, Annamalai University Annamalai nagar.

Induction of diabetes mellitus

The animals were rendered diabetic by a single intraperitoneal injection of 40 mg/kg b.w, streptozotocin (STZ) diluted in 0.1 M sodium citrate buffer (pH 4.5) solution. STZ injected animals were given 20% glucose solution for 24h to prevent initial drug induced hypoglycemia. STZ injected animals exhibited hyperglycemia within a few days .Diabetic condition rats were confirmed by measuring the elevated plasma glucose (by glucose oxidase method) 72 h after injection STZ. The rats with blood glucose above 235 mg/dl were considered to be diabetic and used for experiment.

Experimental Design

The experimental animals were randomly divided into five groups of six animals each detailed as given below. The extract of *Aconitum heterophyllum (AH)* was dissolved in 2% Gum acaia and administered orally at different doses 50, 100, 200 mg/kg/bw. The 200 mg dose exhibited effective as compared to the others. The active dose 200 mg was used for this study and was given to the animals through intragastric tube daily for a period of 28 days. Glibenclamide was dissolved in 2% gum acacia and was used as standard drug.

Group I: Normal control rats (2% gum acacia).
Group II: Normal+AHE (200 mg/kg body weight) in 2% gum acacia
Group III: Diabetic control rats
Group IV :) Diabetic+AHE (200 mg/kg body weight) in 2% gum acacia
Group V: Diabetic+glibenclamide (600µg/kg BW) in 2% gum acacia.

After 28 days of treatment, the animals were sacrificed by cervical decapitation. The blood was collected in heparinized centrifuge tubes and the plasma were collected. The liver and kidney tissues were dissected out immediately and washed with ice-cold saline. A portion of these tissues was weighed using an electronic balance and homogenized using a potter Elvejham homogenizer and centrifuged at 3000xg for 10 min. The supernatant were further used for the assay of glycoprotein components such as hexoses, hexosamine, sialic acid and fucose.

Biochemical analysis

Estimation of plasma and tissue hexoses

Serum and tissue hexose content was estimated by the method of Niebes (1972). 0.2 mL of the serum or tissue homogenate is mixed with 8.5 mL of orcinol-H_2SO_4. The tubes were then heated at 80˚C for 15 min, cooled and read at 540 nm after 20 min. Standard and blank containing 0.2 mL of 0.2N H_2SO_4 were processed similarly. The hexose content of serum is expressed as mg/dL or mg/g wet tissue for tissues.

Estimation of hexosamine

Hexosamine in the plasma and tissue was determined by the method of Elson and Morgon (1933). The method involves 0.1 mL of plasma or tissue homogenate in a test tube graduated at 10 mL, 5 mL of 95% ethanol was added and mixed well, centrifuged for 15 min, decanted, and the precipitate was suspended in 3 mL of 95% ethanol. The solution was centrifuged and decanted. To the precipitated protein 2 mL of 3N HCl were added and the solution was hydrolyzed in a boiling water bath with an air condenser for 4 h.

The hydro lysate was neutralized with 3N NaOH; 1 mL of the acetyl acetone was added to 1 mL of the aliquot, 1 mL of water (blank) and 1 mL of standard. The tubes were capped with marbles to prevent evaporation and were placed in a boiling water bath for 15 min. The tubes were cooled in a tap water. 5 mL of 95% ethanol was added and the solution was mixed well. 1 mL of Ehrlich reagent was added, mixed well, and diluted to 10 mL with 95% ethanol. Absorbance was measured at 530 nm after 30 min. Hexosamine content of the plasma is expressed as mg/dL or mg/g wet tissue for tissues.

Estimation of sialic acid

Sialic acid content in serum and tissues was estimated by the method of Welmer *et al*. (1952). 4.8 mL of 5% TCA was added slowly to 0.2 mL of serum or tissue homogenate, 0.2 mL of or osomucoid standard in separate tubes. The test tube was placed in a boiling water bath for exactly 15 min with a glass marble to prevent evaporation, then the tubes were cooled by immersion in water and filtered. 2 mL of clear filtrate was pipetted out of each tube; 4 mL of diphenylamine (DPA) reagent were added to one of each pair of tubes and 4 mL of acid-mixture without DPA into the other tube. The reagent blank was prepared by adding 2 mL of 5% TCA and 4 mL of DPA reagent. The solutions were mixed well and capped with a glass marble and immersed in a boiling water bath for exactly 30 min. The tubes were cooled in water and the absorbance was determined at 530 nm with a reagent blank set at zero. Sialic acid content of the serum is expressed as mg/dL or mg/g wet tissue for tissues.

Estimation of fucose

Serum fucose content was estimated by the method of Dische and Shettles (1948). To 2.2 mL of serum, 4.8 mL of sulphuric acid reagent was added and heated in a boiling water bath for 3 min. The sample was cooled and 0.1 mL of cysteine hydrochloride reagent was added, 0.5 mL of 0.1 N NaOH was also treated in the same way for blank, after 25 min the optical density was measured at 393 and 430 nm. Fucose content is expressed as mg/dL for serum.

Statistical analysis

Values were represented as means ± S.D for six rats in each group. Data were analyzed by one-way Analysis of Variance (ANOVA) compared with Duncan's multiple range test (DMRT) using SPSS 10 version. The limit of significance was set $P \leq 0.05$.

Results

Tables 1-4 show the changes in the levels of protein bound hexose, hexosamine, fucose, and sialic acid in plasma and tissues of control and experimental rats. The diabetic rats show the significantly higher levels of plasma glycoproteins when compared with normal rats. Treatment with methanolic extract AHE at the dose of 200mg/kg/bw and glibenclamide showed reversal of these parameters towards normal level.

Table 1. Effect of AHE extract on sialic acid in the plasma, liver and kidney of normal and STZ induced diabetic rats.

Name of the group	Plasma sialic acid (mg/dL)	Sialic acid (mg/100 g wet tissue)	
		Liver	Kidney
Normal	$50.22^{a} \pm 3.88$	$7.41^{a} \pm 0.04$	$7.02^{d} \pm 0.58$
Normal + AHE extract (200 mg/kg b.wt.)	$48.21^{a} \pm 3.76$	$7.46^{a} \pm 0.03$	$7.14^{d} \pm 0.54$
Diabetic control	$72.01^{d} \pm 6.54$	$13.96^{d} \pm 0.92$	$3.99^{c} \pm 0.27$
Diabetic + AHE extract (200 mg/kg b.wt.)	$65.72^{c} \pm 5.78$	$10.27^{c} \pm 0.86$	$5.17^{b} \pm 0.22$
Diabetic + glibenclamide (600 µg/kg b.wt.)	$58.46^{b} \pm 4.02$	$8.56^{b} \pm 0.64$	$6.06^{a} \pm 0.05$

Values are means ± S.D for six rats.
Values not sharing a common superscript differ significantly at $P < 0.05$ (DMRT).

Table 2. Effect of AHE extract on hexosamines in the plasma,liver and kidney of normal and STZ induced diabetic rats.

Name of the group	Plasma hexosamines (mg/dL)	Hexosamines (mg/100 g wet tissue)	
		Liver	Kidney
Normal	$62.52^{a} \pm 4.32$	$10.27^{b} \pm 0.78$	$14.27^{a} \pm 0.76$
Normal + AHE extract (200 mg/kg b.wt.)	$64.37^{a} \pm 4.30$	$10.06^{b} \pm 0.72$	$14.06^{a} \pm 0.82$
Diabetic control	$92.86^{d} \pm 8.56$	$16.52^{c} \pm 0.84$	$25.24^{c} \pm 1.27$
Diabetic + AHE extract (200 mg/kg b.wt.)	$85.42^{c} \pm 7.27$	$12.72^{a} \pm 0.69$	$20.56^{b} \pm 1.06$
Diabetic + glibenclamide (600 µg/kg b.wt.)	$79.26^{b} \pm 4.71$	$11.06^{c} \pm 0.82$	$17.09^{b} \pm 0.94$

Values are means ± S.D for six rats.
Values not sharing a common superscript differ significantly at $P < 0.05$ (DMRT).

The levels of glycoproteins in liver and kidney of control and experimental rats were shown in tables 1-4. The levels of the glycoproteins, hexose, hexosamine, and fucose were significantly increased whereas the levels of sialic acid was significantly decrease in diabetic rats. Administration of methanol extract AHE at the dose of 200mg/kg/bw and glibenclamide showed reversal of these parameters towards the normal levels.

Table 3. Effect of AHE on fucose in the plasma , liver and kidney of normal and STZ induced diabetic rats

Name of the group	Plasma fucose (mg/dL)	Fucose (mg/100 g wet tissue)	
		Liver	Kidney
Normal	$23.52^{b} \pm 0.94$	$13.79^{b} \pm 0.88$	$12.14^{a} \pm 0.94$
Normal + AHE extract (200 mg/kg b.wt.)	$22.24^{b} \pm 0.95$	$12.27^{a} \pm 0.84$	$12.02^{a} \pm 0.95$
Diabetic control	$40.56^{a} \pm 0.36$	$25.56^{b} \pm 0.99$	$24.65^{b} \pm 1.42$
Diabetic + AHE extract (200 mg/kg b.wt.)	$32.71^{a} \pm 0.32$	$21.07^{a} \pm 0.81$	$19.16^{c} \pm 1.48$
Diabetic + glibenclamide (600 µg/kg b.wt.)	$30.07^{a} \pm 0.28$	$18.26^{c} \pm 1.02$	$18.56^{a} \pm 0.96$

Values are means ± S.D for six rats.
Values not sharing a common superscript differ significantly at $P< 0.05$ (DMRT).

Table 4. Effect of AHE extract on total hexoses in the plasma, liver and kidney of normal and STZ induced

Name of the group	Plasma total hexoses (mg/dL)	Total hexoses (mg/100 g wet tissue)	
		Liver	Kidney
Normal	$91.56^{a} \pm 7.64$	$25.66^{a} \pm 1.42$	$23.14^{a} \pm 1.72$
Normal + AHE extract (200 mg/kg b.wt.)	$90.22^{a} \pm 7.54$	$24.27^{a} \pm 1.56$	$22.16^{a} \pm 1.74$
Diabetic control	$140.16^{d} \pm 10.16$	$42.11^{d} \pm 2.76$	$40.32^{c} \pm 3.17$
Diabetic + AHE extract (200 mg/kg b.wt.)	$116.41^{c} \pm 9.76$	$35.16^{c} \pm 2.42$	$30.12^{b} \pm 3.09$
Diabetic + glibenclamide (600 µg/kg b.wt.)	$112.56^{b} \pm 8.27$	$32.19^{b} \pm 2.17$	$29.88^{a} \pm 1.84$

Values are means ± S.D for six rats.
Values not sharing a common superscript differ significantly at $P< 0.05$ (DMRT).

Discussion

Diabetes mellitus is becoming gravely fatal health concerns of the 21st century (George *et al.,* 2010). STZ has been extensively used to provoke diabetes mellitus in experimental animal models. The intraperitoneal administration of a single dose of STZ (40mg/kg) selectively destroy some population of insulin secreting β-cells of pancreas ensuing insulin deficiency and causing type-2 diabetes (Balamurugan *et al.,* 2011; Chandramohan *et al.,* 2015) Over production (excessive hepatic glycogenolysis and gluconeogenesis) and declined utilization of glucose by the tissues are the fundamental basis of hyperglycemia in diabetes mellitus (Latner, 1958). Prolonged increase of blood glucose in diabetes may lead to structural and functional alterations of both circulating and membrane bound proteins (Ciftci, 2011).

The glycoprotein metabolism alterations have usually observed in a diabetic state. The increased level of plasma glycoprotein constituents associated with the harshness of diabetes. In this study we have observed the increased level of hexose, hexosamine, fucose and sialic acid in the plasma of streptozotocin induced diabetic rats. The secretion or shedding from cell membrane glycoprotein components in STZ induced diabetic rats showed an important modification in the connective tissue macromolecule (Berenson and Radhakrishnamurthy Dalferes, 1972). This is due to the low utilization of glucose by insulin dependent pathways leads to increase the formation of hexose, hexosamine, sialic acid and fucose for the accumulation of glycoproteins (Spiro and Spiro, 1971). Administration of AHE to diabetic rats decreased the levels of plasma glycoprotein components. This could be due to the decreased hyperglycemic state with the increased levels of plasma insulin in diabetic rats.

The sustained hyperglycemia boosts the expression of glutamic: fructose-6-phosphhate amino transferase (GFAT)) the rate limiting enzyme of the hexosamine pathway resulting an increase in the levels of hexose and hexosamine in plasma and tissue (Brownee, 2005). Protein bound hexose gives hydrophilic nature to the cell membrane and hexosamine through its cationic charges makes cell membrane polarized

(Gamayel *et al*., 2007).The rise in the flux of glucose through hexosamine pathway leads to insulin resistance and vascular complication (McClain *et al*., 2005). In the present study, diabetic rats confirmed increased levels of hexose and hexoseamine in plasma and hepatic and renal tissues. Administration of AHE extract to diabetic rats significantly decreased their levels to the near normal levels. Our results are concordance with the results of Latha and Pari (2005) who reported the administration of aqueous extract of *Scoparia dulcis* improved hexose and hexosamine levels in diabetic rats.

Sialic acid is the terminal residue of the oligosaccharide side chain of the glycoproteins and widely occurs in the exposed positions of the molecules like hormones, enzymes and also tissues (Schaver, 1985). Sialic acid plays a role in cell recognition, Protein targeting, protease resistance, conformational stabilization, adhesion and intracellular signaling in biological systems. In diabetic state, the tissue concentration of sialic acid was found to decline significantly. Decrease in the content of sialic acid in tissues may be due to the utilization for the synthesis of fibronectin, which contains sailic acid residues in the core structure (Schiller, 1957). In our study, a significant elevation in plasma sialic acid with a fall in hepatic and renal tissues was observed in diabetic control rats. Oral administration of AHE to diabetic treated rats significantly restored the levels of sialic acid in plasma, hepatic and renal tissues to near normal which is comparable with glibenclamide.

Fucose is a member of a group of eight essential sugars that the body requires for the optimal functioning of cell to cell communication and its metabolism appears to be altered in various diseases such as diabetes (Sulaiman *et al*., 2012). A rise in fucose levels could be due to increased glycosylation in the diabetic state. (Hunt *et al*., 1991). In our study, an elevated level of fucose was observed in diabetic rats, which on treatment with AHE significantly reduced which are comparable with glibenclamide.

From the above results, the altered glycoprotein components in the plasma, liver and kidney of diabetic rats can be assigned as a direct result of hyperglycemia. In presently observed control over the levels of glycoprotein components following *Aconitum heterophyllum* extract therapy may have been due to the normalization of glucose homeostasis, which may help in the restoration of glycoprotein components in the diabetic rats. The phytochemical investigation revealed the presence of phenols, alkaloids, anthraquinone, glycosides, flavonoids and tannins are biological active constituents in the extract. Hence the observed hypoglycemic property of *Aconitum heterophyllum* may be due to the presence of these active principles in the extract.

Conflict of interest

The authors declare that they have no conflicts of interest concerning this article.

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