Jurnal Ilmiah Mahasiswa Kedokteran Universitas Airlangga

JUXTA: Jurnal Ilmiah Mahasiswa Kedokteran Universitas Airlangga
2024 August, XV (02)

ORIGINAL ARTICLE

Effect of Ajwa Date Fruit (*Phoenix dactylifera*) Methanol Extract on Blood Glucose Levels in Mice with Diabetes Mellitus

Anggita Annisa Wahyu Dewanti[1], Joni Susanto[2*], Dwi Apriliawati[3], Tri Hartini Yuliawati[2]

[1]Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia.
[2]Department of Anatomy, Histology, and Pharmacology, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia.
[3]Department of Public Health and Preventive Medicine, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia.

* Corresponding author: joni-s@fk.unair.ac.id

ABSTRACT

Introduction: High diabetes mellitus (DM) cases result in costly medical expenses. Ajwa date fruit contains triterpenoids, carbohydrates, and flavonoids believed to lower blood glucose, which requires research validation using methanol extract on streptozotocin (STZ)-induced mice. This study aimed to determine the effect of methanol extract of Ajwa dates with several dose levels, namely 3 g/WB, 5 g/WB, and 7 g/WB, given orally to mice induced by STZ.

Methods: This study utilized a randomized pre- and post-test control group design to assess Ajwa date fruit methanol extract effects on blood glucose in Swiss-Webster mice (*Mus musculus*). The mice were divided into four groups: Group K (6 mice without date extract intervention), P1 (6 mice with 3 g/WB/day oral dose date extract intervention), P2 (7 mice with 5 g/WB/day oral dose date extract intervention), and P3 (7 mice with 7 g/WB/day oral dose date extract intervention) and were induced with 100 mg/WB streptozotocin. Administered daily for three weeks, Ajwa dates fruit extract showed varying impacts. Weekly blood glucose measurements and analysis of variance (ANOVA) in the International Business Machines Corporation (IBM) Statistical Package for the Social Sciences (SPSS) version 27.0 disclosed significant group differences, with a $p<0.05$ considered statistically significant.

Results: Post-test blood glucose measurements in the third week showed a significant difference ($p=0.017$), with an optimal reduction in P3 (7 mice with 7 g/WB/day oral dose date extract intervention).

Conclusion: In the third week, Ajwa dates fruit extract, at an optimal 7 g/WB dose, effectively reduced blood glucose levels via flavonoid hypoglycemic mechanisms.

Highlights:
1. The widespread incidence of DM leads to costly treatments and often results in undesirable side effects.
2. Flavonoids in Ajwa date fruit are believed to lower blood glucose levels through several mechanisms.
3. Methanol extract of Ajwa date fruit can effectively lower blood glucose levels in diabetic mice at specific optimal doses.

ARTICLE INFO

Article history:
Received 01/03/2024
Received in revised form 07/19/2024
Accepted 08/05/2024
Available online 08/10/2024

Keywords:
Ajwa date fruit (*Phoenix dactylifera*),
Blood glucose levels,
Diabetes,
Diabetes mellitus,
Mice (*Mus musculus*).

Cite this as:
Dewanti AAW, Susanto J, Apriliawati D, *et al*. Effect of Ajwa Date Fruit (*Phoenix dactylifera*) Methanol Extract on Blood Glucose Levels in Mice with Diabetes Mellitus. *JUXTA J Ilm Mhs Kedokt Univ Airlangga* 2024; 15: 94–99.

JUXTA: Jurnal Ilmiah Mahasiswa Kedokteran Universitas Airlangga
p-ISSN: 1907-3623; e-ISSN: 2684-9453
DOI: https://doi.org/10.20473/juxta.V15I22024.94-99

Introduction

Diabetes mellitus (DM) is a chronic metabolic disease that occurs when the pancreas cannot produce enough insulin or the body cannot use the insulin produced effectively. It is characterized by persistent hyperglycemia and high hemoglobin A1c (HbA1c) levels. Over time, continuous hyperglycemia can cause serious clinical manifestations and can be a source of various diseases, such as stroke, hypertension, kidney failure, blindness, amputation, and even death.[1] DM is also an incurable disease. The patients must undergo lifelong treatment to control blood glucose levels and HbA1c and prevent further complications at a cost that is not cheap.[2] In general, diabetes is divided into 2 main types: type 1 DM, caused mainly by the autoimmune destruction of pancreatic β cells that produce insulin, and type 2 DM, which is caused by impaired insulin secretion and resistance to insulin action.[3]

The World Health Organization (WHO) stated that the number of diabetics worldwide increased from 108 million in 1980 to 422 million in 2014.[4] In 2019, diabetes ranked the 9th highest cause of death, with an estimated 1.5 million cases of death, and 48% of all cases of death from diabetes occurred before the age of 70 years old.[4] In 2021, the number of deaths due to DM reached 6.7 million cases in the world, 747,000 cases in Southeast Asia, and 235,000 cases in Indonesia.[4] According to the International Diabetes Federation (IDF), in 2021, the prevalence of DM between 20-79 years old reached 537 million worldwide and 90 million cases in Southeast Asia.[4] The worldwide health expenditure caused by DM is at least 966 billion dollars and has increased by 316% over the last 15 years. In Indonesia, the prevalence of DM reached around 19 million cases in 2021.[5] According to IDF, in 2021, the number is expected to increase to 23 million cases by 2030 and 28 million cases by 2045.[5] Diabetes treatment is conventionally conducted with pharmacological therapy, which uses several drugs, such as metformin, thiazolidinediones, sulfonylureas, DPP-IV inhibitors, SGLT-2 inhibitors, and insulin therapy.[6] This pharmacological therapy is fairly effective in controlling the blood glucose levels of diabetics. However, this therapy can also cause annoying side effects in some people, such as nausea, tremors, dizziness, constipation, and hypoglycemia.[7] In addition, this therapy can also pose a risk, especially in elderly patients with cognitive impairment, high risk of hypoglycemia, and chronic diseases.[6]

Phoenix dactylifera, better known as Ajwa date fruit, is believed to have potential for antidiabetic therapy. According to some studies, Ajwa dates have a relatively high content of triterpenoids, carbohydrates, and flavonoids.[8] Flavonoids in Ajwa dates include flavanone antioxidants, which have three mechanisms of action in hypoglycemic effects: inhibiting phosphodiesterase, inhibiting intestinal mucosal GLUT-2, and reducing oxidative stress (OS).[9] Inhibition of phosphodiesterase can induce cAMP/cGMP accumulation and has insulin secretagogue activity (promotes insulin production).[10] Inhibition of GLUT-2 can inhibit glucose transport and reduce glucose levels in the blood while reducing OS can reduce the risk of complications from DM by inhibiting intracellular free radical production and increasing the ability of defense enzymes against free radicals.[11,12]

Febrianti (2018) conducted a study by lowering the blood glucose levels of pregnant mice with a methanol extract of Ajwa dates at doses of 3.12 gr/WB mice, 5.2 gr/WB mice, and 7.28 gr/WB mice.[13] In the study, the dose of 7.28 gr/WB became the most optimal dose.[13] Considering the urgency of DM treatment and the hypoglycemic effect of flavonoids through the mechanism of reducing OS, inhibition of intestinal mucosal GLUT-2, and inhibition of phosphodiesterase, the study was conducted to prove the hypoglycemic effect of flavonoids in Ajwa dates through experimental animals with induction of DM. This study was conducted in the Laboratory of Biochemistry Experimental Animal of the Faculty of Medicine, Universitas Airlangga, Surabaya, to determine the effect of methanol extract of Ajwa dates with several dose levels, namely 3 g/WB, 5 g/WB, and 7 g/WB given orally to mice induced by streptozotocin (STZ).

Methods

This experimental study used animal models of DM, white male Swiss-Webster mice (*Mus musculus*) strain as the object of the study. This study used a randomized pre- and post-test control group design, which measured dependent variables at the beginning and the end of the study. This study used four groups: one control group and three treatment groups (divided based on the dose of date extract 3 g/WB/day, 5 g/WB/day, and 7 g/WB/day). The entire group of mice was induced with STZ 100 mg/WB to make mice diabetic. All treatment groups were given date extract according to the dose distribution for 3 weeks. The control group was not given date extract. All control and treatment groups were given a standard diet and drank water ad libitum during the intervention/for 3 weeks. Blood glucose levels were measured weekly.

Methanol extract from Ajwa date fruit made using the maceration method (cold extraction) aims to maintain the integrity of the desired compound during the extraction process. Dates that have been thinly sliced and then oven until dried within 2 x 24 hours with a temperature of 80°C.[13] The flesh of dried dates is weighed as much as 500 grams and mashed into powder. After becoming powder, dates are then macerated using methanol solvent in a ratio of 1:2. The solution is allowed to stand for 2 x 24 hours, then separated until filtrate and residue are obtained. The filtrate obtained is then evaporated using a rotary evaporator.[8] The extraction of Ajwa dates is in the form of a thick brown extract. The results of this extraction are known to still contain glucose, especially glucose, fructose, and sucrose compounds, because these compounds do not have a boiling point and cannot be evaporated.[8] In this study, giving methanol extract of Ajwa dates to DM mice could be assumed to be like people who eat dates.

In this study, the data obtained was collected and tabulated and then tested for normality to determine the use of parametric or nonparametric statistical difference tests. The data were declared normally distributed if the

significance result was $p>0.05$ on the Kolmogorov-Smirnov test. Then, it was continued with the homogeneity test using the International Business Machines Corporation (IBM) Statistical Package for the Social Sciences (SPSS) version 27.0.[14] This homogeneity test was a requirement in one-way analysis of variance (ANOVA), where the data was called homogeneous if the significance value was $p>0.05$. If the data was normally distributed and homogeneous, difference analysis could be performed using the one-way ANOVA test. If a difference was obtained, it could be continued with the post-hoc test. If the data distribution was abnormal, the data was analyzed using Kruskal-Wallis's difference test, which continued with the Mann-Whitney test. If the data was not homogeneous, the ANOVA Brown Forsythe/Welch test was performed.[14]

A post-hoc test was performed to analyze the differences between groups more deeply. SPSS facilitates statistical calculations. If a meaningful price greater than the price of α=0.05 was obtained, the null hypothesis (H0) was accepted, and if a meaningful price was smaller than the price of α=0.05, H0 was rejected.

This study received ethical approval from the Health Research Ethics Committee of the Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia, with reference No. 148/EC/KEPK/FKUA/2023 dated 06/15/2023.

Results

This study divided the intervention group into 4 groups, namely Group K (group of mice with induction of STZ 100 mg/WB, standard diet, and without administration of Ajwa date extract, control), P1 (group of mice with induction of STZ 100 mg/WB, standard diet, and administration of Ajwa date extract per-oral dose 3 g/WB day), P2 (group of mice with induction of STZ 100 mg/WB, standard diet, and Ajwa date extract per-oral dose 5 g/WB day), and P3 (group of mice with STZ induction 100 mg/WB, standard diet, and Ajwa date extract per-oral dose 7 g/WB/day). The treatment was given for 3 weeks, and blood glucose levels were measured weekly.

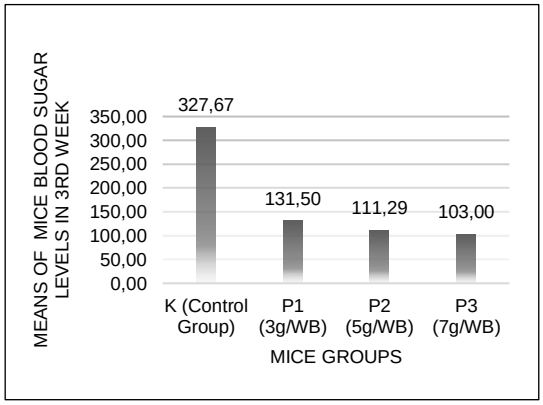

Figure 1. Means of mice blood glucose levels in 3rd week

Table 1 shows paired t-test results, average, and standard deviation of blood glucose levels before and after STZ induction in mice. Based on the paired t-test, there was a significant increase in blood glucose levels before STZ induction and after STZ induction in all groups ($p<0.05$). This suggests that STZ induction can cause hyperglycemia in mice.

Table 1. Blood glucose levels of mice before and after STZ induction

Group	Measurement Time	Mice Blood Glucose Levels (mg/dL) Mean ± SD	Normality Test (Kolmogorov-Smirnov)	Homogeneity Test		Paired T Test	
				Before STZ Induction	After STZ Induction	t	*p*-value
K	Before STZ induction	75.50 ± 35.70	0.200	0.129	0.717	-5.525	0.003*
	After STZ induction	214.16 ± 54.04	0.200				
P1	Before STZ induction	67.71 ± 12.85	0.200			-8.691	0.000*
	After STZ induction	349.33 ± 89.24	0.200				
P2	Before STZ induction	67.42 ± 18.41	0.200			-6.667	0.001*
	After STZ induction	306.42 ± 97.72	0.200				
P3	Before STZ induction	90.16 ± 14.79	0.196			-5.689	0.001*
	After STZ induction	280.00 ± 87.06	0.200				

*Indicating a meaningful difference.
Source: Research data, processed

Table 2 represents the results of the ANOVA test, the average, and the standard deviation of blood glucose levels after administration of the methanol extract of Ajwa dates every week. Based on the ANOVA test, a significant difference was obtained in the third week of treatment with p=0.017 ($p<0.05$). This showed that in the third week of methanol extract treatment, Ajwa date fruit can reduce blood glucose levels. The means of blood glucose levels of mice in the third week can be seen in Figure 1.

Table 2. Blood glucose levels of mice after Ajwa dates fruits extract treatment

Group	n	Mice Blood Glucose Levels (mg/dL) Mean ± SD	Normality Test (Kolmogorov-Smirnov)	Homogeneity Test	ANOVA One-Way Test
				1st Week	
K	6	270.33 ± 162.35	0.200	0.076	0.988
P1	6	272.16 ± 94.68	0.156		
P2	7	268.85 ± 56.67	0.200		
P3	7	253.28 ± 111.42	0.200		
				2nd Week	
K	6	173.66 ± 98.94	0.200	0.760	0.324
P1	6	255.16 ± 66.97	0.200		
P2	7	243.00 ± 80.54	0.200		
P3	7	198.14 ± 93.53	0.200		
				3rd Week	
K	6	327.66 ± 178.89	0.200	0.000	0.017*
P1	6	131.50 ± 40.80	0.064		
P2	7	111.28 ± 26.17	0.061		
P3	7	103.00 ± 26.95	0.200		

*Indicating a meaningful difference
Source: Research data, processed

Post-hoc test of mouse blood glucose levels in the third week showed significant differences between groups of mice. The significance value showed the most optimal reduction in blood glucose levels at a dose of 7 g/WB with a value of p=0.005 (p<0.05).

Table 3. Blood glucose levels of mice before and after Ajwa dates fruit extract treatment in the third week

Group	Measurement Time	Mice Blood Glucose Levels (mg/dL) Mean ± SD	Normality Test (Kolmogorov-Smirnov)	Homogeneity Test		Paired T Test	
				Before Treatment	After Treatment	t	*p*-value
K	Before treatment	214.16 ± 54.04	0.200	0.717	0.076	-2.032	0.098
	After treatment	327.66 ± 178.89	0.200				
P1	Before treatment	349.33 ± 89.24	0.200			5.478	0.003*
	After treatment	131.50 ± 40.80	0.156				
P2	Before treatment	306.42 ± 97.72	0.200			5.381	0.002*
	After treatment	111.28 ± 26.17	0.200				
P3	Before treatment	280.00 ± 87.06	0.200			5.972	0.001*
	After treatment	103.00 ± 26.95	0.200				

*Indicating a meaningful difference
Source: Research data, processed

Table 3 shows paired t-tests of mouse blood glucose levels before and after the third week of treatment. The significance value was significant in the treatment group, while there was no difference in the control group.

Discussion

This experimental study used animal models of DM, white male Swiss-Webster mice (*Mus musculus*) strain as the object of the study. The selection of the male Swiss-Webster mice (*Mus musculus*) strain as an experimental animal was based on the frequent use of this animal as an experimental animal in testing the level of toxicity of toxins and the influence of drugs on humans and several advantages, such as fast breeding, easy to maintain in large quantities, cheap, have considerable genetic variation and have good anatomical and physiological properties.[15] Also, male *Mus musculus* is more hormonally stable than female *Mus musculus*, thereby using experimental animals in scientific research related to the metabolic system is more appropriate. This study used a randomized pre- and post-test control group design, which measured dependent variables at the beginning and the end of the study. This study used four groups: one control group and three treatment groups (divided based on the dose of date extract 3 g/WB/day, 5 g/WB/day, and 7g/WB/day). The entire group was induced with STZ 100 mg/WB to make mice diabetic. All treatment groups were given date extract according to the dose distribution for 3 weeks. The control group was not given date extract. All control and treatment groups were given a standard diet and drank water ad libitum during the intervention/for 3 weeks. The date palm extract as an intervention agent in this study was based on a previous study that stated the suspicion that Ajwa dates contain flavonoids.[13]

Based on a comparative analysis of blood glucose level measurement before and after STZ induction of 100 mg/WB, it showed a significant increase in blood glucose levels p<0.05. This indicates that STZ induction of 100 mg/WB is proven to make mice hyperglycemic. The cytotoxic nature of STZ against pancreatic β cells makes pancreatic β cells experience massive damage, making experimental animals experience absolute insulin deficiency that causes type 1 DM.[15] The sample is expected to have a blood glucose level of >150 mg/dL.[15]

Blood glucose levels in mice were measured every week during the treatment. The treatment was given for 3 weeks. Analysis of blood glucose levels between groups after the first and second weeks of treatment showed no significant difference (p>0.05). Meanwhile, the analysis of blood glucose levels between groups after the third week

of treatment showed a significant difference (p<0.05). In the third week of treatment, the results of the post-hoc test showed a significant difference between group K with P1 (p=0.018), K with P2 (p=0.012), and K with P3 (p=0.005). This showed that the methanol extract of Ajwa dates had a hypoglycemic effect on the blood glucose levels of mice in the third week of treatment. This significant difference also showed the rate of decline in blood glucose levels according to the level of dosing, where the dose in the P3 group (7 g/WB) seemed more significant than the dose in the P2 group (5 g/WB), as well as the dose in the P2 group compared to the dose in the P1 group (3 g/WB). This is by the average blood glucose levels in the four groups, namely 327.67 mg/dL for group K, 131.50 mg/dL for group P1, 111.29 mg/dL for group P2, and 103.00 mg/dL for group P3.[13]

This study showed that the most effective date palm methanol extract was in the P3 group at a dose of 7 gr/WB. This is similar to the study conducted by Febrianti (2018), who reported that the most optimal reduction in blood glucose levels was obtained at a dose of 7.28 g/WB.[13] The decrease in blood glucose levels in this study aligns with the antihyperglycemic mechanism of flavonoid compounds in Ajwa dates, namely flavanone group flavonoids. Ajwa dates are known to have a very strong antioxidant capacity by their inhibiting concentration 50 (IC50) = 26.14 µg/mL.[16] Test positive flavonoid antioxidant compounds contained in Ajwa date fruit with hydrochloric acid reagent and magnesium powder.[16]

People with DM generally experience increased OS and a decrease in antioxidant capacity, which increases the detrimental impact of free radicals.[17] A study showed that cell damage triggered by free radicals plays an important role in the onset of diabetes.[18] Reactive oxygen species (ROS) such as H_2O_2, superoxide (O_2-), and hydroxyl radicals (OH) were identified as the cause of OS during conditions of high blood glucose levels. This is indicated by increased accumulation of lipid peroxides within cells and decreased natural antioxidants.[19] High glucose levels in the blood trigger the formation of ROS that interfere with beta cell function, causing the worsening of DM.[20] The reduction in the number of beta cells due to the increase in apoptosis and the inability of the remaining beta cells to produce insulin and excrete it becomes the cause of beta cell dysfunction.[20] Hyperglycemia in DM has been shown to cause beta cell apoptosis through an intrinsic pathway involving the molecular factor protein B-cell lymphoma 2 (BCL-2). Therefore, preventing beta cell apoptosis can be a solution to managing or treating DM.[20]

Flavonoids are secondary phenolic metabolites found in fruits, vegetables, and mushrooms. Their structure comprises 15 carbon skeletons and two aromatic rings (A and B) connected by three carbon chains. Flavonoids can be classified into six subclasses: flavonols, flavones, flavanones, isoflavones, flavanols, and anthocyanidins.[21] They naturally have anti-diabetic effects.[21] They also function as antioxidants that modulate OS in the body by neutralizing the effects of nitrogen and oxygen species to prevent disease.[22] The antidiabetic activity of flavonoids supports the regulation of carbohydrate digestion, insulin signaling, insulin secretion, glucose uptake, and adipose deposition by targeting several molecules involved in regulating multiple pathways. These include increasing β cell proliferation, promoting insulin secretion, reducing apoptosis, and improving hyperglycemia by regulating glucose metabolism in the liver.[21]

Flavonoids in Ajwa dates can inhibit the production of free radicals in cells and also increase the ability of defense enzymes against free radicals. This aims to prevent OS and vascular complications in DM. Flavonoids can potentially increase nitric oxide (NO) production, which can help improve endothelial dysfunction, improve mitochondrial function in cells, and reduce the activity of the enzyme NADPH oxidase.[12] It can also inhibit phosphodiesterase. Selective pharmacological inhibition of phosphodiesterase targeted at pancreatic β cells may be key to diabetes treatment, especially in type 2 diabetes. The role of phosphodiesterase in the pancreas is largely limited to cAMP/cGMP hydrolysis, and its inhibition can induce cAMP/cGMP accumulation, have insulin secretagogue activity, or promote insulin production.[10] Flavonoids also inhibit intestinal mucosal GLUT-2.[11] GLUT 2 is a major transporter of glucose in the intestine,[23] pancreatic β cells, small intestine, and kidneys.[11] Inhibiting GLUT-2 can inhibit glucose transport and reduce glucose levels in the blood.

Strength and Limitations

This study has several limitations. It was only conducted within 3 weeks of treatment. Therefore, it could not evaluate the effect of giving methanol extract of Ajwa dates for a longer period. Methanol extract of Ajwa dates in this study was limited to 3 doses. Hence, more varied doses are needed to determine the more optimal and toxic doses. Blood glucose levels in this study were measured only per week. More frequent measurement of blood glucose levels is needed, for example, every 3 days, to see the effect of giving Ajwa date fruit extract on blood glucose levels. In this study, extracting Ajwa dates with methanol solvent produced glucose extracts. Thus, an extraction method is needed to produce Ajwa date fruit extract without glucose content.

Conclusion

This study showed that methanol extract of Ajwa Date fruit can lower blood glucose levels with an optimal dose of 7 g/WB in the third week of treatment. However, this study has not been able to analyze toxic doses and doses that are more optimal in lowering blood glucose levels. Further research is needed on questions not answered in this study.

Acknowledgments

The authors would like to thank the Department of Biochemistry and the Department of Anatomy, Histology, and Pharmacology of the Faculty of Medicine, Universitas

Airlangga, Surabaya, Indonesia, for providing facilities to almost all this experimental study.

Conflict of Interest

The authors declared there is no conflict of interest.

Funding

This study did not receive any funding.

Ethical Clearance

This study received ethical approval from the Health Research Ethics Committee of the Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia, with reference No. 148/EC/KEPK/FKUA/2023 dated 06/15/2023.

Authors' Contributions

Conceptualization and design by AAWD, JS, DA, and THY. Conducting research by AAWD. Data retrieval by AAWD. Data collection and assembly by AAWD. Data analysis and interpretation by AAWD, JS, DA, and THY. Article drafting by AAWD. Critical revision of articles into important intellectual content by AAWD, JS, DA, and THY. Final approval of articles by JS, DA, and THY. Provided material studies, including administrative and technical ones by JS, DA, and THY. All authors reviewed and approved the final version of the manuscript.

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