بسم الله الرحمن الرحيم

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تم رفع هذه الرسالة بواسطة / حسام الدين محمد مغربي

بقسم التوثيق الإلكتروني بمركز الشبكات وتكنولوجيا المعلومات دون أدنى مسئولية عن محتوى هذه الرسالة.

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Effect of Grape Seeds *(Vitis vinifera L.)* and Mandarin Peels *(Citrus reticulate L.)* Extracts on the Cardiotoxicity Induced by Cyclophosphamide in Rats

Thesis

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قَالَ تَعَالَىٰ: ﴿وَقُلِ ٱعۡمَلُواْ فَسَيَرَى ٱللَّهُ عَمَلَكُمۡ
وَرَسُولُهُۥ وَٱلۡمُؤۡمِنُونَۖ وَسَتُرَدُّونَ إِلَىٰ عَٰلِمِ ٱلۡغَيۡبِ
وَٱلشَّهَٰدَةِ فَيُنَبِّئُكُم بِمَا كُنتُمۡ تَعۡمَلُونَ ١٠٥﴾

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Abstract

Effect of Grape Seeds *(Vitis vinifera L.)* and Mandarin Peels *(Citrus reticulate L.)* Extracts on the Cardiotoxicity Induced by Cyclophosphamide in Rats. Hanan Kamal Mohamed, MSc. degree, Biochemistry and Nutrition Department, Faculty of Women for Arts, Science and Education, Ain Shams University.

The current study was developed to investigate the influence of grape seeds (GS) and mandarin peels (MP) extracts as a powerful antioxidants on the cardiotoxicity induced by cyclophosphamide (CP) in rats. Sixty adult male Sprague-Dawley rats were divided into 6 groups. Group (1) (Control group): Rats were received distilled water (2.5 ml / kg BW) daily by oral intubation for 6 weeks and injected intraperitoneally (i.p) with saline (0.9 %) as single dose at the end of the sixth week of the experiment. Group (2): Rats were received distilled water and injected with single dose of cyclophosphamide which dissolved in saline (200 mg/kg BW. i.p.) at the end of the sixth week of the experiment**.** Groups (3 and 4): Rats were received grape seeds extracts low and high doses (150 and 300 mg /kg BW), respectively daily by oral intubation for 6 weeks then injected with cyclophosphamide as group 2. Groups (5 and 6): Rats were received mandarin peels extracts low and high doses (150 and 300 mg /kg BW), respectively daily for 6 weeks then injected with cyclophosphamide as group 2. The results of this study documented that CP caused a significant increase in serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALK-P), creatine kinase-MB (CK-MB), lactate dehydrogenase (LDH), creatine kinase (CK) enzymes activities and serum malondialdehyde (MDA) level. While total antioxidant capacity level (TAC) showed a significant decrease. On the other hand cardiac catalase (CAT), superoxide dismutase (SOD) and glutathione peroxidase (GPx) activities and cardiac β cell lymphoma-2 (Bcl-2) level showed a

significant decrease in CP intoxicated group while cardiac p53, caspase-3 and DNA fragmentation levels showed a significant increase in CP intoxicated group. Also, some histopathological changes were observed in liver and heart tissues in CP group. Oral administration of GS and MP caused an ameliorative effect in oxidative and apoptotic biomarkers, liver and heart function enzymes activities with an improvement of histopathological changes in liver and heart tissues. **Conclusion:** Our data proved that the protective effect of grape seeds and mandarin peels in cyclophosphamide intoxicated group may be due to their antioxidant, anti-inflammatory and anti- apoptotic properties.

List of Abbreviations

Abbreviation	Meaning
AAF	Acetylaminofluorene
ADP	Adenosine di phosphate
ALT	Alanine aminotransferase
ADH	Alcohol dehydrogenase.
ALDH	Aldehyde dehydrogenase
ALK-P	Alkaline phosphatase
AST	Aspartate aminotransferase
ATP	Adenosine tri phosphate
BAD	Bcl_2 Associated death promotor
BAX	Bcl_2 Associated X protein
Bcl-2	B Cell lymphoma-2
CAT	Catalase
CCL4	Carbon tetrachloride
CE	Catechin equivalent
CYC	Cytochrome C
CK	Creatine kinase
CK-MB	Creatine kinase-MB
CP	Cyclophosphamide
CPE	Citrus peel extract
CRP	C-reactive protein

CVDs	Cardiovascular diseases
CYP-450	Cytochrome P450
DEN	Diethylnitrosamine
DNA	Deoxyribonucleic acid
DOX	Doxorubicin
ECs	Endothelial cells
ELIZA	Enzyme linked immunesorbent assay
eNOS	Endothelial nitric oxide synthase
FER	Feed efficiency ratio
G6PDH	Glucose-6-phosphate dehydrogenase
GAE	Gallic acid equivalent
GP_X	Glutathione peroxidase
GR	Glutathione reductase
GS	Grape seeds
GSE	Grape seed extract
GSH	Reduced glutathione
GSPE	Grape seed procyanidin extract
GST	Glutathione S-transferase
HDL-C	High-density lipoprotein cholesterol
HDN	Hesperidin
HK	Hexokinase
HPLC	High performance liquid chromatography
HRP	Horse radish peroxidase

i.p.	Intraperitoneally
I/R	Ischemic- reperfusion
IL-6	Interleukin-6
ISO	Isoproterenol
JNKs	c-Jun N-terminal kinases
LDH	Lactate dehydrogenase
LDL-C	Low- density lipoprotein cholesterol
LPO	Lipid peroxidation
MAPK	Mitogen activated protein-kinase
MDA-LDL	Malondialdehyde modified LDL
MG	Methyl gallate
MI	Myocardial infarction
MP	Mandarin peels
MPE	Mandarin peels extracts
NAD	Nicitonamide adenosine di phosphate
+NADP	Nicotinamide adenine dinucleotide phosphate
NADH	Reduced nicotinamide adenine dinucleotide
NADPH	Reduced nicotinamide adenine dinucleotide phosphate
NF-kB	Nuclear factor-kB
NG	Naringin
NOS	Nitric oxide synthase
$ONOO^-$	Peroxynitrites
Ox-LDL	Oxidized- LDL

PARP-1	Poly (ADP-ribose) polymerase-1
PBS	Phosphate buffer solution
PI3K	Phosphoinositide 3-kinase
PMFs	Polymethoxy flavones
PP	Phenoxyl radical
RE	Rutin equivalents
RNS	Reactive nitrogen species
ROO·	Peroxyl radical
ROOH	Hydroperoxide
ROS	Reactive oxygen species
SOD	Superoxide dismutase
STZ	Streptozotocin
TAC	Total antioxidant capacity
TC	Total cholesterol
TFC	Total flavonoid content
TLR-4	Toll-like receptor-4
TNF-α	Tumor necrosis factor-α
TPC	Total phenolic content
TPP	Total polyphenols
VSMCs	Vascular smooth muscle cells
WAT	White adipose tissue