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Research Article

Health Benefits of Dates; Antioxidative and Selected Enzyme Modulation

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Abstract

Dates have been used for centuries to treat illnesses, chronic conditions, and to lower oxidative stress (Khalid et al., 2017; Nasir et al., 2014). The study aims to assess the total phenolics, flavonoids, in-vitro antioxidant potential and inhibitory effects of date fruits (Freeze-dried and oven-dried) extracted using two solvents (ethanol 80% & water) on activity of selected metabolizing (α-glucosidase, α-amylase, and lipase) enzymes. Oven-Dried Aqueous (ODA) extract (783 mg G.A.E/100g DW) of Medjool dates showed 1.13 to 1.48 times higher phenolic content, than Oven dried ethanol (ODE), Freeze-dried Aqueous (FDA), and Freeze-dried Ethanol (FDE). Flavonoid content ranged from 126.22 to 193.11 mg C.E/100g DW dried date samples. DPPH inhibition by date extracts ranged between 25% to 69%. Nitric Oxide Radical Scavenging (NORS) values were 1.09 to 2.74 times higher in ODA compared to other extracts. IC50 values of the fruit extracts ranged differently in terms of inhibition of α-glucosidase (36.26 – 112.93 µg/mL), α-amylase (6.54 – 18.92 µg/mL), and lipase (25.53 – 78.81 µg/mL) activity. Results indicate oven-drying to be most effective method for maintaining total phenolics and flavonoids in dried dates. Dates due to their inhibitory effects on selected enzymes can be used as monotherapy or in combination with other therapies.

Keywords: Dates; Phytochemicals; Antioxidants; Radical scavenging; Nutraceuticals

Abbreviations: FDA- Freeze dried aqueous extract; FDE- Freeze Dried 80% Ethanol extract; ODA- Oven Dried aqueous extract; ODE- Oven Dried 80% ethanol extract.; Total phenolic content- TPC; Total flavonoid content- TFC; 2,2-diphenyl-1-picrylhydrazyl radical- DPPH; ferric reducing antioxidant potential- FRAP; oxygen radical absorbance capacity- ORAC; Trolox equivalent antioxidant capacity- TEAC; nitric oxide radical scavenging- NORS

Introduction

There has been a growing interest in the potential health benefits of natural foods, especially those rich in bioactive compounds with antioxidant properties [1]. The phenolic compounds in fruits and vegetables have attracted attention because of their potent antioxidant effects [2,3]. Foods with the potential to prevent chronic diseases are in higher demand as there is growing awareness of the value of functional foods in preventing diseases. Due to the increased demand for functional foods, dates' phytochemical components and overall health advantages have been evaluated [4].

Since ancient times, humans have used dates to treat illnesses and chronic conditions because they are a vital source of free amino acids and dietary minerals [5]. Additionally, dates have been used to treat diabetes, cancer, atherosclerosis, and high blood pressure and to lower oxidative stress and boost immunity [6]. According to

compositional analysis, date fruits have shown considerable antioxidant potential through their capacity to scavenge free radicals [7]. Consuming diets high in polyphenols over the long term may offer protection against the onset of several chronic diseases, including cancer, diabetes, inflammatory disorders, CVDs, neurodegenerative diseases, and infectious diseases supported by pre-clinical and clinical research [8].

Dates are a significant source of natural antioxidants such as carotenoids, phenolics, tocopherols, flavonoids, and ascorbic acid. Depending on the genotype of the date palm and the post-harvest processing methods, these antioxidants may be present in different concentrations and forms in dates **[9]**. Dates are an excellent source of dietary fiber, even better than cereal because it contains high-quality fiber fractions like cellulose, β -glucans, and arabinoxylans [10].

The redox characteristics of phenolic compounds, which can help absorb and neutralize free radicals, quench singlet and triplet oxygen, or break down peroxides, result in their antioxidant activity [11]. The date fruit has a history of use in traditional medicines to treat cancer and several infectious diseases and to modulate the immune system [12]. The nutrients, phosphorus, iron, potassium, and a significant amount of calcium and carbohydrates are all found in dates, which are good energy sources and make them vitamin and mineral-rich [10].

Due to their capacity to affect the metabolism of glucose, polyphenols are known to have antidiabetic properties. For instance, polyphenols have been demonstrated to modulate digestive enzymes involved in carbohydrate digestion, stimulate insulin secretion by cells, activate insulin receptors, and regulate glycemia by promoting glucose uptake in insulin-sensitive tissue and by modulating hepatic glucose output [13,14]. Due to the inhibition of digestive enzymes such as α-amylase and α-glucosidase by polyphenols, glucose is reduced after eating [15] [16]. Additionally, polyphenols may alter glucose transport by GLUT transporters, particularly the insulin sensitive GLUT4 transporter. Polyphenols have been linked to GLUT4 translocation promotion in skeletal muscles and adipose tissues [17,18].

Drying may affect the quality or quantity of phytochemicals. Understanding the changes in antioxidant potential and enzyme inhibition activity induced by selected processing methods is crucial for optimizing nutritional value and functional benefits of Medjool date's. Moreover, such investigations may offer valuable insights into designing food processing and preparation strategies that preserve or enhance these bioactive properties, empowering consumers to make informed choices about the nutritional quality of the dates they consume. This study was conducted to assess the in-vitro antioxidant potential and the inhibitory effects of date fruit on α-glucosidase and α-amylase levels as an indication of anti-diabetic activity because very few studies have been done assessing the in-vitro antidiabetic impact of Medjool dates grown in California. The modulation of human pancreatic Lipase might be an advancement in the search for therapeutics that can prevent the body from absorbing fat and be used to treat obesity and other related metabolic disorders.

Materials and Methods

Sample Preparation

Medjool Dates (Natural Delights, California) were diced after the removal of seeds and freeze-dried for 72 hours (VirTis Genesis 35L SpScientific, Warminster, PA). Similarly, the dates were diced and oven-dried for 72 hours at 60°C temperature. Freeze Dried and Oven-Dried Dates were ground into a fine paste using a waring blender (Model no. 31BL92, New Hartford, Connecticut, U.S.) before extraction. Ethanol extracts (E.E.) were prepared following the method that Amazu et al. (2010) developed with slight modifications [19]. Five grams freeze-dried and oven-dried dates were soaked in 100 ml of 80 % ethanol with continuous stirring for 3 hours, following which the samples were sonicated (Branson 5800, Branson Ultrasonics Corporation, Danbury, CT 06810, U.S.A.) for 60 minutes and left soaked for 24 hours. Aqueous extracts were prepared using the same method. Both the aqueous and ethanol extracts were centrifuged at 4830×g for 20 minutes. The supernatant was filtered using a Whatman filter paper, and the filtrate was evaporated to dryness at 40°C using a rotary evaporator (Buchi Rotavapor R-215, U.S.A.). The concentrate was stored at -80°C until further use.

Moisture content

Calculation of moisture content and total solids was done using the method mentioned in AOAC, 1999. [20] and the moisture reduction after freeze-drying and oven-drying Medjool dates was calculated as given below.

$$\text{Moisture content (\%) Oven Dried} = \frac{\text{Initial weight} - \text{Dried weight}}{\text{Initial weight}} \times 100$$

Total Phenolic Content

Total polyphenols were determined following the Folin-Ciocalteu's method with slight modifications [21]. Using a gallic acid standard (Acros Organics, Fisher Scientific, Pittsburgh, PA), the absorbance of the sample was measured using distilled water blank at 750nm. The average of three samples was taken and expressed as mg gallic acid equivalents (G.A.E.)/ 100g sample.

Total Flavonoid Content

According to Marinova et al., 2005, an aluminum chloride colorimetric test using catechin as a standard was used to assess the flavonoid concentration [22]. Samples were added to 1 M NaOH along with 7.5 µL of 7.5% sodium nitrite and 15 µL of 10% aluminum chloride. After a five-minute incubation, the absorbance was measured at 520 nm. The amount of total flavonoid in each 100 g was represented as mg of catechin equivalent (C.E.).

Antioxidant Assays

DPPH (2,2-Diphenyl-1-Picrylhydrazyl) Radical Scavenging Activity

The free radical scavenging activity was determined using the Brand-Williams method [23]. DPPH (0.1M) solution was briefly added to 40 µl of samples. The absorbance was read at 517 nm for

90 min at 30 min intervals in the dark at room temperature. The percentage of DPPH inhibition was calculated as follows:

$$\%DPPH = \frac{A_{Control} - A_{Sample}}{A_{Control}} \times 100$$

Ferric Reducing Antioxidative Potential (FRAP)

The method developed by Firuzi et al. in 2005, Jimenez-Alvarez et al. in 2008, and Tsao et al. in 2003 was used to determine the FRAP assay with slight modifications using the standard [24,25] [26]. At 1-minute intervals, the absorbance was measured at 593 nm for 4 minutes. The standard ferrous sulfate () was used to compare any changes in absorbance. The analysis was conducted in triplicate, and the sample's antioxidant potential was given as mM of per 100g.

Trolox Equivalent Antioxidant Capacity (TEAC)

The protocol developed by Miller et al. (1997) was used to determine the TEAC of extracts with slight modifications [27]. A diluted 2,2'-azinobis (3-ethylbenzothiazoline-6-sulphonic acid) (ABTS) radical was added to the extracts. Then, absorbance at the wavelength of 734 nm was measured for 6 minutes at intervals of 1 minute.

Nitric Oxide Radical Scavenging Activity (NORS)

The nitric oxide radical scavenging activity was determined using Griess Illosvoy reagent [28]. Sodium Nitroprusside (10 mM) and 1 mL of extracts or ascorbic acid standard were added in phosphate buffer (pH 7.4) and were incubated at 25˚C for 150 min. Griess reagent was added to the reaction mixture (1:1). The ability of antioxidants to inhibit nitric oxide formation was determined based on the color change at 546 nm.

In-Vitro Enzymatic Assays

α-Glucosidase Inhibition Activity

α-glucosidase inhibition by date fruit extracts was determined using protocol suggested by Apostolidis et al. (2007) [29]. Phosphate buffer (50 mM; pH 6.8), enzyme and date fruit extracts were added. Sodium carbonate (0.1 M) and 1 mM pNPG was added to the samples after incubating for 30 min at 37˚C and absorbance was read at 405 nm. α-glucosidase inhibition was calculated as follows:

$$\text{Inhibition (\%)} = \frac{Abs_{405}(enzyme) - Abs_{405}(extract)}{Abs_{405}(control)} \times 100$$

α-Amylase Inhibition Activity

α-Amylase inhibition by date fruit extracts was analyzed. α-amylase and date fruit extracts were incubated for 10 min at 25˚C. Soluble starch (1%) and dinitro salicylic acid was added to the samples [29]. Samples were incubated for 10 min at 100˚C and the final absorbance was read at 540 nm. α-amylase inhibition activity was calculated as follows:

$$\text{Inhibition (\%)} = \frac{Abs_{540}(enzyme) - Abs_{540}(extract)}{Abs_{405}(control)} \times 100$$

Lipase Activity

Inhibition of pancreatic Lipase by date fruit extracts was determined using p-nitrophenyl butyrate (p-NPB) as a substrate. Date fruit extracts, Lipase and potassium phosphate buffer (pH 7.2) with 0.1% tween 80 was added to the samples and then incubated for 1 hour at 30˚C. After incubation, 25 mM of pNB (2,4 p-nitro phenyl butanoic acid) was added and incubated again for 5 min at 30˚C and absorbance was read at 405 nm [30]. The inhibitory activity of Lipase was calculated as follows:

$$\text{Inhibition (\%)} = \frac{Abs_{405}(enzyme) - Abs_{405}(extract)}{Abs_{405}(control)} \times 100$$

Statistical analysis

The statistical analysis was carried out using a t-test or ANOVA (Analysis of variance). The statistical analysis was conducted using One-way ANOVA using the SAS 9.2 version. Significant differences between means were determined using Tukey's studentized range test, and $p \leq 0.05$ was regarded as significant.

Results & Discussion

Moisture content

Calculation of moisture content was done using the method mentioned in AOAC, 1999. and the percentage moisture loss after freeze-drying was found to be 8% and after oven-drying it was 15.25 %. Therefore, the Total Solids after Freeze drying was 92g/100g and after oven drying it was 84.75g/100g calculated according to the AOAC, 1999 method [20].

Total Phenolic and Flavonoid Content

Table 1: Impact of Freeze drying and Oven drying on Total Phenolic Content and Flavonoid Content of Medjool Date Aqueous and Ethanolic Extracts

Medjool Dates	FDA	FDE	ODA	ODE
Phenolic Content (mg G.A.E /100g DW)	611.85 ± 11.71^{bx}	528.43 ± 12.58^{by}	783.1 ± 18.99^{ax}	695.93 ± 5.78^{ay}
Total Flavonoid Content (mg C.E /100g DW)	193.11 ± 4.68^{ax}	126.22 ± 6.65^{by}	184.02 ± 2.71^{ax}	170.81 ± 5.31^{ay}

*DW- Dry weight; G.A.E- Gallic acid equivalent; CE- Catechin equivalent;(n=3); FDA- Freeze dried aqueous extract; FDE- Freeze Dried 80% Ethanol extract; ODA- Oven Dried aqueous extract; ODE- Oven Dried 80% ethanol extract. The letters abc depict a significant ($p \leq 0.05$) difference between the processing methods & letters xyz depict significant differences between the solvents.

Table 1 shows the total phenolic content of date fruit, which varied significantly ($p \leq 0.05$) with drying methods and solvents. The content ranged from 528.43 to 783.1 mg G.A.E/100g D.W. This is consistent with previous studies indicating varying phenolic content in dates, such as 434.3 to 769.6 mg C.E./100 g [31], and 199.43 to 576.48 mg G.A.E./100 g F.W. [32].

Similar findings were also reported for Deglet Nour and Medjool dates by Wu et al. in 2004 [33]. The Oven-Dried Aqueous (ODA) extract of Medjool date showed the highest phenolic content (783.1 mg G.A.E /100g D.W.) compared to the lowest (528.43 mg G.A.E /100g D.W.) by Freeze-Dried Ethanol (FDE) extracts. Phenolic content was significantly ($p \leq 0.05$) higher in ODA followed by ODE, F.D.A. & FDE. The higher phenolic content was attributed to faster binding of bound phenolic compounds during the breakdown of cellular components [34]. The breakdown of complex phenolic tannins by heat and enzymatic or non-enzymatic oxidation may also contribute to increased phenolic content [35] [36]. Previous studies have shown that heat treatment significantly increases the total phenolic content of many foods, including dried apricots, tomatoes, and raisins [34] [36] [37].Top of Form

The total flavonoid content of dates in Table 1 ranged from 126.22 to 193.11 mg C.E/100g D.W., which is within the range of other studies. However, in Moroccan and Iranian date varieties, the total flavonoid concentration was found to be lower [38] [39]. Variations in flavonoid content may result from factors such as farming location, methods, growing environments, climatic factors, and storage conditions [38] [40] [41]. The flavonoid concentration in FDA extracts was slightly higher than that in ODA extracts, with a percentage difference of around 4.71%. However, this difference was not statistically significant. For ethanol (80%) extracts, oven-drying led to a significantly ($p \leq 0.05$) higher flavonoid content (35.27%) than FDE.

Antioxidant Activity of Medjool Dates

Table 2 shows the Antioxidant capacity of dates measured using DPPH, FRAP, NORS, and TEAC antioxidant assays. The study found that ODE (68.85%) extracts had a significant ($p \leq 0.05$) higher DPPH inhibition (%), followed by F.D.A., FDE, and ODA. Oven drying resulted in approximately 30% significantly($p \leq 0.05$) lower DPPH inhibition (25.35%) for aqueous extracts compared to freeze-dried extracts (54.89%). However, for ethanol (80%) extracts, oven-dried samples showed approximately 20% significantly higher ($p \leq 0.05$) DPPH inhibition (68.85%) compared to freeze-dried samples (48.36%).

The results from this study were in accordance with those from Abbes et al. (2013), who found that the antiradical activity reported for Tunisian date fruits exhibited a wide range from 27.97% to 76.40% [42]. Phenolics have antioxidant activity due to their redox properties, acting as reducing agents, hydrogen donors, and singlet oxygen quenchers. They may also have metal chelating potential [43]. The antioxidant capacity of fruits depend on total phenolic and flavonoid contents [44]. In a DPPH assay, hydrogen-donating antioxidants reduce DPPH radicals [45]. ODE has higher DPPH radical scavenging activity compared to FDA, FDE, and ODA, possibly due to higher phenolic content. A study by Suvarnakuta et al. (2011) found that drying methods significantly affect the degradation of xanthones in α-mangostin and its antioxidant capacity [46]. The data in Table 2 shows the Ferric-reducing antioxidant Potential (FRAP) of Medjool Date extracts, ranging from 127.92 to 168.7 mM Fe (II)/100g D.W. No significant differences were found between the two solvent extracts of freeze-dried samples, but ODE showed a significantly ($p \leq 0.05$) higher FRAP value of 168.7 mM Fe (II)/100g D.W. compared to ODA. Oven-dried samples showed significantly ($p \leq 0.05$) higher values when compared to the freeze-dried samples for both solvents.

Table 2: Impact of Freeze drying and Oven drying on in-vitro antioxidant activity of phytochemicals in Medjool Date Extracts (Aqueous and Ethanolic) using 2,2'-Diphenyl Picryl Hydrazyl (DPPH), Ferric Reducing Antioxidant Potential (FRAP), Nitric Oxide Radical Scavenging (NORS) and Trolox Equivalent Antioxidant Capacity (TEAC) assays

Antioxidant Assays	FDA	FDE	ODA	ODE
DPPH % inhibition	55.89 ± 1.52^{ax}	48.36 ± 4.83^{bx}	25.35 ± 1.49^{by}	68.85 ± 1.84^{ax}
FRAP activity (mM Fe (II)/100g D.W.)	127.92 ± 0.71^{bx}	131.55 ± 1.08^{bx}	150.59 ± 0.71^{ay}	168.7 ± 0.71^{ax}
NORS (mM NO/100g D.W.)	18301 ± 397^{bx}	8172 ± 427.35^{by}	22365 ± 397^{ax}	20395 ± 426^{ay}
TEAC (µg T.E. /100g D.W.)	47.88 ± 0.58^{ay}	60.37 ± 0.28^{ax}	49.54 ± 1.34^{ax}	25.54 ± 0.74^{by}

*DW- Dry weight; DPPH- 2,2-diphenyl-1-picrylhydrazyl; Fe (II)- Ferric; NO- Nitric Oxide; T.E- Trolox Equivalent; FDA- Freeze dried aqueous extract; FDE- Freeze Dried 80% Ethanol extract; ODA- Oven Dried aqueous extract; ODE- Oven Dried 80% ethanol extract. The letters abc depict a significant ($p \leq 0.05$) difference among processing methods & letters xyz depict significant differences between the solvents.

The Nitric Oxide Radical Scavenging (NORS) values for Medjool date show that ODA has significantly higher ($p \leq 0.05$) NORS activity (22365 mM NO/100g D.W.) than other extracts. Oven drying significantly increased ($p \leq 0.05$) NORS activity by 18.17% in aqueous extracts and 59.93% in ethanol extracts. FDE and ODE extracts show a significant decrease ($p \leq 0.05$) by 55.35% and 8.8% compared to FDA and ODA extracts. The antioxidant properties of phenolic compounds are influenced by their redox reaction potential, which neutralizes free radicals [47]. Sodium Nitroprusside, for example, generates nitric oxide, which interacts with oxygen to produce nitrite ions. Nitric oxide scavengers compete with oxygen, reducing nitrite ion production [48]. FDE showed significantly lowered NO activity compared to FDA, ODE, and ODA. Similar results were found for freeze-dried pomegranate extracts as reported by Noda et al. (2002) [49].

Trolox, a water-soluble Vitamin E analog, is used in the Trolox Equivalent Antioxidant Capacity (TEAC) assay. Oven drying resulted in an increase of 3.47% in TEAC value for aqueous extracts compared to freeze-dried extracts. However, oven-dried ethanol extracts showed a ($p \leq 0.05$) significant decrease of 57.69% in TEAC value compared to freeze-dried samples. Similar results for TEAC assay were found in study by Biglari et al., (2008) in which the values ranged from 22 to 54 µM T.E. /100g DW for different varieties of dates. The ABTS radical, generated by potassium persulfate, determines the antioxidant activity of hydrogen-donating antioxidants. FDE had a higher TEAC value due to its ability to donate hydrogen and convert free radicals into stable form [50]. ODE showed a lower TEAC value, possibly due to the decomposition of natural antioxidants through thermal processing. Studies have shown similar results in red grape pomace and blueberries after drying and canning [51- 52].

The present study aimed to determine the correlation between the content of total phenols and antioxidant ability. A strong positive linear association was seen with total phenols in the alcohol and water extracts, with NORS activity (R^2 = 0.91). Whereas the correlation between FRAP activity and the total phenols was found to be lowered to (R^2= 0.66). According to these findings, phenolics were the direct source of the antioxidant action. According to (Wu et al., 2004), the total phenols of the Deglet Noor Variety and antioxidant activity using the ORAC assay have a good linear connection [33]. The discrepancy in the correlation between our results and other studies could be attributed to the characteristics of phenolics, which show that they react favorably in some assays while decreasing in others, as reported by Garcia-Alonso et al (2004) [53]. Furthermore, the Medjool types utilized in this study may not have contained the active ingredients proanthocyanins monomer or polymer [54], which have been shown in studies [55] to contribute significantly to antioxidant capacity.

In-Vitro Enzymatic Assays

Date extracts showed α-glucosidase inhibition ranging from 12% to 54% and lipase inhibition from 17% - 45%. An increase in concentrations increased the α-glucosidase and lipase inhibition. Amylase inhibition ranged from 48.81% - 83.85% at 50 µg/ml concentration of date extracts. Ranilla et al., (2008) in their study found similar results for corn with maple syrups that had the highest alpha-glucosidase inhibitory activity compared to other sugars and syrups (81%, 78%, and 77%), respectively, at 50 µL [56].

In Table 3, ODA (6.54 ± 0.70 µg/ml) has the lowest IC50 value, indicating it is the most effective inhibitor of α-Amylase activity. FDE (18.92 ± 2.48 µg/ml) have higher IC50 values, indicating weaker inhibition as compared to other treatment methods. ODE (36.26 ± 0.37 µg/ml) has the lowest IC50 value, indicating it is the most effective inhibitor of α-Glucosidase activity. ODA (25.53 ± 0.61 µg/ml) has the lowest IC50 value, indicating it is the most effective inhibitor of Lipase activity compared to the other date extracts. Phenolics in *P. dactylifera* are potent inhibitors of alpha glycosidase and alpha-amylase, which can counteract hyperglycemia in Type 2 diabetes. These enzymes are involved in the digestion of carbohydrates, leading to rapid increases in blood glucose levels [56]. Consuming inhibitors naturally from constituents in the diet could be an effective therapy for managing postprandial hyperglycemia with minimal side effects, unlike traditional treatments like acarbose [57]. Some inhibitors of α-glucosidases and α-amylases have structural similarities to sugars, acting as substrate analogs and binding to enzyme catalytic sites [58] [59].

Table 3: In-vitro inhibitory (IC_{50}) property of the phenolic extracts from Medjool dates on metabolic enzymes α-glucosidase, α-amylase, & Lipase activities.

Treatments	IC_{50} (µg/ml)		
	α-Amylase	α-Glucosidase	Lipase
FDA	10.66 ± 1.75^{ax}	112.93 ± 7.55^{cy}	54.45 ± 1.42^{bx}
FDE	18.92 ± 2.48^{by}	51.46 ± 8.17^{by}	78.81 ± 5.61^{cy}
ODA	6.54 ± 0.70^{ax}	109.48 ± 6.20^{cy}	25.53 ± 0.61^{ax}
ODE	10.06 ± 1.54^{ax}	36.26 ± 0.37^{ax}	58.75 ± 0.98^{cy}

***(**n=3), IC-Inhibition Concentration; FDA- Freeze dried aqueous extract; FDE- Freeze Dried 80% Ethanol extract; ODA- Oven Dried aqueous extract; ODE- Oven Dried 80% ethanol extract. The letters abc depict a significant ($p \leq 0.05$) difference between the processing methods & letters xyz depict significant differences between the solvents.

Conclusion

This study explores the impact of freeze-drying and oven-drying methods on the phenolic compounds, antioxidant activity, and enzyme inhibition activity of dates. Results show that oven drying is the best method for maintaining total phenols and flavonoids in dried dates, while freeze-drying with ethanol extracts showed the lowest levels. Sun-drying is more commonly used than freeze-drying and oven-drying in dried date production due to its low cost. The study suggests that oven-drying could be an alternative due to its phenolic compounds, antioxidant activity, and production costs. Dates, due to their inhibitory effects on α-glucosidase and α-amylase levels, can be used as a monotherapy with a suitable diabetic diet and exercise, or in combination with antidiabetic therapy.

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