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Review

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

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A R T I C L E I N F O

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A B S T R A C T

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 *P. 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 *P. 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.

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

Abbreviations: BCCAO, Bilateral common carotid artery occlusion; CD31, Cluster of differentiation 31; COX-2, Cycloxygenase-2; HBA, Hydroxybenzoic acid; HCA, Hydroxycinnamic acids; IL −1, Interlukin −1; IL −1β, Interlukin −1 beta; IL −6, Interlukin −6; LPS, Lipopolysaccharide; MIC, Minimum inhibitory concentration; ROS, Reactive oxygen species; TNF-α, Tumour necrosis factor alpha; VEGF, Vascular endothelial growth factor

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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 *P. dactylifera* L. is the only accepted name for the date palm tree, with available synonyms such as *P. 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, 2016).

The date palm (*P. 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). *P. 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 *P. 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. *P. 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 *P. 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 *P. dactylifera* have revealed the presence of various phytochemicals including phenolic acids, flavonoids, tannins, anthocyanins and carotenoids (Oni et al., 2015). The active constituents of *P. 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.

4.1. Polyphenols

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

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