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EFFICACY AND BIOAVAILABILITY OF SILYMARIN ON PLASMA S100B LEVEL IN CARDIOTOXICITY-INDUCED RATS

By

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COMMITTEE DECISION

This Thesis (Efficacy and Bioavailability of Silymarin on Plasma S100B Level in cardiotoxicity-induced rats) was Successfully Defended and Approved on may, 2019.

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أهداء

الى الداعم الاول الذي اوصلني الى هذه المرحله ،الى الذي وجهني نحو طريق العلم
(أبي)

الى من احبتني دائما وسهرت من اجلي وعلمتني واعتنت بي
(أمي)

الى اخوتي ، الى خالي العزيز الذي اتمنى ان يفرج الله عنه

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°C	Celsius
µg	Microgram
5-HT1A	5-hydroxytryptamine, 1A receptor
AAV	Adeno-associated virus
Akt	Protein kinase B
ALT	Alanine transaminase
ANOVA	Analysis of variance
AP-1	Activator protein 1
AST	Aspartate transaminase
ATPase	Adenosine triphosphatase
AUC	Area under the curve
Bcl-2	B-cell lymphoma 2
bFGF	Basic fibroblast growth factor
Ca^{2+}	Calcium ions
CABG	Coronary artery bypass grafting
cAMP	Cyclic adenosine monophosphate
Cdc42	Cell division control protein 42
Cdk4	Cyclin-dependent kinase 4
CK	Casein kinase
CK-MB	Creatine kinase-muscle/brain
COX-2	Cyclooxygenase-2
CYP450	Cytochrome P450
DMSO	Dimethyl sulfoxide
DNA	Deoxyribonucleic acid
EDTA	Ethylenediaminetetraacetic acid
EGFR	Epidermal growth factor receptor
ERK1/2	Extracellular signal–regulated kinases
Fe^{2+}	Ferrous ion
FGFR	Fibroblast Growth Factor Receptor
FtsZ	Filamenting temperature sensitive mutant Z
G	Gram
GC	Guanylate cyclase
GFAP	Glial fibrillary acidic protein
GLUT 4	Glucose transporter type 4
GM-CSF	Granulocyte-macrophage colony stimulating factor
GPCR	G-protein-coupled receptors
GSH	Glutathione
H	Hour
H&E	Hematoxylin and eosin
HCL	Hydrogen chloride
HIV	Human immunodeficiency virus
HL-60	Human leukemia-60
HMG-CoA	3-hydroxy-3-methylglutaryl coenzyme A
HRP	Horseradish Peroxidase

HSC	Hepatic stellate cell
HSP	Heat shock proteins
I.P	Intraperitoneal
IFN-γ	Interferon gamma
IFs	Intermediate filaments
IGF	Insulin growth factor
IKKβ	Inhibitor of nuclear factor kappa-B kinase subunit beta
IL-1β	Interleukin 1 beta
iNOS	INDUCIBLE synthase
IP	Inducible protein
JNK	C-Jun N-terminal kinase
K^+	Potassium ion
KCl	Potassium chloride
KDa	kilodalton
Kg	Kilogram
LD	Lethal dose
LLD	Lower Limit of Detection
LPA	Lysophosphatidic acid
MAP-2	Microtubule-associated protein 2
MAPK	Mitogen-activated protein kinase
MARKS	Myristoylated alanine-rich C-kinase substrate
MFs	Microfilaments
Mg	Milligram
MI	Myocardial infarction
Min	Minute
Ml	Milliliter
Mm	Millimeters
mRNA	Messenger ribonucleic acid
MTs	Microtubules
MyoD	Myogenic differentiation
Na^+	Sodium ion
NADP	Nicotinamide adenine dinucleotide phosphate
NDR	Nuclear dbf2-related
NF-κB	Nuclear factor kappa-light-chain-enhancer of activated B cells
NGF	Nerve growth factor
Nm	Nanometre
NO	Nitric oxide
O.D	Optical density
PDGFR	Platelet-derived growth factor receptors
Pg	Picograms
PI3K	Phosphatidylinositol-3-kinase
PKC	Protein kinase C
PLA 2	Phospholipases A2
PLC	Phospholipase C
PPAR-γ	Peroxisome proliferator-activated receptor γ
ppm	Parts per million
QT	Quality time

r	Correlation coefficient
RAGE	Receptor for advanced glycation endproducts
RB	Retinoblastoma protein
RNA	Ribonucleic acid
Ros	Reactive oxygen species
RPM	Revolutions per minute
rRNA	Ribosomal ribonucleic acid
RSK	Ribosomal protein S6 kinase
SD	Standard deviation
siRNA	Small interfering
SOD	Superoxide dismutase
SPSS	Statistical Package for the Social Sciences
STAT3	Signal transducer and activator of transcription 3
TGF-β	Transforming growth factor-β
TLR4	Toll-like receptor 4
TNF	Tumor necrosis factor
TMB	Tetramethylbenzidine
UVB	Ultraviolet B-rays
v	Volume
VEGF	Vascular endothelial growth factor
VSMC	vascular smooth muscle cells
α-SMA	α-smooth muscle actin
µL	Microliter
µM	Micromolar

Efficacy and Bioavailability of Silymarin on Plasma S100B Level in cardiotoxicity-induced rats

By

Diyar Majid Jalil khaleel

Supervisor

Dr. Taghreed Altaei

ABSTRACT

Silymarin is the main extract from the seeds of Milk thistle (*Silybum marianum*) and contains approximately 65–80% of silymarin flavonolignans compounds. The major component of the silymarin complex is silibinin. Cardiovascular toxicity is the leading cause of death associated with drugs overdose. The calcium (Ca^{2+})-binding protein S100B is a multifunctional protein primarily expressed by the brain and myocardial tissues, through its interaction with several effector proteins within cells have involved in the regulation of a variety of cellular processes such as protection from oxidative cell damage.

This study was designed to investigate the cardioprotective effect of silymarin on clozapine-induced cardiotoxicity in albino Wistar rats. The heart damage was indicated by elevated levels of the plasma biomarkers such as S100B, troponin, and creatine kinase-MB (CK-MB). S100B levels were correlated with cardiovascular toxic effects induced by clozapine in a rat model.

The results of this study showed that silymarin treated groups presented with significant difference in rat's weight and food consumption, compared to reduction in cardiotoxic groups. Plasma S100B levels were increased in cardiotoxic groups, declined in those treated by silymarin, and abolished by pretreatment with silymarin. Troponin I and CK-MB elevated significantly in cardiotoxic induced rats, which declined with silymarin treatment, and prevented in pretreatment by silymarin.

The observed protective effects of silymarin in end organs, such as the heart, liver and Kidneys, against cardiotoxic agent clozapine were highly significant. The outcome of histopathological analysis of this study showed that the intensity of the evaluated parameters in cardiotoxic induced rats by clozapine was prevented in silymarin pretreatment which describe the cardioprotection by this agent. The correlation study presented with coefficient correlation between S100B and the studied parameters were significant positive correlation with troponin I and CK-MB.

In conclusion, Silymarin significantly attenuated the cardiotoxicity induced by clozapine, and prevents the mediated damage to the heart. The efficacy of silymarin as cardioprotective agent explained by its mechanism of action as cardioprotective agent through anti-inflammatory, antioxidant, decrease S100B, troponin I, and CK-MB levels and correlated to each other.