Effect of Fortified Cake with Papaya (*Carica papaya* L.) on Hypoglycemia of Streptozotocin (STZ) Induced Diabetic in Experimental Rats

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Abstract: The present study was designed to investigate the effect of fortified cake with different levels 20, 30, 50 and 75%, respectively with papaya powder and papaya puree (replacement with wheat flour 72% extract and sucrose) on hypoglycemic, antioxidant activities and some liver and kidneys function in streptozotocin (STZ) induced diabetic rats. Thirty five male rats of Sprague Dawley strain (weighting 90±5 g) were divided into seven groups (each group 5 rats). The first group fed on basal diet, served as a normal control group (-ve). Thirty rats were injected (i.p) with STZ (65mg/kg body weight) to induce hyperglycemia and classified to sex groups, positive control group (+ve) fed on basal diet, C group treated with cake 100% wheat flour (72% extract), C and C groups treated with fortified cake with 20% and 30% papaya powder. Treatment groups C and C were fed on fortified cake with two levels 50 and 75% of papaya puree. After eight weeks, rats were anaesthetized by diethyl ether and sacrificed; blood samples were collected then separate serum to measure some biochemical parameters. Liver and kidneys were removed to demonstrate histopathological observation. Our results showed significant increase in body weight gain, food intake and food efficiency ratio in C, C, C and C groups comparing with positive control (+ve) group, as well as significant reduction in serum glucose, HbA1c, TC, TG, LDL-c and VLDL-c, AST, ALT, creatinine, uric acid, urea and nitric oxide (NO) levels and an increase in insulin, HDL-c, total antioxidant capacity (TAC) and superoxide dismutase (SOD) levels in treated C, C, C and C groups comparing with positive control group (+ve). It is concluded that the examined fortified cake with different levels of *Carica papaya* had a therapeutic protective effect which may be attributed to some potent bioactive constituents of *Carica papaya* against diabetes complications.

Key words: Hypoglycemic · Hypolipidemic · *Carica papaya* · Streptozotocin · Rats

INTRODUCTION

Diabetes mellitus is a public health problem in both undeveloped and developing countries which leads to serious complications over time. It is caused by the deficiency or ineffective production of insulin by pancreas which results in increase or decrease in concentrations of glucose in the blood. It is found to damage many of the body systems, particularly the blood vessels and nerves both insulin-dependent DM (IDDM) and non-insulin dependent DM (NIDDM), thus it is a common and serious metabolic disorder throughout the world [1]. According to the report of World Health Organization [2], 346 million people have diabetes worldwide. It is also estimated that 3.4 million patients died from diabetes-related complications in 2004. Without urgent action, this number is likely to double by 2030. Diabetes mellitus is characterized by dyslipidemia, including increased low-density lipoprotein (LDL) cholesterol levels, low HDL cholesterol levels and increased triglycerides [3].

Many synthetic oral anti-diabetic drugs are associated with drawbacks such as resistance and side effects ranging from liver toxicity, increased abdominal discomfort, flatulence, diarrhea and cardiovascular risk [4]. Streptozotocin induces diabetes by free radical generation. This causes a massive reduction of insulin secreting beta cells of the islets of langerhans, which results in a decrease in endogenous release of insulin [5]. The increasing interest in herbal medicine is not surprising. Plants are recognized as a wonderful source for medicines. It is estimated that there are about 1200 species of plants are used as folk medicines for the treatment and management of diabetes, these plants are...
rich sources of dietary fiber. Recently the impact of natural antioxidants and dietary fiber on human health has received significant attention. Fruit and vegetables are critical components of the human diet due to their high antioxidant capacity, permitting prevention of cellular damage caused by free radicals and also due to their fiber content [6]. Medicinal plants used to treat hypoglycemic or hyperglycemic conditions are of considerable interest for ethno-botanical community [7].

Many plants have been studied for their anti-diabetic potential [8]. Tropical fruit are rich in bioactive compounds such as vitamins and antioxidant compositions [9]. Papaya (Carica papaya L.) is one of the most important fruits cultivated throughout the tropical and subtropical regions of the world [10] and the most economically important fruit in the Caricaceae family [11]. Papaya is commonly known for its food and nutritional values throughout the world. The properties of papaya fruit and other parts of the plant are also well known in traditional system of medicine. During the last few decades considerable progress has been achieved regarding the biological activity and medicinal application of papaya and now it is considered as valuable nutraceutical fruit plant. Papaya possesses excellent medicinal properties for treatment of different diseases [12]. Papaya is a good source of vitamins, minerals and fiber [13-16]. Scientific evidences have shown that Carica papaya has the following activities: anti-diabetes, diuretic, antihyperlipidemic, antihelmintic, anti-amoebic, contraceptive in mice rats, hypoglycemic, nephroprotective, bactericidal, wound healing, antioxidant, anti-nociceptive, anti-inflammatory and anti-ulcer [17]. Dried Carica papaya have bioactive compound that are useful to human health. So, papaya powder can use as an additive to wheat flour as composite flour to be used in bakery products in term of flavoring, antioxidant activities, soluble dietary fiber, resistant starch and water holding capacity [18].

Therefore, this study aims to evaluate hypoglycemic, hypolipidemic, liver and kidneys functions and the antioxidant effect of fortified cake with Carica papaya powder and puree with different levels on streptozotocin induced diabetic rats.

MATERIALS AND METHODS

Materials: American wheat flour (72% extract), sucrose, skim milk, whole egg, salt, baking powder, vanillin, margarine and papaya fruits (Carica papaya L.) Solo variety, were purchased from local market at El-Mansoura city, El-Dakahlia Governorate, Egypt. Streptozotocin and Amaryl drug were obtained from Sigma Chemical Co. (USA) Products. Thirty five male albino rats of Sprague Dawley strain, (weighting 90±5 g) were obtained from the National Research Centre, Dokki, Giza, Egypt.

Methods: Fortified cakes were prepared according to the common method described by Penfield and Campbell [19, 20]. Preparation of cake was carried out by using wheat flour (72% extract), samples replaced separately with 20 and 30% papaya powder, while others were carried out by using sugar (sucrose) replaced separately with 50 and 75% with papaya puree. Rats were kept under standard environmentally controlled and kept under observation for one week for adaption and fed on standard diet which formulated according to AIN [21].

Five rats served as normal control group (-ve), while the other rats were injected (i.p) with streptozotocine (65 mg/kg body weight) dissolved in 0.1M citrate buffer of PH 4.5 then supplied with 5% glucose solution for 48h after injection in order to prevent hypoglycemia [22]. Seven days after streptozotocin administration, blood was collected from the rate eye can thus by means of haematocrite tubes. The Animal showing fasting blood glucose higher than 200 mg/dl were selected and used as diabetic rats, which classified into positive control (+ve) group and five treated rat groups that treated with cake 100% wheat flour (72% extract) (C ), fortified cake with 20% papaya powder (C ), fortified cake with 30% papaya powder (C ), fortified cake with 50% papaya puree (C ) and fortified cake with 75% papaya puree (C ).

Food and water was provided with ad libitum. Food intake was recorded daily and body weight of rats was measured once weekly. At the end of experimental period (eight weeks), the rats were anaesthetized by diethyl ether and sacrificed; blood samples were collected from the aorta of each rat and withdrawn in test tubes. The tubes of blood were left for coagulation then centrifuged at 3000 rpm for 15 minutes to obtain serum for further analysis, glucose (FBS), HbA1c, insulin levels were determined according to the methods of Sasaki et al. [23], Abraham et al. [24] and Wilson and Miles [25], respectively. Serum total cholesterol (TC), serum triglyceride (TG), high density lipoprotein cholesterol (HDL-c) were determined by enzymatic method according to Chon et al. [26], Foster and Dumns [27] and Young [28], respectively. Low density lipoprotein cholesterol (LDL-c), very low density lipoprotein cholesterol (VLDL-c) were calculated by the method described by Friedwald et al. [29]. Serum alanine and aspartate amino
transferase (ALT&AST) enzymes activity were performed according to the method of Burits and Ashwood [30] and Young [31], respectively. Serum creatinine, urea and uric acid were enzymatically determined according to Bohmer [32], Patton and Crouch [33] and Fossati et al. [34], respectively. Superoxide dismutase (SOD) enzyme activity and total antioxidants capacity (TAC) were determined according to Oyanagui [35] and Cao et al. [36], respectively, nitric oxide (NO) was measured by modified gries reaction according to Nagi et al. [37]. Liver and kidney for every rat were collected and immersed in 10% neutral buffered formalin as fixative and sent to Cancer Institute for histopathological examination according to Bancroft et al. [38].

Statistical Analysis: Data were statistically analyzed using computerized SPSS (Statistic Program Signmatat, Statistical Soft-Ware, SAS Institute, Cary, NC). Effects of different treatments were analyzed by one way ANOVA (Analysis of variance) test using Duncan’s multiple range test and p<0.05 was used to indicate significance between different groups according to Snedecor and Cochran [39].

RESULTS AND DISCUSSION

The statistical data in Table 1 presented that, control (±ve) rat group showed a significant decrease in body weight gain as compared to control (-ve) group. The untreated diabetic (positive control) group showed a significant decrease in body weight gain, food intake and food efficiency ratio (FER) comparing with all groups that feeding on fortified papaya cake with different levels. Similar results are in agreement with those obtained by Sonia et al. [40] and Hajzadeh et al. [41], they reported that the weight of diabetic rats were significantly decreased as compared to normal control rats and they suggested that these differences in the food consumption pattern led to important differences in body weight gain at the end of experimental period. As shown in Table 2 serum glucose and insulin levels of the experimental diabetic rats showed that Induction of diabetes led to increase in serum glucose and HbA1c levels as expected in STZ injected rats (positive group) to 411.25 mg/dl and 12.30%, than that of the normal control (-ve) group since STZ causes a massive reduction in insulin 8.60 µ/ml, release by the destruction of the β-cells of the islets of Langerhans and inducing hyperglycemia. These results were confirmed by Prabu and Natarajan [42], who showed that HbA1c percentage is proportionately increased in diabetic patients with ambient hyperglycemic and reflects the extent, as well as management of diabetic condition. Feeding on fortified papaya cake at different incorporated levels to STZ treated diabetic rats caused significant reduction of blood glucose and increase insulin levels as the experiment progressed which was related to the level of fortified cake and duration of treatment.

The maximum reduction in blood glucose was observed at week 6 for groups Cw2, Cw3, Cw1 and Cw5, the reduction is less by 59.9%, 56.11%, 55.56% and 53.25% respectively with that of the positive control group (+ve). At the same time, ratios of glycated hemoglobin (HbA1c) were decreased by 52.03%, 51.06%, 38.46% and 44.31%, respectively. This is in agreement with those reported by Mohammed et al. [43], Montano et al. [44], Krishna et al. [45] and Eze et al. [46]. On the other hand, results showed that feeding on fortified papaya cake with different levels significantly diminished blood glucose levels (p<0.05) in STZ induced diabetic rats. This hypoglycemic effect of Carica papaya is consistent with those reported by Oloyede [47], Sharma et al. [48] and Elekwali et al. [49]. It was also observed that there was a significant reduction of glycated hemoglobin (HbA1c) in the diabetic rat groups that fed on fortified papaya cake with high incorporated levels when comparing with the untreated diabetic rats (+ve) at (P<0.05). It is therefore possible that the Carica papaya may possess active substances which scavenge the free radicals of glucose oxidation, protein glycation and oxidative degeneration or may be making an improvement in insulin secretion. This observation is however supported by Gupta et al. [50].

Table 3 shows the effect of fortified papaya cake with different levels on lipid profile. There was significant increase on the TC, TG, LDL-c, VLDL-c and total lipid levels of untreated diabetic group (+ve) comparing with normal control (-ve). However, there is no significant difference between groups CW2, CW1 and CW2 and normal control group (-ve) for TC, TG, LDL-c and VLDL-c levels. But there is marked increase in the level of HDL-c of treated groups CW2, CW1 and CW2 feeding with fortified papaya cake with different levels when compared to positive control (+ve). A significant increase in serum TC and TG observed in this experiment is in agreement with the findings of Sharma et al. [51].The abnormal high concentration of serum lipids has been associated with diabetes mainly due to the increase in the mobilization of free fatty acids from the peripheral fat deposits [52], because insulin inhibits hormone sensitive lipase production. However, feeding on fortified papaya cake with high incorporated levels to diabetic rats brought the values near to normal levels. Results demonstrated the
Table 1: Body weight gain, food intake and FER of the experimental diabetic rat groups

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Normal control (-ve)</th>
<th>Positive control (+ve)</th>
<th>C</th>
<th>C1</th>
<th>C2</th>
<th>C3</th>
<th>C4</th>
<th>C5</th>
<th>C6</th>
<th>C7</th>
<th>C8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight gain (g)</td>
<td>141.50±11.35^a</td>
<td>122.25±10.52^c</td>
<td>132.50±11.68^b</td>
<td>135.75±11.30^a</td>
<td>136.75±11.91^b</td>
<td>137.84±11.91^a</td>
<td>139.04±11.11^a</td>
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<tr>
<td>Food intake</td>
<td>15.25±1.25^a</td>
<td>11.50±1.29^c</td>
<td>12.50±1.95^b</td>
<td>14.75±1.95^a</td>
<td>14.50±1.73^b</td>
<td>14.50±1.73^a</td>
<td>15.02±1.12^a</td>
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<tr>
<td>FER</td>
<td>0.33±0.001^c</td>
<td>0.24±0.002^a</td>
<td>0.27±0.001^b</td>
<td>0.30±0.001^a</td>
<td>0.32±0.002^a</td>
<td>0.32±0.002^a</td>
<td>0.31±0.001^a</td>
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</table>

Values are expressed as mean ± SD, n=5, Mean values in each column having different superscript (a, b, c,..) are significant at p<0.05 by different and vice versa.

FER: Food efficiency ratio

Table 2: Serum glucose, insulin and levels glycated hemoglobin of the experimental diabetic rat groups

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Normal control (-ve)</th>
<th>Positive control (+ve)</th>
<th>C</th>
<th>C1</th>
<th>C2</th>
<th>C3</th>
<th>C4</th>
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<th>C7</th>
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</thead>
<tbody>
<tr>
<td>FBS (mg/dl) 1week</td>
<td>88.75±7.08^a</td>
<td>355.25±13.04^d</td>
<td>289.75±18.01^a</td>
<td>249.75±18.01^c</td>
<td>258.00±14.14^b</td>
<td>254.75±18.06^c</td>
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<tr>
<td>FBS (mg/dl) 2week</td>
<td>89.00±4.08^b</td>
<td>398.75±10.31^a</td>
<td>274.00±17.02^d</td>
<td>226.15±18.83^a</td>
<td>229.75±13.96^d</td>
<td>219.25±16.18^d</td>
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<tr>
<td>FBS (mg/dl) 6 week</td>
<td>89.50±5.91^c</td>
<td>411.25±18.99^d</td>
<td>251.51±11.29^b</td>
<td>182.75±16.04^a</td>
<td>192.25±14.50^b</td>
<td>180.50±15.58^b</td>
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<tr>
<td>Insulin (µ/ml)</td>
<td>16.05±1.67^a</td>
<td>8.60±1.16^c</td>
<td>14.33±2.24^b</td>
<td>14.74±2.31^a</td>
<td>15.55±1.99^b</td>
<td>15.26±1.99^a</td>
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<tr>
<td>Hb A1C %</td>
<td>5.72±0.71^a</td>
<td>12.30±1.70^c</td>
<td>9.85±0.90^b</td>
<td>7.57±0.68^a</td>
<td>5.90±0.66^c</td>
<td>6.02±0.80^c</td>
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</tbody>
</table>

Values are expressed as mean ± SD, n=5, Mean values in each column having different superscript (a, b, c,..) are significant at p<0.05 by different and vice versa.

FBS: fasting blood glucose, HbA1C: Glycated hemoglobin.

Table 3: Some serum lipids profile (mg/dl) of the experimental diabetic rat groups

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Normal control (-ve)</th>
<th>Positive control (+ve)</th>
<th>C</th>
<th>C1</th>
<th>C2</th>
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<tbody>
<tr>
<td>TC (mg/dl)</td>
<td>63.80±9.34^a</td>
<td>105.55±12.26^a</td>
<td>96.32±10.63^a</td>
<td>84.62±11.48^b</td>
<td>75.77±10.48^b</td>
<td>71.50±5.38^a</td>
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<tr>
<td>TG (mg/dl)</td>
<td>95.77±9.49^b</td>
<td>148.38±11.61^b</td>
<td>133.15±10.71^c</td>
<td>122.18±10.73^c</td>
<td>94.57±8.55^c</td>
<td>97.20±3.35^c</td>
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<tr>
<td>HDL-c (mg/dl)</td>
<td>37.57±3.71^c</td>
<td>26.15±2.43^c</td>
<td>27.82±2.46^b</td>
<td>30.52±2.91^a</td>
<td>33.22±3.43^a</td>
<td>34.77±2.87^a</td>
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</tr>
<tr>
<td>LDL-c (mg/dl)</td>
<td>22.77±2.04^d</td>
<td>41.30±3.92^d</td>
<td>35.07±2.17^c</td>
<td>32.82±2.06^c</td>
<td>30.52±2.18^c</td>
<td>26.32±2.19^c</td>
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<tr>
<td>Total lipids</td>
<td>223.92±11.83^b</td>
<td>333.32±12.10^b</td>
<td>290.80±12.99^a</td>
<td>283.68±14.10^a</td>
<td>265.45±13.36^a</td>
<td>239.55±6.24^a</td>
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<tr>
<td>VLDL-c (mg/dl)</td>
<td>19.15±1.90^c</td>
<td>29.68±2.32^c</td>
<td>19.51±1.90^a</td>
<td>24.44±2.15^a</td>
<td>24.44±2.15^a</td>
<td>19.44±0.67^b</td>
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Values are expressed as mean ± SD, n=5, Mean values in each column having different superscript (a, b, c,..) are significant at p<0.05 by different and vice versa.

TC: Total Cholesterol. TG: Triglycerides. HDL-c: High density lipoprotein. LDL-C: Low density lipoprotein. VLDL-c: Very low density lipoprotein

Table 4: Some liver and kidney function parameters of the experimental diabetic rat groups

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Normal control (-ve)</th>
<th>Positive control (+ve)</th>
<th>C</th>
<th>C1</th>
<th>C2</th>
<th>C3</th>
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</thead>
<tbody>
<tr>
<td>AST (Iu/ml)</td>
<td>27.52±2.16^a</td>
<td>45.12±3.21^a</td>
<td>38.47±2.02^a</td>
<td>35.72±2.46^a</td>
<td>31.35±1.19^a</td>
<td>28.85±2.39^a</td>
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<tr>
<td>ALT (Iu/ml)</td>
<td>16.55±1.95^a</td>
<td>30.37±3.43^a</td>
<td>28.11±2.63^a</td>
<td>26.97±2.31^a</td>
<td>23.85±2.80^a</td>
<td>19.85±1.42^a</td>
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<tr>
<td>Creatinine (mg/dl)</td>
<td>0.85±0.02^a</td>
<td>2.74±0.21^a</td>
<td>2.31±0.06^a</td>
<td>2.11±0.08^a</td>
<td>1.94±0.16^a</td>
<td>1.01±0.09^a</td>
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<tr>
<td>Uric acid (mg/dl)</td>
<td>2.12±0.33^a</td>
<td>4.44±0.33^a</td>
<td>3.30±0.49^a</td>
<td>3.00±0.18^a</td>
<td>2.27±0.26^a</td>
<td>2.15±0.55^a</td>
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<tr>
<td>Urea (mg/dl)</td>
<td>24.80±1.26^a</td>
<td>48.10±3.08^a</td>
<td>38.30±2.15^a</td>
<td>34.25±2.29^a</td>
<td>27.85±1.19^a</td>
<td>25.47±1.38^a</td>
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</table>

Values are expressed as mean ± SD, n=5, Mean values in each column having different superscript (a, b, c,..) are significant at p<0.05 by different and vice versa.

AST: Aspartate aminotransferase. ALT: Alanine aminotransferase

Table 4 shows results of some biochemical parameters as affected by feeding fortified papaya cake with different levels. The AST and ALT activities of positive control group (+ve) were significantly higher than those of normal control group (-ve) and of diabetic rats treated with fortified papaya cake at different levels. Treatment of diabetic rats with fortified cake of (30% papaya powder, 50% papaya puree and 75% papaya

hylolipidemic effects of papaya by reducing the levels of TC, TG, VLDL and LDL. These combined effects can subsequently play a vital role in preventing the incidences of premature occurrence of coronary heart diseases. This is further strengthened by the increase in the levels of high density lipoprotein cholesterol (HDL). Thus fortified papaya cakes exhibited hypocholesterolaemic effects.
puree) reduced the activity of AST and ALT with respect to untreated diabetic group (+ve). While non significant in AST and ALT at treated groups C_{S1} and C_{S2} in comparing with normal control group (-ve). Similar finding was observed by Srinivasan [53], who noticed Hepatoprotective potential of Carica papaya and ascertained by measuring biomarkers and speculated that the protection may be due to the presence of vitamin C. Several enzymes of blood are considered as indicators of hepatic dysfunction and damage and the leakage of hepatic enzymes such as AST and ALT into blood is routinely used as a reliable biochemical index for hepatocellular damage [54]. Therefore the increase in serum Alanine aminotransferase (ALT) and Aspartate aminotransferase (AST) activities may indicate liver tissue damage probably by altered cell membrane permeability leading to the leakage of the enzymes from the tissues to the serum. Serum enzyme measurements are valuable tool in clinical diagnosis, providing information on the effect and nature of pathological damage to any tissue [55]. Creatinine, uric acid and urea levels were significantly highly elevated in positive control group (+ve) comparing with normal control (-ve) group. However treatment with fortified papaya cake in groups C_{w1} and C_{w2} significantly reduced (p<0.05) these parameters to a level similar to normal control group (-ve). The increase in the level of these metabolites (urea and creatinine) in untreated diabetic rats (+ve) may suggest renal damage associated with uncontrolled diabetes mellitus. Blood urea and creatinine are considered as significant markers of renal dysfunction [56]. However, feeding on fortified papaya cake with different levels normalizes these metabolic changes in diabetic rats groups. The observed decrease in these parameters by feeding the rats with fortified cake suggests its potency in management of these ailments. This could be attributed to vitamin C and minerals content [57].

Table 5 shows the effect of fortified papaya cake at different levels on total antioxidant capacity (TAC); superoxide dismutase (SOD) and nitric oxide (NO) of STZ induced diabetic in rats. Treated group C_{S2} had the highest TAC level followed by, C_{w2}, C_{S1} and C_{w1}, compared with positive control group (+ve). On the other hand, the treated rat group C_{S2} feeding on fortified papaya cake with 75% papaya puree had the highest (TAC) and (SOD) levels followed by groups C_{w1} and C_{w2}. Data also show that nitric oxide (NO) recorded the highest level in positive control group (+ve) compared with normal control group (-ve). On the other hand, there was a significant decrease in (NO) level for groups C_{S2}, C_{S1} and C_{w2} compared to the positive control group (+ve). The consumption of these antioxidant enzymes to combat oxidative stress [58, 59]. All living cells protect themselves against free radical damage by enzymes such as superoxide dismutase (SOD) or compounds such as ascorbic acid (vitamin C). Papaya fruit had antioxidant capacity due to their content of vitamin C and vitamin A [57, 60, 61]. In diabetes mellitus these protective mechanism are disrupted. Many synthetic drugs protect against oxidative damage but they have adverse side effects. An alternative solution to the problem is to consume natural anti-oxidants from food supplement and traditional medicine [62].

Table 5: Total antioxidant capacity (TAC), Superoxide dismutase (SOD) and nitric oxide (NO) of the experimental diabetic rat groups.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Normal control (-ve)</th>
<th>Positive control (+ve)</th>
<th>C_{w}</th>
<th>C_{w1}</th>
<th>C_{w2}</th>
<th>C_{S1}</th>
<th>C_{S2}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total antioxidants capacity (TAC) (mmole/L)</td>
<td>3.10±0.22^{a}</td>
<td>1.37±0.15^{b}</td>
<td>1.74±0.06^{b}</td>
<td>2.72±0.06^{c}</td>
<td>2.99±0.06^{c}</td>
<td>2.94±0.06^{c}</td>
<td>3.04±0.12^{c}</td>
</tr>
<tr>
<td>Superoxide dismutase (SOD) (U/mL)</td>
<td>70.13±5.22^{a}</td>
<td>21.25±3.43^{b}</td>
<td>55.87±6.35^{b}</td>
<td>62.29±7.23^{b}</td>
<td>69.76±7.81^{b}</td>
<td>69.94±7.91^{b}</td>
<td>70.04±7.91^{b}</td>
</tr>
<tr>
<td>Nitric oxide NO (µmole/L)</td>
<td>2.68±0.33^{a}</td>
<td>9.45±1.44^{b}</td>
<td>4.23±1.03^{b}</td>
<td>4.02±1.05^{c}</td>
<td>3.76±1.21^{c}</td>
<td>3.46±1.21^{c}</td>
<td>3.17±1.21^{c}</td>
</tr>
</tbody>
</table>

Values are expressed as mean ± SD, n=5, Mean values in each column having different superscript (a, b, c, …) are significant at p<0.05 by different and vice versa
Photo 1: Liver of rat from (normal control) healthy group showing the normal histological structure of hepatic lobule (H and E X400)

Photo 2: Liver of rat from control (+ve) group showing vacuolar degeneration of hepatocytes, congestion of hepatic sinusoids and hepatic necrosis with inflammatory cell infiltration (H and E X 200)

Photo 3: Liver of rat from group C treated with (cake of 100% WF) showing hepatic necrosis associated with mononuclear cells infiltration as well as kupffer cell activation (H and E X 200)

Photo 4: Liver of rat from group C treated with (fortified cake of 20% papaya powder) showing hepatic necrosis associated with mononuclear cells infiltration as well as kupffer cell activation (H &E X 200)

Photo 5: Liver of rat from group C treated with (fortified cake of 30% papaya powder) showing slight hydropic degeneration of hepatocytes and hypergranular cytoplasm (H and E X 200)
Photo 6: Liver of rat from group C₈, treated with (fortified cake of 50% papaya puree) showing cytoplasmic vacuolization of hepatocytes and presence of few leucocytes in the hepatic sinusoids (H and E X400)

Photo 7: Liver of rat from group C₉, treated with (fortified cake of 75% papaya puree) showing no histopathological changes (H and E X 200)

Photo 8: Kidney of rat from (normal control) healthy group showing the normal histological structure of renal parenchyma (H and E X400)

Photo 9: Kidney of rat from control (+ve) group showing hypertrophy of glomerular tuft and thickening of parietal layer of Bowman's capsule (H and E X400)

Photo 10: Kidney of rat from group C₉, treated with (cake of 100% WF) showing congestion of renal blood vessels (H and E × 200)
vacuolization of hepatocytes and presence of few leucocytes in the hepatic sinusoids (Photo 6). While some liver sections of treated group C_{w3} showed no histopathological changes (Photo 7). Serum enzyme measurements are valuable tool in clinical diagnosis, providing information on the effect and nature of pathological damage to any tissue [55]. Therefore, aspartate and alanine amino transaminases are considered sensitive indicators of hepatocellular damage and within limit can provide a quantitative evaluation of the degree
of damage to the liver [63]. According to Neuwinge [64], the fruit of papaya has also been used as a popular hepatoprotective agent. In cases of jaundice and hepatitis, immature fruit is either eaten or used in a decoction.

**Histopathological Results of Kidneys:** Microscopically, kidney of normal control rat group (-ve) revealed normal histological structure of renal parenchyma (Photo 8). Some examined kidney sections of positive control group (+ve) revealed hypertrophy of glomerular tuft and thickening of parietal layer of Bowman's capsule (Photo 9). The examined kidney sections of group C\_w showing congestion of renal blood vessels (Photo 10). Meanwhile, the examined kidney sections of the treated groups C\_w\_1 and C\_w\_2 showing revealed cystic dilatation of renal tubules with cellular cast in their lumen (Photo 11 and 12). While, the examined kidney sections of the treated group C\_s revealed no histopathological changes (Photo 13). Meanwhile, the examined kidney sections of treated rat group C\_s\_2 showed slight congestion of glomerular tufts and vacuolization of renal tubular epithelium (Photo 14). These results are in accordance with those reported by Eze et al. [46], who mentioned that the administration of STZ caused damage to the kidney tissue of induced diabetic untreated group showed severe glomerular necrosis with lymphocyte hyperplasia when compared with normal rats. Our results were similar to the work carried out by Trujillo et al. [65], where they reported an elevation of serum urea usually signifies decreased renal function so plasma urea is recognized markers of glomerular filtration rate (GFR) and in nephropathy [66]. The improved histological nature of the organs studied collaborates by the effectiveness of papaya in preventing organ damage secondary to severe complication of uncontrolled diabetes.

**CONCLUSION**

Our results from this study suggest that fortified cake with *Carica papaya* with different levels had a therapeutic protective effect against diabetes complications. The synergetic hypoglycemic effect is revealed by increased serum insulin levels, decreased serum glucose level as well as improvement of lipid profile. The results of the renal and liver function test have also established that the fortified cake with *Carica papaya* at different levels lacks nephrotoxic and hepatotoxic effects by the high intake levels and duration of administration.

**REFERENCES**


