

بسم الله الرحمن الرحيم





شبكة المعلومات الجامعية التوثيق الالكتروني والميكرو فيلم



جامعة عين شمس

التوثيق الإلكتروني والميكروفيلم

قسم

نقسم بالله العظيم أن المادة التي تم توثيقها وتسجيلها
علي هذه الأقراص المدمجة قد أعدت دون أية تغيرات



يجب أن

تحفظ هذه الأقراص المدمجة بعيدا عن الغبار





بعض الوثائق الأصلية تالفة





بالرسالة صفحات
لم ترد بالأصل





***The potential protective role of
Astaxanthin on Doxorubicin-induced
cardiac toxicity in rats***

Thesis

Submitted for Partial Fulfillment of the Master
Degree in Physiology

By

Marina Sorial Mina Derias

Demonstrator of Physiology
Faculty of Medicine, Ain Shams University

Under Supervision of

Prof. Abd El Rahman Fahmy Ahmed Sabaa

Professor of Physiology
Faculty of Medicine – Ain Shams University

Prof. Abd El Moneim Mahmoud Ali Osman

Professor of Pharmacology
National Cancer Institute – Cairo University.

Dr. Abd El-Hamid Abou el magd Mohamed

Assistant Professor of Physiology
Faculty of Medicine – Ain Shams University

Dr. Doaa Ahmed Abou-bakr Darwish

Lecturer of Physiology
Faculty of Medicine – Ain Shams University

Physiology department
Faculty of Medicine
Ain Shams University
2020

Acknowledgement

First, thanks are all due to **Allah** for Blessing this work until it has reached its end, as a part of his generous help throughout our life.

My profound thanks and deep appreciation to **Prof. Dr. Abd El Rahman Fahmy Ahmed Sabaa**, Professor of Physiology, Faculty of Medicine – Ain Shams University for his great support and advice, his valuable remarks that gave me the confidence and encouragement to fulfill this work.

I am deeply grateful to **Prof. Dr. Abd El Moneim Mahmoud Ali Osman**, Professor of Pharmacology, National Cancer Institute – Cairo University for adding a lot to this work by his experience and for his keen supervision.

I am also thankful to **Dr. Abd El-Hamid Abou el magd Mohamed**, Assistant Professor of Physiology, Faculty of Medicine – Ain Shams University for his valuable supervision, co-operation and direction that extended throughout this work.

I would like to direct my special thanks to **Dr. Doaa Ahmed Abou-bakr Darwish**, Lecturer of Physiology, Faculty of Medicine – Ain Shams University, for her invaluable help, fruitful advice, continuous support offered to me and guidance step by step till this essay finished.

I am extremely sincere to **my family** who stood beside me throughout this work giving me their support.

Marina Sorial Mina Derias

List of Contents

	<u>Page</u>
Acknowledgment	--
List of abbreviations.....	i
List of tables	iv
List of figures	viii
Abstract	x
Introduction	1
Aim of the Work	3
Review of Literature.....	4
• Doxorubicin (Dox).....	4
• Astaxanthin (ATX)	17
Materials and Methods	28
Results	52
Discussion	79
Summary and Conclusion	86
References	90
Appendix	119
Arabic Summary	--

List of Abbreviations

ATP	Adenosine triphosphate
ASK1	Apoptosis-signal regulating kinase-1
ATX	Astaxanthin
BBB	Blood Brain Barrier
BP	Blood pressure
cTnI	Cardiac Troponin I
JNK	c-Jun NH2-terminal kinase
Cu ²⁺	Copper ion
Q-T _c	Corrected Q-T
CRP	C-reactive protein
COX-1	Cyclooxygenase-1 enzyme
DBP	Diastolic blood pressure
DOX	Doxorubicin
DIC	Doxorubicin induced cardiotoxicity
DOXol	Doxorubicinol
ECG	Electrocardiogram
eNOS	Endothelial nitric oxide synthases
ELISA	Enzyme-linked immunosorbent assay
ERK1/2	Extracellular signal-regulated kinase
FBW	Final body weight
HRT	Half relaxation time
HF	Heart failure
HR	Heart rate
HRP	Horseradish peroxidase
HER2	Human epidermal growth factor receptor 2
HFE	Human hemochromatosis protein
H ₂ O ₂	Hydrogen peroxide

List of Abbreviations (Cont.)

OH [·]	Hydroxyl radicals
IR SENSOR	Infrared sensor
IL-1 β	Interleukin-1 β
IL-6	Interleukin-6
i.p.	Intraperitoneal
Fe	IRON
IRP-1	Iron regulatory protein 1
IREs	Iron-responsive elements
I/R	Ischemia/Reperfusion
KHB	Krebs-Henseleit Bicarbonate buffer solution
LSD	Least significant difference
LVEF	Left ventricular ejection fraction
LVW	Left ventricular weight
MMP	Matrix metalloproteinase
MAP	Mean arterial blood pressure
MAPK	Mitogen-activated protein kinase
MFR	Myocardial flow rate
NSCS	Neural stem cells
NADPH	Nicotinamide adenine dinucleotide phosphate
NO	Nitric oxide
NOS	Nitric oxide synthases
NF- κ B	Nuclear factor-kappa β
Q-T _o	Observed Q-T interval
O.D.	Optical Density
O ₂	Oxygen
PT	Peak developed tension
p-ERK	Phospho extracellular signal-regulated kinase
PI3K	Phosphoinositide 3-kinase

List of Abbreviations (Cont.)

PUFA	Polyunsaturated fatty acids
ROS	Reactive oxygen species
RVW	Right ventricular weight
SERCA2a	Sarcoplasmic/ endoplasmic reticulum Ca (2+) ATPase 2a
p-Stat3	Signal transducer and activator of transcription 3
SHR	Spontaneously hypertensive rats
SEM	Standard error of mean
SPSS	Statistical Program for Social Science
O ₂ ⁻	Superoxide
SBP	Systolic blood pressure
USFDA	The United States Food and Drug Administration
TPT	Time to peak tension
TNF- α	Tumor necrosis factor- α

List of Tables

Table	Title	Page
	Materials & Methods	
a	KHB Composition in mmol/L, the stock solutions and the volume used from the stock solutions.	35
	Results	
1	Final Body Weight, Right ventricular weight, Right ventricular weight index, Left ventricular weight and Left ventricular weight index in the different studied groups.	53
2	Systolic Blood Pressure, Diastolic Blood Pressure and Mean Arterial Pressure in the different studied groups.	58
3	Heart Rate, PR interval duration, QRS complex duration, R voltage, observed QT interval duration and corrected QT interval duration in the different studied groups.	60
4	Chronotropic activity from isolated heart study in the different studied groups.	63
5	Peak Tension and Peak Tension/Left Ventricular Weight from isolated heart study in the different studied groups.	66
6	Time to Peak Tension and Half Relaxation Time from isolated heart study in the different studied groups.	69
7	Myocardial Flow Rate and Myocardial Flow Rate/ Left Ventricular Weight from isolated heart study in the different studied groups.	73
8	Plasma cardiac Troponin I, plasma Cytochrome C and Cardiac Tissue Iron in the different studied groups.	76
9	Final Body Weight, Right ventricular weight, Right ventricular weight index, Left ventricular weight and Left ventricular	119

Table	Title	Page
	weight index in Control Group.	
10	Final Body Weight, Right ventricular weight, Right ventricular weight index, Left ventricular weight and Left ventricular weight index in DOX- treated Group.	120
11	Final Body Weight, Right ventricular weight, Right ventricular weight index, Left ventricular weight and Left ventricular weight index in ATX- treated Group.	121
12	Final Body Weight, Right ventricular weight, Right ventricular weight index, Left ventricular weight and Left ventricular weight index in ATX+DOX treated Group.	122
13	Systolic Blood Pressure, Diastolic Blood Pressure and Mean Arterial Pressure in Control Group.	123
14	Systolic Blood Pressure, Diastolic Blood Pressure and Mean Arterial Pressure in DOX- treated Group.	124
15	Systolic Blood Pressure, Diastolic Blood Pressure and Mean Arterial Pressure in ATX- treated Group.	125
16	Systolic Blood Pressure, Diastolic Blood Pressure and Mean Arterial Pressure in ATX+DOX treated Group.	126
17	Heart Rate, PR interval duration, QRS complex duration, R voltage, QT interval observed duration and QT interval corrected duration in Control Group.	127
18	Heart Rate, PR interval duration, QRS complex duration, R voltage, QT interval observed duration and QT interval corrected duration in DOX-treated Group.	128
19	Heart Rate, PR interval duration, QRS	129

Table	Title	Page
	complex duration, R voltage, QT interval observed duration and QT interval corrected duration in ATX-treated Group.	
20	Heart Rate, PR interval duration, QRS complex duration, R voltage, QT interval observed duration and QT interval corrected duration in ATX+DOX treated Group.	130
21	Chronotropic activity from isolated heart study in Control Group.	131
22	Chronotropic activity from isolated heart study in DOX-treated Group.	132
23	Chronotropic activity from isolated heart study in ATX-treated Group.	133
24	Chronotropic activity from isolated heart study in ATX+DOX treated Group.	134
25	Peak Tension and Peak Tesion/Left Ventricular Weight from isolated heart study in Control Group.	135
26	Peak Tension and Peak Tesion/Left Ventricular Weight from isolated heart study in DOX-treated Group.	136
27	Peak Tension and Peak Tesion/Left Ventricular Weight from isolated heart study in ATX-treated Group.	137
28	Peak Tension and Peak Tesion/Left Ventricular Weight from isolated heart study in ATX+DOX treated Group.	138
29	Time to Peak Tension and Half Relaxation Time from isolated heart study in Control Group.	139
30	Time to Peak Tension and Half Relaxation Time from isolated heart study in DOX-treated Group.	140
31	Time to Peak Tension and Half Relaxation	141

Table	Title	Page
	Time from isolated heart study in ATX-treated Group.	
32	Time to Peak Tension and Half Relaxation Time from isolated heart study in ATX+DOX treated Group.	142
33	Myocardial Flow Rate and Myocardial Flow Rate/ Left Ventricular Weight from isolated heart study in Control Group.	143
34	Myocardial Flow Rate and Myocardial Flow Rate/ Left Ventricular Weight from isolated heart study in DOX-treated Group.	144
35	Myocardial Flow Rate and Myocardial Flow Rate/ Left Ventricular Weight from isolated heart study in ATX-treated Group.	145
36	Myocardial Flow Rate and Myocardial Flow Rate/ Left Ventricular Weight from isolated heart study in ATX+DOX treated Group.	146
37	Plasma levels of cardiac Troponin I, Cytochrome C and Cardiac tissue Iron in Control Group.	147
38	Plasma levels of cardiac Troponin I, Cytochrome C and Cardiac tissue Iron in DOX-treated Group.	148
39	Plasma levels of cardiac Troponin I, Cytochrome and Cardiac tissue Iron in ATX-treated Group.	149
40	Plasma levels of cardiac Troponin I, Cytochrome C and Cardiac tissue Iron in ATX+DOX treated Group.	150