Chemical characterisation and the anti-inflammatory, anti-angiogenic and antibacterial properties of date fruit (*Phoenix dactylifera* L.)

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Abstract

Ethnopharmacological relevance: Date fruit, *Phoenix dactylifera* L. has traditionally been used as a medicine in many cultures for the treatment of a range of ailments such as stomach and intestinal disorders, fever, oedema, bronchitis and wound healing.

Aim of the review: The present review aims to summarise the traditional use and application of *Phoenix dactylifera* date fruit in different ethnomedical systems, additionally the botany and phytochemistry are identified. Critical evaluation of *in vitro* and *in vitro* studies examining date fruit in relation to anti-inflammatory, anti-angiogenic and antimicrobial activities are outlined.

Key Findings: The ethnomedical use of *Phoenix dactylifera* in the treatment of inflammatory disease has been previously identified and reported. Furthermore, date fruit and date fruit co-products such as date syrup are rich sources of polyphenols, anthocyanins, sterols and carotenoids. *In vitro* studies have demonstrated that date fruit exhibits antibacterial, anti-inflammatory and anti-angiogenic activity. The recent interest in the identification of the numerous health benefits of dates using *in vitro* and *in vivo* studies have confirmed that date fruit and date syrup have beneficial health effects that can be attributed to the presence of natural bioactive compounds.

Conclusions: Date fruit and date syrup have therapeutic properties, which have the potential to be beneficial to health. However, more investigations are needed to quantify and validate these effects.

Keywords: *Phoenix dactylifera, date fruit, polyphenols, antioxidant, anti-inflammatory*

33 **Abbreviations**

34 BCCAO; Bilateral common carotid artery occlusion

35 CD31; Cluster of differentiation 31

36 COX-2; Cycloxygenase-2

37 HBA; Hydroxybenzoic acid

38 HCA; Hydroxycinnamic acids

39 IL -1; Interlukin -1

40 IL -1β; Interlukin -1 beta

41 IL -6; Interlukin -6

42 LPS; Lipopolysaccharide

43 MIC; Minimum inhibitory concentration

44 ROS; Reactive oxygen species

45 TNF-α; Tumor necrosis factor alpha

46 VEGF; Vascular endothelial growth factor

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1. Introduction

Fruits have always been a major constituent of the human diet. Recently, human food selections, dietary lifestyles and patterns have become increasingly governed by economic necessity, availability and promotion by industry and governments (Heber and Bowerman, 2001). These factors are having a significant impact on diet selection and food intake rather than nutritional significance or health benefits. This has led in some cases to increase in morbidity and mortality associated with food related diseases such as obesity and diabetes (Kris-Etherton et al. 2002).

There is growing epidemiological evidence coupled with clinical and scientific studies strongly supporting the assertion that diets rich in fruits, vegetables, whole grains and fish have a protective role in preventing a wide-range of diseases including type 2 diabetes, cancers, atherosclerosis and cardiovascular diseases. As a result there has been a growing interest in assessing the role of food-based bioactive compounds in preventing the development and the incidence of these diseases.

The health benefits of medicinal foods, plants and herbs are subject to immense interest amongst the public, pharmaceutical companies and health professionals. This interest has resulted in the global health market becoming flooded with products claiming to prevent, reduce symptoms and cure diverse ailments or improve health and prevent chronic diseases (Raskin et al. 2002). Due to this increased commercial exploitation of medicinal foods, almost all varieties of fruit and vegetables are being re-evaluated for their health benefits and phytochemical composition in both clinical settings and under laboratory conditions.

Where access to modern medicines is limited, plants have become increasingly important as a source of alternative medicinal compounds (Raskin et al. 2002). Many plant-based medicines are extracted from diverse sources (Evans, 2009). Primary and secondary metabolites in fruits are numerous with primary metabolites including amino acids, sugars, and chlorophylls whilst secondary metabolites include carotenoids, tannins,

flavonols, phenols, alkaloids and saponins (Evans, 2009). The metabolites in fruits conferring specific appearance, colour, taste, aroma and astringency. Secondary metabolites have been associated with a wide-range of bioactive behaviour, believed to have significant beneficial effects for human health (Balasundram et al. 2006) such as antimicrobial (Taleb et al. 2016a), anti-inflammatory and anti-angiogenic activities (Taleb et al. 2016b). The present review aims to assess the traditional use and application of *Phoenix dactylifera* L. date fruit in different ethnomedical systems, additionally the botany and phytochemistry are identified. Critical evaluation of *in vitro* and *in vitro* uses of date fruit in relation to anti-inflammatory, anti-angiogenic and antimicrobial activities are outlined.

2. Botanical nomenclature and classification

According to Tropicos (Tropicos, 2016), date palm belongs to the Kingdom Plantae, the class Equisetopsida C. Agardh, the subclass Magnoliidae Novák ex Takht, the superorder Lilianae Takht, the order Arecales Bromhead, the family Arecaceae Bercht. & J. Presl and the genus *Phoenix* L. Furthermore, The Plant List identifies that *Phoenix dactylifera* L. is the only accepted name for the date palm tree, with available synonyms such as *Phoenix dactylifera* L. var. *costata* Becc., *P. dactylifera* var. *cylindrocarpa* Mart., *P. dactylifera* var. *gonocarpa* Mart., *P. dactylifera* var. *oocarpa* Mart., *P. dactylifera* var. *oxysperma* Mart., *P. dactylifera* var. *sphaerocarpa* Mart., *P. dactylifera* var. *sphaerosperma* Mart., and *P. dactylifera* var. *sylvestris* Mart. (The Plant List, 2013).

The date palm (*Phoenix dactylifera*) and its fruits are cultivated in dry and semi-arid regions of the world and is the dominant constituent upon which the sustainable biophysical and socio-economic structures of the oasis ecosystem are based (Barreveld, 1993). Furthermore, date palm is the only indigenous wild desert plant definitively domesticated in its native harsh environment (Jaradat and Zaid, 2004). *Phoenix dactylifera* is composed of genetically discrete clones representing thousands of cultivars without the benefits of a dynamic mutation-recombinant system (Chao and Krueger,

2007). It thrives alongside numerous wild palms distributed across the desert belt in the Middle East and North Africa (Zaid and Arias-Jimenez, 1999).

The fruit of the date palm is processed and utilised in various ways but the purported medicinal properties remain largely unknown in the Far East and the West, essentially due to its lack of growth potential and use in these regions but importantly, due to insufficient scientific and clinical data (Vayalil, 2012).

3. Traditional relevance

The historical and religious significance of *Phoenix dactylifera* and date fruit are well documented, they were utilised as anthropomorphic symbols in early as Mesopotamian civilisations, including Sumer and Babylonia, and by the ancient Egyptians in the Nile valley, in the pre-Dynastic era and the Greco-Roman Period (350 AD) (Manickavasagan et al. 2012).

The health and medicinal use of date fruit expanded originally from Middle Eastern folklore to Indian traditional medicine. *Phoenix dactylifera* and date fruit are used as alternative medicine in countries such as Algeria, Egypt, India, Iran and Iraq (Table 1). *Ayurveda* medicine, a medicinal system with historical roots in the Indian subcontinent uses date fruit as a medicinal application for the treatment of lower respiratory tract infections, sciatica, oedema, microbial infections and alcohol intoxication (Kunte and Navre, 1939; The Wealth of India, 1952; Nadkarni, 1976). In the Middle East and across Arabia a decoction of dates with salt is used as a remedy for dehydration associated with diarrhoea (Al-Qarawi et al. 2005). Additionally date products such as date syrup and date paste are administered for treating sore throat and inflammation of the mucus membranes and intestinal disturbances (Souli et al. 2014). Alternative and various uses of *Phoenix dactylifera* in different ethnomedical systems are outlined in Table 2. Despite widespread use, there is limited scientific and clinical evidence to support the aforementioned claims. However the increased understanding of functional composition and phytochemistry of date fruit has begun to provide scientific rationale for date fruit's medicinal ability, which are outlined below.

4. Phytochemical composition

As previously mentioned, secondary metabolites are known to mediate some of the health benefits associated with date fruit. Secondary metabolites form an integral component of a fruit's structural and cellular integrity (Macheix and Fleuriet, 1990) and have gained importance for their potential cancer prevention, diet related disease prevention and cardiovascular associated risk minimisation. Date fruit at the *Tamr* stage consist of a very thin pericarp containing pigments, a colourless thick mesocarp, and a thin endocarp surrounding a single seed. Date fruit, are also sugar rich (Al-Shahib and Marshal, 2002) and the amount of sugar is dependent upon type of cultivar and degree of maturation, with some varieties attaining reducing sugar concentrations of up to 78% (Al-Farsi et al. 2007). Dates are a good source of fibre in particular insoluble fibre approximating 11.5 g /100 g at complete maturation (Al-Shahib and Marshall, 2002). The protein content in date fruit is relatively low 2.5 – 6.5 g /100 g (Chaira et al. 2009), despite this date fruit contain proportionally high levels of essential amino acids including arginine and histadine which are vital to human health (Al-Aswad 1971; Auda et al. 1976; Auda and Al-Wandawi, 1980). Furthermore date fruit are a source of minerals, in particular potassium (864 mg /100 g), calcium (70.7 mg /100 g), sodium (32.9 mg /100 g), iron (0.3 – 6.03 mg /100 g), zinc (0.5 mg /100 g) and magnesium (64.2 mg /100 g) (Al-Farsi et al. 2005; Al-Farsi and Lee, 2008). These micronutrients are essential for physiological functions such as respiration (Na^+), functioning of the immune system (Zn) and physical fatigue (Fe) (Vayalil, 2012). Phytochemical analyses on *Phoenix dactylifera* have revealed the presence of various phytochemicals including phenolic acids, flavonoids, tannins, anthocyanins and carotenoids (Oni et al. 2015). The active constituents of *Phoenix dactylifera* date fruit are volatile compounds (alcohols, esters, aldehydes, lactones, ketones and terpenoids) (Guido et al. 2011; El Arem et al. 2012), phenolic acids (cinnamic acid derivatives, caffeic acid, vanillic acid and protocatechuic acid) and flavonoids (proanthocyanidines, flavonoid glycosides and anthocyanins) (Al-Farsi et al. 2005; Mansouri et al. 2005; Hong et al. 2006). The following chapter summarises the three major phytochemicals characterized for date fruit: polyphenols, carotenoids and tannins.

193 *4.1 Polyphenols*

194 Polyphenols are divided into flavonoids and non-flavonoids. Flavonoids share
195 a common carbon skeleton of diphenyl propanes or two benzene rings joined
196 by a linear 3-carbon chain (Fang et al. 2002). Flavonoids are further
197 subdivided on the basis of their chemical structure, including benzene and
198 pyran rings, examples include flavonols, flavones, anthocyanidins and
199 isoflavones. Non-flavonoids include phenolic acids, which are divided into
200 derivatives of benzoic acids and derivatives of cinnamic acid (Harborne and
201 Baxter, 1993).

202 The phenolic content and subsequent polyphenol content in date fruit is
203 correlated with cultivar, growth and development stages, health and exposure
204 of date fruit to environment and pests (El-Hadrami et al. 2011). The phenolic
205 accumulation is a result of tissue browning involved in the maturation process
206 of date fruit and is biosynthesised by the shikimate pathway.

207 Phenylalanine is the most common precursor in the biosynthesis of
208 polyphenols, and itself is an intermediate in the shikimate pathway (Tsao,
209 2010). The hydroxycinnamic acids, in particular have an important role due to
210 their abundance and diversity as the common structural elements of other
211 phenolic compounds such as flavonoids, condensed tannins, lignin and
212 hydroxycinnamic derivatives (Macheix and Fleuriet, 1990; Rice-Evans et al.
213 1996). Date fruits are rich source of phenolics that vary among different
214 varieties. Phenylalanine concentrations vary significantly during fruit
215 maturation, and increased during dried date cultivars, however, the amounts
216 of protein in date fruit are too low to be considered a vital nutritional source,
217 date fruit contains essential amino acids such as phenylalanine, leucine and
218 threonine (Al-Farsi and Lee, 2008).

219 Date fruits typically show a decline in phenolic compounds with ripening, but
220 an increase in response to stress such as bruising and fungal infection (El-
221 Hadrami et al. 2011). Date palm cultivars exhibit distinct levels and profiles of
222 polyphenol compounds such as gallic, protocatechuic, *p*-hydroxybenzoic,
223 vanillic, caffeic, syringic, *p*-coumaric, ferulic, *o*-coumaric acid, 3-caffeoylquinic
224 acid and 3-O-caffeoylshikimic acid (dactylifiric acid) (Harborne and Baxter,

225 1993; Duke, 2001; Duke and Beckstrom-Sternberg, 2015). The characteristic
226 polyphenols in date fruit are further subdivided into two primary classes
227 hydroxyl benzoic acids and hydroxyl cinnamic acids, which are represented
228 below.

229 *4.1.1 Hydroxy benzoic acids (HBA)*

230 Hydroxy benzoic acids are derived directly from benzoic acid and structural
231 variations are a result of hydroxylations and methoxylations of the aromatic
232 ring. The most common HBAs identified in date fruit include *p*-
233 hydroxybenzoic, vanillic, syringic, protocatechuic and gallic acid (Fig. 1a). The
234 first three acids are constituents of lignin and it is generally assumed that
235 plants lacking lignin lack these acids (Macheix and Fleuriet, 1990). The
236 benzoic acids are often present in bound form, thus making them insoluble as
237 they are often covalently bound to cell wall structural components such as
238 lignin and cellulose (Acosta-Estrada et al. 2014). Furthermore, more than
239 often HBAs constitute hydrolysable tannins or simple molecules by combining
240 with sugars and organic acids (Harborne and Baxter, 1993). *p*-
241 Hydroxybenzoic and vanillic acids are present in numerous fruits and are
242 found as simple combinations with glucose in soft fruits (Robards et al. 1999).
243 Protocatechuic acid has also been detected in date fruit and a number of soft
244 fruits in the form of glucosides (Waterhouse et al. 2000; Hong et al. 2006).

245 Quantitatively, HBA content is generally low in date fruit and other fruits,
246 constituting approximately 24% of the total phenolics, with the exception of
247 blackberry and the *Rosaceae* family (apples, pears, quinces, apricots)
248 (Haslam, 1989; Acosta-Estrada et al. 2014). However, they should not be
249 overlooked since HBAs have a role in the organoleptic qualities of fruits by
250 interaction to form hydrolysable tannins (condensed), which are later
251 discussed in section 4.3.

252 *4.1.2. Hydroxy cinnamic acids (HCA)*

253 Hydroxy cinnamic acids are derived from cinnamic acid and are present as
254 combined forms of four basic molecules: *p*-Coumaric, caffeic, ferulic and
255 sinapic acids (Fig. 1b). Coumarins are also derived from HCAs. There are

numerous coumarins known in nature, and they are essentially lactones derived from *O*-hydroxycinnamic acids by cyclisation and ring closure between the *o*-hydroxy and carboxyl group (Macheix and Fleuriet, 1990). The free forms of HCAs are present in fruits including date fruit (Mansouri et al. 2005; Amira et al. 2012) and exist as two common types of soluble derivatives: an ester bond between the carboxylic group of the phenolic acid and the –OH group of an organic compound, such as chlorogenic acid, or a bond with the phenolic groups of the molecule such as *p*-Coumaric acid O-glucoside.

HCAs are present in fruits in combined forms, and only few exceptional situations result in the accumulation of the free form (Tsao, 2010). Date fruit is one of the exceptions, displaying high free ferulic and *p*-Coumaric acid content (Regnault-Roger et al. 1986; Mansouri et al. 2005; Dhaoudi et al. 2011; Abbès et al. 2013) which is a result of maturation and browning which occurs due to sub-cellular decompartmentation during hydrolysis of combined forms of HCA. Caffeic acid is the most abundant HCA present in fruits, including date fruit approximating an average of 10 mg / 100 g (Vayalil, 2012). Caffeic acid consists of approximately 75% of the total HCA in most fruits (e.g. apples, tomatoes, plums) and is the major representative of the cinnamic acids. *p*-Coumaric acid is also present in a majority of fruits, but is less abundant than caffeic acid. Ferulic acid consists of a small quantity of HCAs in fruits with the exception of peppers and white grapes where its concentration exceeds 50% (Macheix and Fleuriet, 1990).

In addition to their synergistic effects, phenolic compounds and flavonoids, often exhibit pleiotropic effects that in combination may reduce the risk of chronic disease. For instance, curcumin, the active constituent of turmeric (*Curcuma longa*), a root vegetable, has been shown to be beneficial in all three stages of carcinogenesis (Thangapazham et al. 2006). In date fruit, the identified individual phenolic compounds ferulic acid, syringic acid and caffeic acid have been shown to reduce inflammation and angiogenesis (Jung et al. 2007; Lin et al. 2010). Beta-glucan polysaccharides identified in date fruit and more commonly in oats have demonstrated anti-tumour activity and cholesterol lowering potential (Ishurd and Kennedy, 2005). This suggests that

various secondary metabolites in date fruit such as polyphenols, carotenoids, anthocyanins and tannins (discussed below) may interact both synergistically and or as antagonists.

4.2 Carotenoids

A major group of compounds found within the lipid fraction of date fruit are carotenoids. Carotenoids are natural fat-soluble pigments that impart colour to plants (Baliga et al. 2011; Vayalil, 2012). They are biosynthesized by plants, fungi and bacteria (El-Hadrami et al. 2011) and are promising bioactive compounds for the prevention of chronic diseases. Date fruits are a moderate source of carotenoids, however the extent is varied depending on stage of ripening of date and the type of cultivar (Al-Farsi and Lee, 2008; Vayalil, 2012). The major carotenoids in date fruit include lutein, β-carotene and neoxanthin (Fig. 2). Date fruits that are pigmented red contain hydrocarbon carotenoids such as lycopene, neurosporene, γ-carotene and δ-carotene, alternatively; yellow-pigmented dates are rich in α-carotene, β-carotene and carotenol fatty acids (Gross et al. 1983). Some carotenoids are considered as a precursor and great source of Vitamin A. Vitamin A is involved in immune function, vision, cellular communication and reproduction. β-carotene and α-carotene are pro-vitamin A carotenoids. Whilst not all carotenoids found in date fruit are pro-vitamin A; date fruit can contribute to the recommended intake of vitamin A. Boudries et al. (2007) identified a range of 32.6 – 773 µg /100 g carotenoids in dates, alternatively fresh dates (yellow dates) have a higher carotenoid content as demonstrated by Al-Farsi et al. (2005) in Omani dates with 3.03 mg / 100 g.

4.3 Tannins

Tannins are plant polyphenols that function to precipitate proteins from aqueous media (Hammouda et al. 2013). They are sub-divided based on their structure; namely hydrolysable tannins and non-hydrolysable tannins or condensed tannins. Tannins have a number of hydroxyl groups, which give them the ability to bond reversibly with polysaccharides, proteins and alkaloids (Macheix and Fleuriet, 1990). This bonding occurs during the development and maturation of date fruit or during fruit processing.

Hydrolysable tannins are complex polyphenols that can be degraded into sugars and phenolic acids under hydrolytic conditions. Hydrolysable tannins are polyesters based on gallic acid and or hexahydroxydiphenic acid (Fig. 3) and their derivatives. Non-hydrolysable tannins are also termed condensed tannins or proanthocyanidins, they possess the general structure of polymerised flavan-3-ols in which the flavan bonds are most commonly C-4 to C-8 (Hammouda et al. 2013). Fruit bearing plants such as date fruit are rich sources of oligomeric procyanidins, which generally occur unglycosylated, and with one or both of the flavan-3-ols, (+)-catechin or (-)-epicatechin. However, these monomer forms have no tanning properties.

Examination of the tannin content of date fruit, has demonstrated that as the total phenolic content increases, the tannin content decreases, likely as a result of degradation during fruit maturation because of enzymes and/or mechanical processing (Al-Harthi et al. 2015). Martin-Sanchez et al. (2014) have also shown that date fruit and their intermediary fruit products are rich in tannins, however food processing and storage influenced this content. The authors also refer to polyphenol oxidase, a variety of enzymes associated with browning oxidation (Martin-Sanchez et al. 2014). This confirms that date fruit and date fruit products such as date syrup are further susceptible to tannin degradation as a result of processing (such as blanching) and enzyme activation.

More recently, tannins, in particular condensed tannins have been recognised as anti-nutritional factors, whereby they interfere with the absorption of nutrients (AlKurd et al. 2008) and shown to have a greater effect than hydrolysable tannins (Kumar, 1992). Animal studies have revealed that fruits of the date palm at the mature and ripe stage have the lowest tannin content, but in comparison to other fruits and tea, its tannin content is sufficiently low as to not cause a significant anti-nutrition effect (Umaru et al. 2007; Shaba et al. 2015).

The primary function of tannins is in plant defence (Fraenkel, 1959; Harborne, 2001). Furthermore, plants also regulate the synthesis and storage of secondary metabolites such as tannins, so that the more vulnerable tissues

such as fruits and young leaves contain higher concentrations than senescing tissues (Wink, 2004). Tannins are usually located in leaf vacuoles beneath the epidermal surface. The astringent and bitter taste of tannins and alkaloids can be a clear deterrent to predators (Harborne, 2001; Acamovic and Brooker, 2005).

5. Medicinal Properties

The use of date fruit or date fruit concoctions in the application of illness and disorder treatment stems from traditional use. Pollen grains of *Phoenix dactylifera* are mixed with bee-honey and ginger to increase fertility in Sudan (Khalid et al. 2007). In Palestine, consumption of 3-4 date fruits daily is administered for memory increase (Daoud, 2008). “Hurma coffee” from date fruit seeds is an herbal coffee consumed in Turkey for memory enhancing purpose (Sekeroglu et al. 2012). In Mauritius a decoction of a cup of date leaves consumed for 1 week to reduce hyperglycemia (Mootoosamy and Mahomoodally, 2014) In Pakistan dates are administered to relieve backaches and as a potent aphrodisiac whereby un-ripened dates are boiled in water and dried. After drying, 5–10 fruits are taken and boiled in 500 mL milk until half of the milk evaporates. The mixture becomes viscous and reddish (Ullah et al. 2014). Eye problems in Morocco are treated by a mixture of khol (mineral galena, PbS) and medicinal plants including *Piper nigrum*, *Phoenix dactylifera*, *Foeniculum vulgare* and *Nerium oleander* (Texidor-Toneu et al. 2016). The following section emphasises the current literature surrounding date fruit in the *Tamr* stage by examining anti-inflammatory activity, anti-angiogenic and antibacterial activities.

5.1 Anti-inflammatory activity

The anti-inflammatory activity of various parts of *Phoenix dactylifera* have been evaluated (Shabani et al. 2013; El Arem et al. 2014). *Phoenix dactylifera* has been traditionally used to treat inflammatory associated disorders such as asthma, oedema and stomach and intestinal disturbances (Yasin et al., 2015). It has also been incorporated with commercial ibuprofen and paracetamol as a pain reliever (Maryam et al. 2015; Sani et al. 2015). Current literature

384 focusing on date fruit's anti-inflammatory activity are outlined in Table 3, it is
385 evident that both *in vivo* and in *vitro*, date fruit has anti-inflammatory activity,
386 strongly linked to secondary metabolites and antioxidant behaviour.

387 Date fruit flesh exhibited significant neuroprotection against oxidative stress
388 and neuronal damage induced by bilateral common carotid artery occlusion
389 (BCCAO) with reductions in glutathione, glutathione reductase, and
390 glutathione peroxidase (Pujari et al. 2014). The presence of date fruit
391 antioxidants, namely polyphenols, carotenoids and tannins has a significant
392 impact on markers of neuroprotection in particular the anti-oxidative enzymes
393 (Pujari et al. 2014).

394 Moreover, long-term diet supplementation of 2 and 4% acetone extracted
395 date fruit were fed to Alzheimer's disease mice for 14 months and compared
396 to control fed mice. Mice fed with 2 and 4% dates significantly attenuated
397 oxidative stress factors such as lipid peroxidation, protein carbonyl levels and
398 restoration of anti-oxidative stress enzymes (Subash et al. 2014). Methanolic,
399 acidic ethanolic and basic ethanolic extracts of date fruit (1 µg/mL)
400 significantly reduced *E. coli* lipopolysaccharide (LPS) induced inflammation in
401 RAW macrophages at 24-hours, with the methanolic date fruit extract most
402 potent compared to untreated control macrophages. Intracellular ROS
403 measurement demonstrated date extract attenuated LPS induced oxidative
404 stress in a date extract concentration dependent effect. The presence of
405 phenolic compounds and flavonoids in date fruit contributed to the anti-
406 inflammatory activity (Das et al. 2015). Diabetic rats treated with 4 mL/kg
407 body weight of aqueous and methanolic extract of date fruit significantly
408 attenuated fasting blood glucose, and liver parameters serum albumin, serum
409 bilirubin and liver enzymes alanine transaminase and aspartate transaminase
410 compared to diabetic control and normal control rats (Hussein et al. 2015).
411 Pre-treatment with 100 µg/mL aqueous and methanolic extract of date fruit
412 significantly reduced COX-1 and COX-2 enzymes with COX-2 significantly,
413 however not as effective as commercial anti-inflammatory agents Naproxen
414 and Celebrex (Zhang et al. 2015). Moreover, Ajwa dates reduced the
415 expressions of pro-inflammatory cytokines (IL-6, IL-10 and TNF-α) and
416 apoptotic markers (caspase-3 and Bax) in injured Wistar rat heart tissues (Al-

Yahya et al. 2016) further endorsing date fruit's anti-inflammatory and anti-apoptotic potential against myocardial damage.

The mechanisms involved in the anti-inflammatory effect of date fruit appear to be complicated; date fruit has shown efficacy against experimentally induced inflammation as outlined in prostaglandin enzymes, Alzheimer's and diabetes type II. Compositional studies have shown date fruit is a potent radical scavenger, with high antioxidant potential (Al-Farsi et al. 2005; Abbès et al. 2013). The anti-inflammatory effect of dates could be attributed to polyphenol compounds that act as antioxidants, which scavenge free radicals produced during the inflammatory process and prevent unwanted biochemical reactions. This is inferred from the observation that date fruit can inhibit the production of nitric oxide and TNF-α (Schauss, 2013). Date fruit elevates the activity of superoxide dismutase and catalase enzymes, which suggest a potential mechanism whereby date fruit modulates enzymatic behaviour, thus triggering a signalling cascade of the antioxidant defence system (Ceballos-Picot et al. 1996) in an inflammatory situation.

Lastly, numerous bacterial species in the gut are reputed to transform food-derived phenolics, of which the phylogenetically associated *Clostridium* and *Eubacterium* genera are the most common (Selma et al. 2009). This implies that dietary phenolic compounds in date fruit are potentially transformed before they are absorbed and metabolites that reach cells and tissues are chemically, and functionally distinct from the dietary form, and such features underlie their bioactivity (Kroon et al. 2004). A recent study examined the phenolic end products produced by gut microbiota following treatment with date fruit flesh and an extract of date fruit polyphenols (Eid et al. 2014). The metabolised end products were able to induce apoptosis (cell death) in cancerous cell lines similarly to non-metabolised date fruit and date fruit polyphenols. This demonstrated that date fruit polyphenols have anti-inflammatory activity and anti-carcinogenic activity and this bioactive behaviour is maintained following gut microbiota metabolism. Despite the low percentage polyphenol absorption rate, the interaction between date fruit polyphenols and the gut microbiota induce bioactive behaviour.

5.2 Anti-angiogenic activity

Angiogenesis is a process involving the growth of new blood vessels from pre-existing vessels (Oak et al. 2005). Angiogenesis maintains inflammation by providing oxygen and nutrients for cells at inflammatory sites to maintain metabolic activity. The anti-angiogenic and anti-inflammatory effect of bioactive compounds such as polyphenols commonly found in foods, and their role in the prevention and treatment of angiogenic-associated pathogenesis has been previously reported (Tang et al. 2001; Rodriguez et al. 2006; Jung et al. 2007). Inhibition of angiogenesis has become a target for therapeutic treatment in cancer, and inflammatory disorders (Fan et al. 2006). Dates consumed raw is a traditional medicinal remedy used by breast cancer women in Palestine (Jaradat et al. 2016). Date fruit has been implicated in the anti-inflammatory and delay of cancer progression associated with angiogenesis (Table 4).

Khodary date fruit aqueous extract (4 mL/kg) decreased intracellular development of coccidiosis caused by the parasite *Eimeria papillata* in Swiss Albino mice. Treatment of mice with date extract improved inflammation in the jejunum and vacuolation of the epithelium (Metwaly et al. 2012). The effect of date fruit at two maturation stages on the hepatic enzyme system glutathione-S-transferase was studied in rats with 7, 12-dimethylbenz (alpha) anthracene induced mammary cancer. The effect of feeding date fruit (300 mg/kg) was compared to raw soybean seeds for 26 weeks. Injection with sesame oil served as a negative control group and no treatment served as positive control. Livers of rats injected with sesame oil demonstrated highest enzyme activity compared to rats fed date fruit at both maturation stages. Date fruit at both maturity stages possess antioxidant activity that is reflected positively in the prevention of 7, 12-dimethylbenz (alpha) anthracene induced mammary cancer (Al-Sayyed et al. 2013).

Additionally, date fruit flesh attenuates oxidative damage leading to liver fibrosis by reducing inflammatory cytokine TNF-α and angiogenic markers such as VEGF and CD31. The hepatoprotective effect of date fruit is attributed to the reduction of expressions of TNF-α, IL-6, and IL-1β in the

intoxicated liver (Al-Rasheed et al. 2015), this offers a mechanistic approach for future studies. The study also revealed a reduction in fibrotic markers that influence liver fibrosis, and since liver fibrosis is preceded with inflammation and angiogenesis, this could elucidate another mechanism of date fruit by influencing angiogenesis and inflammation via monitoring of fibrotic markers that are considered as a key target in anti-fibrotic therapy (Batalier and Brenner, 2001; Chen et al. 2008).

Taleb et al. (2016b) furthered this by investigating the effect of methanolic extracted date syrup polyphenols in the assessment of inflammatory-associated angiogenesis in endothelial cells. Date syrup polyphenols were found to significantly attenuate IL-6, IL-8 and VEGF, corresponding to a significant attenuation of both COX-2 and VEGF gene expression levels.

Date fruit can protect against coccidiosis-induced infection as demonstrated by the anti-inflammatory activity of date fruit protecting host tissue from injuries induced by the parasite. Furthermore, down regulation of COX-2 and VEGF pathways have been hypothesised to be associated with anti-angiogenic, anti-inflammatory and anti-carcinogenic activity of polyphenols and polyphenol rich foods (Scoditti et al. 2012; Bedran et al. 2015; Medda et al. 2015) in *in vitro* and *in vivo* models of angiogenesis and inflammation. Therefore it can be hypothesised that polyphenols in date fruit that reduce inflammation will also affect angiogenic processes leading to possible reduction in angiogenesis by affecting cytokine stimulation or inhibition.

The anticancer effect of the methanolic extract of Ajwa date on human breast adenocarcinoma (MCF7) cells was evaluated *in vitro*. MCF7 cells treated with concentrations (5, 10, 15, 20 and 25 mg/mL) of methanolic Ajwa date extract inhibited the growth and proliferation of MCF7 cells by inducing cell cycle arrest. It also induced MCF7 cell death via apoptosis in a dose and time dependent manner by the activation and changes in genetic expression associated with apoptosis (Khan et al. 2016). These studies support the indication that the anti-inflammatory and anti-angiogenic activity of date fruit and date syrup and mechanistic activity appears to occur at the protein

expression and genetic level initiating an anti-inflammatory and anti-angiogenic response.

5.3 Antimicrobial activity

A common traditional use for date fruit is the treatment of various infectious diseases with etiologies involving microorganisms. Numerous studies have investigated solvent extracts and preparations of date fruit for its antimicrobial potential, which is summarised below and outlined in Table 5. The underlying mechanisms for the antibacterial activity of date fruit warrant further investigation, despite this numerous factors have been implicated.

The antibacterial activity of date fruit against different microorganisms has been reported (El Sohaimy et al. 2015; Saha and Barnabas, 2015; Bammou et al. 2016; Samad et al. 2016). The antimicrobial activity of *Streptococcus pyogenes* treated with extracted date fruit flesh was investigated by Abuharfeil et al. (1999) *in vitro* and *in vivo*. Date fruit flesh at the greatest concentration 20% decreased the growth of *S. pyogenes* by 88.5% compared to control with no date extract. However a low concentration of date fruit extract (1:64 dilution) inhibited the haemolytic activity of streptolysin O by greater than 90%.

Date syrup crude aqueous-acetone polyphenol extract demonstrated significant antimicrobial potential against Gram-positive compared to Gram-negative microorganisms with an equivalent minimum inhibitory concentration (MIC) of 0.5 mg/mL (Dhaouadi et al. 2011) for *Staphylococcus aureus* and *Staphylococcus epidermidis*, however no bacteriostatic or bactericidal activity was observed for *Escherichia coli*. However commercial antibiotics ampicillin and oxytetrocyclin were more potent inhibitors. Ether, ethanol and water extracts of three varieties of date fruit and different ripening stages showed inhibition at all stages with most potent activity at the *Kimri* stage against Gram-positive bacteria (Saleh and Otaibi, 2013).

Kchaou et al. (2016) investigated the antimicrobial potential of second grade Tunisian date varieties. Aqueous extracts at 10 mg/mL were examined against *S. aureus, Bacillus cereus, Bacillus subtilis, Enterococcus faecalis,*

Micrococcus luteus, E. coli, Klebsiella, and *Salmonella* using the agar disk diffusion method and compared to Ampicillin as a positive control. Inhibition zone diameters were observed ranging from 9 to 19 mm for Gram-positive and from 6 to 25 mm for Gram-negative bacteria. They did not, however, exhibit antimicrobial activities towards *B. cereus* and *M. luteus*, whilst Ampicilin was the most potent inhibitor.

It is evident that date fruit and its phenolic compounds are more efficient at inhibiting Gram-positive bacteria (*S. aureus, S. pyogenes* and *E. faecalis*) than Gram-negative bacteria (*E. coli, Pseudomonas aeruginosa, Yersinia enterocolitica*). The higher resistance is attributed to presence of an outer membrane (Canillac and Mourey, 2004).

Contrary to the antibacterial activity of *Phoenix dactylifera* cited above, Zehra et al. (2015) reported no antibacterial activity in methanolic extracts of three date varieties grown in Oman against *Lactobacillus brevis*, *Salmonella typhimurium*, *E. coli* and *Pseudomonas spp*. However the authors observed antibacterial activity in *Phoenix dactylifera* acetone bark extract (diameter zones of inhibition at 16 mm for *Lactobacillus brevis* and 15 mm for *Pseudomonas spp*). The difference in results is evidence of the effect of various environmental factors such as type of cultivar, geographical location and stage of maturity that we believe strongly influence antibacterial activity.

It is interesting to know that date fruit demonstrates promising antibacterial activity against various microorganisms and that various bioactives such as phenolic compounds from various extracts of date fruit have been isolated and investigated. In respect to the traditional use of date fruit, methanolic extracts of phenolic compounds in date syrup were compared against whole date syrup treated with *S. aureus* and *E. coli*. Extracted phenolic compounds had a significantly lower bactericidal concentration compared to whole date syrup (32 mg/mL for *E. coli* and 23 mg/mL for *S. aureus*). It was further demonstrated that the sugar content had no impact on its antibacterial potential (Taleb et al. 2016a). Methanolic extract of Kimia dates was investigated for antimicrobial activity by Ravishanker and Raut (2016) using the agar cup method against *S. typhi* with zone of inhibition at 53 mm,

additionally the ethyl acetate fraction resulted in zones of inhibition of 38 mm against *S. aureus* and 35 mm against *E. coli* using the disk diffusion method. The bioactive compound in the ethyl acetate fraction contributing to the antimicrobial activity was identified as beta-Amyrin acetate ($C_{32}H_{52}O_2$) a triterpene involved in antimicrobial, antifungal and anti-inflammatory activity

Fractionation and isolation of different extracts of date fruit have identified phenolic compounds, flavonoids and flavonols. These sub-classes of polyphenols have been well documented as antimicrobials (Hamilton-Miller, 1995; Cowan, 1999) and potent antioxidants and are attributed to the structural interactions between phenolic compounds and microorganisms (Daglia, 2012). We hypothesise therefore that the phenolic compounds such as those present in date fruit utilise redox active metals such as iron and copper when interacting with bacteria in particular Gram-positive, facilitate reactive oxygen species generation due to the formation of highly reactive quinones that participates in the Fenton reaction, whereby the inherent SOS system of bacteria are unable to effectively manage.

6. Conclusions and future directions

Date fruit is a commodity that is frequently consumed and prescribed in various ethnomedical systems especially throughout the Middle East. This review outlined the botanical nomenclature and summarised the phytochemistry and medicinal applications of date fruit (*Phoenix dactylifera*) at the *Tamr* stage. A robust body of scientific evidence has enabled the emergence of an evidence base on which the medicinal properties of date fruit now stands, but despite this it is clear that much remains to be discovered.

Ethnomedical evidence has demonstrated the traditional use and application of date fruit as a medicinal agent to treat inflammation, infection and disease. It is becoming increasingly apparent that polyphenols mediate many of these effects. These findings verify the traditional applications of *Phoenix dactylifera* in the treatment of wounds, fever, stomach disturbances and oedema.

Furthermore, compounds within date fruit have the potential to be utilized as natural preservatives in the food and pharmaceutical industry.

However, full characterization of the different polyphenol compounds at specific maturation stage, cultivar and geographic location is necessary to further develop an understanding of the beneficial contribution of individual date fruit polyphenols in human health. Eventually, this would mitigate any cultivar variability to ensure that the health benefit are fully realised and supported scientifically.

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List of Captions

Fig. 1a. Hydroxybenzoic acids identified in date fruits

Fig. 1b. Hydroxycinnamic acids and derivatives identified in date fruits

Fig. 2. Carotenoids identified in date fruits.

Fig. 3. Tannin sub-components for non-hydrolysable tannins identified in date fruits.

Table 1.
Traditional medicinal use of *Phoenix dactylifera* L. across different countries

Table 2.
Traditional use of *Phoenix dactylifera* L. across different ethno-medical systems

Table 3.
Anti-inflammatory activity of different date fruit extract investigated *in vivo* and *in vitro.*

Table 4.
Anti-proliferative activity of date fruit in different experimental models

Table 5.
Antimicrobial activity of *Phoenix dactylifera* L. as demonstrated in experiments.