Ajwa Seeds (*Phoenix dactylifera* L.) Suspension Exerted Antidiabetic and Antihyperlipidemic Effects Against Streptozotocin-Induced Diabetes in Rats by Downregulating Insulin Expression in the Pancreatic Beta Islets

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Submitted: 18 April 2021 – Revised version received: 29 April 2021 – Accepted: 11 May 2021 – Published online: 26 August 2021

**Abstract**

**Objectives** This study investigated the antidiabetic and antihyperlipidemic effects of the powdered seeds of Ajwa Al-Madina in streptozotocin (STZ)-induced diabetes in rats. Besides investigating the possible underlying mechanisms.

**Methods** Rats were assigned to one of six groups (*n* = 5) as follows: normal control, vehicle control, Ajwa seeds control, diabetic control, Diabetic + Metformin, and Diabetic + Ajwa seeds. Metformin and Ajwa seeds were injected into rats orally via oral gavage 6 days/week along 4 weeks period.

**Results** Ajwa seeds decreased fasting serum glucose, increased fasting serum insulin and decreased fasting serum triglycerides cholesterol, low-density lipoprotein, and increased fasting serum high-density lipoprotein. Besides, it upregulated insulin protein immunoexpression in the beta cells of Langerhans islets. Ajwa seed also preserved the normal histological structure of the pancreatic beta cells tissue.

**Conclusion** Ajwa seeds produced significant hypoglycemic and hypolipidemic effects in diabetic rats mainly through enhancement of insulin secretion. The plant is a promising adjunctive therapy in diabetes mellitus treatment.

**Keywords** Ajwa seeds, glucose, insulin, histopathology, lipids, immunoexpression

**Introduction**

Diabetes mellitus (DM) is one of the world’s fastest-growing health issues in the twenty-first century. It is one of the leading causes of death worldwide. If not treated properly, it can cause chronic health problems, especially cardiovascular, renal, and nerve complications. According to the International Diabetes Federation (IDF), the global prevalence of DM is projected to rise from 425 million patients in 2017 to 629 million in 2045. In the Middle East, DM claimed the lives of 38.7 million people between the ages of 20 and 79 years in 2017.1,2 DM is one of the most prevalent health problems in Saudi Arabia (SA).3 DM has also increased tenfold in SA over the last three decades.4 While there are several oral drugs available to treat DM, the majority of them are ineffective at preventing serious complications, regulating blood glucose levels, and are associated with numerous side effects.5

In the last century, herbal medicines have gained popularity. Before the introduction of medications, traditional healers used herbal products to cure DM. A plant extract is a mixture of organic chemicals derived from some portion of the plant. As a result, they are healthy since they are organic and thus less dangerous and have fewer adverse reactions.6,7 Many fruits’ seeds are used in traditional and herbal medicine to prevent diseases, relieve stress, and minimize side effects.7

Dates (*Phoenix dactylifera* L., family Arecaceae) are a common fruit in the Arab World. It is regarded as a major nutritional and economic product.8 In Egypt, SA, and other Middle East countries, it is the most important crop.9 *Phoenix dactylifera* (*Ph. dactylfera*) seeds are normally discarded by the fruit industry as byproducts. These seeds have often been roasted, ground, and used as a caffeine-free coffee substitute, either pure or mixed with coffee, as well as animal feed.10 The various parts of *Ph. dactylfera* are popularly used to manage a variety of ailments, including neurological diseases, memory deterioration, paralysis, hyperthermia, and coma.11 Date fruits and seeds, in the form of powder, pulp, and infusion, are commonly used in research to treat atherosclerosis, malignancy, asthenia, pulmonary ailments, and throat infections. Date fruits and seeds are also used as an antidiarrheic, hypoglycemic, expectorant, tonic, aphrodisiac, and mouthwash.12

Ajwa is a form of the date that is only grown in SA/Al-Madinah Al-Munawara and has a high medicinal value. The health benefits of Ajwa dates have been recorded in hadith, with Saud (R.A) narrating, “If anyone takes seven Ajwa dates in the morning, neither magic nor poison can harm him that day”.13 Ajwa date seed extracts were found to have an antihyperglycemic activity in laboratory animals in several recent studies.14,15 However, the mechanism underlying this effect remains unknown and requires further investigation and evidence.

This study aims to examine if the powdered seeds of Ajwa Al-Madina have a therapeutic impact on DM induced by streptozotocin (STZ) in rats, and if so, what the mechanism is.

**Materials and Methods**

**Drugs and Chemicals**

STZ was obtained from Sigma-Aldrich, USA. Metformin (Glucophage, 500 mg, Merck Santé, France) from Alnahdi pharmacy, SA. Ajwa seeds were gathered from Ajwa dates, Oasis Lina, Al-Madinah Al-Munawara, SA.

**Ajwa Seeds Aqueous Suspension**

The seeds were separated from the fleshes, and the deposit was cleaned. Seeds were air-dried at ambient temperature for 15–21 days. The dried seeds were ground into a fine powder using a hammer mill. One-gram Ajwa seeds powder was mixed with 10 ml Tween-80 to make seeds suspension (Figure 1).
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Determination of Ajwa Seeds Volatile Constituents

Solid-phase extraction-gas chromatography/mass spectrometry (SPE-GC/MS) analysis was performed based on the recently published method of \(^{17}\) at the Analytical Chemistry Unit, Assiut University, Assiut, Egypt.

Animals

Thirty adult Wistar rats (150 g - 250 g body weight) were obtained from King Fahad Research Centre, King Abdulaziz University (KAU), Jeddah, SA. The rats were maintained for one week under the standard laboratory circumstances of temperature, humidity, and light/dark cycle (12:12 h). During the adaptation period, the rats could drink and eat free.

Ethical Approval

The study design was accepted by the Biomedical Ethics Research Committee (registration number: 346-19), College of Medicine, KAU, Jeddah, SA.

Induction of Diabetes

The rats were given a single injection of STZ (35 mg/kg) intraperitoneally.\(^{18}\) Fasting blood glucose levels were measured using the ACCU-CHEK apparatus after seven days. Glucose levels higher than 200 mg/dl were identified as diabetes rats\(^{19}\) (Figure 2).

Experimental Groups

Rats were assigned to one of six groups (\(n = 5\)) as follows:

1- Normal control (NC) group: rats received 2 ml distilled water.
2- Vehicle control (VC) group: rats received 2 ml tween 80.
3- Ajwa seeds control (AC) group: rats received 2 ml Ajwa seeds suspension (1 g/kg).\(^{20}\)
4- Diabetic control (DC) group: diabetic induced rats received 2 ml distilled water.
5- Diabetic + Metformin (DM) group: diabetic rats received 2 ml metformin solution (150 mg/kg).\(^{21}\)
6- Diabetic + Ajwa seeds (DA) group: diabetic rats received 2 ml Ajwa seeds suspension (1 g/kg).

Metformin and Ajwa seeds were injected into rats orally via oral gavage 6 days/week along 4 weeks period (Figure 2).

Obtaining Samples

Four weeks after treatment protocol administration, rats were starved overnight and were sedated with ether for blood withdrawal from the heart (heart puncture technique). Blood samples were centrifuged at 3500 rpm for 15 minutes under cooling conditions then the sera were separated and kept frozen at \(-80^\circ C\). After that, the rats were killed and dissected, and all pancreases were excised, washed in 0.9 percent saline, and stored either frozen at \(-80^\circ C\) or in a 10% buffered formalin solution (Figure 2).

Assessment of Fasting Serum Glucose

Fasting serum glucose concentrations were determined using Diagnostics Reactivos GPL, Barcelona, Spain colorimetric kit according to the brochure instructions.

Assessment of Fasting Serum Insulin

Fasting serum insulin concentrations were determined using Immunospec, CA ELISA kit according to the brochure instructions.

Assessment of Fasting Serum Lipid Profile

The fully automated technique using ELISA, (Dynex) was used to measure fasting serum lipid profile (triglyceride (TG), cholesterol (CHOL), low-density lipoprotein (LDL), and high-density lipoprotein (HDL)) according to the instruction brochure accompanying the kits.

Histopathological Study (Hematoxylin and Eosin (H & E) Staining)

Formalin-fixed pancreases were processed in the histology lab, pathology department, King Abdulaziz University, SA, and were stained with H & E. The sections were then examined under the light microscope by a blind pathologist.
**Immunohistochemical Study (Insulin and Nuclear Factor kappa Beta (NF-κB))**

For determining the presence and secretion of insulin in pancreatic beta cells, the sections were stained immunohistochemically for insulin using. For determining the inflammatory cells in the sections, the pancreas sections were stained immunohistochemically for NF-κB.

An immunoperoxidase (peroxidase/anti peroxidase, PAP) protocol was utilized to stain the pancreas segments for insulin and NF-κB proteins. The antibodies (bought from Lab Vision, Fremont, CA) were diluted in 1:200 dilution. The segments were analyzed and phototed, utilizing light microscopy.

**Data Analysis**

The averages ± standard errors were used to display the data. The data were analyzed statistically using a one-way analysis of variance (ANOVA) and Tukey's post-hoc test. A P-value of less than 0.05 was used as the significant level. SPSS for Windows, version 22, Armonk, NY was used to conduct the data analysis.

**Results**

**Ajwa Seeds Volatile Constituents**

Table 1 showed of the volatile active constituents of Ajwa seeds powder.

**Effect of Ajwa Seed and Metformin on Fasting Serum Glucose Measured in Control and Diabetic Rats**

There were no significant differences between the serum glucose concentration of the three control groups (NC, VC, and AC). The DC group showed a significantly increased serum glucose concentration compared to the NC group (P < 0.001). Treatment of DC group with metformin and Ajwa seed suspension significantly decreased serum glucose concentration compared to DC group (P < 0.001). Ajwa seed suspension significantly decreased serum glucose concentration compared to the DM group (P < 0.05) (Fig. 3).

**Effect of Ajwa Seed and Metformin on Fasting Serum Insulin Measured in Control and Diabetic Rats**

The DC group showed a significantly decreased serum insulin concentration compared to the NC group (P < 0.001). Treatment of DC group with metformin and Ajwa seed suspension significantly increased serum glucose concentration compared to DC group (P < 0.001). Ajwa seed suspension significantly increased serum glucose concentration compared to the DM group (P < 0.001) (Fig. 4).

**Effect of Ajwa Seed and Metformin on Serum Lipids Profile Measured in Control and Diabetic Rats**

There were no significant differences between various serum lipids concentrations of the three control groups (NC, VC, and AC). The DC group showed significantly increased serum TG, CHOL, and LDL concentrations compared to the NC group (P < 0.001). On the other hand, serum LDH concentration was decreased in the DC group compared to the NC group (P < 0.001). Treatment of DC group with metformin and Ajwa seed suspension significantly decreased serum TG, CHOL, and LDL concentrations compared to DC group (P < 0.001). Furthermore, treatment of DC group with metformin and Ajwa seed suspension significantly increased serum HDL concentration compared to the DC group (P < 0.001). Ajwa seed suspension significantly decreased serum LDL concentration compared to the DM group (P < 0.001) (Table 2).
Fig. 3 Effect of Ajwa seed and metformin on fasting serum glucose measured in control and diabetic rats. Data were displayed as averages ± standard errors. ‘*’ displayed significant difference compared to NC. ‘*’ displayed a significant difference compared to DC. ‘**’ displayed a significant difference compared to DM. ‘***’ displayed significant difference at P < 0.001. ‘*’ displayed significant difference at P < 0.05.

Fig. 4 Effect of Ajwa seed and metformin on fasting serum insulin measured in control and diabetic rats. Data were displayed as averages ± standard errors. ‘*’ displayed significant difference compared to NC. ‘*’ displayed a significant difference compared to DC. ‘**’ displayed a significant difference compared to DM. ‘***’ displayed significant difference at P < 0.001.

**Table 2. Effect of Ajwa seed and metformin on serum lipid profile measured in control and diabetic rats**

| Groups | TG (mg/dl) | CHOL (mg/dl) | LDL (mg/dl) | HDL (mg/dl) |
|--------|------------|--------------|-------------|-------------|
| NC     | 101 ± 1.4  | 117 ± 2.9    | 29 ± 0.27   | 21 ± 0.78   |
| VC     | 97 ± 3.2   | 125 ± 0.34   | 29 ± 0.92   | 17 ± 1.9    |
| AC     | 102 ± 0.5  | 125 ± 0.73   | 27 ± 1.2    | 19 ± 1.3    |
| DC     | 124 ± 2.9  | 144 ± 1.7    | 43 ± 0.63   | 8 ± 0.15    |
| DM     | 105 ± 1.3  | 127 ± 2.1    | 36 ± 0.77   | 13 ± 0.15   |
| DA     | 101 ± 1.2  | 132 ± 2.2    | 29 ± 1.6    | 13 ± 0.2    |

Data were displayed as averages ± standard errors. ‘*’ displayed significant difference compared to NC. ‘*’ displayed a significant difference compared to DC. ‘**’ displayed a significant difference compared to DM. ‘***’ displayed significant difference at P < 0.001.

**Effect of Ajwa Seed and Metformin on Histopathological Changes in Control and Diabetic Rats Pancreas**

As shown in Fig. 5 islets of Langerhans of NC pancreas revealed normal morphology. Also, there were normal density and distribution of different cell populations. The Beta cells were apparently larger in size and were most central in position, their nuclei were lightly stained (active) and centrally located. Blood capillaries between the cells were thin-walled and compressed. In VC and AC groups there was no alteration in the normal cell density of islets cells. In the DC group, the islets showed central cells with a larger size, homogenous acidophilic cytoplasm, degenerated small, and even lost nuclei. In the DM group preservation of normal islet morphology, and cell density was observed. The apparent increase in the size of central cells is evident. More evident preservation was observed in the islets of the DA group.

**Effect of Ajwa Seeds on Pancreatic Immunoperoxidase of Insulin Observed in Control and Diabetic Rats’ Pancreas**

As shown in Fig. 6 islets of Langerhans of NC pancreas showed highly positive staining for insulin which was observed in a large population of centrally located cells in Langerhans islets. In VC and AC groups no alteration was observed in immunostaining for insulin compared to the NC group. In the DC group, a significant decrease in positive insulin-immunostained cells was observed where they apparently looked enlarged compared to those of the NC. In DM and DA treated groups a significant increase of insulin-immunostained cells was observed compared to the DC group.

**Discussion**

Diabetes mellitus is a long-term condition that is linked to several metabolic problems. Hyperglycemia, or high blood glucose, is the most prevalent sign of diabetes. The underlying causes of diabetes are either a lack of insulin production or insulin resistance or both. Chemical medicines have been
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**Conclusion**

Ajwa seeds possess antidiabetic and antihyperlipidemic effects against STZ-induced diabetes in rats. The preservation of beta cells in the pancreas and induction of insulin secretion is the most likely mechanism by which Ajwa seeds exerted their antidiabetic action in this model. As a result, Ajwa seeds could be used in conjunction with dietary and pharmacological therapy to improve diabetes control.

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