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Phoenix dactylifera Linn as a potential novel anti-oxidant in treating major opioid toxicity

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ABSTRACT

The use of opioids has gain popularity in the field of medicine especially in treating chronic terminally ill patients. Unfortunately, several adverse effects in relation to its use have been reported. Literature search on the adversity of opioids in treating pain, its paradoxical hyperalgesic effects and susceptibility to addiction were conducted using Pubmed, Embase and Google Scholar without species limitation. This brief article focuses on the corresponding neuro-protective, hepato-protective, anti-inflammatory, ulcero-protective and nephron-protective functions of (*Phoenix dactylifera L)* to elaborate on evidences, mechanisms, modulatory and pharmacological significance to counteract adverse effects of opioid treatment and provide insight on the underlying mechanisms of addiction.

INTRODUCTION

Phoenix dactyliferaL is one of the species of date palm that grow abundantly in countries around the Arabian Gulf. It belongs to family *Arecaceae*. The plant is considered as one of the oldest cultivated fruit trees in the Middle East since 6000 BC. Due to its abundance and historical tradomedical applications, it has been described as "tree of life" among the Arabian nations. *P. dactyliferaL* is identified by several names in different areas of the globe; the Arabs term it as 'nakhla', the Brazilians call it 'tamareira', while the Chinese and Japanese refer to it as 'wu low zi' and 'natsumeyashi' respectively (Quattrocchi, 1999). Medicinal plants continue to provide valuable therapeutic agents, both in modern and in traditional medicine (Krentz and Bailey, 2005). The role of natural products in curing health problems is gaining acceptance at the global level. There has been a great interest in medicinal uses of *P. dactylifera* as evidenced by the huge research works conducted in the last few decades (Vyawahare *et al.*, 2008). Various parts of date palm are widely used as remedies for numerous disorders, they include memory disturbances, fever, inflammation, paralysis, loss of consciousness, nervous disorders, etc. (Abdelrahman *et al.*, 2012). Phoenix *dactylifera* L. contains 44-88% carbohydrates, 6.4-11.5% dietary fibre, 2.3-5.6% protein, 0.2-0.5% fat, 15 different mineral salts and vitamins. Details essentiality of dietary contents found in dates led to its consideration as an ideal food and a balanced diet (Al-Shahib and Marshall, 2003). Date fruit is a good source of energy and rich in nutrients that constitute a significant part of a balanced diet to meet the body need (Ossi *et al.*, 2008; Sadiq *et al.*, 2013). Most of the carbohydrates in dates exist in the form of fructose and glucose, which are easily absorbed by the human body (Ahmed *et al.*, 1995; Myhara *et al.*, 1999). The dietary fiber content of dates enhances their suitability as ingredients for preparation of fiber-based foods and dietary supplements. Dietary fibers have important therapeutic application and protective effect against conditions such as hypertension, coronary heart disease, obesity, hyperlipidemia and diabetes. It also possesses anticancer, antioxidant, hepato-protective, anti-ulcerative, anti-inflammatory, anti-proliferative, anti-mutagenic, antibacterial, antifungal and antiviral potentials (Tariq *et al.*, 2000; Mallhi *et al.*, 2014).

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An opioid is defined as any psychoactive chemical that is characterized by morphine or other opiates in its pharmacological effects. The opioid drugs have the potential to produce profound analgesia, mood change, physical dependence, tolerance and a rewarding effect which may lead to compulsive drug use. It exerts its effect by binding to opioid-specific receptors, which are principally localized in central and peripheral nervous systems, as well as in the gastrointestinal tract (Reisine and Bell, 1993). The receptors in those organ systems mediate both the beneficial effects and the side effects of the drugs. Opium and its derivatives have been used for centuries, both in a medicinal and leisure manner. Indeed, findings of opium poppy seeds dating as far back as 30,000 years ago suggest the use of opium by Neanderthal man (McDonald and Lambert, 2005), the birth of opioid pharmacology can be traced in 1799, when Friedrich Serturner discovered morphine as the major active ingredient of opium. Morphine and its derivatives are not only used today for the treatment of acute and chronic pain, but also participate in modulation of gastrointestinal, endocrine and autonomic function, as well as a possible role in altered cognitive function (McDonald and Lambert, 2005).

The molecular basis for the acute action of opioids is established via interaction with its specific receptors, of the three pharmacologically distinct opiod receptor types i.e. mu, delta and kappa. Of these receptors, μ-receptor is the main receptor responsible for the action of morphine and some other abused drugs (DeLander *et al.*, 1984). The result of cloning the three different types opioid receptors revealed the interaction of their molecular structures and mechanisms through which mu and other opioid receptors exert their cellular effects through inhibition of adenylyl cyclase activity, closing of voltage-sensitive calcium channel (VSCC) and stimulation of potassium efflux by opening the voltage-gated potassium channels causing hyperpolarization (McDonald and Lambert, 2005; Reisine and Bell, 1993). However opioids have been shown to have predominant inhibitory effects on calcium entry through voltage-gated calcium channels in various cell lines and tissue preparations (Toselli *et al.*, 1997). All these inhibitory actions underlie the decrease in neurotransmitter release and reduction of cellular excitability produced by opioid through Gi or Go subunits (Rabbani *et al.*, 2003). Long-term use of these drugs is associated with undesirable adverse effects, such as oxidative damage to brain, liver, kidney and infertility, as well as constipation.

Thus, safe and effective approach is needed for prevention and treatment of these conditions (Skrabalova *et al.*, 2013). *Phoenix dactylifera* as a potent antioxidant is rich in potassium, phenolics, flavonoids and low calcium level. Additionally, because of its magnesium content, it is expected that date palm may exert antagonistic effect on adversity of opioid drugs. Opioids have been implicated in oxidative damage to brain, liver and kidney, various studies have shown that long term usage of opioids especially morphine is associated with decrease level of antioxidants and antioxidases (Zhou *et al.*, 2000; Abdelzaher *et al.*, 2010; Zhou *et al.*, 2011; Sumathi *et al.*, 2011). Moreover studies have shown that various parts of *P. dactylifera* are widely used in traditional medicine for the treatment of various disorders which include memory disturbances, fever, inflammation, paralysis, loss of consciousness and nervous disorders (Biglari *et al.*, 2008; Abedi *et al.*, 2012).

Studies have shown that date extract enhances antioxidant processes and prevent oxidative stress. A hydromethanolic extract of *P. dactylifera* fruit showed high antioxidant activity, reducing power, free radical scavenging activity, the antioxidant potential was attributed to phytoconstituents (flavonoids, saponins, tannins, steroids) and vitamin C (Naskar *et al.*, 2010). Furthermore, aqueous *P. dactylifera* extract was found to inhibit significantly the lipid peroxidation, protein oxidation and also exhibited a potent superoxide and hydroxyl radical scavenging activity in a dose dependent manner in vitro (Vyawahare *et al.*, 2008). It can be suggested that *P. dactylifera* extracts can exhibit antagonist effects to oxidative stress induced by opioid adversity.

Neuroprotection

Studies indicated that opioids especially morphine has been implicated in oxidative damage to brain (Zhou *et al.*, 2000; Abdelzaher *et al.*, 2010; Zhou *et al.*, 2011). Nevertheless, the neuro-protective effect of *P. dactylifera* may counteract the destructive activity of the reactive oxygen species (ROS) that could originate from the opioid abuse. According to the previous reports, pharmacologic agents that possess free radical scavenging or antioxidant properties do have the tendency to reduce brain damage that accompanied by brain ischemia and consequently prevents neurological deficits as observed in *P. dactylifera* use (Gemma *et al.*, 2002; Majid *et al.*, 2008; Al-Taher, 2008). The high concentrations of total phenolic content, flavonoids and anthocyanins as well as the presence of significant quantity of selenoproteins in *P. dactylifera* makes it an excellent candidate for antioxidant processes (Baliga *et al.*, 2011; Wan Ismail *et al.*, 2013), most notably, neuro-protective agents exert their function by protecting nerve cells against oxidative injury. Aqueous Date Fruit Extract (ADFE) was proven to be effective in shielding local neuronal circuitry against focal cerebral ischemia, a property that is most closely related to the oxygen free radical scavenging property of the fruit (Majid *et al.*, 2008).

However similar study conducted to investigate the role of date seed extracts (DSE) in protection against cerebral ischemic damage in rats and suggested that DSE protected cortical neuronal damage induced by middle cerebral artery occlusion credited to its antioxidant activity (Kalantaripour *et al.*, 2012). Moreover, various studies did emphasize on the neuro-protective activity of *P. dactylifera* (Pujari *et al.*, 2014; Mallhi *et al.*, 2014). Zangiabadi and colleagues (2011) reported that *P. dactylifera* could prevent diabetic deterioration and improve pathological parameters of diabetic neuropathy in rats as compared with control groups. Another study by Pujari *et al.* (2014) did verify the neuromodulatory role of aqueous date extract in reversing adverse effect of bilateral carotid artery occlusion.

With the aim of exploring the possible anticonvulsant effect of *P. dactylifera*, Al-Taher (2008) observed significant delay in seizure onset time and 50% reduction in mortality rate among pentylenetetrazole (PTZ) induced seizure mouse models following intraperitoneal administration of 3,4-Dimethoxy toluene (DMT), the major constituent of the *P. dactylifera.* In picrotoxin (Pic), nicotine (Nic) and maximal electroshock (MES)-induced seizure models, DMT administration showed complete inhibition of tonic hind-limb extension (THLE) and exhibited complete protection against mortality. Similarly, injection of DMT (100 mg/kg) to picrotoxin (12mg/kg) induced seizure model resulted in delayed onset time of convulsions and reduced death cases. However, DMT exhibited complete protection against nicotine-induced convulsions (0.8 mg/kg), the findings suggest involvement in GABAnergic or noradrenergic pathways and possible DMT induced increase in GABA level (Al-Taher, 2008).

Nephroprotection

Kidneys are delighted organs because they maintain the constancy of the extracellular fluid and receive 20-25% of cardiac output yet make up less than 1% of total body mass, they are metabolically active, and thus principally susceptible to toxic injury from agents that disrupt metabolism. Most nephrotoxicity causes either acute or chronic tubular injury, although glomerular injury may sometimes result from drugs or chemicals (Gheshlaghi, 2012; Prakash *et al.*, 2003). Drug-abuse nephropathy and infection in substance abuser causes chronic renal failure (CRF) and nephrotic syndrome in long term usage of drugs. Amphetamine by polyvasculitis mechanism induces CRF (Cooksey, 2012; Gheshlaghi, 2012). Morphine, heroin and cocaine are the most commonly abused drugs, and their use is associated with various types of renal toxicity, including a wide range of glomerular, interstitial and vascular diseases leading to acute or chronic renal failure (Singh *et al.*, 2013). However study conducted by Atici *et al.* (2005) showed that the histopathological and biochemical changes that follow chronic usage of morphine or tramadol in rat's kidneys pointed out that the risk of increased lipid peroxidation, renal damage due to long term use of opioids, especially morphine. However another study showed that feeding rats with *Phoenix dactylifera* fruit extract could reduce the levels of plasma creatinine and urea concentration and ameliorate gentamicin-induced damage to the proximal tubular regions of the rat kidneys (Al-Qarawi *et al.*, 2008). Nevertheless researchers suggested that vitamins, ascorbic acid, mineral selenium, quercetin and melatonin fractions in date fruit may be responsible for nephron protective activity (Abdel-raheem *et al.*, 2009).

Hepatoprotection

Chronic opioid intoxication has been shown to cause pathologic changes in the liver in nearly 100% of cases (Poppers, 2001). Morphine is a widely used opioid in recent years, as an effective analgesic drug for the management of severe pain. It is metabolized mainly in the liver with risk of increased lipid peroxidation and liver damage. Several reports pointed out the risk of hepatic damage due to long term usage of morphine via disturbance of oxidant-antioxidant balance (Samarghandian *et al.*, 2014; Atici *et al.*, 2005). Morphine causes serious oxidative stress in mice hepatocytes and hence results in hepatotoxicity. Antioxidants have shown promising protective effects against morphine caused hepatotoxicity as indicated by decreased plasma alanine content and aspartate transaminase activity (Zhang *et al.*, 2004). However, similar facts suggest the hepatotoxicity induced by morphine and heroin are due to the generation of reactive oxidative species that leads to oxidative stress, leading to increased lipid peroxidation in the liver of abusers (Panchenko *et al.*, 1999). *Phoenix dactylifera* is famous for its use in treating jaundice and in women before and after delivery in traditional medicine practice. Naskar *et al.* (2010) reported that water-methanolic extract of date fruit possesses potent antioxidant effect and free radical scavenging activity in addition to its hepatoprotective effect. Date syrup can replace honey by 75% because of their similarity in sugar content. Palm date syrup showed significant hepatoprotective activity in carbon tetrachloride (CCl_4) induced hepatotoxicity among New Zealand rabbits (Mallhi *et al.*, 2014). Similar Study conducted by Al-Qarawi *et al.* (2004) described the reduction of CCl_4-induced elevation in plasma enzyme and bilirubin concentration and improved morphological and histological liver damage in rats following administration of aqueous extracts of the flesh and pits of *Phoenix dactylifera*. The antioxidative and hepatoprotective effects of palm syrups during the first and second experimental periods (4 and 20 h) were very clear, since results of plasma ALT and AST and TBARS (from liver homogenate) of the control were significantly higher than those obtained from animals treated with syrups (Zakaria *et al.*, 2012). Moreover, similar study by Ahmed *et al* (2008) indicated that treatment with aqueous extract of date flesh or by ascorbic acid significantly reduced thioacetamide-induced elevation in plasma bilirubin concentration and enzymes and this study suggests that thioacetamide-induced liver damage in rats can be ameliorated by administration of extract of date flesh or ascorbic acid and this signified the potency of antioxidant activity in date fruit.

Fertility and Sexual Function

Clinical studies have consistently associated medical and recreational opioid use with hypogonadism and hormone imbalance in both genders. Most studies proposed that the majority of chronic opioid usage are associated with hormonal imbalances and interfere with menstruation in women by limiting the production of luteinizing hormone (LH). Opioid-induced endocrinopathy likely causes the strong association of opioid use with osteoporosis and bone fracture which is likely caused their agonist of opioid receptors in the hypothalamus and the pituitary gland (Brennan, 2013; Colameco, 2009). Studies also have shown that opioid treatment results in hypogonadism (Vuong *et al.*, 2010) by disrupting the normal pulsatility of gonadotropin releasing hormone (GnRH) secretion with subsequent reduction of the release of luteinizing hormone (LH) and follicle-stimulating

hormone (FSH) from the pituitary gland and of testosterone or estradiol (E2) from the gonads (Adams *et al.*, 1993). The *Phoenix dactylifera*, date palm is used as therapy for male infertility and impotency in traditional medicine. The presence of α-amirin, triterpenoidalsaponins, estrone, estradiol, estriol and flavonoids in date palm may explain the facilitatory role of the fruit on sexual function by increasing the release of dopamine (DA) in the nucleus accumbens (Abedi *et al.*, 2014). Oral administration of date fruit suspensions at doses of 120 and 240 mg/kg improved the sperm count, motility, morphology and DNA quality with an associated increase of the weight of testis and epididymis (Bahmanpour *et al.*, 2006). However similar study conducted by Abedi*et al* (2012) indicated that *Phoenix dactylifera* pollens can enhance penile erection, influence sexual arousal and improve performance. It seems the primary site of its action may be the testis; however, its possible effect on the hypothalamo-hypophyseal axis may serve as a better candidate. *Phoenix dactylifera* fruit extract have been shown to increase sperm count in guinea pigs and to enhance spermatogenesis and increase the concentration of testosterone, follicle stimulating hormone (FSH) and luteinizing hormone (LH) in rats (Elgasim *et al.*, 1995).

Study conducted by Abedi*et al* (2014) reveal that male rats treated with aqueous date extract has high sexual behavior when exposed to estrous female counterpart than control. However similar study conducted by Bajpayee (1997) and Bahmanpour*et al* (2006), indicated that the effect of *P. dactylifera* in reproductive system of adult male rats and is exerted by improving the quality of sperm parameters and consequently improves fertility. *P. dactylifera* pollens were reported to contain estrogenic materials, estrone, which gives the fruit its characteristic of gonadal stimulating potency that improve male infertility and promote gonadotrophin activity in the rat (Bajpayee, 1997).

Gastrointestinal Protection

Treatment of opioid-induced gut dysfunction: Opioid analgesics are the mainstay in the treatment of moderate-to-severe pain, unfortunately, adverse effects can severely compromise the therapeutic use offered by these drugs, the gastrointestinal tract (GIT) is one of the main targets of their unwanted actions, the most common and devastating being constipation (Holzer, 2004). Constipation develops in many people on opioid because it directly inhibits and disrupts normal functions of the intestinal tract. Since tolerance to this problem does not develop readily, most patients on long-term opioid will need a laxative (McCarberg, 2013). The opioid-induced motor stasis results from blockade of gastrointestinal peristalsis and fluid secretion pathways, and reflects the action of the endogenous opioid system in the gut (Holzer, 2004). *P. dactylifera* fruit with its high fibers and laxative property has been demonstrated by quantifying their effect on gastrointestinal transit in mice, compared with the control, the animals that received date fruits extracts emptied more of their gastrointestinal content which ranged from 4 to 22% (Al-Qarawi *et al.*, 2003). However study conducted by Al-Qarawi*et al* (2005) indicated that the aqueous and ethanolic extracts of the *P. dactylifera* fruit and pits were effective in ameliorating the severity of gastric ulceration and mitigating the ethanol-induced increase in histamine and gastrin concentrations, and the decrease in mucin gastric levels. The ethanolic extract was more effective than the rest of the other extracts used. It is suggested that the basis for the gastro protective action of date extracts may be multi-factorial, and may include its antioxidant action.

Anti-Inflamatory and Analgesic Function

Inflammation is a complex phenomenon comprising of a humoral (cytokines) and cellular (leukocytes, monocytes and macrophages) mechanisms. It is usually a self-limiting event. Chronic inflammation continuously produces inducible cyclooxygenase (COX-2) that increases the production of prostaglandin E2 (PGE2) and reduces the E-cadherin protein (Sciarra *et al.*, 2008). It also produces free radicals as several reactive oxygen species (ROS) (Rigas and Sun, 2008). Opioid-induced hyperalgesia has been observed in some patients, whereby individuals using opioids to relieve pain may paradoxically experience more pain as a result of their medication. This phenomenon, although uncommon, as seen in some palliative care patients, most often when dose is escalated rapidly (Vella-Brincat and Macleod, 2007). Additionally, intravenous opioid drug users are at high risk of various infections including hepatitis and human immunodeficiency virus infection. The various parts of *Phoenix dactylifera* are widely used in traditional medicine for the treatment of various disorders which may include memory disturbances that follows neuro inflammation (e.g postoperative cognitive dysfunction), fever, systemic inflammation and neuropathic pain (Abedi *et al.*, 2012). *P. dactylifera* possesses significant anti-inflammatory activity and recent report on the Ajwa dates showed that ethyl acetate, methanolic, and water extracts of Ajwa dates inhibit the lipid peroxidation, cyclooxygenase enzymes COX-1 and COX2 activity (Zhang *et al.*, 2013). However a study by Elberry *et al.* (2011) suggested that anti-inflammatory and antiproliferative activities of *P. dactylifera* pollen may serve a potential protective effect in atypical prostatic hyperplasia (APH) in Wistar rats through modulation of cytokine expression and/or upregulation of their autocrine/paracrine receptors. Shabani *et al.* (2013) have reported that *P. dactylifera* extract decreases thermal hyperalgesia and can prevent pain resulting from diabetic neuropathy. Mohamed and Al-okbi (2004) suggested the use of *the* fruits in the treatment of headache and arthritis. Moreover, in a similar context, anti-arthritis activity of Phoenix dactylifera was demonstrated in rats (Doha *et al.*, 2004).

CONCLUSION

Although increased education on prescription and use of opioids is important in achieving good pain management, adverse effects such as pruritus, postoperative nausea and vomiting (PONV), sedation, hypotension, respiratory depression and opioid induced constipation do need pharmacologically active agents that have the capacity to individually counteract these complications by

interfering with opioid activity and their receptor activation pathways. Interestingly, phytochemistry and immense pharmacologic properties of *Phoenix dactylifera* such as its haemopoietic, antioxidant, neuro protective, anti-ulcerative, hepato protective and cerebro protective activities can be exploited to ameliorate adverse effects of opioid use. This may lead to development of novel therapeutic approach to managing side effects of opioid administration.

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