An extract from date seeds having a hypoglycemic effect

Is it safe to use?

Ahmed F. El Fouhil, MSc, PhD, Aly M. Ahmed, MSc, PhD, Hasem H. Darwish, MD, Muhammad Atteya, MSc, PhD, Ali H. Al-Roalle, BSc, MSc.

ABSTRACT

The aim was to investigate the safety of seed extract administration, and to compare between toxic effects of diabetes on rats treated with insulin versus rats treated with insulin-seed extract.

Methods: This study was performed in the Anatomy Department, College of Medicine, King Saud University, Riyadh, Kingdom of Saudi Arabia from August to December 2010. One hundred rats were divided into 5 groups. Group 1 served as control. Group 2 was given daily ingestions of 10 ml of date seed extract. Animals of groups 3 and 4 were made diabetic by streptozotocin injection, and were given daily subcutaneous injections of 3 IU/day of insulin for 8 weeks. Group 4 received, in addition, daily ingestions of 10 ml of seed extract. Group 5 were made diabetic with streptozotocin and then given the seed extract only. At the end of experiment, rats were decapitated, and the sera were separated for estimation of alanine aminotransferase (ALT), aspartate aminotransferase, gamma glutamyl transferase, blood urea nitrogen, and serum creatinine levels. Livers and kidneys were processed for light microscopic study.

Results: The mean values of all tested serum levels were significantly higher in Group 3 compared to Groups 1, 2 and 4 (with the exception of ALT in the case of Group 4). There was no significant change when comparing the mean values of Groups 1, 2, and 4. Livers and kidneys of rats in Groups 1, 2, and 4 showed normal histology, while those of Group 3 showed histopathological changes.

Conclusion: Date seed extract administration is safe on the liver and kidney. In addition, insulin-date seed extract combination minimizes the toxic effects of diabetes on these organs.


From the Department of Anatomy, College of Medicine, King Saud University, Riyadh, Kingdom of Saudi Arabia.

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Address correspondence and reprint request to: Dr. Ahmed F. El Fouhil, Department of Anatomy, College of Medicine, King Saud University, PO Box 2925 (28), Riyadh 11461, Kingdom of Saudi Arabia. Tel. +966 (1) 4671314. Fax. +966 (1) 4671300. E-mail: ahmedfathala@hotmail.com
Diabetes is a predominant public health concern affecting a large population in the whole world. The disease causes substantial morbidity, mortality, and long-term complications. Conventional hypoglycemic drugs are widely used. Considering insulin as the drug of choice for type 1 diabetes, its disadvantages were discussed in previous studies. There is an increasing use of complementary and alternative medicine among the general public. Date seeds have been used in folk medicine to treat diabetes mellitus (DM) for many years without scientific basis. The efficacy of an aqueous extract from date seed has been tested successfully in the glycemic control of type 1 DM in rats. Compared to insulin, date seed extract is easily administered (by oral route), easily available, and almost costless. The use of any medication might be associated with possible unwanted effects (side effects) on vital organs. Liver and kidney are important organs of metabolism, detoxification, storage and excretion, and therefore, are especially vulnerable to damage. This work is carried out to provide information on the effect, if any, of the administration of date seed extract on the structure and functions of rat liver and kidney. It would also provide a comparison between the effect of diabetes on such organs, in cases of rats treated with a combination of insulin and date seed extract, and those treated with insulin as a single drug for the treatment of diabetes. The present study would be a preliminary step for testing the efficacy of such extract in the treatment of DM in humans.

Methods. This study was performed in the Department of Anatomy, College of Medicine, King Saud University, Riyadh, Kingdom of Saudi Arabia (KSA) from August to December 2010. One hundred male adult Sprague Dawley albino rats weighing 250-300 gm were used in this study. The Deanship of Scientific Research, King Saud University, Riyadh, KSA approved this research. This study followed the International Guidelines for the Care and Use of Laboratory Animals. The present study would be a preliminary step for testing the efficacy of such extract in the treatment of DM in humans.

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Preparation of the date seed extract. Seeds obtained from “Sukkary” dates were washed with tap water, left to dry, roasted, and crushed. The crushed seed powder...
was added to distilled water to prepare a mixture of 50 g/L. The mixture was boiled until it becomes brownish in color, and then finally filtered.

Statistical analysis. Results were expressed as mean ± standard deviation (SD). The significance of the difference between the values from different groups was determined using the one way analysis of variance (ANOVA) followed by the post-Hoc Duncan test for multiple comparisons. Results were considered significant when \( p \leq 0.05 \). Data were analyzed using the Statistical Package for Social Sciences version 16.0 (SPSS Inc, Chicago, Illinois, USA).

Results. Biochemical results. Table 1 shows the results of liver and kidney function tests, expressed as mean ± SD in the 4 groups.

Liver function tests. The mean values of serum AST and serum \( \gamma \)-GT were significantly higher in rats of Group 3 (insulin-treated) when compared to Groups 1, 2, and 4. No significant change was detected in the mean values of serum AST and serum \( \gamma \)-GT when comparing Groups 1, 2, and 4 with each other. The mean value of serum ALT was significantly higher in Group 3 compared to Groups 1 and 2, but not statistically significant when compared to Group 4. No statistically significant differences were observed when comparing the mean value of serum ALT of Groups 1, 2, and 4 with each other.

Kidney function tests. The mean values of both BUN and serum creatinine were significantly higher in Group 3 compared to Groups 1, 2, and 4. No statistically significant differences were observed when comparing Groups 1, 2, and 4 with each other.

Histological results. Liver. Stained liver sections from rats of Groups 1, 2, and 4 showed normal hepatic architecture. Hepatocytes were arranged in

<table>
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<th>Groups</th>
<th>ALT (U/L)</th>
<th>AST (U/L)</th>
<th>( \gamma )-GT (U/L)</th>
<th>BUN (mg/dl)</th>
<th>Creatinine (mg/dl)</th>
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<td>1</td>
<td>45.575 ± 5.875</td>
<td>52.050 ± 6.283</td>
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<td>2</td>
<td>45.775 ± 7.561</td>
<td>51.925 ± 5.239</td>
<td>66.550 ± 3.623</td>
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<td>0.4275 ± 0.045</td>
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<tr>
<td>3</td>
<td>54.300 ± 2.815*</td>
<td>69.050 ± 6.140†</td>
<td>78.475 ±6.409†</td>
<td>28.225 ± 3.551†</td>
<td>1.3400 ± 0.414†</td>
</tr>
<tr>
<td>4</td>
<td>50.450 ± 2.812</td>
<td>53.275 ± 4.496</td>
<td>67.025 ± 2.394</td>
<td>19.975 ± 1.063</td>
<td>0.6650 ± 0.113</td>
</tr>
</tbody>
</table>

*significant compared to Groups 1 and 2, †significant compared to groups 1, 2 and 4 (\( p \leq 0.05 \)). ALT - alanine aminotransferase, AST - aspartate aminotransferase, \( \gamma \)-GT - gamma glutamyl transferase, BUN - blood urea nitrogen

Figure 1 - Histological results showing: a) section of the liver from the control rat (Group 1), showing normal hepatic architecture with normal central vein (CV), and plates of hepatocytes separated by normal hepatic blood sinusoids (arrows). b) Section of the liver from the group receiving seed extract only (Group 2), showing normal hepatic architecture. c) Section of the liver from a diabetic rat injected with insulin (Group 3), showing some dilatation of the CV and blood sinusoids (arrows). d) Section of the liver from a diabetic rat injected with insulin and received seed extract (Group 4), showing normal hepatic architecture. Hematoxylin and eosin stain, scale bars 100 μm.
plates radiating from the central veins. These plates of hepatocytes were separated by blood sinusoids (Figures 1a, b, d). Liver sections from Group 3 showed dilatation and congestion of both the central veins and the blood sinusoids (Figure 1c).

**Renal cortex.** Stained sections of the renal cortex from rats of Groups 1, 2, and 4 showed normal renal corpuscles, and proximal and distal renal tubules. The renal corpuscles showed patent capsular space with no proliferation of mesangial cells. Sections of the proximal

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**Figure 2** - Histological results showing: a) section of the kidney cortex from a controlled rat (Group I), showing a normal renal corpuscle with patent capsular space (arrow) and numerous proximal (P) but fewer distal (D) convoluted tubules, b) section of the kidney cortex from a control rat receiving seed extract only (Group 2), showing normal renal cortex architecture, arrow - capsular space; P - proximal convoluted tubules, D - distal convoluted tubules, c) section of the kidney cortex from a diabetic rat injected with insulin (Group 3), showing thickening of the arterial walls (A), venous dilatation (V), perivascular mononuclear cellular infiltration (arrowheads), and shrinkage of some glomeruli (arrow), d) section of the kidney cortex from a diabetic rat injected with insulin and received seed extract (Group 4), showing almost normal renal cortex architecture (Hematoxylin and Eosin stain, scale bars 100 µm).

**Figure 3** - Histological results showing: a) section of kidney medulla from a control rat (Group 1), showing normal collecting tubules, b) section of kidney medulla from a control rat receiving seed extract only (Group 2), showing normal collecting tubules, c) section of kidney medulla from a diabetic rat injected with insulin (Group 3), showing disintegration of tubular cells with their necrosis and desquamation (arrows), d) Section of kidney medulla from a diabetic rat injected with insulin and received seed extract (Group 4), showing normal collecting tubules (Hematoxylin and Eosin stain, scale bars 100 µm).
convoluted tubules were more numerous in comparison to fewer sections of distal convoluted tubules (Figures 2a, b, & d). Sections of the kidney cortex from rats of Group 3 showed thickening of the arterial walls, venous dilatation, and perivascular mononuclear cellular infiltration. Many renal corpuscles showed shrinkage or segmentation of their glomeruli (Figure 2c).

Renal medulla. Stained sections of the renal medulla from rats of Groups 1, 2, and 4 showed normal renal collecting tubules with normal interstitium (Figures 3a, b, d), while sections from rats of group 3 showed marked degeneration, necrosis, and desquamation of collecting tubular epithelium (Figure 3c).

Discussion. The efficacy of an aqueous extract from date seeds has been tested successfully in the glycemic control of type 1 DM in rats. The previous results encouraged the authors to conduct a study aiming to investigate the safety of the date seed extract administration by studying the biochemical and histopathological changes in the liver and kidney of healthy rats treated with the date seed extract. This study also aimed to compare between the effect of diabetes on liver and kidney of rats treated with the combination of insulin and date seed extract versus those treated with insulin as a single drug for treatment of diabetes.

Biochemical studies were performed to test the liver and kidney functions of rats in all groups. The biochemical indices evaluated in the present study are useful parameters to indicate impairment in the functional capacities of such organs. Liver functions were evaluated by measuring serum ALT, AST, and γ-GT activities. The levels of BUN and serum creatinine were estimated to assess the functional capacity of the kidney. The present results showed an increase in the mean values of the biochemical indices in the sera of rats of Group 3. Similar changes in the mean values of those indices in the case of diabetic rats and human were reported before. The mean values of all parameters tested were significantly higher in rats of Group 3 compared to those of Groups 1 and 2. With the exception of serum ALT, a significant difference was also observed between the values in rats of Group 3, and those in rats of Group 4. No significant change was detected in the mean values of all parameters tested when comparing Groups 1, 2, and 4 with each other. Accordingly, there is no apparent toxic effect of the date seed extract on the liver and kidney functions of healthy rats when administered daily for 8 weeks. Furthermore, the use of a combination of insulin and date seed extract decreases significantly the mean values of all tested parameters toward normal, when compared with insulin used as a single drug, thus improving liver and kidney functions, and minimizing toxic effects of diabetes on such organs.

Histological results showed that the liver of healthy rats treated with date seed extract for 8 weeks (Group 2) exhibited normal hepatic architecture. The picture was more or less similar in the case of diabetic rats treated with insulin and date seed extract (Group 4). On the other hand, liver sections from diabetic rats treated with insulin (Group 3) showed histopathological changes in the form of dilatation and congestion of both central veins and blood sinusoids. Regarding the kidney, sections obtained from rats of Groups 2 and 4 showed normal renal cortex and medulla. However, sections of kidney from rats of Group 3 showed the picture of vasculitis with thickening of the arterial walls and perivascular mononuclear cellular infiltration. In addition, focal shrinkage of glomeruli, as well as, focal degeneration and necrosis of collecting tubular epithelium were also observed. Similar histopathological changes in liver and kidney of diabetic rats and human were reported before. The present results reported the absence of histopathological changes in liver and kidney of healthy rats taking a daily ingestion of date seed extract for 8 weeks (Group 2) indicating the safety of extract ingestion for the given period. Furthermore, the apparently normal histological picture of liver and kidney of rats of Group 4 versus the damage observed in rats of Group 3 would suggest that the combination of insulin and date seed extract minimize the histopathological effects of diabetes on liver and kidney when compared to insulin administration for the same period.

The effect of multiple dosages of the extract, as well as the effect of extract for longer durations was not tested, and this limits our study. Furthermore, histopathological data observed were not evaluated quantitatively. In addition, this study had aimed to include a fifth group of diabetic rats taking daily ingestion of 10 ml of seed extract alone, however, most animals died in the beginning of the experiment. A previous study on the efficacy of date seed extract as a hypoglycemic agent reported a lag period of approximately 2 weeks between the time of administration of the extract and the manifestation of its effect, and suggested that this lag period with no apparent hypoglycemic effect was the possible cause of high mortality rate of rats in Group 5. Animals of such group might suffer from high blood glucose levels for a relatively long period without effective treatment.

In conclusion, date seed extract administration is apparently safe. Compared with insulin administration as a single drug, insulin-date seed extract combination minimizes the toxic effects of diabetes on the liver and kidney. The present results would encourage further studies to investigate the effect of dosage variations.
and duration of administration of the extract on the structure and function of vital organs. Investigation of the mechanism of action, by which insulin-date seed extract combination minimizes the toxic effects of diabetes would be also essential to determine whether this is due to the additive hypoglycemic effect of the extract, and/or to an additional property of the extract.

The results would encourage testing of the efficacy of the date seed extract, as a supplement for insulin in the treatment of DM in humans.

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References