

# **EXPERIMENTAL STUDY OF THE POTENTIAL ANTI-INFLAMMATORY ROLE OF REBAMIPIDE IN SOME EXPERIMENTAL ANIMAL MODELS**

**thesis**

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بسم الله الرحمن الرحيم

”يُؤْتِي الْحِكْمَةَ مَنْ يَشَاءُ وَمَنْ يُؤْتَ الْحِكْمَةَ فَقَدْ  
أُوتِيَ خَيْرًا كَثِيرًا وَمَا يَذَّكَّرُ إِلَّا أُولُو الْأَلْبَابِ“

صدق الله العظيم

سوره البقره: الايه ٢٦٩

*Dedication*

*To my parents and my husband  
who gave me continuous guidance  
and support*



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## *Abstract*

**Background:** Inflammation contributes to the pathophysiology of many chronic diseases. Chronic inflammatory diseases, such as asthma, rheumatoid arthritis and inflammatory bowel disease. TNF $\alpha$  plays a pivotal role in pathogenesis of them. Although Corticosteroids, Immunosuppressive agents, and Biological agents such as TNF $\alpha$  inhibitors, they alleviate the symptoms but do not cure the disease and have some limitations owing to their severe side effects. Consequently, looking for new agents that are equally or more effective and cause fewer side effects are needed. One of these drugs is rebamipide. Recent pharmacological studies have demonstrated that rebamipide has many pleiotropic pharmacological effects including Anti-Inflammatory, free radical scavenging and immunomodulatory are the most important effects.

**Aim of the work:** we intended to elucidate, compare and evaluate possible anti-inflammatory and immunomodulatory role of rebamipide in some experimental animal models of colitis, asthma and arthritis

### **Methods and experimental designs**

Acetic acid 4% induced ulcerative colitis, OVA sensitized guinea pig model of bronchial asthma and acute non immunological formaldehyde 1% induced arthritis

### **Results and Conclusion**

In the present study we verified the well established protective therapeutic effect of rebamipide in amelioration of AA induced ulcerative colitis in rats, which could be explained by its potent anti-inflammatory, antioxidant and cytoprotective effects. The significant attenuation of pathological changes associating the OVA sensitized guinea pig model of bronchial asthma could be attributed anti-inflammatory and immunomodulatory role.

Its insignificant role in ameliorating pathological changes associating formaldehyde induced arthritis could explain that its immunomodulatory role is more obvious in ulcerative colitis and asthma models in which cell mediated immunity was elicited or the chosen dose of the rebamipide in this study could not illicit anti-inflammatory and immunomodulatory

### **Key words**

**Inflammation, ulcerative colitis, Asthma, Arthritis, Rebamipide, Dexamethazone, TNF $\alpha$ , MPO, IgE, Acetic acid, Ovalbumin, Formaldehyde**

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*List of abbreviations*

<b>5-ASA</b>	<b>5-amino salycilic acid</b>
<b>5HT</b>	<b>Sertonin</b>
<b>AA</b>	<b>Acetic acid</b>
<b>ADAMT</b>	<b>Adesintegrin and metalloprotease with thrombospondintype 1 motif</b>
<b>AHR</b>	<b>Airway hyperresponsiveness</b>
<b>ANOVA</b>	<b>Analysis of variance</b>
<b>APC</b>	<b>Antigen presenting cell</b>
<b>AZA</b>	<b>Azathioprine</b>
<b>C<sup>0</sup></b>	<b>Degree centigrade</b>
<b>CAM</b>	<b>Cellular adhesion molecule</b>
<b>CARD</b>	<b>Caspase recruitment domain</b>
<b>CD</b>	<b>Cluster of differentiation</b>
<b>COX</b>	<b>Cyclooxygenase enzyme</b>
<b>CTL</b>	<b>Cytotoxic Tlymphocytes</b>
<b>CW/BW</b>	<b>Colonic weight to body weight ratio</b>
<b>CXCR</b>	<b>Chemokine receptor</b>
<b>DAI</b>	<b>Disease activity index</b>
<b>DEX</b>	<b>Dexamethazone</b>
<b>DMARD</b>	<b>Disease modifying anti rheumatic drugs</b>
<b>DSS</b>	<b>Dextran sulphate sodium</b>
<b>ERK</b>	<b>Extracellular signal regulated kinase</b>
<b>EPR</b>	<b>electron paramagnetic resonance</b>
<b>FADD</b>	<b>Fas –associated death domain</b>
<b>GINA</b>	<b>Global initiative for asthma</b>
<b>GM-CSF</b>	<b>Granulocyte macrophage colony stimulating factor</b>
<b>H&amp; E</b>	<b>Haematoxyllin and Eosin staining</b>
<b>HCQ</b>	<b>Hydroxychloroquine</b>
<b>HIF<math>\alpha</math></b>	<b>Hypoxia inducible factor<math>\alpha</math></b>
<b>HO-1</b>	<b>Hemoxygenase -1</b>
<b>IBD</b>	<b>Inflammatory bowel disease</b>
<b>ICS</b>	<b>Inhaled corticosteroids</b>
<b>IFN</b>	<b>Interferron</b>
<b>IgE</b>	<b>Immunoglobulin E</b>
<b>I<math>\kappa</math>B</b>	<b>Inhibitor of NF-<math>\kappa</math>B</b>
<b>IKK</b>	<b>Inhibitor for kappa<sub>B</sub> kinase</b>

<b>IL</b>	<b>Interlukin</b>
<b>JAM</b>	<b>Juxta adhesion molecules</b>
<b>JUK</b>	<b>C-jun-N-terminal kinase</b>
<b>LABA</b>	<b>Long acting beta2 agonist</b>
<b>LEF</b>	<b>Leflunomide</b>
<b>LOX</b>	<b>Lipooxygenase enzyme</b>
<b>LT</b>	<b>Leukotrien</b>
<b>MADCAM</b>	<b>Mucosal addressin cellular adhesion molecule</b>
<b>MAPK</b>	<b>Mitogen activated protein kinase</b>
<b>MCP</b>	<b>Monocyte chemoattractant protein</b>
<b>M-CSf</b>	<b>Macrophage colony stimulating factor</b>
<b>MEKK1</b>	<b>MAP/ERK kinase kinase1</b>
<b>MHC</b>	<b>Major histocompatibility</b>
<b>MKK7</b>	<b>MAP kinase kinase7</b>
<b>MPO</b>	<b>Myeloperoxidase enzyme</b>
<b>mM</b>	<b>Milli mole</b>
<b>MTX</b>	<b>Methotrexate</b>
<b>NF-K<sub>B</sub></b>	<b>Nuclear factor kappa</b>
<b>NK</b>	<b>Natural killer cell</b>
<b>NSAID</b>	<b>Nonsteroidal inflammatory drugs</b>
<b>OVA</b>	<b>Ovaalbumin</b>
<b>PAF</b>	<b>Platlet activating factor</b>
<b>PG</b>	<b>Prostaglandin</b>
<b>PKC</b>	<b>Protein kinase c</b>
<b>PLA2</b>	<b>Phospholipase A2</b>
<b>PMNs</b>	<b>Polymorphnuclear cell</b>
<b>PPAR</b>	<b>peroxisome proliferator-activated receptor</b>
<b>PSGL</b>	<b>P selectin glycoprotein ligand</b>
<b>RANKL</b>	<b>Receptor activator of nuclear factor kappa</b>
<b>Reb</b>	<b>Rebamipide</b>
<b>RIP</b>	<b>Receptor interacting protein</b>
<b>SABA</b>	<b>Short acting beta agonist</b>
<b>SOD</b>	<b>Superoxide dismutase</b>
<b>SPZ</b>	<b>Sulphazalazine</b>
<b>TAK1</b>	<b>TGF-<sub>B</sub> transforming growth factor beta activated kinase</b>
<b>Th</b>	<b>T helper</b>
<b>TIMP</b>	<b>Tissue inhibitors of metalloprotenases</b>
<b>TNBS</b>	<b>Trinitrobenzene sulphonic acid</b>
<b>TNF</b>	<b>Tumer necrosis factor</b>
<b>TRADD</b>	<b>TNF receptor associated death domain</b>
<b>TRAF<sub>2</sub></b>	<b>TNF activated factor 2</b>



<b>TXA</b>	<b>Thromboxane</b>
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# **INTRODUCTION**

Inflammation is considered the cornerstone of pathology in that the changes observed are indicative of injury and disease. It is recognised that inflammation is far more complex than might first appear and is a major response of the immune system to tissue damage and infection. These processes involve the major cells of the immune system, including neutrophils, basophils, mast cells, T-cells, B-cells, etc. These events are controlled by a host of extracellular mediators and regulators, including cytokines, growth factors, eicosanoids (prostaglandins, leukotrienes, etc), complement and peptides. Inflammation is now considered as the full circle of events, from initiation of a response, through the development of the cardinal signs of inflammation to healing and restoration of normal appearance and function of the tissue or organ. However, in certain conditions there appears to be no resolution and a chronic state of inflammation develops that may last the life of the individual. Such conditions include the inflammatory disorders rheumatoid arthritis, osteoarthritis, inflammatory bowel diseases, retinitis, multiple sclerosis, psoriasis and atherosclerosis. (Neville et al., 2004).

It was postulated that any discussion of inflammation must involve consideration of the molecular level, and should also include the full range of cell types involved in the acute and chronic injury response. Thus, the positive or negative outcome of the process is influenced by the simultaneous responses and interactions of these cell types (Scott et al., 2004).

The concept that some cytokines function primarily to induce inflammation is based on the genes coding for the synthesis of small