EVALUATION OF ANTIDIABETIC EFFECT OF BERBERINE IN TYPE 2 DIABETIC RATS MODELS

Thesis

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ABSTRACT

Berberine exists in a number of medicinal plants and displays many pharmacological effects on type 2 diabetes mellitus. The study aimed to determine the hypoglycemic effects of berberine in rats with type 2 diabetes, on inflammatory biomarkers, insulin, adiponectin, lipid profile, liver oxidative stress biomarkers, mRNA expression levels of PPARγ and resistin. Diabetes was induced by feeding rats with high fat diet for 4 weeks followed by injection of STZ, Oral doses of 50 and 100 mg/kgberberine were daily given for 4 weeks after diabetes induction.

Key Words:- Berberine **-** type 2 diabetes **–** insulin resistance**.**

List of Abbreviations

4-AP	**4–aminophenazone**
A	**Absorbance**
AD	**Alzheimer's disease**
ADA	**American Diabetes Association**
AAI	**Antiatherogenic index**
Akt	**Protein kinase B**
ALT	**Alanine aminotransferase**
AMPK	**Adenosine monophosphate kinase**
ANOVA	**Analysis of variance**
AST	**Aspartate aminotransferase**
BBR	**Berberine**
CAT	**Catalase**
cDNA	**Complimentary DNA**
CHD	**Coronary heart disease**
CK-MB	**Creatine kinase MB**
CMC	**Carboxy methyl cellulose**
COX-2	**Cyclooxygenase-2**
DNA	**Deoxyribonucleic acid**
DTNB	**5,5'dithiobis (2-nitrobenzoic acid)**
EDTA	**Ethylenediaminetetraacetic acid**
ELISA	**Enzyme-linked immunosorbent assay**
ERK	**Extracellular-signal-regulated kinase**
FBS	**Fetal bovine serum**
FFA	**Free fatty acids**
FPG	**Fasting plasma glucose**
GK	**Glycerol kinase**
GLP	**Glucagon like peptide**

GLUT	**Glucose transporter**
GPO	**Glycerol-3-phosphate oxidase**
GPx	**Glutathione peroxidase**
GR	**Glutathione reductase**
GSH	**Reduced glutathione**
H_2O_2	**Hydrogen peroxide**
HDAC3	**Histone deacetylase-3**
HDL	**High density lipoprotein**
HFD	**High fat diet**
HOMA-IR	**Homeostasis model assessment of insulin resistance**
IC	**Inhibitor concentration**
IDDM	**Insulin-dependent diabetes mellitus**
IGF-1	**Insulin-like growth factor 1**
IL	**Interleukin**
INF	**Interferon**
iNOS	**Inducible nitric oxide synthase**
ip	**Intraperitoneal**
IR	**Insulin receptors**
IRS	**Insulin receptor substrate**
LDH	**Lactate dehydrogenase**
LDL	**Low density lipoprotein**
LDLR	**Low density lipoprotein receptor**
LPL	**Lipoprotein lipase**
LPL	**Lipoprotein lipase**
MAPK	**Mitogen-activated protein kinase**
MDA	**Malondialdehyde**
MDH	**Malate dehydrogenase**
mRNA	**Messenger RNA**
NAD	**Nicotinamide adenine dinucleotide**

NADH	**Nicotinamide adenine dinucleotide +Hydrogen**
NF-κB	**Nuclear factor kappa-B**
NO	**Nitric oxide**
NOD	**Nonobese diabetic**
NOS	**Nitric oxide synthase**
Nrf2	**Nuclear factor erythroid-2-related factor-2**
OD	**Optical Denisty**
OGTT	**Oral glucose tolerance test**
PCR	**Polymerase chain reaction**
PI-3K	**Phosphatidylinositide 3-kinase**
PKB	**protein kinase B**
POD	**Peroxidase**
PPAR	**Peroxisome proliferator activated receptor**
PPREs	**PPAR response element**
r.p.m	**Round per minute**
RNA	**Ribonucleic acid**
RNS	**Reactive nitrogen species**
ROS	**Reactive oxygen species**
RT-PCR	**Reverse transcriptase polymerase chain reaction**
RXR	**Retinoid X receptor**
SD	**Standard deviation**
SEM	**Standard error mean**
SIRT1	**Sirtuin**
SOD	**Superoxide dismutase**
SREBP	**Sterol regulatory element-binding protein**
STAT	**Signal transducer and activator of transcription**
STZ	**Streptozotocin**
T2D	**Type 2 diabetes**
TBA	**Thiobarbituric acid**

TBARS	**Thiobarbituric acid reacting substance**
TCA	**Trichloroacetic acid**
Th	**T helper**
TNF-α	**Tumor necrosis-factor alpha**
UCP2	**Uncoupling protein 2**
VEGF	**Vascular endothelial growth factor**
vLDL	**Very low density lipoprotein**
WHO	**World Health Organization**

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INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder caused by defects in insulin secretion, insulin action or both. If ineffectively controlled, the resulting chronic hyperglycaemia is associated with numerous disabling complications **(Tripathy and Chavez, 2010)**. It is the most common form of the disease, which accounts for more than 90% of all diabetic patients **(Tripathi and Srivastava, 2006)**. The incidence of diabetes is increasing worldwide and T2DM and its complications constitute a major public health problem **(Wu et al., 2014)**. It is predicted that T2DM will continue to increase in developing countries with the majority of patients being 45-64 years old **(Wild et al., 2004)**. Health spending on diabetes accounted for 10.8% of the total health expenditure worldwide and the disease caused 5.1 million deaths in 2013 **(International Diabetes Federation, 2013)**. According to the International Diabetes Federation, the number of patients with diabetes mellitus in 2015 was estimated to be 415 million, and is expected to increase to 642 million by 2040 **(International Diabetes Federation, 2015)**.

A wide variety of lifestyle factors, such as sedentary lifestyle **(Zimmet et al., 2001)**, physical inactivity **(Hu et al., 2002)**, smoking **(Manson et al., 2000)**, and alcohol consumption **(Cullmann et al., 2012)**, are of great importance to the development of T2DM.The main mechanisms of insulin resistance in T2DM are oxidative stress, endoplasmic reticulum stress, amyloid deposition in the pancreas, ectopic lipid deposition in the muscle, liver and pancreas, and lipotoxicity and glucotoxicity **(Weir and Bonner-Weir, 2004)**. Although it is difficult to determine which mechanism is the most important, among those with

T2DM these processes can be caused by overnutrition. It is important to note, however, that each of these stresses could either induce an inflammatory response or be associated with inflammation **(Hotamisligil and Erbay, 2008)**.

The association between inflammation and insulin resistance and future development of T2DM has been shown **(Donath et al., 2009)**. The production of tumour necrosis factor (TNF)-α by cells in the adipose tissue of rodents provided early evidence of a link between tissue inflammation and the pathogenesis of insulin resistance and T2DM **(Hotamisligil et al., 1993)**. In addition, interleukin (IL)-1β contributes to the glucose-induced impairment of β-cell function and apoptosis **(Maedler et al., 2002)**.

Adipose tissue is now recognized as a secretory organ that plays important role in insulin sensitivity and energy expenditure **(Attie and Scherer, 2009)**, and dysfunction in adipocytes is associated with insulin resistance and type 2 diabetes **(Blüher, 2009)**. Adipocytes are understood to secrete diverse pro-inflammatory cytokines such as IL-6 and TNF-α, as well as anti-inflammatory cytokines such as adiponectin **(Sowers, 2008)**. Increased levels of TNF-α and IL-6, and reduced level of adiponectin can exacerbate insulin resistance in adipose tissue **(Blüher, 2009)**.

Berberine, an isoquinoline alkaloid originally isolated from the Chinese herb Coptischinensis (Huanglian), is one of the main components of R. coptidis **(Leng et al. 2004)**. Recent studies have demonstrated that berberine has remarkable effects as an anti-hyperglycemic and anti-hyperlipidemic, and it reduces weight gain in type 2 diabetes patients **(Yin et al. 2008a; Zhang et al. 2010 and Zhao et al. 2008)**. Therefore, we have attempted to demonstrate the benificial effects of berberine in