

بسم الله الرحمن الرحيم





شبكة المعلومات الجامعية التوثيق الالكتروني والميكروفيلم



جامعة عين شمس

التوثيق الإلكتروني والميكروفيلم

قسم

نقسم بالله العظيم أن المادة التي تم توثيقها وتسجيلها
علي هذه الأقراص المدمجة قد أعدت دون أية تغيرات



يجب أن

تحفظ هذه الأقراص المدمجة بعيدا عن الغبار





بعض الوثائق الأصلية تالفة





بالرسالة صفحات
لم ترد بالأصل



B1 ✓ < 90

**POSSIBLE MODIFICATION OF RESPONSES OF
CERTAIN ANTIHYPERTENSIVE AGENTS BY
CONCURRENT ADMINISTRATION OF ANTIOXIDANTS**

THESIS

**SUBMITTED FOR THE DEGREE OF DOCTORATE OF
PHILOSOPHY IN PHARMACOLOGY AND TOXICOLOGY**

BY

ASHRAF KAMAL BAHGAT

*B.Pharm., M.Pharm.Sc.(Pharmacology)
Assistant Lecturer of Pharmacology & Toxicology
Faculty of Pharmacy, Cairo University*

UNDER THE SUPERVISION OF

Prof. Dr. Ezz-Eldin S. Eldenshary

*Professor of
Pharmacology & Toxicology
Faculty of Pharmacy
Cairo University*

Dr. Laila G. Mahran

*A. Professor of
Pharmacology & Toxicology
Faculty of Pharmacy
Cairo University*

**Faculty of Pharmacy
Cairo University
2002**

Examination Board Approval Sheet

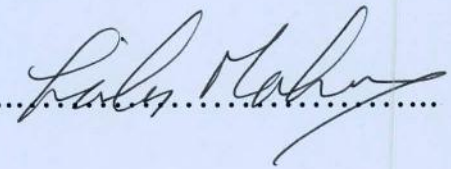
Thesis Approval Committee:

Signature

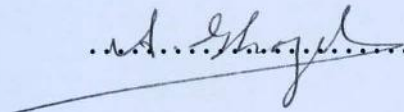
1. Prof. Dr. Ezz-Eldin S. Eldenshary

.....
.....

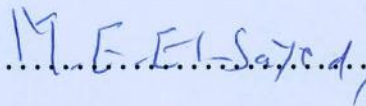
2. Dr. Laila G. Mahran

.....
.....

3. Prof. Dr. Abdel-Rehim Ghazal

.....
.....

4. Prof. Dr. Mostafa El-Sayed El-Sayed

.....
.....

Date: 5 / 11 / 2002

ACKNOWLEDGEMENTS

I would like to express my deepest profound thanks and sincere gratitude to **Prof. Dr. Ezz-Eldin S. Eldenshary**, Professor of Pharmacology and Toxicology, Faculty of Pharmacy, Cairo University for suggesting the point, his kind supervision, generous assistance, providing me with many helpful literature as well as his efforts to get many of the drugs used in this research. I would also thank him for his constructive comments throughout the experimental investigations as well as writing and revising the thesis.

Neither words nor the available space can describe my greatest appreciation and sincere thanks and gratitude to **Dr. Laila G. Mahran**, Assistant Professor of Pharmacology and Toxicology, Faculty of Pharmacy, Cairo University. She really acted like my sister pushing me forward by her excellent supervision, continuous encouragement, support and backup, kind relation, assistance, and restful smile. She helped me through providing some of the chemicals and instruments used in this study as well as with her valuable comments during writing and revising the thesis.

Finally, I would like to extend my special gratitude to my colleagues in the Pharmacology & Toxicology Department for their help and cooperation.

Ashraf Bahgat

LIST OF ABBREVIATIONS

- **2K-1C**: two kidney-one clip.
- **ACE**: angiotensin converting enzyme.
- **Ang II**: angiotensin II.
- **BH₄**: tetrahydrobiopterin.
- **BP**: blood pressure.
- **CCBs**: calcium channel blockers.
- **CHD**: Coronary heart disease.
- **CHF**: Congestive heart failure.
- **CVD**: Cardiovascular disease.
- **DHP**: dihydropyridine calcium channel blockers.
- **GSH**: reduced form of glutathione.
- **GSSG**: oxidized form of glutathione.
- **LDL**: low density lipoprotein.
- **LVH**: Left ventricular hypertrophy.
- **MDA**: malondialdehyde.
- **MI**: Myocardial infarction.
- **NO**: nitric oxide.
- **NOS**: nitric oxide synthase.
- **PRA**: plasma renin activity.
- **PUFAs**: polyunsaturated fatty acids.
- **RHR**: renal hypertensive rats.
- **ROS**: reactive oxygen species.
- **RVH**: renovascular hypertension.
- **SBP**: systolic blood pressure.
- **SHR**: spontaneously hypertensive rats.
- **SHRSP**: stroke-prone spontaneously hypertensive rats.
- **SOD**: superoxide dismutase.
- **TBARS**: thiobarbituric acid reactive substances.
- **TIA**: Transient ischemic attack.
- **TXA₂**: thromboxane A₂.
- **VSM**: vascular smooth muscle.
- **VSMCs**: vascular smooth muscle cells.

CONTENTS

SUBJECT	PAGE
INTRODUCTION	
Hypertension.....	1
The Renin-Angiotensin-Aldosterone System.....	11
Calcium Channel Blockers.....	20
Free Radicals and Oxidative Stress.....	29
Reactive Oxygen Species and Hypertension.....	39
Biological Antioxidants.....	46
AIM OF THE WORK	63
MATERIALS	66
EXPERIMENTAL DESIGN	69
METHODS	
I. Blood Pressure Experiments.....	71
II. Free Radical Markers.....	75
III. Nitric Oxide Metabolites.....	84
IV. Statistical Analysis.....	88
RESULTS	
I. Results of The Lisinopril Group.....	89
II. Results of The Isradipine Group.....	115
DISCUSSION	141
SUMMARY AND CONCLUSION	169
REFERENCES	173
ARABIC SUMMARY	

LIST OF TABLES

TABLE	PAGE
1. Classification of blood pressure.....	1
2. Causes of secondary hypertension.....	2
3. Complications of hypertension.....	4
4. Risk stratification and treatment of hypertensive patients.....	6
5. Types and distribution of voltage-sensitive Ca^{2+} channels.....	21
6. Tissue selectivity and pharmacokinetics of some Ca^{2+} channel blockers..	23
7. Effect of 30-day treatment with lisinopril and certain antioxidants (β -carotene, α -tocopherol, coenzyme Q_{10} , ascorbic acid, selenium, fish oil) on systolic blood pressure of renal hypertensive rats.....	90
8. Effect of 30-day treatment with lisinopril and certain antioxidants (β -carotene, α -tocopherol, coenzyme Q_{10} , ascorbic acid, selenium, fish oil) on serum MDA concentration, blood GSH concentration, and blood SOD activity of renal hypertensive rats.....	100
9. Effect of 30-day treatment with lisinopril and certain antioxidants (β -carotene, α -tocopherol, coenzyme Q_{10} , ascorbic acid, selenium, fish oil) on serum total nitrite concentration of renal hypertensive rats.....	108
10. Effect of 30-day treatment with isradipine and certain antioxidants (β -carotene, α -tocopherol, coenzyme Q_{10} , ascorbic acid, selenium, fish oil) on systolic blood pressure of renal hypertensive rats.....	116

11. Effect of 30-day treatment with isradipine and certain antioxidants (β -carotene, α -tocopherol, coenzyme Q ₁₀ , ascorbic acid, selenium, fish oil) on serum MDA concentration, blood GSH concentration, and blood SOD activity of renal hypertensive rats.....	126
12. Effect of 30-day treatment with isradipine and certain antioxidants (β -carotene, α -tocopherol, coenzyme Q ₁₀ , ascorbic acid, selenium, fish oil) on serum total nitrite concentration of renal hypertensive rats.....	134

LIST OF FIGURES

FIGURE	PAGE
1. Factors involved in the control of blood pressure.....	3
2. Chemical classification and structures of some ACE inhibitors.....	17
3. Drug binding sites of the L-type Ca^{2+} channel and their allosteric interaction.....	22
4. Chemical classification and structures of some Ca^{2+} channel blockers	24
5. Sequential generation of ROS from molecular oxygen.....	35
6. Lipid peroxidation.....	36
7. Scavenging reactions of α -tocopherol.....	51
8. Typical recording of the systolic blood pressure of a hypertensive rat using Harvard rat tail blood pressure system.....	73
9. Standard curve of lipid peroxides measured as MDA.....	77
10. Standard curve of SOD.....	80
11. Standard curve of reduced glutathione.....	83
12. Standard curve of nitrite.....	87
13. Effect of 30-day treatment with lisinopril alone and with a combination of lisinopril and β -carotene on SBP of RHR.....	91
14. Effect of 30-day treatment with lisinopril alone and with a combination of lisinopril and α -tocopherol on SBP of RHR.....	92

15. Effect of 30-day treatment with lisinopril alone and with a combination of lisinopril and coenzyme Q ₁₀ on SBP of RHR.....	93
16. Effect of 30-day treatment with lisinopril alone and with a combination of lisinopril and ascorbic acid on SBP of RHR.....	94
17. Effect of 30-day treatment with lisinopril alone and with a combination of lisinopril and selenium on SBP of RHR.....	95
18. Effect of 30-day treatment with lisinopril alone and with a combination of lisinopril and fish oil on SBP of RHR.....	96
19. Effect of 30-day treatment with lisinopril alone and with a combination of lisinopril and β -carotene on serum MDA concentration (A), blood GSH concentration (B), and blood SOD activity (C) in RHR.....	101
20. Effect of 30-day treatment with lisinopril alone and with a combination of lisinopril and α -tocopherol on serum MDA concentration (A), blood GSH concentration (B), and blood SOD activity (C) in RHR.....	102
21. Effect of 30-day treatment with lisinopril alone and with a combination of lisinopril and coenzyme Q ₁₀ on serum MDA concentration (A), blood GSH concentration (B), and blood SOD activity (C) in RHR.....	103
22. Effect of 30-day treatment with lisinopril alone and with a combination of lisinopril and ascorbic acid on serum MDA concentration (A), blood GSH concentration (B), and blood SOD activity (C) in RHR.....	104
23. Effect of 30-day treatment with lisinopril alone and with a combination of lisinopril and selenium on serum MDA concentration (A), blood GSH concentration (B), and blood SOD activity (C) in RHR.....	105
24. Effect of 30-day treatment with lisinopril alone and with a combination of lisinopril and fish oil on serum MDA concentration (A), blood GSH concentration (B), and blood SOD activity (C) in RHR.....	106

25. Effect of 30-day treatment with lisinopril alone and with a combination of lisinopril and β -carotene on serum total nitrite concentration of RHR.....	109
26. Effect of 30-day treatment with lisinopril alone and with a combination of lisinopril and α -tocopherol on serum total nitrite concentration of RHR.....	110
27. Effect of 30-day treatment with lisinopril alone and with a combination of lisinopril and coenzyme Q ₁₀ on serum total nitrite concentration of RHR.....	111
28. Effect of 30-day treatment with lisinopril alone and with a combination of lisinopril and ascorbic acid on serum total nitrite concentration of RHR.....	112
29. Effect of 30-day treatment with lisinopril alone and with a combination of lisinopril and selenium on serum total nitrite concentration of RHR.....	113
30. Effect of 30-day treatment with lisinopril alone and with a combination of lisinopril and fish oil on serum total nitrite concentration of RHR.....	114
31. Effect of 30-day treatment with isradipine alone and with a combination of isradipine and β -carotene on SBP of RHR.....	117
32. Effect of 30-day treatment with isradipine alone and with a combination of isradipine and α -tocopherol on SBP of RHR.....	118
33. Effect of 30-day treatment with isradipine alone and with a combination of isradipine and coenzyme Q ₁₀ on SBP of RHR.....	119
34. Effect of 30-day treatment with isradipine alone and with a combination of isradipine and ascorbic acid on SBP of RHR.....	120
35. Effect of 30-day treatment with isradipine alone and with a combination of isradipine and selenium on SBP of RHR.....	121
36. Effect of 30-day treatment with isradipine alone and with a combination of isradipine and fish oil on SBP of RHR.....	122