



Cardioprotective effect of Date Palm Fruit Extract (*Phoenix Dactylifera* L.) against Doxorubicin-induced cardiotoxicity in rats

Thesis

submitted for the degree of Doctor of Philosophy of Science in
Biochemistry

Presented by

Shimaa Mubarak Fahmy Mubarak

(M.Sc. in Biochemistry-Faculty of Science, Ain Shams University, 2013)

Under Supervision of

Prof. Dr.

Shadia Abdel Hamid Fathy

*Professor of Biochemistry,
Biochemistry Department,
Ain Shams University*

Prof. Dr.

Jihan Seid Hussein

*Professor of Medical Biochemistry,
Medical Biochemistry Department,
National Research Centre*

Prof. Dr.

Abdel Razik Hussein Farrag

*Professor of Histochemistry,
Pathology Department,
National Research Centre*

Ass.Prof. Dr.

Nahla Samir Hassan

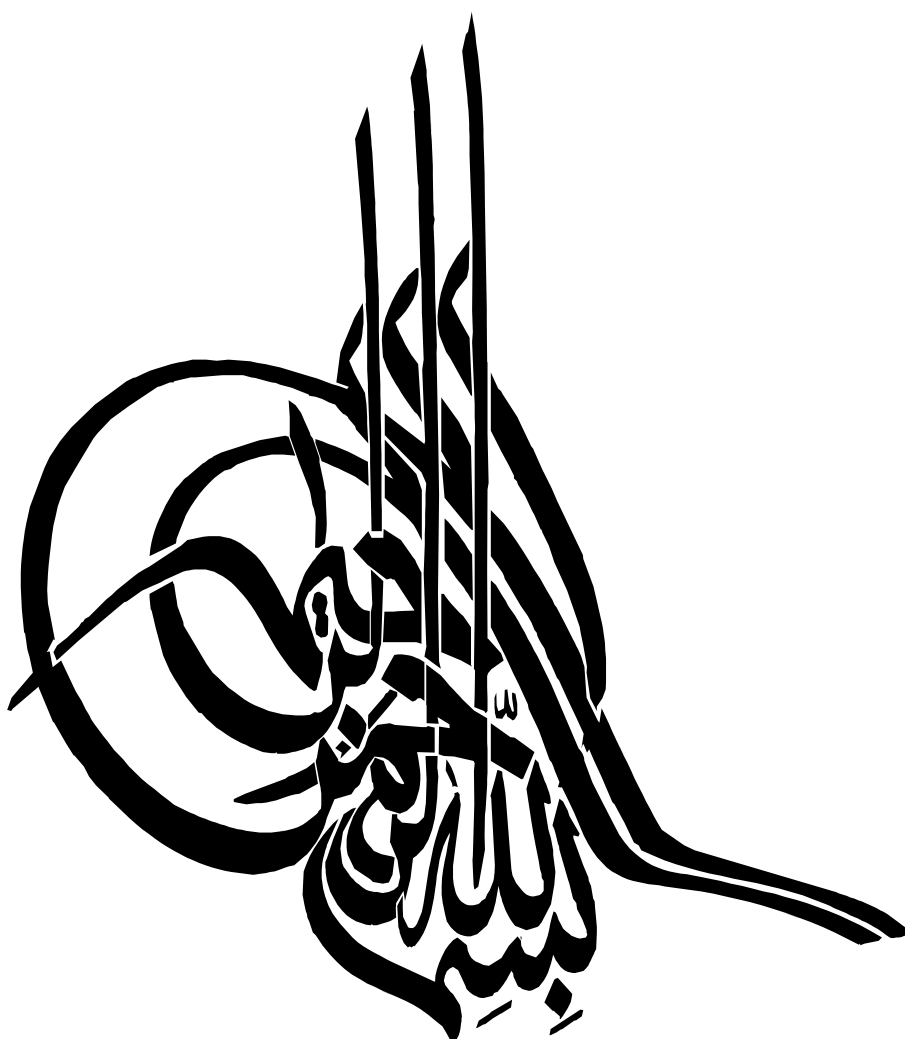
*Assistant Prof. of Biochemistry,
Biochemistry Department,
Ain Shams University*

Department of Biochemistry

Faculty of Science

Ain Shams University

2018



ACKNOWLEDGMENT

First and foremost. I feel always indebted to Allah, the most kind and the most merciful thanks to who made me able to accomplish this work.

I would like to express my good indebtedness and sincere gratitude to Prof. Dr. Shadia Abdel Hamid Fathy, Professor of Biochemistry, Faculty of Science, Ain Shams University, to whom I am deeply indebted for her supervision, kind guidance and care during the progress of this study , continuous encouragement and support, valuable advice and constructive criticism . No words can express my sincere gratitude to her.

I wish to express my deepest heartfelt appreciation , gratefulness and sincere thanks to Prof. Dr. Jihan Seid Hussein, Professor of Medical Biochemistry, Medical Biochemistry Department, National Research Centre for her supervision , helping me in the experimental work ,her continuous encouragement, patience, useful feedback , insightful comments . I owe her more than i can express for all the time she spent in revising every detail in this thesis.

I would like to express my great respect and gratitude to Prof. Dr. Abdel Razik Hussein Farrag, Professor of Histochemistry, Pathology Department, National Research Centre for his continuous instructive supervision, fruitful discussions and guidance, his efforts exerted in the pathology part and its related data interpretations, continuous corporation and his kind care.

I would like to express my sincere gratitude and appreciation to Dr. Nahla Samir Hassan, Assistant Prof. of Biochemistry, Faculty of Science, Ain Shams University for her supervision, endless help, generous support, continuous encouragement, valuable advice.

My deepest thanks and appreciation to Prof. Dr. Zakaria El-Khayat, Professor of Medical Biochemistry, Medical Biochemistry Department, National Research Centre , for his valuable advice , endless cooperation , and unique support throughout the development of this thesis.

A word of gratitude is due to the Medical Biochemistry Department, National Research Centre, for providing the research facilities needed to achieve this work.

I'm also grateful to Prof. Dr. Mahmoud Ibrahim Nassar, Professor of natural products chemistry, Natural Compounds Chemistry Department, National Research Centre for his preparing the extract of date palm fruit.

I would like to express my gratitude to all my colleague in the Laboratory Department of Al-waraq Central Hospital, for their endless support and ultimate encouragement.

Finally, I want to express my deep love and most profound gratitude to my family especially my father and my mother.

Name:	Shimaa Mubarak Fahmy Mubarak.
Date of graduation:	June 2006, Faculty of women for Arts, Sciences and Education, Biochemistry & Nutrition Department, Ain Shams University.
Degree awarded:	B.Sc. in Biochemistry & Nutrition 2006(very good). M.Sc. in Biochemistry, Faculty of Science, Ain Shams University, 2013.
Occupation:	Medical chemist at Al-waraq Central Hospital.

This thesis has not been submitted to
this or any other University

Shimaa Mubarak Fahmy Mubarak

Abstract

Antitumor therapy usually destructs the physiological homoeostasis and affects various organs during cancer treatment process. Doxorubicin (Dox) an anthracycline antibiotic has been widely used to treat cancer, principally haematological malignancies and solid tumors. The administration of Dox is a topic of concern in the medical community, as it frequently related to dose-dependent cardiotoxicity. Therefore, the present study was designed to investigate the protective potential of date palm fruit extract on Dox-induced cardiotoxicity. Forty female albino rats were used in this study and classified into four groups including control, date palm fruit extract, Dox and protected groups. Myocardial toxicity of Dox appeared in the elevation of serum total cholesterol (TC), triglycerides (TG), low density lipoprotein cholesterol (LDL-C) levels and atherogenic indices, while level of high density lipoprotein cholesterol (HDL-C) decreased; it also decreased the activities of cardiac glutathione peroxidase (GPx) and superoxide dismutase (SOD), but increase levels of cardiac malondialdehyde (MDA) and also of urinary 8-hydroxy-2-deoxyguanosine (8-OHdG).

Abstract

Dox produced a significant increase in creatine kinase-MB (CK-MB) & lactate dehydrogenase (LDH) activities and serum troponin-I level .It also showed changes in electrocardiography (ECG) pattern. Histopathological studies revealed alteration of cardiac tissue structure by Dox. Meanwhile, pretreatment with date palm fruit extract restored the aforementioned parameters indicating its cardioprotective influence on the heart tissue against toxicity induced by Dox.

Key words: *Phoenix dactylifera* L., Cardioprotective, Doxorubicin, Cardiotoxicity, Atherogenic indices, 8-OHdG, HPLC, ECG.

List of content

Title	Page
Abstract.....	I
List of abbreviations.....	III
List of figures.....	VI
List of tables.....	XI
1. Introduction	1
Aim of the work	5
2. Review of literature	6
3. Materials and methods	58
3.1 Materials	58
3.1.1 Chemicals	58
3.1.2 Plants	58
3.1.3 Experimental animals.....	58
3.2 Methods.....	59
3.2.1 Plant extraction.....	59
3.2.2 Induction of cardiotoxicity.....	59
3.2.3 Experimental design.....	59
3.2.4 Blood sampling.....	60
3.2.5 Preparation of tissue homogenate.....	61
3.2.6 Biochemical assays.....	61
3.2.6.1 Lipid profile.....	61
3.2.6.2 Oxidant and antioxidant parameters...	67
3.2.6.3 Cardiac profile parameters.....	75
3.2.7 Electrocardiography (ECG) monitoring...	79
3.2.8 Histopathological examination.....	79
3.2.9 Statistical analysis.....	80
4. Results	81
4.1 Biochemical parameters.....	81
4.1.1 Lipid profile.....	81
4.1.2 Atherogenic indices.....	83
4.1.3 Oxidant and antioxidant parameters.....	98
4.1.4 Cardiac profile parameters.....	112

4.2 Electrocardiography (ECG) monitoring..... 120

4.3 Histopathological examination of the heart..... 136

5.Discussion..... 143

6. Summary..... 159

7. References..... 165

8. Arabic summary..... 212

List of abbreviations

AC	Atherogenic Coefficient
AF	Atrial Fibrillation
AI	Atherogenic Index
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AMPK	AMP-Activated Protein Kinase
ANTs	Anthracyclines
APH	Atypical Prostatic Hyperplasia
AST	Aspartate Aminotransferase
ATP	Adenosine Triphosphate
AV block	Atrio-Ventricular Block
AZT	Azithromycin
CAT	Catalase
CCl₄	Carbon Tetrachloride
CK	Creatine Kinase
CK – MB	Creatine Kinase – MB
CPK	Creatine Phosphokinase
CPT I	Carnitine Palmitoyl-Transferase System
CRR	Cardiac Risk Ratio
DNA	Deoxyribonucleic Acid
Dox	Doxorubicin
DPL	Date Palm Leaves
DPP	Date Palm Pollen
DSE	Date Seed Extract
DZR	Dexrazoxane
EAC	Ehrlich Ascites Carcinoma
ECG	Electrocardiography