STUDYING THE EFFECT OF DEFERIPRONE IN IMMUNOLOGICAL MODEL OF LIVER FIBROSIS

Thesis Presented By:

Dalia Abdulazim Ismail Ibrahim El-Khouly

B. Pharm. Sc. Ain Shams University (2004)

Assistant Lecturer of Pharmacology & Toxicology

Faculty of Pharmaceutical Sciences & Pharmaceutical Industries, Future University

Submitted for the Partial Fulfillment of PhD Degree in Pharmaceutical Sciences
(Pharmacology & Toxicology)

Supervised By:

Prof.Dr. Ebtehal El-Demerdash Zaki

Professor & Head of Pharmacology & Toxicology Department
Faculty of Pharmacy, Ain Shams University

Prof.Dr. Azza Sayed Mohamed Awad

Professor & Head of Pharmacology & Toxicology Department
Faculty of Pharmacy, Ahram Canadian University

Ass.Prof. Dr. Wesam Soliman El-Bakly

Associate Professor of Pharmacology & Therapeutics
Faculty of Medicine, Ain Shams University

Dr. Reem Nabil Abulnaga

Lecturer of Pharmacology & Toxicology
Faculty of Pharmacy, Ain Shams University

Faculty of Pharmacy- Ain Shams University

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Examination Board Approval Sheet

Name of candidate:

Dalia Abdulazim Ismail Ibrahim El-Khouly

Submitted to the Pharmacology and Toxicology Department, Faculty of Pharmacy, Ain Shams University.

Approved by the committee in charge:

1. **Dr. Samira Saleh Mostafa**
   Professor of Pharmacology and Toxicology, Faculty of Pharmacy, Cairo University.

2. **Dr. Gouda Kamel Helal**
   Professor of Pharmacology and Toxicology, Faculty of Pharmacy, Al-Azhar University.

3. **Dr. Ebtehal El Demerdash Zaki**
   Professor of Pharmacology and Toxicology, Faculty of Pharmacy, Ain Shams University.

4. **Dr. Azza Sayed Awad**
   Professor of Pharmacology and Toxicology, Faculty of Pharmacy, Ahram University.

Head of Pharmacology and Toxicology Department

Prof.Dr. Ebtehal El Demerdash Zaki

Date: / / 2017

Pre-requisite Post-Graduate Courses

Besides the work presented in this thesis, the candidate has attended the following courses:

Special courses:

1. Pharmacology.
2. Clinical Pharmacology and Therapeutics.
3. Clinical Toxicology.
4. Selected topics in Pharmacology and Toxicology.

She has successfully passed examination in these courses and the comprehensive exam with general grade ***Excellent.***

Head of Pharmacology and Toxicology Department

Prof .Dr. Ebtehal El-Demerdash Zaki

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ABSTRACT

Chronic hepatitis C (CHC) virus infection; affecting more than 170 million people worldwide; is a leading cause of progressive liver fibrosis, liver cirrhosis and hepatocellular carcinoma. Iron overload is one of mechanisms by which hepatitis C virus causes oxidative stress that may contribute to fibrosis and carcinogenesis in the liver. The present study was designed to assess the potential antifibrotic effect of the oral iron chelator deferiprone (DFP) and whether it can attenuate the severity of oxidative stress and inflammatory response during concanavalin A (Con A)-induced liver fibrosis in rats. Moreover, we assessed its additional usefulness to interferon-based therapy. To screen the hepatoprotective dose of DFP, rats were randomized and given different doses of DFP (5, 10, 25, 40 mg/kg, oral, respectively), 1 h before they were injected with Con A. For studying the potential antifibrotic mechanisms of DFP in chronic immunological model, male wister rats were treated with either DFP (5 mg/kg/day, oral, 3 times/week for 6 weeks) and/or pegylated interferon-α2b (1.5 µg/kg/week, s.c., for 6 weeks). Different markers of liver fibrosis were assessed including biochemical measurement of hydroxyproline content and immunohistochemical detection of alpha-smooth muscle actin and collagen expression using Masson trichrome stain. Markers of hepatotoxicity, oxidative stress and inflammation were also assessed. Histological examination was done using light and electron microscope. Fibrosis, oxidative stress & inflammatory markers were significantly ameliorated by treatment with DFP in comparison to the co-treatment with pegylated interferon-α2b and DFP. Furthermore, histopathological examination and electron microscope confirmed the antifibrotic effect of DFP. Collectively these findings indicate that DFP can have potential antifibrotic effect in CHC patients.

Keywords: concanavalin A - deferiprone - fibrosis - hepatitis C - hepcidin - iron overload - immunological

Contents

List of abbreviations

A	Absorbance
4-AAP	4-aminoantipyrine
Ab	Antibody
ACEIs	Angiotensin-Converting Enzyme Inhibitors
ADP	Adenosine Diphosphate
Ag	Antigen
AI	Anemia of Inflammation
ALT	Alanine Aminotransferase
ANOVA	Analysis of Variance
AP-1	Activator Protein 1
ARB	Angiotensin-II Receptor Blockers
AST	Aspartate Aminotransferase
α- SMA	Alpha-Smooth Muscle Actin
ATF-6	Activating Transcription Factor-6
ATP	Adenosine Triphosphate
AUC	Area Under the Curve
BAX	BcL-2-Like Protein 4
BCG	Bromocresol Green
BcL-2	B-cell Lymphoma 2

BSA	Bovine Serum Albumin
Ca^{+2}	Calcium
Caspases	Cysteine-aspartic proteases
CBT	Cognitive Behavioral Therapy
CCl_4	Carbon tetrachloride
CD4^{+}	Cluster of Differentiation 4^{+}
cDNA	Complement DNA
CE	Cholesterol Esterase
CHC	Chronic Hepatitis C
Cmax	Maximum Serum Concentration
CO	Cholesterol Oxidase
Con A	Concanavalin A
CoNS	Coagulase-Negative Staphylococci
COX-2	Cyclooxygenase-2
Ct	Cycle threshold
CT	Connective Tissue
CTGF	Connective Tissue Growth Factor
CV	Central Vein
CYP	Cytochrome P
CYP 450	Cytochrome P450
DFO	Deferoxamine

DFP	Deferiprone
DMT1	Divalent Metal Transporter 1
DNA	Deoxyribonucleic acid
DNase	Deoxyribonuclease
dNTPs	Deoxynucleotide triphosphates
ECM	Extracellular Matrix
e.g.	Example
ELISA	Enzyme-Linked Immunosorbent Assay
ER	Endoplasmic Reticulum
Fas-L	Fas Ligand
FDA	Food and Drug Administration
Fe	Iron
Fe^{2+}	Ferrous
Fe^{3+}	Ferric
FG	FibroGen
FMASU-REC	Faculty of Medicine Ain Shams University-Research Ethics Committee
gadd153	growth arrest and DNA-damage-inducible gene 153
GAS	Interferon-Gamma-Activated Site
GCS	D-Glutamyl-Cysteine Synthetase
G-CSF	Granulocyte-Colony Stimulating Factor
GGT	Gamma-Glutamyl Transferase

GK	Glycerol Kinase
GPO	Glycerol Phosphate Oxidase
GRP78	Glucose Regulated Protein 78
GSH	Reduced Glutathione
HA	Hyaluronic Acid
H & E	Hematoxylin and Eosin
HBV	Hepatitis B Virus
HCC	Hepatocellular Carcinoma
HCV	Hepatitis C Virus
HIF1-α	Hypoxia-Inducible Factor 1 alpha
4-HNE	4-hydroxy-2-nonenal
H_2O_2	Hydrogen Peroxide
HRP	Horseradish Peroxidase
HSCs	Hepatic Stellate Cells
IFN	Interferon
IFN-α	Interferon-alpha
IFN-γ	Interferon-gamma
IgG	Immunoglobulin G
IL-1	Interleukin 1
IL-6	Interleukin 6
IL-10	Interleukin 10
ILs	Interleukins