

Original Article



Anti-Inflammatory Effects of Ivermectin in Carrageenan-Induced Paw Edema in Rats

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Abstract

Introduction: Ivermectin has shown potential anti-inflammatory properties in some studies, although the results are conflicting. Therefore, this study investigated the anti-inflammatory effects of ivermectin in rats using the carrageenan-induced paw edema model.

Methods: Thirty male Wistar rats were randomly assigned to carrageenan, dimethyl sulfoxide, and indomethacin groups and two ivermectin-treated (at 0.2 mg/kg and 10 mg/kg doses) groups (n=6 each). Paw edema was induced by the subcutaneous injection of carrageenan, and ivermectin was intraperitoneally injected at doses of 0.2 mg/kg and 10 mg/kg. Then, paw thickness was hourly measured for 5 hours. Finally, myeloperoxidase (MPO) activity, malondialdehyde (MDA) levels, and histopathological changes in paw tissues underwent assessment.

Results: At the second hour post-carrageenan injection, ivermectin at 0.2 mg/kg ($P<0.01$) reduced inflamed paw thickness. At the third hour, ivermectin at 0.2 mg/kg ($P<0.001$) and 10 mg/kg ($P<0.01$) also decreased inflamed paw thickness. Likewise, both doses of ivermectin ($P<0.01$) contributed to a similar extent to diminishing inflammation at the fourth hour. Moreover, ivermectin at doses of 0.2 mg/kg and 10 mg/kg could reduce MPO activity ($P<0.01$) and MDA levels ($P<0.01$), respectively. Ultimately, histopathological evaluation revealed a dose-dependent decline in leukocyte infiltration and inflammation in ivermectin-treated rats.

Conclusion: Ivermectin demonstrated anti-inflammatory activity by decreasing paw edema, oxidative stress, neutrophil activity, and leukocyte infiltration, suggesting its potential as an anti-inflammatory agent.

Keywords: Inflammation, Carrageenan, Ivermectin, Edema, Oxidative stress

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Introduction

Inflammation is a phenomenon during which the body's defense mechanisms combat external irritants, typically accompanied by edema, swelling, pain, and warmth. Numerous studies have provided evidence implicating inflammation in different processes, such as aging (1), cancer (2), cardiovascular disorders, and other life-threatening conditions (3). In addition, inflammation manifests in two forms. Acute inflammation lasts from minutes to days, with histological features, including plasma protein exudation from the vessel walls of the affected area and neutrophil accumulation. Further, chronic inflammation persists for a longer period (days to years), which is histologically characterized by the presence of lymphocytes and macrophages in the tissue, along with vascular proliferation and connective tissue formation (4). Inflammatory stimuli can be microbiological, chemical, or physical. Likewise, inflammation may result from autoimmune responses (5-7).

The animal models of inflammation, while providing

valuable insights into potential damage, do not completely reflect a specific disease but rather highlight its certain aspects. The carrageenan-induced paw inflammation model is a model of inflammatory edema, specifically paw edema, which is generally controllable with nonsteroidal anti-inflammatory drugs and serves as a moderate model for pain (8).

Carrageenan is a red seaweed, and its mucopolysaccharide extract contains a complex group of polysaccharides, including lambda, kappa, and iota forms. The injectable lambda form induces acute, non-immune, and highly reproducible inflammation (9). This model further exhibits a biphasic inflammatory response. The initial phase takes place within the first two hours following carrageenan injection, and the later phase occurs after two hours and is marked by the infiltration of neutrophil, pro-inflammatory cytokines, and prolonged prostaglandin production (10, 11).

Ivermectin is used for controlling and treating parasitic infections, available in oral and topical forms since



1981. Moreover, it is extensively employed in veterinary medicine. The drug stimulates both humoral and cellular immune systems and acts as a ligand for gamma-aminobutyric acid (GABA) receptors and glutamate-mediated chloride channels (12). According to research, its anti-inflammatory effects are linked to the reduction in inflammatory cytokine production and inhibition of the nuclear factor-kappa β (NF- κ B) pathway (13). The anti-inflammatory effects of ivermectin in coronavirus disease 2019 (COVID-19) patients have been reported in recent years, with suggestions of its antiviral potential in these patients (14); nonetheless, multiple robust clinical studies have demonstrated its lack of efficacy in treating COVID-19 (15). In 2008, it was first shown that ivermectin reduced mortality by 50% in rats with severe inflammation induced by bacterial lipopolysaccharide injection (16). Additionally, two studies reported that systemic and topical ivermectin interventions in rats with allergic inflammation exhibited anti-inflammatory effects, with the systemic effect observed at a 2 mg/kg dose (13, 17). Similarly, Seyyedabadi et al found that a three-day course of ivermectin significantly decreased cerebral infarct size, oxidative stress (OS), and myeloperoxidase (MPO) activity while enhancing memory and learning abilities in rats subjected to cerebral ischemia-reperfusion. These beneficial effects are likely mediated through activate adenosine monophosphate-activated protein kinase (AMPK)-dependent pathways (18). Conversely, evidence suggests a pro-inflammatory role for ivermectin. One study showed that ivermectin injection induced inflammation, leading to neurotoxicity in fish (19), while another indicated that this drug weakens the immune system in macrophages via the NF- κ B pathway (20).

Given the conflicting evidence, it has been hypothesized that ivermectin's anti-inflammatory effects would predominate in the acute, non-immune carrageenan-induced paw inflammation model, which may be through the inhibition of NF- κ B and OS pathways, as supported by prior studies in similar acute inflammation contexts (16, 21). This is based on ivermectin's established role in modulating innate immune responses without significant pro-inflammatory activation in non-immune acute models.

Materials and Methods

Animals

This study utilized thirty male Wistar rats, aged 8–10 weeks and weighing 250 ± 30 g. The animals were maintained at a standard condition throughout the experiment. In addition, the study was conducted following approval from the Ethics Committee of Urmia University of Medical Sciences (IR.UMSU.AEC.1402.008).

Reagents

Lambda carrageenan was procured from Sigma Pharmaceutical Company, while indomethacin and ivermectin were obtained from Jalinous and Royan Darou Pharmaceutical Companies (Iran), respectively.

Study Design

The rats were randomly allocated to five groups of six:

carrageenan, dimethyl sulfoxide (DMSO; as the solvent of indomethacin), indomethacin at 10 mg/kg (positive control), and two treatment groups receiving ivermectin at doses of 0.2 mg/kg and 10 mg/kg (as low and high doses, respectively).

The DMSO group received an equivalent volume (0.1 mL) and concentration (10%) of DMSO as used to dissolve indomethacin, ensuring matched solvent exposure. This allows the attribution of effects to DMSO itself, which has mild anti-inflammatory properties at this concentration (22).

Initially, the thickness of the right paw was measured with a digital caliper (time zero). Then, 0.1 mL of carrageenan was subcutaneously injected into the right hind paw of each rat. The ivermectin treatment group, subdivided into two groups, received intraperitoneal ivermectin at 0.2 mg/kg and 10 mg/kg 20 minutes before carrageenan administration. Another group received indomethacin at 10 mg/kg. At the end of the experiment, the animals were deeply anesthetized with a 200 mg/kg pentobarbital injection and euthanized. Next, tissue samples were immediately excised and either frozen or placed in 10% formalin for subsequent procedures. It should be noted that the doses determined in this study were selected based on previous research: 0.2 mg/kg based on systemic anti-inflammatory efficacy in colitis (23) and ischemia (24) models, as well as 10 mg/kg based on high-dose efficacy in neuroinflammation and seizure models without apparent toxicity (25).

Investigators were blinded to group allocation for paw measurements and biochemical assays.

Assessing Hind Paw Thickness

Paw swelling was quantified using a digital micrometer at hourly intervals (1–5 hours) following carrageenan administration (26).

Assessment of Myeloperoxidase Activity

After excision, the tissue was homogenized in phosphate-buffered saline containing hexadecyltrimethylammonium bromide and then reacted with o-dianisidine hydrochloride (27).

Measurement of Tissue Lipid Peroxidation

Malondialdehyde (MDA), as a product of LPO, was determined by reaction with thiobarbituric acid (28).

Histopathological Analysis

For histopathological analysis, the rat paw was excised and fixed in 10% formalin, and then hematoxylin and eosin staining was used to assess histology, neutrophil infiltration, edema, inflammation, and necrosis. Additionally, histopathological evaluation was independently performed by two blinded observers: a pathologist and a trained researcher. Edema, neutrophil infiltration, tissue disruption, and overall inflammation were scored using a semi-quantitative 0–4 scale (0 = absent, 1 = mild, 2 = moderate, 3 = severe, 4 = very severe) based on established carrageenan-induced paw edema protocols (26,

28). Due to the semi-quantitative nature of the scoring and the involvement of an expert pathologist, inter-rater discrepancies were resolved by consensus rather than statistical reliability testing.

Statistical Analysis

All data are presented as the mean $\pm$ standard error of the mean. Normal distribution of data was verified using the Kolmogorov–Smirnov test. Furthermore, a one-way analysis of variance (ANOVA) was utilized to evaluate the results. When statistically significant differences were identified, group comparisons were further examined using Tukey's post hoc test.

Results

Ivermectin's Effect on Hind Paw Thickness

The thickness of the right paw of rats in different groups was measured using a digital caliper five hours post-carrageenan injection (Figure 1).

At the first hour post-carrageenan injection, paw thickness increased in all groups, indicating carrageenan-induced edema (6.79 ± 0.15), though this increase was significantly less ($P < 0.0001$) in the indomethacin group (5.83 ± 0.08). At the second hour, the carrageenan group continued to demonstrate increased paw thickness and edema (6.88 ± 0.11), while other groups exhibited reduced edema. This reduction was significant for the DMSO group (6.24 ± 0.09 ; $P < 0.01$), ivermectin at 0.2 mg/kg (6.27 ± 0.1 ; $P < 0.01$), and indomethacin (5.6 ± 0.08 ; $P < 0.0001$) compared to the carrageenan group. At the third hour, all groups indicated decreased edema, with significant

reductions for DMSO and ivermectin at 0.2 mg/kg (6.07 ± 0.07 and 6.03 ± 0.09 ; $P < 0.01$), ivermectin at 10 mg/kg (6.13 ± 0.05 ; $P < 0.05$), and indomethacin (5.49 ± 0.07 ; $P < 0.0001$) when compared with the carrageenan group. At the fourth hour, the trend of inflammation reduction continued across all groups. The ivermectin treatment groups at 0.2 mg/kg and 10 mg/kg (5.75 ± 0.08 and 5.76 ± 0.07 ; $P < 0.01$) similarly contributed to reducing inflammation in comparison to the carrageenan group (6.15 ± 0.05), maintaining this effect until the end. At the fifth hour, paw thickness was similar in the carrageenan and DMSO groups, with no significant difference between the ivermectin-treated groups and the carrageenan group. However, indomethacin substantially reduced paw edema ($P < 0.001$). Figure 2 displays a summary of the results.

Ivermectin's Effect on Myeloperoxidase Activity

Figure 3 depicts MPO activity in all groups, including treatment and control (carrageenan) groups. As observed, MPO activity decreased in all groups compared to the carrageenan group, but this decline was significant only in the ivermectin 0.2 mg/kg (68.75 ± 6.75 ; $P < 0.01$) and indomethacin (84.2 ± 5.91 ; $P < 0.05$) groups in comparison to the carrageenan group (130.2 ± 9.82). Finally, the ivermectin 0.2 mg/kg group exhibited a greater reduction in MPO activity when compared to the indomethacin group.

Ivermectin's Effect on Tissue Lipid Peroxidation

Figure 4 illustrates MDA levels in all groups, including treatment and control groups. Based on the results, MDA

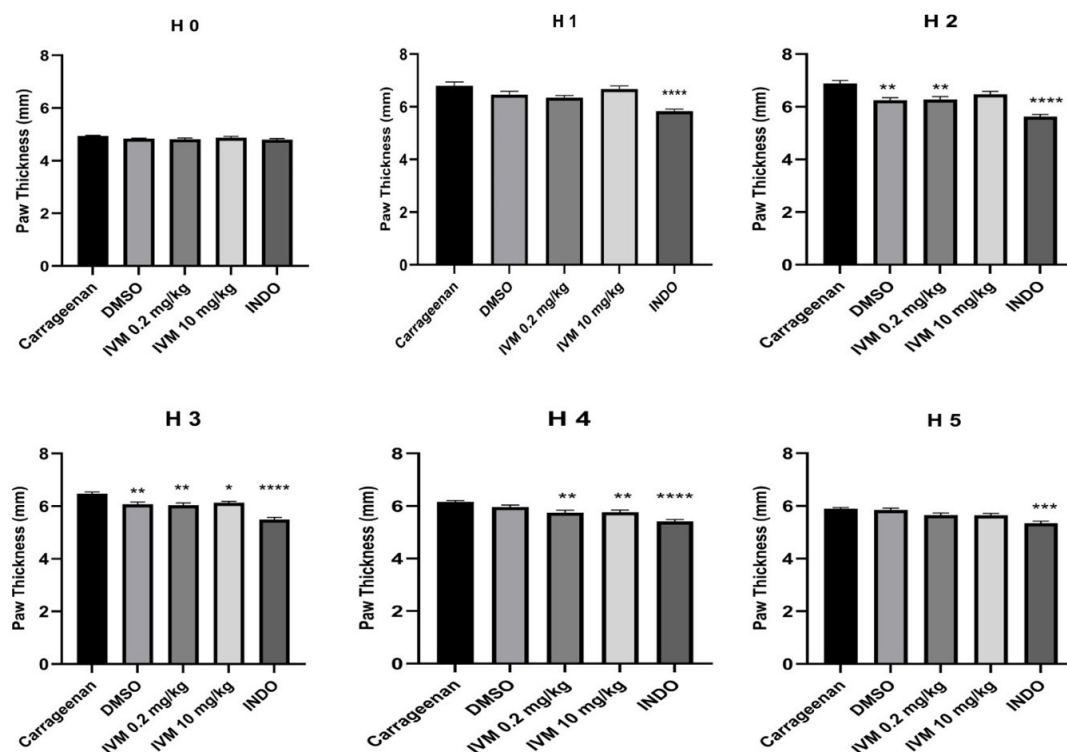


Figure 1. The Effects of Ivermectin on Paw Thickness at 0 Hour, 1 Hours, 2 Hours, 3 Hours, 4 Hours, and 5 Hours Following the Injection of Carrageenan
 Note. ANOVA: Analysis of variance; DMSO: Dimethylsulfoxide; IVM: Ivermectin; INDO: Indomethacin; SEM: Standard error of the mean. Values are provided as means $\pm$ SEM (n=6 per group). * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$, and **** $P < 0.0001$ compared to a carrageenan group (one-way ANOVA followed by Tukey's post-hoc test)

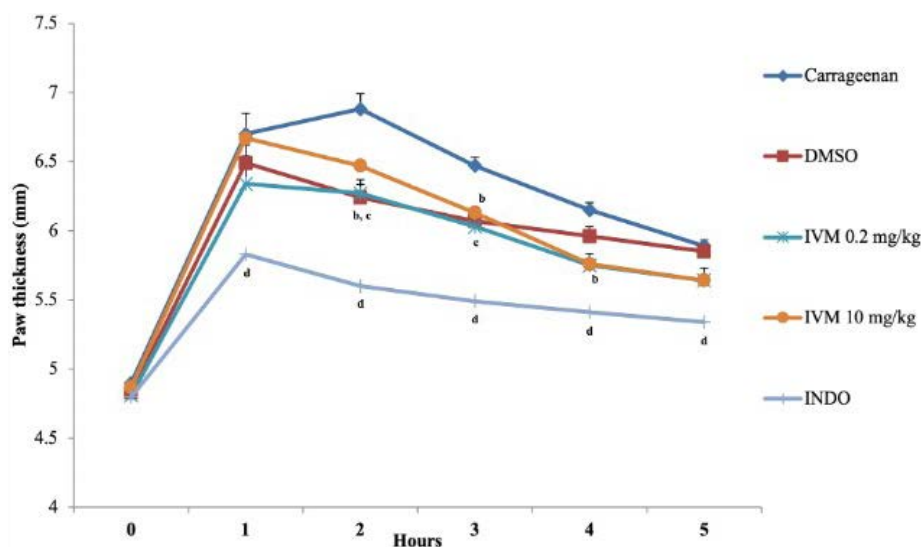


Figure 2. Effect of Ivermectin on Paw Thickness in the Carrageenan-Induced Inflamed Paw Model From Hours Zero to Five

Note. ANOVA: Analysis of variance; DMSO: Dimethylsulfoxide; IVM: Ivermectin; INDO: Indomethacin; SEM: Standard error of the mean. Values are mean $\pm$ SEM (n = 6 per group). ^a $P < 0.05$, ^b $P < 0.01$, ^c $P < 0.001$, and ^d $P < 0.0001$ in comparison with the carrageenan group (one-way ANOVA followed by Tukey's post-hoc test)

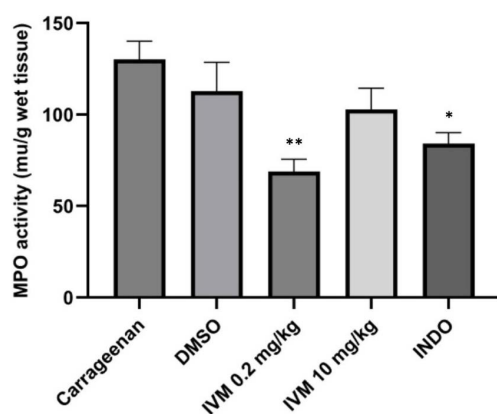


Figure 3. The Effects of Ivermectin on MPO Activity

Note. MPO: Myeloperoxidase; ANOVA: Analysis of variance; DMSO: Dimethylsulfoxide; IVM: Ivermectin; INDO: Indomethacin; SEM: Standard error of the mean. Values are presented as means $\pm$ SEM (n = 6 per group). ^{*} $P < 0.05$ and ^{**} $P < 0.01$ compared to the carrageenan group (one-way ANOVA followed by Tukey's post-hoc test)

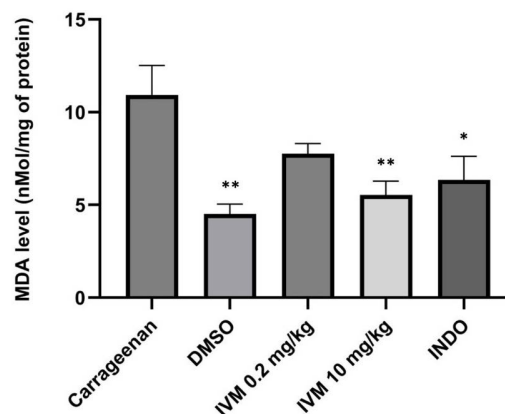


Figure 4. The Effects of Ivermectin on MDA Level

Note. ANOVA: Analysis of variance; DMSO: Dimethylsulfoxide; IVM: Ivermectin; INDO: Indomethacin; SEM: Standard error of the mean. Values are shown as means $\pm$ SEM (n = 6 per group). ^{*} $P < 0.05$ and ^{**} $P < 0.01$ compared to the carrageenan group (one-way ANOVA followed by Tukey's post-hoc test)

levels decreased in all groups compared to the carrageenan group. This reduction was remarkable in the ivermectin 10 mg/kg (5.53 ± 0.74 ; $P < 0.01$) and DMSO (4.5 ± 0.53 ; $P < 0.01$) groups and the indomethacin group (6.34 ± 1.27 ; $P < 0.05$) in comparison to the carrageenan group (10.93 ± 1.59).

Histopathological Analysis

The histological sections of the carrageenan-induced inflamed paw were examined using a light microscope and graded from 1 to 4 (low, moderate, high, and very severe damage) based on histopathological changes (e.g., edema, neutrophil accumulation, and tissue disruption) by two individuals in a double-blind manner. The carrageenan group displayed significant leukocyte accumulation. Ivermectin treatment at all doses reduced leukocyte accumulation compared to the carrageenan group ($P < 0.05$ for 0.2 mg/kg and $P < 0.001$ for 10 mg/kg). Similarly, indomethacin administration significantly decreased leukocyte accumulation ($P < 0.001$) when compared to the carrageenan group (Figures 5).

It should be noted that inter-rater agreement was high; discrepancies occurred in fewer than 10% of sections and did not exceed one grade point, with all cases resolved by consensus review. A formal Cohen's Kappa statistic was not pre-specified, representing a methodological limitation.

Discussion

The anti-inflammatory effects of ivermectin were investigated using the carrageenan-induced paw edema model in rats. The results demonstrated that ivermectin reduced paw thickness, MDA levels, and MPO activity. Moreover, histopathological findings indicated a reduction in leukocyte infiltration and edema in the inflamed area.

The significant reduction in paw edema observed in the DMSO group at certain time points (hours 2 and 3) is consistent with previous reports, indicating mild anti-inflammatory and antioxidant properties of DMSO at low concentrations. Furthermore, these effects have been attributed to its ability to scavenge free radicals, inhibit prostaglandin synthesis, and reduce neutrophil activation

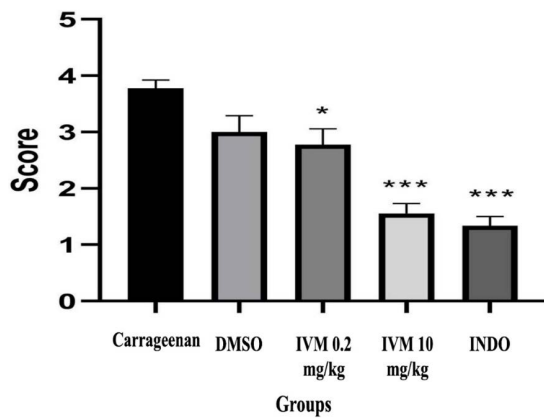


Figure 5A. The Effects of Ivermectin on Histopathological Analysis

Note. ANOVA: Analysis of variance; DMSO: Dimethylsulfoxide; IVM: Ivermectin; INDO: Indomethacin; SEM: Standard error of the mean. Histopathological changes were graded from zero to four based on objective criteria: 0=no changes; 1 (mild)=minimal neutrophil infiltration (<10% tissue involvement) and slight edema; 2 (moderate)=10–50% infiltration with moderate edema and minor disruption; 3 (severe)=>50% infiltration with marked edema, necrosis, and disruption; 4=very severe with extensive necrosis, by two individuals in a double-blind manner. Values are expressed as means±SEM (n=6 per group). * $P<0.05$ and *** $P<0.001$ when compared to the carrageenan group (one-way ANOVA followed by Tukey's post-hoc test)

(22). Although DMSO was primarily included as a vehicle control for indomethacin, its mild protective effects in this model should be acknowledged and do not confound the primary findings regarding ivermectin.

Ivermectin is widely used for controlling and treating parasitic infections, stimulating both humoral and cellular immune systems (12). As an indicator of inflammation and edema, paw thickness was significantly reduced by ivermectin in this study, demonstrating its anti-edematous effects. However, these effects were less pronounced than those of the standard treatment, indomethacin, appearing with a slight delay and diminishing earlier, suggesting that ivermectin has short-term anti-inflammatory effects. The mechanism by which ivermectin reduces edema may involve direct inhibition of NF- κ B-dependent inflammatory pathways (13, 29). Similar research has shown that ivermectin can inhibit the release of these cytokines, thereby reducing the inflammatory response (30). Our data confirmed that ivermectin primarily acts during the late phase (2–4 hours) of carrageenan-induced inflammation, which is dominated by neutrophil infiltration, prostaglandin production, and OS (10, 11). This is evidenced by peak reductions in paw thickness at hours 2–4 and sustained decreases in MPO activity, MDA levels, and histopathological damage in contrast to weaker or delayed effects in the early phase (0–2 hours). Such phasing aligns with ivermectin's potential modulation of neutrophil-related pathways rather than early histamine/serotonin-mediated vascular permeability.

The transient anti-edematous effect of ivermectin (<5 hours), as evidenced by the return of paw thickness to the carrageenan group level by 5 hours, contradicts the sustained histopathological improvements observed at the endpoint. This may be explained by the initial effect of ivermectin on vascular permeability and fluid accumulation (reflected in paw thickness), which resolves rapidly, versus

its longer-lasting inhibition of neutrophil migration and oxidative injury as reflected in MPO activity and tissue histology.

Moreover, the short therapeutic window observed in this study (2–4 hours) may be most relevant in acute, self-limiting inflammatory conditions or settings where brief anti-inflammatory coverage is necessary (e.g., post-procedural inflammation or helminth-associated tissue inflammatory pathology); however, clinical translation from this preclinical model requires substantially further investigation, including pharmacokinetic studies and disease-specific models.

As a byproduct of lipid breakdown, MDA signals heightened oxidative damage and amplifies inflammatory processes (31). Previous studies have reported the conflicting effects of ivermectin on MDA levels. For instance, Seyyedabadi et al and Cheraghi et al demonstrated reduced LPO and OS in cerebral ischemia-reperfusion and myocardial ischemia models, respectively (18, 24), while Sharmeen et al attributed ivermectin's anti-cancer effects to increased chloride influx into cancer cells, leading to reactive oxygen species production and cell death (32). Consistent with most prior research, a significant reduction in MDA levels was observed in the ivermectin-treated group in this study, indicating antioxidant effects in this model, potentially inhibiting free radical oxygen production and reducing oxidative damage in inflamed tissues.

MPO, a key enzyme in neutrophil leukocytes, plays a critical role in inflammatory responses by producing hypochlorite acid, which is a potent oxidative agent that exacerbates inflammation (33). Leukocyte accumulation is a hallmark of inflammation in animal models. Histopathological analysis in this study revealed that ivermectin significantly reduced leukocyte accumulation, suggesting it may prevent neutrophil migration and accumulation at the inflammation site, possibly linked to the reduced activity of cell adhesion molecules, such as intercellular adhesion molecule-1 and vascular cell adhesion molecule-1 (34). In this study, the sharp reduction in MPO activity is consistent with the hypothesis that ivermectin may mitigate inflammation partly by inhibiting neutrophil migration and activity in the inflamed area, though direct mechanistic evidence was not obtained in this study. Recent studies indicate that ivermectin, beyond its antiparasitic effects, possesses notable anti-inflammatory properties. A primary mechanism is the inhibition of the NF- κ B pathway, which regulates the expression of inflammatory genes (21). Additionally, ivermectin may reduce inflammatory responses by activating the peroxisome proliferator-activated receptor gamma (PPAR- γ) pathway, which is a negative regulator of inflammation (35). Fathi et al demonstrated that GABA dietary supplements can reduce OS and inflammatory responses (36), effects that could also be expected from ivermectin as a GABA agonist (12). Likewise, research has shown that ivermectin functions as a selective allosteric modulator of P2X4 receptors (37). P2X receptors have recently attracted significant interest for their roles in immune regulation and inflammation. Among them, the P2X7 receptor is recognized as a major

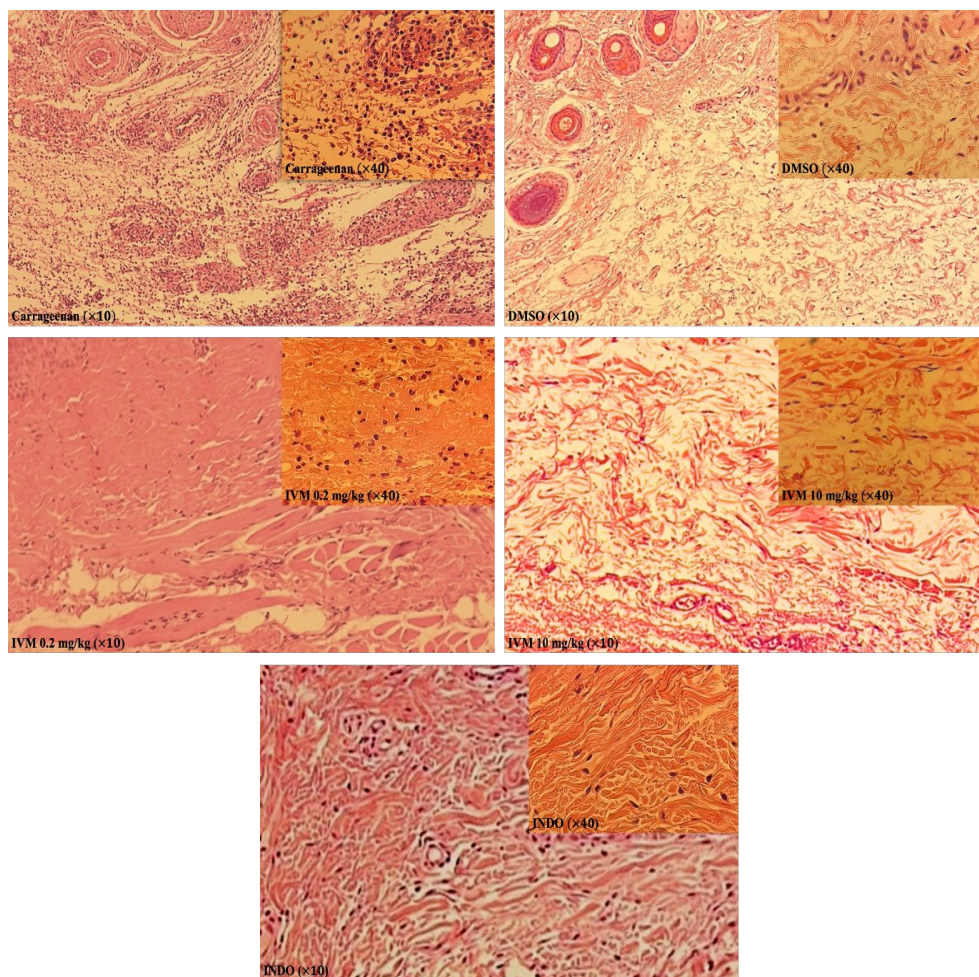


Figure 5B. Histopathological Changes of Rat Paw Tissues in Different Experimental Groups
 Note. DMSO: Dimethylsulfoxide; IVM: Ivermectin; INDO: Indomethacin

modulator of immune responses, although P2X1 and P2X4 receptors have been implicated in these processes as well. This purinergic signaling pathway is currently being investigated as a promising target for novel anti-inflammatory therapies (38).

Beyond the NF- κ B, PPAR- γ , AMPK, and P2X4 pathways central to our stated hypothesis, several additional mechanisms have been proposed in the broader ivermectin literature that may contribute to its anti-inflammatory effects and warrant future investigation in this model, though they were not directly tested in this study.

The observed dissociation in dose-response effects, where the lower dose (0.2 mg/kg) considerably reduced MPO activity but not MDA levels, while the higher dose (10 mg/kg) substantially reduced MDA but not MPO, likely reflects distinct underlying mechanisms. As a marker of neutrophil accumulation and activation, MPO activity appears more sensitive to lower, clinically relevant doses of ivermectin, potentially through the modulation of neutrophil migration or GABAergic pathways. In contrast, LPO (MDA) reflects broader OS, which may require higher concentrations to achieve significant antioxidant effects, possibly via enhanced AMPK activation or other pathways. Similar dissociations between neutrophil-related and OS markers have been reported in prior ivermectin studies in ischemia models (18, 24, 39). This biphasic-like response

highlights the multifaceted actions of ivermectin across different inflammatory and oxidative pathways. It must be emphasized that these mechanistic interpretations are speculative in the absence of direct molecular evidence from the current experiment, representing testable hypotheses to be addressed in future mechanistic studies.

The anti-inflammatory effects of ivermectin have found in specific models, such as lung inflammation (13), cerebral ischemia-reperfusion (18), chronic colitis (23), and autoimmune diseases (40). However, conflicting reports exist, with some studies suggesting the pro-inflammatory effects of ivermectin. For example, Zhang et al indicated that ivermectin may induce inflammation and neurotoxicity in fish (19), while another study reported weakened immune responses in macrophages via the NF- κ B pathway (20). These inconsistencies underscore the need for further investigation into the general anti-inflammatory potential of ivermectin.

Unlike these studies, the present research is the first to evaluate the broad-spectrum anti-inflammatory effects of ivermectin using the carrageenan-induced paw edema model in rats. This model, characterized by acute, non-immune inflammation with biphasic mediator release and neutrophil infiltration (9, 10), allowed us to assess ivermectin's efficacy in a generalized inflammatory context. Our findings not only align with previous

reports of ivermectin's anti-inflammatory properties but also provide novel evidence of its effectiveness in mitigating acute inflammation in a standardized model. Nonetheless, this study had several limitations. The sample size was relatively small, and no cytokine measurements or mechanistic assays were performed. Consequently, the proposed mechanisms, including NF- κ B inhibition, PPAR- γ activation, GABAergic modulation, and P2X4 receptor involvement, remain speculative due to the absence of direct molecular evaluations such as protein quantification or receptor agonist/antagonist studies.

Conclusion

In general, our results confirmed that the administration of ivermectin in carrageenan-induced paw edema model in rats reduced paw thickness, MDA levels, and MPO activity while inhibiting leukocyte accumulation and edema in the inflamed area, suggesting ivermectin as a potential anti-inflammatory agent. The findings of this study further revealed that ivermectin is a potential anti-inflammatory agent for acute and short-term inflammatory conditions, with a therapeutic window of 2–4 hours.

Overall, these results should be interpreted as preclinical and exploratory. Finally, further studies incorporating larger sample sizes, extended time-course analyses, and direct molecular assessments of inflammatory signaling pathways are required to clarify the therapeutic relevance and mechanistic basis of ivermectin's anti-inflammatory actions.

Authors' Contribution

Conceptualization: Hamid Soraya

Data Curation: Erfan Norouzifard, Farhang Mehrnia

Formal Analysis: Hamid Soraya

Project Administration: Erfan Norouzifard, Farhang Mehrnia

Writing–Original Draft: Erfan Norouzifard, Farhang Mehrnia

Writing–Review & Editing: Hamid Soraya

Competing Interests

The authors have no relevant financial or non-financial interests to disclose.

Ethical Approval

This protocol was approved by the Ethics Committee of Urmia University of Medical Sciences (ethical No. IR.UMSU.AEC.1402.008).

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