Review

iMedPub Journals
http://www.imedpub.com/

Journal of Nutraceuticals and Food Science

2016
Vol.1 No.2:9

Date Palm (*Phoenix dactylifera*): Protection and Remedy Food

Ali Hafez El-Far[1], Hazem Mohammed Shaheen[2], Mohamed M. Abdel-Daim[3], Soad K. Al Jaouni[4] and Shaker A. Mousa[5]

[1]Department of Biochemistry, Faculty of Veterinary Medicine, Damanhour University, Egypt

[2]Department of Pharmacology, Faculty of Veterinary Medicine, Damanhour University, Egypt

[3]Department of Pharmacology, Faculty of Veterinary Medicine, Suez Canal University, Egypt

[4]King Abdel Aziz University, College of Medicine, Hematology and Director of Prophetic Medicine Chair, Jeddah, KSA

[5]Pharmaceutical Research Institute, Albany College of Pharmacy and Health Sciences, Albany, NY, USA

Corresponding author: Shaker A. Mousa, The Pharmaceutical Research Institute, Albany College of Pharmacy and Health Sciences, 1 Discovery Drive, Rensselaer, USA, Tel: +1-518-694-7397; Fax: +1-518-694-7567; E-mail: shaker.mousa@acphs.edu

Received: June 07 2016; **Accepted:** July 25 2016; **Published:** July 27 2016

Citation: El-Far AH, Shaheen HM, Abdel-Daim MM, et al. Date Palm (*Phoenix dactylifera*): Protection and Remedy Food. Curr Trends Nutraceuticals. 2016, 1: 2.

Abstract

Phoenix dactylifera belongs to the *Arecaceae* family; its leaves, barks, pits, fruits and pollens have antioxidant, anticancer, hepatoprotective, n europrotective, nephroprotective, gastrointestinal protective, antidiabetic, antihyperlipidemic, sexual improvement and antimicrobial potentials. The broad pharmacological effects of *P. dactylifera* may be attributed to the powerful and beneficial ingredients including phenolics, flavonoids, carotenoids, vitamins, minerals, amino acids, fatty acids and organic acids. This review was conducted to explain the pharmacological preventive and curative potentials of *P. dactylifera* by searching through PubMed and Google scholar databases until January, 2016 by selection of some unique studies under each pharmacological potential of *P. dactylifera*.

Introduction

Natural products can be good remedies because they are inexpensive and easy to access. Some herbs are recommended as a remedy for some diseases by the Prophet Mohammed (Peace Be upon Him) [1] as he said dates cure several disorders. The importance of dates has been documented in the Qur'an in Surah Maryam, at the point when Mary brought forth the Christ Jesus (Peace Be upon Him) under a palm tree, she heard a voice advising her: "Shake the trunk of the palm tree towards thee: it will drop new, ready dates upon thee. Eat, then, and drink, and let thine eye be cheered!" (Qur'an 19: 25-26) [2]. The health benefit of Ajwa dates has been documented in hadith as Saud (R.A) narrated that I heard Allah's Apostle saying, "If Somebody takes seven Ajwa dates in the morning, neither magic nor poison will hurt him that day" [3].

Table 1: A summary of the pharmacological potentials of *P. dactylifera*.

Activity	*P. dactylifera* / Extracts	Study type	Conclusions	Reference
Antioxidant	Aqueous extract (fruits)	In vitro	Hydroxyl radical scavenging potential	[13]
			Superoxide scavenging potential	
	Phenolic and flavonoid fractions (fruits)	In vitro	Antioxidant capacity	[14]
			Radical scavenging potential	
	Aqueous-methanol extracts (fruits)	In vitro	Total phenolic contents	[15]
			Total flavonoid contents	
	Methanolic extract (fruits)	In vitro	Antioxidant capacity	[16]
			Total phenolic contents	
Anticancer	Date extract (DDE) and polyphenol-rich extract (DPE)	In vitro	Growth inhibition of Caco-2 cells	[18]

	Fruits	Mice	β-glucan anti-tumorigenesis	[19]
Hepatoprotective	Aqueous extract (fruits)	Rabbit	Elevation in serum GSH level	[21]
			Serum MDA level, ALT and AST activities restoration	
			Elevation in serum IgM, IgG and IgA levels	
	Aqueous extract (flesh and seeds)	Rat	Reduction in elevated serum activities of ALT, AST and ALP due to CCl_4	[22]
	Aqueous extract (fruits)	Rat	Significant reduction in thioacetamide-induced elevation in plasma bilirubin concentration and enzymes activities of AST, ALT, LDH and γ-GT	[23]
	Aqueous extract (fruits)	Rat	Pretreatment with date palm fruit extract restored the liver damage induced by dimethoate, as revealed by inhibition of hepatic lipid peroxidation, amelioration of SOD, GPx and CAT	[24]
	Aqueous extract (fruits)	Rat	The aqueous extract attenuated oxidative stress induced by trichloroacetic acid by decreasing the extent of hepatic TBARS (thiobarbituric acid reactive substances) formation, restoring the activities of SOD, CAT and GPx	[25]
Nephroprotective	Aqueous extract (seeds)	Rat	Significant amelioration in the elevated levels of glucose, urea, creatinine, ALT, and AST due to streptozotocin.	[26]
			Significant enhancement in GSH level and SOD, GST and CAT enzyme activities with significant reduction in MDA and nitric oxide levels in both liver and kidneys	
	Pro-anthocyanidin-rich seed extract	Rat	Significant suppression in the elevated serum levels of creatinine due to CCl_4	[27]
			Significant decrease in MDA in renal tissue	
	Aqueous extract (fruits and seeds)	Rat	Significant decrease in plasma creatinine and urea levels due to gentamicin nephrotoxicity	[28]
	Aqueous extract (fruits)	Rat	Significant reduction in renal MDA due to dimethoate	[29]
Neuroprotective	Methanolic extract (fruits)	Rat	Attenuation of GSH levels and SOD and CAT activities depletions induced by ischemia	[30]
	Aqueous extract (fruits)	Rat	Significant reductions in grooming frequency and sciatic motor nerve conduction velocity	[31]
Gastrointestinal protective	Various extracts (fruits and seeds)	Mice	Aqueous and ethanolic extracts were emptied from the gastrointestinal tract contents	[32]
	P. dactylifera sap.	Rat	Significant increase of GIT transit time	[33]
	Aqueous extract (pulp)			
	Aqueous and ethanolic non dialyzed and dialyzed extracts (fruits and seeds)	Rat	Marked amelioration of gastric necrosis, hemorrhage, congestion and edema in stomach histological sections and biochemical levels of plasma gastrin and histamine in gastric mucosa induced by ethanol	[34]

	Ethanolic extract (leaves)	Rat	Oral administration of extract or its fractions in alloxan-induced diabetic rats significantly reduced serum glucose, triacylglycerol and cholesterol	[36]
	Aqueous, ethanol, methanol and acetone extracts (seeds)	In vitro	All extracts possess significant antidiabetic activity	[37]
Antihyperlipidemic	Methanol-water extract (leaves)	Rat	Significant decrease in serum LDL-C levels	[38]
Antimicrobial	Aqueous extract (fruits)	In vitro	Significant reduction in *C. albicans, C. tropicalis* and *C. kefyr* adhesion to human buccal epithelial cells	[40]
	Aqueous extract (fruits)	In vitro	Weakness and distortion of *C. albicans* cell wall	[41]
	Aqueous extract (fruits)	In vitro	Growth inhibition of *Bacillus subtilis, Staphylococcus aureus, Salmonella typhi,* and *Pseudomonas aeruginosa*	[42]
Sexual Improvement	Ethanolic extract (pollen)	Rat	Restoration to the significant reduction in sperm count and motility and with sperm abnormalities along with increased testicular MDA and decreased GSH levels due to cadmium chloride	[43]
	Ethanolic extract (pollen)	Rat	Alleviation of significant lowering in genital sex organs weight, sperm count and motility, serum LH, FSH and testosterone due to induced hyper- and hypothyroidism	[45]
	Fruits	Human	Significant increase in the mean cervical dilatation, proportion of intact membranes and spontaneous labor in comparison to control	[46]

ALT: Alanine Transaminase; AST: Aspartate Transaminase; Caco-2: Human Epithelial Colorectal Adenocarcinoma; CAT: Catalase; CCl_4: Carbon Tetrachloride; FSH: Follicle Stimulating Hormone; γ-GT: γ-Glutamyl Transferase; GIT: Gastrointestinal Tract; GPx: Glutathione Peroxidase; GSH: Reduced Glutathione; GST: Glutathione S-Transferase; LH: Luteinizing Hormone; LDL-C: Low Density Lipoprotein-Cholesterol; LDH: Lactate Dehydrogenase; MDA: Malondialdehyde; SOD: Superoxide Dismutase

Date palm (*Phoenix dactylifera*) belongs to the *Arecaceae* botanical family, which contains about 200 genera with around 3,000 species [4]. *P. dactylifera* have been developed in the Middle East over the last 6,000 years [5]. Numerous research studies have proven the preventive effect of *P. dactylifera* against different environmental chemicals that may be toxic for some tissues in animal and human [6]. Phenolics of powerful antioxidants have been isolated from *P. dactylifera* such as ferulic, gallic, catechin, chlorogenic, caffeic, coumaric, resorcinol, protocatechuic, dactyliferic, 3-o-caffeoylshikimic, sinapic, p-hydroxybenzoic, vanillic, syringic, procyanidin and isochlorogenic acids [7-9]. The anthocyanins, apigenin, isoquercetrin, quercetin, quercetrin, procyanidins, luteolin and rutin constitute the flavonoid content of P. dactylifera. Moreover, *P. dactylifera* contains considerable amounts of antioxidant vitamins C, A and E [10-12].

The therapeutic potentials of *P. dactylifera* in this study were searched in PubMed and Google scholar databases and will be discussed in the following topics with a subsequent summary (Table 1).

Therapeutic potentials of *Phoenix dactylifera*

Antioxidant activity

Oxidative stress is an imbalance between oxidant production and antioxidants. Enzymatic and non-enzymatic antioxidants reduce the reactive oxygen species (ROS) induced by oxidation. Superoxide dismutase (SOD), catalase (CAT), reduced glutathione (GSH), oxidized glutathione (GSSG) and glutathione S-transferase (GST) are the enzymatic antioxidants of concern. *P. dactylifera* has antioxidant potential via its phenolics, flavonoids and small molecules such as vitamin C, vitamin E and GSH. These antioxidant constituents of *P. dactylifera* may directly react with ROS to destroy them by accepting or donating electrons to eliminate the unpaired condition of ROS, or they may indirectly decrease the cellular free radicals by enhancing the activities and expressions of antioxidant enzymes that lead to prevention of lipid peroxidation, DNA damage and protein modification.

An in vitro study was conducted to evaluate the antioxidant potential of *P. dactylifera* fruit aqueous extract by determination of its hydroxyl-radical-scavenging potential.

Various concentrations of *P. dactylifera* extract in a Fe^{2+}/ascorbate/EDTA/H_2O_2 system were measured with a thiobarbituric acid method. They also studied the superoxide scavenging potential of date fruit extract in a photo-reduction of riboflavin assay measured with/by nitroblue tetrazolium reduction method. There was a significant dose dependent relationship in the inhibition of hydroxyl-radical inhibition by *P. dactylifera* extract with complete inhibition shown at a concentration of 4.0 mg/mL [13]. The antioxidant effects of *P. dactylifera* were found to hinder lipid peroxidation and inhibit free radical-mediated oxidation of lysine, arginine, and proline residues of proteins, leading to prevention of the formation of carbonyl derivatives. This potential of *P. dactylifera* may be due to their total phenolic content, flavonoids, vitamins C, A and E and β-carotene and GSH. However, the authors didn't quantify the active ingredients present in *P. dactylifera* and studied only the aqueous extract.

A 2015 study was done on the antioxidant potentials of *P. dactylifera* fruit's phenolic or flavonoid fractions from two date varieties, Amari and Hallawi, through determination of ferric-reducing antioxidant power, free radical scavenging capacity, inhibition of Cu^{2+}-induced LDL oxidation, and enhancement of HDL-mediated cholesterol efflux from macrophages [14]. The flavonoid fraction was found to have greater inhibition of LDL oxidation than phenolic fractions, with IC50 of 9-31 nmol/GAE mL versus 85-116 nmol/GAE mL, respectively. The phenolic and flavonoid fractions of both Amari and Hallawi dates exhibited variable capacities to reduce ferric ions, scavenge radicals, and inhibit LDL oxidation. In addition, only the flavonoid fractions stimulated cholesterol removal from macrophages (Table 1).

Another in vitro study to evaluate the antioxidant activity of different Tunisian common varieties of *P. dactylifera* was done on Korkobbi, Bouhattam, Baht, Bekreri, Garn ghzal, Smiti, Mermilla, Kenta, Nefzaoui and Rotbi [15]. The authors evaluated the phenolic content (54.66 mg/100 g fresh weight Korkobbi) and flavonoids (54.46 quercetin equivalents/100 g fresh weight Korkobbi). The percentage of lipoperoxyl radical inhibition reached 83% in the Korkobbi variety, while it was about 95% in the Rotbi variety. The antioxidant activity of each variety differs according to the phenolics and flavonoids; Korkobbi had the most capacity against free radicals. A similar study confirmed a high positive correlation between total phenolics in methanolic extract of Mauritanian *P. dactylifera* varieties (Tamr and Blah fruit) and Trolox equivalent antioxidant capacity, suggesting that phenolics were the major contributor to the antioxidant activity [16].

Anticancer activity

Cancer is a lethal disease that attacks more than one-third of the world's population. Smoking, viral infection, chemicals, radiation, environmental factors, and dietary factors are the main predisposing causes of cancer. Chemotherapy, radiotherapy and surgery are the primary conventional treatments along with complementary and alternative therapies of natural origin. Phenolics and flavonoids of medicinal plants have been used as powerful anticancer drugs through up-regulation of anti-apoptotic molecules such as p53, caspases and Bcl-2-associated X protein (Bax) or by down-regulation of apoptotic molecules as Akt, B cell lymphoma-2 (Bcl-2) and nuclear factor κB (NFκB) [17].

One study of digested date extract (DDE) and polyphenol-rich extract (DPE) tested the growth inhibition of human epithelial colorectal adenocarcinoma (Caco-2) cells before and after pH-controlled batch culture fermentation in comparison to untreated cells [18]. In 24-well plates, Caco-2 cells were seeded at low confluence (5×10^4 per well) and exposed to DDE and DPE (0.2 mg/mL). After 24, 48 and 72 h the cells were harvested and fixed by the addition of 125 µl ice-cold trichloroacetic acid. The medium was removed and the cells washed, and total biomass was determined using sulforhodamine B. At 48 h, DDE had a significantly greater growth inhibition percentage of Caco-2 cells than DPE, with DDE inhibiting about 90%. After 48 h fermentation, the DDE induced 70% inhibition while DPE induced 30% inhibition.

β-glucan is another phytochemical constituent of *P. dactylifera* that exhibits anticancer activity. β-glucan was isolated from Libyan *P. dactylifera* and had potent antitumor activity correlated to their (1→3)-β-D-glucan linkages. This was the first report on β-glucan antitumor effect [19]. There is a completed trial investigating the anticancer effect of low molecular weight β-glucan derived from oats in cancer cells: human melanoma (Me45), human epidermoid carcinoma (A431) and normal immortal human keratinocyte (HaCaT) and murine macrophages (P388/D1) [20]. The β-glucan significantly deceased cancer cells' viability, while no toxic effect on the normal cells was seen. Moreover, β-glucan induced a significant expression of caspase-12, the inflammatory caspase, in both cancer cell lines (Me45 and A431), while in HaCaT cells was significantly lower and in P388/D1 cell line was negative. The data revealed strong anticancer properties of new low molecular weight β-glucan from oat. This study is of particular interest and directs researchers to investigate the anticancer effect of β-glucan isolated from *P. dactylifera* against numerous cancer cell lines in both in vitro and in vivo studies.

Hepatoprotective activity

The liver is a vital organ of the digestive system that regulates a wide variety of anabolic and catabolic biochemical reactions necessary for normal vital functions. It protects organisms from toxic chemicals through its capacity to convert lipophilic into more water-soluble metabolites that can be efficiently eliminated from the body via urine. This protective ability of the liver is from the enzymes that catalyze the oxidation, reduction and hydrolysis (Phase I) and conjugation (Phase II) of functional groups on drug and chemical molecules. Some toxic chemicals such as carbon tetrachloride (CCl_4), thioacetamide, dimethoate and dichloroacetic acid induced oxidative stress and morphological changes in liver that induces liver injuries and defects in hepatic detoxification ability. These changes restored by *P. dactylifera* as it enhances the liver's detoxification ability will now be discussed.

An example is a study on the protective effect of Siwa *P. dactylifera* flesh aqueous (1:3 w/v) against CCl_4 hepatotoxicity in rabbits [21]. Rabbits were pretreated with a single dose of 15 mL of Siwa date palm extract orally. CCl_4 solution was prepared in paraffin oil (50% v/v) and injected subcutaneously with a dose of 1.0 and 2.0 mL CCl_4 solution/kg. *P. dactylifera* extract significantly ameliorated the elevated levels of malondialdehyde (MDA) and GSH depletion in the liver tissue caused by CCl_4 along with marked ameliorations of elevated alanine transaminase (ALT) and aspartate transaminase (AST). Moreover, *P. dactylifera* induced an elevation in serum immunoglobulin M (IgM), immunoglobulin G (IgG), and immunoglobulin (IgA) levels (Table 1).

A study of CCl_4 in rats and the hepatoprotective effect of both *P. dactylifera* flesh and seeds was conducted by soaking either *P. dactylifera* flesh or seeds powder in distilled water in a ratio of 1:3 w/v [22]. Rats were treated by either extract before and after CCl_4 intraperitoneal injection. The results revealed a significant reduction in elevated ALT, AST, and alkaline phosphatase (ALP) activities due to CCl_4 in rats subjected to both pre- and post-treatments with the aqueous extracts of *P. dactylifera* flesh and seeds. To complete the experimental design of this study, we recommend an additional group injected by olive oil alone as a control because the CCl_4 was prepared in olive oil, and to inject it intraperitoneally at a dose of 0.2 mL/100 g B.W. of rats.

There have been several studies of the ameliorative effect of the aqueous extract of *P. dactylifera* against the elevated serum hepatic markers due to induced hepatotoxicity by thioacetamide (400 mg/kg/single dose), dimethoate (20 mg/kg/day) and dichloroacetic acid (0.5 and 2 g/L water) in rats [23-25]. *P. dactylifera* extracts induced significant reduction in the elevated activities of serum ALT, AST, ALP, lactate dehydrogenase (LDH) and γ-glutamyl transferase (γ-GT) due to chemicals. The topics of these studies are of great importance toward investigating the protective role of *P. dactylifera* against environmental chemicals that have serious hazards. Further studies on the protective role *P. dactylifera* against various pollutants were recommended for future research.

Nephroprotective activity

The kidneys are a vital organ for detoxification of environmental chemicals or drugs by methylation, sulphation, glucuronidation, glycine conjugation and glutathione conjugation by GST. Metabolism of drugs by the kidneys produces toxic metabolites and ROS that favor renal injury through lipid peroxidation, protein damage, and DNA strand breaks. In the same context, numerous studies that evaluated the nephroprotective activity of *P. dactylifera* have proven that the protective *P. dactylifera* effect against various nephrotoxicity may be due to the phenolics and antioxidant vitamins content present in *P. dactylifera* and will now be discussed.

A study of the protective role of *P. dactylifera* seeds aqueous extract against diabetes induced by streptozotocin in rats has been done [26]. Orally administered extracts to diabetic rats at a dose of (1 g/kg/d) for 4 weeks significantly ameliorated the elevated levels of glucose, urea, creatinine, ALT, and AST due to streptozotocin. Furthermore, significant enhancement in GSH level and SOD, GST and CAT enzyme activities with significant reduction in thiobarbituric acid reactive substances (TBARS) and nitric oxide levels in both liver and kidneys were stated for the *P. dactylifera* treated groups. The enhancement in both liver and kidney functions was attributed to the antioxidant property of *P. dactylifera* seeds extract.

In another study the renal protective activity of proanthocyanidin-rich date seed extract against CCl_4-induced toxicity model in rats in a dose of 100 mg of extract/kg rat was evaluated [27]. Relative to the control CCl_4-intoxicated group, pretreatment with extract significantly suppressed the elevated serum levels of creatinine, 5.41 versus 7.07 mg/dl. The authors attributed the protective effect against CCl_4 nephrotoxicity to the free radical scavenging potentials of proanthocyanidin-rich date seed that was determined by a significant decrease in MDA in renal tissue.

In a study of the protective role of *P. dactylifera* flesh and seeds extract against nephrotoxicity due to gentamicin, an antibiotic used to treat many types of bacterial infections, rats were given either the *P. dactylifera* flesh extract (50 % w/w) mixed with the food or the seeds extract in the drinking water in a ratio of 2:1 w/v [28]. Gentamicin was injected intramuscularly at a dose of 80 mg/kg/day during the last 6 days of treatment after 28 consecutive days of *P. dactylifera* extract treatments. The *P. dactylifera* flesh and seeds significantly decreased plasma creatinine and urea levels due to gentamicin nephrotoxicity in comparison to control. This antioxidant activity may be attributed to melatonin, vitamin E, and ascorbic acid components of *P. dactylifera*. Characterization and quantification of antioxidant components of both *P. dactylifera* flesh and seeds extracts were not done in this study by HPLC or GC-MS; these techniques may be helpful in understanding the mechanism by which the extracts protected the rats against gentamicin nephrotoxicity.

Another study investigated the nephroprotective activity of *P. dactylifera* in rats. Two experiments were done; in the first, rats received daily treatment with date extract of 4 mL/kg, 30 minutes prior to oral administration of dimethoate 20 mg/kg for 2 months as a protective experimental design. In the second experiment, rats received dimethoate alone for a month and then began receiving the experimental treatment in the second month [29]. In both experiments, *P. dactylifera* groups had no significant difference in plasma creatinine, urea, uric acid, and renal SOD when compared to control, while MDA levels were significantly decreased due to *P. dactylifera* in comparison to the dimethoate injected group. Further studies should be done to investigate the protective role of *P. dactylifera* along with different nephrotoxic drugs or environmental chemicals with molecular and histopathological studies on the anatomical elements of the kidney, such as the glomerulus, tubules, and medulla.

Neuroprotective activity

Brain injuries are of numerous etiologies involving genetic, metabolic, nutritional, endocrinological, toxic, and infectious mechanisms in antenatal or postnatal periods. Both peripheral neurotoxicity and central neurotoxicity are associated with chemotherapies such as paclitaxel, cisplatin, cytarabine, ifosfamide and methotrexate or environmental neurotoxicants such as lead and mercury.

In a study on the neuroprotective effect of *P. dactylifera* against bilateral common carotid artery occlusion, rats were pretreated with methanolic extract of *P. dactylifera* fruits at a dose of 30, 100 and 300 mg/kg for 15 consecutive days [30]. All depletion induced by ischemia in GSH levels and SOD and CAT activities was attenuated by *P. dactylifera* extract at a dose of 100 and 300 mg/kg, while no significant changes were recorded at the low dose (30 mg/kg). Hence, the *P. dactylifera* methanolic extract protected against induced oxidative stress and neural damage in a dose-dependent manner.

Diabetic neuropathy in streptozotocin-induced diabetic rats and the effect of *P. dactylifera* fruits aqueous extract has been studied [31]. Diabetes was induced in rats by intraperitoneally injection of 45 mg/kg freshly prepared streptozotocin dissolved in 0.1 mol/L citrate buffer. After one week, fasting blood sugar was determined and rats with fasting blood glucose levels over 200 mg/dl were considered diabetic. After confirmation of diabetes, aqueous extract of *P. dactylifera* in a dose of 4 mL/kg rats was administrated by gavage daily for 6 weeks. *P. dactylifera* induced significant reductions in grooming frequency and sciatic motor nerve conduction velocity in comparison to control, whereas in rearing status, total distance moved, and mobility duration no significant changes were recorded. It would be useful for this study to be extended to include multiple doses to decide on the most suitable one to induce neuroprotection.

Gastrointestinal protective activity

Prophet Muhammad (Peace Be Upon Him) recommended Muslims to break their fasting during the holy month of Ramadan (Iftar) with date fruits. Research studies have proven that eating date fruits after fasting has benefits for our nutrition and gastrointestinal tract (GIT) health [2, 10]. The Prophet (Peace Be Upon Him) said, "When you break the fast, you should do it with a date-fruit for there is blessing in it, and if you do not find a date-fruit, break it with water for it is pure". Date-fruits are easy to digest so they don't exhaust the empty stomach of the fasting person to receive the food after being inactive throughout the day, activating the release of digestive secretions and preventing constipation.

In a 2003 study the GIT transit time effects of different extracts of *P. dactylifera* fruit and seeds were studied in comparison to yohimbine, a drug that increased the GIT transit time, and clonidine, a drug that decreased the GIT transit time, in doses of 1 mg/kg and 2 mg/kg, respectively, by intraperitoneal injection in mice [32]. The aqueous extracts of the *P. dactylifera* fruit and seeds were prepared by adding distilled water to coarsely pounded *P. dactylifera* fruit in a ratio of 3:1 (w/v), and leaving for 48 h at 4^0C with continuous stirring. Parts of aqueous extracts were dialyzed with dialysis tube and running tap water for 24 h. The dialyzed aqueous extract was kept refrigerated and used daily for 14 consecutive days. The *P. dactylifera* fruit and seeds were added in a ratio of 1:3 (w/v) to ethanol at 4^0C with continuous stirring. Each mouse was fasted from food but not water 16 h prior to administration of extracts of either *P. dactylifera* fruit or seeds by oral gavage at doses of 0.01, 0.02 or 0.04 mL/kg. After 2 h, all animals were given a test meal containing charcoal and gum arabic in water. Thirty minutes after that they were stunned and sacrificed by cervical dislocation. The travelled distance of the charcoal column along the small intestine was determined to evaluate GIT transit time. Aqueous and ethanolic extraction of *P. dactylifera* fruits and seeds were emptied from the gastrointestinal tract contents in a dose-dependent manner.

Another study compared GIT transit time due to *P. dactylifera* sap (0.4 and 4 mL/kg rat), aqueous *P. dactylifera* pulp extract (150 and 300 mg/kg rat), clonidine (1 mg/kg rat) and yohimbine (2 mg/kg rat) orally [33]. The *P. dactylifera* sap and aqueous *P. dactylifera* pulp extract significantly increased the GIT activity in rats in a dose-dependent manner that confirmed their use in traditional Tunisian medicine for the treatment of constipation. For further study, the phytochemical composition of *P. dactylifera* sap and aqueous *P. dactylifera* pulp extract should be measured to determine the active ingredients that influenced the GIT transit time.

A study by the same group evaluated the protective effects of 3 different extracts of *P. dactylifera* fruits and seeds against ethanol-induced gastric ulceration in rats [34]. All extracts of *P. dactylifera* fruit and seeds aqueous, dialyzed or ethanolic were orally administrated in a dose of 4 mL/kg for 14 consecutive days. On the last day rats were given 1 mL of ethanol 80% 1 h before sacrifice. The data revealed marked amelioration of gastric necrosis, hemorrhage, congestion and edema in stomach histological sections and biochemical levels of plasma gastrin and histamine in gastric mucosa induced by ethanol. The authors did not use a positive control group of rats treated with extracts without administration of ethanol, for proper comparison with ethanol treated rats.

Anti-diabetic activity

Diabetes mellitus (DM) is one of the common metabolic disorders in which about 2.8% of the population suffers from DM and its complications worldwide. Numerous natural herbs are used as alternatives for treatment of diabetes. The normoglycemic effect of *P. dactylifera* may be due to its minerals, phenolics and phytoestrogens constituents. The minerals that are present in *P. dactylifera* have a vital role in DM management such as magnesium that plays a key role in regulation of insulin action and insulin-mediated-glucose uptake. Zinc induces the insulin formation and release, while chromium potentiates the insulin action, and selenium, which has been shown to stimulate glucose uptake, regulates glycolysis and pentose phosphate pathways. Phenolics present in *P. dactylifera* are considered to be a potent inhibitor of alpha glycosidase and alpha amylase, leading to reduction of

carbohydrates' digestion and absorption that may counteract the hyperglycemia present in DM [35].

The antidiabetic effect of *P. dactylifera* leaves ethanolic extract (PDE) and its organic and aqueous fractions on diabetes induced by alloxan in male rats was investigated by Mard et al [36]. Freshly prepared solution of alloxan monohydrate in normal saline solution was injected intraperitoneally in a dose of 150 mg/kg to rats that had fasted overnight. After 1 h, the animals were allowed to feed ad libitum. Their blood glucose level was checked before and 1 week after alloxan injection. The treatment groups received different doses of PDE (100, 200, and 400 mg/kg), PDE fractions (50, 100, and 200 mg/kg), or glibenclamide (4 mg/kg), whereas diabetic control animals received saline (5 mL/kg) orally once a day for 14 days. Blood samples (20 µL) were obtained from the tail tip of fasted rats at 1st, 6th, 10th, and 14th days, and blood glucose levels were monitored. Oral administration of PDE or its fractions in alloxan-induced diabetic rats significantly reduced blood glucose, serum triacylglycerol and cholesterol when compared with the control group. Plasma insulin levels were increased in the treated groups relative to the control group. This result may be considered as a scientific explanation for the hypoglycemia in alloxan-diabetic rats treated by *P. dactylifera*.

The antidiabetic effects of aqueous, ethanol, methanol and acetone extracts of different varieties of Omani *P. dactylifera* seeds were evaluated via an in vitro experiment [37]. All extracts of *P. dactylifera* seeds of all date varieties possess significant antidiabetic activity, whereas aqueous extract induced the maximum inhibition of α-glucosidase and α-amylase, suggesting presence of some non-phenolic water soluble compounds as inhibitors of these enzymes. The inhibitory effect of aqueous extract on α-glucosidase and α-amylase levels may guide the researcher to analyze extracts with HPLC and GC-MS to know the phytochemical constituents that are responsible for inhibition of α-glucosidase and α-amylase activities. Inhibition of α-amylase enzyme retards the digestion of starch and glycogen and α-glucosidase inhibitors also decrease the digestion of carbohydrates. Hence, *P. dactylifera* seeds extract reduces the impact of carbohydrates on blood sugar and may be useful along with antidiabetic diets and drugs.

Antihyperlipidemic activity

Hyperlipidemia is the major risk factor for atherosclerosis that leads to morbidity and mortality in Western society; therefore, scientists are trying to discover new therapeutics to counteract hyperlipidemia. There are many mechanisms by which herbs can reduce hyperlipidemia through improvements of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase activity that have a potential role in regulating serum lipid profile. In addition, some herbal extracts induce inhibition of lipid accumulation during adipogenesis or inhibit the lipid production, leading to lowering serum triacylglycerol, total cholesterol and low-density lipoprotein cholesterol (LDL-C).

A study of the hypolipidemic effect of *P. dactylifera* leaves (DPL) along with flax seeds (FS) extracts was done in alloxan-diabetic rats for 4 weeks [38]. At the 4th week, either FS or DPL extract induced significant decrease in serum total cholesterol levels by 40 and 31% in FS and DPL, respectively. At the 2nd week, serum LDL-C levels were significantly decreased by both extracts, while no significant changes were recognized in serum high density lipoprotein cholesterol (HDL-C) levels. The results suggest that FS and DPL extracts could have hypolipidemic effects in diabetic rats. In order to counteract the diabetic complications, the duration of the experiment should be extended to investigate the effect of both extracts on glycation product such as hemoglobin A1c (HbA1c) and advanced glycation end products. A study of the hypolipidemic mechanism of *P. dactylifera* would also be useful.

Antimicrobial activity

According to the reports of World Health Organization (WHO), infectious diseases are responsible for over 50% of worldwide deaths, occurring mainly in tropical and developing countries [39]. Many studies have described the traditional use of some medicinal plants in the treatment of some infectious diseases through the antibacterial, antifungal, and antiviral activities of those plants.

In 2000 an in vitro study of the *P. dactylifera* (Berhi date) aqueous extract on adhesion of *Candida* species to human buccal epithelial cells (BEC) was done [40]. Amounts of 50, 100 and 200 g of *P. dactylifera* were suspended in 500 mL sterile distilled water for 24 h, homogenized and filtered. Then, 37 g of brain heart infusion broth was added to each filtrate and the final concentrations were 5, 10 and 20% (w/v). Significant reduction (between 25 % and 52 % in relation to control) in *C. albicans*, *C. tropicalis* and *C. kefyr* adhesion to BEC at the different *P. dactylifera* aqueous extracts' concentrations was observed. The in vivo application of this study on either animals or human would be beneficial for future research.

A study of the Berhi date effect on the cellular ultrastructure of *C. albicans* was examined with electron microscopy [41]. Weakness and distortion of *C. albicans* cell wall was seen by scanning electron microscopy when yeast was exposed to 5 % (w/v) *P. dactylifera* extract. More extensive damage due to cell lysis and concurrent death of *C. albicans* was noticed at high concentration of *P. dactylifera* extract (20 %, w/v). Another antimicrobial study of Berhi date extract (20%, w/v) on *Bacillus subtilis*, *Staphylococcus aureus*, *Salmonella typhi*, and *Pseudomonas aeruginosa* was done by Sallal and Ashkenani [42]. *P. dactylifera* extract induced about 80 to 99% growth inhibition in nutrient broth cultures of all bacteria. *B. subtilis* was extensively affected by extract treatment through cell elongation. An application of these results may be that *P. dactylifera* extract could be included in antimicrobial drugs and in topical ointment manufacture.

Sexual improvement activity

Reproduction can be affected by exposure to a wide variety of pollutants, including dioxins, poly-chlorinated biphenyls,

heavy metals, chlorination of water, organic solvents and poly-aromatic hydrocarbons. Phenolics and flavonoids present in some herbs can induce enhancement of the expression and/or activities of antioxidant enzymes and improve fertility. *P. dactylifera* pollen is a strong chelator of environmental chemicals especially of heavy metals and their produced ROS as will be discussed.

Adult male rats were injected intraperitoneally by a single dose of cadmium chloride 1 mg/kg, then after 24 h, rats were treated with ethanolic extract of *P. dactylifera* pollen (40 mg/kg/day) orally for 56 successive days [43]. Cadmium exposure caused significant reduction in sperm count and motility and with sperm abnormalities along with increased testicular MDA and decreased GSH levels. *P. dactylifera* pollen (DPP) restored the deleterious effects of cadmium toxicity on spermatogenesis with increase in serum testosterone. The pretreatment of rats by *P. dactylifera* pollen before cadmium injection should be studied to evaluate the protective potential of *P. dactylifera* pollen to testis.

Another study was conducted to evaluate the protective effect of DPP ethanolic extract on thyroid disorder-induced testicular dysfunction in male rats. Hyper- and hypothyroidism were induced by intraperitoneal injections of L-thyroxine (300 µg/kg/day) and propylthiouracil (10 mg/kg/day) for 56 days. For the same duration, DPP extract was orally administrated in a dose of 150 mg/kg. Hyper- and hypothyroidism induced significant lowering in genital sex organs weight, sperm count and motility, serum levels of luteinizing hormone (LH), follicle stimulating hormone (FSH) and testosterone. DPP extract alleviated the reproductive dysfunction in male rats induced either by hyper- or hypothyroidism [44]. In a similar study DPP was administrated orally in doses of 120, 240 and 360 mg DPP /kg rat for 35 days [45]. In comparison to control rats, DPP significantly raised the ratio of testis and epididymis to body weight, sperm count and sperm motility at the of 120 and 240 mg/kg doses. Serum LH and testosterone levels noticeably increased at 120 mg/kg of DPP. Therefore, these studies have proven that DPP could improve fertility factors in rats. However, the mechanism by which DPP induces a reproduction improvement in male rats still needs more research in comparison to fertility medications.

A human study was carried out on 69 pregnant women who at 4 weeks prior to their estimated date of delivery ate 6 *P. dactylifera* fruits per day and were compared with 45 pregnant women as control subjects. In the pregnant women who ate *P. dactylifera*, there was a significant increase in the mean cervical dilatation (3.52 cm) vs 2.02 cm in the control group, proportion of intact membranes (83% vs 60%, respectively) and spontaneous labor (96% vs 79%, respectively). The women who ate *P. dactylifera* had a shortened mean latent phase of the first stage of labor by 510 vs 906 minutes for the control group. *P. dactylifera* at the last 4 weeks of gestation significantly augmented labor [46]. These results came in accordance with the voice heard advising to Mary: "Shake the trunk of the palm tree towards thee: it will drop new, ready dates upon thee. Eat, then, and drink, and let thine eye be cheered!" that may aid you in labor. The relationship between *P. dactylifera* and oxytocin hormone is a research point of interest because oxytocin has a pivotal role in labor.

Conclusion

P. dactylifera possesses numerous curative potentials as antioxidant, anticancer, antidiabetic, anti-hperlipidemic and antimicrobial along with protection of various cells against different environmental toxic chemicals and side effects of chemotherapy. Most studies relate the pharmacological potentials of *P. dactylifera* to its antioxidant activity.

The antioxidant activity of *P. dactylifera* varies according to its varieties and geographical area of cultivation due to variation in phytochemical constituents of *P. dactylifera*. Therefore, the phytochemical analysis of *P. dactylifera* fruit, leaves, seeds, pollen, sap and pulp of different extraction solvents has a central role in the protective mechanism of *P. dactylifera*.

From the above mentioned data about the therapeutic potentials of *P. dactylifera* we can recommend some ideas for future research:

- Standardize of *P. dactylifera* doses and frequencies in human and animal.
- Study the therapeutic potentials of *P. dactylifera* fruits, seeds and pollens.
- Isolate and characterize active components, and their mechanism of actions.
- Study the protective effect of *P. dactylifera* against various toxic substances in acute and chronic diseases.
- Study if *P. dactylifera* chelates various toxic substances via in vitro and in GIT.
- Study the effect of *P. dactylifera* on the expressions and activities of free radical generating enzymes.
- Study the metal chelating property of *P. dactylifera*.
- Study the possible anticancer mechanisms of *P. dactylifera* in in vitro and in vivo models.
- Evaluate the benefit of *P. dactylifera* for newly born children.

References

1. Marwat SK, Khan MA, Rehman F, Bhatti IU (2009) Aromatic plant species mentioned in the Holy Qura'n and Ahadith and their ethnomedicinal importance Pak J Nut 8: 1472-1479.
2. Rahmani AH, Aly SM, Ali H, Babiker AY, Srikar S, et al. (2014) Therapeutic effects of date fruits (Phoenix dactylifera) in the prevention of diseases via modulation of anti-inflammatory, anti-oxidant and anti-tumour activity. Int J ClinExp Med 7: 483-491.
3. Al-Bukhari MI, Al-Bukhari S (1976) The collection of authentic sayings of Prophet Mohammad (peace be upon him), division 71 on medicine. (2nd edition), Ankara, Turkey: Hilal Yayinlari.
4. Barreveld WH (2015) Date palm products. FAO Agricultural Services Bulletin No 101.

5. Copley MS, Rose PJ, Clampham A, Edwards DN, Horton MC, et al. (2001) Detection of palm fruit lipids in archaeological pottery from QasrIbrim, Egyptian Nubia. Proc R Soc London 593-597.

6. Yasin BR, El-Fawal HA, Mousa SA (2015) Date (Phoenix dactylifera) polyphenolics and other bioactive compounds: A traditional Islamic remedy's potential in prevention of cell damage, cancer therapeutics and beyond. Int J Mol Sci 16: 30075-30090.

7. Hamad I, Abdelgawad H, Al JS, Zinta G, Asard H, et al. (2015) Metabolic analysis of various date palm fruit (Phoenix dactylifera L.) cultivars from Saudi Arabia to assess their nutritional quality. Molecules 20: 13620-13641.

8. Mansouri A, Embarek G, Kokkalou E, Kefalas P (2005) Phenolic profile and antioxidant activity of the Algerian ripe date palm fruit (Phoenix dactylifera). Food Chemistry 89: 411-420.

9. Hammouda H, Cherif JK, Trabelsi-Ayadi M, Baron A, Guyot S (2013) Detailed polyphenol and tannin composition and its variability in Tunisian dates (Phoenix dactylifera L.) at different maturity stages. J Agric Food Chem 61: 3252-3263.

10. Al-Shahib W, Marshall RJ (2003) The fruit of the date palm: it's possible use as the best food for the future? Int J Food Sci Nutr 54: 247-259.

11. Benmeddour Z, Mehinagic E, Le MD, Louaileche H (2013) Phenolic composition and antioxidant capacities of ten Algerian date (Phoenix dactylifera L.) cultivars: A comparative study. J Func Foods 5: 346-354.

12. Mohamed RM, Fageer AS, Eltayeb MM, Mohamed AIA (2014) Chemical composition, antioxidant capacity, and mineral extractability of Sudanese date palm (Phoenix dactylifera L.) fruits. Food Sci Nutr 2: 478-489.

13. Vayalil PK (2002) Antioxidant and antimutagenic properties of aqueous extract of date fruit (Phoenix dactylifera L. Arecaceae). J Agric Food Chem 50: 610-617.

14. Borochov-Neori H, Judeinstein S, Greenberg A, Volkova N, Rosenblat M, et al. (2015) Antioxidant and antiatherogenic properties of phenolic acid and flavonol fractions of fruits of 'Amari' and 'Hallawi' date (Phoenix dactylifera L.) varieties. J Agric Food Chem 63: 3189-3195.

15. Chaira N, Smaali MI, Martinez-Tome M, Mrabet A, Murcia MA, et al. (2009) Simple phenolic composition, flavonoid contents and antioxidant capacities in water-methanol extracts of Tunisian common date cultivars (Phoenix dactylifera L.). Int J Food Sci Nutr 60 Suppl 7: 316-329.

16. Mohamed LFM, Mohamed AMV, Ben MML, Bouna ZA, Samb A, et al. (2014) Antioxidant activity of various Mauritanian date palm (Phoenix dactylifera L.) fruits at two edible ripening stages. Food Sci Nutr 2: 700-705.

17. Rodriguez ML, Estrela JM, Ortega AL (2013) Natural polyphenols and apoptosis induction in cancer therapy. J Carcinogene Mutagene S6: 1-10.

18. Eid N, Enani S, Walton G, Corona G, Costabile A, et al. (2014) The impact of date palm fruits and their component polyphenols, on gut microbial ecology, bacterial metabolites and colon cancer cell proliferation. J Nutr Sci 3: e46.

19. Ishurd O, John FK (2005) The anti-cancer activity of polysaccharide prepared from Libyan dates (Phoenix dactylifera L.). Carbohyd Polymers 59: 531-535

20. Choromanska A, Kulbacka J, Rembialkowska N, Pilat J, Oledzki R, et al. (2015) Anticancer properties of low molecular weight oat beta-glucan - An in vitro study. Int J Biol Macromol 80: 23-28.

21. El-Gazzar UB, El-Far AH, Abdel MHA (2009) The ameliorative effect of Phoenix dactylifera extract on CCl4 hepatotoxicity in New Zealand rabbits. J Appl Sci Res 5: 1082-1087.

22. Al-Qarawi A, Mousa HM, Ali BH, Abdel-Rahman H, El-Mougy SA (2004) Protective effect of extracts from dates (Phoenix dactylifera L.) on carbon tetrachloride-induced hepatotoxicity in rats. Intern J Appl Res Vet Med 2: 176-180.

23. Ahmed MB, Hasona NaS, Selemain HAH (2008) Protective effects of extract from dates (Phoenix Dactylifera L.) and ascorbic acid on thioacetamide-induced hepatotoxicity in rats. Iran J Pharm Res 7: 193-201.

24. Saafi EB, Louedi M, Elfeki A, Zakhama A, Najjar MF, et al. (2011) Protective effect of date palm fruit extract (Phoenix dactylifera L.) on dimethoate induced-oxidative stress in rat liver. Exp Toxicol Pathol 63: 433-441.

25. El Arema A, Ghrairia F, Lahouara L, Thouria A, Saafia EB, et al. (2014) Hepatoprotective activity of date fruit extracts against dichloroacetic acid-induced liver damage in rats. J Func Foods 9: 119-130.

26. Abdelaziz DH, Ali SA, Mostafa MM (2015) Phoenix dactylifera seeds ameliorate early diabetic complications in streptozotocin-induced diabetic rats. Pharm Biol 53: 792-799.

27. Ahmed AF, Al-Qahtani JH, Al-Yousef HM, Al-Said MS, Ashour AE, et al. (2015) Proanthocyanidin-rich date seed extract protects against chemically induced hepatorenal toxicity. J Med Food 18: 280-289.

28. Al-Qarawi AA, Abdel-Rahman H, Mousa HM, Ali BH, El-Mougy SA (2008) Nephroprotective action of Phoenix dactylifera in gentamicin induced nephrotoxicity. Pharm Biol 46: 227–230.

29. Saafi-Ben SEB, El AA, Louedi M, Saoudi M, Elfeki A, et al. (2012) Antioxidant-rich date palm fruit extract inhibits oxidative stress and nephrotoxicity induced by dimethoate in rat. J Physiol Biochem 68: 47-58.

30. Pujari RR, Vyawahare NS, Kagathara VG (2011) Evaluation of antioxidant and neuroprotective effect of date palm (Phoenix dactylifera L.) against bilateral common carotid artery occlusion in rats. Indian J Exp Biol 49: 627-633.

31. Zangiabadi N, Asadi-Shekaari M, Sheibani V, Jafari M, Shabani M, et al. (2011) Date fruit extract is a neuroprotective agent in diabetic peripheral neuropathy in streptozotocin-induced diabetic rats: a multimodal analysis. Oxid Med Cell Longev 2011: 976948.

32. Al-Qarawi AA, Ali BH, Al-Mougy SA, Mousa HM (2003) Gastrointestinal transit in mice treated with various extracts of date (Phoenix dactylifera L.). Food Chem Toxicol 41: 37-39.

33. Souli A, Sebai H, Rtibi K, Chehimi L, Sakly M, et al. (2014) Effects of dates pulp extract and palm sap (Phoenix dactylifera L.) on gastrointestinal transit activity in healthy rats. J Med Food 17: 782-786.

34. Al-Qarawi AA, Abdel-RH, Ali BH, Mousa HM, El-Mougy SA (2005) The ameliorative effect of dates (Phoenix dactylifera L.) on ethanol-induced gastric ulcer in rats. J Ethnopharmacol 98: 313-317.

35. Ranilla LG, Kwon YI, Genovese MI, Lajolo FM, Shetty K (2008) Antidiabetes and antihypertension potential of commonly

consumed carbohydrate sweeteners using in vitro models J Med Food 11: 337-348.

36. Mard SA, Jalalvand K, Jafarinejad M, Balochi H, Naseri MKG (2010) Evaluation of the antidiabetic and antilipaemic activities of the hydroalcoholic extract of Phoenix dactylifera palm leaves and its fractions in alloxan-Induced diabetic rats. Malays J Med Sci 17: 4-13.

37. Khan SA, Al Kiyumi AR, Al Sheidi MS, Al Khusaibi TS, Al Shehhi NM, et al. (2016) In vitro inhibitory effects on α-glucosidase and α-amylase level and antioxidant potential of seeds of Phoenix dactylifera L. Asian Pac J Trop Biomed 6: 322-329.

38. Abuelgassim AO (2010) Effect of flax seeds and date palm leaves extracts on serum concentrations of glucose and lipids in alloxan diabetic rats. Pak J Biol Sci 13: 1141-1145.

39. WHO/UNICEF (2000) Global water supply and sanitation assessment 2000 Report.

40. Abu-Elteen KH (2000) Effects of date extract on adhesion of Candida species to human buccal epithelial cells in vitro. J Oral Pathol Med 29: 200-205.

41. Shraideh ZA, Abu-Elteen KH, Sallal AK (1998) Ultrastructural effects of date extract on Candida albicans. Mycopathologia 142: 119-123.

42. Sallal AK, Ashkenani A (1989) Effect of date extract on growth and spore germination of Bacillus subtilis. Microbios 59: 203-210.

43. El-Neweshy MS, El-Maddawy ZK, El-Sayed YS (2013) Therapeutic effects of date palm (Phoenix dactylifera L.) pollen extract on cadmium-induced testicular toxicity. Andrologia 45: 369-378.

44. El-Kashlan AM, Nooh MM, Hassan WA, Rizk SM (2015) Therapeutic potential of date palm pollen for testicular dysfunction induced by thyroid disorders in male rats. PLoS One 10: e0139493.

45. Mehraban F, Jafari M, Toori MA, Sadeghi H, Joodi B, et al. (2014) Effects of date palm pollen (Phoenix dactylifera L.) and Astragalus ovinus on sperm parameters and sex hormones in adult male rats. Iran J Reprod Med 12: 705-712.

46. Al-Kuran O, Al-Mehaisen L, Bawadi H, Beitawi S, Amarin Z (2011) The effect of late pregnancy consumption of date fruit on labour and delivery. J Obstet Gynaecol 31: 29-31.