



**Cairo University**  
**Faculty of Veterinary Medicine**  
**Pharmacology Department**

=====

**Effects of Ivermectin and Doramectin Drugs in Concurrent with  
Vitamin E on the Fertility in Male Rats**

**Thesis Presented**

**By**

**Shimaa Ramadan Emam Mohamed**

**(M.V. Sc., Cairo University, 2011)**

**For Ph.D. Degree**

**(Veterinary Pharmacology)**

**Under Supervision of**

**Prof. MOSTAFA ABBAS SHALABY**

**Professor of Pharmacology**  
**Faculty of Veterinary Medicine**  
**Cairo University**

**Prof. HOSSNY AWAD EL-BANNA**

**Professor of Pharmacology**  
**Faculty of Veterinary Medicine**  
**Cairo University**

**(2015)**

**Cairo University**

**Faculty of Veterinary Medicine**

**Department of Pharmacology**



=====

**Supervision sheet**

**Under Supervision of :**

**Prof. MOSTAFA ABBAS SHALABY**

**Professor of Pharmacology  
Faculty of Veterinary Medicine  
Cairo University**

**Prof. HOSSNY AWAD EL-BANNA**

**Professor of Pharmacology  
Faculty of Veterinary Medicine  
Cairo University**



**Cairo University**  
**Faculty of Veterinary Medicine**  
**Department of Pharmacology**

=====

**Name: Shimaa Ramadan Emam**  
**Date of birth: November 10, 1985**  
**Degree: Ph.D.**  
**Supervisors:**  
**Prof. Dr. Mostafa Abbas Shalaby**  
**Prof. Dr. Hossny Awad El-banna**

**Nationality: Egyptian**  
**Place of birth: Cairo**  
**Specialization: Pharmacology**

**Title of thesis: Effects of Ivermectin and Doramectin Drugs in Concurrent with Vitamin E on the Fertility in Male Rats**

## **ABSTRACT**

The protective effect of ivermectin (IVM) and doramectin (DOM) concomitantly with vitamin E (Vit. E) against testicular toxicity induced by sodium valproate (SVP) in rats was investigated. Seventy mature male rats were randomized into 2 main groups; the 1<sup>st</sup> for IVM and the 2<sup>nd</sup> for DOM. Each group was subdivided into 7 subgroups which given orally either IVM or DOM alone and concurrently with vitamin E to rats with testicular toxicity. Blood samples were withdrawn for determination of testosterone, FSH and LH serum levels. Semen samples were collected from for analysis. Sex organs weight, semen analysis, serum biochemical analysis, blood criteria and histopathology of testes, liver and kidneys were the parameters used in this study. The results denoted that oral pretreatment with IVM or DOM concomitantly with Vit. E increased the relative weight of testes and sperm motility, count and viability in SVP-intoxicated rats. There were also significant increases in serum testosterone and FSH levels and testicular antioxidant enzymes activity associated with amelioration of degenerative changes in the testis. The previous treatments increased biochemical markers of liver and kidney function, but have no adverse effects on blood pictured in the treated rats. In conclusion, oral pretreatment with IVM and DOM concomitantly with Vit. E exerts protective and antioxidant effects against testicular toxicity in rats; produces no effect of blood picture, but induces hepatorenal toxicity.

**Key words: Ivermectin- Doramectin- Vitamin E- Male fertility- Sperms- Testosterone.**

## **ACKNOWLEDGEMENT**

*Firstly, I offer my great thanks to our Merciful God who gives us every things we have.*

*I wish to express my sincere gratitude, grateful thanks and deep appreciation to **Prof. Dr. Mostafa Abbas Shalaby**, Professor of Pharmacology, Faculty of Veterinary Medicine, Cairo University, for his close supervision throughout the work, valuable guidance and offering me his cumulative experience and valuable time for completing this work,*

*I would like also to express my sincere gratitude and grateful thanks to **Prof. Dr. Hossny Awad El-banna**, Professor of Pharmacology, Faculty of Veterinary Medicine, Cairo University, for his kind supervision, careful guidance and assistance during preparation of my thesis.*

*I am greatly appreciated to **Dr. Reham Abdel-Salam**, Lecturer of Pathology, Faculty of Veterinary Medicine, Cairo University and to my colleague **Sara El-Sayed**, Assistant Lecturer of Physiology, Faculty of Veterinary Medicine, Cairo University for their continuous help during histopathological and physiological procedures in my work,*

*I wish to express my grateful thanks and deep appreciation, which would never be sufficient to my Family with special regards to my Father, Mother and my Husband **Dr. Mohammed** and my Daughter **Jwireah**.*

## CONTENTS

Subject	page
<b>1-INTRODUCTION.....</b>	<b>1</b>
<b>2-REVIEW OF LITERATURES:</b>	
<b>I- Effect of avermectins .....</b>	<b>4</b>
<b>II–Effect of valporic acid .....</b>	<b>35</b>
<b>III –Effect of vitamin E.....</b>	<b>37</b>
<b>3-MATERIAL AND METHODS</b>	
<b>I-MATERIAL</b>	
A) Drugs.....	39
B) Animals.....	44
C) Experimental design .....	46
<b>II-METHODS</b>	
<b>I-Effect on the male fertility.....</b>	<b>46</b>
<b>1-Organ weight analysis .....</b>	<b>46</b>
<b>2-Examination of epididymal spermatozoa.....</b>	
(a)-Progressive motility of sperms .....	46
(b)- Sperm cell concentration .....	47
(c) Epididymal sperm abnormalities .....	47

### **3- Antioxidant activity and lipid peroxidation**

(a) Determination of catalase enzyme.....	48
(b) Determination of superoxide dismutase (SOD).....	52
(c) Determination of total antioxidant capacity (TAC).....	53
(d) Determination of lipid peroxide (MDA).....	55
(e) Determination of reduced glutathione (GSH).....	57

### **4- Sex hormone assay**

(a) Serum testosterone .....	59
(b) Serum FSH .....	60
(c) Serum LH.....	61

## **(II)- Effect on hepatorenal function**

### **(1) Effect on liver function**

(a) Determination of alkaline phosphates activity (ALP)....	63
(b) Determination of activity of transaminases.....	64
(c) Determination of total protein .....	65
(d) Determination of albumin .....	66

### **(2) Effect on kidney function**

(a) Determination of serum Creatinine.....	67
(b) Determination of blood urea nitrogen (BUN).....	68

(c) Determination of serum uric acid.....	69
<b>(3) Effect on serum total cholesterol and triglycerides</b>	
(a) Determination of serum cholesterol level.....	72
(b) Determination of serum triglycerides level.....	73
<b>III) Effect of blood criteria</b>	
<b>1- Blood cell counts</b>	
a) Red blood cell count (erythrocytic count) .....	73
b) Total leucocytic count (TLC) .....	75
c) Differentia leucocytic count (DLC) .....	76
<b>2- Hemoglobin concentration (Hb) .....</b>	<b>77</b>
<b>3 - Packed cell volume (Hematocrit) .....</b>	<b>77</b>
<b>4 - The erythrocyte indices .....</b>	<b>78</b>
a- Mean corpuscular volume (MCV) .....	76
b- Mean corpuscular hemoglobin (MCH) .....	76
c- Mean corpuscular hemoglobin concentration .....	77
<b>V- Histopathological examination.....</b>	<b>78</b>
<b>RESULTS .....</b>	<b>83</b>
<b>DISCUSSION. ....</b>	<b>141</b>
<b>CONCLUSION.....</b>	<b>149</b>

<b>SUMMARY .....</b>	<b>150</b>
<b>REFERENCE.....</b>	<b>153</b>
<b>ABSTRACT .....</b>	
<b>ARABIC SUMMARY .....</b>	
<b>ARABIC ABSTRACT .....</b>	



## LIST OF TABLES

<b>No.</b>	<b>Title</b>	<b>Page</b>
(1)	Showing animal groups and their treatments.	45
(2)	Effect of ivermectin (IVM) at therapeutic and double therapeutic (Td and 2Td) dose and vitamin E (Vit. E) on relative weights of sexual organs of rats with testicular damage induced by sodium valproate. (n= 5 rats).	84
(3)	Effect of doramectin (DOM) at therapeutic and double therapeutic (Td and 2Td) dose and vitamin E (Vit. E) on relative weights of sexual organs of rats with testicular damage induced by sodium valproate. (n= 5 rats).	86
(4)	Effect of ivermectin (IVM) at therapeutic and double therapeutic (Td and 2Td) dose and vitamin E (Vit. E) on sperm parameters of rats with testicular damage induced by sodium valproate. (n= 5 rats).	89
(5)	Effect of doramectin (DOM) at therapeutic and double therapeutic (Td and 2Td) dose and vitamin E (Vit. E) on sperm parameters of rats with testicular damage induced by sodium valproate. (n= 5 rats).	91
(6)	Effect of ivermectin (IVM) at therapeutic and double therapeutic (Td and 2Td) dose and vitamin E (Vit. E) on levels of catalase (CAT) and superoxide dismutase (SOD) in testis tissue of rats with testicular damage induced by sodium valproate. (n= 5 rats).	94
(7)	Effect of doramectin (DOM) at therapeutic and double therapeutic (Td and 2Td) dose and vitamin E (Vit. E) on levels of catalase (CAT) and superoxide dismutase (SOD) in the testis tissue of rats with testicular damage induced by sodium valproate. (n= 5 rats).	96
(8)	Effect of ivermectin (IVM) at therapeutic and double therapeutic (Td and 2Td) dose and vitamin E (Vit. E) on malondialdehyde (MDA) content, total antioxidant capacity (TAC) and reduced glutathione (GSH) content in testis tissue of rats with testicular	99

	damage induced by sodium valproate. (n= 5 rats).	
<b>(9)</b>	Effect of doramectin (DOM) at therapeutic and double therapeutic (Td and 2Td) dose and vitamin E (Vit. E) on malondialdehyde (MDA) content, total antioxidant capacity (TAC) and reduced glutathione (GSH) content in testis tissue of rats with testicular damage induced by sodium valproate. (n= 5 rats).	101
<b>(10)</b>	Effect of ivermectin (IVM) at therapeutic and double therapeutic (Td and 2Td) dose and vitamin E (Vit. E) on serum levels of sex hormones testosterone (T), FSH and LH in rats with testicular toxicity induced by sodium valproate. (n= 5 rats).	104
<b>(11)</b>	Effect of doramectin (DOM) at therapeutic and double therapeutic (Td and 2Td) dose and vitamin E (Vit. E) on serum levels of sex hormones testosterone (T), FSH and LH in rats with testicular toxicity induced by sodium valproate. (n= 5 rats).	106
<b>(12)</b>	Effect of ivermectin (IVM) at therapeutic and double therapeutic (Td and 2Td) dose and vitamin E (Vit. E) on serum liver enzymes ALT, AST and ALP activities in rats with testicular damage induced by sodium valproate. (n= 5 rats).	109
<b>(13)</b>	Effect of doramectin (DOM) at therapeutic and double therapeutic (Td and 2Td) dose and vitamin E (Vit. E) on serum liver enzymes ALT, AST and ALP activities in rats with testicular damage induced by sodium valproate. (n= 5 rats).	111
<b>(14)</b>	Effect of ivermectin (IVM) at therapeutic and double therapeutic (Td and 2Td) dose and vitamin E (Vit. E) on serum concentrations of urea, creatinine and uric acid in rats with testicular damage induced by sodium valproate. (n= 5 rats).	114
<b>(15)</b>	Effect of doramectin (DOM) at therapeutic and double therapeutic (Td and 2Td) dose and vitamin E (Vit. E) on serum concentrations of urea nitrogen, creatinine and uric acid in rats with testicular damage induced by sodium valproate. (n= 5 rats).	116

<b>(16)</b>	Effect of ivermectin (IVM) at therapeutic and double therapeutic (Td and 2Td) dose and vitamin E (Vit. E) on serum total cholesterol (TC) and triglycerides (TG) levels in rats with testicular damage induced by sodium valproate. (n= 5 rats).	119
<b>(17)</b>	Effect of doramectin (DOM) at therapeutic and double therapeutic (Td and 2Td) dose and vitamin E (Vit. E) on serum total cholesterol (TC) and triglycerides (TG) levels in rats with testicular damage induced by sodium valproate. (n= 5 rats).	121
<b>(18)</b>	Effect of ivermectin (IVM) at therapeutic and double therapeutic (Td and 2Td) dose and vitamin E (Vit. E) on the differential leucocytic count (TLC) in rats with testicular damage induced by sodium valproate. (n= 5) rats).	124
<b>(19)</b>	Effect of doramectin (DOM) at therapeutic and double therapeutic (Td and 2Td) dose and vitamin E (Vit. E) on the differential leucocytic count (TLC) in rats with testicular damage induced by sodium valproate. (n= 5) rats).	125
<b>(20)</b>	Effect of ivermectin (IVM) at therapeutic and double therapeutic (Td and 2Td) dose and vitamin E (Vit. E) on RBCs count, hemoglobin (Hb) concentration and packed cell volume (PCV) in rats with testicular damage induced by sodium valproate. (n= 5) rats).	127
<b>(21)</b>	Effect of doramectin (DOM) at therapeutic and double therapeutic (Td and 2Td) dose and vitamin E (Vit. E) on RBCs count, hemoglobin (Hb) concentration and packed cell volume (PCV) in rats with testicular damage induced by sodium valproate. (n= 5) rats).	128

## LIST OF FIGURES

<b>No.</b>	<b>Title</b>	<b>Page</b>
(1)	Showing the chemical structural formula of Ivermectin.	40
(2)	Showing the chemical structural formula of Doramectin.	41
(3)	Showing the chemical structural formula of sodium valproate.	42
(4)	Showing the effect of ivermectin (IVM) at therapeutic and double therapeutic (Td and 2Td) dose concomitantly with vitamin E (Vit. E) on the relative weight of testes of rats with testicular damage induced by sodium valproate. (n= 5 rats).	85
(5)	Showing the effect of doramectin (DOM) at therapeutic and double therapeutic (Td and 2Td) dose and vitamin E (Vit. E) on relative weights of testes of rats with testicular damage induced by sodium valproate. (n= 5 rats).	87
(6)	Showing the effect of ivermectin (IVM) at therapeutic and double therapeutic (Td and 2Td) dose and vitamin E (Vit. E) on sperm parameters of rats with testicular damage induced by sodium valproate. (n= 5 rats).	90
(7)	Showing the effect of doramectin (DOM) at therapeutic and double therapeutic (Td and 2Td) dose and vitamin E (Vit. E) on sperm parameters of rats with testicular damage induced by sodium valproate. (n= 5 rats).	92
(8)	Showing the effect of ivermectin (IVM) at therapeutic and double therapeutic (Td and 2Td)	95

	dose and vitamin E (Vit. E) on levels of catalase (CAT) in testis tissue of rats with testicular damage induced by sodium valproate. (n= 5 rats).	
<b>(9)</b>	Showing the effect of ivermectin (IVM) at therapeutic and double therapeutic (Td and 2Td) dose and vitamin E (Vit. E) on levels of superoxide dismutase (SOD) in testis tissue of rats with testicular damage induced by sodium valproate. (n= 5 rats).	95
<b>(10)</b>	Showing the effect of doramectin (IVM) at therapeutic and double therapeutic (Td and 2Td) dose and vitamin E (Vit. E) on levels of catalase (CAT) in testis tissue of rats with testicular damage induced by sodium valproate. (n= 5 rats).	97
<b>(11)</b>	Showing the effect of doramectin (DOM) at therapeutic and double therapeutic (Td and 2Td) dose and vitamin E (Vit. E) on levels of superoxide dismutase (SOD) in the testis tissue of rats with testicular damage induced by sodium valproate. (n= 5 rats).	97
<b>(12)</b>	Showing the effect of ivermectin (IVM) at therapeutic and double therapeutic (Td and 2Td) dose and vitamin E (Vit. E) on malondialdehyde (MDA) content, total antioxidant capacity (TAC) and reduced glutathione (GSH) content in testis tissue of rats with testicular damage induced by sodium valproate. (n= 5 rats).	100
<b>(13)</b>	Showing the effect of doramectin (DOM) at therapeutic and double therapeutic (Td and 2Td) dose and vitamin E (Vit. E) on malondialdehyde (MDA) content, total antioxidant capacity (TAC)	102

	and reduced glutathione (GSH) content in testis tissue of rats with testicular damage induced by sodium valproate. (n= 5 rats).	
<b>(14)</b>	Showing the effect of ivermectin (IVM) at therapeutic and double therapeutic (Td and 2Td) dose and vitamin E (Vit. E) on serum levels of sex hormones testosterone (T), FSH and LH in rats with testicular toxicity induced by sodium valproate.(n= 5 rats).	105
<b>(15)</b>	Showing the effect of doramectin (DOM) at therapeutic and double therapeutic (Td and 2Td) dose and vitamin E (Vit. E) on serum levels of sex hormones testosterone (T), FSH and LH in rats with testicular toxicity induced by sodium valproate. (n= 5 rats).	107
<b>(16)</b>	Showing the effect of ivermectin (IVM) at therapeutic and double therapeutic (Td and 2Td) dose and vitamin E (Vit. E) on serum liver enzymes ALT, AST and ALP activities in rats with testicular damage induced by sodium valproate. (n= 5 rats).	110
<b>(17)</b>	Showing the effect of doramectin (DOM) at therapeutic and double therapeutic (Td and 2Td) dose and vitamin E (Vit. E) on serum liver enzymes ALT, AST and ALP activities in rats with testicular damage induced by sodium valproate. (n= 5 rats)	112
<b>(18)</b>	Showing the effect of ivermectin (IVM) at therapeutic and double therapeutic (Td and 2Td) dose and vitamin E (Vit. E) on serum concentrations of urea, creatinine and uric acid in	115

	rats with testicular damage induced by sodium valproate. (n= 5 rats).	
<b>(19)</b>	Showing the effect of doramectin (DOM) at therapeutic and double therapeutic (Td and 2Td) dose and vitamin E (Vit. E) on serum concentrations of urea nitrogen, creatinine and uric acid in rats with testicular damage induced by sodium valproate. (n= 5 rats).	117
<b>(20)</b>	Showing the effect of ivermectin (IVM) at therapeutic and double therapeutic (Td and 2Td) dose and vitamin E (Vit. E) on serum total cholesterol (TC) and triglycerides (TG) levels in rats with testicular damage induced by sodium valproate. (n= 5 rats).	120
<b>(21)</b>	Showing the effect of doramectin (DOM) at therapeutic and double therapeutic (Td and 2Td) dose and vitamin E (Vit. E) on serum total cholesterol (TC) and triglycerides (TG) levels in rats with testicular damage induced by sodium valproate. (n= 5 rats).	122
<b>(22)</b>	Showing C.S. of a testis of normal control rat showing normal histological findings of mature seminiferous tubules and normal spermatogenic series. (H&E X 200).	130
<b>(23)</b>	Showing C.S. of a testis of rat given sodium valproate showing severe testicular degeneration with decreased in spermatogonial cells to complete loss of spermatogenic series (arrow). (H&E X 200)	130
<b>(24)</b>	Showing C.S. of a testis of rat given sodium valproate showing severe testicular hemorrhage	131