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EXPERIMENTAL PHARMACOTHERAPEUTIC STUDY OF SOME ANTIOXIDANTS AND INSULIN RECEPTOR SENSITIZERS IN DIABETIC RATS

Thesis Submitted in Partial Fulfillment of the Requirements of the Degree of Master in Pharmaceutical Sciences (Pharmacology & Toxicology)

By

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2010

Prerequisite Postgraduate Courses

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

General Courses:

1. **Computer and its application.**
2. **Literature search and scientific English language.**
3. **Basic statistics.**

Special Courses:

1. **Pharmacometrics.**
2. **Toxicometrics.**
3. **Immunopharmacology.**
4. **Pathophysiology of diseases.**

He had successfully passed examination in these courses with grade "Good"

Prof. Dr. Hekma Abdel Tawab

Head of Pharmacology & Toxicology Department

Examination Board Approval Sheet

Thesis Approval Committee: **Signature**

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Date: / / 2010

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The Most Graceful, The Most Merciful

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ABSTRACT

Oxidative stress is implicated in the pathogenesis of diabetes mellitus and its complications. This disease may be associated with increased levels of peroxides in plasma and tissues of humans and experimental animals.

Continuous hyperglycemia is likely to increase the formation of reactive oxygen and nitrogen species which might be responsible for occurrence of diabetic complications. Consequently antioxidants emerged as good supplements for treatment of diabetes mellitus. Furthermore free radicals resulting from continuous reaction of glucose with body proteins have been assumed to cause insulin resistance. So antioxidant administration is beneficial in the management of diabetes mellitus due to protection against glucose toxicity and improvement of insulin activity.

Taken together with insulin, antioxidants would represent a good approach towards delaying the onset or progression of diabetic complication. In addition, insulin resistance can be successfully managed by insulin resistant receptor sensitizers such as rosiglitazone.

In this study effectiveness of some antioxidants such as ascorbic acid, L-carnitine and α-lipoic acid, in reducing oxidative stress in diabetes mellitus, which would reflect their action on glycemic control and delaying of diabetic complications was investigated. Insulin resistant rats were used in order to evaluate the possible enhancement of such compounds in controlling diabetes. These

animals were subjected for treatment with insulin receptor sensitizers including chromium and a thiazolidinedione namely rosiglitazone before and after treatment with insulin. The oxygen status in blood was assessed by determination of malonedialdehyde (MDA), superoxide dismutase (SOD) and glutathione peroxidase (GPX). The glycemic status was assessed by determination of blood glucose level and glycated haemoglobin content.

Results of the present study indicated that blood glucose level reached a diabetic value by day twenty first of sucrose feeding, whereupon the rats became insulin resistant diabetic animals.
These animals showed abnormalities in blood glucose level associated with exaggerated oxidative stress status. This was evidenced by a significant elevation in blood sugar and glycated hemoglobin levels as well as MDA level, together with significant reductions in blood GSH-PX and SOD activities.

Treatment of IRD rats with insulin lowered blood glucose and glycated hemoglobin levels to values that remained higher than those of normoglycemic animals. Treatment with chromium, rosiglitazone, α-lipoic acid, ascorbic acid and L-carnitine produced consistent reductions in blood glucose level and inconsistent lowerings in glycated hemoglobin content.

Coadministration of insulin and each of the investigated insulin receptor sensitizers namely chromium and rosiglitazone as well as the antioxidents α-lipoic acid, ascorbic acid and L-carnitine produced significant additive or synergetic antihyperglycemic effects as indicated by a greater significant reduction in blood glucose or glycated hemoglobin level of insulin resistant diabetic rats. Moreover