ROLE OF Achyranthes aspera (Linn) SEEDS ON HIGH FRUCTOSE DIET INDUCED DIABETES IN RATS

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Abstract

The high fructose-fed rats are good experimental and most probably used as a model of insulin resistance (IR). Achyranthes aspera (A. aspera) has been shown to improve insulin sensitivity in this model. The present study investigated whether A. aspera could prevent inflammatory and hepatic damage in HFFD rats. Male Wistar rats were fed a diet containing starch (control) or 60 % fructose (insulin-resistant model). Group I rats and Group II rats also received normal diet. Groups III and IV are received high fructose fed diet (HFFD). After 45 days, markers enzymes of liver injury, C-Reactive Protein (CRP), Interleukin (IL-6), Tumor Necrosis Factor (TNF), α-leptin and adiponectin in the plasma, serum and liver were quantified. The marker enzymes Aspartate Transaminase (AST) and Alanine Transaminase (ALT), Alkaline Phosphatase (ALP), Gamma-glutamyl transferase (GGT) and Lactate dehydrogenases (LDH) levels and Inflammatory Markers TNF-α and IL-6 levels significantly increased in HFFD rats as compared to control. Administration of A. aspera to fructose-fed rats significantly reduced these hepatic and inflammatory markers abnormalities. A. aspera activates the decreases IL-6 and TNF-α and a marker enzyme (AST, ALT, ALP, GGT and LDH) concentrations, prevent liver damage, and ameliorates adiponectin in IR rats.

Article History

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Key words: Aspartate transaminase, High fructose fed rats, Insulin resistance, Inflammatory markers and Leptin.

1. Introduction

Diabetes mellitus (DM) is a metabolic disorder characterized by ameliorated glucose level and insulin deficiency and defects of insulin action (Sellamuthu et al., 2013). Obesity-associated insulin resistance (IR) is a one of the main risk factor for Type 2 diabetes, the predominant form of diabetes (Tsai et al., 2015). In addition, IR is associated with metabolic syndrome, a cluster of metabolic abnormalities, including glucose intolerance, hypertension, hyperlipidemia, and a non-infective inflammatory state (Guo, 2014). According to the International Diabetes Federation, the number of patients with DM in 2013 was estimated as 382 million and is expected to increase 592 million by 2035. In addition, health spending on diabetes accounted for 10.8 % of the total health expenditure worldwide and the disease caused 5.1 million
deaths in 2013 (International Diabetes Federation, 2013). That risks modern world to face big health problem. Food and beverages rich in energy, fat, and/or sugar are commonly consumed in modern societies (Shridhar et al., 2015). Fructose intake in the form of high fructose corn syrup or sucrose, one of the sweeteners of carbonated beverages, has increased dramatically in the last 30 years (Madero et al., 2011).

The sites of fructose - induced IR are documented to be the liver, skeletal muscle and adipose tissue (Suganthi et al., 2005). The previous research studies confirmed that high-fructose diet (HFFD) leads to insulin resistance and increased hepatic oxidative stress (Cummings et al., 2010). Oxidative stress is defined as the persistent imbalance between the production of Reactive Oxygen Species (ROS) and antioxidant defense culminating in irreversible cellular alterations (Karpaga selvi et al., 2015). IR and C-reactive protein (CRP) levels are strongly correlated in adults (Gelaye et al., 2010). It has also been reported that increased CRP concentrations may reflect not only local inflammation at atherosclerotic lesions but also predict future cardiovascular disease (CVD) risk including IR (Ridker, 2007). An emerging body of evidence documents associations of elevated CRP concentrations in individuals with IR (Nakanishi et al., 2005). These observations are very important because an accumulation of body fats leads to an increase of pro-inflammatory cytokines such as TNF-α, IL-6 (Muniyappa, 2007). In previous epidemiological studies have demonstrated an increase in plasma levels of inflammatory markers such as CRP, IL-6 and TNF-α in patients with metabolic syndrome as well as T2D clinically overt T2D (Christiana et al., 2016). It is authentic that liver plays an important role in the maintenance of normal glucose levels in any condition. AST, ALT and GGT are the common liver enzymes which together comprises liver function tests (Hanley et al., 2004). AST and ALT are the well-known markers of hepatocellular health while GGT also shows biliary tract function. ALT is another major marker of liver function, but AST and GGT are the less specific markers because both they are present in other tissues (Lee et al., 2014). In addition, these components of liver function tests have been shown to be positively correlated with the risk of future Type 2 diabetes. A recent meta-analysis on this topic showed that both elevated ALT and GGT were associated with increased risk of diabetes, while GGT might be a better risk factor than as compare to ALT (Ko et al., 2015). A. aspera Linn. belonging to family Amaranthaceae, is commonly found as a weed on wayside throughout India. It is known as Apamarg in Sanskrit, Chirchitta in Hindi and Prickly chaff flower in English, Naayuruvi in Tamil. A. aspera is having phytoactive constituents and alteration of lipid peroxidation and enhancement in free radical scavenging activity of the herbal seed crude powder. A. aspera seeds are rich in protein, and used to treatment of night blindness and cutaneous diseases, antipyretic activity, hepatoprotective potency (Nehete et al., 2009). A. aspera leaves have been assessed for cancer chemo preventive activity (Chakraborty et al., 2002).

A. aspera Linn is well known medicinal plant and found enormous information about drug in ancient literature such as Ayurvedic, Unani, Tibba, Siddha, Allopathy, Homeopathy, Neuropathy and Home remedies. Earlier phytochemical studies reported that it contains saponins, alkaloids (betaine, achyranthine), amino acids, steroids (stigmasterol), triterpenoids (oleanolic acid and its glucoside), phenolic content (indole acetic acid oxidase), and flavonoids It has also been reported to have antiarthritic, antirheumatic activity as per folklore practice (Veerappan and Malarvili, 2017). A. aspera having Alkaloids, flavonoids, saponin glycosides, steroids and terpenoids were found strong positive in A. aspera (Ningwal et al., 2016). A. aspera is having phytoactive constituents and reduction of lipid peroxidation and enhancement in free radical scavenging activity of the herbal seed crude powder (Malarvili and Gomathi, 2009). Our previous work shows that A. aspera has antihyperlipidimic activity in high fructose fed diet (HFFD) rats (Malarvili et al., 2011). The present study aimed to investigate the effects Achyranthes aspera (A.aspera) in high fructose fed induced that obesity. The parameters are chosen to assess
that CRP, leptin, marker enzymes and inflammatory markers.

2. Materials and methods

Animals

Healthy male adult albino rats (Wistar strain) 6 - 7 weeks old, weighing 160 – 180 g was procured from “Sri Venkateswara Enterprises”, Bangalore, India. They have been housed in clean sterile polypropylene cages with proper aeration and lighting (12±1 hrs day/night rhythm) throughout the experimental period. In throughout the experimental period, the temperature was maintained between 27 ºC ± 2 ºC. The animals were fed with commercially energy rich available pelleted rat feed (Gold-Mohur, M/S Hindustan Lever Ltd, Mumbai, India) during the acclimatization period and water ad libitum. The usage and handling of experimental rats was done by following the rules and regulations given by the Institutional Ethics Committee.

After one week of acclimatization, the animals were divided into two batches. One batch was provided with a control diet containing starch as the source of carbohydrate and the other was fed a fructose-enriched diet for 45 days. Group I (CON) received the control diet and tap water ad libitum. The composition of the diets was given in Table - 1. Group II (CON+ A. aspera) control rat orally supplemented with A. aspera, at last, 15 days of experimental period group III are HFFD rats and group IV (HFFD + A. aspera) were fed HFFD and oral supplemented with A. aspera. The total experimental duration was 45 days. A. aspera was given orally for the last 15 days of the experimental period. Blood samples from all the groups of animals were collected from the tail vein on the 10th, 20th and 30th days and estimated glucose levels to ensure diabetic status. The following experimental groups, consisting of six rats each, were maintained as follows:

Experimental Design

The rats were divided into four groups, each group consisting of six animals.

a) Group I : Normal control rats.

b) Group II : Control rats treated with the crude powder of A. aspera seeds (100 mg kg\(^{-1}\) body weight) twice daily for a period of last 15 days of the experimental period.

c) Group III : High Fructose fed rats (>60 % fructose for 45 days).

d) Group IV : High Fructose fed rats treated with the crude powder of A. aspera seeds (100 mg kg\(^{-1}\) body weight) twice daily for a period of last 15 days of the experimental period.

Chemicals

Fructose, bovine serum albumin, G-6-P, γ-glutamyl parainitroaniline, nicotinamide adenine dinucleotide (NAD\(^{+}\), NADH) nicotinamide adenine dinucleotide phosphate (NADP\(^{+}\), NADPH), reduced glutathione, oxidized glutathione, adenosine triphosphate, adenosine monophosphate, thiobarbituric acid and 1,2,4-aminonapthol sulphonic acid were obtained from Sigma Chemical Company, ST. Louis, MO, USA. All other chemicals and reagents used were of highest purity and of analytical grade marketed by Glaxo Laboratories, Mumbai, SD Fine Chemicals, Mumbai and Sisco Research Laboratories, Pvt. Ltd., India.

Collection of Samples

At the end of the 45 days, the rats were fasted overnight and killed by cervical decapitation under mild ether anesthesia. Blood was collected in heparin rinsed tubes to separate the plasma. Blood collected in another set of test tubes without anticoagulant was used to separate the serum. Liver, kidney was perfused in situ with cold 0.15 M NaCl at 37 ºC.

Analytical method

CRP was measured using a specific immunoassay kit (Imunospec Corporation, CA, USA). Pro-inflammatory cytokines (TNF-α, IL-6, and were measured in duplicate using Milipore’s MILLIPLEX rat CVD cytokine panel (Millipore, Billerica, MA, USA). The plasma and serum levels of leptin (ng/ml) and TNF- α, (pg/ml) were also estimated by solid-phase enzyme-linked immunosorbent assay (ELISA) based on the sandwich principle using test reagent kits (DRG Instruments, GmbH, Germany) and (ID labs, Canada), respectively. The marker enzymes activities of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were estimated by the method of Reitman and Frankel (1957).
Lactate dehydrogenase (LDH) and was determined by the method of King (1965). Alkaline phosphatase (ALP) and γ-glutamyl transferase (GGT) were estimated using the method of King and King (1954), and Rosalki (1972).

Table - 1: Composition of diets fed to rats for the determination of insulin resistance

<table>
<thead>
<tr>
<th>Ingredient (g/100 g)</th>
<th>Control diet</th>
<th>High fructose diet</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corn starch</td>
<td>60</td>
<td>-</td>
</tr>
<tr>
<td>Fructose</td>
<td>-</td>
<td>60</td>
</tr>
<tr>
<td>Casein</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>Methionine</td>
<td>0.7</td>
<td>0.7</td>
</tr>
<tr>
<td>Groundnut oil</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Wheat bran</td>
<td>10.6</td>
<td>10.6</td>
</tr>
<tr>
<td>Salt mixture†</td>
<td>3.5</td>
<td>3.5</td>
</tr>
<tr>
<td>Vitamin mixture‡</td>
<td>0.2</td>
<td>0.2</td>
</tr>
</tbody>
</table>

†Composition of the mineral mix (g/kg): MgSO₄·7H₂O, 30.5; NaCl, 65.2; KCl, 105.7; KH₂PO₄, 200.2; 3MgCO₃·Mg(OH)₂·3H₂O, 38.8; FeC₆H₅O₇·5H₂O, 38.8; CaCO₃, 512.4; KI, 0.8; NaF, 0.9; CuSO₄·5H₂O, 1.4; MnSO₄, 0.4; and CONH₃, 0.05.

‡One kilogram of vitamin mix contained: thiamine mononitrate, 3 g; riboflavin, 3 g; pyridoxine HCl, 3.5; nicotinamide, 15 g; d-calcium pantothenate, 8 g; folic acid, 1 g; d-biotin, 0.1 g; cyanocobalamin, 5 mg; vitamin A acetate, 0.6 g; α-tocopherol acetate, 25 g; and choline chloride, 10 g.

Statistical analysis

Values or mean ± SD for six rats in the each group and statistical differences between mean values were determined by one way analysis of variance (ANOVA) followed by DMRT test for multiple comparisons. The values of P<0.05 were considered to be significant. Statistical Package for Social Studies (SPSS Inc., Chicago, IL) 19.0 versions were used for this analysis.

3. Results

The Table - 2 illustrates the effect of A. aspera seeds on body weight and glucose in normal and fructose fed rats. The level of glucose and body weight significantly increased in fructose fed rats when compared with normal rats. A significant improvement in insulin level with a marked reduction in fructose-induced elevation in the levels of glucose and body weight was observed in rates administered with A. aspera seeds. The acquired information introduced in Table – 3 and 4 shows that significantly elevated (P<0.05) CRP, leptin, serum, IL-6 and TNF-α and significantly decreased the level of adiponectin in HFFD rats as compared to control rats. Oral supplementation of A. aspera seeds significantly decreased the levels of CRP, leptin, serum, IL-6 and TNF-α concentrations and increased the level of adiponectin of the HFFD rats as compared to group III. No significant differences between Group I and II.

The Table – 5 and 6 shows the activity of liver marker enzymes as AST, ALT, ALP, GGT and LDH in serum and liver of control and experimental rats. Activity of AST, ALT, GGT and LDH were observed to substantially attenuate in the HFFD treated the group as compared with control rats. Administration of A. aspera seeds significantly (P < 0.05) decreased the levels of AST, ALT, ALP, GGT and LDH Group IV as compared to Group III. There are no significant changes of Group I and II. Administration of A. aspera seed extract (100 mg/kg of B.W) is an effective dose for all parameters significant effect in HFFD rats as compared to control rats. A. aspera in normal control rats didn’t show any significant.
Table - 2: Effect of *A. aspera* seeds in diet on body weight, blood glucose and insulin in normal and fructose fed animals.

<table>
<thead>
<tr>
<th>Group</th>
<th>Body weight (g)</th>
<th>Blood glucose (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before treatment</td>
<td>After treatment</td>
</tr>
<tr>
<td>I (Normal Control)</td>
<td>188.25 ± 16.1 ^a</td>
<td>218.59 ± 18.13 ^a</td>
</tr>
<tr>
<td>II (Control + <em>A. aspera</em>)</td>
<td>188.68 ± 15.3 ^a</td>
<td>189.47 ± 13.57 ^a</td>
</tr>
<tr>
<td>III (HFFD Control)</td>
<td>261.41 ± 19.5 ^b</td>
<td>311.25 ± 19.12 ^b</td>
</tr>
<tr>
<td>IV (HFFD+ <em>A. aspera</em>)</td>
<td>263.59 ± 21.1 ^b</td>
<td>190.07±18.87 ^c</td>
</tr>
</tbody>
</table>

Values are means ± SD for six rats in each group.
Values not sharing a common superscript (a, b, and c) differ significant at (P < 0.05, Duncan's Multiple Range Test [DMRT]).

Table - 3: Levels of adipocytokines in plasma at the end of experimental study

<table>
<thead>
<tr>
<th></th>
<th>I (Normal Control)</th>
<th>II (Control + <em>A. aspera</em>)</th>
<th>III (HFFD Control)</th>
<th>IV (HFFD + <em>A. aspera</em>)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRP (lg/mL)</td>
<td>1.54±0.04 ^a</td>
<td>1.51±0.01 ^a</td>
<td>3.05±0.24 ^b</td>
<td>1.61±0.01 ^c</td>
</tr>
<tr>
<td>Leptin (ng/mL)</td>
<td>0.32±0.01 ^a</td>
<td>0.31±0.02 ^a</td>
<td>2.01±0.06 ^b</td>
<td>0.35±0.03 ^c</td>
</tr>
<tr>
<td>Adiponectin (µg/mL)</td>
<td>4.71±0.31 ^a</td>
<td>4.70±0.30 ^a</td>
<td>1.76±0.15 ^b</td>
<td>4.63±0.29 ^c</td>
</tr>
<tr>
<td>TNF-α (pg/mL)</td>
<td>19.5±0.96 ^a</td>
<td>19.1±0.97 ^a</td>
<td>56.8±4.27 ^b</td>
<td>21.1±0.17 ^c</td>
</tr>
<tr>
<td>IL-6 (pg/mL)</td>
<td>77.2±5.13 ^a</td>
<td>76.19 ± 6.84 ^a</td>
<td>218.28 ± 11.97 ^b</td>
<td>80.34 ± 6.82 ^c</td>
</tr>
</tbody>
</table>

Values are mean ± S.D for six rats in each group.
Values not sharing a common superscript (a, b, and c) differ significant at (P < 0.05, Duncan's Multiple Range Test [DMRT]).

Table - 4: Levels of adipocytokines in serum at the end of experimental study

<table>
<thead>
<tr>
<th></th>
<th>I (Normal Control)</th>
<th>II (Control + <em>A. aspera</em>)</th>
<th>III (HFFD Control)</th>
<th>IV (HFFD + <em>A. aspera</em>)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRP (mg/dL)</td>
<td>14.62±0.91 ^a</td>
<td>14.1±0.85 ^a</td>
<td>69.28±4.24 ^b</td>
<td>16.61±0.99 ^c</td>
</tr>
<tr>
<td>Leptin (ng/mL)</td>
<td>23.5±1.91 ^a</td>
<td>22.91±1.82 ^a</td>
<td>43.51±4.16 ^b</td>
<td>25.35±1.83 ^c</td>
</tr>
<tr>
<td>Adiponectin (ng/mL)</td>
<td>74.6±6.38 ^a</td>
<td>75.04±6.18 ^a</td>
<td>58.6±4.24 ^b</td>
<td>72.11±6.14 ^c</td>
</tr>
<tr>
<td>TNF-α (pg/mL)</td>
<td>59.15±4.87 ^a</td>
<td>58.14±4.75 ^a</td>
<td>126.8±11.45 ^b</td>
<td>61.54±5.28 ^c</td>
</tr>
<tr>
<td>IL-6 (pg/mL)</td>
<td>81.47±7.58 ^a</td>
<td>80.19 ± 7.17 ^a</td>
<td>189.04 ± 11.97 ^b</td>
<td>85.07 ± 7.93 ^c</td>
</tr>
</tbody>
</table>

Values are mean ± S.D. for six rats in each group.
Values not sharing a common superscript (a, b, and c) differ significant at (P < 0.05, Duncan's Multiple Range Test [DMRT]).

Table - 5: Levels of marker enzymes in serum at the end of experimental study

<table>
<thead>
<tr>
<th></th>
<th>I (Normal Control)</th>
<th>II (Control + <em>A. aspera</em>)</th>
<th>III (HFFD Control)</th>
<th>IV (HFFD + <em>A. aspera</em>)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AST (IU/L)</td>
<td>29.74 ± 1.02 ^a</td>
<td>29.13 ± 1.92 ^a</td>
<td>68.86 ± 3.11 ^b</td>
<td>33.42 ± 1.27 ^c</td>
</tr>
<tr>
<td>ALT (IU/L)</td>
<td>22.61 ± 1.53 ^a</td>
<td>21.99 ± 1.24 ^a</td>
<td>48.94 ± 3.43 ^b</td>
<td>24.71 ± 1.51 ^c</td>
</tr>
<tr>
<td>ALP (IU/L)</td>
<td>78.18 ± 6.54 ^a</td>
<td>77.18 ± 6.39 ^a</td>
<td>148.25 ± 11.67 ^b</td>
<td>80.18 ± 8.47 ^c</td>
</tr>
<tr>
<td>LDH (IU/L)</td>
<td>116.48 ± 10.95 ^a</td>
<td>115.27 ± 10.12 ^a</td>
<td>199.25 ± 14.12 ^b</td>
<td>119.05 ± 10.7 ^c</td>
</tr>
<tr>
<td>GGT (IU/L)</td>
<td>19.98 ± 1.89 ^a</td>
<td>18.85 ± 1.36 ^a</td>
<td>46.14 ± 3.28 ^b</td>
<td>22.05 ± 1.82 ^c</td>
</tr>
</tbody>
</table>

Values are mean ± S.D. for six rats in each group.
Values not sharing a common superscript (a, b, and c) differ significant at (P < 0.05, Duncan's Multiple Range Test [DMRT]).

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Table - 6: Liver injury marker enzymes, total protein, albumin to globulin ratio, interleukin-6 and tumour necrosis factor-a in the different groups

<table>
<thead>
<tr>
<th></th>
<th>I (Normal Control)</th>
<th>II (Control +A. aspera)</th>
<th>III (HFFD Control)</th>
<th>IV (HFFD + A. aspera)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AST a</td>
<td>70.69 ± 6.91 a</td>
<td>69.48 ± 6.12 a</td>
<td>145.62 ± 13.13 b</td>
<td>74.68 ± 7.63 c</td>
</tr>
<tr>
<td>ALT a</td>
<td>65.11 ±5.19 a</td>
<td>64.65 ± 5.12 a</td>
<td>140.26 ± 13.1 b</td>
<td>69.79 ± 5.72 c</td>
</tr>
<tr>
<td>ALP</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>GGT b</td>
<td>2.29 ± 0.19</td>
<td>2.28 ± 0.16</td>
<td>4.97 ± 0.36</td>
<td>2.33 ± 0.11</td>
</tr>
<tr>
<td>LDH c</td>
<td>319.1 ±29.1 a</td>
<td>317 ± 30.28 a</td>
<td>422.15 ± 39.4 b</td>
<td>326.5 ± 30.1 c</td>
</tr>
<tr>
<td>IL-6 (pg/dL)</td>
<td>80.63 ±7.64 a</td>
<td>79.6 ±6.18 a</td>
<td>104 ± 9.27 b</td>
<td>86.14 ± 7.9 c</td>
</tr>
<tr>
<td>TNF-α (pg/dL)</td>
<td>5.81 ± 0.49 a</td>
<td>5.81 ± 0.51 a</td>
<td>11.89 ± 1.90 b</td>
<td>5.94 ± 0.52 c</td>
</tr>
</tbody>
</table>

Values are mean ± S.D. for six rats in each group.
Values not sharing common superscript are significant with each other at P<0.05 (Duncan’s multiple range test).
α-Values are lmol p-nitro aniline formed/min.
β-Values are lmol pyruvate formed/min.
γ-Values are lmol NADH used/min.
AST, aspartate aminotransferase; ALT, alanine aminotransferase; IL-6, interleukin-6; TNF-α, tumour necrosis factor-α.

4. Discussion

In our studies shows significant attenuated in the serum and liver concentrations of CRP, leptin, serum, IL-6 and TNF-α with significant increased and significantly decreased the level of Adiponectin in HFFD rats is compared to control rats. C-reactive protein (CRP), is one of most important hepatic acute phase protein highly regulated by circulating levels of IL-6, predicts coronary heart disease incidence in healthy subjects. Another one valuable point, CRP is primarily synthesize in the liver and regulated by the pro-inflammatory parameters such as cytokine IL-6 and tumor necrosis factor-alpha (TNF-α) (Gabay and Kushner, 1999) in adiposities. That previous information suggests that the correlations of CRP concentrations with both fasting insulin and glucose could be due to the presence of a chronic systemic sub-clinical inflammation (Nakanishi et al., 2005). CRP is also providing downstream integration to overall cytokine activation, is bound to the membranes of damaged vascular cells where it activates complement proteins or enhances the production of thrombogenic agents (Fukuchi et al., 2008) depending on conventional risk factors and other markers of inflammation (Kaptoge et al., 2010). These instances of vascular inflammation might be induced development of IR (Fukuchi et al., 2008). Previous researchers’ intimate of CRP over the last decade has increased markedly. CRP has been shown to be a useful marker and mediator of inflammation and a powerful predictor of future CVD event (Ndumele et al., 2006). The researcher workers strongly suggests that systemic inflammation, as evidenced by triggered CRP, might be of etiologic importance in IR and DM. Administration of A. aspera alter the insulin signaling pathway due to decrease the level of CRP.

Leptin moves around at levels proportional to body fat and is a key afferent signal linking adiposity level and nutritional status. HFFD induced obesity, even though leptin levels rise proportionally with adiposity, these elevated leptin levels fail to prevent weight gain (Scarpace et al., 2007). Huang and colleagues (2004) indicated that after the experimental period intervention, the leptin levels were approximately 100 % higher in animals HFFD than those fed chow diet. Adiponectin is a 244 – amino acid collagen-like protein that is secreted independently by adipocytes and acts as a hormone with anti-inflammatory and insulin-sensitizing properties (Kadowaki et al., 2006). It is well known that circulating adiponectin concentrations decrease with increasing levels of obesity is a good understanding one, which may be heavily comorbid condition between this adipokine and
diabetes risk. The major, hypothesized role of adiponectin against impairment of glucose metabolism is its favorable effect on insulin sensitivity. Metabolic studies show that adiponectin can induce the insulin sensitivity by stimulating glucose utilization and oxidative fatty acid in the skeletal muscle and liver through improving AMP-activated protein kinase. Supplementation of A. aspera is reverse the changes of leptin and adiponectin levels, it may A. aspera have is having insulin sensitivity

Obesity leads to expanded of adipose tissue mass, and one explanation for obesity-related IR is the production of certain factors, including TNF-α and IL-6, by adipose tissue (Bal et al., 2010). Early research studies showed that pro-inflammatory cytokines impair insulin sensitivity and glucose regulation in IR and diabetes. Klover and coworkers have represented that both acute and chronic exposure to IL-6 inhibits insulin action in vivo (Klover et al., 2003). TNF-α expression correlated positively with the degree of obesity and level of hyperinsulinemia and negatively with adipose tissue lipoprotein lipase activity (Kawamata et al., 2007). Importance of adipokines in influencing IR is authentically proved by earlier researchers. TNF-α interferes with early steps of insulin signaling and causes ubiquitinylation (Medina et al., 2005).

In previous researchers intimate that plasma concentrations of IL-6 and TNF-α were increased in fructose-fed rats in the present study. Because accumulation of fats in the liver, there is sustained hepatic generation of pro-inflammatory cytokines from the Kupffer cells, leading to a vicious cycle of worsening insulin resistance and severity of steatohepatitis. Increased TNF-α production to suppress insulin receptor signal transduction in fructose-fed rats has been suggested as a link between inflammation and IR (Miller Adeli, 2008). In our study report is also agreed with the above statement due to increases the level of inflammatory parameters. Effects of A. aspera alters the inflammatory markers such TNF-α, IL-6 and reduced inflammation as well as improvements in insulin sensitivity and liver function, alleviation of endotoxic injury.

In our experimental studies observed that marker enzymes as like as AST, ALT, ALP GGT and LDH levels are significantly increased in serum and liver markers in HFFD rats as compared to control. Increased in serum levels of AST and ALT are directly induced liver damage because they also present in the cytoplasm in location and are released into circulation after cellular damage. Investigate of liver function can be made by estimating the activities of serum AST, ALT and ALP, which are enzymes originally present in much more concentration in the cytoplasm (Parmar et al., 2013), when there is hepatopathy, these enzymes leak into the blood stream which leads to with the extent of liver damage (Venukumar and Latha, 2004). ALT is also subsequently estimated biochemical profile for the purpose of assessing hepatic injury. The elevation of ALP indicates the disturbed excretory function of liver. GGT is also membrane bound enzymes, which are released imbalancely depending on the pathological conditions. Elevation of serum GGT concentrations is regarded as another important indicator of hepatic damage. LDH is catalyses the conversion of lactate to pyruvate using NAD+ as coenzyme of NAD. The increased in LDH activity in serum as same mechanism of AST and ALT. So an elevation of the serum marker enzymes in generally regarded as one of the most sensitive index of the hepatic damage (Parmar et al., 2013).

Thus, GGT could serve as a marker of the IR syndrome in the pathogenesis of diabetes. Another possible mechanism is that GGT plays an important role in antioxidant systems. Experimental studies have reported that GGT has a central role in the maintenance of intracellular antioxidant defenses through its mediation of extracellular glutathione transport into most types of cells (Karp et al., 2001). Hence, raised GGT concentrations could be a marker of oxidative stress, which might also play a role in the cause and development of diabetes (Lee et al., 2003). Previous researcher’s treatment with the extract of A. aspera significantly decreased
levels of serum enzyme markers as AST, ALT and ALP, thus suggesting that the extract possessed compounds that protected the hepatocytes from alcohol induced liver injury and subsequent leakage of the enzymes into the circulation. In our studies accepted the same mechanical action of supplementation of A. aspera reduced the marker enzymes as like as AST, ALT, ALP, GGT and LDH in the experimental group as compared to HFFD rats.

5. Conclusion
On the basis of the results obtained in the present study, it is concluded that HFFD rats induced IR and hepatic damage is amenable to attenuation by A. aspera seed crude extract as compared to control. The protective effect of A. aspera seed crude extract can be correlated directly with its ability to reduce the rate of inflammatory markers as well as it restored the liver marker enzymes. The findings of this study suggest that A. aspera seed can be used as a safe, cheap, and effective alternative chemopreventive and a protective agent in the management of HFFD rats.

6. References


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