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Effect of Sildenafil Citrate on Some Physiological and Hematological Parameters in Diabetic Male Albino Rats

A Thesis

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Dedication

I Dedicate this Work

- ✓ *To my dear father*
- ✓ *To my kind mother*
- ✓ *To my wonderful husband, Mohamed and my lovely kids, Roma and Medo*
- ✓ *To my lovely sister, Zenab and her sweet kids, Yossef and Kareem*
- ✓ *To my dear brother, Mohamed*
- ✓ *To my best friend, Mona*

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Contents

List of Abbreviations

4-AA	4-aminoantipyrine
APTT	Activated partial thromboplastin time
AT-III	Antthrombin III
cAMP	Cyclic adenosine monophosphate
cGMP	Cyclic guanosine monophosphate
EDTA	Ethylene diamine tetra acetic acid
eNOS	Endothelial nitric oxide synthase
GLUT 2	Glucose transporters
GMP	Guanosine monophosphate
GOD	Glucose oxidase
GRISS	Golombok rust inventory of sexual satisfaction
GTP	Guanosine triphosphate
H_2O_2	Hydrogen peroxide
HbA1c	Glycohemoglobin
I L-1	Interleukin-1
i.p.	Intraperitoneal
i.v.	Intravenous
IDDM	Insulin–dependent diabetes mellitus
LADA	Latent autoimmune diabetes of adults
LPO	Lipid peroxidation

MDA	Malondialdehyde
NIDDM	Non-insulin dependent diabetes mellitus
NO	Nitric oxide
NOS	Nitric oxide synthase
PDE5	phosphodiesterase Type 5
PDE5I	Phosphodiesterase type 5 inhibitor
POD	Peroxidase
PT	Prothrombin time
ROS	Reactive oxygen species
-SH groups	Sulphydryl groups
SOD	Sodium oxide dismutase
TAC	Total antioxidant capacity
TNFα	Tumor necrosis factor-α

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ABSTRACT

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Effect of Sildenafil Citrate on Some Physiological and Hematological Parameters in Diabetic Male Albino Rats.

Key words: Alloxan, Hyperglycemia, Hyperfibrinogenemia, Protein C, Protein S, Sildenafil citrate.

Diabetes is a group of metabolic disorders characterized by a chronic hyperglycemic condition resulting from defects in insulin secretion, insulin action or both. Phosphodiesterase type 5 inhibitors (PDE5Is) like sildenafil citrate that blocks the degradative action of cyclic guanosine monophosphate (cGMP) in the smooth muscle cells lining the blood vessels provide a novel therapeutic option for treating diabetes complications and improving the quality of life in diabetic patients, they acting by various mechanisms including nitric oxide (NO) donor effect and antioxidant effect. The purpose of this study is to evaluate the oral treatment effect of sildenafil on some biochemical and hematological parameters in alloxan-induced diabetes in male rats. Thirty-two adult male Wistar albino rats were divided randomly into II classes. Class I consists of two healthy groups: control group (not received any medication) and sildenafil-treated group (10 mg/kg body weight).

Class II consists of two diabetic groups (received single intraperitoneal (i.p.) injection of alloxan (150 mg/kg body weight): alloxan-treated group and alloxan plus sildenafil-treated group. Blood samples were collected after 7 and 14 days of sildenafil treatment in all experimental groups. The present

investigation showed that alloxan-treated group induces elevation in glucose, glycohemoglobin (HbA1c), malondialdehyed (MDA), prothrombin time (PT), activated partial thromboplastin time (APTT), fibrinogen (factor I), indicated by reduction in protein C and proteins S. Oral treatment of diabetic rats with sildenafil significantly improved the most signs of the diabetic complications including hyperglycemia, oxidative stress, glycation of proteins and hyperfibrinogenemia induced by alloxan in male rats. The modulatory effects obtained here were partial, but significant and time dependent. No harmful effects were detected for sildenafil consumption on all parameters measured in healthy treated rats. The present study supports the hypothesis that sildenafil may have beneficial effects against some diabetic complications.

INTRODUCTION

Diabetes is a chronic metabolic disease that occurs when the pancreas does not produce enough insulin which is the hormone regulates blood sugar or when the body cannot effectively use the insulin it produces. The overall risk of dying among people with diabetes is at least double the risk of their peers without diabetes **(WHO, 2016)**.

The two main types of diabetes are type I diabetes and type II diabetes. A third type, gestational diabetes, develops only during pregnancy. Other types of diabetes are caused by defects in specific genes, diseases of the pancreas, certain drugs or chemicals, infections, and other conditions. Some people show signs of both types I and type II diabetes **(Inzucchi *et al.*, 2015)**.

Type I diabetes is caused by a lack of insulin due to the destruction of insulin-producing β cells in the pancreas. In type I diabetes an autoimmune disease the body's immune system attacks and destroys the β cells. Normally, the immune system protects the body from infection by identifying and destroying bacteria, viruses, and other potentially harmful foreign substances, but in autoimmune diseases, the immune system attacks the body's own cells. In type I diabetes, β cell destruction may take place over several years, but symptoms of the disease usually develop over a

short period of time. Type I diabetes typically occurs in children and young people, though it can appear at any age. In the past, type I diabetes was called juvenile diabetes or insulin-dependent diabetes mellitus **(Seino, *et al.*, 2010 and Vasilakou *et al.*, 2013)**.

Type II diabetes the most common form of diabetes is caused by a combination of factors, including insulin resistance, a condition in which the body's muscle, fat, and liver cells do not use insulin effectively. Type II diabetes develops when the body can no longer produce enough insulin to compensate for the impaired ability to use insulin. Symptoms of type II diabetes may develop gradually and can be subtle; some people with type II diabetes remain undiagnosed for years **(Marín-Peñalver et al., 2016)**.

Type II diabetes develops most often in middle-aged and older people who are also overweight or obese. The disease, even it is rare in youth, it is becoming more common in overweight and obese children and adolescents. Scientists think genetic susceptibility and environmental factors are the most likely triggers of type II diabetes **(Bonner-Weir *et al.*, 2014)**.

The microvascular complications of diabetes encompass long term complications of diabetes affecting small blood vessels. These classically have included

retinopathy, nephropathy and neuropathy. Macrovascular complications of diabetes include coronary artery disease, stroke and peripheral vascular disease. Early macrovascular disease is associated with atherosclerotic plaque in vessels supplying blood to the heart, brain, limbs, and other organs. Late stages of macrovascular disease involve complete obstruction of these vessels which can include myocardial infarction, stroke and gangrene **(Chawla *et al.*, 2016)**.

Alloxan induced diabetes mellitus is a classical experimental model used to study diabetes in experimental animals, it acts by causing irreversible damage of β cells in pancreas **(Carvalho *et al.*, 2003)**. Several potential mechanisms have been proposed to explain abnormal endothelium dependent vasodilation in patients with diabetes. These include: decreased synthesis of nitric oxide (NO) by the endothelium, increased inactivation of NO, decreased responsiveness of the nitric oxide-guanylate cyclase pathway at the level of the vascular smooth muscle, and increased release of vasoconstrictor prostanoids that counteract the vasodilation by NO **(Williams *et al.*, 1996)**.

NO is a biological mediator plays an important role in a variety of biological processes and is a fundamental component in the fields of biochemistry, physiology, immunology and neuroscience. NO is synthesized from L-arginine by the enzyme nitric oxide synthase (NOS). Most of