Comparative analysis of Withania somnifera and Rhus coriaria on hyperglycemia and insulin sensitivity in type 2 diabetic rats

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Tarique Anwer

Abstract

We investigated and compared the effects of an aqueous extract of Withania somnifera (WS) and methanolic extract of Rhus coriaria (RC) on hyperglycemia and insulin sensitivity in type 2 diabetic rats. Type 2 diabetes was induced by single intraperitoneal injection of streptozotocin (STZ, 100 mg/kg) to 2 days old rat pups. WS & RC (200 mg/kg and 400 mg/kg) was administered orally once a day for 5 weeks after the animals were confirmed diabetic (i.e., 90 days after STZ injection). A group of citrate control rats were also maintained which had received citrate buffer on the 2nd day after birth. Significant increases in blood glucose, glycosylated hemoglobin (HbA1c) and serum insulin levels were observed in type 2 diabetic control rats. Treatment with WS & RC reduced the elevated levels of blood glucose, HbA1c and insulin in the type 2 diabetic rats. An oral glucose tolerance test (OGTT) was also performed on the same groups, in which we found a significant improvement in glucose tolerance in the rats treated with WS & RC. The insulin sensitivity was assessed for both peripheral insulin resistance and hepatic insulin resistance. WS & RC treatment significantly improved the insulin sensitivity index (KITT) which was significantly decreased in type 2 diabetic control rats. There was a significant rise in homeostasis model assessment of insulin resistance (HOMA-R) in type 2 diabetic control rats whereas WS & RC treatment significantly prevented the rise in HOMA-R in type 2 diabetic treated rats. Based on our findings, it is possible to postulate that RC is more effective than WS in controlling hyperinsulinemia and glucose tolerance and improved insulin sensitivity thus normalizing hyperglycemia in type 2 diabetic rats.

Keywords Rhus coriaria; hyperglycemia; streptozotocin; insulin sensitivity; diabetes mellitus

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Introduction

Type 2 diabetes mellitus (DM) is possibly the world’s fastest growing metabolic disorder which results from defects in insulin secretion (Kahn, 2001) on one side, and insulin resistance on the other (Polonsky et al., 1996). The progression of type 2 DM begins with an impairment of glucose tolerance (Zimmet and Thomas 2003) and is often associated with a state of insulin resistance, which means insulin that is secreted by the β-cells and IS bound to the liver, muscle and fat cells is subnormally efficacious in carrying out its metabolic actions (Robertson and Harmon, 2006). In recent years there has been an upsurge in the clinical use of indigenous drugs. Management of type 2 DM without any side effects is still a challenge to the medical system. The conventional pharmacological treatments for type 2 diabetes have a number of limitations, such as adverse effects and high rates of secondary failure (Kim et al., 2006). Medicinal plants with antidiabetic activities were used for many centuries and sometimes as regular constituents of the diet, it is assumed that they do not have many side effects (Halim and Hussain, 2002). This leads to increasing demand for natural products which have antidiabetic activity with fewer side effects and are relatively economical as compared to oral hypoglycaemic agents. It is assumed that herbal medicine can only be effective as an alternative to oral hypoglycaemic agents in the treatment of type 2 DM, where pancreatic islets are not totally destroyed. Withania somnifera (WS) Dunal (Family: Solanaceae), commonly known as ashwagandha is widely used in the Ayurvedic system of medicine in India. It is an official drug and is mentioned in the Indian Pharmacopoeia (1985). Several studies of this plant indicate that it possesses anti-inflammatory, antitumor, antistress, antioxidant, immunomodulatory, hematopoietic and rejuvenating properties besides its positive influence on the endocrine, cardiopulmonary and central nervous system (Ghosal et al., 1989; Bhattacharya et al., 1995; Mishra et al., 2000). In a previous report (Anadulla and Radhika 2000), it was found that WS reduces blood glucose level in mild type 2 diabetic subjects. An Ayurvedic herbal formulation (Tarsina) containing WS as one of the ingredients have been found to attenuate STZ-induced hyperglycaemia and pancreatic islet superoxide dismutase activity in type 1 diabetic rats (Bhattacharya et al., 1997). Dried fruit extract of Withania coagulans Dunal (other species of Withania) has been shown to have hypoglycaemic activity in type 1 diabetic rats (Hemlatha et al., 2004).

Rhus coriaria (RC) L. (Family: Anacardiaceae), commonly known as sumac (also spelled as sumach) is a well-known spice in the Middle-East and grown in the central region of Turkey. Maulyanov et al., (1997) has reported that sumac contains flavonols, phenolic acids, hydrolysable tannins, anthocyanins, and organic acids. Phytochemicals in RC are being used as antibacterial, antidiarrhoeal, antispasmodic, antiviral, astringent, candidicide, hepatoprotective, antiasthmatic, anti-inflammatory, antioxidant, antiulcer, fungicide, cyclooxygenase-
inhibitor and lipoxygenase inhibitor due to their contents of ellagic acid, gallic acid, quercetin, isoquercitrin, myricetin and tannic acid (Duke et al., 2003). Recently, the hypoglycaemic efficacy of sumac (Rhus coriaria L.) has been investigated through inhibition of a glycoside hydrolase: alpha-amylase in the treatment and prevention of diabetes (Giancarlo et al., 2006). Methanolic extract (FROM THE water-soluble part) of RC was found to be an uncompetitive inhibitor of xanthine oxidase and scavenger of superoxide radicals (Canadan, 2003).

Hence, the present study was undertaken to evaluate and compare the effects of WS and RC on hyperinsulinemia, glucose intolerance and insulin sensitivity in type 2 diabetic rats.

Materials and Methods

Animals
Healthy albino Wistar rats were kept for breeding. The animals were maintained under controlled conditions of illumination (12 hr light/12 hr darkness) and temperatureS between 20-25 0C. They were housed under ideal laboratory conditions, maintained on A standard pellet diet and given water ad libitum throughout the experimental period.

Preparation of plant extract
Rhus coriaria L. seeds were collected and washed with water and dried in shade. Dried RC seed was extracted with methanol at room temperature three times with 5 volumes of methanol (w/v). The solvent was evaporated at 35-40 oC under reduced pressure of -760 mmHg to give methanolic extract, yielding approximately 10% (w/w). A dark semi-solid (greenish black) material was obtained. It was stored at 4 0C until used. When needed the residual extract was suspended in distilled water and used in the study.

Drugs and Chemicals
Standardized powdered, aqueous root extract of Withania somnifera (Batch No. WS/05002) was a gift sample by Natural Remedies, Bangalore, India. It was stored at 4 0C until used. When needed the residual extract was dissolved in distilled water and used in the study. It contains total withanolides (3.9% w/w). Streptozotocin was procured from Sigma Aldrich, USA. The enzyme-linked immunosorbent assay (ELISA) kit for insulin assay was purchased from Mercodia, Sweden. All the other biochemicals and chemicals used for the experiment were of analytical grade.

Induction of diabetes
To induce type 2 diabetes, STZ (100 mg/kg) in citrate buffer (pH-4.5) was administered intraperitoneally to 2 days old rat pups (Shinde and Goyal, 2003). Another group of pups received only citrate buffer on the 2nd day of their birth. All the surviving pups were kept (mortality ≤ 30%) to adulthood. 90 days after STZ treatment, the development of diabetes was confirmed by measuring blood glucose level. Rats with fasting blood glucose levels of 200 mg/dl or higher were considered to be diabetic.

Experimental design
The rats were divided into eight groups consisting of six animals in each group as follows:
• Group I: Citrate control, received citrate buffer (0.1 ml/kg, i.p)
• Group II: Type 2 diabetic control, received STZ in a single dose (100 mg/kg, i.p)
• Group III: WS only treated rats, received WS (400 mg/kg, p.o)
• Group IV: Type 2 diabetic treated rats, received WS (200 mg/kg, p.o)
• Group V: Type 2 diabetic treated rats, received WS (400 mg/kg, p.o)
• Group VI: RC only treated rats, received RC (400 mg/kg, p.o)
• Group VII: Type 2 diabetic treated rats, received RC (200 mg/kg, p.o)
• Group VIII: Type 2 diabetic treated rats, received RC (400 mg/kg, p.o)

WS (200 mg/kg and 400 mg/kg; Visavadiya & Narasimhacharya 2007) was dissolved in water and given until the end of the study (5 weeks) to groups III, IV and V animals. RC (200 mg/kg and 400 mg/kg) was also dissolved in water and given until the end of the study (5 weeks) to groups VI, VII and VIII animals. On the last day of the experiment, blood samples were collected for biochemical estimations.

Biochemical Parameters Studied
Glucose was estimated by glucose oxidase method (Braham and Trinder, 1972), glycosylated haemoglobin was estimated by Bannon (1982). Plasma insulin level was assayed by ELISA kit (Morgan and Lazarow, 1963). Oral glucose tolerance test (OGTT) was measured according to the method of Pari and Saravanan (2002). Insulin sensitivity index (KITT) was measured for the determination of peripheral insulin resistance (Murali et al., 2002). Homeostasis model assessment of insulin resistance (HOMA-R) was calculated using fasting blood glucose (FBG) and fasting insulin (FI) level and was used for the determination of hepatic insulin resistance (Uno et al., 2005).

Statistical analysis
Data were expressed as the mean ± standard error (S.E) of the means. For a statistical analysis of the data, group means were compared by one-way analysis of variance (ANOVA) with post hoc analysis. The Tukey-Karmer post hoc test was applied to identify significance among groups. P < 0.05 was considered to be statistically significant.

Results
Effect of WS and RC on hyperglycemia in type 2 diabetic rats
Table 1 shows the effect of WS and RC on blood glucose levels. Significant (P < 0.001) increases in blood glucose levels were observed in type 2 diabetic control rats when compared with citrate control rats. Oral administration of WS and RC at two doses (200 mg/kg and 400 mg/kg) reduced the blood glucose levels significantly (P < 0.001) in a dose-dependent manner when compared with type 2 diabetic control rats. RC was found to be more effective than WS in controlling hyperglycemia. WS and RC (400 mg/kg) per se effect did not produce any significant (P < 0.001) change in the blood glucose levels when compared with citrate control rats.

Effect of WS and RC on HbA1c levels in type 2 diabetic rats
Table 1 shows the effect of WS and RC on glycosylated haemoglobin levels. It was observed that type 2 diabetic control rats showed significant ($P < 0.001$) increase in HbA1c levels when compared with citrate control rats. Oral administration of WS and RC at two doses (200 mg/kg and 400 mg/kg) decreased the HbA1c levels significantly ($P < 0.01$) in a dose-dependent manner when compared with type 2 diabetic control rats. The effect of RC on HbA1c was greater than those of WS. There was no significant change in HbA1c levels of WS and RC (400 mg/kg) per se treated rats when compared with citrate control rats.

The data are expressed in mean ± S.E.; n=6 in each group. *$P<0.001$ compared with the corresponding value for citrate control rats (group II vs I). $yP<0.001$ compared with the corresponding value for type 2 diabetic control rats (group II vs IV, V, VII, VIII). *$P<0.01$ compared with the corresponding value between WS & RC (200 mg/kg; group IV vs VII). ns$P>0.05$ compared with the corresponding value between WS & RC (400 mg/kg; group V vs VIII)

**Table 1**: Effect of Withania somnifera (WS) and Rhus coriaria (RC) on blood glucose and glycosylated haemoglobin levels in type 2 diabetic rats.

<table>
<thead>
<tr>
<th>Groups</th>
<th>Treatment</th>
<th>Blood Glucose (mg/dl)</th>
<th>Glycosylated Haemoglobin (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Citrate Buffer (1 ml/kg, i.p)</td>
<td>97.18±3.02</td>
<td>5.70±0.265</td>
</tr>
<tr>
<td>II</td>
<td>STZ (100 mg/kg, i.p)</td>
<td>324.66±10.87$^x$</td>
<td>12.18±0.322$^x$</td>
</tr>
<tr>
<td>III</td>
<td>Only WS (400 mg/kg, p.o)</td>
<td>98.60±1.16</td>
<td>5.67±0.155</td>
</tr>
<tr>
<td>IV</td>
<td>Type 2 diabetic + WS (200 mg/kg, p.o)</td>
<td>151.01±4.08$^y$, $^*$</td>
<td>9.30±0.118$^y$, $^*$</td>
</tr>
<tr>
<td>V</td>
<td>Type 2 diabetic + WS (400 mg/kg, p.o)</td>
<td>121.28±1.80$^{y, ns}$</td>
<td>6.95±0.169$^{y, ns}$</td>
</tr>
<tr>
<td>VI</td>
<td>Only RC (400 mg/kg, p.o)</td>
<td>96.66±1.89</td>
<td>5.90±0.134</td>
</tr>
<tr>
<td>VII</td>
<td>Type 2 diabetic + RC (200 mg/kg, p.o)</td>
<td>139.65±1.89$^y$, $^*$</td>
<td>8.87±0.109$^y$, $^*$</td>
</tr>
<tr>
<td>VIII</td>
<td>Type 2 diabetic + RC (400 mg/kg, p.o)</td>
<td>117.08±1.87, ns</td>
<td>6.83±0.129, ns</td>
</tr>
</tbody>
</table>
Effect of WS and RC on OGTT in type 2 diabetic rats

Table 2 shows the blood glucose levels of citrate control, type 2 diabetic control, WS and RC treated rats after oral administration of glucose (2 gm/kg). In type 2 diabetic control rats the peak increase in blood glucose levels were observed after 1 h. The blood glucose levels remained high over the next hour. WS and RC treated rats showed significant (P < 0.01) decrease in blood glucose levels at 1 and 2 h when compared with type 2 diabetic control rats. The effect was most pronounced at 2 h intervals. RC was found to be more effective in improving glucose tolerance than WS. WS and RC (400 mg/kg) per se treatment did not produce any significant change in the blood glucose levels at 1 and 2 h during OGTT when compared with citrate control rats.

Table 2: Effect of Withania somnifera (WS) and Rhus coriaria (RC) on oral glucose tolerance test in type 2 diabetic rats.

<table>
<thead>
<tr>
<th>Groups</th>
<th>Treatment</th>
<th>0 min</th>
<th>15 min</th>
<th>30 min</th>
<th>60 min</th>
<th>120 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Citrate Buffer</td>
<td>82.82±</td>
<td>112.20±</td>
<td>149.49±</td>
<td>124.14±</td>
<td>98.43±</td>
</tr>
<tr>
<td></td>
<td>(0.1 ml/kg, i.p)</td>
<td>1.67</td>
<td>2.05</td>
<td>2.92</td>
<td>1.69</td>
<td>1.28</td>
</tr>
<tr>
<td>II</td>
<td>STZ</td>
<td>256.56±</td>
<td>301.51±</td>
<td>328.78±</td>
<td>42.92±</td>
<td>318.18±</td>
</tr>
<tr>
<td></td>
<td>(100 mg/kg, i.p)</td>
<td>5.84x</td>
<td>7.72x</td>
<td>5.69x</td>
<td>9.78x</td>
<td>6.83x</td>
</tr>
<tr>
<td>III</td>
<td>Only WS</td>
<td>85.34±</td>
<td>120.20±</td>
<td>156.06±</td>
<td>127.77±</td>
<td>92.92±</td>
</tr>
<tr>
<td></td>
<td>(400 mg/kg, p.o)</td>
<td>2.69</td>
<td>3.29</td>
<td>3.51</td>
<td>2.34</td>
<td>3.51</td>
</tr>
<tr>
<td>IV</td>
<td>Type 2 diabetic + WS</td>
<td>140.90±</td>
<td>166.77±</td>
<td>189.56±</td>
<td>166.77±</td>
<td>150.50±</td>
</tr>
<tr>
<td></td>
<td>(200 mg/kg, p.o)</td>
<td>1.67y</td>
<td>1.48y</td>
<td>2.58y</td>
<td>1.86y</td>
<td>1.39y</td>
</tr>
<tr>
<td>V</td>
<td>Type 2 diabetic + WS</td>
<td>119.26±</td>
<td>138.20±</td>
<td>173.88±</td>
<td>150.30±</td>
<td>128.18±</td>
</tr>
<tr>
<td></td>
<td>(400 mg/kg, p.o)</td>
<td>2.17y</td>
<td>2.53y</td>
<td>5.73y</td>
<td>1.76y</td>
<td>2.8y</td>
</tr>
<tr>
<td>VI</td>
<td>Only RC</td>
<td>83.14±</td>
<td>115.32±</td>
<td>157.69±</td>
<td>140.73±</td>
<td>96.08±</td>
</tr>
<tr>
<td></td>
<td>(400 mg/kg, p.o)</td>
<td>1.73</td>
<td>2.91</td>
<td>2.63</td>
<td>2.92</td>
<td>2.26</td>
</tr>
<tr>
<td>VII</td>
<td>Type 2 diabetic + RC</td>
<td>137.32±</td>
<td>164.07±</td>
<td>184.30±</td>
<td>165.36±</td>
<td>148.90±</td>
</tr>
<tr>
<td></td>
<td>(200 mg/kg, p.o)</td>
<td>1.92y</td>
<td>1.81y</td>
<td>1.51y</td>
<td>1.52y</td>
<td>2.69y</td>
</tr>
<tr>
<td>VIII</td>
<td>Type 2 diabetic + RC</td>
<td>114.71±</td>
<td>130.31±</td>
<td>155.45±</td>
<td>137.79±</td>
<td>120.02±</td>
</tr>
<tr>
<td></td>
<td>(400 mg/kg, p.o)</td>
<td>1.83y</td>
<td>2.23y</td>
<td>2.41y</td>
<td>1.90y</td>
<td>1.61y</td>
</tr>
</tbody>
</table>
The data are expressed in mean ± S.E.; n=6 in each group. xP<0.001 compared with the corresponding value for citrate control rats (group II vs I). yP<0.001 compared with the corresponding value for type 2 diabetic control rats (group II vs IV, V, VII, VIII).

**Effect of WS and RC on insulin levels in type 2 diabetic rats**

Table 3 shows the effect of WS and RC on insulin levels. Hyperinsulinemia was observed in type 2 diabetic control rats when compared with citrate control rats. WS and RC treatment significantly (P < 0.01) reduced the elevated levels of insulin when compared with type 2 diabetic control rats. RC was found to be more effective than WS in preventing hyperinsulinemia. WS and RC (400 mg/kg) per se treatment did not induce any significant change in the levels of insulin.

**Effect of WS and RC on insulin sensitivity in type 2 diabetic rats**

Table 3 shows the levels of KITT, an index of insulin sensitivity and HOMA-R, an index of hepatic insulin resistance. Type 2 diabetic control rats showed a significant decrease in KITT levels with a significant increase in HOMA-R levels when compared with citrate control rats. Treatment with WS and RC significantly (P < 0.001) increased the levels of KITT and prevented rises in HOMA-R levels when compared with type 2 diabetic control rats. The effect of RC on improving the insulin sensitivity was found to be more effective than those of WS. There was no significant change in the levels of KITT and HOMA-R in WS and RC (400 mg/kg) per se treated rats when compared with citrate control rats.

**Table 3:** Effect of Withania somnifera (WS) and Rhus coriaria (RC) on insulin levels, KITT and HOMA-R in type 2 diabetic rats.

<table>
<thead>
<tr>
<th>Groups</th>
<th>Treatment</th>
<th>Insulin Level (mU/L)</th>
<th>K_{ITT}</th>
<th>HOMA-R</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Citrate Buffer (0.1 ml/kg, i.p)</td>
<td>13.13±0.245</td>
<td>10.15±0.162</td>
<td>3.14±0.037</td>
</tr>
<tr>
<td>II</td>
<td>STZ (100 mg/kg, i.p)</td>
<td>24.09±0.329</td>
<td>4.61±0.162</td>
<td>19.28±0.541</td>
</tr>
<tr>
<td>III</td>
<td>Only WS (400 mg/kg, p.o)</td>
<td>13.57±0.137</td>
<td>10.24±0.213</td>
<td>3.29±0.130</td>
</tr>
<tr>
<td>IV</td>
<td>Type 2 diabetic + WS (200 mg/kg, p.o)</td>
<td>20.01±0.283</td>
<td>6.10±0.180</td>
<td>7.38±0.097</td>
</tr>
<tr>
<td>V</td>
<td>Type 2 diabetic + WS (400 mg/kg, p.o)</td>
<td>16.95±0.228</td>
<td>8.72±0.135</td>
<td>5.07±0.085</td>
</tr>
<tr>
<td>VI</td>
<td>Only RC (400 mg/kg, p.o)</td>
<td>12.88±0.235</td>
<td>10.19±0.197</td>
<td>3.088±0.068</td>
</tr>
<tr>
<td>VII</td>
<td>Type 2 diabetic + RC (200 mg/kg, p.o)</td>
<td>19.09±0.222</td>
<td>6.66±0.115</td>
<td>6.57±0.060</td>
</tr>
<tr>
<td>VIII</td>
<td>Type 2 diabetic + RC (400 mg/kg, p.o)</td>
<td>15.89±0.200</td>
<td>9.18±0.164</td>
<td>4.59±0.056</td>
</tr>
</tbody>
</table>
The data are expressed in mean ± S.E.; n=6 in each group. xP<0.001 compared with the corresponding value for citrate control rats (group II vs I). yP<0.001 compared with the corresponding value for type 2 diabetic control rats (group II vs IV, V, VII, VIII). *P<0.01 compared with the corresponding value between WS & RC (200 & 400 mg/kg; group IV vs VII & V vs VIII). **P<0.001 compared with the corresponding value between WS & RC (200 & 400 mg/kg; group IV vs VII & V vs VIII).

**Discussion**

Type 2 diabetes mellitus results from a combination of tissue resistance (or insulin sensitivity) to insulin action and an adequate compensatory insulin secretory response (American Diabetes Association, 1999). Treatment that is inadequate or instituted too late predisposes the affected individual not only to the basic metabolic disturbances but also to a number of serious complications of diabetes. STZ is frequently used to induce DM in experimental animals (Szkudelski, 2001; Yamagishi et al., 2001). Although, it is generally accepted that the cytotoxicity produced by STZ depends on DNA alkylation and subsequent activation of poly ADP-ribose synthetase that causes rapid and lethal depletion of NAD in pancreatic islets (Bennet and Pegg, 1981; Bolzan and Bianchi, 2002), several lines of evidence indicate that the free radicals may play an essential role in the mechanism of β-cell damage and diabetogenic effect of STZ (Ohkuwa et al., 1995).

The method of type 2 diabetes induction was first described by Portha et al. (1974). At 8–10 weeks of age and thereafter rats neonatally treated with STZ manifest hyperglycaemia, an impaired response to the glucose tolerance test (Portha et al., 1979) and loss of β-cell sensitivity to glucose (Giroix et al., 1983). People who develop diabetes usually pass through the phases of excessive adipogenesis, nuclear peroxisome proliferator-activated receptor (PPAR) modulation, insulin resistance, hyperinsulinemia, pancreatic β-cell stress and impaired glucose postprandial and fasting levels (Porte and Kahn, 2001; Hayden and Tyagi, 2002). Hyperinsulinemia has generally been considered as a marker of insulin resistance, i.e. a decrease in the effect of insulin to stimulate glucose uptake at a given serum insulin concentration ((Tenenbaum et al., 2003). Those considered as at risk for developing type 2 DM tend to exhibit a constellation of risk factors i.e, abdominal obesity, hypertension, dyslipidaemia, and insulin resistance (Reaven, 1988; Cordain et al., 2003). Hence in addition to glycemic control, management of hyperinsulinemia is also essential for controlling insulin resistance and thus limiting the complications of type 2 diabetes.

Type 2 diabetic control rats exhibited persistent hyperglycaemia. Recently Giancarlo et al. (2006) has shown that RC has hypoglycaemic activity. Previously dried fruit extract of Withania coagulans Dunal (other species of Withania) has been shown to have hypoglycaemic activity in type 1 diabetic rats (Hemlatha et al., 2004). Treatment with WS and RC (200 mg/kg and 400 mg/kg) to type 2 diabetic rats reduced the elevated blood glucose levels thereby
showing its antihyperglycaemic activity. In diabetes, there is an increased glycosylation of a number of proteins including haemoglobin and β-crystalline of lens (Alberti and Press, 1982). Measurement of glycosylated haemoglobin (HbA1c) has proven to be particularly useful in monitoring the effectiveness of therapy in diabetes (Goldstein, 1995). The levels of HbA1c were increased in type 2 diabetic control rats when compared with citrate control rats. Agents with antioxidant or free radical scavenging properties may inhibit oxidative reactions associated with protein glycation (Elgawish, 1996). Some recent studies have shown that WS has antioxidant properties and prevents lipid peroxidation (Chaudhary et al., 2003; Bhattacharya et al., 2001). A previous report has shown that methanolic extracts of RC fruits have considerable antioxidant activity against free radicals and lipid peroxidation (Candan and Sokmen, 2004). Administration of WS and RC to type 2 diabetic rats reduced the glycosylation of haemoglobin by virtue of its free radical scavenging properties and thus decreased the levels of HbA1c. A decrease in blood glucose levels might also contribute to decreased levels of glycated haemoglobin in WS and RC treated type 2 diabetic rats.

Hyperinsulinemia appears to be a compensatory mechanism that responds to increased levels of circulating glucose and is often associated with the progression to insulin resistance (Goldstein, 2002). The β-cells normally compensate insulin resistance by secreting greater amounts of insulin to maintain glucose homeostasis. Bonora et al., (1983) has reported that hyperinsulinemia is associated with decreased hepatic insulin clearance and hypersecretion of β cells in mild glucose intolerance obese subjects. Results of the present study clearly showed that hyperinsulinemia (as evident by increased serum insulin level) was seen in type 2 diabetic control rats. Therefore, the hyperinsulinemia in type 2 diabetic rats could be either due to decreased hepatic clearance of insulin or by down-regulation of insulin receptors and desensitizing postreceptor pathways (Olefsky et al., 1985), resulting in decreased insulin binding and degradation. Even people with diabetes who take oral medication or require insulin injections to control their blood glucose levels can have higher than normal blood insulin levels due to insulin resistance. Despite high insulin levels (hyperinsulinemia), the glucose levels were greater in type 2 diabetic control rats than type 2 diabetic treated rats. However, WS and RC treatment was found to be effective in reducing insulin levels of type 2 diabetic rats thereby preventing hyperinsulinemia. It seems that both WS and RC exert antihyperglycaemic effect by attenuating hyperinsulinemia.

An insulin-resistant state is a key phase of the metabolic syndrome, constituting the major risk factor for the development of glucose intolerance and diabetes mellitus (Groop, 2000). Thus interventions to decrease insulin resistance may postpone the development of type 2 diabetes and its complications. When animals were subjected to OGTT, increased blood glucose levels were found with the increase of time and were maintained for up 2 h in type
Comparative analysis of Withania somnifera on glucose tolerance and insulin sensitivity. Treatment with WS and RC significantly improved glucose tolerance, as indicated by reduction in peak blood glucose levels at 1 and 2 h in type 2 diabetic treated rats during OGTT. In the present investigation the rate of glucose disposal was found to be significantly decreased in type 2 diabetic control rats when compared with citrate control rats. WS and RC might enhance glucose utilization by peripheral tissues and increase the glycogen stores in the liver due to restoration of delayed insulin response because they significantly decreased the blood glucose levels in glucose loaded rats.

Our results showed that WS and RC decreased blood glucose levels, prevented hyperinsulinemia and improved glucose tolerance in type 2 diabetic rats. These results suggest that WS and RC can improve insulin sensitivity. Thus, KITT was determined to check peripheral insulin resistance (Murali et al., 2002) whereas HOMA-R was determined to check hepatic insulin resistance (Bonora et al., 2000). The results obtained clearly showed that KITT was significantly improved by WS and RC treatment in type 2 diabetic rats. Additionally, WS and RC treatment significantly prevented the rise in HOMA-R in type 2 diabetic rats. This suggests that WS and RC are pharmacologically effective in improving insulin sensitivity. In the present study the treatment of RC showed most significant results in decreasing the levels of blood glucose and HbA1c and preventing hyperinsulinemia as compared to WS treatment. Similarly RC treatment showed the most significant results in improving glucose tolerance and insulin sensitivity as compared to WS treatment.

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Abstract

Comparative analysis of Withania somnifera and Rhus coriaria on hyperglycemia and insulin sensitivity in type 2 diabetic rats

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(Arabic) Abstract

Keywords Rhus coriaria; hyperglycemia; streptozotocin; insulin sensitivity; diabetes mellitus

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