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

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the Master's Degree in Pharmaceutical Science**

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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 المرحلة ،الى الذي وجهني نحو طريق العلم
(أبي)

الى من احببني دائما وسمررت من اجلي وعلمتني واعتنت بي
(أمي)

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

الى جميع افراد عائلتي واصدقائي

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List of Contents

Content	Pages
Committee decision	III
Dedication	IV
Acknowledgement	V
List of content	VI
List of table	VIII
List of figure	VIII
List of abbreviation	X
Abstract	XIII
Chapter one	
1.Introduction	1
1.1.Objectives	4
Chapter two	
2. Literature review	5
2.1 Silymarin	5
2.1.1. Chemical composition of silymarin	6
2.1.2. Pharmacokinetics of Silymarin	8
2.1.3. Pharmacodynamics of Silymarin	9
2.1.4. Mechanisms of Action of Silymarin	12
2.1.5. Therapeutic activity	16
2.1.6. Drug interactions	18
2.1.7. Adverse Effects and Interactions	19
2.1.8. Toxicity	20
2.2. Cardiotoxicity by drugs	20
2.3. The Protein S100B	21
2.3.1. The functions of S100B	25
2.3.1.1. Intracellular regulatory activities	27
2.3.1.1.1. Inhibition of Protein Phosphorylation	27
2.3.1.1.2. Cytoskeleton interactions	28
2.3.1.1.3. Cell proliferation and survival	29
2.3.1.1.4. Cell differentiation	30
2.3.1.1.5. Ca ²⁺ homeostasis	31
2.3.1.1.6. Enzyme activity regulation	32
2.3.1.2. Extracellular regulatory activities	33
2.3.1.2.1. Effects of S100B on neurons	34
2.3.1.2.2. Effects of S100B on astrocytes	35
2.3.1.2.3. Effects on microglia	37
2.3.1.2.4. Effects on monocytes/macrophages	39
2.3.2. S100 proteins as therapeutic targets in disease	41
2.3.3. Role of S100 proteins in tissue repair	42
2.3.4. S100 proteins as biomarker in specific diseases	43

2.3.5. Renal Elimination.	44
Chapter three	
3. Materials and methods	45
3.1. Setting	45
3.2. Materials	45
3.2.1. Chemicals	45
3.2.2. Instruments and equipment	46
3.3. METHODS	47
3.3.1. Rats and housing	47
3.3.2 Experimental design	47
3.3.2.1. Study groups	47
2.3.3. Dosage and samples preparation	48
3.4. Bioavailability of Silymarin	49
3.5. Enzyme linked Immune Sorbent Assay	50
3.5.1. Rat s100b assay	50
3.5.1.1. Test principle	50
3.5.1.2. Assay procedure	50
3.6. Cardiac Troponin and Ck-MB	51
3.6.1. Determination of Troponin I	52
3.6.2. Determination of CK-MB	52
3.7. Histopathology study: Fixation and Staining	53
3.8. Statistical analysis	53
Chapter four	
4. Results	55
4.1. The efficacy of different doses of Silymarin as cardioprotection for cardiotoxicity-induced rats.	55
4.1.1. Silymarin efficacy on the rats' weight	55
4.1.2. Silymarin efficacy on the rats' food consumption	56
4.2. The Bioavailability of Silymarin	56
4.3. The Efficacy of Silymarin on Studied Biomarkers	57
4.3.1. The plasma S100B level	58
4.3.2. Cardiac Troponin	58
4.3.3. Cardiac CK-MB	59
4.4. Microscopically appearance and histopathology study:	60
4.4.1. Histopathology of the heart	60
4.4.2. Histopathology of the Rat's Liver	64
4.4.3. Histopathology of the Rat's Kidney	65
4.5. The Correlation study	67
4.5.1. Analysis of S100B correlation to weight, and food consumption	67
4.5.2. Analysis of S100B correlation to cardiac Troponin	67
4.5.3. Analysis of S100B correlation to cardiac CK-MB	68
4.5.4. Analysis of Troponin I correlation to cardiac CK-MB	69
Chapter five	
5. Discussion	70
Chapter six	
6. Conclusion	81

6.1. Future work	82
REFERENCE	83

List of tables

Tables	Pages
Table 1: Chemicals used in this study with their suppliers.	45
Table 2: The instruments used in this study.	46

List of figure

Figures	Pages
Figure 1: Milk thistle	6
Figure 2. Chemical structure of silymarin.	6
Figure 3. Structures of flavonolignan isomers of silymarin	7
Figure 4. Different therapeutic activities of silymarin	18
Figure 5: The Ca ²⁺ -dependent S100-target protein interactions	23
Figure 6. Schematic representation of putative receptors for S100B, S100A8/S100A9, the S100A8-like CP-10 protein, S100A2, and S100A7.	25
Figure 7: S100s function as Ca ²⁺ -signaling proteins. S100s bind and regulate protein targets as well as other Ca ²⁺ -signaling proteins in a Ca ²⁺ -dependent manner.	26
Figure 8. Schematic representation of proposed intracellular regulatory effects of S100B.	28
Figure 9: Schematic representation of extracellular effects of S100B in brain, heart, and vasculature	34
Figure 10. Proposed model of effects of extracellular S100B on neurons.	35
Figure 11. Proposed model of effects of S100B on astrocytes and microglia	36
Figure 12. Involvement of S100 proteins in stress and inflammation-mediated responses.	41
Figure 13. The average rat's weight during study period.	55
Figure 14. Rat's food consumption in all studied groups during the study period.	56
Figure 15. Plasma concentration time profile of Silymarin levels following IP administration.	57
Figure 16. The plasma levels of S100B in all tested groups.	58
Figure 17. Plasma Troponin I levels pre and post treatment in all tested groups.	59
Figure 18. Plasma CK-MB levels pre and post treatment.	60
Figure 19. Sections showed normal myocardium architecture of silymarin treated groups;	61
Figure 20. Heart tissues of group 4 treated by clozapine then by silymarin, showed less inflammation compared to group 6.	62

Figure 21. Heart tissues of group 5, which treated by silymarin first then treated by clozapine, the section shows normal myocardium architecture.	62
Figure 22. Heart tissues of clozapine induced cardiotoxicity group 6.	63
Figure 23. Heart tissues of normal saline control rat group 7.	63
Figure 24. Microscopic section of rat's liver, silymarin treated group 1, 2 and 3.	64
Figure 25. A: Liver section showed normal architecture for 4, 5, 6, and 7 groups.	65
Figure 26. Histopathological section showed rat's kidney of silymarin treated group 1, 2 and 3.	66
Figure 27. Microscopic section of rat's kidney of groups 4, 5, 6, and control group 7.	66
Figure 28. The correlation study between plasma S100B concentrations and Troponin I levels.	68
Figure 29. The correlation study between plasma S100B concentrations and CK-MB levels.	68
Figure 30. The correlation study between plasma Troponin I concentrations and CKMB levels.	69

List of abbreviations

°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
IKK β	Inhibitor of nuclear factor kappa-B kinase subunit beta
IL-1 β	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- κ B	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
μ L	Microliter
μ M	Micromolar

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

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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.