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Effect of Fosinopril on Some Serum Constituents in Experimentally Induced Diabetes Mellitus in Rats

Thesis

Submitted for the Partial Fulfillment of the M.D. Degree in Pharmacology

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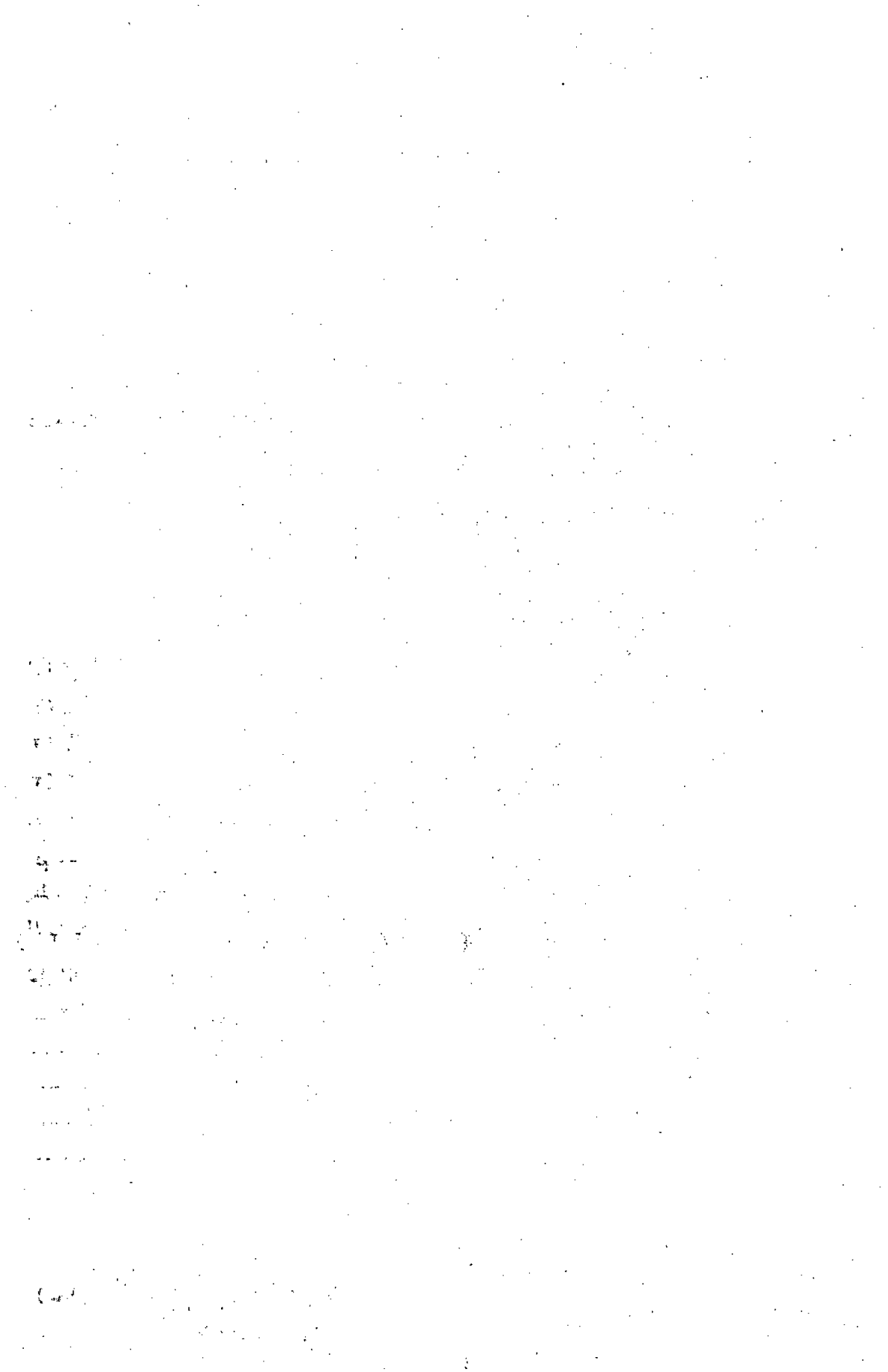
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Content

	Page
List of Table	
Introduction	1
Review of Literature	3
* The renin-Angiotensin System	3
* Angiotensin-Converting Enzyme (ACE) Inhibitors	6
* Fosinopril	19
* Diabetes Mellitus	27
* Lipoproteins	42
* Diabetes and Hyperlipidemia	46
Aim of the Work	47
Materials and Methods	48
Results	55
Discussion	88
Summary & Conclusion	98
References	106
Appendix	
Arabic Summary	

Table (18)	Comparison of plasma glucose, serum triglyceride (TG), total cholesterol (TC), high density lipoprotein cholesterol (HDLc), Total cholesterol/high density lipoprotein cholesterol (TC/HDLc) and low density lipoprotein cholesterol (LDLc) between group V (diabetic + insulin + hypercholesterolemia + 25 mg therapy) and controls	77
Table (19)	Comparison of plasma glucose, serum triglyceride (TG), total cholesterol (TC), high density lipoprotein cholesterol (HDLc), Total cholesterol/high density lipoprotein cholesterol (TC/HDLc) and low density lipoprotein cholesterol (LDLc) between group VI (diabetic + insulin + hypercholesterolemia + 50mg therapy) and controls	78
Table (20)	Comparison of results of 4 weeks therapy with 25 mg/kg fosinopril versus 4 weeks group IV.	79
Table (21)	Comparison of results of 4 weeks therapy with 25 mg/kg fosinopril versus 8 weeks group IV.	79
Table (22)	Comparison of results of 8 weeks therapy with 25 mg/kg fosinopril versus 4 weeks group IV.	80
Table (23)	Comparison of results of 8 weeks therapy with 25 mg/kg fosinopril versus 8 weeks group IV.	80
Table (24)	Comparison of results of 4 weeks therapy with 50 mg/kg fosinopril versus 4 weeks group IV.	81
Table (25)	Comparison of results of 4 weeks therapy with 50 mg/kg fosinopril versus 8 weeks group IV.	81
Table (26)	Comparison of results of 8 weeks therapy with 50 mg/kg fosinopril versus 4 weeks group IV.	82
Table (27)	Comparison of results of 8 weeks therapy with 50 mg/kg fosinopril versus 8 weeks group IV.	82
Table (28)	Comparison of results of 8 weeks therapy with 25 mg/kg fosinopril versus 4 weeks therapy with 50mg/kg fosinopril.	82

List of Tables

	Page
Table (1) Plasma glucose levels of group I and group II	69
Table (2) Serum Triglyceride (TG) levels of group I and group II	69
Table (3) Serum total cholesterol (TC) levels of group I and group II	70
Table (4) Serum levels of high density lipoprotein cholesterol (HDLc) of group I and group II	70
Table (5) Serum total cholesterol / high density lipoprotein cholesterol (TC/HDLc) ratio of group I and group II	71
Table (6) Serum levels of low density lipoprotein cholesterol (LDLc) of group I and group II	71
Table (7) Results of variable of group I and group II (Control)	72
Table (8) Results of variable of group III (4 weeks)	72
Table (9) Results of variable of group III (8 weeks)	72
Table (10) Results of variable of group IV (4 weeks)	73
Table (11) Results of variable of group IV (8 weeks)	73
Table (12) Results of variable of group V (4 weeks)	73
Table (13) Results of variable of group V (8 weeks)	74
Table (14) Results of variable of group VI (4 weeks)	74
Table (15) Results of variable of group VI (8 weeks)	74
Table (16) Comparison of plasma glucose, serum triglyceride (TG), total cholesterol (TC), high density lipoprotein cholesterol (HDLc), Total cholesterol/high density lipoprotein cholesterol (TC/HDLc) and low density lipoprotein cholesterol (LDLc) between group III (diabetic + insulin) and controls	75
Table (17) Comparison of plasma glucose, serum triglyceride (TG), total cholesterol (TC), high density lipoprotein cholesterol (HDLc), Total cholesterol/high density lipoprotein cholesterol (TC/HDLc) and low density lipoprotein cholesterol (LDLc) between group IV (diabetic + insulin + hypercholesterolemia) and controls	76

Introduction

Diabetes mellitus is a major health care issue. It is not a single disease entity, it is a systemic disease that includes a variety of metabolic disorders (*Ziemmet and Kelly, 1992*).

The chronic hyperglycemia of diabetes is associated with long-term damage, dysfunction and failure of various organs, especially the eyes, kidney, nerves, heart and blood vessels (*The Expert Committee on The Diagnosis of D.M., 1997*).

Premature cardiovascular disease resulting from accelerated atherosclerosis is one of the most common and serious complications of diabetes (*Sharpe et al., 1988*).

The frequency of hyperlipidemia in diabetes is indeed very high, depending on the type of diabetes and its degree of control (*Balassa, 1985*). It consists of hypertriglyceridemia with raised VLDL, total cholesterol and LDL.

The class of angiotensin-converting enzyme (ACE) inhibitors has emerged as one of the most important to modern cardiovascular medicine. Its efficacy in the treatment of hypertension, congestive heart failure, ventricular dysfunction and diabetic nephropathy has been established (*Krommer et al., 1990 ; Morgan and Andersson, 1992 ; Böhlen et al., 1994*).

Fosinopril (monopril) is the ester produg of an angiotensin-converting enzyme (ACE) inhibitor, fosinoprilat. It is the first member of a novel chemical class of angiotensin-converting enzyme (ACE) inhibitors, the phosphinic acids (*Hui et al., 1991*).

In the present work, the effect of the angiotensin-converting enzyme (ACE) inhibitor "fosinopril" on the plasma glucose, serum triglyceride, total serum cholesterol, high-density lipoprotein cholesterol and low-density lipoprotein cholesterol was investigated in experimentally induced type I diabetes mellitus (IDDM) in rats.

The Renin-Angiotensin System

Tiegerstedt and Bergman in 1898, demonstrated that saline extracts of the kidney elicited a very potent pressor response because they contained a pressor substance which they named renin. In 1934, *Goldblatt* and his colleagues showed that sustained hypertension could be produced by clamping the renal artery of a dog. In 1940, *Braun-Menendez* and his colleagues in Argentina and *Page and Helmer* in the United state reported that renin was an enzyme that acted on a plasma protein substrate to catalyze the formation of the actual pressor material, a peptide, which was named hypertensin by the former group and angiotonin by the latter. These two terms persisted for nearly 20 years, until it was agreed to rename the pressor substance angiotensin and to call the plasma substrate angiotensinogen. In the mid-1950s, two forms of angiotensin were recognized, the first a decapeptide (angiotensin I) and the second an octapeptide (angiotensin II) formed by enzymatic cleavage of angiotensin I by another enzyme, termed angiotensin converting enzyme. The octapeptide was shown to be more active form (*Skeggs et al., 1954*).

Further progress came in 1958, when *Gross* suggested that the renin-angiotensin system was involved in the regulation of aldosterone secretion.

In 1965, *Ferreira* described bradykinin-potentiating factor, which was present in the venom of the Brazilian pit viper, *Bothrops Jararaca*.