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REVIEW ARTICLE

Date Palm (*Phoenix dactylifera*): Novel Findings and Future Directions for Food and Drug Discovery

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Abstract: *Phoenix dactylifera* is a useful traditional medicinal plant, mainly the fruit is used, which is the edible part of the plant (Ajwa date). It is now considered to be a valuable source of natural medicinal products against various diseases. Phytochemical investigations have shown that the fruit contains anthocyanins, phenolics, sterols, carotenoids, and flavonoids. The fruits are a rich source of carbohydrates, vitamins, and proteins. *P. dactylifera* is considered as a complete diet because it also contains different fatty acids, amino acids, proteins, and steroidal substances. This review highlights the phytochemical composition, nutritional significance, and potential health benefits of *P. dactylifera* and discusses its potential as a functional food for disease prevention, management, and treatment.

Keywords: *Phoenix dactylifera*, biological activities, phytochemicals, future directions, drug discovery, medicinal plant.

1. INTRODUCTION

Over the years, it has become increasingly evident that nature has numerous medicinal plants that contain phytochemicals with potent pharmacological activities, including promising antitoxic properties [1]. It is estimated by the World Health Organization that up to 80 percent of humans still rely on traditional medicines [2].

P. dactylifera is a useful traditional medicinal plant belonging to the family *Arecaceae.* [3]. The genus *Phoenix* contains 14 species including *P. dactylifera* that have been cultivated in the Middle East for at least 6000 years [4]. Its phytochemical investigation has revealed that the fruits contain anthocyanins, phenolics, sterols, carotenoids, procyanidins, and flavonoids, compounds known to possess free radical scavenging, antioxidant, antimutagenic, antimicrobial, anti-inflammatory, antihyperlipidemic, gastroprotective, hepatoprotective, nephroprotective, anticancer, and immunostimulant activities [5, 6].

All *P. dactylifera* products such as fruits, seeds, pollen, leaves, and syrup have beneficial uses for human and animals. This attracts researchers to study the different pharmacological potentials of *P. dactylifera* products. Our previous study showed antioxidant and immune stimulant activities of *P. dactylifera* seeds supplemented to broiler chickens as a feed additive [7].

P. dactylifera products are widely used daily food in Islamic countries due to their history of more than 1400 years. Ajwa dates, a special kind of date present in Arab countries, have been mentioned by the Prophet as he said, “If Somebody takes seven Ajwa dates in the morning, neither magic nor poison will hurt him that day” [8]. In addition, the Prophet mentioned the benefits of dates from Medina, a city

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in Saudi Arabia, and said, "He who ate seven dates (of the land situated) between these two lava plains in the morning, no poison will harm him until it is evening" [9].

2. *P. DACTYLIFERA* ACTIVE INGREDIENTS

P. dactylifera can be considered as a complete food in addition to its curative effects against various complaints. *P. dactylifera* is considered as a complete diet because it contains different fatty acid, amino acid, proteins, and steroidal substances [10-13]. It contains phytochemicals like phenolics, flavonoids, and carotenoids, which have anticancer and antioxidant potentials [14-16]. The protective effects of *P. dactylifera* are thought to be due to not only the fiber, vitamins, and minerals, but also to a diversity of plant secondary metabolites as flavonoids and phenolics [17, 18]. Also, the polyphenolic proanthocyanidins may act in combination with other phenolics as free radical scavengers or heavy metal chelators, and in turn, they can prevent the oxidative stress and inflammation [19].

P. dactylifera contains considerable amounts of vitamins of water and fat-soluble origins that are very important for vitality. Moreover, it contains vitamins with powerful antioxidant potentials that are capable of chelating different radicals in the non-enzymatic reaction such as vitamin A, C, and E [18, 20]. Additionally, it contains amounts of macro- and micronutrients that play an important role in many biological functions in the body [21-23]. Selenium, copper, zinc, and manganese are of great importance for antioxidant metalloenzymes such as superoxide dismutase (SOD) and glutathione peroxidase (GPx) [24]. The phytochemical constituents of *P. dactylifera* fruits are listed in Tables **S1-4** and illustrated in Fig. (**1**).

3. BIOLOGICAL ACTIVITIES OF *P. DACTYLIFERA*

3.1. Antioxidant Activity

Studies concerning the antioxidant effect of *P. dactylifera* have shown that oxidative stress induced by reactive oxygen species (ROS) and reactive nitrogen species (RNS) reduced the body antioxidant defense system and led to cellular oxidative damage as listed in Table **S5**. *P. dactylifera* have shown antioxidant activities in the Trolox equivalent antioxidant capacity (TEAC) test, 2,2′-azinobis (3-ethylbenzothiazoline-6-sulphonic acid) radical cation ($ABTS^{+}$) assay, and the ferric reducing/antioxidant power method (FRAP assay) [25]. Also, *P. dactylifera* contains a high percentage of vitamin C, A, and E plus a high total phenolic content [26, 27]. These results of *in vitro* studies encouraged researchers to investigate the antioxidant activity of *P. dactylifera* extracts *in vivo* against different toxicants as carbon tetrachloride (CCl_4), isoproterenol, cadmium, and streptozotocin-induced diabetic rats [28-31]. The protective effect of *P. dactylifera* may be related to the accelerated activities of antioxidant enzymes such as catalase (CAT), SOD, GPx, glutathione reductase (GR), glutathione S-transferase (GST) along with significant reduction in malondialdehyde (MDA) [7, 30, 32, 33]. Conclusively, it can be said that *P. dactylifera* is a good antioxidant food.

3.2. Anticancer Activity

Constituents of *P. dactylifera* fruits have shown antitumor activity, as listed in Table **S6**. *In vitro* trials were done to determine the anticancer activity of *P. dactylifera* extracts towards different cancer cell lines such as human epithelial colorectal adenocarcinoma (Caco-2) [34], and the human melanoma-derived cell line (IGR-39) [35]. Khan and colleagues investigated the mechanism by which the methanolic extract of Ajwa date (15 and 20 mg/ml) inhibited the growth of human breast adenocarcinoma (MCF7) through upregulation of proapoptotic molecules, p53, Bcl-2-associated X protein (Bax), Fas, and Fas ligand (FasL) along with downregulation of B-cell lymphoma 2 (Bcl-2) [36].

3.3. Antidiabetic, Anti-Hyperglycemic, and Antihyperlipidemic Activities

We found four studies in the literature on the antidiabetic activity of *P. dactylifera* (Table **S7**). Some studies proofed the antidiabetic effect of *P. dactylifera* through elevation of plasma insulin with normalization of plasma glucose, triacylglycerol, and cholesterol in alloxan-induced diabetes in rats [37]. It is important to investigate the real cause of plasma insulin increment as to whether this is due to increase in the efficiency of healthy β-cells or due to the regeneration of alloxan-injured cells.

One of the antihyperglycemic effects of *P. dactylifera* is the inhibition of either α-glucosidase and α-amylase *in vitro,* potentially delaying the digestion and absorption of carbohydrates, leading to normalization of plasma glucose levels. Such an effect was induced by *P. dactylifera* leaves' hydro-alcoholic extract [35] and *P. dactylifera* seeds' aqueous extract [38]. Also, Hasan and Mohieldein [39] treated streptozotocin-induced diabetic rats with 10 ml of *P. dactylifera* seeds' aqueous extract per day for each rat. The tested extract significantly reverted the elevated serum glucose, cholesterol, and triacylglycerol levels of the diabetic rats to near normal values.

3.4. Anti-Inflammatory Activity

The anti-inflammatory effects of *P. dactylifera* could be shown as a reduction of paw edema volume [40], wound healing activities [41], and cardioprotective [30]. In line with these facts, we summarize the anti-inflammatory properties of *P. dactylifera* as reported in the literature (Table **S8**).

Al-Qarawi and coworkers found that aqueous and ethanolic undialyzed and dialyzed extracts from *P. dactylifera* fruit have been effective in ameliorating the severity of gastric ulceration and mitigating the ethanol-induced increase in histamine and gastrin concentrations and decreasing mucin gastric levels. According to the authors, the anti-inflammatory ability of the extract may be explained by the antioxidant action of the extract [42].

The phenolics and flavonoids content could inhibit the formation of prostaglandin endoperoxide, leading to termination of inflammation mediators like prostaglandins and thromboxane [43]. Ali Haimoud and colleagues evaluated the anti-inflammatory activity of methanolic extracts of

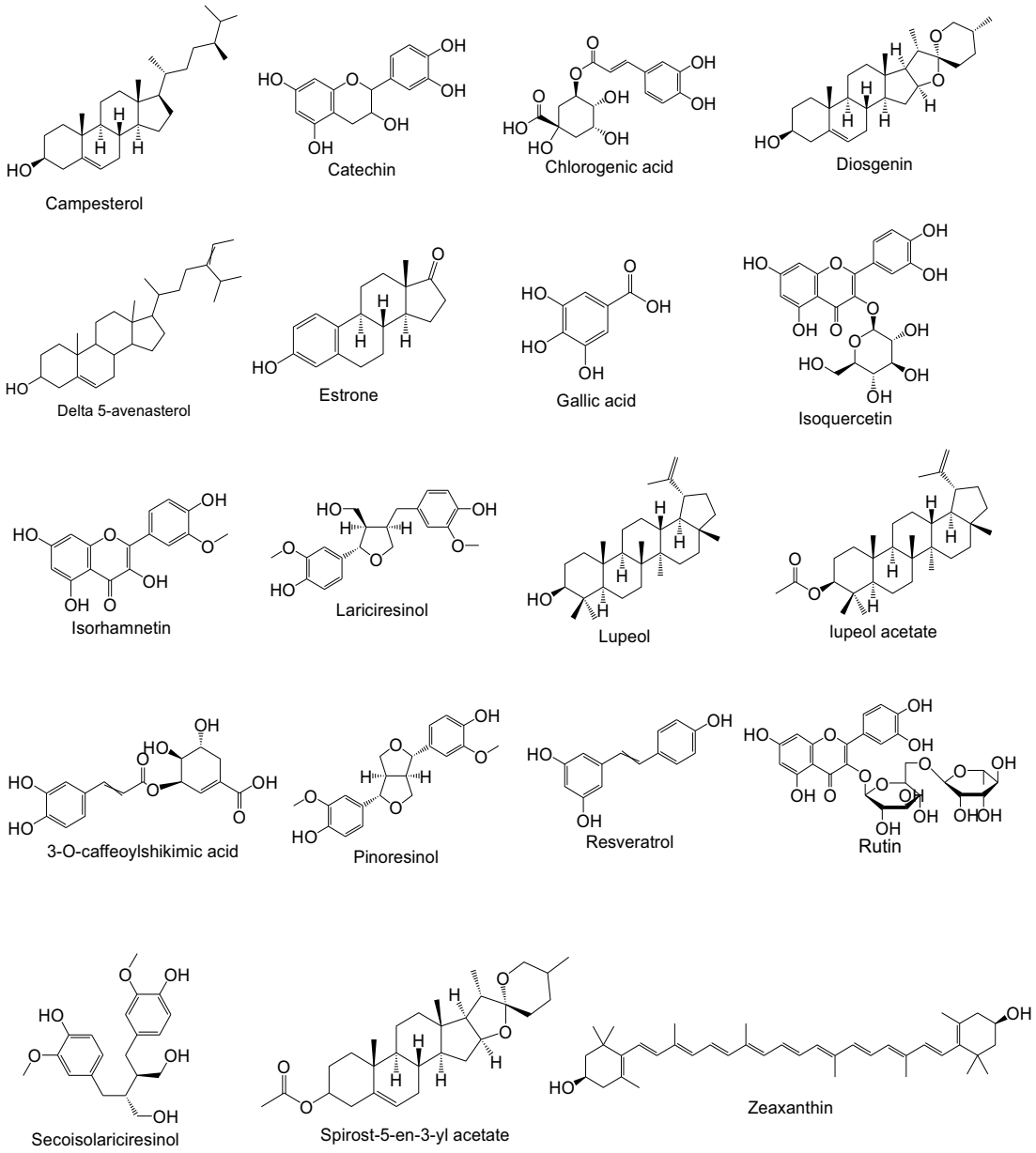

Fig. (1). The structures of some secondary metabolites characterized in *P. dactylifera*.

P. dactylifera fruits grown in Algeria. They found a noticeable reduction in paw volume in the experimental model of carrageenan-induced acute paw edema in Swiss albino mice ranging from 35.64 to 67.56% as a response to oral administration of 250 mg/kg dose of the methanolic extract [40].

In traditional medicine, *P. dactylifera* has been used to treat inflammatory-associated diseases [44] and recently was presented as a pain reliever along with chemical agents such as ibuprofen and paracetamol [45, 46]. There is no clear mechanism for such effects but it has been reported that *P. dactylifera* had active substances that can interfere with prostaglandin synthesis [47], inhibiting the expression of inflammatory cytokines such as IL-6, IL-8, IL-10, TNF-α, and IGF-1 [30], analgesic effects due to the presence of vitamin C and E [46], and increasing the expression of TGF-β [48]. On the other hand, potentiating of the antioxidant system as described previously can be a possible mechanism for anti-inflammatory effects of *P. dactylifera*.

3.5. Antimicrobial Activity

Different extracts and oils of *P. dactylifera* show strong antimicrobial activities (Table **S9**).

Abuharfeil *et al*. [49] studied the effect of *P dactylifera* against the hemolytic activity of streptolysin O and stated that the *P. dactylifera* fruit extract resulted in a decrease in the growth of *Streptococcus pyrogens* by 88.5% compared to control. In a disc diffusion method, it has been determined that aqueous and ethanol extracts of *P. dactylifera* fruits had a strong antibacterial activity against *Escherichia coli*, *Salmonella enterica*, and *Bacillus subtilis* and moderately inhibited *Staphylococcus aureus* and *Enterococcus faecalis*. This antibacterial effect is due to the presence of esculetin,

tannic acid, a moderate concentration of gallic acid, itaconic acid, and traces of ferulic acid present in *P. dactylifera* extracts [50].

In another study, the antibacterial activity of methanol and acetone extract of the Saudi Arabian *P. dactylifera* variety Mabroom, Safawi, and Ajwa, as well as Iranian *P. dactylifera* variety Mariami were evaluated. The methanolic extract of Mabroom was more potent against *Staphylococcus aureus* than the methanolic extract of Ajwa and Mariami (100 mg/ml for Mabroom *vs*. 300 mg/ml for Ajwa and Mariami). The lowest concentration of methanolic extracts of Mabrooom and Mariami that could inhibit *Bacillus cereus* growth was 500 mg/ml while methanolic extracts of Safawi and Ajwa could inhibit the growth of this bacterial species at 400 mg/ml [27].

Finally, antimicrobial activities of hydroalcoholic extract of six Moroccan date fruit varieties including Bouskri, Bousrdon, Bousthammi, Boufgous, Jihl, and Majhoul against Gram-positive (*Bacillus subtilis*, *B. cereus*, and *S. aureus*) and Gram-negative bacteria (*E. coli*, *Pseudomonas aeruginosa*, *Salmonella abony*) were examined by Bouhlali and colleagues using a disc diffusion method. All the tested *P. dactylifera* fruit extracts showed antibacterial activity except Majhoul and Bouskri extracts, but this antibacterial effect was still lower than that of gentamicin. The Bousrdon and Jihl extracts were more potent inhibitors with minimum inhibitory concentration (MIC) values ranging from 2.5-10 mg/ml for all bacterial strains tested [51].

As noted above, *P. dactylifera* can be effective against Gram-positive and -negative bacteria. However, it has been reported that *P. dactylifera* fruits are more efficient against Gram-positive bacteria than against Gram-negative bacteria due to the presence of an outer membrane. On the other hand, the most effective substances in *P. dactylifera* that are attributed to the antimicrobial effects are phenolic compounds by generating hydrogen peroxide that mediates bacterial growth inhibition [52]. It has been postulated that phenolic compounds utilize redox active metals when interacting with bacteria, in particular, gram-positive [47].

3.6. Antitoxic Activities

The studies concerning the hepatoprotective, nephroprotective, and neuroprotective effects of *P. dactylifera* against oxidative stress, and xenobiotics-induced toxicity are listed in Table **S10**.

3.6.1. Antihepatotoxicity

The hepatoprotective potential of *P. dactylifera* was examined in a study by Al-Qarawi and coworkers on the effect of aqueous extracts of the flesh and seeds against CCl_4-induced hepatotoxicity in rats. The *P. dactylifera* seeds' extract was added to drinking water. β-Sitosterol, one of the bioactive compounds present in the extract, may be responsible for the observed protective effect against CCl_4-induced hepatic injury in a rat model [53]. In screening and developing of hepatoprotective drugs for the treatment of hepatocellular injuries, the ability of the constituents of such drugs to inhibit the aromatase activity of cytochrome P-450, thereby favoring liver regeneration, is an important factor to consider [54]. Based on the aforementioned results, Kowalska *et al*. in 1990 suggested that the flavonoids content of *P. dactylifera* could be a factor contributing to its hepatoprotective ability through the inhibition of cytochrome P-450 aromatase [55].

Saafi and coworkers reported a protective effect of the aqueous fruit flesh extract of *P. dactylifera* against dimethoate-induced oxidative stress in rat liver. Oral administration of dimethoate (20 mg/kg) resulted in the elevation of all hepatic biomarker enzymes examined. The elevation witnessed in the hepatic biomarker enzymes examined was an indication of a certain degree of damage to the liver. Taken together, their results demonstrated that when animals challenged with dimethoate are treated with aqueous fruit flesh extract (4 ml/kg) of *P. dactylifera*, the extract can mitigate diminished hepatic antioxidant activities, notably SOD, GPx, and CAT activities, and inhibit hepatic lipid peroxidation as well as restore various degrees of alterations observed in hepatic biomarker enzymes, thereby preventing against hepatocellular damage [56].

3.6.2. Antinephrotoxicity

P. dactylifera has also been reported to play a crucial role in the treatment and management of various nephrotoxicities arising from different xenobiotics. In a study conducted by Ahmed and coworkers, using a CCl_4-induced toxicity model in rats, a hydroacetone extract (50 or 100 mg/kg/rat) prepared from seeds of *P. dactylifera* was demonstrated to confer a noticeable protection on the kidney in a dose-dependent manner. According to the authors, the nephroprotective ability of the extract may be explained by its ability to effectively scavenge the free radical generated during CCl_4 metabolism, probably because the extract contained a high quantity of proanthocyanidins (49.0 % CT – 0.52 % CT *w*/*w*), which exhibited high antioxidant activity [57]. Another study conducted by Hasan and Mohieldein revealed that prolonged administration of aqueous *P. dactylifera* extracts (100 g/L in a dosage of 10 ml/day/rat) could restore kidney function. In this study, it was observed that there were various degrees of renal dysfunction among diabetic rats while treatment with aqueous *P. dactylifera* extracts ameliorated the progressive decline in renal dysfunction among the treated rats [39].

Al-Ghasham and coworkers reported that aflatoxin B_1 (AFB_1) induces histopathological changes in the kidney that are associated with renal dysfunction, as indicated by the elevations in the levels of plasma creatinine and urea. Toxicity was induced by intraperitoneal administration of AFB_1 (50 µg/kg). Treatment with aqueous *P. dactylifera* extract for two weeks resulted in a marked reduction in levels of plasma creatinine and urea as well as a significant improvement in the kidney architecture. They concluded that the observed effect may be attributed to the antioxidant properties of *P. dactylifera* extract [58]. Al-Qarawi and coworkers also investigated the effect of *P. dactylifera* extract on gentamicin (GM) nephrotoxicity in rats. Toxicity was induced by administration of GM (80 mg/kg/day) intramuscularly. *P. dactylifera* extracts were administered to the animals by mixing the *P. dactylifera* flesh extract with the food (50 % *w*/*w*) or by mixing the seed extract in the drinking water (2:1 *w*/*v*). GM administration was found to cause a significant elevation in the plasma levels of

creatinine and urea and induced a marked necrosis of the renal proximal tubules. Interestingly, administration of either *P. dactylifera* flesh extracts with the food (50% *w*/*w*) or seeds extract in the drinking water (2:1 *w*/*v*) resulted in a significant reversal effect in observed indices of toxicity in the kidney. Melatonin, vitamin E, and ascorbic acid, which are abundantly present in the extract and may synergistically act to counteract the overwhelming effect of the free radicals generated, were suggested to be the basis of the nephroprotection [59].

3.6.3. Antineurotoxicity

The impact of free radical generation, mediated by oxidative stress in the pathogenesis of various neurological diseases such as a cognitive decline in aging, Alzheimer's disease, Parkinson's disease, and vascular dementia has been widely documented in the literature [60]. Antioxidants from plant-derived food in the form of nutraceuticals are now being considered as an alternative therapy against solemn neuronal loss due to their capability to counteract free radicals generated and neutralize them, thereby conferring neuroprotection [61]. Pujari and co-workers investigated the neuroprotective and antioxidant effect of *P. dactylifera* fruits against permanent bilateral common carotid arteries (BCCA) in rats at doses of 30, 100, and 300 mg/kg. They reported that chronic occlusion of BCCA resulted in a noticeable increase in lipid peroxidation as evidenced by the elevation in malondialdehyde levels. They also observed that there was a general decline in the endogenous antioxidants, notably glutathione, GPx, GR, GST, CAT, and SOD. They concluded that 100 and 300 mg/kg of the extract significantly ameliorated these alterations, confirming the protective role of the extract in ischemia hypoperfusion [62]. The polyphenolic constituents in the extract such as flavonoids and plant sterols as well as its ascorbic acid content may account for the observed neuroprotective effect.

A similar study conducted to investigate the neuroprotective effect of aqueous *P. dactylifera* fruit extract in focal cerebral ischemia in rats reported that a 250 mg/kg dose of the extract significantly inhibited neuronal damage induced by cerebral ischemia. Rats were maintained on varying doses of the extract (125, 250, 500, and 1000 mg/kg). The extract was administered once per day for two weeks; the largest protective effects of the extract were observed at a dose of 250 mg/ kg. At 500 mg/kg, a lower protective effect was observed, and 1000 mg/kg showed a negative effect, which may be attributed to high concentration of antioxidants that may be harmful. They concluded that the extract at 250 mg/ kg could protect neurons against ischemia-reperfusion-induced insults [63]. Taken together, in search for a promising antitoxic agent in the treatment and management of hepatotoxicity, nephrotoxicity, and neurotoxicity, *P. dactylifera* is a candidate to explore.

3.7. Reproductive and Labor Induction Activities

Plants and their constituents play a significant role as pain relievers and cause relaxation in childbirth. Several medicinal plants show an effect in the stimulation of all phases of labor [64]. *P. dactylifera* has a pivotal role in the enhancement of male fertility and induction of labor as stated in Table **S11** that may be related to its antioxidant activity [65, 66]**.**

An *in vivo* trial was started to evaluate the effect of the normal and acid-treated powdered *P. dactylifera* seeds on male rat fertility [67]. The normal *P. dactylifera* seeds concentrations of 7 and 14% caused a significant increase in the plasma testosterone, while the acid-treated seeds (14%) significantly increased the plasma level of luteinizing hormone (LH). In another study, the authors injected 0.3 ml of diluted *P. dactylifera seeds* oil (15 and 20% of oil in saline 0.9%) and reported significant increases in the sperm count, motility, and viability in male mice [68].

Another study reported the reproductive potential of *P. dactylifera* pollen through treatment of rats by 1 ml of aqueous extract of pollen using concentrations of 120, 240, 360 mg/kg body weight by gavage. The doses of 120 and 240 mg/kg significantly raised the ratio of testis or epididymis to body weight, sperm count, sperm motility, and estradiol level compared to the control group, with noticeable increases in serum LH and testosterone levels [69]. Where LH and testosterone are responsible for spermatogenesis and male fertility, estradiol that is produced by Leydig cells of the mammalian testis prevents the apoptosis of male sperm cells. These findings were confirmed by the study of El-Kashlan, *et al*. [70] in which they administered 150 mg ethanolic extract of *P. dactylifera* pollen per kg in male rat and recorded marked an increase in sperm count and motility, serum levels of LH, testosterone, and estradiol hormones. The authors also recognized potentiation in the activities of testicular 3β-hydroxysteroid dehydrogenase (3β-HSD) and 17β-hydroxysteroid dehydrogenase (17β-HSD) that contribute to the testosterone biosynthesis.

3.8. Cardiovascular Protective Activity

P. dactylifera fruit has been used as an antihypertensive food for centuries. Because *P. dactylifera* seeds can be used as edible oils and also in pharmaceutical industry, it has been proposed that it may exert beneficial effects on cardiovascular conditions [20]. Braga *et al*. showed that this fruit is a potent angiotensin-converting enzyme inhibitor. This is an effective strategy for reducing blood pressure [71]. Also, high sodium and low potassium intake have a major role in raising blood pressure [72]. Because *P. dactylifera* fruit contains a high amount of potassium and a low amount of sodium, it can control blood pressure by maintaining the electrolyte balance. Also, the magnesium and calcium contents of *P. dactylifera* fruit play key roles in this subject [73].

Hypercholesterolemia is an important risk factor because of its major impact on the progression of cardio- and cerebrovascular disorders. It was reported that *P. dactylifera* fruit supplementation could modulate cholesterol absorption and metabolism [74]. This effect is related to *P. dactylifera* fiber and phytochemicals by three mechanisms: reduction in cholesterol absorption and reabsorption of bile acids, and inhibition of hepatic cholesterol biosynthesis after production of short-chain fatty acids due to *P. dactylifera* fiber fermentation. Also, phytochemicals such as phytosterols and

phytoestrogens inhibit cholesterol absorption from intestinal lumen [75].

Ahmed *et al*. [76] demonstrated that for *Aseel*, the best varieties of Pakistani dates, efficiency was the same as atorvastatin with respect to lowering of some markers such as fasting blood sugar, cholesterol, triacylglycerol, LDL, and VLDL. Generally, this experiment showed that *Aseel* lowered the blood lipid levels. The presence of some constituents like phytochemicals, β-sitosterol, proanthocyanidin, catechin, quercetin, anthocyanins, and selenium may contribute to cardioprotective and antihyperlipidemic effects of *P. dactylifera* [77].

4. FUTURE DIRECTIONS

Suggestions for future research directions to give a complete understanding of the biological and nutritive roles of *P. dactylifera* are:

- Phytochemical constituents of *P. dactylifera grown* in Arabian countries.
- Comparative phytoconstituents of Aliya, Medina and other countries (The Middle East and North Africa).
- Differences between *P. dactylifera* eaten in the early morning (empty stomach) and other times of the day.
- Protective effect of *P. dactylifera* against different toxicants in different models.
- Plasma amino acid pool, growth hormone, and insulin-like growth hormone levels.
- Growth hormone receptor and myogenic genes in muscles.
- Plasma lipid profiles and non-esterified fatty acids (NEFA).
- Experimentally induced non-alcoholic fatty liver concerning triacylglycerol and cholesterol biosynthesis-related genes.
- The relationship between *P. dactylifera* and intestinal amino acid transporters such as oligopeptide transporter (PepT1), excitatory amino acid transporter 3 (EAAT3), Na^+-independent branched-chain and aromatic amino acid transporter (LAT1), Na^+-independent cationic amino acid transporter (CAT1), Na^+-independent cationic amino acid transporter (CAT2).
- Purification of active substances responsible for antioxidant activity.
- Application of different extracts of *P. dactylifera* in different routes as an alternative treatment for different diseases with a base of oxidative stress.
- Pro-apoptotic proteins such as caspase-3, caspase-8, caspase-9, phosphatase and tensin homolog (PTEN), p53 upregulated modulator of apoptosis (PUMA), phorbol-12-myristate-13-acetate-induced protein 1 (NOXA), integrins, and E-cadherin.
- Anti-apoptotic molecules like mitogen-activated protein kinase (MAPK), nuclear factor kappa B (NF-κB), actin, cyclin-dependent kinases (CDKs), matrix metallopeptidases (MMPs), mammalian target of rapamycin (mTOR), signal transducer and activator of transcription 3 (STAT3), and receptor for advanced glycation end-products (RAGE) signaling pathways.
- The combination between *P. dactylifera* and the already established anticancer drugs of either natural or synthetic nature.
- The relationship between *P. dactylifera* and intestinal monosaccharide transporters such as Na^+-dependent glucose and galactose transporter (SGLT1), glucose transporter (SGLT5), Na^+-independent glucose, galactose and fructose transporter (GLUT2), and Na^+-independent fructose transporter (GLUT5).
- Glucose uptake by peripheral tissues with evaluation of glucokinase and hexokinase genes and protein expression.
- Gluconeogenic, glycogenic, and glycogenolytic enzymes' gene and protein expression.
- Fatty acid β-oxidation enzymes' gene and protein expression.
- Regeneration of injured β-cells in diabetic-induced models.
- Beneficial effects of extracts of *P. dactylifera* in the experimental model of human inflammatory diseases.
- Proteomic analysis of differentially expressed proteins in the liver, kidney, and brain of animal models in xenobiotics-induced toxicity (CCl_4 or ethanol) should be investigated as identification of these differentially expressed proteins will help us to understand the molecular events occurring during xenobiotics' toxicity and will also help us in elucidating the exact mechanism of action of *P. dactylifera*.
- Molecular mechanisms of *P. dactylifera* reproductive activity through evaluation of the gene expression of the enzymes of testosterone and estradiol biosynthesis.
- Effect of *P. dactylifera* on female reproductive enzymes such as LH, follicle-stimulating hormone (FSH), estrogen, and progesterone.

- The role of *P. dactylifera* in the regulation of irregular menstrual cycle and silent heat in human and animals.
- The role of *P. dactylifera* in labor induction concerning oxytocin, gonadotropin-releasing hormone (GnRH), and Prostaglandin $F_2\alpha$ ($PGF_2\alpha$).

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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Declared none.

SUPPLEMENTARY MATERIAL

Supplementary material is available on the publisher's web site along with the published article.

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