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# Date Seeds Drinking as Antidiabetic: A Systematic Review

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**Abstract.** Diabetes mellitus are metabolic disorder diseases due to poor blood glucose control. The diabetic case continues increasing and efforts are needed to prevent it. This study aims to examine the effect of consumption of date palm seeds in regulating blood glucose levels. This study uses a systematic review design. A comprehensive literature search through several online databases such as Google Scholar, PubMed, and Science Direct. Articles are limited to publications between 2014-2018. The keywords used are "date seeds", "date pits", "antidiabetic", "hyperglycemia", and "antiglycemic". Results: A total of 173 articles have been identified. Based on the inclusion criteria and critical assessment of the article, 4 articles were suitable for review. Conclusion: the active substances in date palm seeds can improve oxidative stress in pancreatic beta cells so that it can restore insulin production. Consumption of date seeds has the potential to reduce blood glucose levels in hyperglycemic patients and does not change the glycemic index in normal people. It means that dates are beneficial for diabetic patients.

## 1. Introduction

The incidence of diabetes is increasing year by year. If it is not managed properly and not prevented, it will increase burden of health care cost. The prevalence of diabetes in several regions in Indonesia is quite high, thus it potentially reduces life expectancy [1]. Diabetes mellitus tends to cause complications of various disorders such as atherosclerosis, microvascular diseases of the eyes, kidneys, nerves and diabetic ulcers. There is a relationship between disorders of uric acid metabolism, albuminuria and atherogenic index in patients with diabetes mellitus [2].

Treatment of diabetic patients includes insulin therapy, diet and exercise. The use of insulin-like chemical drugs in Diabetes patients increases the risk of organs damage due to drug toxicity such as liver and kidney disorders, redness of the skin, diarrhea, and others [3]. The use of herbal medicine, which is date seeds, becomes one of the choices. The active compounds in date seeds and the role of date seeds in the health sector are getting attention. Phytochemical tests showed that dates contain many alkaloids, flavonoids, anthraquinones, saponins, terpenoids, and tannins [4]. These polyphenols play an important role as antioxidants to capture free radicals. Other study also show that the water extract of Ajwa dates contains high antioxidant [5].

Studies has shown that dates contain many active compounds such as antioxidants, antidiabetic, antibacterial, antimicrobial and immunostimulant [6-10]. Previous research has also proven that dates seed extract can reduce inflammation, through its role as an antioxidant to reduce oxidative stress [11]. Research on the use of dates flesh has been done [12-15], but the use of dates seeds still needs to be studied further. This systematic review aims to explore the working mechanism of date seeds as antidiabetic drinking.

## 2. Research methods

A comprehensive search is done on original research articles published between 2014-2018 through scientific databases in the form of, PubMed, Google Scholar, and Science Direct. The combination of keywords used is "date pits", "date seed", "hyperglycemia", "antiglycemia", and "antidiabetic". Search is done using terms in combination with Boolean operators „AND', and „OR'. Details of the methods used are listed in Figure 1. The inclusion criteria used in the systematic review of this study are original research, published in English, available full text, using experimental design and having control.

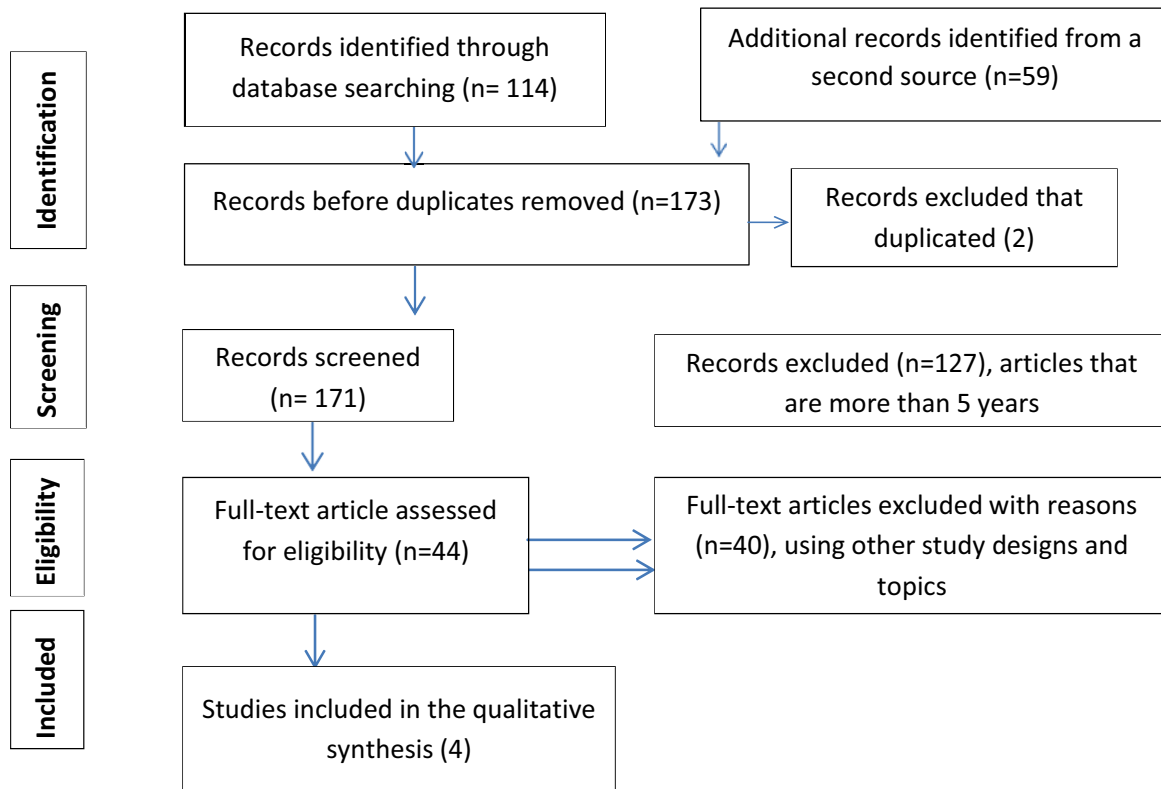


### 3. Data extraction

Critical appraisal conducted on research that meets the inclusion criteria. Data is extracted independently from research that meets the criteria in the form of structured extraction data in the table.

### 4. Data synthesis

The narrative results are summarized based on the findings from each study. Narrative synthesis is an approach in a systematic review carried out by reviewing findings in research relating to the review topic.



**Figure 1.** The selection process for articles

## 5. Result

### 5.1. Oxidative stress and diabetes

Several studies have shown that diabetes is associated with oxidative stress. Antioxidant deficiency is found either in prediabetes or diabetes stages. Free radicals can oxidize pancreatic beta cells, result in reduced insulin production. After diabetes occurs, this condition will also increase the production of free radicals so that oxidative stress gets higher. Under hyperglycemic condition, glucose in the form of a straight chain (aldehyde) is able to modify proteins, lipids, phosphatidylethanolamine, and DNA (glycation). This reaction of glucose with protein (Maillard reaction) can also occur in physiological aging. The Maillard reaction will produce various types of advanced glycosylated end products (AGEs). The buildup of AGEs will cause oxidative reactions with free radical chains, thus accelerating the occurrence of atherosclerosis, nephropathy, neuropathy, retinopathy, and cataracts in diabetes. The high

level of glucose in diabetes can also cause autoxidation, producing free radicals in the form of hydrogen peroxide, and superoxide radicals [16].

Uncontrolled hyperglycemia can cause abundant free radicals in several ways, namely increased glycolysis, activation of intercellular sorbitol pathways, glucose autoxidation, activation of NAD (P) H oxidase which depends on protein kinase C, increased flux of the hexosamine pathway, increased intracellular AGEs formation, increased receptor expression and activation of ligand AGEs and non-enzymatic glycation.

The mechanism of STZ (C<sub>8</sub>H<sub>15</sub>N<sub>3</sub>O<sub>7</sub>) and alloxan in inducing diabetes in experimental animals proves that toxic compounds (oxidants) can damage pancreatic beta cells. This compound will produce ROS, lead to an increase in the levels of radical superoxides, hydrogen peroxide and hydroxyl radicals which can potentially damage macromolecules [17].

### 5.2. *The active compound in date seeds*

Dates contain many active compounds that act as antioxidants. The antioxidant capacity of date palm seeds varies greatly depending on type and origin. The antioxidant level of Moroccan varieties varies between 10,966–22.86 mmolTrolox equivalent / 100 g DW, 4,807–8,021 mmolTrolox equivalent / 100 g DW and 0.166–0.112 g / l for FRAP, ABTS and IC<sub>50</sub> of DPPH respectively. The phenolic and flavonoid content of date seeds were found between 2697–5342 mg Gallic acid equivalent / 100 g DW and 1224–1844 mg Rutin equivalent / 100 g DW respectively [18]. The results of high-performance liquid chromatography (HPLC) analysis, date palm seeds contain the most phenolic compounds, namely Pyrogallol (59.49), Cinnamic acid (39.24), Benzoic acid (39.02), Ellagic acid (38.32), Catechol (24.68), Gallic acid (19.08), Protocatechuic acid (18.05), Syringic acid (17.84), Vanillic acid (8.33). While the main flavonoid contents are Hesperidin, Naringin, Rutin, Hesperetin, Quercetin, and Kaempferol [19].

Compare to fruit and date seeds, date has more contain of active compounds. Vitamin C, oxidative value, total phenolic, total flavonoids and more energy and protein content in dates than fruit (Herchi, Kallel and Boukhchina, 2014). Therefore, consumption of date seeds can be used as a scientific alternative to improve health and improve disruption of body cell function compared to dates [20].

### 5.3. *The antidiabetic mechanism of date seeds*

There is a relationship between high levels of free radicals and diabetes mellitus. The presence of free radicals will damage pancreatic beta cells so that insulin production is disrupted, lead to diabetes mellitus. After diabetes mellitus occurs, high free radicals will increase the risk of complications. Dates are proven to have high flavonoids and phenolics which can increase the capacity of endogenous antioxidants such as superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPx) levels and reduce free radical oxidation products [21], [22]. High antioxidant capacity can reduce oxidative stress, thereby reducing cell damage, especially pancreatic cells.

The results of other studies showed that date seed extract can stimulate endogenous insulin secretion in type 1 DM mice induced by Streptozotocin (STZ). C-peptide levels as an indicator of increased endogenous insulin secretion experienced a significant increase in diabetic mice given dates rather than that fed insulin alone [23]. The administration of dates in normal mice did not show a hypoglycemic effect. Therefore, dates are safe for consumption in healthy people. Giving seeds of dates to healthy controls was also not harmful, which is seen based on liver function tests (ALT, AST, and gamma-GT) and kidney function (BUN and creatinine), although consumed every day for 8 weeks [24]. The combination of dates with insulin can also minimize the side effects (toxic) of insulin [25].

A study *in vitro*, date seed extract 5 mg / mL has a moderate to a good inhibitory effect on  $\alpha$ -glucosidase enzymes (in the range 5,91-51,71%). While the water extract in dates has the best antidiabetic activity by inhibiting the  $\alpha$ -glucosidase enzyme, followed by methanol and ethanol [26]. Inhibition of the  $\alpha$ -amylase enzyme activity is also shown by water extracts compared to other solvents. Inhibition of the activity of  $\alpha$ -amylase and  $\alpha$ -glucosidase enzymes is one of the strategies in controlling postprandial hyperglycemia in diabetes by reducing the speed of carbohydrate hydrolysis. Both of these enzymes function to hydrolyze starch, disaccharides and long-chain carbohydrates into glucose. Glucose

absorption in the intestine decreases due to decreased activity of this enzyme. The high inhibitory ability of these two enzymes is not related to their phenolic levels.

Dates are a source of dietary fiber, phenolic compounds, and natural antioxidants. Giving dates to diabetic rats can significantly increase body weight compared to those not given dates. Giving dates for 70 days can also increase sperm count, motility and viability in diabetic rats. The higher the concentration of date palm seeds, the lower the sperm abnormality in diabetic rats [27]. Blood glucose levels also decrease along with the increasing dose of dates.

A previous studies also proved that date seed extracts can inhibit the activity of  $\alpha$ -amylase and pancreatic lipase[28]. Inhibition of the  $\alpha$ -amylase enzyme will inhibit digestion of starch, so that absorption is inhibited. This lipase enzyme has functions to digest fat so that the fat absorption process will be inhibited. If the absorption process is inhibited, blood sugar also decreases and diabetes can be prevented. The use of methanol extract showed the best results in inhibiting lipase enzyme activity. Phenolic compounds such as gallic acid, catechin, epicatechin, ellagic acid myricetin, quercetin, kaempferol, resveratrol, and anthocyanins are thought to play a role in inhibiting the activity of these enzymes.

Dates also reduce pancreatic cancer cell proliferation and DNA damage so that insulin production is maintained [29]. Aliphatic compounds in date palm seeds also have the potential to be anticancer and antibacterial [30]. Glucan compounds in dates can work as antitumors.

## 6. Conclusion

Dates contain active compounds in the form of polyphenols and phenolics. This compound works as an antidiabetic by fighting the oxidation of free radicals, repairing pancreatic cells, decreasing lipid peroxidation in the cell membrane, and inhibiting the  $\alpha$ -amylase, pancreatic  $\alpha$ -glucosidase, and lipase enzymes. Consumption of steeping dates can improve blood sugar levels and keep blood sugar levels normal. Need further research on long-term use in humans.

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Table 1. Characteristics of research using dates as antidiabetic

No	Ref.	Purpose	Design	Groups intervention	Indicator/variable	Major finding
1	[31]	to find the effect of bread supplemented with date pits on the metabolic control of diabetes through biological and histopathological evaluations	Experiments with control	The first group (6 rats) fed on a basal diet as a (negative control group). The second main group (6 rats) was injected with alloxan to induce hyperglycemia (positive control group) and then the rats fed on the same basal diet. The other 12 rats after being injected with alloxan were divided into 2 groups (3 & 4) and received basal diets containing fortified bread with 10% and 15% date pits powder for 45 days respectively.	Biological evaluation was carried out by determination of body weight gain and food intake. At the end of the experimental period: glucose, insulin, HbA1c, total cholesterol, and other lipids, and also to determine each of kidney and liver functions. Liver and Pancreas were removed to demonstrate histopathological observation.	Our results showed a significant reduction in the glucose, HbA1c, TC, TG, LDL-C, and VLDL-C, as well as reducing hazards on liver and kidney functions compared with positive control group. Histopathological observation proved that the last group diet (with 15% date pits) looked like the negative control group.
2	[32]	to evaluate the anti-diabetic, hypolipidaemic and antioxidant activities of date seed extract in diabetes-induced rats.	Experiments with control	Group I: Normal control with water (NCWT). Group II: Normal controls with Ajwa seed extract (NASE) 10 ml/day of aqueous seed extract orally. Group III: Normal controls with Sukkari seed extract (NSSE) 10 ml/ day of aqueous seed extract orally. Group IV: Diabetic control (DC). Group V: Diabetic with Ajwa seed extract (DASE) 10 ml/day of aqueous seed extract orally. Group VI: Diabetic with Sukkari seed extract (DSSE) 10 ml/day of aqueous seed extract orally. Group VII: Diabetic with Insulin treatment (DCIN) insulin 2U/Rat once per day	Fasting glucose, body weight HbA1C, insulin level SOD, MDA, 8OHdG Urea, creatinine, Lipid profile	antidiabetic property of aqueous seed extracts of two different varieties of dates namely Ajwa and Sukkari of the Kingdom of Saudi on streptozotocin-induced Diabetic rats. Prolong treatments with the extract restores the function of liver and kidney and balances the oxidative stress condition in diabetic treated rats



3	[33]	To investigate the protective effect of <i>P. dactylifera</i> seeds against diabetic complications in rats.	Experiments with control	Twenty-one rats were randomly divided into three groups, seven rats in each group: Group I (Control group): received a single intraperitoneal injection of citrate buffer vehicle. Group II (Untreated diabetic group): received a single intraperitoneal injection of STZ (50 mg/kg). Group III (aqPDS-treated group): received a single intraperitoneal injection of STZ (50 mg/kg) and daily administration of aqPDS (1 g/kg/d) by oral gavage for 4 weeks.	MDA, nitric oxide (NO), reduced glutathione, superoxide dismutase (SOD), glutathione S-transferase, and catalase. Glucose level Urea, creatinine, ALT, AST	Results: Oral administration of aqPDS significantly ameliorated the elevated levels of glucose (248 $\pm$ 42 versus 508 $\pm$ 60 mg/dl), urea (32 $\pm$ 3.3 versus 48.3 $\pm$ 5.6 mg/dl), creatinine (2.2 $\pm$ 0.35 versus 3.8 $\pm$ 0.37 mg/dl), ALT (29.6 $\pm$ 3.9 versus 46.4 $\pm$ 5.9 IU/l), and AST (73.3 $\pm$ 13 versus 127.8 $\pm$ 18.7 IU/l) compared with the untreated diabetic rats. There was a reduction in TBARS and NO levels and improvement of the histopathological architecture of the liver and kidney of diabetic rats. The aqPDS showed potential protective effects against early diabetic complications of both liver and kidney.
4	[34]	to investigate the effects of aqueous extract of black pepper and ajwa seed on liver enzymes in alloxan-induced diabetic Wister albino rats to show the preventive and ameliorating effects in hyperglycemic rats	Experiments with control	Rats were divided into 6 groups; normal control rats, diabetic control rats, glibenclamide-treated rats, black pepper treated rats, ajwa seed treated rats and black pepper plus ajwa seed treated rats. Hyperglycemia was induced in the treatments groups by a single intraperitoneal injection of alloxan at 150 mg/kg body weight. Doses were glibenclamide 10 mg/kg, black pepper 50 mg/kg, ajwa seed 500 mg/kg and their mixture 500 mg/kg body weight for a period of 8 weeks	Serum glucose, AST, ALT, and ALP	Ajwa seed and mixture significantly reduced glucose level. AST level was significantly reduced by mixture treated group. No significant difference was observed between different aqueous extract treated group in ALT and ALP level. The study indicates that black pepper and ajwa seed extract to some extent normalized the glucose and liver enzyme activities in alloxanized diabetic rats.