

# LIST OF CONTENTS

Chapter	Page
<b>ACKNOWLEDGMENT</b> .....	<b>i</b>
<b>LIST OF CONTENTS</b> .....	<b>ii</b>
<b>LIST OF TABLES</b> .....	<b>iv</b>
<b>LIST OF FIGURES</b> .....	<b>v</b>
<b>LIST OF ABBREVIATIONS</b> .....	<b>vii</b>
<b>I. INTRODUCTION</b> .....	<b>1</b>
• Epidemiology .....	1
• Changing in Epidemiological Pattern of Peptic Ulcer Disease .....	1
• Pathogenesis .....	2
• Role of oxidative stress in peptic ulcer .....	5
• Malondialdehyde (MDA).....	6
• Nuclear E2_ related factor 2 in oxidative stress.....	6
• Mechanism of functioning of the keap1/nrf2/are signaling system .....	7
• Etiology of peptic ulcer .....	8
• Clinical manifestations of peptic ulcer .....	9
• Complication of peptic ulcer .....	9
• Treatment .....	10
• Refractory ulcers .....	13
• Experimental models of peptic ulcer.....	13
• Rebamipide .....	15
• Tianeptine.....	19
• Oleum cinnamomi .....	21
<b>II. AIM OF THE WORK</b> .....	<b>25</b>
<b>III. MATERIALS AND METHODS</b> .....	<b>26</b>
• Experimental animals .....	26
• Experimental design .....	26
• Assessment of ulcer index and protective ratio.....	27
• Determination of the level of superoxide dismutase in the gastric mucosa .....	28
• Determination of the level of malondialdehyde in the gastric mucosa .....	29

- Determination of the level of glutathione peroxidase in the gastric mucosa .....29
- Determination of Nuclear factor erythroid related factor(Nrf2) in gastric mucosa.....31

**IV. RESULTS .....35**

**V. DISCUSSION .....49**

**VI. SUMMARY .....55**

**VII. CONCLUSIONS .....58**

**VIII. RECOMMENDATIONS.....59**

**IX. REFERENCES.....60**

**PROTOCOL**

**ARABIC SUMMARY**

## LIST OF TABLES

Table	Page
(I) Degree of ulceration according to the scales of Abouzeit-Har.....	27
(II) Effect of rebamipide (60mg/Kg), tianeptine (12mg/Kg) and oleum cinnamomi (2.5ml/Kg) orally for seven days before indomethacin administration (100mg/Kg) on ulcer score.....	35
(III) Effect of rebamipide (60mg/Kg), tianeptine (12mg/Kg) and oleum cinnamomi (2.5ml/Kg) orally for seven days before indomethacin administration (100mg/Kg) on gastric activity of superoxide dismutase (U/gm tissue). .....	37
(IV) Effect of rebamipide (60mg/Kg), tianeptine (12mg/Kg) and oleum cinnamomi (2.5ml/Kg) orally for seven days before indomethacin administration (100mg/Kg) on gastric content of Malondialdehyde (nmol/gm tissue).....	38
(V) Effect of rebamipide (60mg/Kg), tianeptine (12mg/Kg) and oleum cinnamomi (2.5ml/Kg) orally for seven days before indomethacin administration (100mg/Kg) on gastric content of glutathione peroxidase activity (U/gm tissue). .....	39
(VI) Effect of rebamipide (60mg/Kg), tianeptine (12mg/Kg) and oleum cinnamomi (2.5ml/Kg) orally for seven days before indomethacin administration (100mg/Kg) on gastric level of Nuclear factor erythroid related factor content (ng/ml). .....	41
(VII) Effect of rebamipide (60mg/Kg), tianeptine (12mg/Kg) and oleum cinnamomi (2.5ml/Kg) orally for seven days before ethanol administration (1ml 70%) on ulcer score.....	42
(VIII) Effect of rebamipide (60mg/Kg), tianeptine (12mg/Kg) and oleum cinnamomi (2.5ml/Kg) orally for seven days before ethanol ulcer (1ml 70%) on gastric activity of superoxide dismutase (U/gm tissue).....	43
(IX) Effect of rebamipide (60mg/Kg), tianeptine (12mg/Kg) and oleum cinnamomi (2.5ml/Kg) orally for seven days before ethanol administration (1ml 70%) on gastric content of Malondialdehyde (nmol/gm.tissue). .....	45
(X) Effect of rebamipide (60mg/Kg), tianeptine (12mg/Kg) and oleum cinnamomi (2.5ml/Kg) orally for seven days before ethanol ulcer (1ml 70%) on gastric of glutathione peroxidase activity (U/gm tissue).....	46
(XI) Effect of rebamipide (60mg/Kg), tianeptine (12mg/Kg) and oleum cinnamomi (2.5ml/Kg) orally for seven days before ethanol administration (1ml 70%) on gastric content of Nuclear factor erythroid related factor (ng/ml).....	48

## LIST OF FIGURES

Figure		Page
(1)	Schematic presentation of gastric mucosal defense mechanisms. ....	3
(2)	Physiology of gastric acid secretion. ....	4
(3)	Key aspects of Nrf2 activation: 1) binding to Keap1 inhibitor; 2) ubiquitination and proteasome degradation; 3) phosphorylation and transport into the nucleus; 4) binding to ARE; 5) export from the nucleus. ....	7
(4)	Chemical structure of cimetidine. ....	12
(5)	Biosynthesis of prostaglandins. ....	15
(6)	chemical structure of Rebamipide. ....	16
(7)	Action of Rebamipid. PGs induce increase of inflammatory mediators. ....	17
(8)	chemical structure of Tianeptine. ....	19
(9)	Standard Curve for Rat NFE2L2 ELISA. ....	32
(10)	Effect of rebamipide (60mg/Kg), tianeptine (12mg/Kg) and oleum cinnamomi (2.5ml/Kg) orally for seven days before indomethacin administration (100mg/Kg) on ulcer score. ....	36
(11)	Effect of rebamipide (60mg/Kg), tianeptine (12mg/Kg) and oleum cinnamomi (2.5ml/Kg) orally for seven days before indomethacin (100mg/Kg) on gastric activity of superoxide dismutase (U/gm tissue). ....	37
(12)	Effect of rebamipide (60mg/Kg), tianeptine (12mg/Kg) and oleum cinnamomi (2.5ml/Kg) orally for seven days before indomethacin administration (100mg/Kg) on gastric content of Malondialdehyde (nmol/gm tissue). ....	38
(13)	Effect of rebamipide (60mg/Kg), tianeptine (12mg/Kg) and oleum cinnamomi (2.5ml/Kg) orally for seven days before indomethacin administration (100mg/Kg) on gastric mucosal glutathione peroxidase activity (U/gm tissue). ....	40
(14)	Effect of rebamipide (60mg/Kg), tianeptine (12mg/Kg) and oleum cinnamomi (2.5ml/Kg) orally for seven days before indomethacin administration (100mg/Kg) on gastric level of Nuclear factor erythroid related factor content (ng/ml). ....	41
(15)	Effect of rebamipide (60mg/Kg), tianeptine (12mg/Kg) and oleum cinnamomi (2.5ml/Kg) orally for seven days before ethanol administration (1ml 70%) on ulcer score. ....	42

<b>Figure</b>	<b>Page</b>
<b>(16)</b> Effect of rebamipide (60mg/Kg), tianeptine (12mg/Kg) and oleum cinnamomi (2.5ml/Kg) orally for seven days before ethanol administration (1ml 70%) on gastric activity of superoxide dismutase (U/gm tissue). .....	<b>44</b>
<b>(17)</b> Effect of rebamipide (60mg/Kg), tianeptine (12mg/Kg) and oleum cinnamomi (2.5ml/Kg) orally for seven days before ethanol ulcer (1ml 70%) on gastric content of Malondialdehyde.....	<b>45</b>
<b>(18)</b> Effect of rebamipide (60mg/Kg), tianeptine (12mg/Kg) and oleum cinnamomi (2.5ml/Kg) orally for seven days before ethanol administration (1ml 70%) on gastric activity of glutathione peroxidase (U/gm tissue). .....	<b>47</b>
<b>(19)</b> Effect of rebamipide (60mg/Kg), tianeptine (12mg/Kg) and oleum cinnamomi (2.5ml/Kg) orally for seven days before ethanol administration (1ml 70%) on gastric content of Nuclear factor erythroid related factor (ng/ml). .....	<b>48</b>

## LIST OF ABBREVIATIONS

<b>5-HT</b>	5-hydroxytryptamine
<b>AC</b>	Adenylate cyclase
<b>Ach</b>	Acetylcholine
<b>AGE</b>	Advanced glycation end products
<b>ALT</b>	Alanine transferase
<b>ARE</b>	Antioxidant responsive element,
<b>AST</b>	Aspartate transferase
<b>C. parapsilosis</b>	Candida parapsilosis
<b>C. burmanii</b>	Cinnamon. Burmanii
<b>C. orthopsilosis</b>	Candida orthopsilosis
<b>C.tritaeniorhynchus</b>	Culex tritaeniorhynchus
<b>CA</b>	Cinnamaldehyde
<b>CCK</b>	Cholecystokinin
<b>CCL4</b>	Carbon tetrachloride
<b>CDF</b>	Choledocho-duodenal fistulisation
<b>COX</b>	Cyclooxygenase, COX-1 and COX-2
<b>ECL</b>	enterochromaffine-like cells
<b>EP<sub>3</sub></b>	Procyclin EP <sub>3</sub>
<b>FOXO3a</b>	Forkhead transcription factor
<b>GP</b>	glutathione peroxidase
<b>GSH</b>	glutathione
<b>H.pylori</b>	Helicobacter pylori.
<b>H/K<sup>+</sup>ATPase</b>	Hydrogen/potassium adenosine triphosphate enzyme system
<b>H<sub>2</sub>RAs</b>	Histamine receptors antagonists
<b>Hist</b>	Histamine
<b>IFN <math>\gamma</math></b>	Interferon gama

<b>IL-</b>	Interleukin
<b>iNOS</b>	Inducible nitric oxide synthase
<b>MDA</b>	Malondialdehyde
<b>NADPH</b>	reduced nicotinamide adenosine dinucleotide phosphate
<b>Nrf2</b>	Nuclear E2_related factor 2
<b>NSAIDs</b>	Nonsteroidalantiinflammatory drugs.
<b>P.aeruginosa</b>	Pseudomonas. Aeruginosa
<b>PGs</b>	Prostaglandins
<b>PPAR</b>	Peroxisome proliferator activated receptor
<b>PPAR<math>\gamma</math></b>	Peroxisome proliferator activated receptor $\gamma$
<b>PPIs</b>	Proton pump inhibitors
<b>PPRE</b>	Peroxisome proliferator response elemen
<b>PUD</b>	Peptic ulcer disease
<b>ROS</b>	reactive oxygen species
<b>SOD</b>	superoxide dismutases
<b>SSRE</b>	Selective Seretonin Reuptake Enhancer
<b>SSRIs</b>	Selective serotonin reuptake inhibitors
<b>Tc</b>	Trans-cinnamaldehyde
<b>TCA</b>	Tricyclic antidepressants
<b>TNF-</b>	Tumor necrosis factor
<b>UC</b>	Ulcerative colitis
<b>VCAM-1</b>	Vascular cell adhesion molecule-1
<b>VEGF</b>	Vascular endothelial growth factor
<b>VEGF</b>	Vascular endothelial growth factor