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The potential antioxidant bioactivity of date palm fruit against [](http://crossmark.crossref.org/dialog/?doi=10.1016/j.biopha.2021.112154&domain=pdf) gentamicin-mediated hepato-renal injury in male albino rats

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A R T I C L E I N F O

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GC-MS

A B S T R A C T

Gentamicin (GM) is a commonly prescribed antimicrobial drug used for treatment of infections but associated hepatic and renal complications restrict its efficacy. Overproduction of free radicals and inflammation are involved in GM-induced hepato-renal damage. Date palm is renowned to have antioxidant and anti-inflammatory bioactive composites. In this context, the current research was purposed to assess the ameliorative influence of date palm extract (DE) supplementation against GM-induced hepato-renal injury. Gas chromatography-mass spectrometry (GC–MS) was used to detect the bioactive constitutes in DE. The protective action of high and low doses of DE was assessed alongside the GM remediation (80 mg/kg) in rats. GM evoked significant alter- ations in liver and kidney function biomarkers (aminotransferases, albumin, creatinine, and blood urea). Furthermore, notable elevations in malondialdehyde (MDA) level and increment expression of inducible nitric oxide synthase (iNOS) along with reduction in catalase (CAT) activity were observed in both organs after GM treatment. Oxidative stress was the main modulatory mechanism in GM-induced hepato-renal toxicity. However, DE could mitigate the GM-inflicted liver and kidney damage, in a dose-response pattern, due to its high content of phenolics and flavonoids.

*Abbreviations:* ABTS+, 2,2'-azino-bis (3-ethylbenzothiazoline-6-sulfonate) diammonium salt; ALT, alanine transferase; AST, aspartate transferase; BUN, blood urea nitrogen; CAT, catalase; DAB, 3,3-diaminobenzidine tetrahydrochloride; DE, date palm extract; DPPH•, 1,1-diphenyl-2- picrylhydrazyl; GC–MS, Gas chromatography-

mass spectrometry; GM, gentamicin; H2O2, hydrogen peroxide; iNOS, inducible nitric oxide synthase; IS, intensity score; LPO, lipid peroxidation; MDA, malon- dialdehyde; NIST, National Institute Standard and Technology; NO, nitric oxide; O2•—, superoxide anions; OH%, hydroxyl radicals; PBS, phosphate buffered saline; PS, proportional score; ROS, reactive oxygen species; TFC, total flavonoid content; TPC, total phenolic content; TS, total score.

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## Introduction

Gentamicin (GM) is a commonly utilized aminoglycoside as a ther- apy for severe gram-negative bacterial infections and possesses a higher potency compared to other aminoglycosides [[1]](#_bookmark26). In spite of its wide therapeutic uses, it is well renowned for giving rise marked cytotoxicity, including renal and hepatic toxicity [[2–4]](#_bookmark27). The liver and kidney are highly susceptible to drug toxicities due to its contribution in metabolic pathways, detoxification, and excretion of drugs and their metabolites [[5,6]](#_bookmark33). The pathogenesis of GM-induced injury is multi-factorial; how- ever, the overgeneration of harmful free radicals with subsequent oxidative damage plays a major role in GM mediated-renal and hepatic tissue injuries [[7]](#_bookmark0). Reactive oxygen species (ROS) such as superoxide

anion, O2•–; hydrogen peroxide, H2O2; and hydroxyl radical, OH•, have

been confirmed to be generated by GM and reactive nitrogen species such as nitric oxide (NO).

Additionally, Rashid and Khan [[3]](#_bookmark31) have documented the affinity of GM to the intracellular iron, forming iron-GM complex, which is assumed to be involved in GM-induced oxidative stress. The generated ROS can directly attack the cellular components resulting in lipid per- oxidation (LPO), protein denaturation, and DNA damage. These events are known to be accompanied by exhaustion of endogenous enzymatic and non-enzymatic antioxidant defense mechanisms [[8]](#_bookmark1). These mecha- nisms dedicate the potential use of antioxidant supplementations to counteract the GM-induced oxidative damage.

The date palm (*Phoenix dactylifera* L.) is an ancient plant that belongs to the Arecaceae species and globally popular, which is widely grown, especially in the Middle East and North Africa [[9]](#_bookmark2). It has been recog- nized for its high nutritional value and medicinally active constituents thus utilized as folk remedies in the medicament of atherosclerosis [[10]](#_bookmark3), hypercholesterolemia [[11,12]](#_bookmark4), tumors [[13]](#_bookmark9), renal [[14]](#_bookmark15), hepatic [[5]](#_bookmark33), gastric [[15]](#_bookmark19), cerebral [[16]](#_bookmark20) and cardiovascular ailments [[17]](#_bookmark21). It has a striking antioxidant property which is mainly endorsed for the high content of flavonoids and phenolic compounds [[18]](#_bookmark22) that formerly evi- denced opposed to the oxidative harm triggered by various toxicants including CCl4 [[9]](#_bookmark2), trichloroacetic acid [[5]](#_bookmark33), paracetamol [[19]](#_bookmark23), and

dimethoate [[20]](#_bookmark24).

In line with this assertion, we proposed that DE supplementation could mitigate the GM-triggered oxidative stress and promote tissue renovation due to its antioxidant capability. Wherefore, the current investigation was destined to assess the palliative potentiality of DE on GM-stimulated oxidative stress in the liver and kidney tissues. Bio- markers of liver and kidney, oxidative status, histopathological alter- ation, and inducible nitric oxide synthase (iNOS) expression were evaluated.

## Materials and methods

* 1. *Drugs*

Gentamicin (Garamycin 80®; gentamicin sulfate 80 mg/2 ml vial) was got by Memphis Co. for Pharm. Chem. Ind., Cairo, Egypt.

* 1. *Plant material and date extract (DE) preparation*

Fresh date palm fruit (*Phoenix dactylifera L*.) was gained at the Tamr phase (Khodry type) from the local market, Al Madinah Al Munawara, Saudi Arabia. Date fruits were washed under streaming tap water for the removal of dust and macroscopic contaminants. Subsequently, the date fruits were manually pitted, and the flesh was collected and minced into teeny pieces. Next, 1 g of minced date flesh was soaked and blended in

7.5 ml distilled water for preparation of date extract (DE) at a concen- tration of 1 g/7.5 ml, namely DE high and kept for 24 h at 4 ◦C. Apart of

the obtained DE high solution was twofold diluted with distilled water to acquire a concentration of 0.5 g/7.5 ml, namely DE low. The obtained date extract (DE high) was kept for further phytochemical

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characterization and animal treatment.

* 1. *Phytochemical screening of date extract (DE) by gas chromatography-mass spectrometry (GC/MS) assessment*

Identification of phytochemical constituents of DE was carried out by GC/MS analysis (GC-Trace Ultra-ISQ mass spectrometer, Thermo Sci- entific, Austin, USA). Known weight of dried date plam fruit was placed in absolute methyl alcohol for five days, followed by filtration and 0.1 ml of the extract containing polar and non-polar compounds was injected the GC/MS. Compounds were isolated on a “TG–5MS Capillary

Standard Column”. Its temperature was set as isothermal (55 ◦C/min)

and progressively elevated to160 ◦C at a rate of 10 ◦C per min and kept for 2 min, then continuously raised to 280 ◦C at a ratio of 5 ◦C per min and kept till 9 min. Helium was utilized as a carrier gas and was deliv- ered at a regular flow-ratio (1 ml per min) with injection of 1 µl of

sample at 2 min solvent delay. The samples and solvents were auto- matically injected by an autosampler (AS3000), which was connected to the GC and adjusted at the splitting mode. At a full scan mode, electron

ionization voltage was commenced at 70 eV within the spectrum of 40–650 (*m/z*). The temperature of the ion source was set at 200 ◦C. The identity of active compounds in DE was obtained utilizing the National Institute Standard and Technology (NIST) database and WILEY mass

spectral libraries with more than 62,000 patterns.

* 1. *Identification of total phenolic content (TPC)*

The TPC of DE was specified depending on the Folin-Ciocalteu pro- cedure [[21]](#_bookmark25). In a nutshell, 3.5 ml of distilled water was applied to 100 µl of the extract and shaken well, subsequently adding 250 µl of Folin-Ciocalteau reagent for oxidation. Next 5 min, the admixture was neutralized by adding 1.25 ml of Na2CO3 (20% solution) and scramble well for 30 s. The absorbance was calculated utilizing a UV/visible spectrophotometer at 725 nm versus a solvent blank after 40 min. The TPC was specified using a gallic acid calibration curve and presented as mg of gallic acid equivalent (mg GAE) per gram of date palm. When Y 0.0242X 0.0187 (where X mg GAE / g of date palm; Y optical density), the gallic acid calibration curve was determined, and the

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correlation coefficient was R2 = 0.999.

* 1. *Identification of total flavonoid content (TFC)*

The TFC of DE was calculated utilizing a colorimetric assay with aluminium chloride (AlCl3) [[22]](#_bookmark28). Briefly, 2 ml of DE was applied to 600 µl of 5% NaNO2 and mingled with 600 µl AlCl3 (10%); the volume was set to 2.5 ml by distilled water. Following 5 min of room temperature incubation, 4 ml of 1 M NaOH was mixed then carefully vortexed. TFC was expressed as mg catechin equivalents /100 g dry weight for each sample. Finally, using a spectrophotometer (TU-1810 series of UV–vi- sible, General Analysis of General Instrument Co. Ltd., Beijing, China), the absorbance was recorded at 510 nm versus a solvent blank. The TFC was calculated utilizing a catechin-based calibration curve and expressed as mg of catechin equivalent (mg CE)/g of date palm [[23]](#_bookmark29). The catechin calibration curve was calculated using the formula Y 0.0125X 0.0086 (where X mg CE/g of date palm; Y optical den-

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sity), with an R2 of 0.999.

* 1. *Detection Scavenging activity of radical DPPH*•

As reported by Hwang and Thi [[24]](#_bookmark30), the stable DPPH• was used to evaluate DE’s free radical scavenging ability. For DPPH•, the final concentration was 200 µM, and the reaction volume was 3 ml. After 60

min of incubation in dim, the absorbance was estimated at 517 nm versus a blank of pure methanol. The following equation was used to

measure the percent suppression of the DPPH• free radical:

2



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