



# Potential utility of angiotensin two receptor blocker in a rat model of ulcerative colitis

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بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

﴿وَعَلَّمَكَ مَا لَمْ تَكُنْ تَعْلَمُ وَكَانَ

فَضْلُ اللَّهِ عَلَيْكَ عَظِيمًا﴾

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**List of Abbreviations**

<b>ACE</b>	Angiotensin converting enzyme
<b>ADHP</b>	10-Acetyl-3,7-dihydroxyphenoxazine
<b>Ang II</b>	Angiotensin II
<b>ARB</b>	Angiotensin receptor blocker
<b>5-ASA</b>	5-Aminosalicylic acid
<b>AT1</b>	Angiotensin II receptor, type one
<b>BHT</b>	Butylated hydroxy toluene
<b>BSA</b>	Bovine serum albumin
<b>CAMs</b>	Cell adhesion molecules
<b>CD</b>	Crohn's disease
<b>CD1</b>	Cluster of differentiation 1
<b>CMC</b>	Carboxy methyl cellulose
<b>CRC</b>	Colorectal cancer
<b>COX</b>	Cyclo-oxygenase enzyme
<b>DAI</b>	Disease activity index
<b>DMSO</b>	Dimethyl sulfoxide
<b>DSS</b>	Dextran sodium sulphate
<b>DTPA</b>	Diethylene triamine penta acetic acid
<b>EGF</b>	Epidermal growth factor
<b>ELISA</b>	Enzyme-linked immunosorbent assay
<b>GSH</b>	Reduced glutathione
<b>HRP</b>	Horseradish peroxidase
<b>IBD</b>	Inflammatory bowel diseases
<b>ICAM-1</b>	Intracellular adhesion molecule-1
<b>IFN-<math>\gamma</math></b>	Interferon gamma
<b>IgG</b>	Immunoglobulin G
<b>IL</b>	Interleukin
<b>iNOS</b>	Inducible nitric oxide synthase
<b>KGF</b>	Keratinocyte growth factor
<b>5-LO</b>	5-Lipo-oxygenase enzyme
<b>MDA</b>	Malondialdehyde
<b>MPA</b>	Metaphosphoric acid
<b>MPO</b>	Myeloperoxidase
<b>NADPH</b>	Nicotinamide adenine dinucleotide phosphate
<b>NF-KB</b>	Nuclear Factor kappa-light chain enhancer of activated B cells
<b>NKT</b>	Natural killer T cells
<b>OLM-M</b>	Olmesartan medoxomil
<b>PBS</b>	Phosphate buffer saline
<b>PGE<sub>2</sub></b>	Prostaglandin E <sub>2</sub>
<b>PG-PS</b>	Peptidoglycan-polysaccharide
<b>P.O.</b>	Per os (oral)
<b>RAAS</b>	Renin angiotensin aldosterone system
<b>ROS</b>	Reactive oxygen species

<b>SASP</b>	Salicylazosulphapyridine
<b>SDS</b>	Sodium dodecyl sulfate
<b>SH</b>	Sulfhydryl
<b>SP</b>	Sulfapyridine
<b>TBA</b>	Thiobarbituric acid
<b>TBARS</b>	Thiobarbituric acid reactive substances
<b>Th2</b>	T helper cell type-2
<b>TMB</b>	Tetra methyl benzidine
<b>TNBS</b>	2,4,6-Trinitrobenzene sulphonic acid
<b>TNF-<math>\alpha</math></b>	Tumor necrosis factor-alpha
<b>UC</b>	Ulcerative colitis

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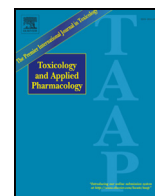
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## Anti-inflammatory and anti-oxidant activities of olmesartan medoxomil ameliorate experimental colitis in rats

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### ABSTRACT

Ulcerative colitis (UC) is a chronic inflammatory bowel disease (IBD) driven through altered immune responses with production of proinflammatory cytokines. Many therapies are used, but side effects and loss of response limit long-term effectiveness. New therapeutic strategies are thus needed for patients who don't respond to current treatments. Recently, there is suggested involvement of the proinflammatory hormone angiotensin II in inflammatory bowel disease. The aim of this study was to investigate the possible role of olmesartan medoxomil (OLM-M), an angiotensin II receptor blocker in ameliorating ulcerative colitis. Colitis was induced in male Wistar rats by administration of 5% dextran sodium sulphate (DSS) in drinking water for 5 days. OLM-M (1, 3 and 10 mg/kg) was administered orally during 21 days prior to the induction of colitis, and for 5 days after. Sulfasalazine (500 mg/kg) was used as reference drug. All animals were tested for changes in colon length, disease activity index (DAI) and microscopic damage. Colon tissue concentration/activity of tumor necrosis alpha (TNF- $\alpha$ ), myeloperoxidase (MPO), prostaglandin E2 (PGE2), reduced glutathione (GSH) and malondialdehyde (MDA) were assessed. Results showed that the OLM-M dose-dependently ameliorated the colonic histopathological and biochemical injuries, an effect that is comparable or even better than that of the standard sulfasalazine. These results suggest that olmesartan medoxomil may be effective in the treatment of UC through its anti-inflammatory and antioxidant effects.

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### Introduction

Crohn's disease (CD) and ulcerative colitis (UC) are the two major forms of chronic inflammatory bowel disease (IBD) (Blumberg and Strober, 2001). UC primarily affects the mucosal lining of the colon and rectum, whereas CD can involve any segment of the gastrointestinal tract (Podolsky, 2002). Although the etiology remains unclear, yet studies showed that a combination of genetic susceptibility factors and altered immune response driven by microbial factors in the enteric environment are involved in the pathophysiology of these chronic disorders (Korzenik and Podolsky, 2006). The activation of the intestinal immune system results in the production of pro-inflammatory cytokines, such as tumor necrosis factor (TNF- $\alpha$ ) and interleukin-1 $\beta$  (IL-1 $\beta$ ), prostaglandins and leukotrienes (Krimsky et al., 2003). IL-1 $\beta$  appears to be a primary stimulator of diarrhea, the main symptom of intestinal inflammation (Siegmund et al., 2001). In addition, TNF- $\alpha$  and IL-1 $\beta$  are the key immunoregulatory cytokines that amplify the inflammatory response by activating a cascade of

immune cells, such as neutrophils and others (Jainu et al., 2006). Infiltration of neutrophils assessed by myeloperoxidase (MPO), result in the production of cytotoxic reactive oxygen species (ROS) that are destructive on intestinal cell macromolecules, ultimately leading to mucosal disruption and ulceration (Fiocchi, 1998).

Currently available treatments for IBD are only effective in ameliorating the disease symptoms while having many concomitant disadvantages. Antibiotics, one of the commonly used therapies, could adversely change the environmental conditions of microflora and also trigger resistance. Moreover, immunosuppressant and anti-inflammatory drugs (as corticosteroids) have many undesirable side effects (Sartor, 2004).

Angiotensin II (Ang II) is the primary effector peptide of the renin-angiotensin-aldosterone system (RAAS) through its action on both angiotensin receptors Ang II type 1 (AT1) and AT2 receptors (Padia and Carey, 2012). Activation of the AT1 receptor by Ang II is responsible for all of the known cardiovascular effects of Ang II: acute vasoconstriction, aldosterone secretion and sympathetic overactivity, while activation of the AT2 receptor results in the opposite effects (Burnier, 2001). Ang II is a proinflammatory hormone that participates in several key events of the inflammatory response: it increases vascular permeability (via release of prostaglandins and vascular endothelial cell growth factor/vascular permeability factor) (Suzuki et al., 2000) and enhances neutrophil infiltration, possibly contributing to intestinal ulceration.

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