


Ajwa Nanopreparation Prevents Doxorubicin-Associated Cardiac Dysfunction: Effect on Cardiac Ischemia and Antioxidant Capacity

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Abstract

Background: This study evaluated the cardioprotective effect of Ajwa nano-preparation against doxorubicin-associated cardiotoxicity. **Methods:** Twenty-four male Wistar rats (200–250 g) were divided into 3 groups. One group was given the nanopreparation containing both Ajwa fruit and pit in a dose of 1.4 g/kg orally 1 hour before doxorubicin infusion (Dates-DOX group). Another group was given the vehicle for 1 hour before doxorubicin infusion (DOX group). The third group received the vehicle but no DOX infusion (time control). Cardiac hemodynamics, blood pressure, cardiac contractility, and conductivity were recorded before and after 45 minutes of infusion of doxorubicin (15 mg/kg, slow intravenous over 45 minutes). Blood samples were collected before and after doxorubicin infusion. Heart tissue samples were collected and snap frozen until assay of reduced glutathione. **Results:** Rats pre-administered Ajwa nanopreparation were protected from doxorubicin-associated systolic and diastolic dysfunction based on the significant elevation in the rate of rise in left ventricular pressure (dp/dt_{max}) and (dp/dt_{min}) compared with the DOX group. In addition, it prevented the doxorubicin-associated ischemia based on the significant shortening in QT interval, JT interval, and $T_{peak} - T_{end}$ interval versus the DOX group. There was no effect on atrial conductivity (PR interval and P duration). Ajwa pretreatment increased the antioxidant capacity of cardiac tissue, as evidenced by increasing the cardiac content of reduced glutathione compared with the untreated doxorubicin group. **Conclusion:** Ajwa nanopreparation protects from doxorubicin-associated cardiotoxicity through alleviating cardiac ischemia and increasing cardiac antioxidant capacity.

Keywords

doxorubicin, chemotherapy, cardiotoxicity, Ajwa, nanoformulation

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Introduction

The anticancer drug doxorubicin is widely used for the treatment of various malignancies.¹ However, cardiotoxicity has limited its clinical uses.² Cardiotoxicity associated with doxorubicin could be due to production of reactive oxygen species (ROS), dysfunction of mitochondria, and formation of peroxynitrite.³ Oxidative stress leads to cardiovascular diseases through disruption of vascular endothelial layers and may cause atherosclerosis, hypertension, coronary heart diseases, and myocardial infarction.⁴

Date seeds increase the antioxidant status by increasing the activity of superoxide dismutase, vitamin E, and glutathione peroxidase.⁵ Production free radicals plays an important role

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in doxorubicin toxicity. Compounds having antioxidant properties can be examined for potential protective and therapeutic effects. Polyphenols are agents that protect against oxidative myocardial injury. Among these compounds are Ajwa fruits that possess antioxidant properties due to their high levels of polyphenolic compounds.^{6,7} In a clinical trial from our institution, Ajwa intake during the standard treatment of pediatric cancer patients improved the treatment outcome.⁸

Therefore, we hypothesized that Ajwa fruits and seeds may have a cardioprotective effect. The present study was done to investigate the protective effect of Ajwa fruits and seeds on doxorubicin-associated cardiotoxicity in Wistar rats by studying the hemodynamic, electrocardiological, and biochemical changes in doxorubicin-associated cardiac toxicity.

Material and Methods

Instrumentation

An Agilent 6420 Triple Quad mass spectrometer (TQ-MS) was used for characterization and quantification. The system was connected to an HPLC (high-performance liquid chromatography)-Agilent 1200 system equipped with an autosampler, a quaternary pump, diode array detector (DAD), and a column compartment (Agilent, Palo Alto, CA). The HPLC column was Nucleodor Gravity, 150 × 4.6 mm, 5 μm (Macherey Nagel, Duren, Germany), and kept at 25°C.

Qualification of Ajwa Pits and Mixture of Ajwa Fruit/Pits Using HPLC-DAD

Principle. The major constituents in Ajwa fruit/pits are flavonoids such as aglycone and glucoside conjugate.

Habib et al⁹ described an HPLC-ultraviolet-mass spectrometry method for quantitative analysis of total flavonoids, and we followed their procedure for the hydrolysis of glycone to produce unconjugated flavonoids, followed by reaction with phloroglucinol to produce one major peak corresponding to epicatechin-phloroglucinol adduct. All peaks that corresponded to other phloroglucinol derivatives that eluted between epicatechin-phloroglucinol and epicatechin were also calculated. The sum of epicatechin-phloroglucinol, epicatechin, and other phloroglucinol derivatives corresponded to the total flavonoids.

Preparation of the Nano Formulation of *Phoenix dactylifera* L

One type of *Phoenix dactylifera* L date fruit, known as Ajwa, was obtained from a certain date farm in Al-Madina Al-Monawara City (Saudi Arabia) that cultivates a known Ajwa variety using organic methods of cultivation, and stored in a refrigerator at 4°C. Date palm fruits were washed and dried. Nanoparticles of date seeds were prepared in millimeter size by grinding seeds in a ball mill for 40 hours. They

were milled in steel cells (250 mL) using hardened steel balls (diameter 15 mm, weight 32 g) in ambient atmosphere. The mechanical milling was performed in a horizontal oscillatory mill (Retsch, PM 400, Germany) operating at 25 Hz. The mixture ratio of steel balls and the grounded seeds powder was around 15:1 by weight. The milled material was used directly without added milling media. Five balls were kept in each cell along with 10 g of the sample powder.

Sample Characterization. The samples were characterized with field emission scanning electron microscopy (SEM), JSM-7500 F (JEOL, Tokyo, Japan). The morphology of the ball milled date seeds powder sample was also analyzed with tapping mode atomic force microscopy (AFM) with scanning area of 1 × 1 μm. The system used is a variable temperature UHV AFM/scanning tunneling microscope model XA 50/500 (Omicron, Erlangen, Germany).

Preparation of Nano-Dates Mixture

1. Twenty dates were weighed separately to determine the mean weight of dates.
2. Dates were separated into seeds and fruits, and the seeds milled to nanoparticles as described above, and the fruits were cut to very small pieces using a meat grinder to give semisolid form.
3. The semisolid ground fruit was mixed with the nanoparticles of seeds by the same ratio as the weight of the original dates in the planetary mixer for 20 minutes.

Equal portions of the fruit paste and seeds nanopowder were mixed and the nanopreparation was administered orally to rats with an intragastric feeding tube at a dose of 1.4 g/kg daily.

Animal Groups

Twenty-four male Wistar rats (Animal House, King Abdulaziz University, Kingdom of Saudi Arabia) were divided into 3 groups (8 rats each). One group was given the nanopreparation containing both the Ajwa fruit and pit in a dose of 1.4 g/kg by oral gavage in rats (equivalent to 200 mg/kg in human, 1 date per adult) 1 hour before doxorubicin infusion (Dates-DOX group). Another group was given the vehicle for 1 hour before doxorubicin infusion (DOX group). The third group received the vehicle but no DOX infusion (time control).

Experimental Design

The experimental protocol was approved by the Unit of Biomedical Ethics Research Committee, King Abdulaziz University, Kingdom of Saudi Arabia (Approval Number: 173-19). Cardiac hemodynamics and blood pressure was

recorded using a microtip catheter inserted in the right carotid artery through a small opening in the artery and advanced to the left ventricle as described in our previous studies.^{10,11} Cardiac conductivity was determined using surface electrocardiogram (ECG).¹² Cardiac contractility and conductivity were recorded before and after 45 minutes of infusion of doxorubicin (15 mg/kg, slow intravenous [IV] over 45 minutes). In addition, blood samples were collected before and after doxorubicin infusion. Heart tissue samples were collected and snap frozen until assay of reduced glutathione.

Hemodynamic Recording. Following anesthetization as described above, the animals' body temperature was maintained at 37°C using a rectal probe and controlled heating pads. A microtip pressure catheter (Millar Instruments, Houston, TX) was inserted through a small incision into the right carotid artery and advanced into the left ventricle. The pressure catheter is capable of measuring ventricular pressure continuously from the intact beating hearts of rats. After a 5-minute stabilization period, the signals were continuously recorded. The microtip catheter was connected to a Power Lab Data Interface connected to a PC running LabChart professional software (v8.0, AD Instruments, Bella Vista, Australia) including the ventricular pressure modules. The module determines and calculates the isovolumic relaxation constant (Tau), rate of rise in left ventricular (LV) pressure (dp/dt_{max}), rate of fall in LV pressure (dp/dt_{min}), developed pressure (P_{dev}), end systolic pressure, end diastolic pressure, and heart rate.

ECG Recording. The standard surface ECG was recorded according to the method in recent publications from our laboratory^{11,13} using a Powerlab system (AD Instruments) connected to a PC running LabChart professional software with the ECG module. The ECG module quantitatively determines different components of the ECG.

Biochemical Analysis. Cardiac tissue reduced glutathione level was measured using Abcam assay kit (Abcam, Cambridge, England).

Statistical Analysis

Values are expressed as mean \pm SEM (standard error of mean). Statistical analysis was done with 2-way analysis of variance (ANOVA) followed by Newman-Keuls' post hoc test using statistical software Prism 5 (GraphPad, San Diego, CA). Probability levels less than .05 were considered statistically significant.

Results

Qualification of Ajwa Pits and Fruit/Pits

As shown in Figure 1 and Table 1, Ajwa pits were found to contain 47.4 g/kg of total flavonoids, and the Ajwa pits/fruits were found to contain 23.84 g/kg of total flavonoids.

Nanoformulation of Ajwa

Figure 2 shows SEM images at different magnifications (a-d) of the ball milled Ajwa seeds. These images show nanostructures with sizes of 20 to 40 nm. At this particle size, AFM images were also obtained. The black/white and colored images in Figure 2 display similar nanoparticles to those observed with SEM. A mixture of individual nanoparticles and clusters can be seen. These clusters are also of nanoparticles with sizes in the same range (ie, 20-40 nm).

Effects on Cardiac Systolic and Diastolic Functions

Intravenous infusion of doxorubicin (13 mg/kg over 5 minutes) led to a reduction in cardiac systolic hemodynamics as apparent from the significant reduction in the rate of rise in LV pressure (dp/dt_{max} , Figure 3A and C) and reductions in diastolic function as apparent from the fall in LV pressure (dp/dt_{min} , Figure 3A and D). The reductions in both systolic and diastolic functions were gradual and reached a plateau and statistical significance after 20 and 30 minutes (both at $P < .05$) from doxorubicin injection. However, rats pre-administered Ajwa nanopreparation of both fruit and pit in a dose of 1.4 g/kg were protected from the doxorubicin-associated systolic and diastolic dysfunctions, as was observed from the significant elevation in the rate of dp/dt_{max} and dp/dt_{min} versus the DOX group ($P < .05$).

Effects on Heart Rate and Cardiac Cycles

As shown in Figure 4A, IV infusion of doxorubicin (13 mg/kg over 5 minutes) did not significantly affect the heart rate of animals. However, doxorubicin gradually decreased both systolic and diastolic duration, reaching a plateau and statistical significance after 20 and 30 minutes from doxorubicin injection (both at $P < .05$, Figure 3B and C). Pretreatment of rats with Ajwa nanopreparation of both fruit and pit in a dose of 1.4 g/kg did not have any significant effect on the decreased systolic or diastolic duration associated with doxorubicin infusion (Figure 4B and C).

Effects on Ventricular Ischemia

Intravenous infusion of doxorubicin (13 mg/kg over 5 minutes) led to cardiac ischemia as observed from the gradual prolongation of the QT interval (Figure 5A), JT interval (Figure 5B), and $T_{peak} - T_{end}$ interval (Figure 5B), reaching a plateau and statistical significance after 20 and 30 minutes from doxorubicin injection (all at $P < .05$). Pretreatment of rats with Ajwa nanopreparation of both fruit and pit in a dose of 1.4 g/kg completely prevented the doxorubicin-associated ischemia as observed from the significant shortening in QT interval (Figure 5A), JT interval (Figure 5B), and $T_{peak} - T_{end}$ interval versus DOX group (all at $P < .05$).

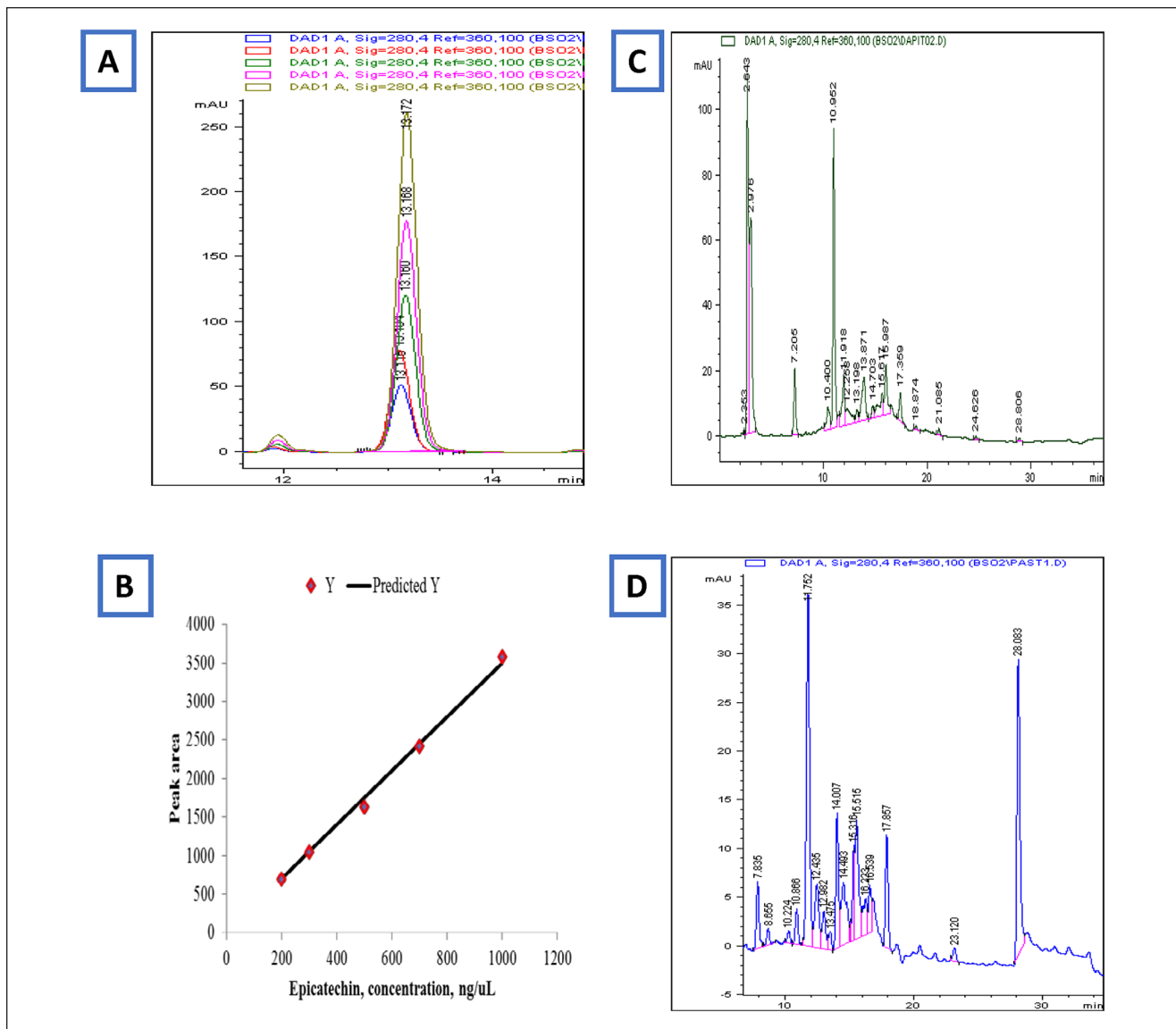


Figure 1. The overlaid chromatogram of serial concentrations of epicatechin (A), the calibration curve of epicatechin (B), and representative chromatogram of analyzed date pits samples (C) and fruit/pits samples (D).

Effects on Atrial Conductivity

As shown in Figure 6A and B, neither IV infusion of doxorubicin (13 mg/kg over 5 minutes) nor Ajwa pretreatment significantly affected the atrial conductivity as evidenced by the non-significant change in the PR interval and P duration.

Effects on Cardiac Reduced Glutathione Level

As shown in Figure 6C, Ajwa pretreatment increased the antioxidant capacity of cardiac tissue as evidenced by the increase in the cardiac content of reduced glutathione compared with the untreated doxorubicin group.

Discussion

This study deals with the effect of Ajwa nanopreparation on doxorubicin-associated cardiac toxicity. Doxorubicin use in patients is limited by its cardiac toxicity, which is related to oxidative stress.

In the present study, IV infusion of doxorubicin-associated cardiac dysfunction was manifested by a reduction in cardiac systolic and diastolic hemodynamic function as observed from the significant reduction in the rate of rise in LV pressure (dp/dt_{\max}) and (dp/dt_{\min}). Hence, dp/dt_{\max} and dp/dt_{\min} are direct indicators of cardiac systolic and diastolic function. Pretreatment with Ajwa nanopreparation of both fruit and pit gave protection from these systolic and

Table 1. The Flavonoids Contents of the Ajwa Pits Powder (A) and the Ajwa Fruits/Pits Powder (B) as Quantified Using HPLC-DAD.

(A) Date Pits Powder			
#	Time	Area	mg/g
<i>Sample 1</i>			
	7.25	260.90	5.97
	10.41	213.70	4.89
Epicatechin phloroglucinol	10.96	1096.10	25.09
	11.93	283.90	6.50
	12.26	175.40	4.01
Epicatechin	13.21	65.70	1.50
	Total		47.96
<i>Sample 2</i>			
	7.205	260.1	5.95
	10.4	163.3	3.74
Epicatechin phloroglucinol	10.952	1090.8	24.96
	11.918	287.2	6.57
	12.258	179.3	4.10
Epicatechin	13.198	64.9	1.49
	Total		46.82
	Average		47.4
(B) Date Fruit/Pits Powder Mix			
#	Time	Area	mg/g
<i>Sample 1</i>			
	7.331	233.8	5.35
	8.34	13.00	0.30
	9.35	45.90	1.05
	10.01	17.90	0.41
Epicatechin phloroglucinol	10.61	106.90	2.45
	11.21	22.10	0.51
	12.88	43.50	1.00
Epicatechin	13.98	511.30	11.70
	Total		22.76
<i>Sample 2</i>			
	7.84	105.70	2.42
	8.66	31.30	0.72
	10.22	18.50	0.42
Epicatechin phloroglucinol	10.87	55.70	1.27
	11.75	618.50	14.16
	12.44	151.30	3.46
	12.98	80.70	1.85
Epicatechin	13.48	26.90	0.62
	Total		24.91
	Average		23.84

Abbreviation: HPLC-DAD, high-performance liquid chromatography-diode array detector.

diastolic dysfunctions as observed from the significant elevation in the rate of rise in dp/dt_{\max} and dp/dt_{\min} versus the DOX group ($P < .05$). These results could be explained by the ability of doxorubicin and its metabolites to inhibit calcium pumps, so that it could abolish the calcium loading activity of the cardiac sarcoplasmic reticulum and therefore lower LV systolic pressure (LVSP), dp/dt_{\max} and dp/dt_{\min} .¹⁴

Treatment with doxorubicin not only causes hemodynamic changes but also electrophysiological changes as reflected by the changes of the ECG, which include prolongation of QT interval, JT interval, and $T_{\text{peak}}-T_{\text{end}}$ interval.

Data of the present study showed that treatment with Ajwa nanopreparation attenuated the prolongation of QT interval, JT interval, and $T_{\text{peak}}-T_{\text{end}}$ interval, which means

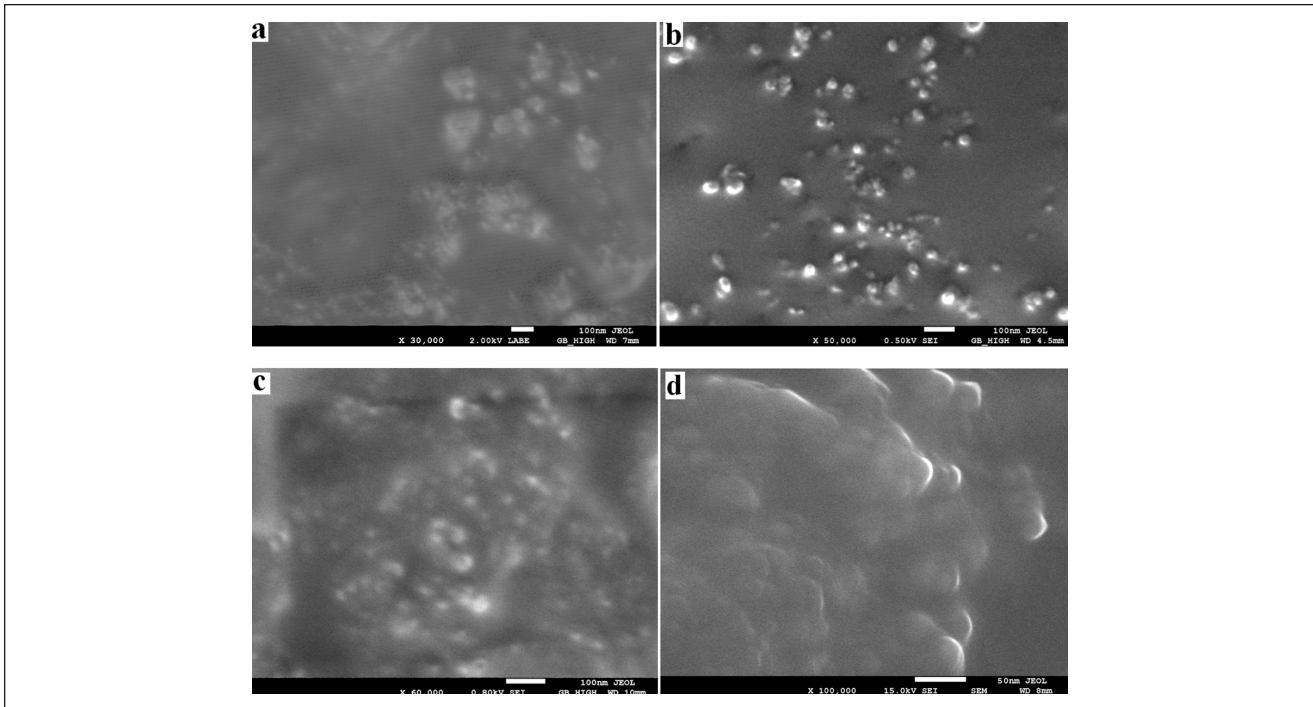


Figure 2. SEM images at different magnification (a-d) of the ball milled date seeds.

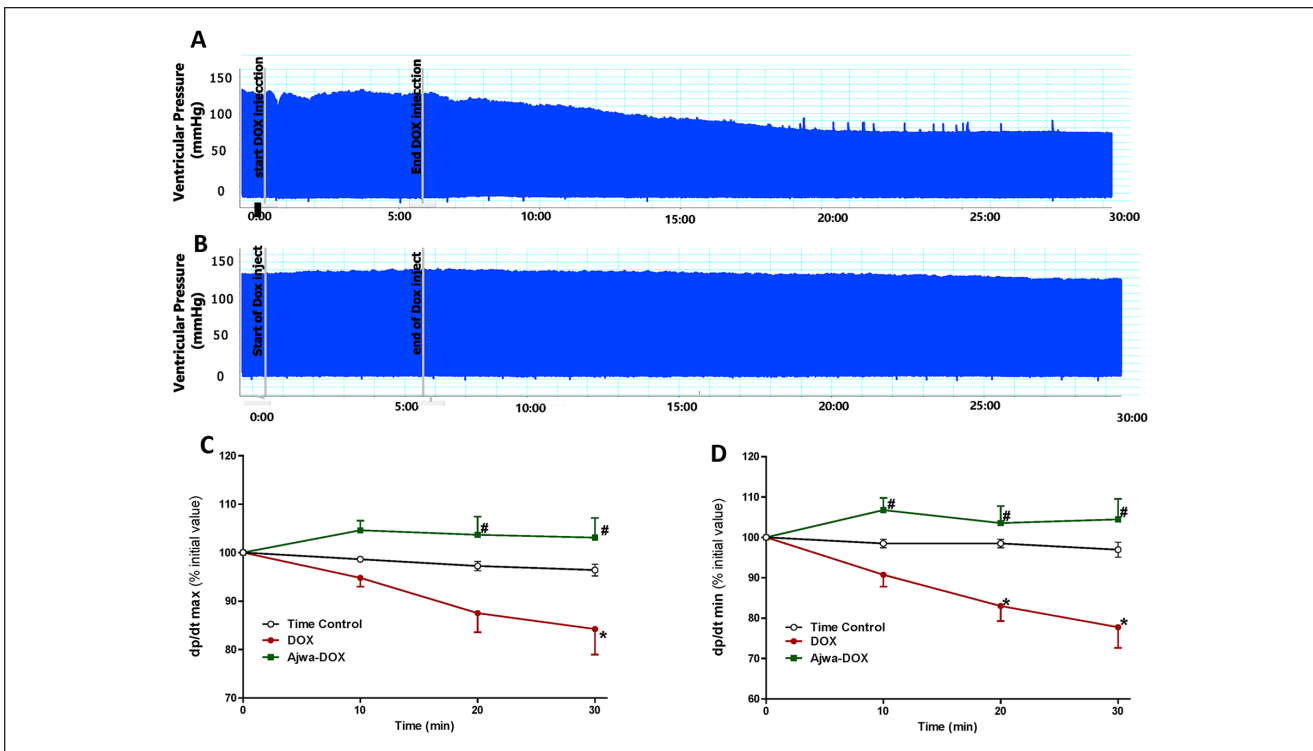


Figure 3. Effect of pretreatment with Ajwa nanopreparation (1.4 g/kg, Ajwa-DOX) on the doxorubicin (15 mg/kg DOX) associated effects on the rate of increment (dp/dt_{max} , C) and the rate of decrement (dp/dt_{min} , D) in left ventricular pressure. A and B are representative traces of the left ventricular pressure recording of rats exposed to DOX alone or pretreated with Ajwa before DOX, respectively. Values are presented as the mean \pm SE of 6 to 8 animals. *Significantly different from the corresponding control values at $P < .05$; #Significantly different from the corresponding DOX values at $P < .05$, by 2-way ANOVA and Newman Keuls post hoc test.

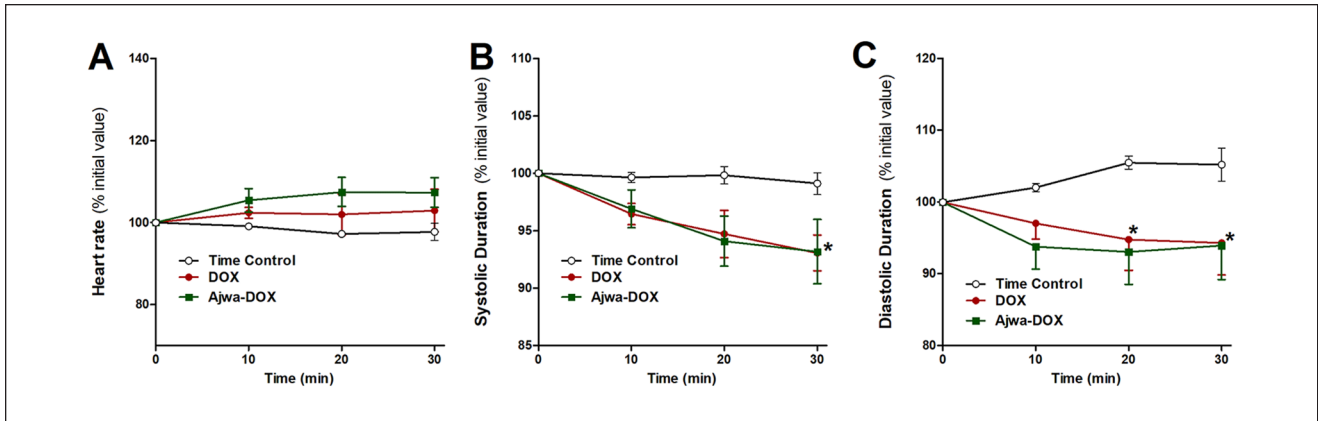


Figure 4. Effect of pretreatment with Ajwa nanopreparation (1.4 g/kg, Ajwa-DOX) on the doxorubicin (15 mg/kg DOX) associated effects on the heart rate (A), systolic duration (B), and diastolic duration (C). Values are presented as the mean \pm SE of 6 to 8 animals. *Significantly different from the corresponding control values at $P < .05$; #Significantly different from the corresponding DOX values at $P < .05$, by 2-way ANOVA and Newman Keuls post hoc test.

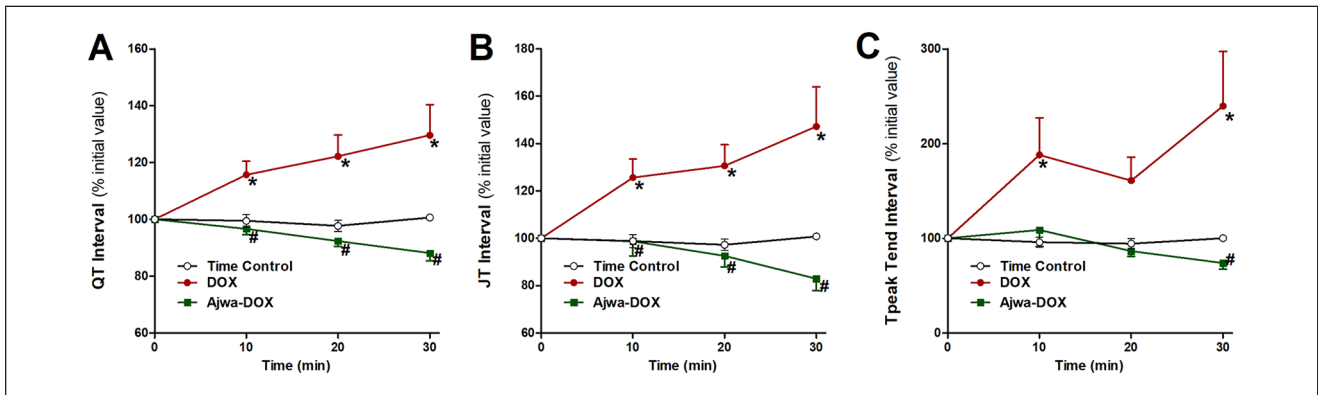


Figure 5. Effect of pretreatment with Ajwa nanopreparation (1.4 g/kg, Ajwa-DOX) on the doxorubicin (15 mg/kg DOX) associated effects on QT interval (A), JT interval (B), and $T_{peak} - T_{end}$ interval (C). Values are presented as the mean \pm SE of 6 to 8 animals. *Significantly different from the corresponding control values at $P < .05$; #Significantly different from the corresponding DOX values at $P < .05$, by 2-way ANOVA and Newman Keuls post hoc test.

that the injury of cardiomyocyte was attenuated and the LV function was preserved. Treatment with Ajwa nanopreparation significantly reversed the LVSP, which reflects the increase in cardiac function.

Oxidative stress (ROS) plays an important role in cardiac toxicity associated with doxorubicin as manifested by a significant decrease in the antioxidant-reduced glutathione. This is due to consumption of the reduced glutathione due to the interactions of free radicals induced by doxorubicin with the bio-membrane that leads to lipid peroxidation. Doxorubicin is metabolized into toxic, short-acting semiquinone metabolites in cardiac tissue that react with molecular oxygen to produce ROS. The other mechanism dealing with doxorubicin-associated cardiotoxicity is the formation of an anthracycline-iron free radical complex. The latter interacts with hydrogen peroxide, leading to formation of the OH[•] radical. ROS

interact with cellular contents, tissue lipids, and protein, causing damage to cell membranes and mitochondria of the cardiomyocytes.¹⁵

This study observed that Ajwa nanopreparation caused an increase in reduced glutathione because of its antioxidant property which inhibited the oxidative process in the heart. Ajwa date contains anthocyanins, phenolics, sterols, carotenoids, and flavonoids.¹⁶ The antioxidant property of Ajwa dates could be related to phenolic compounds. Hamad et al⁶ found that p-coumaric acid, gallic acid, and ferulic acid derivatives were the most dominant phenolic compounds in Ajwa dates. Similarly, Eid et al¹⁷ found protocatechuic acid, hydroxybenzoic acid, vanillic acid, gallic acid, isovanillic acid, chlorogenic acid, ferulic acid, isoferulic acid, caffeic acid, hydroxycinnamic acid, and chlorogenic acid as the main phenolic compounds and acid with different ripening stages of Ajwa date. In addition, Ajwa

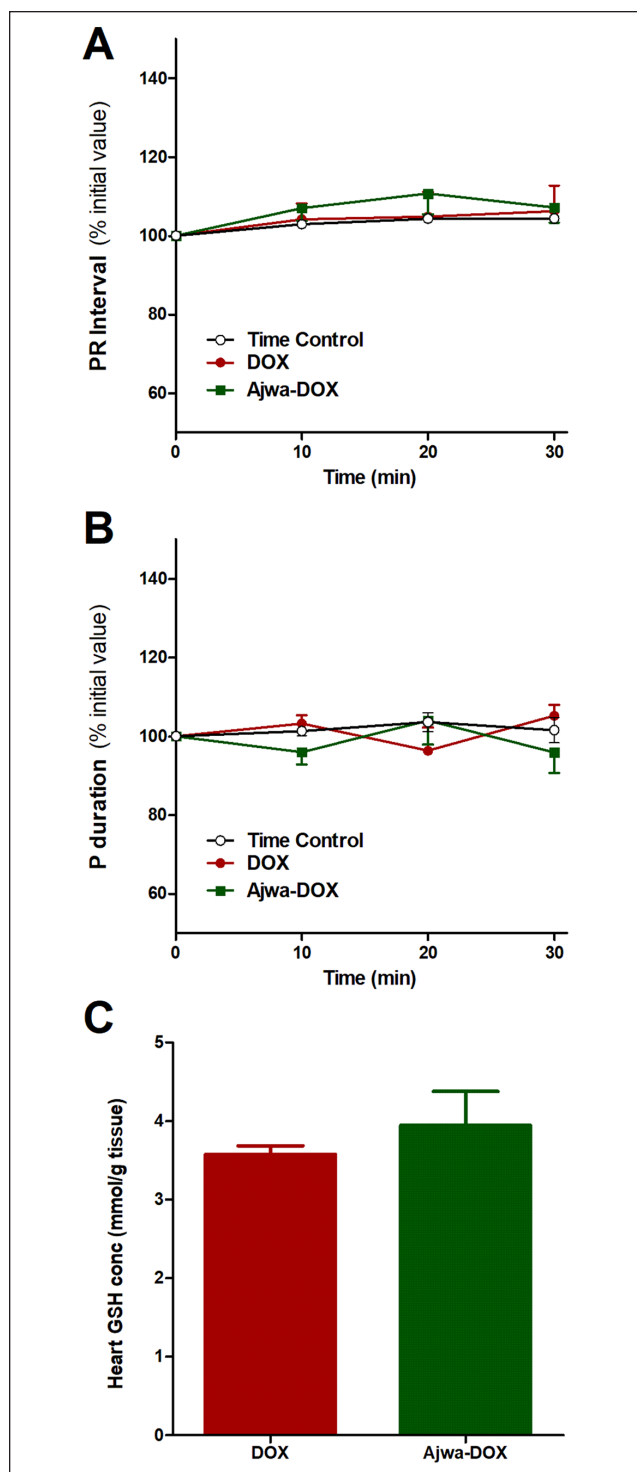


Figure 6. Effect of pretreatment with Ajwa nanopreparation (1.4 g/kg, Ajwa-DOX) on the doxorubicin (15 mg/kg DOX) associated effects on PR interval (A), P duration (B), and on the heart reduced glutathione (GSH) concentration (C). Values are presented as the mean \pm SE of 6 to 8 animals. *Significantly different from the corresponding control values at $P < .05$; #Significantly different from the corresponding DOX values at $P < .05$, by 2-way ANOVA and Newman Keuls post hoc test or unpaired Student's t test as appropriate.

date fruit is enriched with active flavonoids including quercetin, isoquercetin, luteolin, apigenin, and rutin.⁶

Results of Al-Yahya et al¹⁸ revealed that Ajwa prevented the depletion of endogenous antioxidants (catalase, superoxide dismutase, non-protein sulfhydryl, and nitric oxide), inhibited lipid peroxidation (malondialdehyde and myeloperoxidase), and myocyte injury marker enzymes. The pro-inflammatory cytokines (IL-6 [interleukin], IL-10, and tumor necrosis factor- α) and the apoptotic markers (caspase-3 and Bax) are downregulated by Ajwa. The anti-apoptotic protein Bcl2 is upregulated. Moreover, Ajwa reduced myonecrosis and restored the cardiomyocytes' architecture and therefore attenuated the cardiac cytotoxicity.

Conclusion

In the present study, Ajwa nanopreparation is proven to have a cardioprotective effect against doxorubicin-associated cardiotoxicity. The Ajwa cardioprotection seems to be mediated, at least in part, by alleviating the cardiac ischemia and increasing cardiac antioxidant capacity.

Authors' Note

The use of the Ajwa Nano-Preparation described in the current work in treating ischemic heart disease is protected by United States Patent No. US9,861,675 B1 (January 9, 2018).

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Declaration of Conflicting Interests

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