The Potential Hepatoprotective Effect of Quercetin on Cholestatic Liver Injury in Rats

Thesis

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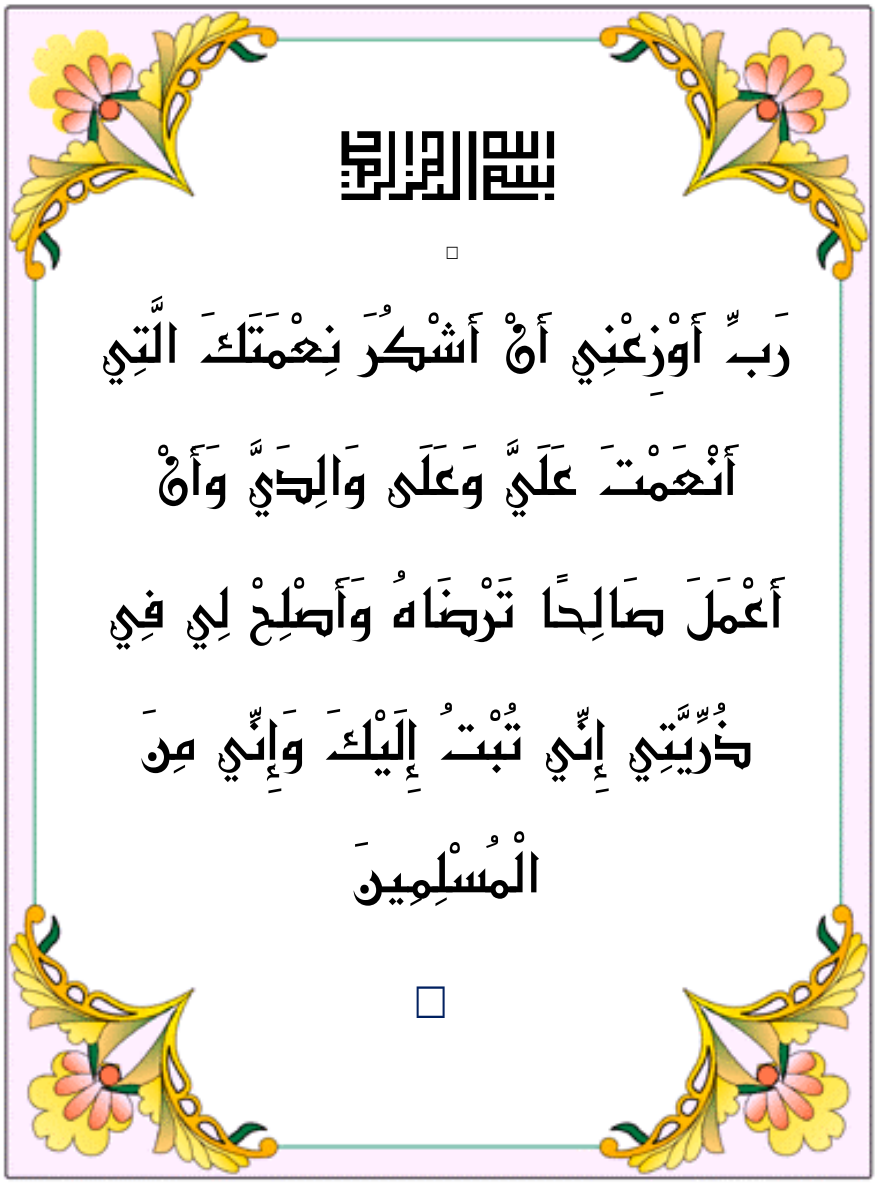
بسم الله الرحمن الرحيم
رَبِّ أَوْزِعْنِي أَنْ أَشْكُرَ نِعْمَتَكَ الَّتِي
أَنْعَمْتَ عَلَيَّ وَعَلَى وَالِدَيَّ وَأَنْ
أَعْمَلَ صَالِحًا تَرْضَاهُ وَأَصْلِحْ لِي فِي
ذُرِّيَّتِي إِنِّي تُبْتُ إِلَيْكَ وَإِنِّي مِنَ
الْمُسْلِمِينَ

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Gehad Salah

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List of Abbreviations

Abb.	Full Term
%BW	Percentage of body weight gain
ABC	ATP-binding cassette transporters
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANOVA	Analysis of variance
AST	Aspartate aminotransferase
BDL	Bile duct ligated-group
BDL-Q	Bile duct ligated quercetin-treated group
BSEP	Bile salt export pump
BW_f	Final body weights
BW_i	Initial body weights
CD18	Cluster of differentiation 18
COX	Cyclooxygenase
DAMPs	Damage associated molecular pattern molecules
ECM	Extracellular matrix
EGFR	Epidermal growth factor receptor
Egr-1	Early growth response factor 1

Abb.	Full Term
GPX	Glutathione peroxidase
GR	Glutathione reductase
GSH	Reduced glutathione
GSSG	Oxidized glutathione
H&E	Hematoxylin & Eosin
HSC	Hepatic stellate cell
ICAM1	Intracellular adhesion molecule 1
LOX	Lipoxygenase
LPS	Lipopolysaccharide
LW	Liver weight
LW%	Liver index
MAPK	Mitogen-activated protein kinase
MPO	Myeloperoxidase
MPT	Mitochondrial permeability transition pore
MRP-2	Multi-drug resistant related protein 2
MTC	Masson's trichrome
NF-kB	Nuclear factor kappa
NO	Nitric oxide
NTCP	Na+ dependent taurocholate transporter
O.D.	Optical density

Abb.	Full Term
OATP2	Organic anion transporter
PDGF	Platelet derived growth factor
ROS	Reactive oxygen species
SAP	Serum amyloid P
SHAM	Sham-operated
SPSS	Statistical Program for Social Science
SW	Spleen weight
SW%	Spleen index
TGF-β1	Transforming growth factor- beta 1
TIMP1	Tissue inhibitor of metalloproteinase 1
TNF-α	Tumor necrosis factor- alpha
TP	Total proteins
UDCA	Ursodeoxycholic acid
α-SMA	Alpha smooth muscle antigen

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The Potential Hepatoprotective Effect of Quercetin on Cholestatic Liver Injury in Rats

Abstract

Background: cholestasis is a prevalent health problem associated with liver oxidative stress, inflammation, and fibrosis. Quercetin has been shown to afford a beneficial effect in a variety of liver diseases.

Aim: This study was designed to investigate the potential protective effect of quercetin on liver cholestasis and the possible underlying mechanisms in a rat model of bile duct ligation (BDL).

Design: Experimental study

Methods: This study was carried out on adult male Wister rats which were randomly divided into: Sham, BDL and BDL- quercetin treated (BDL- Q) groups. Quercetin was given by gavage in a dose of 50 mg/kg/day.

Results: Bile duct ligation resulted in a significant increase in serum levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), and liver levels of myeloperoxidase (MPO), tumor necrosis factor alpha (TNF-α),and transforming growth factor beta 1(TGF-β1), along with a significant decrease in serum levels of total proteins (TP) and liver glutathione peroxidase(GPX) in BDL group versus sham group . Quercetin treatment significantly lowered serum levels of AST, ALT, ALP, and MPO, TNF-α, and TGF-β1 in liver tissues associated with a significant increase in serum TP and liver GPX in BDL-Q group versus BDL rats. Histological studies revealed enhancement of inflammation and a significant increase in the percentage area of collagen deposition in BDL versus sham group. These changes were attenuated in BDL-Q group compared to BDL rats.

Conclusions:

Quercetin alleviated cholestasis induced liver injury and improved liver function possibly via attenuating liver oxidative stress, inflammation and fibrosis.

Key words: Cholestasis, quercetin, oxidative stress, inflammation, fibrosis

Introduction

Chronic cholestasis is a prevalent health problem produced by impairment of bile flow, and accumulation of toxic bile acids in hepatocytes, evoking severe liver injury which may progress to cirrhosis and liver failure ***(Hirschfield et al., 2010).*** It is caused by various aetiologies such as primary biliary cirrhosis, primary sclerosing cholangitis and progressive familial intrahepatic cholestasis ***(Ghonem et al., 2015).*** Ligation of the common bile duct in rodents represents a well settled experimental model of cholestasis that initiates a complex cascade of pathological events similar to that of human ***(Dondorf et al., 2017).*** This model enabled the scientists to recognize the pathophysiology of the cholestasis and to develop different treatments to human cholestatic liver diseases.

Recently, evidence has accumulated that the progression of liver injury in cholestasis is heavily dependent on overproduction of reactive oxygen species (ROS) as well as pro-inflammatory cytokines ***(Gonzalez-Sanchez et al., 2015).*** Exposure of hepatocytes to high concentrations of potentially toxic bile acids initiates hepatocellular injury, followed by a leukocytic phase in which activated neutrophils infiltrate and attack the bile

acid stressed hepatocytes through ROS formation ***(Rust et al., 2009; Copple et al., 2010).*** Excessive production of ROS has been demonstrated to induce cellular damage ***(Cesaratto et al., 2004)*** and promote inflammation by upregulating tumor necrosis factor-alpha (TNF-α) signaling pathway, and IL-6 mRNA expression in chronic liver diseases ***(Elsharkawy et al., 2005; Ghatak et al., 2011).*** Transforming growth factor beta-1(TGF-β1), a potent profibrotic cytokine, was also activated by oxidative stress ***(Poynard et al., 2010)*** and in a consequence stimulates the transformation of hepatic stellate cells into myofibroblasts which increase the extracellular matrix formation, promoting liver fibrosis ***(Elsharkawy et al., 2005).*** During the past decades, the mechanisms of liver cholestasis have been investigated, but few therapeutic strategies are available to efficiently interrupt the progression of liver injury. According to the aforementioned reports, oxidative stress, and inflammation are potential targets for therapeutic intervention in treating cholestatic liver disorders. Therefore, antioxidants might have a relevant benefit and restrain the hepatocellular injury in chronic cholestasis.

Quercetin (3,3’,4’,5,6-Pentahydroxyflavon), a natural flavonoid compound found in vegetables and fruits, has a