

# Treating Doxorubicin associated Cardiotoxicity using Ajwa Dates

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**Abstract:** Cardiovascular disease is a leading cause of death worldwide, presenting an immense public and economic burden, phoenix dactylifera is rich in polyphenols, flavonoids and certain micronutrients, dietary fibres which can impact vascular health and diseases in humans. According to data collected from animal study reported that consumption phoenix dactylifera or extracts can modulate selective markers of vascular health, particularly plasma lipid levels including triglycerides and cholesterol indices of oxidative stress and inflammation. Recently studies performed that Ajwa dates are beneficial for ischemic heart disease and Also showed that pre treatment with Ajwa extract helps in mitigate myocyte injury and indicating a potential for Ajwa extract used to preserve cardiac function in patient at high risk for IHD. Ajwa dates regularly less susceptible to disease and infections. They are delightful soft and cultivated only in Saudi Arabia. They have antioxidant, anti hyperlipidemic, anti inflammatory, anti mutagenic, hepato-protective nephro-protective & anti atherogenic properties. Study has assessed the cardio protective effect of Ajwa nano-preparation against doxorubicin-associated cardiotoxicity. Doxorubicin are the most efficacious anti-cancer drugs, however, its use as a chemotherapeutic agent is severely hindered by its dose-limiting toxicities. Doxorubicin degrades the other organs too, but mostly the toxicity is observed in the cardiac tissue. Therefore we hypothesized that Ajwa fruits and seeds may have a cardio protective effect. The present study was aimed to identify the protective effects of Ajwa fruit and seeds on doxorubicin associated cardio toxicity in wistar rats.

This article also contains health benefits of various Dates (phoenix dactylifera) with their nutritional value per 100 grams and therapeutic uses. Methodology used to prove the effect on cardiac dysfunction by Ajwa and preparation of Nano pharmaceutical formulations of phoenix dactylifera.

**Keywords:** phoenix dactylifera, doxorubicin, Ajwa nano preparations, cardiotoxicity, p-coumaric, ferulic, and sinapic acids, flavonoids, procyanidins.

## Introduction:

Cardiovascular diseases affect the Physiology or Structure of heart causing various complication like Arrhythmias, Aorta disease and Congenital heart condition, Deep vein thrombosis, Heart attack, Coronary failure, cardiomyopathy, Heart valve disease, Pericardial disease, Peripheral vascular disease, Rheumatic heart condition, Stroke, disease. (1-4) Heart disease is a combined term, it describes that many conditions affect a person's heart health, heart valves, heart muscles, coronary arteries, or heart rhythm. These plays an important role in overall heart health. When a person acquire knowledge of heart disease, it's important for them to make changes in their lifestyle modification to slow the progression of the disease. Heart disease can leads to many potentially fatal complications if left untreated. It is estimated that 1 in 4 deaths in the United States is due to heart disease, According to the Centres for Disease Control and Prevention Trusted sources. (5) Date palm,, commonly called as date or phoenix dactylifera,(6) Family: Arecaceae, cultivated for its edible sweet fruit. There is an archaeological evidence of cultivating dates in Arabia from the 6th millennium BCE. (7) Dates are rich in calories, Proteins, vitamins and other essential nutrients that may help to regain your energy immediately. Health benefits : good source of energy, boost brain health, prevent heart disease, may relieve constipation & Anemia, helps to treat chronic diarrhoea.(8) They contains fibres which helps to decrease the cardiac disease & prevent constipation, selenium, magnesium, copper good for bone health, potassium helps to support nervous system, vitamins such as B<sup>1</sup>,B<sup>2</sup>,B<sup>3</sup>, B<sup>5</sup>,A,K,&D. (9-12) They are various types of dates Medjool, Piarom, Deglet Noor, Mazafati, Barhi, Rabbi, Thoory, Sayer, Dayri, Khudri, Zahidi, Safawi, halawy, Ajwa. (13-16) dates are soft dry variety of fruit from Saudi Arabia. Cultivated in Madina. Date features a sugar content of 77%, high proportion of minerals (3%), especially In calcium (1.2he g/100 g) (Gasim, 1994).(17-19).There are 200 varieties of Dates(phoenix dactylifera) some are listed below:

DATES(Phoenix dactylifera)	Average nutritional value per 100 grams of dates	Uses	Reference
Medjool	Calories-133, Carbohydrates-36, proteins-0.8g, fats-0g, vitamin B6 (b <sup>6</sup> x)-7%, Calcium-2%, magnesium-6% of DV (daily value)	Heart health, healthy digestion, bone health, high in antioxidants, natural fuel of body	18-19
Mazafati (Rutab)	Sodium-0.01, phosphorus-0.07, iron- 0.2, calcium- 0.22, carbohydrates-51g, energy-264 k cal	During pregnancy, diarrhoea, osteoporosis, cancer, cholesterol and high blood pressure, constipation	18,20-21
Piarom (Maryami)	Carbohydrates- 51 g, sugar- 46 g, energy- 300 Cal, dietary fibres-26g, fat-5.6 g, proteins-1.61 g, fructose, sodium 2 grams	Diabetes, blood pressure, improves vision, lesions and cancer cells	18,22
Sayer	Calories-277, carbs 75g, fibres-7g, Proteins 2g, potassium 20%, magnesium 14%, iron 5%, vitamin b6 12%, sugar 68 g	Gastrointestinal, digestion, high antioxidant, anemia, hair growth, fatty liver disease, heart attack, cancer	18,23
Rabbi	Energy 289 cal, carbohydrates-2.2%, sugar 64g, proteins 0.6%, calcium, potassium, magnesium, vitamin A, B& vitamin c(vit cx) lactose and abundant fructose, dietary fibre 10g	Prevents cancer of digestive system, gastrointestinal function, relief nervous tensions and treatment of disease such as anaemia, high blood sugar, diabetes	18,24,25,26,44
Deglet noor	Calories- 20gms, total fat-0.03 gms, carbohydrate-5.33g, dietary fibre-0.6g, protein-0.17g, iron 0.7g, flavonoids	Helps with inflammation, reducing diabetes, Alzheimer's and types of cancers	27, 42
Barhi	Potassium- 0g, energy-163k cal, proteins-1.46 g, carbohydrates-8.0g, fat-0.2g, sodium-0.01g, iron-1.28 g	Promotes brain health, natural labor, bone health, high blood sugar	28
Thoory (Bread date)	Contains vitamins, minerals, cholesterol free food, good source of fibre-50%, more potassium	High concentration of antioxidants, improves bowel movements, diabetes, heart diseases, brain functions	29,42
Dayri date	Dietary fibres, potassium 20%, iron 5%, folic acid, vitamin B	Pregnancy, Anemia, gastrointestinal, high blood pressure, cancer	30,42
Khudri	Glucose and fructose, energy-275k cal, protein-1.80g, fats- 0.20g, carbohydrates-63.00g, cholesterol-0,	Heart health, prevent abdominal cancers, easing baby birth, improves vision	31,32,42
Zahidi	Dietary fibres, iron 2%, potassium, vitamin B, antioxidant, flavonoids, carbohydrate-31g, calcium-2%, almost 20 amino acid	Works as anti inflammatory agents, bone health, heart diseases, diabetes, hair growth, digestion	33,34, 42
Safawi	Calories-202(10%), carbohydrates-46g, proteins-2g, fat-2.8g, fibres-7g, iron-1%	Constipation, diarrhoea, abdominal cancer, heart, anemia, sexual dysfunction	35, 43, 42
Halawy	Carbohydrates-10%, dietary fibres-12%, proteins-1g, iron, potassium, flavonoids	Improves brain functionality, prevent microbial infection, skin, protect kidney	36,37,42
Ajwa	Dietary fibre- 4%, energy-277 kcal, moisture-9.45%, protein-1.85%, Ash-1.71%, fats-2.47%, fibre-51.4%, carbohydrates-33.12%, calcium-1%, potassium-4%, iron-5%, magnesium-10%, vitamin A and B -2%, vitamin k-2.7mg, polyphenols, flavonoids.	Strengthen heart, bone health, teeth density, highly nutritious, regulate blood pressure, diabetes, boosts the immune system, strengthen to nervous system, concentration of antioxidant, pregnancy, benefits to male infertility, avoid atherosclerosis, reduces the pain of childbirth, prevent abdominal cancer, prevents anemia, improves eyesight, protects from pellagra, reduces triglycerides cholesterol levels(LDL) in the blood, helps in treatment hypertension, treat dementia & fatigue	38,39,40,41,44,45,46,4

Ajwa dates are delightful soft and fruity, dark in colour and dry variety of date cultivated only in Saudi Arabia. They are rich in vital nutrients and have good source of natural occurring antioxidant & other bioactive compounds(48,49) it has both flesh and pits rich in phenolic and flavonoids which have diverse effect on human health because to their strong anti-oxidant properties, Ajwa dates have antioxidant, anti hyperlipidemic, anti inflammatory, anti mutagenic, hepato-protective nephro-protective & anti atherogenic properties. (50-52,55) recently studies performed that Ajwa dates are beneficial for ischemic heart disease and Also showed that pre treatment with Ajwa extract helps in mitigate myocyte injury and indicating a potential for Ajwa extract used to preserve cardiac function in patient at high risk for IHD.(53)Ajwa dates regularly less susceptible to disease and infections.(54)

Consumption of fruits and vegetables high in polyphenol have shown to exert cardio-protective effect. phenolic extracts of Ajwa dates have shown to reduce the TC, LDL-C, and lipids VLDL-C and improved HDL-C and the antioxidant, improving health condition.(56) Polyphenols are potential substances against cancers and cardiovascular, metabolic(57)neurodegenerative diseases(58), Polyphenols are nutrient antioxidants, The classification of polyphenols mainly includes flavonoids (60%), phenolic acids (30%), and other polyphenols including stilbenes and lignans(59). Antioxidant activity is recognized acknowledgement to the wide selection of phenolic compounds present in dates including p-coumaric, ferulic, and sinapic acids, flavonoids, and procyanidins (60,61) Potassium, magnesium are the minerals which play a important role in controlling vital signs, normal cardiac rhythm, and contraction. The contained potassium also has function to take care of elasticity of arterial walls which prevent deterioration of vascular under high blood pressure. studies revealed that reduction of systolic blood pressure by 14.23 mmHg due to the potassium contained in dates (Deglet Noor), the presence of high level of potassium and low level of sodium in Ajwa dates are apparently beneficial for individuals with hypertension. Furthermore, the magnesium in Ajwa dates also functions to activate as regulator of  $\text{Na}^+/\text{K}^+$  pump, which results in lowering of diastolic blood pressure.

#### METHODOLOGY USED TO PROVE THE EFFECT ON CARDIAC DYSFUCTION BY AJWA:

Studies revealed that cardio protective effects of Ajwa nano preparations against doxorubicin the associated cardiotoxicity, is a anticancer drug used to treat various malignancies (62)such as skin, lungs, breasts, pancreas, and other organs and glands. Cardiotoxicity has limited clinical uses.(63) cardiotoxicity associated with doxorubicin could be due to production of reactive oxygen species, formation of peroxynitrite, and dysfunction of mitochondria.(64) oxidative stress leads to cardiovascular disease through disruption of vascular endothelial layers may causes hypertension, coronary heart disease, atherosclerosis.(65) numerous researches suggested that free radicals is responsible for doxorubicin induced cardiotoxicity, (66) and also demonstrated that some natural products causes high antioxidant activities which prevents some chronic non infectious diseases initiated by oxidative stress (67-69). A freeze drying extract was found to improve cardiomyogenesis up to about half of the propagation and reversed the suppression of endogenous antioxidant and repressed lipid peroxidation(70) hence the present studies was designed to investigate the probable antioxidative efficacy of Ajwa date against doxorubicin induced cardiotoxicity in wistar albino rat.

#### PREPARATION OF NANO-PHARMACEUTICAL FORMULATION OF PHOENIX DACLIFERA L

Ajwa is obtained from a certain date farm in Al-Madina Al-Munawara City (Saudi Arabia) that cultivates a known Ajwa variety using organic methods of cultivation, and stored in a refrigerator at 4°C. Dates were washed and dried. Nanoparticles of date seeds were grounded for 40 hours in a ball mill forming millimeter size. They were crushed in 250ml steel cells in a suitable atmosphere. The mixture ratio of steel balls and thus the grounded seeds powder was around 15:1 by weight. The milled material was used directly without added milling media. Five balls with 10 g of the sample powder were placed in each cell

Preparation of nano-date mixture:

1. 20 dates were weighed separately to work out the mean weight of dates.
2. Dates were separated into seeds and fruits, and therefore the seeds milled to nanoparticles as described above, and therefore the fruits move very small pieces Employing a meat grinder to give semisolid form.
3. The semisolid ground fruit was mixed with the nanoparticles of seeds by an equivalent ratio because the weight of the first dates within the planetary mixer for 20 minutes.

Equal proportions of the seeds powder and fruit paste were mixed, this mixture was subsequently administered orally to rats with an intragastric feeding tube at a dose of 1.4 g/kg daily.

Preparation of tablets:

The tablet is formed by mixing the nanoparticles of the date seed with direct compressing material such as avicel and passing it through sieve number 40, then mixing the powder with lubricating material such as magnesium stearates. This mixture was compressed using a single punch tablet press machine with oblong flat faced press. The compression force was adjusted to obtain tablets with hardness in the range of 4.5-5.5 Kg.

#### Preparation of suspensions:

The suspension was formed by mincing the fruit of the date. The seed nanoparticles powder was mixed with the flesh in the planetary mixer, maintaining the ratio of their original form. The suitable vehicle in required amount was drop wise added to the above mixture until a uniform suspension was achieved. Next 0.2% methyl paraben as preservative was added into the mixture.

ANIMAL TESTING:

According to study1:

24 wistar rats were divided into three groups about (200-250g) one group was given the nano preparation containing both the Ajwa fruit and pith in a dose of 1.4 g/kg by orally (equivalent to 200mg/kg in human) one hour before doxorubicin infusion (Dates- Dox group) Second group was given the vehicle for one hour before doxorubicin infusion (Dox group) third group received the vehicle but no dox infusion (time control). Blood samples were collected before and after infusion, blood pressure, cardiac hemodynamic,

cardiac contractility were recorded before and after 45 minutes of Dox infusion. Hard tissue samples were collected and kept frozen until assay reduced glutathione.

According to study: 2

10 Wistar rats were taken, An extra ten rats from the same were used as a control untreated group. In nano-formulation group, 13.3 mg/kg of the Ajwa nanoparticle mixture was given orally twice daily for 5 days. Then Vasopressin was injected (3 IU/kg; intravenous) to induce experimental cardiac ischemia and animals were investigated for hemodynamic, biochemical parameters and Immunofluorescence staining of angiotensin II, angiotensin I receptor, 4HNE (4-Hydroxynonenal) and collagen protein expression in both treated and untreated groups.

RESULT: according to study 1 &2 pre administration of Ajwa nano preparations were protected from doxorubicin associated systolic and diastolic dysfunction. It prevents the doxorubicin associated ischemia based on the significant shortening in QT interval, JT interval and Tpeak -T end interval versus dox group. There is no effects on Ariel conductivity PR interval and P duration. Pre-treatments increases antioxidant capacity of cardiac tissue by increasing the carrier content off reduced glutathione. Results-2 administration of Nano pharmaceutical formulation of Ajwa for 5 days decreases the systolic pressure, diastolic pressure, mean blood pressure in heart rate compared to control group, systolic duration is more in the Ajwa treatment group then the control group. Ajwa group shows a significant decrease in angiotensin 1 in both the coronary and heart tissue compared to control as detected immunofluorescent confocal microscope.

Conclusion: Ajwa nano preparations from doxorubicin associated cardiotoxicity through alleviating cardiac ischemia and increasing cardiac anti-oxidant capacity.

Dexrazoxane is hydrolyzed to its active form intracellularly and binds iron to prevent the formation of superhydroxide radicals, thus preventing mitochondrial destruction. The effect of dexrazoxane on the prevention of doxorubicin-induced cardiotoxicity is impressive in both animal and human studies.

#### Biomarkers involved in IHD:

There are a number of biomarkers – hFABP, GPBB, S100, PAPP-A, RP, TNF, IL6, IL18, CD40 ligand, MPO, MMP9, cell-adhesion molecules, oxidized LDL, glutathione, homocysteine, fibrinogen, and D-dimer procalcitonin. Usually, the diagnosis of IHD is confirmed when a patient has an increase or decrease in at least two of the following cardiac markers: (eg, CK-MB isoenzymes), BNP, myoglobin, preferably serum troponins (cTnI or cTnT), or a typical ECG trace with Q waves that indicate a diagnosis of AMI (71, 72)

Amongst these markers, myoglobin is considered as an important one in early detection of cardiac damage. During an injury it is rapidly released from the myocardium and also subsequently released from kidneys within 24 hours (73). Due to its rapid onset and rapid kinetics, it is an important biomarker (73). TnC per gram of myocardium is 13–15 times more than that of CK-MB, which depicts the higher sensitivity of cTn compared with CK-MB in the early period (74).

There are certain biomarkers which potentially be exploited in the diagnosis of IHD. The hfABP marker release begins just 3 hours after the onset of chest pain and returns to normal in 12- 24 hours, it is detected in lesser amounts than myoglobin. Hence, it is more useful in diagnosing AMI. GPBB, is considered quite sensitive marker.

There is a characteristic difference between the sensitivities of biomarkers release within the first 4 hours. The sensitivity differences are GPBB 0.77, CK-MB mass and myoglobin 0.47, TnT 0.40, CK activity 0.20) (75).

There are certain other cardiac peptides which can be utilized in the future in diagnosis which include irisin and plasma- induced markers PAPP-A, LpA, ApoA, ApoB (76).

Product	Quantity	Response	Reference
Dates	No data available	↓ACE Activity	77
Date phenolic acid and flavonol fractions	Amari PhA: 4.27 µmol GAE/g Hallawi PhA: 0.38 µmol GAE/g Amari Fl: 1.37 µmol GAE/g Hallawi Fl: 0.43 µmol GAE/g	All PhA and Fl fractions: ↓Ferric ions, scavenge radicals, LDL oxidation via TBARS and lipid peroxide assays Only Fl fractions: ↑ Cholesterol removal from macrophages	78
Date syrup derived-polyphenols	60 and 600 µg/mL	IL-6, IL-8, VEGF ↓ COX-2 & VEGF induced by TNF-α at protein level and gene expression	79
Date extract	100	a potent co-agonist ligand for FXR Regulates FXR-target gene expression in Caco-2 cells	80
Dates	Date pulp mixed with chow powder (1:1, w/w)	↓Serum cholesterol, TG, LD	81
Datefruit suspension	300 and 600 mg/kg	300 mg/kg: ↓ Serum cholesterol, TG, LDL, VLDL, C-HDL, LDL-HDL 600 mg/kg: ↓ TG, VLDL	82

Date palm seed	1.0 g/kg	↓AST, ALT, ALP, TBARS, NO, liver lesions ↑ SOD, GST	83
Date palm seed	1 g/kg/day	ALT, AST, TBARS, NO↑ SOD, GST, CA	84
Date extract	Ex vivo: 250 µg/mL In vivo: 250 and 500 mg/kg body weight	Ex vivo: Attenuated cytotoxicity and enhanced H9C2 proliferation (40%) In vivo: ↑ CAT, SOD, NO, Bcl2 ↓ IL-6, IL-10, TNF-α, MDA, caspase-3 and Bax	85
Date pollen extract	40 mg kg <sup>-1</sup>	MDA ↑ Glutathione	86
Dates	1.4 g/kg	Rate of rise in left ventricular pressure (dp/dtmax) and (dp/dtmin), glutathione ↓ QT interval, JT interval, and Tpeak-Tend interval	87
Date extract	200 and 400 mg/kg body weight	↑ GSH, SOD, CAT ↓ TBARS, troponin-T, LDH, CK, and AST ↑ CD34 and CD133 positive progenitor cells Improved histopathological indices of MI	88
Dates	100day	↓TG, TBARS, and AAPH-induced serum lipid peroxidation ↑ PON1 aryl esterase activity	89
Dates	3 dates/day	↓ Total cholesterol Suggestive ↓ LDL	90

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