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Cardio protective effects of dates

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Abstract

Date palm (*Phoenix dactylifera* L.) fruit is promising and significant source of high nutritional value compounds such as carbohydrates, proteins, dietary fibers, minerals, and vitamins as well as also enrich by anthocyanins, isoquercetrin, quercetin, quercetrin, procyanidins, apigenin, luteolin, and rutin, respectively. Due to the presence of phytochemicals, date palm causes significant reduction in low density lipoproteins, very low density lipoproteins cholesterol and enhancement in high density lipoprotein They also increase the antioxidant enzymes such as paraoxonase 1 arylesterase, glutathione peroxidase and superoxide dismutase in serum that block free radicals production. Phytochemicals from date fruit lowered the creatine kinase-MB, lactate dehydrogenase activities and levels of cardiac malondialdehyde. Moreover, phytosterols inhibit cholesterol absorption in small intestine by preventing the attachment of cholesterol with micellar bindings. Besides, these bioactive compounds also inhibit the bio synthesis of cholesterol by restricting gene expression of HMG-CoA reductase enzyme. The current review highlight the preventive role of phytochemicals from date fruit against cardiovascular abnormalities via controlling lipid profile, preventing free radicals production, maintaining sodium metabolism and improving cardiac muscles contraction.

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Introduction

Dates are the members of the palm family (Arecaceae). The name of date originated from two greek words, one is dáktulos "date" and other is ferō "stem". Botanical name of date fruit is *Pheonix dactylifera*. Dates are grown abundantly in North Africa and Middle East countries. Date palm is a perennial, dioecious, diploid and monocotyledonous plant with unique biological and developmental characteristics. It is used for 6000 years among humans and also known as oldest crop (Sulieman *et al.*, 2012). There are more than two hundred types of dates throughout the worldwide (Bakr Abdu S., 2011). Native origin of dates is the Persian Gulf and also main crop of Saudi Arabia, Egypt and Middle Eastern countries (Chao T and Krueger R., 2007) According to a survey the worldwide date production was 6,924,975 t in 2005 (ZaidA *et al.,* 2002). Egypt is largest producer of phoenix dactylifera whereas Pakistan is ranked on 5th largest producing country. More than 150 date varieties are produced in Pakistan (Zahoor T *et al.,* 2011). Worldwide yearly production is almost 6 to 8 million tons (Niazi S *et al.,*). These are potential source of carbohydrates (70%) as fructose and sucrose 100gm flesh can provide approx 314 kcal of energy as well as also rich in nutrients such as micronutrient vitamins and minerals. High in riboflavin, lycopene (Ried K and Fakler P. 2011) biotin, ascorbic acid (Ambali S*et al* 2007), folic acid and thiamin and other fat soluble vitamins, date fruit is also abundant in minerals like calcium, iron, zinc(Ali A *et al.,* 2009), phosphorus, potassium and copper required for different metabolic functions (Ismail B *et al.,* 2008). It also contains ingredients such as flavonoids, phenolics carotenoids (Boudries S *et al.,* 2007), procynidines, and phytosterols.

These compounds show health beneficial and functional properties (Al-Farsi *et al.,* 2008) such as anticancer, hepatoprotective, antioxidant, neuroprotective, anti-atherogenic (Rosenblat M *et al.*, 2015),antidiabetic nephroprotective, gastrointestinal protective, antihyperlipidemic, antimicrobial, sexual improvement and antihyperlipidemic potentials (Hassan W *et al.,* 2018).

Cardiovascular disease (CVD) is the combination of heart and blood vessels diseases basically heart diseases are the major cause of death at that time. Cardiovascular diseases are responsible for one-third of deaths in individuals over age 35. Aproximately one-half of all middle-aged men and women in the United States will develop some symptoms of Coronary Heart Diseases. According to 2016 Heart Disease and Stroke Statistics overall death rate from CHD was 102.6 per 100,000. Heart Disease and Stroke Statistics update of the AHA reported that 15.5 million people in the USA have CHD. The prevalence of heart diseases increases with age for both men and women (Sanchis-Gomar F *et al.,* 2016). Currently Pakistan is facing the dual Burden of Communicable and Non- Communicable Diseases according to World Health Organization (NCD Country Profiles, 2014).The World Health Organization (WHO) profile shows that in 25.3% individuals in Pakistan were hypertensive and 19% had Cardiovascular diseases (Naseem S*et al.*, 2016). Dyslipedemia a metabolic disorder, which is identified by high total cholesterol, low density lipoprotein (LDL) cholesterol, triglyceride contents and a low in high-density lipoprotein (HDL) cholesterol levels in the blood. Increased level of Low-density lipoproteins, triglycerides and cholesterol cause fat deposition and plaque formation in arteries which lead towards ischemic heart disease (Kim SJ *et al.*, 2018). Atherosclerosis, more common now a day's which is caused by oxidation of excessive cholesterol cells (Al-Farsi M*et al.*, 2005). Basic aim of this review is to find out cardioprotective impacts of date fruit.

Date (Phoenix dactylifera)

Phytochemicals in date fruit

Carotenoids: Carotenoids are isoprenoid pigments. They act as active physical quenchers of reactive oxygen species and other free radicals (Fiedor and Burda, 2014). They can also act as chemical quenchers (Wolak and Paran, 2013) by irreversible oxygenation. Antioxidant potential of carotenoids helps to improve human health by reducing the progression of pathogenic disease such as cancer and cardiovascular diseases (Eggersdorfer and Wyss, 2018).

Quercetin**:** A polyphenol derived from plant quercetin (Li *et al.*, 2016), has a vast range of biological actions including anti-inflammatory, anti-carcinogenic and antiviral activities. It reduces the chances of cardiovascular diseases through the prevention of platelet aggregation, lipid peroxidation (Brüll *et al.,* 2015) and capillary permeability (Dower *et al.*, 2015). Jung *et al.* in 2013 determined the effect of quercetin on hyperlidimia in High-Fat diet (HFD) -induced obesity in mice. It was found that HFD-induced altered lipid metabolism which increased body weight, LDL levels liver weight, and adipose tissue. After providing quercetin supplementation there was a sudden reduction in weight, lipid levels and liver weight. Serum cholesterol and lipid level also were reduced. Further investigations showed that Quercetin supplementation altered expression of several lipid metabolism-related genes (including Pon1, Aldh1b1, Abcg5, Acaca, and Fdft1). Collectively, findings determined that quercetin prevents HFD-induced obesity and other complications by altering gene expression.

Anthocyanins**:** Anthocyanins are flavonoids belongs to polyphenolic compounds (Chen *et al.*, 2016). Anthocyanins provide red and blue colors to fruits, flowers, and plants. Different studies showed that anthocyanins have many health-promoting properties (Zhu *et al.*, 2014). These compounds act the components of functional foods and help in the prevention of many chronic diseases (Pojer *et al.,* 2013).

Rutin**:** Rutin is an important flavonoid with chemical formula (3, 3′, 4′, 5, 7-pentahydroxyflavone-3-rhamnoglucoside) (Ganeshpurkar A and Saluja A. K. 2017) and also known as vitamin P and quercetin-3-*O*-rutinoside. Rutin is a unique molecules with some therapeutic properties (Al-Dhabi*et al.,* 2015). Its neutraceutical effects including hepatoprotective, gastroprotective and anti-diabetic effects have been studied in different experimental studies (Hosseinzadeh H and Nassiri-Asl M. 2014). Dates contain a significant amount of rutin that helps to prevent many cardiovascular diseases and maintains kidney health by vasodilating and anti-inflammatory effect (Diwan *et al.*, 2017).

Sterols: Sterols are the subgroup of steroids with ahydroxyl group at the 3-position of the A-ring. These are also known as amphipathic lipids. Plant based sterols are called phytosterols and are responsible for varios health benefits (Liolios *et al.*, 2008). The sterols of date fruit contain cholesterol, stigmasterol, β-sitosterol, campesterol and isofucosterol (Aliga *et al.*, 2011). Plant sterols are capable of reducing blood cholesterol and LDL levels (Gylling *et al.*, 2014) in this way plant sterols prevent the progression or coronary artery disease such as atherosclerosis (Ras *et al.*, 2015). It has been observed that plant sterols supplement can also cure the end points of cardiovascular diseases (Gylling *et al.*, 2014).

Phenolic acids: Phenolic acids are the main classes of secondary metabolites and.contain a hydroxylated benzene ring with one or more carboxyl groups. Different types of date fruit contain various phenolic compounds including p-coumaric, sinapic and ferulic acids (Chaira *et al.*, 2009). Main function of phenolic acids is to prevent damages caused by free radicals (Dimitrios, 2006) and are known as more effective anti-oxidants (Sánchez-Maldonado *et al.*, 2011).

Function as cardiovascular disease preventive

Anti-oxidant potential

Multiple factors are involved in the development of cardio-vascular disease (CVD). Pathological changes or dysregulation of physiological functions increase performance of immune cells which lead towards systemic inflammation characterized by high levels of reactive oxygen species (ROS) (Zorov *et al.,* 2014). In patients suffering from inflammatory diseases antioxidants levels are very low due to poor intake of antioxidant rich foods (Mangge *et al.,* 2014). Antioxidants are substances that remove potentially damaging oxidizing agents in a living organism (Forman *et al.,* 2014).

Excessive production of reactive oxygen species (ROS) increase the chance of cardiovascular disease.

A study showed that Ajwa extract inhibit cyclooxygenase (COX), COX 1 and COX 2 these enzymes are responsible to initate oxidative stress. Similarly it had proved that "Ajwa," a variety of date fruits, consumed by rats prevented the depletion of superoxide dismutase (SOD) and catalase (CAT). SOD and CAT both are endogenous antioxidants which prevent lipid oxidation and inflammation diseases including cardiac hypertrophy, atherosclerosis, cardiomyopathy, hypertension, heart failure and myocardial infarction. It is Important to prevent these free radicals production by consuming a significant amount of antioxidants (Bonner and Arbiser, 2014). Different antioxidants such as beta carotene, quercetin, CoQ10, reserveterol, lycopene, vitamin E and vitamin C have shown therapeutic benefits in several types of CVD (Jain A *et al.,* 2015). Not only CVD antioxidants also reduce the chance of other metabolic and inflammatory diseases such as diabetes and cancer (Zhang *et al.,* 2015).

Total antioxidants and flavonoids contents vary in different types of date palm. Dates are good source of antioxidants such as vitamin C, phenols and flavonoids. Trabzuni DM and his colleagues determined the levels of antioxidants in their study. Findings revealed that solleg were high in antioxidants levels about 0.12g/ml (Trabzuni *et al.,* 2014). In another study, antioxidant values were found out by the ABTS in Deglet Nour (1300 µmolTE/g), Shahia (776 µmolTE/g), Khudri (341) and Barni(452 µmolTE/g) (Al-Jasass *et al.,* 2015).

Different studies determined the antioxidant activity of date fruit.According to a research Ajwa date extract is beneficial for ischaemic heart disease. In a study by Zhang *et al.* (2013) percentages of nutritional components in Ajwa date fruit were measured, according to this measurement percentages of moisture, fructose, glucose, seeds, soluble proteins and fiber were 6.21, 39.06, 26.35, 13.24, 1.33, and 11.01 respectively. The extract of Ajwa date in water inhibited lipid peroxidation about 91% and also inhibited the activity of cyclooxygenase enzymes COX-1 upto 31-32% and COX-2 about 45%at 100µg/ml. the soluble protein was also very effective to perform both anti-inflammatory and antioxidants activities (Zhang *et al.,* 2013).

A study was conducted in oman by Khan *et al.* (2016) to find out total phenolic contents (TPC) of various types of Date fruit to checked out their antioxidant capacity. In this study, four seeds extracts(ethanol, water, methanol, acetone) were prepared from each date fruit variety and antioxidant activities were determined by H ydrogen peroxide (H_2O_2) scavenging method, 1,1-diphenyl-2-picrylhydrazyl and reducing free radicals power methods. TPCs were also measured. This study confirmed that seeds of Omani dates were rich in dietary antioxidant due to high TPC (Khan SA *et al.,* 2016).

Another study was conducted to investigate antioxidant and cardioprotective effects of date fruit (Ajwa dates). In 2016, Al-Yahya *et al.* found the cardioprotective and antioxidant effect of lyophilized Ajwa extract (AJLE) in injured Wister rats. Cardioprotective effect of Ajwa dates was determined on Dichloro-dihydro-fluorescein diacetate (DCFH)-toxicated cardiomyoblast cells (H9C2). Basically this effect was evaluated by measuring cardiac function, hemodynamics, myocardial antioxidant, serum cardiac enzymes and inflammatory bio markers in induced pluripotent stem cells IPS-injured Wistar rat heart tissues. Oral administration of Ajwa date fruit extract 250 and 500 mg/kg body weight prevented the breakdown of endogenous antioxidants and myocyte injury marker enzymes, and inhibited lipid peroxidation. Biochemical data showed that lyophilized Ajwa extract reduced edema, myonecrosis, and infiltration of inflammed cells and restored the structure of cardiomyocytes. This study revealed that lyophilized Ajwa extract had strong antioxidant, hypolipidimic, cardioprotective, anti-apoptotic and anti-inflammatory potential against myocardial damage. The mechanisms behind these activities include reduction of free radicals production, inhibition of degradation of endogenous antioxidants (Salah *et al.,* 2012) and lipid peroxidation. Ajwa extract also helps to alleviate

myocyte injury after ischaemia or heart attack (Al-Yahya *et al.,* 2016).

A study showed that Ajwa extract inhibit cyclooxygenase (COX), COX 1 and COX 2 these enzymes are responsible to initate oxidative stress. Similarly it had proved that "Ajwa," a variety of date fruits, consumed by rats prevented the depletion of superoxide dismutase (SOD) and catalase (CAT). SOD and CAT both are endogenous antioxidants which prevent lipid oxidation and inflammation (Khan and Siddiqui, 2017).

Anti-hypercholestrolemic and hypolipidemic activity

Hypercholesterolemia is a major threat for the development of cardiovascular diseases. Currently, many studies have been reported the hypocholestolemic effect of phoenix dactylifera (Sureka *eta al.,* 2016). In a study, conducted by Vayalil *et al* in 2012 hamsters were induced with cholesterol supplements to increases cholesterol and lipids levels in blood. One specific group of cholesterol fed hamsters was fed with date fruit supplement. After sometime measurements showed a considerably reduction in total plasma cholesterol levels, organ weights, triglycerides and LDL levels which were increased by cholesterol-induced supplements.This study shows that date fruit supplementation have a potential to change the absorption or metabolism of cholesterol. In this way date fruit supplement may prevent the chance of atherosclerosis and other heart diseases. Different mechanisms are used to explain hypocholestrolemic effect of dates. First, date fruit contains small amount of fats and this fat is avaible in the form of small fatty acids which are easily absorbable. Second, as Dates are good source of dietary fiber (Berry *et al.,* 2011) and fiber content of dates reduces the absorption and reabsorption bile acids in gastrointestinal track. Dietary fiber also inhibits the biosynthesis of cholesterol by producing small chain fatty acids on fermentation. Third, the date fruit also rich in phytosterols (plants sterols) which work similar to cholesterol lowering drugs (AL Saif *et al.,* 2007). Phytosterols inhibit cholesterol absorption in small intestine by preventing the attachment of cholesterol with micellar bindings.in this way phytochemicals in date fruit lower cholesterol and lidids levels in blood (John *et al.,* 2007). *β*-sitosterol is a phytosterol that have an obvious effect in lowering cholesterol levels in humam beings. It inhibits bio synthesis of cholesterol by restricting gene expression of HMG-CoA reductase enzyme required for cholesterol synthesis (Batta *et al.,* 2006). Plasma triglycerides levels were also decreased in hamsters fed with date fruit supplementation (Vayalil, 2012).

A study reported by Mushtaq and their colleagues (2017), they investigated that administration of ajwa date seed powder on diet induced hyperlipidemic rabbits. They found that ajwa seed powder caused significant reduction in concentrations of very low density lipoproteins cholesterol, low density lipoprotein, cholesterol and enhancement in levels of high density lipoprotein (Mushtaq *et al.,* 2017).

In 2016 Ahmed *et al.* found that date fruit extract had similar properties to Atorvastatin drug, A drug which is used to maintain blood lipid profile. It was examined when date fruit exact about 300mg and 600mg/kg was given to hyperlipidemic- induced mice and another group was served with the drug (Atorvastatin). After 14 days lipid and hepatic profile was measured and there was a significant decrease in LDL, VLDL and cholesterol level in blood without any increase in lipid enzymes (Ahmed *et al.,* 2016). Hypolipidemic effect of phoenix dactylifera in their experiment. Experiment was conducted on albino wistar rats who were fed with the extract of phoenix dactylifera and result showed decrease in low density lipoproteins and very low density lipoproteins while high density lipoprotein level was increased (Huseen et al., 2020).

Jung and his fellows (2006) determined that various types of date palm fruit have antihyperlipidemic and antihypercholestrolemic activity for example Aseel fruit (dates) suspension has hypolipidemic effect and control fat's breakdown in liver with the help of phenolic compounds. Flavonoids and Vitamin C are

splendidly present in date fruit which reduce plasma cholesterol,LDL and VLDL levels, the combined effects of Vitamin C, flavonoids, polyphenols, folate and antioxidants in phoenix dactylifera are responsible for healthy biological activities (Jung *et al.,* 2006).

Date fruit seeds also have ability to lower lipids levels in blood stream. Date Seed Extract (DSE) increased paraoxonase and aryl esterase activity of serum in hypercholesterolemia rats. Due to presence of soluble poly phenols and flavonoids. These enzymes are required for the reduction of long chain fatty acids which are also known as Bad fats and high lipids in blood (Takaeidi *et al.,* 2014). A study by Rock *et al.* (2009) on humans showed hypocholesterolemic effect of phoenix dactylifera when they had consumed 100g/day of date fruit for 4 weeks, after 4 weeks there was significant decrease in serum Low Density Lipoprotein (LDL) and triglycerids. Results also shown an increase in antioxidant enzymes such as paraoxonase 1 arylesterase in serum that block free radicals production.

Anti-Inflammatory

A study was performed in 2017 by Kehili *et al* to find out anti-inflammatory activity of date fruit (*Phoenix dactylifera*). About 50 mg/kg extract of the *P. dactylifera* was given to formalin-induced edema mice. At end the inflammation level in mice was measured by the size of edema, level of C-reactive protein (CRP) and homocysteine content in the blood. There was a significant decrease in the edema size and reduction of CRP and homocysteine levels in blood.

This study suggests that date fruit extract have power to reduce inflammation because inflammatory disorders causes a secondary immune cell activation, which result in heart diseases and the atherogenesis (Kehili *et al.,* 2016). Flavonoids and phenolic contents in dates vary depending upon their type. According to Mohammad Al-Mamary *et al.* (2014) Rotab date-syrup had more antioxidant capacity then Saudi-syrup and Iraq-syrup because it had more flavonoids and phenolic contents. These flavonoids had ability to scavenge free radicals or ions to prevent the production of free radicals (Al-Mamary *et al.,* 2014).

Atherosclerosis

Oxidation of accumulated fat cells causes atherosclerosis which is the leading cause of cardiovascular diseases. As mentioned in previous studies Phenolic compounds and flavonoids, are effective natural nutritional antioxidants which are capable of scavenging free radicals, metal ions and preventing lipid peroxidation. Epidemiological studies showed that high consumption of diet rich in polyphenols directly linked with reduced morbidity and mortality rate from cardiovascular disease. Borochov-Neori et al determined the atherogenic property and polyphenolic contents in nine different types of date fruit. They examined atherogenic properties by measuring free radical induced oxidation, it's effect on LDL levels in serum and phenolic content was examined by revese phase high pressure liquid chromatography (RP-HPLC), commom phenolic compounds were hydroxycinnamates, hydroxybenzoates and flavonols. There was a clesr difference between phenolic contents of all varieties of date fruit and all types had shown the inhibition of cholestrol and lipid peroxidation. Phenolic content of all types were varied and most varieties also showed the athrogenic property. According to this study soluble phenolic compounds in date fruit had atherogenic property to prevent cardiac diseases (Borochov-Neori *et al.,* 2013).

Myocardial injury

Date fruit also help to prevent cell damage and improve cell induced injury to make healthy organs. The cells protective effect of date fruit determined by Asadi-Shekaari M et al in a study in 2008. In this study they showed that aqueous extract of date fruit had protective effect against hydrogen peroxide (H_2O_2) induced cytotoxicity In addition, the total antioxidant capacity of aqueous extract of date fruit was very high about 1.97±0.04 mmol on measuring. The results investigated that date fruit extract

inhibited H_2O_2 induced cell damage. In this study two aqueous date fruit extract were used 0.1% and 10%. Findings showed that both percentages of aqueous solutions had preventive effect but 10% date fruit solution showed more protective capacity than 0.1% because it had more concentration and apoptotic features. So these results show that aqueous date fruit extract has protective and proliferative effect against H_2O_2induced cytotoxicity (Asadi-Shekaari *et al.,* 2008).

Doxorubicin (Dox), is an antibiotic (anthracycline) most commonly used for the treatment of cancer. High administration of Doxorubin causes cardiotoxicity. Carditoxity is determinsd by high levels of LDL, VLDL and decreased HDL level in blood. A study was conducted by MUBARAK *et al.* (2018) to determine the protective effect of date fruit extract on Dox-induced cardiotoxicity. In this study 40 female albino rats were used and divided into four groups including control, date fruit extract, Dox, and treated date palm fruit extract groups. Doxorubin produced increase in creatine kinase-MB and lactate dehydrogenase activities. It also reduced the activities of cardiac glutathione peroxidase and superoxide dismutase but increased levels of cardiac malondialdehyde. High different Histopathological studies showed the alteration of cardiac tissue structure by Doxorubicin. Treatment with date palm fruit extract recovered the cardiac tissue injury caused by Doxorubincin. So it can be said that phoenix dactylifera have a cardioprotective effect on the heart tissue against cardiotoxicity induced by Dox (Mubarak *et al.,* 2018).

Alhaider et al. (2017) investigated the potential of date fruit fruit extracts in repairing tissue injury such as myocardial infarction by increasing circulating progenitor cells. Extract of four different types of date fruit had been used, all extracts were rich in flavonoids and phenolic compounds which were involved in antioxidant activities and protection of cardiac tissues damaged by myocardial infraction. All date fruit extract showed the ability to improve cardiac muscles and increase the number of progenitor cells from bone marrow to the place of myocardial infraction. So date fruit extract showed the ability to promote tissue repairing.

Blood control

Hypertention is one of the major causes of the onset of CVD (De Puala *et al.,* 2012). Daily dietary consumption of phytochemicals reduce the chance of hypertention and other coronary diseases (Cassidy *et al.,* 2011). It is well known that the Phoenix dactylifera fruit has a considerable amount of phytochemical compounds. Now a days natural remedies are used to treat human diseases because some modern drugs have potential drawbacks. Most commonly cardiovascular disease are controlled with anticoagulants like aspirin and warfarin. Basic aim to prevent coagulation main cause of strokes, heart attacks and ischemic heart disease. Due to some clinical complications these drug should be replaced with some natural source. That's why a study was conducted in 2018 by Hasson *et al.* to check the anticoagulant ability of date fruit. In that study the efficacy of different types of Phoenix dactylifera was determined by evaluating PT (prothrombin time) and BT (bleeding time) activities. There was a significant prolongation in Prothrombin time. The results were further confirmed by platelet aggregation and platelet mass which were low (Hasson *et al.,* 2018). Dates contain a significant amount of Spotassium, magnesium, calcium ,iron and sodium these minerals helps to maimtain electrolyte balance for example Potassium control sodium concentration and prevent hypertention It also helps to regulate heartbeat and maintain heart rhythm (Tahraoui *et al.,* 2007; El Fouhil *et al.,* 2013).

Conclusion

*Phoenix dactylifera i*s a fruit with many healthy pharmacological activities, it helps to prevent cardiac diseases, cancers and other chronic disorders due to presence of some beneficial components.

It is well known that current allopathic drugs have some drawbacks and cause other health related complications as we discussed about doxorubicin. So

date fruit is the best natural source to prevent heart diseases and other diseases.

Despite the prevention of diseases date fruit is the best source to fulfill nutritional requirements such as vitamins, minerals and energy. Daily consumption of 3-7 dates helps to prevent nutritional deficiencies and follow prophet's Sunnah as a Muslim.

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