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Modulatory Role of *Asparagus racemosus* on Glucose Homeostasis in Aged Rats

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Abstract: Normal aging is usually associated with a progressive deterioration in most endocrine functions that may be responsible for serious disturbances of metabolic homeostasis. Impairment of glucose homeostasis is a well-known feature of aging. Regulation of glucose metabolism is a key aspect of metabolic homeostasis and insulin is the dominant hormone influencing this regulatory system. Glucose seems to be central to the phenomenon of aging and age-related diseases. Medicinal plants are believed to be much safer and proved elixir in the treatment of various ailments. The modulatory effect of *Asparagus racemosus* on plasma glucose, insulin, insulin resistance index and metabolic liver enzymes such as hexokinase, glucose-6-phosphatase and fructose-1,6-bisphosphatase were evaluated in young and aged rats. In aged rats, the increased levels of all the variables except the activity of hexokinase were observed. Supplementation of *Asparagus racemosus* root extract (ARRE) to aged rats restored the age associated altered activity of enzymes and plasma parameters. The results of the present study suggest that the ARRE regulated the glucose homeostasis in aged rats as like young rats. Supplementation could maintain the activity of enzymes and plasma parameters in young rats. These modulatory effects of ARRE may be attributed to the presence of enriched therapeutic phytochemical constituents.

Key words: *Asparagus racemosus* root extract, glucose, aging, insulin

INTRODUCTION

Aging is associated with progressive accumulation of deleterious changes resulting in a gradual functional decline and an increasing probability of disease including cancer, diabetic mellitus, artheriosclerosis etc., (Terman *et al*., 2006). Aging is usually associated with a progressive deterioration in most endocrine functions that may be responsible for serious disturbances of metabolic homeostasis and is associated with an impairment of glucose homeostasis in both humans and experimental animals (Novelli *et al*., 2000). Regulation of glucose metabolism is a key aspect of metabolic homeostasis and insulin is the predominant hormone influencing this regulatory system. Insulin played a key role in the maintenance of glucose homeostasis and provides the major modulator of glucose storage and utilization (Dilman, 1994). Glucose seems to be central to the phenomenon of aging and age-related diseases (Suji and Sivakami, 2004). Hyperglycemia is an important aging factor involved in generation of Advanced Glycosylation End products (AGEs) (Facchini *et al*., 2000; Elahi *et al*., 2002). Aging has been implicated in the development of insulin resistance in both rats and humans (Ferrannini *et al*., 1996).

Plant and plant products are being used as a source of medicine since long. Medicinal plants are assuming greater importance in the primary health care of individuals and communities in many developing countries. There has been an increase of demand in international trade because of very effective, cheaply available, supposedly have no side effects and used as alternative to allopathic medicines. Medicinal plants are believed to be much safer and proved elixir in the treatment of various ailments (Ghosh, 2003).

In Indian system of medicine *Asparagus racemosus* is an important medicinal plant and its root paste or root juice has been used in various ailments and as health tonic (Pandey *et al*., 2005; Goyal and Singh, 2003). *Asparagus racemosus* (Liliaceae) (Eng: Willd asparagus, Tamil: Thanner Vittan Kizhangu), is a well known ayurvedic rasayana which prevent aging, increase longevity, impart immunity, improve mental function and add vigor and add vitality to the body and also used in nervous disorders, dyspepsia, tumors, inflammation, hyperdipsia, neuropathy and hepatopathy (Sharma, 2001).

Reports indicate that the pharmacological activities of *A. racemosus* root extract (ARRE) include antiulcer (Sairam *et al*., 2003), antioxidant (Kamat *et al*., 2000), anti-diarrhoeal (Venkatesan *et al*., 2005), antidiabetic

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(Govindarajan *et al*., 2004) and immunomodulatory activities (Thatte and Dahanukar, 1988). Previously was reported that ARRE contains saponins (Hayes *et al*., 2006), alkaloids (Sekine, 1995), polysaccharides (Kamat *et al*., 2000), polyphenols, favonoids and vitamin-C (Visavadiya and Narasimhacharya, 2005). *Asparagus racemosus* has also been reported to have potent adaptogenic activity (Rege *et al*., 1999).

Hence in the present study to investigate the modulatory role of *Asparagus racemosus* root extract on glucose homeostasis in young and aged rats through the determination of plasma glucose, insulin, insulin resistance index and the activity of hexokinase, glucose-6-phosphatase and fructose-1,6-bisphosphatase in liver.

MATERIALS AND METHODS

Animals: Male albino rats of Wistar strain approximately 3-4 months young rats weighing approximately 140-160 g and 24-26 months old rats weighing approximately 380-410 g (aged) were used in this study. They were healthy animals obtained from Sri Venkateswara enterprises, Bangalore, India. The animals were housed in spacious polypropylene cages and were given food and water *ad libitum*. The animal room was well ventilated and had 12 h light/dark cycle throughout the experimental period. The study protocol was carried out as per the rules and regulation of the Institutional Animal's Ethics Committee (IAEC).

Preparation of plant extract: The roots of the *Asparagus racemosus* were collected from the kolli hills, Tamil Nadu, South India. The collected roots were identified and authenticated by a botanist Prof. Dr. M. Jegadeesan, Department of Herbal and Environmental Science, Tamil University, Thanjavur, Tamil Nadu. A Voucher specimen (Specimen No: 29) has been deposited at the Herbarium of the department. *Asparagus racemosus* root powder (5 g) was suspended in a measured amount of distilled water (600 mL). The suspension was boiled until the quantity was reduced to 100 mL. The concentration of resultant decoction was 50 mg mL^{-1}. The effective dose as 500 mg kg^{-1} b wt^{-1}. of ARRE was selected based on the dose dependent studies carried out in aged rats (Velavan *et al*., 2006).

Experimental design: The animals were divided into 4 groups of 6 animals each: Group I- control young rats; Group II-young rats administered ARRE (500 mg kg^{-1} b.wt day^{-1}) for 4 weeks; Group III-control aged rats; Group IV-aged rats administered ARRE (500 mg kg^{-1} b.wt day^{-1}) for 4 weeks. After the completion of experimental regimen, the rats were fasted over night and blood samples were collected by cervical decapitation. Blood was collected and plasma was separated. Liver was dissected out, washed in ice-cold saline and used for biochemical studies.

Analytical determination: Plasma insulin was assayed by Enzyme-linked Immunosorbent Assay (ELISA) kit (Diagnostic production corporation, UK) The kit included human insulin as standard and labelled human insulin antibody, which cross reacts with rat insulin. Plasma glucose levels were assayed by glucose oxidase/peroxidase method (Trinder, 1969). Hexokinase, glucose-6-phosphatase and fructose-1,6-bis phosphatase were assayed according to the method of Brandstrup *et al*. (1957), Baginsky *et al*. (1974) and Gancedo and Gancedo (1971) and the inorganic phosphate (Pi) liberated was estimated by the method of Fiske and Subbarow (1925). Homeostasis Model Assessment (HOMA) was used as an index to measure the degree of insulin resistance and was calculated by the formula: [insulin ($\mu U\ mL^{-1}$) x glucose in mmol L^{-1}) /22.5] (Pickavance *et al*., 1999).

Statistical analysis: All the values were expressed as means±SD of 6 rats from each group and statistically evaluated by one-way analysis of variance (ANOVA). The means were tested for significance by Tukey's test for multiple comparisons (Harvey and Paige Searle, 1998). A value of $p<0.001$ and $p<0.05$ were considered as significant.

RESULTS AND DISCUSSION

The use of traditional medicine and medicinal plants in most developing countries, as a normative basis for the maintenance of good health, has been widely observed. Medicinal plants are a major source of biodynamic compounds of therapeutic values. The beneficial multiple activities like manipulating carbohydrate metabolism by various mechanisms, preventing and restoring integrity and function of β-cell and insulin-releasing activity, improving glucose uptake and utilization. The antioxidant properties present in medicinal plants offer exciting opportunity to develop them into novel therapeutics (Tiwari and Madhusudana Rao, 2002).

Glucose uptake and utilization decline in the liver and muscle but increased in the adipose tissues as the animals aged. These changes may cause the increased adiposity that is currently proposed to be responsible for the onset of age-related insulin resistance. The rate of glucose uptake was severely reduced between 18 and 32 weeks of

age in all tissues (Higgins *et al*., 1999). The relationship between aging and insulin resistance has attracted substantial attention in last several decades (Fulop *et al*., 2003). Pancreatic synthesis and secretion of insulin, Insulin Receptor (IR) and post-receptor changes associated with aging are critical factors of the glucose homeostasis in aging (Lamberts *et al*., 1997). Aging has been associated with peripheral insulin resistance in both humans and rats (Escriva *et al*., 1997).

Glucose was measured as a metabolic control of insulin action. The impairment of glucose homeostasis and increase in plasma glucose level are associated with aging (Dembe *et al*., 1997; Escriva *et al*., 1997). Insulin is the dominant hormone which influencing the regulation of glucose metabolism. One of the major effects of insulin is to enhance overall glucose disposaland this is achieved by stimulation of glucose uptake into the target tissues (Tiwari and Madhusudana Rao, 2002).

The plasma glucose level was increased in aged rats as compared to young rats. Supplementation of ARRE to aged rats significantly decreased the age associated increased plasma glucose (Table 1). The levels of insulin and insulin resistance index were significantly elevated in aged control rats as compared to young and aged ARRE treated rats. Supplementation of ARRE to aged rats restored the age-associated increased in plasma glucose, insulin and insulin resistant index. In young rats, supplementation with ARRE the levels of plasma glucose, insulin and insulin resistance index were remains unaltered. The degree of insulin resistance as measured by HOMA was higher in aged control rats while in ARRE treated rats the values were normal.

The elevated insulin levels in the face of increased glucose levels suggest an insulin resistant state (Fink *et al*., 1983). Age related glucose intolerance is characterized by a increased insulin resistant and age associated alterations in insulin clearance, insulin sensitivity of hepatic and peripheral tissues (Chen *et al*., 1985). In present study, we also observed the increased level of insulin, insulin resistant index and glucose in aged rats. ARRE treatment to aged rats prevented the increases indicates that ARRE improves the insulin action, decreased insulin resistance index and thereby promote the glucose uptake into target tissues. Present findings is in agreement with the Govindarajan *et al*. (2004) studies. The possible biochemical mechanisms of the ARRE in aged rats are: the insulin like action/reduce the insulin resistance or by other mechanisms such as stimulation of glucose uptake by peripheral tissues, inhibition of endogenous glucose production, as similar mechanisms have been reported for plant extracts (Burcelain *et al*., 1995).

Table 1: Effect of *Asparagus racemosus* on plasma glucose, insulin and insulin resistance index in control and experimental animals

Parameters	Plasma glucose (mg dL^{-1})	Insulin (μU mL^{-1})	Insulin resistance index (©HOMA)
Young control	81.22±7.79	55.21±4.03	12.52±1.24
Young+ARRE	84.99±6.62	57.40±8.04	12.70±1.56
Aged control	97.35±2.37*	90.70±4.00*	21.59±1.0*
Aged+ARRE	87.52ª±6.22***	59.63ª±5.49**	13.56ª±0.67**

Values are given as mean±SD for six rats in each group, *Significantly different from young control ($p<0.001$), **Significantly different from aged control ($p<0.001$), ***Significantly different from aged control ($p<0.05$), ªNon-significant from young control

$$^{©}\text{HOMA} = \frac{\text{Insulin } (\mu\text{U mL}^{-1}) \text{ x glucose (mmol L}^{-1})}{22.5}$$

Table 2: Changes in activities of hexokinase, glucose-6-phosphatase and fructose-1,6-bisphosphatase in liver of control and experimental animals

Parameters	Hexokinase (U^a g^{-1} protein)	Glucose-6-phosphatase (U^b mg^{-1} protein)	Fructose-1,6-bisphosphatase (U^c mg^{-1} protein)
Young control	147.07±7.66	0.168±0.011	0.359±0.01
Young+ARRE	150.56±8.02	0.166±0.010	0.349±0.01
Aged control	109.81±5.18*	0.248±0.020*	0.584±0.04*
Aged+ARRE	142.42#±6.35**	0.185#±0.012**	0.384#±0.02**

Values are given as mean±SD for six rats in each group, ªMicromoles of glucose phosphosylated per min, ᵇMicromoles of Pi liberated per min, ᶜMicromoles of Pi liberated per h, *Significantly different from young control ($p<0.001$), **Significantly different from aged control ($p<0.001$), #Non-significant from young control

Liver is one of the main target organs for insulin action. Glucose transport into liver is independent of insulin. However, insulin by decreasing intracellular glucose, indirectly promotes glucose entry into liver cells. Insulin participates in regulation of hepatic glycolysis and gluconeogenesis (Fulop *et al*., 2003). The action of insulin is known to be a suppressor of gluconeogenesis and also a potent stimulator of key glycolytic enzymes. One of the key enzymes in the catabolism of glucose is hexokinase, which phosphorylates glucose and converts it into glucose-6-phosphate (Laakso *et al*., 1995). Hexokinase exhibit high affinity to glucose and are subject to feedback inhibition by Glucose-6-phosphate. Glucose-6-phosphatase is a gluconeogenic enzyme essential for the regulation of blood glucose homeostasis. Frouctose-1,6-bisphosphatase catalyzes one of the irreversible steps in gluconeogenesis and serves as a site for the regulation of this process. These enzymes are present in a significant amount in liver and kidney (Moorthy *et al*., 2004).

The changes in the activities of hepatic hexokinase, glucose-6-phosphatase and fructose-1,6-bisphosphatase of control and experimental groups are shown in Table 2. A marked decrease in the activities hexokinase was observed in aged animals. A similar result was observed in Moorthy *et al*. (2004) studies in aged rats. The activities of hepatic gluconeogenic enzymes glucose-6-phosphatase and fructose-1,6-bisphosphatase were

significantly increased in the aged rats. Administration of ARRE to aged rats significantly reversed the age-associated changes in the activities of gluconeogenic enzymes. The administrations of ARRE to young rats show an insignificant effect on hepatic enzymes as compared to young control.

The increased activity of hexokinase can cause increased glycolysis and increased utilization of glucose for energy production. The decrease in the concentration of blood glucose in aged rats given ARRE may be due to increased glycolysis (increased liver hexokinase activity). Previous reports indicates that *Asparagus racemosus* root extract reduce the levels of glucose in the blood (Govindarajan *et al*., 2004). Glucose-6-phosphatase and fructose-1,6-bisphosphatase, are the regulatory enzymes in gluconeogenic pathway. The decreased activities of these enzymes may be due to the insulinomimetic activity of ARRE. A sequential metabolic correlation between increased glycolysis and decreased gluconeogenesis stimulated by ARRE suggest that the possible mechanism through which glucose homeostasis is regulated in aged rats.

The altered activity of hexokinase and gluconeogenic enzymes in aged rats may relate to the diabetes. The chemically induced model of diabetes is characterized by a partial or total deficiency of insulin that results in decrease in the enzymatic activity of hexokinase (Hikino *et al*., 1989). The activity of hexokinase potentiate by insulin (Weber *et al*., 1966). The activities of hepatic glucose-6-phophatase and fructose-1,6-bisphophatase were increased significantly in diabetic rats (Baquer *et al*., 1998) and decreased with insulin administration. The presence of all the gluconeogenic enzymes in the liver indicates that the complete pathway is operative and may be of significance under conditions where enough intracellular glucose is not available for utilization, although the circulating blood glucose levels may be high. One such hormonal condition is diabetes where the absence of insulin adversely influences the normal transport of glucose into the cells. The availability of these enzymes may also be beneficial to the liver under conditions like hypoglycemia. Results of the present study indicates that aged and diabetic rats having similar mechanism in intracellular level while extracellularly aging is associated with insulin resistance but diabetic is related to partial or total deficiency of insulin. Type-2 diabetes is complicated by several factors including insulin resistance (Chakrabarti and Rajagopalan, 2002).

The suggested mechanism of action of the ARRE extract on the activities of enzymes in aged rats through the stimulation of glucose uptake by tissues or increase in insulin sensitivity to tissues, insulinomimetic, inhibition of endogenous glucose production, or inactivation of gluconeogenesis in liver. It is also possible that other mechanisms like delay or inhibition of intestinal glucose absorption.

Flavonoids are considered as active principles in many medicinal plants and natural products with positive effect for human health (Wollenweber, 1988). These natural compounds may act separately or synergistically to regulate glucose homeostasis. Our earlier reports reveals that the quantitative analysis of ARRE indicated the presence of flavonoids (36.7±3.9 mg 100 mL^{-1}), polyphenol (88.2±9.3 mg 100 mL^{-1}) and vitamin-C (42.4±5.1 mg 100 mL^{-1}) (Velavan *et al*., 2007) exhibits the regulation of glucose homeostasis through the maintenance of blood glucose level in young and aged rats treated with ARRE.

In summary, aging is associated with the impairment of glucose homeostasis. Nature has given herbs immense power to circumvent various harmful influences of various factors including aging. The present investigation was carried out to evaluate the activity of *Asparagus racemosus* on glucose homeostasis in young and aged rats. The findings of the present study indicates that supplementation of ARRE to aged rats restored the age associated increased glucose levels, insulin action and the activity of hexokinase, glucose-6-phosphatase and fructose-1,6-bisphosphatase. The results of the present study suggest that the ARRE regulated the glucose homeostasis in aged rats as like young rats. Supplementation could maintain the activity of enzymes and plasma parameters in young rats. These modulatory effects of ARRE may be attributed to the presence of enriched therapeutic phytochemical constituents.

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