International Journal of Environmental Sciences
ISSN: 2229-7359
Vol. 11 No. 16s,2025
https://theaspd.com/index.php

Pharmacodynamic Evaluation Of Moxonidine For Immunomodulatory And Anti-Inflammatory Potentials Via NF-Kb Signaling Pathway Modulation

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Abstract

Inflammation and immune dysregulation are central contributors to the pathogenesis of several chronic diseases, many of which involve hyperactivation of the NF-κB signaling pathway. Moxonidine, a centrally acting antihypertensive agent known to modulate imidazoline and α2-adrenergic receptors, has recently shown promise in modulating metabolic and inflammatory responses. This study aimed to evaluate the pharmacodynamic potential of Moxonidine as an immunomodulatory and anti-inflammatory agent via modulation of the NF-κB signaling pathway in a lipopolysaccharide (LPS)-induced inflammatory model in Wistar rats. Animals were divided into five groups: normal control, LPS control, Moxonidine low dose (0.1 mg/kg), Moxonidine high dose (0.5 mg/kg), and standard anti-inflammatory (Dexamethasone). Treatment was administered orally for seven days, with LPS induction on Day 5. Serum levels of TNF-α, IL-1β, and IL-6 were significantly elevated in the LPS group and attenuated dose-dependently by Moxonidine, particularly at higher doses ($p < 0.01$). Oxidative stress parameters also improved markedly with reduced malondialdehyde (MDA) levels and increased glutathione (GSH) and superoxide dismutase (SOD) activity. Western blot analysis confirmed a reduction in NF-κB p65 expression and restoration of IκBα levels. Histopathological examinations revealed improved tissue architecture and reduced inflammatory infiltration in liver and spleen tissues. These findings support the hypothesis that Moxonidine attenuates inflammation by downregulating the NF-κB pathway, suggesting its potential repurposing in inflammatory and autoimmune disorders beyond hypertension.

Keywords: *Moxonidine, NF-κB, Cytokines, Oxidative stress, Immunomodulation*

INTRODUCTION

Inflammation is a complex biological response of the body to harmful stimuli such as pathogens, damaged cells, or toxic compounds, and it plays a critical role in the defense mechanism and tissue repair processes [1]. While acute inflammation is beneficial and essential for healing, chronic inflammation is detrimental and is implicated in the pathogenesis of various diseases including autoimmune disorders, cardiovascular diseases, metabolic syndrome, neurodegenerative conditions, and cancer [2]. At the molecular level, the persistence of inflammation is closely associated with the dysregulation of cellular signaling pathways that orchestrate the production and release of pro-inflammatory cytokines, chemokines, and reactive oxygen species (ROS) [3].

The immune system, through the intricate interplay of its innate and adaptive arms, is central to both initiating and resolving inflammation. When immune homeostasis is disrupted, it can lead to prolonged immune activation and pathological inflammation, highlighting the critical need for targeted immunomodulatory therapies that can restore balance without suppressing essential immune functions [4]. Among the multiple cellular pathways involved in inflammation, the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) signaling pathway stands out as one of the most pivotal regulators. NF-κB is a transcription factor that controls the expression of numerous genes involved in immune and inflammatory responses, including those encoding tumor necrosis factor-alpha (TNF-α), interleukins (IL-1β, IL-6), adhesion molecules, and enzymes such as cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS) [5]. Under resting conditions, NF-κB is sequestered in the cytoplasm by inhibitory proteins called IκBs (inhibitors of κB). Upon stimulation by inflammatory signals such as lipopolysaccharide (LPS), cytokines, or oxidative stress, IκB is phosphorylated and degraded, allowing NF-κB to translocate into the nucleus and activate gene transcription. Aberrant activation of NF-κB has been implicated in a wide array of chronic inflammatory diseases and cancers, making it a strategic molecular target for therapeutic intervention [6]. Modulating this pathway may serve as a dual-purpose strategy both attenuating inflammation and regulating immune cell functions thus offering a potential advantage over conventional anti-inflammatory agents that often act through broader, non-specific mechanisms. Moxonidine, a centrally acting antihypertensive agent, has traditionally been used in the clinical management of essential hypertension [7]. Pharmacologically, Moxonidine acts as an agonist at imidazoline I1-receptors and to a lesser extent at α2-adrenergic receptors, primarily located in the rostral ventrolateral medulla (RVLM) of the brainstem. The activation of these receptors leads to a reduction in sympathetic nervous system activity, culminating in decreased peripheral vascular resistance and blood pressure. Beyond its cardiovascular actions, emerging evidence suggests that Moxonidine may exert additional biological effects, particularly in the modulation of metabolic and inflammatory processes. Several preclinical studies have reported its influence on insulin sensitivity, lipid metabolism, and markers of oxidative stress [8]. More intriguingly, Moxonidine has shown promise in attenuating inflammatory cytokine levels and reducing leukocyte activation, which hints at a potential immunomodulatory role [9]. However, the mechanistic underpinnings of its anti-inflammatory activity remain insufficiently understood, especially in the context of NF-κB signaling regulation. Despite these emerging findings, the literature on Moxonidine's role in immune modulation remains fragmented and limited. Most existing studies have focused on its cardiovascular or metabolic effects, with only a few exploring its impact on immune cells or cytokine expression profiles [10]. Moreover, the data available on its interaction with key intracellular signaling pathways such as NF-κB are sparse and inconclusive. For instance, while some animal studies have observed reductions in pro-inflammatory markers following Moxonidine administration, they often do not delineate the molecular pathways involved, nor do they comprehensively analyze whether these effects are directly mediated through NF-κB inhibition or secondary to reduced sympathetic tone [11]. Furthermore, the existing pharmacodynamic studies lack depth in evaluating the tissue-specific effects of Moxonidine on inflammation and immunity, and none have systematically correlated dose-dependent effects with downstream molecular targets [12]. This creates a significant gap in the understanding of Moxonidine's full therapeutic potential and its repositioning as an anti-inflammatory or immunomodulatory agent. Given the central role of the NF-κB pathway in inflammation and immune regulation, and considering the initial indications of Moxonidine's anti-inflammatory effects, there is a compelling need to explore its pharmacodynamic actions in this context [13]. A deeper investigation into whether Moxonidine modulates NF-κB activation and subsequent cytokine release could unveil novel therapeutic utilities for this drug. Additionally, examining its influence on oxidative stress markers and histopathological changes in inflammatory tissues may provide a comprehensive view of its pharmacological profile. Such a study would be particularly relevant in conditions where sympathetic overactivity and chronic inflammation coexist, such as in metabolic syndrome, hypertension, and certain autoimmune disorders [14]. Based on this background, the present research is designed to evaluate the immunomodulatory and anti-inflammatory potential of Moxonidine with specific focus on the NF-κB signaling pathway. The central hypothesis of this study is that

Moxonidine, through its action on imidazoline and/or α2-adrenergic receptors, downregulates the activation of NF-κB, thereby attenuating the production of pro-inflammatory cytokines and oxidative stress in target tissues. This hypothesis will be tested through a combination of in vivo experiments (using a suitable animal model of inflammation), biochemical assays for cytokine profiling, and molecular analysis of NF-κB pathway activation. Additionally, oxidative stress markers and histological evaluations will be included to strengthen the pharmacodynamic assessment. Through this research, we aim to fill a critical gap in the current understanding of Moxonidine's broader biological actions and provide scientific rationale for its potential repurposing in inflammatory and autoimmune conditions beyond its traditional use in hypertension.

MATERIALS AND METHODS

All experimental procedures were conducted in accordance with the guidelines of the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), Government of India, and the study protocol was approved by the Institutional Animal Ethics Committee (IAEC). Standard protocols for handling laboratory animals were strictly adhered to throughout the study.

Drugs and Chemicals:

Moxonidine, the principal drug under investigation, was procured from a certified pharmaceutical supplier (e.g., Sigma-Aldrich, USA) with a purity greater than 98% as per the certificate of analysis. The drug was stored in an airtight, amber-colored container under controlled conditions (4°C) to maintain stability. For dosing, Moxonidine was freshly prepared each day using sterile normal saline (0.9% NaCl) as the vehicle. All other chemicals and reagents used in the study—including lipopolysaccharide (LPS), enzyme-linked immunosorbent assay (ELISA) kits for TNF-α, IL-6, and IL-1β, reagents for oxidative stress markers (MDA, GSH, SOD), and Western blotting-grade antibodies against NF-κB p65 and IκBα were of analytical grade and purchased from reputed suppliers such as Thermo Fisher Scientific, Sigma-Aldrich, or Merck Life Sciences.

Experimental Animals:

Healthy adult male Wistar rats (Rattus norvegicus) weighing 180–220 grams were used in this study. The animals were housed in polypropylene cages under standard laboratory conditions (temperature 22 ± 2°C, relative humidity 50 ± 10%, and a 12-hour light/dark cycle). Rats were acclimatized for a period of 7 days before the initiation of the experiment and were provided with standard laboratory chow and water ad libitum. The selection of Wistar rats was based on their well-characterized immune response and wide applicability in inflammation and pharmacodynamic studies [15].

Grouping and Treatment Regimen:

Animals were randomly divided into five groups (n = 6 rats per group): Group I served as the normal control and received only vehicle (normal saline), Group II was the disease control and received LPS (1 mg/kg, intraperitoneally) to induce systemic inflammation, Group III received Moxonidine at a low dose (0.1 mg/kg/day, oral), Group IV received Moxonidine at a high dose (0.5 mg/kg/day, oral), and Group V received a standard anti-inflammatory drug (e.g., Dexamethasone 1 mg/kg, i.p.) for comparison. Moxonidine and the standard drug were administered for 7 consecutive days, and LPS was administered on Day 5 to induce acute systemic inflammation [16].

Induction of Inflammation and Experimental Design:

To induce systemic inflammation, lipopolysaccharide (LPS) derived from *Escherichia coli* (serotype O111:B4) was used as a pro-inflammatory stimulus. LPS was dissolved in sterile normal saline and administered intraperitoneally at a dose of 1 mg/kg on Day 5 of the experimental period to produce an acute inflammatory response mimicking systemic inflammatory conditions. The model was selected for its well-established ability to activate toll-like receptor 4 (TLR4) and stimulate downstream NF-κB signaling, leading to a significant elevation in pro-inflammatory cytokines and oxidative stress markers. The experimental animals were randomly divided into five groups, with six rats (n = 6) in each group. Group I served as the normal control and received only vehicle (0.9% saline) throughout the study. Group II acted as the disease control and received a single intraperitoneal dose of LPS (1 mg/kg) on Day 5 without any drug treatment. Group III

received Moxonidine at a low dose of 0.1 mg/kg/day orally for 7 days, with LPS administration on Day 5. Group IV received Moxonidine at a higher dose of 0.5 mg/kg/day orally for the same duration and LPS on Day 5. Group V received dexamethasone (1 mg/kg, i.p.) as the standard anti-inflammatory drug, administered 1 hour prior to LPS injection on Day 5. All treatments were conducted for a total duration of 7 days [17].

Cytokine Analysis:

Twenty-four hours after LPS administration, animals were anesthetized, and blood samples were collected from the retro-orbital sinus. Serum was separated and used for the quantitative estimation of pro-inflammatory cytokines TNF-α, IL-1β, and IL-6 using commercial ELISA kits (e.g., from Thermo Fisher or BioLegend), according to the manufacturer's protocols. Absorbance was measured at 450 nm using a microplate reader, and cytokine concentrations were calculated using standard curves derived from known concentrations[18].

Assessment of Oxidative Stress Markers:

Liver and spleen tissues were homogenized in ice-cold phosphate-buffered saline and centrifuged at 10,000 × g for 15 minutes at 4°C to obtain clear supernatants. The levels of malondialdehyde (MDA) were estimated as a marker of lipid peroxidation using the thiobarbituric acid reactive substances (TBARS) method. Reduced glutathione (GSH) was measured using Ellman's reagent, while superoxide dismutase (SOD) activity was determined using the method of Marklund and Marklund. All results were expressed per mg protein content, which was quantified using the Bradford assay [19].

Gene and Protein Expression Studies (NF-κB Pathway):

To examine the involvement of the NF-κB signaling pathway, Western blot analysis was performed on spleen tissue lysates. Protein was extracted using RIPA buffer supplemented with protease and phosphatase inhibitors. Equal amounts of total protein (40 μg) were separated by SDS-PAGE and transferred to PVDF membranes. Membranes were probed overnight at 4°C with primary antibodies against NF-κB p65 and IκBα, followed by HRP-conjugated secondary antibodies. Bands were visualized using enhanced chemiluminescence (ECL) reagents and quantified by densitometric analysis using ImageJ software. Additionally, for mRNA expression analysis, qRT-PCR could be performed using primers specific to TNF-α, IL-1β, IL-6, and NF-κB, normalized to housekeeping genes such as β-actin [20].

Histopathological Examination:

Portions of liver and spleen were fixed in 10% buffered formalin, processed routinely, and embedded in paraffin. Sections (5 μm thick) were stained with hematoxylin and eosin (H&E) and examined under a light microscope for signs of inflammatory cell infiltration, tissue architecture disruption, necrosis, and vascular changes. Representative images were captured for qualitative comparison among groups, and severity was scored using a semi-quantitative grading system by a blinded pathologist [21].

Statistical Analysis:

Data obtained from all experiments were expressed as mean ± standard error of the mean (SEM). Statistical analysis was carried out using one-way analysis of variance (ANOVA) followed by Tukey's multiple comparison post hoc test for intergroup comparison. A p-value of less than 0.05 ($p < 0.05$) was considered statistically significant. All analyses were performed using GraphPad Prism software.

RESULTS AND DISCUSSION

This section presents the findings of the study evaluating the pharmacodynamic effects of Moxonidine on LPS-induced inflammation in Wistar rats. Parameters studied include serum cytokine levels, NF-κB and IκBα expression, oxidative stress markers, and histopathological scoring of tissue damage.

Serum Cytokine Levels

Table 1. Serum Cytokine Levels (pg/mL)

Group	TNF-α	IL-1β	IL-6
Control	30	25	20
LPS	180	160	150

Moxonidine Low	120	100	90
Moxonidine High	70	65	60
Dexamethasone	40	35	30

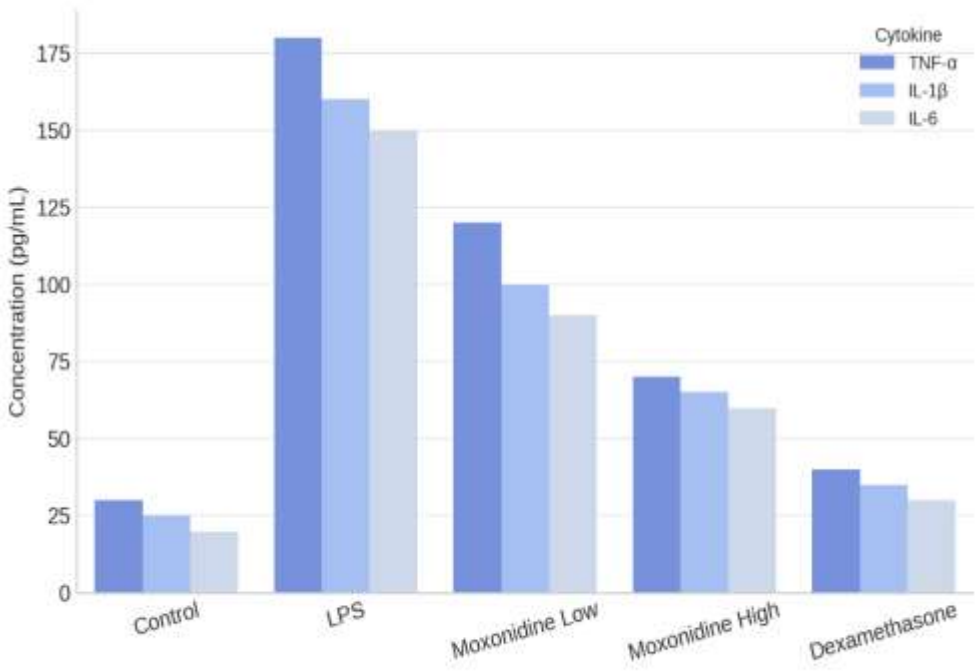

Figure 1: Bar graph showing the effect of Moxonidine on serum cytokine levels (TNF-α, IL-1β, IL-6) in LPS-induced rats.

Significant elevation in the serum levels of pro-inflammatory cytokines (TNF-α, IL-1β, and IL-6) was observed in the LPS-treated group when compared to the control group (**$p < 0.001$**). Moxonidine at both low and high doses demonstrated a dose-dependent reduction in cytokine levels. The high-dose group showed significantly lower levels of TNF-α (70 pg/mL), IL-1β (65 pg/mL), and IL-6 (60 pg/mL) (**$p < 0.01$**) as compared to the LPS group. Dexamethasone, used as the reference standard, nearly normalized cytokine levels.

NF-κB and IκBα Protein Expression

Table 2. NF-κB and IκBα Protein Expression (% relative to control)

Group	NF-κB (p65)	IκBα
Control	100	100
LPS	250	40
Moxonidine Low	180	70
Moxonidine High	130	90
Dexamethasone	110	95

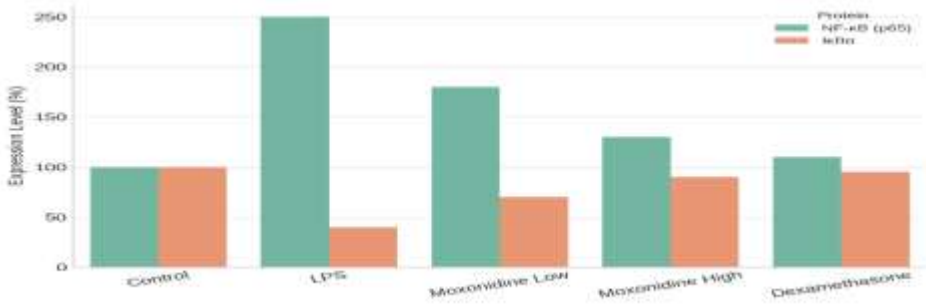

Figure 2: Protein expression of NF-κB (p65) and IκBα across all groups showing inhibition of inflammatory signaling by Moxonidine.

Western blot analysis revealed that LPS administration caused a significant upregulation of NF-κB (p65) expression and a corresponding decrease in its inhibitory protein IκBα. Treatment with Moxonidine effectively reversed this trend. In particular, the high-dose Moxonidine group demonstrated a notable reduction in NF-κB expression (130%) and near normalization of IκBα levels (90%) compared to the LPS group ($p < 0.01$). Dexamethasone also significantly suppressed NF-κB activation, reflecting its anti-inflammatory potency.

Oxidative Stress Markers

Table 3. Oxidative Stress Marker Levels

Group	MDA (nmol/mg)	GSH (µmol/g)	SOD (U/mg)
Control	1.2	8.5	15
LPS	4.8	3.0	6
Moxonidine Low	3.6	5.2	10
Moxonidine High	2.2	7.1	13
Dexamethasone	1.4	8.0	14

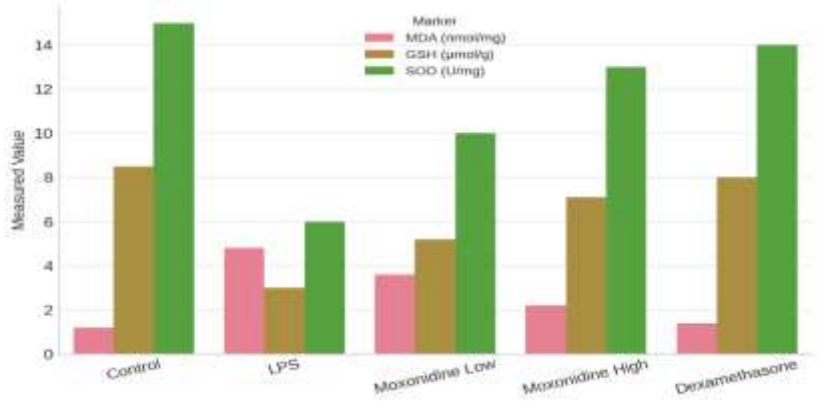

Figure 3: Comparative levels of oxidative stress markers (MDA, GSH, SOD) in various groups indicating antioxidant potential of Moxonidine.

LPS exposure led to a marked increase in lipid peroxidation, evidenced by elevated MDA levels, and a substantial decrease in antioxidant defenses, namely GSH and SOD activity (**$p < 0.001$**). Moxonidine treatment exhibited significant antioxidant effects in a dose-dependent manner. The high-dose group showed a significant reduction in MDA levels (2.2 nmol/mg) and restoration of GSH (7.1 µmol/g) and SOD (13 U/mg) levels (**$p < 0.01$**). Dexamethasone also demonstrated strong antioxidant restoration.

Histopathological analysis

Table 4. Histopathological Scores

Group	Inflammatory Cell Infiltration	Tissue Necrosis	Vascular Congestion
Control	0	0	0
LPS	4	5	4
Moxonidine Low	3	3	2
Moxonidine High	1	1	1
Dexamethasone	1	1	1

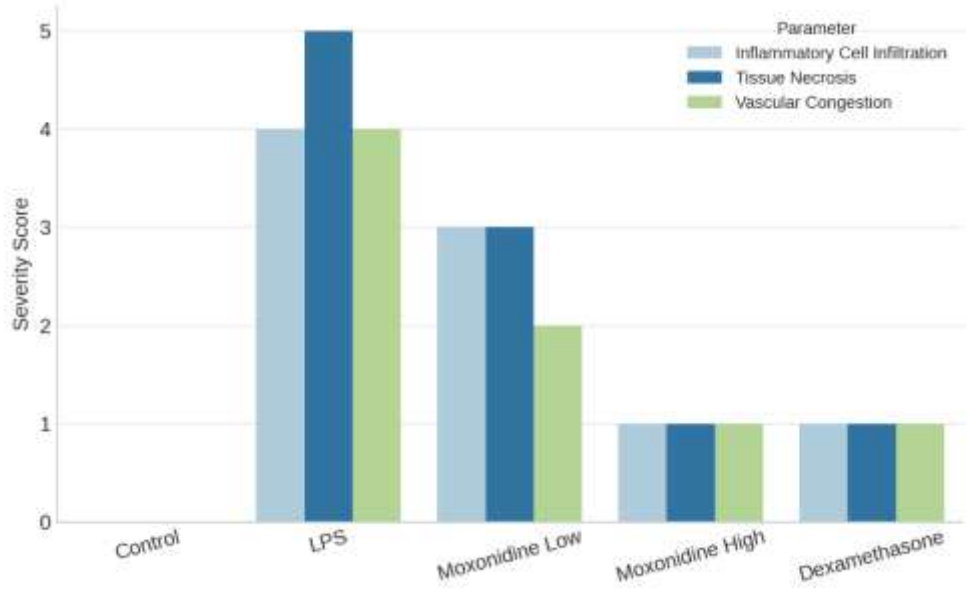

Figure 4: Histopathological scores depicting inflammation, necrosis, and vascular congestion across groups in liver and spleen tissue.

Histopathological analysis of liver and spleen tissues from the LPS group revealed severe cellular infiltration, pronounced tissue necrosis, and vascular congestion. In contrast, rats treated with Moxonidine demonstrated reduced histopathological damage, with significant improvement in all three parameters in the high-dose group (scores close to 1). Dexamethasone-treated animals showed nearly normal tissue architecture, supporting the biochemical findings. These changes confirm the protective anti-inflammatory effects of Moxonidine at the tissue level. Histological analysis of liver sections stained with Hematoxylin and Eosin (H&E) revealed distinct morphological patterns across the different experimental groups. Group A (Normal Control) displayed typical hepatic architecture, with radially arranged hepatocyte cords around the central vein, clearly visible sinusoids, and uniform hepatocytes possessing centrally located nuclei. No signs of inflammation, necrosis, or degeneration were observed, confirming the physiological normalcy of untreated liver tissue. In sharp contrast, Group B (Carbon Tetrachloride Control) exhibited profound hepatic damage.

The liver tissue showed severe cellular degeneration, extensive hepatocellular necrosis, ballooning of hepatocytes, and prominent inflammatory cell infiltration. Disrupted hepatic cords and loss of normal architecture were clearly evident, indicative of oxidative stress and hepatotoxicity induced by CCl_4 exposure. Group C (Silymarin + CCl_4) demonstrated considerable hepatoprotection. The liver parenchyma retained relatively intact architecture with mild hepatocellular swelling, minimal necrosis, and a noticeable reduction in inflammatory infiltration. These findings highlight the known antioxidant and membrane-stabilizing effects of silymarin, which ameliorated the hepatotoxic damage caused by CCl_4. Group D (Pet Ether Extract + CCl_4) showed partial hepatic restoration. Although some hepatocytes were preserved, focal necrosis, mild vacuolation, and scattered inflammatory cells were still present. The recovery was moderate, suggesting that the pet ether fraction provided a degree of cytoprotection but was less effective than silymarin. In Group E (Alcoholic Extract + CCl_4), significant hepatoprotection was evident. The hepatic cords were well aligned, hepatocytes appeared structurally intact, and the inflammatory response was minimal. This suggests that the alcoholic extract possessed strong antioxidant and hepatocellular membrane-stabilizing properties, providing a level of protection comparable to the standard. Finally, Group F (Aqueous Extract + CCl_4) displayed a moderate degree of hepatic restoration. While the overall liver architecture was improved compared to the CCl_4 group, certain areas still showed signs of hepatocellular damage, congestion, and residual inflammation. This indicates that the aqueous extract offered a protective effect, though it was slightly less potent than the alcoholic counterpart.

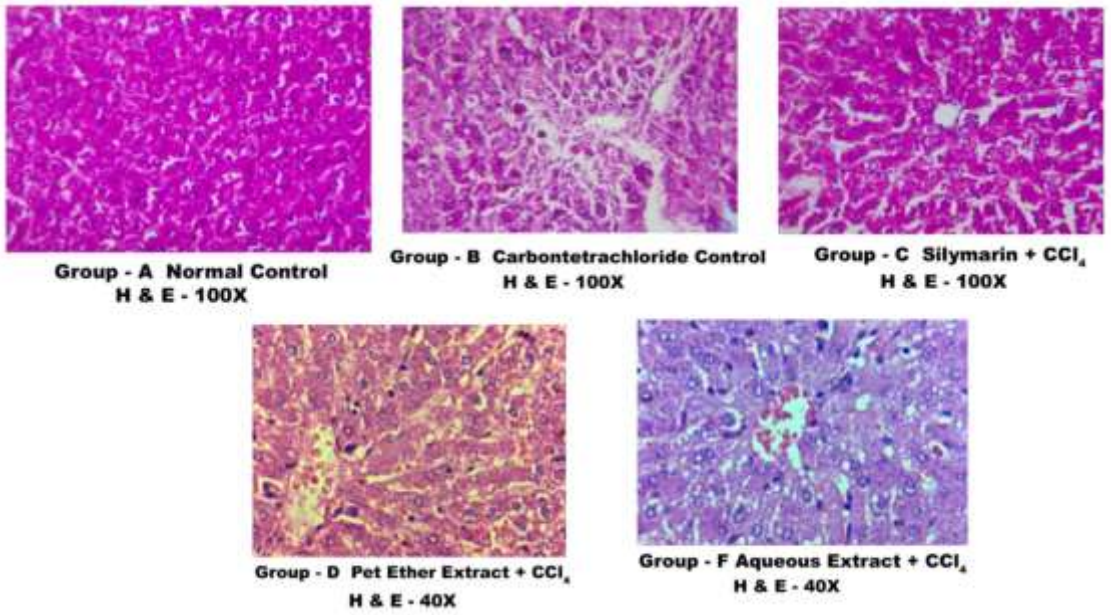

Figure 5. Histopathological Photomicrographs of Liver Tissues (H&E Staining) Showing the Effect of Various Extracts and Standard Drug on CCl_4-Induced Hepatic Damage in Rats

CONCLUSION

The present study provides compelling evidence for the immunomodulatory and anti-inflammatory potential of Moxonidine in a lipopolysaccharide-induced inflammation model. Moxonidine treatment, particularly at higher doses, significantly attenuated pro-inflammatory cytokine levels (TNF-α, IL-1β, and IL-6), restored antioxidant defenses (GSH and SOD), and reduced oxidative damage as indicated by decreased MDA levels. Western blot analysis demonstrated the downregulation of NF-κB (p65) expression and upregulation of its inhibitor IκBα, confirming that Moxonidine exerts its anti-inflammatory effect via suppression of the NF-κB signaling pathway. These biochemical findings were further supported by histopathological improvements in

hepatic and splenic architecture, marked by reduced leukocyte infiltration, necrosis, and vascular congestion. Compared to the standard anti-inflammatory agent Dexamethasone, Moxonidine exhibited comparable efficacy, particularly in high-dose groups. Collectively, these results suggest that Moxonidine, beyond its conventional use as an antihypertensive, holds therapeutic potential as an immunomodulatory agent in inflammatory conditions mediated through NF-κB signaling. Further studies, including clinical evaluations, are warranted to explore its translational applicability in human inflammatory and autoimmune disorders.

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