Date Palm Fruit against Diabetes

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Diabetes is a chronic metabolic disorder triggered by disturbances in carbohydrate, protein, and lipid metabolisms, where either reduced secretion or sensitivity of insulin is observed coupled with poor glucose control. Date palm fruits are one of the fruits reported to have good potential in diabetes treatment due to its presence of polyphenols exerting strong antioxidant activities. Other possible mechanisms of action include the polyphenolic compounds, which can inhibit enzymes like α-amylase and α-glucosidase. Flavonoids in dates can stimulate β-cells by increasing the number of islets and β-cells, recovering endocrine pancreatic tissues, reducing β-cell apoptosis, activating insulin receptors following the increase in insulin secretion, in addition to improving diabetes-induced complications.

date palm | Phoenix dactylifera | dates | polyphenols | flavonoids | diabetes | anti-diabetic

1. Introduction

Diabetes mellitus (DM) is a disease that is universally emerging, incurring long-standing complexities on organs, including the heart, kidneys, retina, and peripheral nerves. Natural products, which are often free from side effects, are good alternatives for disease amelioration [1][2][3]. Additionally, natural products have potentially effective roles in regulating diabetes and its complications [2][4][5].

Date palm fruit (*Phoenix dactylifera*) is from the Arecaceae or Palmae family. It is one of the oldest cultivated plants and originates from the Arabian Peninsula. There are more than 2000 distinct assortments of dates, including Ajwa, Khalas, Ruthana, Sukkary, Sefri, Segae, Khodry, Lulu, Hilali, and Munifi [6][7]. Dates are very nutritious and are rich in starch, salts, minerals, nutrients, unsaturated fats, proteins and fibres [8][9].

The presence of variable active constituents in dates including flavonoids, steroids, phenol, and saponins are postulated to exert anti-diabetic activities mainly by scavenging the free radicals via antioxidant activities and by inhibiting α-amylase and α-glucosidase enzymes [10][11][12][13]. Fibres and fructose are glucose-lowering, where consumption of dates up to 76.2 g as a snack is purported to be beneficial in Arabic culinary tradition, and can maintain the postprandial glucose levels in patients with diabetes [14][15]. Additionally, the date palm has numerous therapeutic potentials, including cell reinforcement, anti-mutagenic, antibacterial, antifungal, antitumor, neuroprotective, and gastroprotective properties [16][17]. The antioxidant potential in dates is perceived to be contributed by the wide range of phenolic components present, including *p*-coumaric, flavonoids, procyanidins,

ferulic, and sinapic acids. Other investigations indicated that the date palm possesses thirteen flavonoid glycosides, including luteolin, quercetin, and apigenin. Ajwa date, also known as a “super date”, and found only in Saudi Arabia, has good nutritional and medicinal values, making it one of the most expensive date varieties [18][19][20].

2. Date Fruit Seed

2.1. Evidence from In Vivo Studies

2.1.1. Antihyperglycemic Activity

Date seeds are promising source of nutrients, fibres and oil with functional properties [17][21][22]. In a 2-week in vivo study [23], date seed significantly reduced blood glucose levels and body weight ($p < 0.005$) of alloxan-induced diabetic rats when compared to control. Besides reduced glucose level, a significant ($p < 0.05$) increase in SOD, CAT, glutathione levels and a significant ($p < 0.05$) decrease in the MDA level were noted in the diabetic rats as compared to the untreated diabetic rats (444.3 ± 6.0 vs. 388.0 ± 4.5 mg/dL) administered with date palm seed extract [24]. Thouri et al. [25] detected in vivo glucose lowering and anti-inflammatory activities of Tunisian date seed which was eventually attributed to the presence of phenolics and flavonoids and antioxidant activities. The seed extracts of two Saudi date varieties (Ajwa and Sukkari) were evaluated in streptozotocin-induced diabetic rats in an eight-week experimental procedure. Following the intervention, blood glucose levels of diabetic rats which received Ajwa date seed extracts were significantly reduced (434.0 ± 20.0 mg/dL vs. 148.0 ± 28.7 mg/dL; $p < 0.001$) as compared to control. This is similarly seen in rats, which received Sukkari date seed extracts as compared to control (434.0 ± 20.0 mg/dL vs. 171.0 ± 9.2 mg/dL, $p < 0.001$). In addition, the two varieties also reduced diabetic rats’ body weight after eight weeks (Ajwa: 279.0 ± 2.1 g to 276.0 ± 7.4 g and Sukkari: 280.0 ± 1.0 g to 275.0 ± 3.1 g), thus, indicating that both varieties can reduce blood glucose levels and therefore have the potential to be investigated as anti-diabetics [26].

Abdelaziz et al. [27] estimated the effect of *Phoenix dactylifera* date seed in treating early complications of diabetes in streptozotocin-induced diabetic rats. Following the administration of aqueous suspension of date seed for four weeks, glucose level was decreased in date seed-treated rats when compared to untreated rats (248.0 ± 42.0 mg/dL vs. 508.0 ± 60.0 mg/dL). Khalil et al. [28] demonstrated that blood glucose level was significantly ($p < 0.05$) reduced from baseline (284.7 mg/dL vs. 172.5 mg/dL) following a 30-day administration with date seed powder (Zahdi variety) given in combination with fine bran to streptozotocin-induced diabetic rats. Furthermore, date seed supplementation at 5%,10%, and 15% can significantly reduce blood glucose levels in a concentration-dependent manner in male diabetic rats to 176.7 ± 11.0 mg/dL ($p < 0.05$), 130.7 ± 9.0 mg/dL ($p < 0.01$) and 121.1 ± 11.5 mg/dL ($p < 0.001$), respectively. It is plausible that the date seeds ameliorated glucose levels via its high dietary fibre and high chromium levels, essential for the synthesis of glucose tolerance factors. Date seed may also increase the activity of glucose-6-phosphate dehydrogenase by increasing insulin secretion, thus increasing the influx of glucose into pentose monophosphate shunt and reducing blood glucose levels [29]. In an eight-week in vivo experiment [30], oral administration of date seed extracts along with insulin demonstrated a significant ($p <$

0.05) antihyperglycemic effect on streptozotocin-induced diabetic rats as compared to administration of insulin alone. There was also a significant lowering ($p < 0.05$) of HbA1c levels due to stimulation of undifferentiated pancreatic islet cells to differentiate into newly formed β-cells. In fact, other research from a similar group demonstrated that date seed can stimulate endogenous insulin secretion from β-cell of pancreatic islets in type I diabetic rats [31]. Finally, date seed extract is reported to reduce blood glucose levels in male albino rats ($n = 24$) in a concentration-dependent manner. In the experiment, 10% and 15% date seed extracts which were mixed with fortified bread caused significant reduction in glucose levels from 152.5 ± 3.4 mg/dL to 119.8 ± 4.7 mg/dL (for the former) and to 105.6 ± 4.1 mg/dL (for the latter) [32]. It was hypothesized that the effects occur due to the high presence of the dietary fibres which are insoluble in water (including cellulose, hemicellulose and lignin), in addition to micro- and macro elements of date seed [33][34].

2.1.2. Antihyperlipidemic Activity

Ayatollahi et al. [23] perceived that date seeds have the potential to significantly ($p < 0.05$) reduce LDL and cholesterol levels in diabetic rats as compared to the control group. Abiola et al. [24] and Khalil et al. [28] also detected a significant decrease ($p < 0.05$) in the levels of cholesterol, TG, and LDL with improved levels of HDL in diabetic treated rats as compared to the untreated diabetic rats. Similar results were depicted in other in vivo studies on diabetic rats [32][35]. Hasan et al. [26] detected Saudi date seeds have the potentials to reduce the levels of cholesterol and TG in diabetic rats compared to untreated diabetic rats.

2.1.3. Against Diabetes-Induced Testicular Toxicity

Interestingly, in male rats administrated with date seed, testicular antioxidant enzyme status were dramatically improved [35] indicating that date seed has promising effects against diabetic-induced reproductive disorders.

2.1.4. Ameliorating Liver and Kidney Functions

In other multiple in vivo studies [23][32], date seeds exhibited the potential to reduce serum levels of creatinine, urea, and ALP in diabetic rats indicating date seeds can ameliorate kidney and liver functions in T2DM. In addition, no acute toxicity was detected even after high dosage of extract administration. Another study [27] also demonstrated that the levels of antioxidant enzymes including glutathione S-transferase, CAT and SOD were also significantly improved in both the kidneys and liver of date seed treated diabetic rats compared to the untreated rats. Subsequently, El Fouhil et al. [36] demonstrated that date seed extract was not only safe, but also minimised the toxic effects in the liver and the kidneys by improving ALT, aspartate aminotransferase, gamma glutamyl transferase, blood urea nitrogen, and creatinine levels.

Taken together, based on the T2DM animal model studies, date seeds are potential anti-diabetic agent due to its glucose and HbA1c lowering capacities in addition to improving the liver, the kidneys, reproductive system, and overall lipid profile.

2.2. Evidence from Clinical Studies

Antihyperglycemic Activity

Gharib et al. [37] evaluated the phenolic content and anti-diabetic effect of date kernels coffee among diabetic patients. Date kernels are a rich source of antioxidants due to the presence of numerous phenolic compounds including epicatechin, ellagic, chlorogenic, gallic, and caffeic acids. In this study, two cups of date kernels coffee in 200 mL were administered daily for three months (with each cup containing 10 g date kernels). After three months, fasting glucose to insulin ratio was significantly decreased ($p < 0.001$) with significant improvement in β-cell function ($p < 0.001$). Therefore, due to the overall improvement of serum glycaemic profile, it was recommended that date kernel has the potentials to be incorporated into an anti-diabetic regimen. However, more clinical studies are required to fully establish this fact.

3. Date Fruit Leaf

3.1. Evidence from In Vivo Studies

3.1.1. Antihyperglycemic Activity

In a recent study conducted on streptozotocin-induced diabetic male Wistar rats [38], when date leaf extract was administered orally, blood glucose, HbA1c and MDA levels were significantly decreased ($p < 0.05$), while plasma insulin along with a number of β-cells significantly increased ($p < 0.05$) in treated diabetic rats compared to control rats. Ismail et al. [39] observed after a 28-day follow-up that extracts of palm leave tops did not significantly decrease blood glucose levels in streptozotocin-induced diabetic Sprague–Dawley rats (before: 411.1 ± 84.2 mg/dL vs. after: 399.7 ± 172.2 mg/dL, $p = 0.90$) as compared to controls. The effect of phenolic compounds extracted from Iraqi date palm leaves were evaluated in alloxan-induced diabetic rabbits ($n = 12$) in a 24-h procedure [40]. When date palm leaf extracts were administered at different intervals, such as 2, 4, 6, and 24 h, blood glucose levels of the diabetic rabbits significantly decreased (392.3 ± 4.7 mg/100 mL to 325.5 ± 4.7 mg/100 mL ($p < 0.05$), 280.6 ± 2.7 mg/100 mL ($p < 0.01$), 238.3 ± 8.1 mg/100 mL ($p < 0.01$) and 134.5 ± 4.8 mg/100 mL ($p < 0.001$), respectively). The subsequent reduction indicates that date palm leaf extract has strong glucose-lowering effects in a time-dependent manner. Chakroun et al. [41] reported the presence of ten phenolic compounds in date palm leaf extract and conducted an in vivo study for 28 days in alloxan-induced diabetic mice. They identified that α-glucosidase and α-amylase enzymes were inhibited by the date palm leaves extract. Significant anti-diabetic activity was observed from date palm leaves extract when compared to Glucor® (acarbose) administered at 50 mg/kg. This finding confirms that date palm leaf extract can reduce blood glucose levels and may have superior anti-diabetic effect as compared to Glucor®.

Following the administration of *Ziziphus jujube* (jujube date) leaf extract in alloxan-induced diabetic rats, there were significant ($p < 0.001$) reduction in blood glucose levels (from 767.8 mg/dL to 250.9 mg/dL) although when compared with glibenclamide-administrated group, the difference was not significant as reported by Eddine et al. [13]. The mechanism behind this discovery could be hypothesised as due to the contribution of jujube date in stimulating β-cells and activating insulin receptors and subsequently lowering the blood glucose level [42]. In an

interesting study [43], upon subacute administration of *Phoenix dactylifera* leaf extract in alloxan-induced male Wister rats, blood glucose and insulin levels significantly improved. Similar results were confirmed by Abuelgassim et al. [44] where date palm leaf extract was incorporated in alloxan-induced male Wister diabetic rats. Subsequently after 4 weeks, there was a significant glucose reduction in diabetic rats (17.43 ± 0.76 to 16.77 ± 0.28 mmol/L/) as compared to controls. It is hypothesised that the leave extract promotes insulin secretion by closing the K^+ ATP channels. Additionally, some components of leaves extract such as flavonoids, phenols, steroids and saponins have free radical scavenging abilities. It may also reduce water intake and improve body weight with a reverse dyslipidaemia effect [45][46].

3.1.2. Antihyperlipidemic Activity

In an in vivo study, Mard et al. [43] demonstrated that upon administration of subacute *Phoenix dactylifera* leaf extract, both cholesterol and TG levels improved in diabetic male Wister rats compared to the control group. Abuelgassim et al. [44] also confirmed that administration of date palm leaf can significantly improve cholesterol ($p < 0.001$) and LDL levels ($p < 0.001$), however, no significant improvement on serum HDL levels.

3.1.3. Ameliorating Haematological Parameters

Nuha et al. [40] reported from an in vivo study that the phenolic compounds identified in date leaves possessed no toxic effects on red blood cells.

Therefore, these results suggest that date leaves have potential roles in lowering plasma glucose, HbA1c, regulating lipid profile, protecting haematological parameters and, subsequently, improving diabetes and diabetes-associated complications in animal models.

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