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Phytochemical and Therapeutic Evaluation of Date (Phoenix dactylifera). A Review

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Abstract
Phoenix dactylifera belongs to Arecaceae family and its leaves, barks, pits, fruits and pollens contain antioxidant, hepatoprotective, antihypertensive, anti diabetic, anti-ulcerative, anti-inflammatory, anti mutagenic, ant diarrheal, antifungal, antibacterial, antiviral, ant proliferative, anticancer activity. Date fruit also increases estrogen, testosterone, PCV, Hb levels. It also reduces side effects of methyl prednisolone, lead induced heamotoxicity, male and female infertility. It is also neuroprotective, cerebroprotective agent. It is used in different medical complications. There is an overview of pharmacological properties of date palm. Date fruit has potent constituents that have therapeutic implication in prevention of diseases through anti-oxidant, anti-inflammatory, anti-tumor and ant diabetic effect. This review will highlight the phytopharmacological and other traditional uses of *Phoenix dactylifera* that will evoke scientists to search out its further uses in field of medicine
Keywords: *Phoenix dactylifera*, phytochemicals, pharmacological activity, date fruit

History
Dates (*Phoenix* dactylifera) are the members of the palm family Arecaceae. The species name *dactylifera* "date-bearing" came from two word Greek dáktulos means "date" and the Greek word ferō. The date palm (*Phoenix dactylifera L.*) stated by Arshad H. Rahmani in 2012 it is one of the oldest cultivated plants of earth and being used as food for 6000 years. More than two hundred varieties of dates are available worldwide. Mainly it is found in Saudi Arabia, Middle Eastern countries and Egypt. The native origin of dates is around the Persian Gulf and has been cultivated from Mesopotamia to prehistoric Egypt in 4000 B.C (Al-Qarawi *et al.,* 2004). The exact date of origin is difficult to identify due to old historical prospective. It is said that it originated 4000 BC from the ancient Mesopotamia area or western India (Hassan at al 2012). For thousands of years date fruit is used as staple food in Middle East. Different types of dates namely khodry, khalas, sefri, ajwa, hilali, munifi, ruthana have been found and have also shown medicinal uses. In the ancient times in Egypt's Nile valley it was used as symbol of the year. It was cultivated in Mehrgarh in 7000 B.C Ammar *et al.,* 2009. Its fruit has important place in religion as it is used to break the day long during the holy month of Ramadan in Islam. It was the belief of Jews that it is one of the seven holy fruits in the world (Ahmed at al 2008).

Introduction
Phoenix dactylifera is also known as date palm cultivated for its edible sweet fruit. For all over the world dates are of very important and have been mentioned in the Holy Quran for many times. It is medium sized plant 15-25m tall, grows single or forms clumps with other stems of same root (Bahmanpour *et al*., 2009). Its leaves are 4-6 cm long having spines on petioles and pinnate with 150 leaflets of 30cm long and 2cm wide, span of crown ranges from 6 to 10m.Fruits are oval and cylindrical 3-7cm long and 2-7cm diameter. Date contained 20-70 calories. It turns from bright red to bright yellow on ripening. Single stone of date is 2-2.5cm and 6-8mm thick (Waffa *et al.,* 2012). Date palm is dioeciously having female and male parts originating from one seed but only 50% part is female i.e. fruit bearing. Its natural constituents like phytochemicals, sterols, carotenes and flavonoids have been screened for various medicinal activities to reduce the side effects of artificial drugs that bring harm to human body systems (Abdu, 2011). The pulp is rich in iron calcium cobalt copper, fluorine, manganese, sodium, copper and zinc etc.

Phytochemical Analysis
Whole plant contains Carbohydrates, steroids, alkaloids, flavonoids, tannins and vitamins. Its phenolic profile shows that it contains cinnamic acids, falconoid glycosides and flavones. Steroids are like cholesterol, sigmasterol, campesterol and alpha sitosterol were identified by thin layer chromatography (TLC). Vembuet al in 2012 stated that fresh dates contain anthcyanins. Dates contain nutrients as carbohydrates (44-88%), (Abdu, 2011), dietary fibers (6.4-11.5%), fats (0.2-0.5%) and proteins (2.3-5.6%). Dates contain fatty acids as palmitolieic acid, Oleic, linoleic and linolenic acid. In dates 23 amino acids are found. Furthermore vitamin A, B1, B2 and nicotinic acid are also found in dates stated by Abdu, 2011.

Antioxidant and Hepatoprotective
In body free radicals cause oxidative damage leading to carcinogenesis, aging, mutagenesis, atherosclerosis,

neurogenerative diseases and depression. Free radicals attack on lipids, proteins and nucleic acids and cause complications. It was proved by in-vitro studies that *Phoenix dactylifera* has antioxidant and anti-mutagenic properties. In an experiment, hepatotoxicity was induced in 25 New Zealand rabbits by carbon tetrachloride and palm date syrup was tested on them. Mainly ALT and AST levels were tested by the enzymatic kits and NADH disappearance was measured by spectrophotometer. The blood was taken from heart. NADH disappearance is directly proportional to activity of ALT and AST. Significant reduction of ALT and AST levels was predicted. In this experiment three different types of syrups were used Saudi, Iraqi and Rotab that showed different reduction in enzyme levels. It was concluded that hepatoprotective activity depends on the total phenolic contents and flavonoids in *Phoenix dactylifera* among those varieties. Rotab has strongest antioxidant and hepatoprotective effects due to high total phenolic contents and high flavonoids in it. Iraqi syrup has lowest hepatoprotective and antioxidant properties due to low phenolic contents and flavonoids. From this study shoaibi Z.A *et al.,* emphasized that date palm should be used in daily diet for better health. In another study flesh of *Phoenix dactylifera* was used to determine its hepatoprotective activity in rabbits. 60 New Zealand rabbits were used in six groups (10/group). Hepatotoxicity was induced by CCl4 and after treatment with water extracts; the levels of AST, ALT, IgM, IgG and IgA were seen. Rabbits' livers were also homogenized for the detection of malondi aldehyde (MDA) and (Glutathione) GSH that are biomarkers of lipid per-oxidation and anti-oxidative stress respectively. Significant ameliorating of ALT, AST was caused by water extraction. In this study hepatotoxicity (lipid per-oxidation products; MDA) is increased and endogenous antioxidant (GSH) decreased while pretreatment with the extract, ameliorates increased and decreased level of MDA and GSH respectively. Increased level of IgM, IgG and IgA (near to control level) showed potent antioxidant property of *Phoenix dactylifera* as hepatotoxicity decreased the level of these proteins especially IgG. Mechanisms of action of *Phoenix dactylifera* in hepatoprotectivity was revealed in this study. It was observed that Beta-sito sterol in *Phoenix dactylifera* is responsible for protective effects, Flavonoids inhibit cytochrome P450 aromatization that favors liver regeneration and T-Ascorbic acid contents of *Phoenix dactylifera* are useful in liver protection. This study suggested that CCl4 induced hepatotoxicity can be prevented by aqueous flesh extract of *Phoenix dactylifera* (El-Gazzar *et al.,* 2009). In some other studies, it was stated that plant phenolic compounds including flavonoids are effective antioxidants with anti-mutagenic and anti-carcinogenic effects. Date palms also have a role in neutralizing free radicals and suppressing various types of diseases development and progression. Another report showed that aqueous extracts of dates have antioxidant, antimicrobial and anti-mutagenic activity. Another study has shown that dates have the highest concentration of polyphenols among the dried fruits. The antioxidant activity of phenolic compounds is a due to their redox properties, which have an important role in absorbing and neutralizing free radicals. Phytochemical studies showed significant antioxidant capacities and capabilities to lower the prevalence and mortality rates of cancer. Dates are a good source of antioxidants due to the carotenoids and phenolics with quantity 3942mg/100g and antioxidants constituents 80400µmol/100g. In recent study, the antioxidant activities in different types of dates such as Fard, Khasab and Khalas were observed and stated that Khalas is having best quality, has higher antioxidant activity, total carotenoids and bound phenolic acids as compared to other types of dates.

In another study Ajwa date was tested as functional food by using 28 wistar rats in which orchatoxin A was used to induce hepatotoxicity. This 4-weeks study determined the effects of aqueous extracts of flesh of *Phoenix dactylifera* in affected rats by analyzing the levels of ALT, total bilirubin and by examining the liver tissues. Extract showed strong antioxidant activity in tested animals. Levels of bilirubin and ALT were lower as compared to control group. And normal tissues were observed under the microscope after treatment with *Phoenix dactylifera* aqueous extract. Many histological alterations were reduced by extract application as compared to rats treated with orchatoxin A. In 2011, Abdu SB concluded from this study that *Phoenix dactylifera* may increase antioxidant enzymes that provide protection to hepatocytes against oxidative stress. *Phoenix dactylifera* has significant role in protecting cellular damage caused by oxidative stress generated by free radicals production in body (Pujari *et al.,* 2011).

Anti-diabetic activity

Synthetic medicines are effective but also have adverse effects and alter metabolic pathways. Natural products and their constituents is a good approach in the control of diabetes as they are less toxic and free from side effects. Plants also show significant effects in managing function of pancreatic tissues by an increase in insulin production and inhibit the intestinal absorption of glucose. The exact mechanism of action of dates in controlling diabetes is not fully understood but it might be due to increase the output of insulin and inhibit absorption of glucose. Various active compounds present in *Phoenix Dactylifera* extract (PDE) such as flavenoids, steroids, phenol and saponins, which play a role as anti-diabetic. Flavonoid compounds in date fruits' epicarp play a significant role in the improvement of the different biochemical results in diabetic rats. It prevents diabetic's neuropathy. Male wistar rats were made diabetics with alloxan. Ethanolic leaf extract of *Phoenix dactylifera,* phytochemical analysis of extract was carried out that shows presence of flavonoids, saponins, steroids and

phenols while tannins, alkaloids and terpenoids were not found in the extract. Results of this study determined pronounced antihyperglycemic and antihyperlipidimic activity. Mechanism of action was also illustrated.

Anti-Cancer and Antimutagenesis activity

Cancer is a multi-fact disease worldwide. The alteration in normal mechanism of action of genes is a major cause in the development and progression of cancer. The current treatment based on radiotherapy and chemotherapy is effective but also shows adverse consequences. Constituents of medicinal plants such as flavanoids and phenol play a significant role in cancer control through the regulation of genetic pathways without any side effect The dates fruits constituents have shown the antitumor activity but its exact mechanism of action in the prevention of tumor is not known exactly. Study on animal model showed that glucans, constituents of date fruits exhibited a dose dependant anticancer activity with an optimum activity at a dose of 1mg/kg in tumor.

An experimental study stated that if rats were pretreated with ajwa dates extract before ochratoxin as compared to OTA treated rats, severity of the histological lesions as well as the serum levels of total bilirubin and ALT enzyme activity were greatly reduced.

The date's constituents show a vital effect in the inhibition of phase I enzymes such as CYP450 and enhance the activity of phase II enzyme. An experimental study showed that the antigen toxicity of date pits is due to its ability to scavenge the alkyl radical or inhibit the aromatize activity of cytochrome P-450. It has been proved that foods having antioxidant activity is beneficial in cancer and cardiovascular problems and increase life by 60%. By using vital capacity tests and Ames test, anticancer effects of date palm were determined on Salmonella typhimurium. Prevention percent was determined by rat liver extract of *Phoenix dactylifera* pollen grains when applied on thebacterium. In this way Gita *et al.,* in 2011 displayed anticancer and ant mutagenic activity. In another study, it was observed that fruit extract of *Phoenix dactylifera* has potent anti mutagenic activity and this study also demonstrates free radical scavenger like activity of fruit extract of *Phoenix dactylifera by* (Avail, 2002). Glucan, (a polysaccharide) was isolated from the Libyan dates and its anticancer study showed that glucan has potent antitumor activity may be due to (1-3)-β-D-glucan linkages. This was first study performed on dates for its anticancer activity stated by (Ishurd and Kennedy, 2005).

Ant diarrheal activity

Aqueous extract of *Phoenix dactylifera* can also be used for the treatment of diarrhea that reduces mean number of defecations when compared to control saline group. *Phoenix dactylifera* can reduce severity of diarrhea in dose dependent way. In this study diarrhea was induced by castor oil (Kumar *et al.,* 2010; Al–Taher, 2008).

Anti Inflammatory and Anti Proliferative Activity

Inflammation is important physiologic defense mechanisms against various factors such as infection, burn, toxic chemicals, allergens and other stimuli. The unbalance inflammatory process shows a vital role in development and progression of various diseases. Transcription factors like LOX and NF-kB play a significant role in the inflammation, cancer, diabetes and other diseases. Regulation of transcription factors is important and critical step in the prevention of disease. Inhibitors of transcription factors are important.Inhibitors used show an adverse effect and are expensive as well. Natural products are a good remedy in the suppression of NF-kB and acts as anti-inflammatory agents. Studies showed that constituents of plants such as phenolics and flavonoids act as excellent anti-inflammatory agents. Date fruits play a significant role as anti-inflammatory and recent studies predict that that ethyl acetate, methanolic, and water extracts of Ajwa dates inhibit the lipid peroxidation cyclooxygenase enzymes COX-1 and COX2. A study in animal model showed that *Phoenix dactylifera* pollen has potential protective effect via modulation of cytokines expressions another finding in the of dates fruits reported that the methanolic extract of edible portion of the fruit showed a vital role in reducing foot swelling and plasma fibrinogen. A study in the support of dates as anti-inflammatory showed that the leaves of dates are good source of natural antioxidant and anti-inflammation drugsinduction of pollen suspension and extract in rats having atypical hyperplasia (APH) t demonstrated protective effects of suspension as well as extract in APH induced rats. They cause modulation in cytokine expression and/or up regulation in autocrine/paracrine receptors said by (Elberry *et al,* 2011). In 2011 Karasawa *et al* stated that hot water fruit extract of *Phoenix dactylifera* can also stimulate cellular immune system in mice.

Gastroprotective Activity

In an experiment gastric ulcer induced by ethanol was treated with aqueous and ethanolic extracts of fruits and pits of *Phoenix dactylifera*. It was observed that levels of histamine and gastrin that had been raised due to ulcer induced by ethanol were normalized mainly by the fruit extracts. Results showed that these extracts can reduce severity of ulcer. Ethanolic undialyzed extracts most effective for this purpose .Al-Qarawi et al demonstrated that gastroprotective activity of *Phoenix dactylifera* is may be due to its antioxidant potential. He also said that Gastric emptying can be increased by ingestion of water and ethanolic extracts of fruits of *Phoenix dactylifera.*

Antibacterial Activity

Drug resistance against microbial pathogens is increasing significantly worldwide. Treatment is based on antibiotics, which are expensive and also causes adverse side effects. Natural products and their constituents can be a good choice in the control of infection as they are inexpensive, effective without side effects. *Phoenix dactylifera* and its constituents play a significant effect in the prevention or treatment of bacterial diseases. Sooad and Ramesa determined antibacterial activity of *Phoenix dactylifera* by using leaf, seed, fruit and bark of plant. Three extracts (aqueous, methanol and acetone) were tested against standard gram positive (*S. aurous, S. pyogenes*) and gram negative strain (*E. coli, P. aeruginosa*) and antibacterial activity was measured by disc diffusion method through zone of inhibition and kanamycin was used as standard drug. It was stated that all parts of plant have antibacterial potential in all extracts. Aqueous extracts were less antimicrobial thanmethanol and acetone. Fruit and leaf extracts had better antibacterial activity than seed and bark. Acetone fruit extract and methanol leaf extract has highest activity against *S. aureus* and *E. coli* respectively. But all the extracts were less effective than standard kanamycin. This study also gives authentic photochemical profile of *Phoenix dactylifera* plant. It is stated that leaf and fruit are effective antibacterial than seed and bark.

Effectiveness of methanol and acetone extract is due to their ability to extract wide range of constitutes than water and it proves methanol a better and suitable solvent for antimicrobial investigations. As fruit part has maximum constituents so it has highest antibacterial activity except *E. coli*. Antibacterial activity of *Phoenix dactylifera* is may be due to its alkaloids, flavonoids and tannins. Al-Daihan stated that Pits of *Phoenix dactylifera* have activity against gram negative bacteria.

Another recent study showed that *P. dactylifera* is helpful as antimicrobial in reducing side effects related to use of drugs like methyl prednisolon. Its extract is also useful in treating enteric diseases.

Cerebroprotective and neuroprotective activity

Rats suffering from cerebral ischemia were examined by treating with extract of date seed for its cerebroprotective effects. This study stated that seed extract significantly reduces neuronal damage. Ultra structures of cortical neurons were also preserved by treatment with seed extract. Latency time was also improved, reduction in oxidative stress in brain and restoration of anti-oxidative enzymes also occurred. *Phoenix dactylifera* seed extract also attenuates muscle weakness that shows protective effect against ischemic reperfusion damage. This cerebroprotective effect of *Phoenix dactylifera* is due to its antioxidant activity. In 2012 Kalantaripour et al stated *Phoenix dactylifera* used beneficial to manage brain ischemia fruits of *Phoenix dactylifera have also neuroprotective* effects it was examined when applied to mice in which ischemia was induced by bilateral common carotid artery occlusion. Results demonstrate that due to anti-oxidative properties and poly phenolic compounds like flavonoids, plant sterols and ascorbic acids of *Phoenix dactylifera* it is a Neuroprotective agent. (Pujari*et al.,* 2011)

Antiviral Activity

Antiviral activity of acetone pits extract of *Phoenix dactylifer* was studied by Jassim and Naji in 2007a against lytic pseudomonas phage using *Pseudomonas aureginosa* as host cell. Results stated antiviral activity with MIC <10ug/ml for *Pseudomonas* phage. Extract strongly inhibit infectivity of *pseudomonas* phage. The decimal reduction time, concentration exponent and phage inactivation kinetics strongly agree with antiviral potential of *Phoenix dactylifera*. According to Jassim and Naaji Inhibition of infectivity of phage and bacterial lysis with *Phoenix dactylifera* pits extract shows that *Phoenix dactylifera* may be an inexpensive way to protect from viral infections and further studies on *Phoenix dactylifera* may be useful for HIV treatment.

Antifungal activity

In 2012, Bukhari and Perveen determined that leaves and pits of *Phoenix*
Dactylifera has antifungal properties. They tested water, methanol and acetone extract of leaves and ptis on seven pathogenic fungi *F.oxysporum, Fusarium sp., F. solani, A. flavus, A.alternata, Alternaria sp. and Trichoderma sp.* by agar well diffusion and agar dilution method test fungi was treated with two types of dates Barhee and Rothna. Water extracts of both varieties showed no effect on growth of tested fungi. Strong antifungal activity was seen with methanol pits and leaves extract against *A. alternate*. Poor to negligible antifungal activity was seen with all extracts against *A. flavus*. Methanolic extracts of both varieties showed good activity against all fungi except *A.flavus*. Order of activity according to zone of inhibition against almost all fungi is as follows: Methanolic pitsextract>Methanolic leaves extract>Acetone pits extract>Acetone leaves extract. Results of this study demonstrate that two varieties of *Phoenix dactylifera* extracts have antifungal properties. Difference in degree of inhibition of fungi growth may be due to phytochemicals present in two varieties (Bokhari and Perveen, 2012).
(Boulenouar *et al.,* 2011 stated that dichloromethane extract of date fruit has also antifungal activity.

Delivery and labor relaxation

Constituents of date fruit play a significant role as pain-relievers and also cause relaxation in childbirth. Several medicinal plants show an effect in the stimulation of all phase of labor. An important and first study on the date's role in labor has shown that dates showed a significant effect as higher mean cervical dilatation reduced the induction and labor rise in women who ate dates fruits as compared to non-date fruit consumers.

Male Infertility and Testicular Dysfunction

Use of herbal medicines for improvement of sexual life is improving. *Phoenix dactylifera* pollens can increase level of testosterone in cirrhotic patients thus improve sexual quality of life (Ahmed *et al.,* 2008). In experiment 50 Sprague-Dawley rats were feed on *Phoenix dactylifera* pollen suspension for 35days. Investigating parameters were blood and serum samples and morphology of testis, epididimis, seminal vesicle and prostate was determined under microscope. After treatment it was seen that after treatment sperm parameters e.g. motility, count and morphology improved especially with dose 120 mg/kg. *Phoenix dactylifera* pollen suspension has also cause reduction in DNA denaturation especially with high doses. Weight of testis and epididimis also increased during this study while there was little affect of *Phoenix dactylifera* pollens on prostate and seminal vesicle or histology of reproductive tissues. It is demonstrated that dates contain estradiol and flavonoids that increase sperm health thus improving male reproductive activity. *Phoenix dactylifera* also has gonadotrophin like effects may be due to steroidal components. Thus pollens of *Phoenix dactylifera* can be used to treat male infertility problems (Bahmanpour *et al.,* 2006)

Female infertilitily and harmone levels

Women have three estrogenic hormones as Estradiol, Estrone and Estriol, among them estradiol is most potenthormone of reproductive age and estrone is a hormone inmenopausal women. It has also been reported that estrone is present in Egyptian palm pollens. First determination of estradiol and estriol was carried out during a study in which extract of pollen grains of date palm was subjected to column chromatography. N-Hexane and Ethyl Acetate fractions of pollen extracts were examined that demonstrated 10 and 5 compounds respectively including estradiol and estrone. In this study estradiol presence in dates was first determined by using HPLC. This study also supports strong antioxidant activity of *Phoenix dactylifera* pollen extract. This a first study that demonstrate phytochemical analysis of *Phoenix dactylifera*. We can conclude from this study that *Phoenix dactylifera* can also be used for Female infertility due to hormonal deficiency (Abbas and Ateya, 2011). Estradiol like activity of *Phoenix dactylifera* was also determined by another study in which 24 immature white female albino rats were used in which polar (methanol and anhydrous methanol) and non polar (petroleum ether and ether) extract of seeds of *Phoenix dactylifera* was used to study its effects on uterine weight and degree of opening of vagina. The effects of these two extracts were compared with estradiol. After investigating, it was seen that estradiol has maximum effects on said parameters followed by polar extract while non polar extract has lowest effect. Results of this study suggest that both extracts have estrogen like activity in rats but at different degrees. Interestingly this study also proved the safety of both extracts because acute toxicity studies was also conducted on adult male and female albino mice (Ammar *et al.,* 2009)

CONCLUSION

Stated Pharmacological activities of *Phoenix dactylifera* support its traditional use in different diseases and also confirm its importance in Islamic teachings. The use of dates has positive effects on human health and results of these findings suggest that it can also be a useful commercial drug after identification and isolation of active components that will assist in the treatment of cardiac, gastric and neuronal diseases. The current treatment approach for the diseases on synthetic drugs is expensive, shows unwanted adverse effects, alter the genetic and metabolic pathways. Thus, a safe, effective and affordable approach is needed to control the disease development and progression. Dates and their constituents are a good remedy as they are inexpensive, effective and easy to access. Earlier finding showed that therapeutic effect of dates in the diseases management via anti-oxidant, anti-inflammatory and anti-tumor properties. Dates fruits in the control of diseases create optimism towards the novel therapeutic strategy. Keeping all information in hand as anti-oxidant, anti-inflammatory and anti-tumor, further research based on clinical trial and animal model is required to authenticate the exact mechanism the of action of dates and their constituents in diseases prevention.

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