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Review Article

Unveiling the Cardiovascular-Guarding Secrets of *Phoenix dactylifera*: A Systematic Review

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ABSTRACT

Cardiovascular disease is a significant cause of global mortality, creating a substantial burden on public health and economy. Research focusing on beneficial food and its active ingredients is essential to mark the health needs. Dates are abundant in polyphenols, particularly flavonoids, micronutrients and dietary fibers, that can influence cardiovascular health and potentially alleviate vascular illness. Based on this, we aimed to systematically review the cardiovascular effects of *P. dactylifera*. In this study, a systematic-research was performed according to the PRISMA guidelines to collect all relevant studies on "cardio-protective effect of *P. dactylifera*" using various databases up-to 2024. A total of 109 studies were obtained and evaluated in accordance with pre-selected criteria for inclusion/exclusion and finally 21 studies were included in this review. Evidence from *in vitro, in vivo*, clinical studies, histological and genetic data indicated that consuming date fruit entirely or its extracts could regulate specific indicators of cardiovascular health, especially level of lipids (triglycerides and cholesterol), markers of inflammation and oxidative stress. Emerging evidence suggest that integrating date fruit and extracts into one's diet could be a beneficial factor of cardiovasculary healthy life.

Keywords: Cardiovascular disease, *P. dactylifera* (dates), Dietary fibres, Polyphenols.

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INTRODUCTION

Lifestyle decisions including nutrition and physical exertion can establish risk elements for various chronic illnesses, like diabetes, specific malignancies and cardiovascular disease (Ezzati and Riboli, 2013). Globally, these chronic conditions are predicted to produce 17.3 trillion USD in total economic loss from 2011 to 2030 because of decreased productivity, elevated expenditure on healthcare and wasted capital (Mozaffarian, 2016). Mitigation and reduction of risk initiatives, like dietary guidelines, are critical to alleviate this load. Nutritional recommendations advocate advantageous trends which possess a number of important features, including plentiful consumption of fruits, seeds, vegetables, legumes, nuts, grains, sea food, yoghurt, vegetable oils and minimising consumption of processed and red meat, refined grains, starch and added sugars (McGuire, 2016). Vegetables and fruits including apples, berries, citrus, cruciferous and green leafy vegetables are abundant in various vital nutrients and other biochemicals that may give preservation from a variety of chronic illnesses (Zurbau *et al*., 2020). The dietary guidelines suggest the eating of a minimum 5-9 servings of various kinds of vegetables and fruits per day in a 2k-calorie diet (McGuire, 2016) that provides copious levels of vitamins including folate, pro-vitamin A, ascorbic acid, minerals (potassium, magnesium and calcium), fibres and along with phenolic acids, flavonoids and carotenoids (Liu, 2013). Higher consumption of polyphenols, specifically flavonoids, reduces the risk of cardiovascular diseases (Parmenter *et al*., 2020) via improving endothelial function and lowering low-density lipoprotein (LDL), platelet reactivity and blood pressure (Williamson, Kay, and Crozier, 2018).

Phoenix dactylifera (*P. dactylifera*, date), belongs to the family, *Arecaceae*. Its culture was thought to have originated in Iraq and developed as early as 3000 BCE (Yahia, 2011). Although more than 2000 date palm varieties have been found, but quality of only few have been examined. The date fruit is regarded as succulent fruit that is widely consumed worldwide. It has thick, flavourful flesh and may be consumed dry, semi-dry or soft (Ali, Parveen, and Ali, 2018). *P. dactylifera*, is extensively cultivated in Arabian Peninsula, Middle East and North Africa. This resilient plant is capable of thriving in extreme conditions, tolerating temperatures as high as 50°C, little humidity and minimal rainfall (Oladzad, Fallah, Mahboubi, Afsham, and Taherzadeh, 2021). Different types

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of dates have been noted, with Ajwa, Medjhool and Deglet Nour being the most common (Mohamad Fawzi Mahomoodally *et al.*, 2023). Saudi Arabia's 24 million date palm trees generate around one million tons of dates annually, accounting for 15 percent of global production. Date palm is a significant socioeconomic resource in the Gulf and Middle East (El Hadrami and Al-Khayri, 2012). Saudi Arabia has a wide range of over 400 different types of date cultivars, with 10 specific varieties, like Khalas, Sheshi and Reziz, being particularly favoured by consumers, particularly in Eastern portion of the country (Arabia, 2006). The date palm and its fruit have long been revered in many religions. The Prophet Muhammad (PBUH) employed the date fruit to treat different diseases and it is widely consumed by Muslims. According to the Bible, the plant is a treasured gift from God and is used to decorate Christian religious services (Indrayani, Rahmadi, Diana, and Zeranika, 2018). The Quran frequently mentions this tree, with references to palm gardens in four verses, date fruits in five verses and date palms in nine verses (Ali *et al.*, 2018). This crop is widely used for both religious and medicinal purposes in Egypt, Africa and Arabia (Selmani, Chabane, and Bouguedoura, 2017). Dates are utilized in various Ayurveda preparations because of their wide range of therapeutic effects. Ayurveda and Ayurvedic practitioners employ dates to treat dental issues, respiratory, urinary tract infections, nervous, dermal, cardiovascular, kidney and liver disorders, anxiety, gastroprotective, anti-inflammatory, immunomodulatory, anti-cancer activities anti- microbial and viral infections (Younas *et al.*, 2020).

As far we know, this study is the first systematic review addressing the potential cardioprotective effects of *P. dactylifera*. The aim is to address the following questions based on the given text.

(a)What are the effects of *P. dactylifera* on different cardiovascular conditions through animal studies and clinical trials (b) What are possible mechanisms behind these effects.

MATERIALS AND METHODS

We carried out a systematic and comprehensive research using Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline (Moher, Liberati, Tetzlaff, Altman, and PRISMA Group*, 2009) along with PICO framework (Moher *et al.*, 2009) for organizing the review process.

Participants (P) include free animals/patients (*in vivo* studies or clinical trials) with cardiac diseases and/or effected enzymes or cardiac cells (*in vitro* studies).

Intervention (I) include enzymes/cardiac cells/animals/patients treated with date fruit or extract.

Comparison (C) include enzymes/cardiac cells/animals/patients treated with control drug.

Outcomes (O) include changes in the enzymes/cardiac cells/animals/patients treated with date fruit or extract.

Search strategy

A systematic search was conducted to find out scientific papers relevant to the cardio-protective effect of *P. dactylifera* published from 2007 to 2024, in various databases including Google Scholar, PubMed and Scopus. Keywords included were "dates", "dates fruit", "*Phoenix dactylifera*", "dates palm", "cardio-protective", "cardiac effects".

Process of study selection

We started by initially choosing all research based on the study goal (examining the cardioprotective effects of *P. dactylifera*) mentioned in title and abstract. Then, we moved on to evaluating the full-text papers that met the criteria of (a) being in English, (b) containing substantial findings, (c) not being restricted by publication year and (d) encompassing *in vivo, in vitro*, or clinical studies for inclusion in this systematic review. In addition, we excluded irrelevant papers, book chapters, review articles, case studies, letters to the editors, posters, editorials and oral presentations from the current study.

Data extraction process

Each qualifying the article was investigated separately by two authors. When there was a disagreement between them, it was addressed by engaging the third author. The following information was then retrieved regarding every relevant study: (a) author name and publication year (b) models for *in vitro/ in vivo* experiment/clinical study (c) activity (d) forms of dates used (e) outcomes derived from *P. dactylifera* administration on cardiac cells/tissue/enzymes/animals/patients.

RESULTS

We collected 109 papers till 2024. After deleting duplicate research (n=34), seventy-five studies were screened based on their titles and abstracts. Eleven papers were subsequently removed, leaving 64 studies eligible for full-text review and finally 21 studies were included in the current systematic review. Figure 1 illustrates the study's selection process. Table 1 summarises the data from twenty-one eligible studies.

Phytochemistry

Phytochemicals are biologically active compounds which provide flavour, colour, aroma and protection to plants (Watson, Singh, and Takahashi, 2018). Various components of *P. dactylifera* have been analysed, showing significant levels of bioactive compounds. Examination of plant chemicals indicated that date palm tree contains abundant phenolics, alkaloids, saponins, carotenoids, terpenes, phytoestrogens, phytosterols and sterols. The tree contains phenolics as the most commonly found groups in nearly all of its parts (Mohamad Fawzi Mahomoodally *et al.*, 2023). Methanol, water, ethanol and acetone are commonly used solvents for extracting its phytochemicals. It's important

Table 1: The Characteristics included in the studies.

Sl. No.	References	Model	Activity	Form of dates used	Outcomes
1	(Anwar *et al.*, 2022)	*In vitro*	Antioxidant	Methanolic extract of Ajwa extract.	DPPH inhibition.
2	(Anwar *et al.*, 2022)	Molecular docking	Antioxidant	11 active components of Ajwa seeds.	Interaction with catalase (1DGH) and superoxide dismutase (5YTU).
3	(Khan *et al.*, 2016)	*In vitro*	Antioxidant	Four seed extracts including water, ethanol, methanol and acetone for each date Omani date variety, namely, Fardh, Naghal, Khalas, Khinazi and Khasab.	DPPH inhibition.
4	(Al-Yahya *et al.*, 2016)	*Ex vivo* (DCFH-toxicated cardiomyoblast cells (H9C2).	Cardioprotective	Lyophilized Ajwa extract.	Attenuated cytotoxicity and enhanced the H9C2 proliferation by up to 40%.
5	(Al-Yahya *et al.*, 2016)	*In vivo* (Wistar rats)	Hemodynamics, Cardiac function, Serum cardiac enzymes, Myocardial antioxidant, Inflammatory and apoptotic biomarkers, histopathological parameters.	Lyophilized Ajwa extract.	Depletion of endogenous antioxidants (CAT, SOD, NP-SH and NO) and myocyte injury marker enzymes and inhibited lipid peroxidation (MDA, MPO). Moreover, AJLE downregulated the expressions of proinflammatory cytokines (IL-6, IL-10 and TNFα) and apoptotic markers (caspase-3 and Bax) and upregulated the anti-apototic protein Bcl2. Histological data showed that AJLE pretreatment reduced myonecrosis, edema and infiltration of inflammatory cells and restored the cardiomyocytes architecture.
6	(Alsaif *et al.*, 2007)	*In vivo* (hamsters)	Antihyperlipidemic	50% (w/w) date pulp with chow.	Significant reduction in plasma cholesterol, LDL levels and organ weights. Increase in hepatic triglycerides.
7	(Mushtaq, Kausar, Kousar, and Chiragh, 2017)	*In vivo* (rabbits)	Antihyperlipidemic	Ajwa date seed powder.	Elevation in HDL, decrease in serum cholesterol, triglycerides, LDL, atherogenic index of plasma and LDL/HDL ratio.
8	(Ahmed, Alam Khan, and Jamil, 2016)	*In vivo* (albino rats)	Antihyperlipidemic	Date fruit suspension.	Decrease in cholesterol, triglycerides, LDL and VLDL along with cholesterol- HDL and LDL-HDL ratio.

Sl. No.	References	Model	Activity	Form of dates used	Outcomes
9	(Bouhlali *et al.*, 2023)	*In vivo* (male albino Wistar rats)	Antihyperlipidemic	Methanolic extract of Moroccan date fruit varieties (*Majhoul* and *Bousrdoun*).	both varieties displayed a significant decline in serum total cholesterol, triglycerides and LDL, levels as well as an elevation in HDL.
10	(Kehili, Zerizer, Beladjila, and Kabouche, 2016)	*In vivo* (adult male albino mice)	Anti-inflammatory (formalin-induced paw edema test)	Algerian date fruit extract.	Significant decline in the size of an edema size, homocysteine level in blood, CRP values.
11	(Borochov-Neori *et al.*, 2013)	*In vitro*	Anti-atherogenic	Ethanol and acetone extracts of nine Israeli date varieties Including 'Amari', 'Barhi', 'Deglet Noor', 'Deri', 'Hadrawi', 'Hallawi', 'Hayani', 'Medjool' and 'Zahidi' fruit.	Inhibition of LDL oxidation by all extracts and stimulation of cholesterol removal from macrophages by most of the extracts.
12	(Asadi-Shekaari *et al.*, 2008)	*In vitro* (hydrogen peroxide H_2O_2- induced cytotoxicity in HEPG-2, A172, U937 and PC12 cell lines).	Cytoprotective	Aqueous extract of Fruits of the date palm.	Inhibition of H_2O_2- induced cell damage in a concentration dependent manner.
13	(Mubarak, Hamid, Farrag, Samir, and Hussein, 2018)	*In vivo* (female albino rats).	Cardioprotective on Dox-induced cardiotoxicity	Hydro-methanolic extract of date palm fruit.	Reversal of cardiac tissue injury.
14	(Al-Jaouni, Abdul-Hady, El-Bassossy, Salah, and Hagras, 2019)	*In vivo* (Wistar rats).	Cardioprotective on Dox-induced cardiotoxicity	Nanopreparation (Ajwa fruit and pit).	Rats pre-treated with Ajwa nanopreparation received protection from doxorubicin-induced systolic and diastolic dysfunction. In addition, it inhibited doxorubicin-induced ischemia. There was no effect on atrial conductivity. Ajwa pre-treatment enhanced the antioxidant capability of cardiac tissue.
15	(Alhaider, Mohamed, Ahmed, and Kumar, 2017)	*In vivo* (rats).	Cardioprotective on induced Myocardial infarction	Ethanolic extract of four different varieties of Saudi Arabia date palm fruits including Berhi, Khalase, Khenizi and Reziz.	All date fruit extracts demonstrated the capacity to enhance cardiac muscles and elevate the number of progenitor cells migrating from the bone marrow to the site of myocardial infarction.
16	(Hasson *et al.*, 2018)	*In vivo* (CD1 mice).	Anticoagulant	Ethanolic extract of three different cultivars of dates including Ajwa, Khalas and Fardh.	Elevation in both prothrombin time and bleeding-time. Khalas date displayed a potential property to enhance wound healing in contrast to other dates.

Sl. No.	References	Model	Activity	Form of dates used	Outcomes
17	(Cifuentes *et al.*, 2024)	*In vivo* (L-NAME-induced hypertension and spontaneously hypertensive rats).	Vascular relaxation	Hydroalcoholic extracts of seeds of three varieties including Sukkari seed, Ajwa seed and Mabroom seed.	All extracts induced relaxations exceeding 60% in the aortic rings precontracted with 10^{-6} M phenylephrine in normotensive rats, with the Sukkari seed extract demonstrating the highest potency
18	(Nawaz, Grieve, Muzaffar, Iftikhar, and Anwar, 2024)	*In vivo* (Wistar albino rats).	Cardio-protective effect in Diabetic Cardiomyopathy (DCM).	Extract of *Phoenix dactylifera.*	Improvement in glucolipid balance and reduced oxidative stress in the DCM rats, maintaining the structural integrity of pancreas and heart. Upregulation in the expression of insulin signaling genes in pancreatic tissue and downregulation in the profibrotic gene expression in ventricular tissue.
19	(Rock *et al.*, 2009)	Clinical trial (healthy individuals, crossover design).	Anti-atherogenic	Medjool and Hallawi date.	No significant effect on BMI, serum total cholesterol, LDL, VLDL and HDL. Decrease in serum triacylglycerol by 8 % and 15% after consumption of Medjool and Hallawi date, respectively. Hallawi reduced basal serum oxidative status and susceptibility of serum to AAPH-induced lipid peroxidation and increase in serum activity of the HDL-associated antioxidant enzyme paraoxonase 1.
20	(Alalwan *et al.*, 2020)	Randomized, controlled and parallel arm clinical trial (Bahraini diabetic adults).	Anti-hyperlipidemic	Whole dates	Improvement in the lipid profile including decrease in total cholesterol and LDL.
21	(Nasrullah *et al.*, 2023)	Randomized clinical trial (patients).	Anti-hyperlipidemic	Ajwa dates pits powder.	Decline in body weight, fat mass, BMI, body fat percentage, waist circumference, visceral fat area, levels of total cholesterol in the serum and LDL.

to consider that highly polar solvents, such as methanol, are preferred to achieve the highest extraction efficiency. For instance, the yield from methanol was 33.2%, whereas chloroform, with lower polarity, yielded only 7.2%. Additionally, phenolics were predominantly present in distilled water, while chloroform was high in terpenoids (Mohamad Fawzi Mahomoodally *et al.*, 2023). The leaves were analyzed using HPLC/MS and 53 phenolic compounds were identified, with 33 of them being previously unreported. These compounds include kaempferol and malonyl derivatives. Different varieties of date palm cultivars such as

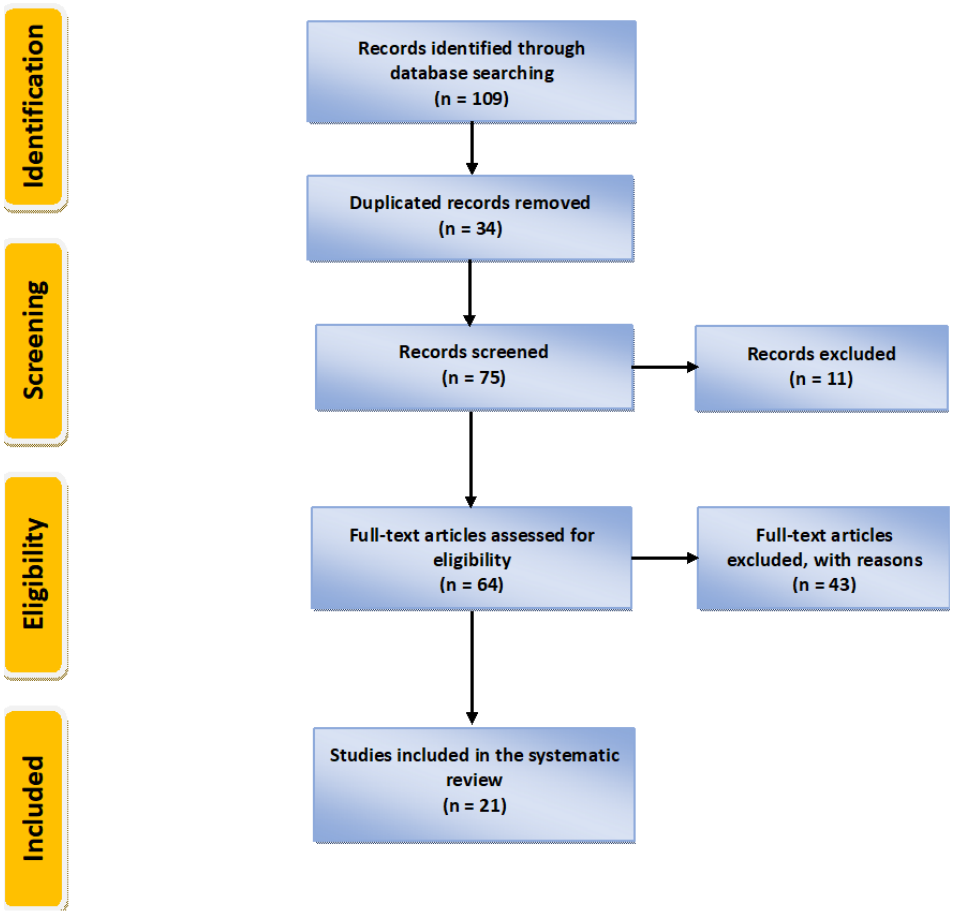

Figure 1: PRISMA flow diagram of study's selection process.

Deglet Nour, Medjhool and Barhee were distinguished based on their dried leaves. Solvents with varying polarities, including methanol, ethyl acetate, hexane and water, were employed, all of which demonstrated antioxidant and radical scavenging abilities attributed to their phenolic content.

Methanol exhibited the highest potency and contained the greatest amounts of phenolic compounds for all three varieties in descending order (69.06±0.41, 79.71±2.95, 146.46±2.61 mg/g), followed by ethyl acetate (10.69±0.09, 6.51±1.70, 4.03±0.47 mg/g), hexane and water. The most notable potential was observed in Deglet Nour, possibly due to the influence of other compounds present in the extract and the choice of solvent. Leaves of Barhi contained double quantity of phenolic content in comparison to the latter, while Deglet Nour possessed 5.5 times more tannins (Mohamad Fawzi Mahomoodally *et al.*, 2023). The only fruit that has been reported to contain flavonoid sulfates is dates (Yahia, 2011). The major flavonoids discovered were quercetin, apigenin and luteolin. Quercetin and kaempferol are connected to sugar molecules, which affects their bioavailability and bioactivity. Before absorption into the bloodstream, the sugar moiety in quercetin is hydrolyzed, which enhances the lipid solubility of the consumed compound (Li *et al.*, 2022). A study reported the chemical composition of three top-quality date varieties: Ajwa, Sukkari and Khalas. The findings showed that water extract possessed a higher phenol content of 308 mg/100g compared to ethanol extract, which had 276 mg/100 g. This was particularly evident in case of Ajwa variety, with 455.88 mg/100g in water extract and 245.66 mg/100 g in ethanol extract.

However, Sukkari variety exhibited the highest rutin concentration at 8.10 m/kg, with the levels of catechin being almost identical at 7.50 mg/kg and 7.30 mg/kg, respectively (Saleh, Tawfik, and Abu-Tarboush, 2011). Dates with a dark color such as Ajwa are rich in polyphenols, whereas light-colored dates have the lowest concentration of polyphenols. In 1978, a crystalline mixture of plant sterol was obtained from edible part of date fruit, which included, stigmasterol, β-sitosterol, campesterol and isofucosterol. Phytosterols have been shown to reduce cholesterol absorption and lower LDL-C levels because their structure is similar to cholesterol and competes with it for absorption. They are primarily found as fatty acid esters, hydroxycinnamic acid esters and glycosides. Specific enzymes in the GI tract break down all the ester bonds, producing free phytosterols and stanols.

Due to their higher hydrophobicity in comparison to cholesterol in micelles, the absorption of cholesterol in intestine is reduced (Li *et al.*, 2022).

In a separate study, various phytoestrogens including daidzein, glycitein, genistein, formononetin, lariciresinol, matairesinol, secoisolariciresinol, coumestrol and pinoresinol have been identified (Thompson, Boucher, Liu, Cotterchio, and Kreiger, 2006). A different research study examined the levels of carotenoids in three distinct types of dates during the latter stages of ripening. Specifically, it identified Lutein and β-carotene as the primary carotenoids. The Khalas variety exhibited the highest quantity of this compound. Conversely, the Ajwa contained a greater amount of polyphenols, whereas lighter colored dates had the lowest concentration (Boudries, Kefalas, and Hornero-Méndez, 2007). It has been found that Saudi dates contained high levels of p-coumaric acid, gallic acid and ferulic acid during their analysis (Hamad *et al.*, 2015). In Nigeria, Yahaya and colleagues carried out a chemical analysis of fresh dates and found no presence of flavonoids and steroids. They also investigated three different cultivars from Pakistan, specifically Dora, Dhakki and Karbalance. Among these, methanol extract of Karbalance demonstrated the highest yield. Dora was found to have the highest phenolic content including 55.648±0.11 mg/g dry extract (Yahaya, Omokhudu, Abdulahi, and Sanusi, 2015). Furthermore, examination of Egyptian cultivars involved analysing secondary metabolites through spectroscopic analysis, resulting in isolation of two compounds from epicarps: diosmetin 7-O-b-L-arabinofuranosyl, b-D-apiofuranoside and diosmetin 7-O-b-Dapiofuranoside (M. F. Mahomoodally *et al.*, 2023). Hong *et al.*, analysed the presence of flavonoid glycoside and procyanidin in Deglet Noor variety of date fruit.

They used liquid chromatography-electrospray ionisation/ tandem mass spectrometry to identify 13 flavonoid glycosides of luteolin, apigenin and quercetin, along with 19 isomeric forms (Hong, Tomas-Barberan, Kader, and Mitchell, 2006). In addition, it was discovered that oil obtained from date fruit is a crucial source of phenolics. The Modified Bligh-Dyer extraction method yielded the highest flavonoids content in extracted oil, with a level of 38 mg/100g oil. This was followed by Soxhlet method, which resulted in a flavonoids content of 34 mg/100g oil (Besbes *et al.*, 2004). The ultimate source of phenolics found in date seeds includes flavonoids such as anthocyanins, flavones, flavonols and phenolic acids, encompassing hydroxycinnamic acid and hydroxybenzoic acid. Date seeds also represent a potential means of carotenoids. Lycopene, lutein, zeaxanthin, β-cryptoxanthin and α-carotene have been identified. The pollen from date palms contains a high amount of saponin, alkaloids, steroids and phenolics, particularly flavonoids, as evidenced by their presence in the aqueous extract (Gu *et al.*, 2003).

Effect of *P. dactylifera* on different cardiovascular conditions

In 2017, an estimated 17.8 million lives were lost due to Cardiovascular Diseases (CVD), making it the primary cause of death globally. It is projected that CVD will be responsible for over 22.2 million deaths in 2030 (Virani *et al.*, 2020). Several risk elements are linked to onset and advancement of CVD. Although non-changeable elements like age, family history and gender may not be altered, lifestyle aspects tied to high cholesterol, elevated blood pressure and blood sugar, lack of physical activity, obesity and smoking can be adjusted and can have a substantial effect on heart health (Benjamin *et al.*, 2019). A healthy lifestyle requires diet and physical activity, both of which are crucial for preventing chronic diseases like CVD. Healthy dietary patterns related to heart are rich in vegetables, fruits, nuts, seeds and whole grains, which contain bioactive dietary components, such as mono and polyunsaturated fats, minerals and essential vitamins, phytochemicals like polyphenols and various non-digestible carbohydrates including fibers and resistant starch. These components, independently or via their combined impact, are believed to contribute to cardiovascular health (James *et al.*, 2014). The vascular-related effects of dates have been the main focus of many studies, which have centred on regulating cholesterol and lipid levels, defending against oxidants and managing inflammatory responses (Al-Dashti, Holt, Keen, and Hackman, 2021).

Antioxidant effect

Higher Reactive Oxygen Species (ROS) production raises the risk of CVD (Khalid *et al.*, 2020). A study used *in vitro* tests to evaluate the health-promoting properties of methanolic extracts of Ajwa date seed and fruit pulp extracts, confirmed that Ajwa dates have potential antioxidant activity. Molecular docking studies revealed that eleven active components of Ajwa seeds interact with important antioxidant enzymes catalase (1DGH) and superoxide dismutase (5YTU) (Anwar *et al.*, 2022). Various types of antioxidants, including beta carotene, CoQ10, quercetin, resveratrol, vitamin E, lycopene and vitamin C have demonstrated therapeutic advantages in treating various forms of cardiovascular disease (Jain, Mehra, and Swarnakar, 2015). Another research was carried out to explore the antioxidant and heart-protecting benefits of date fruit. In injured Wistar rats, a study discovered the antioxidant and cardioprotective impact of lyophilized Ajwa extract. The results obtained from this study showed that Ajwa date fruit extract prevented the depletion of natural antioxidants and enzymes that signal myocyte injury and it also inhibited lipid peroxidation. The biochemical analysis indicated that freeze-dried Ajwa extract lessened swelling, myocyte death and influx of inflamed cells while restoring the structure of heart muscle cells. This research demonstrated that freeze-dried Ajwa extract exhibited potent antioxidant, hypolipidemic, cardioprotective, antiapoptotic and anti-inflammatory properties, as shown

in the Figure 2, (Al-Yahya *et al.*, 2016). In Oman, a research group prepared four seed extracts (ethanol, water, methanol and acetone) from each variety of date fruit and evaluated the antioxidant activities via hydrogen peroxide scavenging method, DPPH and reducing free radicals power methods along with determination of TPCs. The study made sure that Omani date seeds are abundant in dietary antioxidants due to their high TPC (Khan *et al.*, 2016).

Antihyperlipidemic activity

In a study, hamsters were given cholesterol supplements to raise their levels of cholesterol and lipid. The measurements taken later displayed a significant reduction in plasma cholesterol, LDL levels and organ weights that had been elevated by the cholesterol supplements in the group given date fruit supplements. However, hepatic triglycerides were elevated. The study indicates that supplementation of date fruit has the potential to alter the cholesterol absorption or metabolism (Alsaif *et al.*, 2007). It has been studied that Ajwa seed powder resulted in a significant decline in serum cholesterol, triglycerides, LDL, atherogenic index of plasma and LDL/HDL ratio and rise in HDL level in diet-induced hyperlipidemia in rabbits (Mushtaq *et al.*, 2017). In another study, date fruit extract significantly reduced LDL, cholesterol, VLDL levels in blood, all without an elevation in lipid enzymes, showing atorvastatin like effect in mice model (Ahmed *et al.*, 2016). In most recent study, methanolic extract of two Moroccan date fruit varieties was tested for its anti-hyperlipidemic effect using Triton-WR-1339 and chronic hyperlipidemic rat models induced by fat rich diet. The research also involved analysing serum lipid profile and measuring peroxidation of lipid using egg yolk homogenate as a lipid-sufficient medium. The findings revealed a substantial reduction in serum total cholesterol, triglycerides and LDL level, along with an elevation in level of HDL along with decrease in body weight. Furthermore, the extracts were found to significantly inhibit peroxidation of lipid, as indicated by test of thiobarbituric acid reactive substances (Bouhlali *et al.*, 2023).

Anti-inflammatory activity

Similarly, the anti-inflammatory properties of date fruit have been assessed in mice model and the result showed a significant reduction in edema size, decreased C-Reactive Protein (CRP) and homocysteine level in blood (Kehili *et al.*, 2016). Another experiment showed that dates can reduce oxidative damage, apoptosis and inflammation in the heart tissue of rats (Al-Yahya *et al.*, 2016).

Anti-atherogenic activity

In a study, the anti-atherogenic properties and polyphenolic contents in nine different types of date fruit were investigated. The atherogenic potentials were assessed by determining the oxidation induced by free radicals and its impact on level of serum LDL. The phenolic content was analysed using reverse phase high pressure liquid chromatography and common phenolic components identified included hydroxycinnamates, flavonols and hydroxycinnamates. The study revealed clear differences in phenolic contents among all varieties of date fruit, with all types demonstrating the inhibition of cholesterol and peroxidation of lipids. The soluble phenolic compounds in date fruit were found to have atherogenic properties, effectively preventing cardiac diseases based on the findings of the study (Borochov-Neori *et al.*, 2013).

Myocardial injury

A study was performed to investigate the cardio- protective effect of date fruit. The results revealed a protective effect against cytotoxicity induced by Hydrogen peroxide (H_2O_2). The findings indicated that the extract efficiently inhibited cell damage induced by H_2O_2 (Asadi-Shekaari *et al.*, 2008). A study was performed to assess the potential protective impact of date fruit extract on doxorubicin-induced cardiotoxicity. This cardiotoxicity/heart tissue injury was reversed by administering date palm fruit extract, suggesting a protective effect on cardiac tissue induced by doxorubicin (Mubarak *et al.*, 2018). A study was conducted to explore the cardioprotective benefits of nano-preparation containing seeds and fruits of Ajwa date on doxorubicin-induced cardiotoxicity *in vitro*, focusing on analysing hemodynamic, electro-cardiological and biochemical alterations. The findings indicated a significant protective effect from a notable rise in left ventricular pressure (Al-Jaouni *et al.*, 2019). A study was conducted on the ability of date fruit extracts in repairing tissue damage, including that caused by myocardial infarction, by enhancing circulation of progenitor cells. The findings indicated that all date fruit extracts demonstrated the capacity to enhance cardiac muscles and elevate the number of progenitor cells migrating from bone marrow to the site of myocardial infarction, indicating their potential to facilitate tissue repair (Alhaider *et al.*, 2017).

Effect on blood

The anticoagulant properties of different varieties of *P. dactylifera* has been assessed by examining their prothrombin time and bleeding time. A substantial extension in prothrombin time was noted. The findings were later verified through low platelet aggregation and platelet mass levels (Hasson *et al.*, 2018). A recent investigation examined the effects of hydroalcoholic extracts of seeds of various types of *P. dactylifera* on relaxation of vascular system. The findings revealed that all extracts induced relaxations exceeding 60% in the aortic rings pre-contracted with 10^{-6} M phenylephrine in normotensive rats, with Sukkari seed extract, demonstrating the highest potency (Cifuentes *et al.*, 2024).

Diabetic cardiomyopathy

Cardiovascular disorders are increasingly common and there are currently no effective medications for treating heart failure

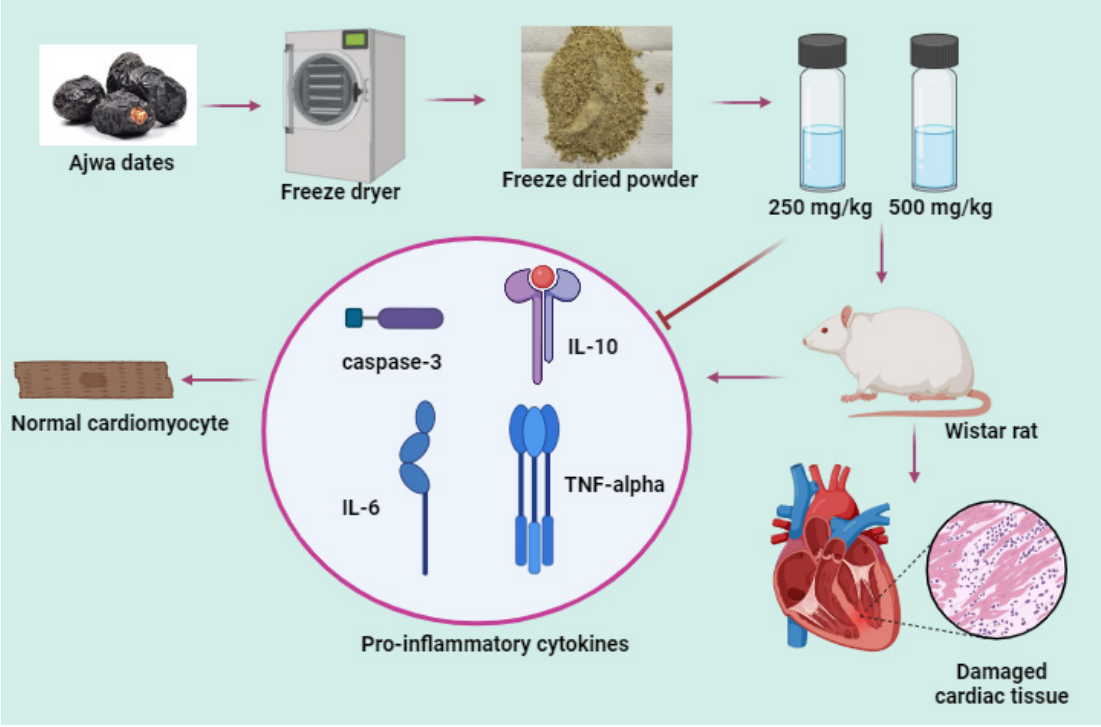

Figure 2: Cardioprotective effect of Ajwa dates.

linked to diabetes. Therefore, it is crucial to investigate alternative methods, such as exploiting plant extracts, that have been successfully used for medical treatment. A recent study examined the potential heart-protective effects of *P. dactylifer* in Diabetic Cardiomyopathy (DCM), tested its effects on glucolipid levels, myocardial blood and serum indicators. The results revealed that treatment with *P. dactylifera* improved glucolipid balance and reduced oxidative stress *in vitro*, maintaining the structural integrity of pancreas and heart. The analysis of gene expression showed that treatment with *P. dactylifera* increased the expression of insulin signalling genes in pancreas and reduced expression of genes associated with fibrosis in heart's ventricular tissue, suggesting cardio-protection in DCM by modulating glucolipid balance and metabolic signalling, (Figure 3), (Nawaz *et al.*, 2024).

Clinical trials

Two clinical trials on date consumption were found by searching English and Arabic language databases. One study was a crossover design in a preliminary trial involving ten healthy individuals, consumed 100 g/day of Hallawi or Hallawi dates for four weeks, with a four-week washout period among the groups. The study observed 15% decrease in serum triglycerides with Hallawi dates. The individuals who consumed Hallawi dates showed significantly elevated triglyceride levels compared to those in the Medjool group. However, it's difficult to precisely ascertain the specific values as they are only demonstrated in a bar graph. The research also observed that consuming Hallawi dates, led to a significant reduction in oxidative stress markers, as evidenced by TBARS assay, the 2,2′-Azobis (2-amidinopropane) hydrochloride-induced serum lipid peroxidation assay and higher serum paraoxonase 1 aryl esterase activity. The noteworthy decrease in oxidative stress following the consumption of Hallawi dates, as opposed to Medjool dates, may be attributed to notably higher total phenolic content in Hallawi dates (Rock *et al.*, 2009). In both types of dates, majority of soluble phenolics were phenolic acids, but only dates of Hallawi variety had a substantial amount of catechins, known for their strong antioxidant properties. Variances in absorption, processing and effects of various phenolic compounds in two types of dates may account for the differing results. Unluckily, the criteria for including or excluding participants were not clearly defined and no information was given on whether the values returned to their original baseline after the crossover and washout period. Considering greater fiber content of dates, that may impact gut microbiome characteristics, it's important to consider the potential carry-over effect from consuming one type to another. For studies in future, it would be ideal to include a separate control group with no intervention, or use a parallel arm design or confirm that primary lipid outcome measures, as well as gut microbiome environment at beginning of period of second treatment, reverted to baseline values.

In another research involving humans, impact of consuming three Khudary dates daily for about 16 weeks was examined. This trial, which was randomized, controlled and parallel-arm, revealed a notable enhancement in plasma cholesterol level of date-consuming group, showing an approximate five percent improvement from the initial levels. Additionally, there was an observed tendency for decreased LDL-C levels (Alalwan *et al.*, 2020). The comparison of the treatment group with control did not

show statistically significant results, indicating that the decrease in cholesterol could have been influenced by participation in the project rather than the consumption of dates. Additional limitations involve the absence of information on the dates exact weight given, total distribution and amount of macronutrients in diets.

Recently another research was carried out to evaluate the influence of powder obtained from Ajwa Dates Pit (ADP) on the body composition, lipid profile and blood pressure in patients having hyper-lipidemia. This study involved 40 patients and they all received a daily dose of 10 mg of either Rosuvastatin or Atorvastatin as prescribed by their doctor. Additionally, 2.7 g of ADP or an equivalent amount of wheat flour was administered daily prior to breakfast with warm water for 40 days. Body composition, blood pressure and lipid profile were determined at the beginning of the experiment, as well as after 20 and 40 days. Findings indicated that compared to control group, ADP resulted in a significant decline in BMI, body weight body fat percentage, fat mass, waist circumference and visceral fat area. Furthermore, ADP was associated with a substantial decline in serum cholesterol and LDL. The study suggested that ADP could potentially contribute to the improvement of dyslipidemia and obesity (Nasrullah *et al.*, 2023).

The above-mentioned reports collectively indicate that dates have the potential to improve indicators of cardiovascular health state, especially lipid levels in plasma, inflammatory and oxidative stress markers and presence of Circulating Progenitor Cells (CPC). These findings are initially based on experiments conducted in test tubes and animal subjects, which could be beneficial as preliminary models. However, variations in the way studies were designed, the quantity and makeup of dates or extracts used in the studies and insufficient information regarding the control groups hinder specificity and minimize the potential to make conclusions regarding the mechanistic pathways and the applicability to human beings. When examining the cardiovascular effects of date products or extracts, the selection of a control substance is crucial, as control items may contain substantial amounts of biologically active components that could significantly impact the function of cardiovascular system.

Phytonutrients and their possible mechanisms behind the effects

The impact of date polyphenols has been studied in relation to various cardiovascular factors. Fractions of flavonol and phenolic acid extracted from Amari and Hallawi varieties of dates at ripening state have been analyzed for their antioxidant and antiatherogenic properties. Both fractions displayed different abilities to decrease Ferric ions (FRAP assay), neutralize radicals and prevent oxidation of LDL-C through assays of lipid peroxide and TBARS, with flavonol fractions demonstrating the most potent effects. Cholesterol removal from macrophages was only enhanced by the flavonol fractions. The Amari dates showed significantly higher yields of isolated fractions, with about 10 times more phenolic acids and about 3.5 times more flavonols, as compared to the Hallawi dates with regard to µmol GAE per g fruit. The main component in the two separated fractions was ferulic acid, along with relatively small quantities of coumaric

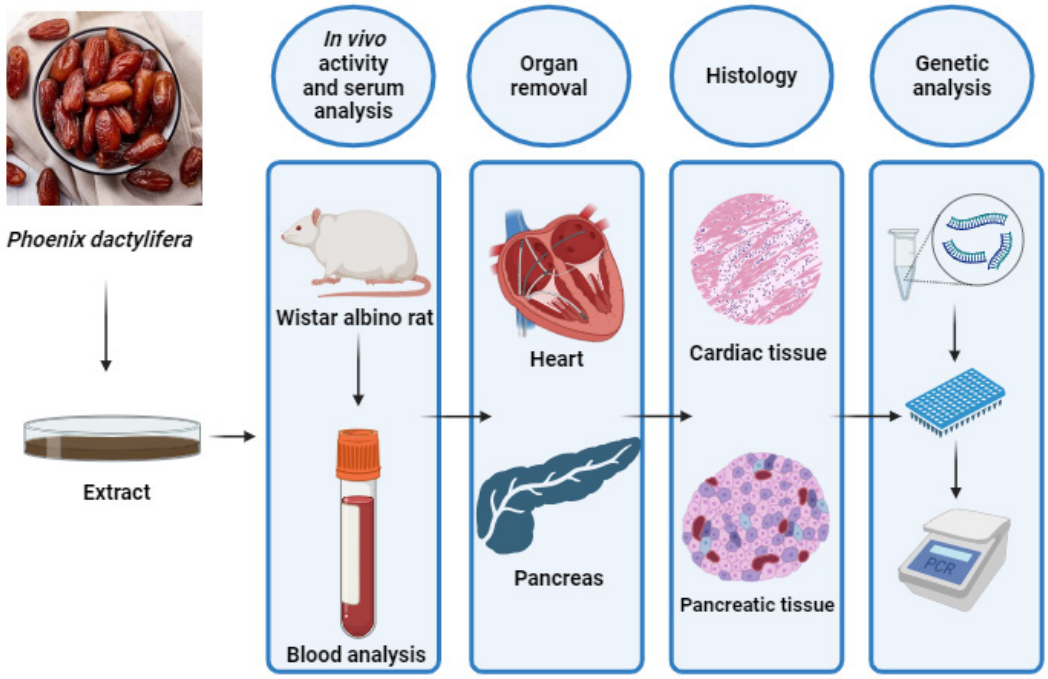

Figure 3: Representing the schematic diagram of cardio-protective effect of *Phoenix dactylifera* extract.

acid, but they significantly varied in their complementary phenolic acid composition. Amari dates mainly had derivatives of caffeic acid, while the Hallawi mostly contained a derivative of salicylic acid. Seven distinct peaks of flavonols were observable and all peaks were temporarily categorized as kaempferol derivatives based on a standard library. The two separated date flavonol fractions had notably different compositions. Apart from one prominent flavonol peak present in both fractions, Amari comprised significant concentrations of five other flavonols, whereas Hallawi exhibited a single flavonol as its major constituent. The findings illustrated a firm relationships between structure and function of date polyphenols and recognized date flavonols as biologically active materials with antiatherogenic properties (Al-Dashti *et al*., 2021). The polyphenols extracted from date syrup mainly from derivatives of cinnamic acid and catechin, were observed to effectively decrease the levels of IL-6, IL-8 and Vascular Endothelial Growth Factor (VEGF) in Human Vascular Endothelial Cells (HECVs). These findings correlated with a potent decrease in both COX-2 and VEGF induced by TNF-α at both levels including protein and gene expression, when evaluating inflammatory-related angiogenesis in HECVs (Taleb, Morris, Withycombe, Maddocks, and Kanekanian, 2016). Many researchers have conducted studies on individual polyphenols found in dates in laboratory and tissue culture systems to understand their impact on indicators of function of vascular system. Protocatechuic acid [by product of anthocyanin Cyanidin-3-Glucoside (C3G)] and its metabolites of phase II have shown to regulate the synthesis of core inflammatory markers including IL-6 and Vascular Cell Adhesion Molecule-1 (VCAM-1), especially the conjugated of sulphate in human umbilical vein endothelial cells when stimulated with oxidized LDL or a group of differentiated CD40L (Amin *et al*., 2015). It was also found that C3G and its metabolites decreased the production of IL-6 in cells stimulated by CD40L, while both C3G and its metabolite called ferulic acid, lowered the synthesis of VCAM-1. Additionally, ferulic acid and anthocyanins were discovered to effectively decrease monocyte adhesion to human umbilical vein endothelial cells under conditions related to physiology, which is a crucial step in reducing the development of atherosclerosis (Krga *et al*., 2016). Similarly, extract of California-grown dates including varieties of Deglet Noor and Medjool, was found to be powerful co-agonist ligand *in vitro* for Farnesoid X Receptor (FXR) in human intestinal cells. This receptor is essential for maintaining triglyceride and cholesterol balance. The extract has 13% proanthocyanidin based on a dry weight, equivalent to 131.3 mg PACs/g of extract of date palm. This research suggests a potential explanation for the observed hypotriglyceridemic effect of dates in humans (Rock *et al*., 2009). The effect on vascular relaxation caused by hydroalcoholic extracts obtained from seeds of three varieties of dates is attributed to endothelial Nitric Oxide (NO) cascade, as it reduced vascular relaxation in denuded-endothelium rat aorta and when treated with an inhibitor including 10^{-4} M L-NAME of endothelial Nitric Oxide Synthase (eNOS). Validation using confocal microscopy confirmed that NO generation in intact aortic rings enhanced by SS extract as indicated by DAF-FM fluorescence. In line with the mentioned discoveries, there was a noteworthy decline by SS extract in L-NAME-induced hypertensive rats, in vascular relaxation in intact aortic rings (endothelial dysfunction model), but not in SHR. The uncovered endothelium hindered relaxation of vascularity in both models. This effect may be influenced by existance of phenolic compounds, including protocatechuic acid and caftaric acid, which were recognized by UHPLC-ESI-MS/MS (Cifuentes *et al*., 2024). The methanolic extract of two Moroccan varieties of date fruit including Majhoul and Bousrdoun, was studied for its anti-hyperlipidemic effect. Among the varieties, Bousrdoun exhibited the most significant lipid-lowering effects, primarily due to its high inhibition of lipid peroxidation, attributed to its abundant content of caffeic, gallic, p-coumaric, vanillic acids, luteolin and rutin (Bouhlali *et al*., 2023).

In addition to polyphenols, dates have nutrients that are good for the cardiovascular system, such as potassium, magnesium, selenium, folate, fiber and vitamin C. The majority of date cultivars are high in potassium but having low sodium content, both of which are crucial components of diet for regulating blood pressure (Staruschenko, 2018). The body needs folic acid to convert homocysteine into methionine. Higher quantity of homocysteine in blood have been linked to a greater chance of developing Cardiovascular Disease (CVD) (Wald, Law, and Morris, 2002). The exact ways in which elevated homocysteine contributes to cardiovascular disease are not fully understood, but potential changes involve reduced vascular function due to lower availability of nitric oxide and higher levels of endothelin-1, encouragement of harmful reactive oxygen species and inflammation of endothelium and initiation of blood clotting process (Barroso, Handy, and Castro, 2019). Dates contain a minimum quantity of vitamin C compared to citrus fruits but can still assist in scavenging free radicals through enzymatic and non-enzymatic activities, as well as in protecting lipoproteins from oxidative damage (Kiokias, Proestos, and Oreopoulou, 2018). Moreover, vitamin C has the potential to enhance factors like arterial stiffness and endothelial function, while insufficient vitamin C level in blood has been linked with increased risk of cardiovascular condition including developing cardiac failure and death (Morelli, Gambardella, Castellanos, Trimarco, and Santulli, 2020; Plantinga *et al*., 2007).

Dietary fibers, which are known to lower lipids, are thought to contribute to some of the heart-protective benefits of dates (Surampudi, Enkhmaa, Anuurad, and Berglund, 2016). Dates contain mostly insoluble fibers. These fibers have the ability to attach to cholesterol and triacylglycerols in intestines, aiding in their expulsion from body. This process contributes to reducing the levels of circulating cholesterol (Lunn and Buttriss,

2007). Consequently, there is also a decreased susceptibility to oxidation for less lipoprotein, thereby decreasing its impact on atherogenesis (Threapleton *et al.*, 2013). Additionally, foods high in fiber can support the development of helpful symbiotic bacteria and restrict proliferation of recognized harmful pathogens (Tang, Kitai, and Hazen, 2017). Reportedly, a diet rich in fiber was found to boost the growth of microbiota that produce acetate, reduce blood pressure and lower fibrosis and cardiac hypertrophy in mice with hypertension (Marques *et al.*, 2017).

Future directions

The cardiovascular benefits of certain fruits, berries and nuts, high in specific polyphenols including apples, walnuts and strawberries have been studied in animals and humans for their health-promoting properties. However, as far as we know, there are no similar studies available on date fruits (Borkowski *et al.*, 2019). The polyphenol and fiber levels in dates make it worthwhile to conduct studies on vascular function and gut microbiome. Two common non-invasive methods for evaluating vascular function are peripheral arterial tonometry in fingertip and flow-mediated dilation of the brachial artery (Matsuzawa, Kwon, Lennon, Lerman, and Lerman, 2015). The evaluation of burden related to cardiovascular risk factor has been shown to have prognostic value for both methods (Freemark, 2019). Consuming high amounts of certain polyphenols, like flavanols and proanthocyanidins present in red grapes, berries, tea and cocoa, has been shown to greatly enhance peripheral arterial tonometry and flow-mediated dilation in different segments of population (Curtis *et al.*, 2019). The effects of products of date and their polyphenols on the dysfunction of vascular system has not been studied through measurement of FMD and PAT. This means there is no existing data on this topic. Most nutrition studies face a significant challenge in finding appropriate control groups, especially when investigating the significant health impacts of entire foods containing multiple bioactive compounds that may act individually or in combination with additional elements in food. One approach to test extracts or food involves using a control product that deeply matches the test fraction or compound in terms of calories, macro-nutrients and micro-nutrients, colour and taste. The usefulness of this approach has been demonstrated, examining the consequences of a dietary strawberry powder and beverage containing high levels of flavanols derived from cocoa (Djurica *et al.*, 2016). Using a no-intervention control group is another approach, but practically, it could affect the results because some participants in the control group might drop out of the study before it ends and the ones who stay may not accurately reflect the original study population. When conducting future research on dates, it is important to carefully choose the study participants and concentrate on populations susceptible to CVD. Therefore, it is essential to take into account hormonal condition, age and gender, as these elements may lead to considerable differences in the responses of cardiometabolic system to phenolic compounds. Other factors including microbial metabolism and variations in genetics can also play a key role in the variability of outcomes (Milenkovic *et al.*, 2017). In human nutrition research, there is a growing focus on the need for reproducibility and accuracy. Instead of solely measuring the total concentration of GAEs, which is a rough indicator of the amount of flavonoid present, it is essential to have more comprehensive compositional profiles of dates. To improve the quality of research, it is crucial to provide detailed descriptions of the employed products, model systems and reagents as well as to enhance the correctness and transparency in experimental designs, procedures and data analysis. It is important to highlight that the lack of these elements has been a hindrance in the discussed *in vitro* and *in vivo* studies (Sorkin, Kuszak, Williamson, Hopp, and Betz, 2016).

CONCLUSION

Recent data suggests that consuming dates may have positive consequences on indicators of vascular well-being. Mostly, effects have been noted in studies using the fruit as a whole or extracts in animals, which is a compelling rationale to carry out epidemiological research along with the randomized clinical trials. Consumption of products related to date or its polyphenol components appears to cause improvement in the lipid level of blood, reduction in oxidative stress and inflammation, that ultimately result in the better cardiovascular health conditions. In addition to measuring alterations in cholesterol or indicators of antioxidant activity, it would be valuable to assess functional indicators. Study protocols that examine the connection between circulating metabolites obtained from dates or date-derived polyphenols and physiological responses would be beneficial. As current guidelines promote eating habits rich in plant-based foods and dates can be a great option for achieve these objectives.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; **USD:** United States dollar; **LDL:** Low-density lipoprotein; **PICO:** Patient, Intervention, Comparison and Outcome; **DPPH:** 2,2-diphenyl-1-picrylhydrazyl; **DCFH:**

Dichlorodihydrofluorescein; **CAT:** Catalase; **SOD:** Superoxide dismutase; **NP-SH:** Non-protein thiols; **NO:** Nitric oxide; **MDA:** Malondialdehyde; **MPO:** Myeloperoxidase; **IL:** interleukin; **TNF:** Tumor necrosis factor; **Bcl2:** B-cell lymphoma 2; **AJLE:** Ajwa lyophilized extract; **HDL:** High-density lipoprotein; **CRP:** C-reactive protein; **H_2O_2:** Hydrogen peroxide; **DCM:** Diabetic cardiomyopathy; **BMI:** Body mass index; **HPLC/MS:** High-performance liquid chromatography-mass spectrometry; **CVD:** cardiovascular diseases; **TPC:** Total phenolic content; **L-NAME:** Nω-nitro-L-arginine methyl ester; **TBARS:** Thiobarbituric acid reactive substances; **FRAP:** Ferric reducing antioxidant power; **FMD:** Flow-mediated dilatation; **PAT:** Peripheral artery tonometry.

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