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School of Pharmacy & Pharmaceutical Sciences
Isfahan University of Medical Sciences

Original Article

Evaluation of the anti-ulcerative effects of lacosamide in a rat model of acetic acid-induced colitis

Mohsen Minaiyan[1,*] and Niloufar Mottaghi[2]

[1]*Department of Pharmacology and Toxicology, School of Pharmacy and Pharmaceutical Sciences Research Centre, Isfahan University of Medical Sciences, Isfahan, Iran.*
[2]*School of Pharmacy and Pharmaceutical Sciences, Isfahan University of Medical Sciences, Isfahan, Iran.*

Abstract

Background and purpose: Colitis is a type of inflammatory bowel disease (IBD) with an unknown and complex etiology. Lacosamide is a known antiepileptic drug for which anti-inflammatory effects have been reported. This study investigates the ameliorative effects of lacosamide on acetic acid-induced colitis in rats.
Experimental approach: Male Wistar rats were divided into different interventional groups, including normal and control colitis groups (normal saline, 5 mL/kg), two colitis groups (dexamethasone, 1 mg/kg) and mesalazine (100 mg/kg), four colitis groups received oral lacosamide (10, 20, or 40 mg/kg), or lacosamide enema (10 mg/kg). The treatments were conducted for five days following disease induction by acetic acid (3.5%, 2 mL). Colitis indices in tissue samples, as well as biochemical factors such as myeloperoxidase (MPO), malondialdehyde (MDA), and ferric reducing antioxidant power (FRAP), were assessed.
Findings/Results: The trend of body weight drop was stopped by using lacosamide. Colon weight as well as ulcer index significantly decreased in the groups that received lacosamide (10-40 mg/kg *via* oral or rectal) compared to the control group. Histological findings showed that lacosamide (10 and 20 mg/kg *via* oral and enema) reduced inflammation markers and tissue damage while causing tissue regeneration. Levels of MDA and MPO significantly decreased while FRAP increased in lacosamide (10 and 20 mg/kg) groups, both oral and *via* enema.
Conclusion and implications: Findings highlight the potential of lacosamide as an effective treatment in reducing inflammation and promoting ulcer healing. However, further studies are needed to elucidate the precise mechanisms of lacosamide's anti-inflammatory effects and to confirm these results in human disease.

Keywords: Acetic acid; Inflammation; Lacosamide; Rats; Ulcerative colitis.

INTRODUCTION

Inflammatory bowel disease (IBD) is a common gastrointestinal illness that includes two main conditions: ulcerative colitis and Crohn's disease. Ulcerative colitis is a chronic, recurrent disease with no specific known cause, characterized by symptoms such as weight loss, bloody diarrhea, passage of stool with mucus, and abdominal pain (1). The unknown etiology of ulcerative colitis and the limitations of existing therapies, including insufficient efficiency, adverse effects, and patient dissatisfaction, have driven the research for new therapeutic approaches (2). Current medications, such as 5-aminosalicylic acid derivatives, corticosteroids, immunosuppressants, and biological agents like infliximab, have shown varying degrees of success but are often limited by significant side effects (3). Also, long-term IBD can greatly impact mental well-being. Research indicates that those with IBD have a higher prevalence of psychological issues compared to the general population, while these issues intensify during flare-up periods. Depression, for instance, is notably frequent during remission, affecting around 30% of patients, while during relapses, about 55% face it. Additionally, some psychiatric disorders, such as depression and anxiety, can act as risk factors for relapse (4-6).

*Corresponding author: M. Minaiyan
Tel: +98-3137927088, Fax: +98-313-6680011
Email: minaiyan@pharm.mui.ac.ir

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Antiepileptic drugs exhibit anti-inflammatory properties beyond their primary role in seizure control, while some of them have the capacity to be added to antidepressant or anti-anxiety medications. Sodium valproate, levetiracetam, pregabalin, gabapentin, and topiramate have shown efficacy in reducing inflammatory markers like tumor necrosis factor alpha (TNF-α), interleukin (IL)-6, IL-1β, and myeloperoxidase (MPO), while enhancing antioxidant activity in experimental colitis models (7-11). For instance, sodium valproate significantly reduces oxidative stress and improves colonic tissue integrity in acetic acid-induced colitis (7). Topiramate also demonstrates protective effects in tri-nitrobenzene sulfonic acid (TNBS)-induced colitis, reducing macroscopic and microscopic damage. These findings support exploring lacosamide as a potential anti-inflammatory agent for managing IBD (8).

Lacosamide, a third-generation antiepileptic drug, was first approved in 2008 for adjunctive treatment of partial seizures and later as a monotherapy (12). Its unique mechanism of action includes selective inhibition of depolarized sodium channels and binding to collapsin response mediator protein-2 (CRMP-2), which are involved in neuronal growth and differentiation (13). Beyond its anticonvulsant properties, lacosamide has shown potential neuroprotective and anti-inflammatory effects in preclinical studies (14). For instance, studies have demonstrated that lacosamide can enhance antioxidant enzyme activity and reduce oxidative stress in models of transient cerebral ischemia (15). Additionally, it has been effective in alleviating chronic pain in animal models of osteoarthritis and inflammation-based pain (16).

According to the aforementioned topics, this study was conducted to investigate the anti-colitis effects of lacosamide in a laboratory model of acute colitis caused by acetic acid in rats, with the potential for future clinical applications, if promising results are obtained.

MATERIAL AND METHODS

Materials and reagents

This study utilized a variety of high-grade reagents and materials. Lacosamide was sourced from Pars Darou Co., Iran. Dexamethasone and mesalazine were prepared as pure powders from Daru-Pakhsh Co., Iran. Biochemical reagents such as orthodianisidine dihydrochloride (ODZ) and hexadecyltrimethylammonium bromide (HTAB) were procured from Sigma-Aldrich Co., Germany, and applied for MPO activity assessment. Biochemical analyses were supported by malondialdehyde (MDA) assay kits and antioxidant capacity assay kit, based on the ferric reducing antioxidant power (FRAP) method, both manufactured by Navand Salamat Co, Iran.

Animals

Male Wistar rats (200 ± 20 g, 3-4 months old) were prepared from the nest of animals belonging to Isfahan School of Pharmacy, Isfahan University of Medical Sciences, Isfahan, Iran. Eight separate groups, each consisting of six animals, were chosen. The rats were housed at a temperature of about 21-23 °C, under a 12/12-h light/dark cycle and ambient humidity of 30-50%. Throughout the study, the animals were fed standard pellet-form feed concentrates. All procedures involving the animals were conducted in accordance with local guidelines for the care and handling of laboratory animals at Isfahan University of Medical Sciences. The study was approved by the Ethics Committee of Isfahan University of Medical Sciences, Isfahan, Iran (Ethic code: IR.MUI.AEC.1402.038).

Grouping and study design

The normal group received normal saline (5 mL/kg) orally (p.o.), once daily, 2 h before rectal administration of normal saline, and continued for 4 consecutive days, making the total duration of treatment 5 days. The normal group received normal saline, the colitis control group received normal saline (5 mL/kg), while induction of colitis was accomplished by acetic acid (3.5%, 2 mL). Groups 3-5 received lacosamide at three doses (10, 20, and 40 mg/kg, p.o.), 2 h before colitis induction. The lacosamide enema group (group 6) was treated with lacosamide (10 mg/kg, rectally) in rats with colitis. Groups 7 and 8 were treated with dexamethasone intraperitoneally (1 mg/kg, i.p.) or mesalazine (100 mg/kg, p.o.), respectively (17). All interventional groups were similarly treated to the normal group. The doses of

lacosamide were selected based on previous studies on its anti-inflammatory and/or anti-nociceptive effects (16,18).

Disease induction

Animals were kept in groups of 3, in polycarbonate cages with free access to water, but were fasted for one day (24 h) before colitis induction. Acute colitis was triggered using acetic acid (3.5%, 2 mL), following the method outlined in previous studies in our laboratory (19). The rats were anesthetized using desflurane (5%), an inhalation anesthetic, administered in a special chamber to ensure ethical handling during the procedures. Once the animal was sedated, an 8 cm tube was gently inserted into the colon through the anus. To minimize leakage of the solution, the rats were kept in a head-down position for 30 s. The rats' body weights were recorded at both the beginning and the end of the experiment to assess changes in body weight.

Tissue collection

Twenty-four hours after the last treatment, the animals were sacrificed in a CO_2-saturated chamber, and 8 cm of the distal colon was excised from 3 cm from the anus. The colons were subjected to macroscopic assessments as follows, and thereafter split into four sections for histopathological assessment, measurement of MPO activity, as well as MDA and FRAP parameters. The tissue segments designated for histopathological evaluation were preserved in10% buffered formalin, while those intended for assessing biochemical parameters were stored at -20 °C in a freezer (20).

Colon injury assessment macroscopically

First, clear photos of the inner surface of the colon tissue were taken with a digital camera, and the analysis of the lesion surface was performed using Fiji-win 32 software. To macroscopically evaluate the severity of colitis, an independent observer used a four-point scoring system. The following grades were used to determine the macroscopic score: 0 for non-visible changes,1 for mild erythema and mucosal edema or erosion, 2 for moderate edema, bleeding, or erosion, and 3 for severe edema, ulcers, or necrosis. Ulcer index was calculated according to the method previously described by the authors (19,20).

Ulcer index = Ulcer area (cm^2) + macroscopic score (0-3)

Colon injury assessment microscopically

The colon sections preserved in formalin buffered solution (pH 7) were dehydrated, embedded in paraffin, and then sliced into 5-µm-thick sections. The paraffin was removed using xylene, and the sections were stained following the hematoxylin and eosin (H&E) staining protocol. The stained sections were then evaluated according to a modified version of the scoring method described previously (20). The total colitis index was determined by adding 4 parameters, including scores for inflammation severity (0-3), extent of inflammation (0-3), infiltration of leukocytes (0-3), and crypt damage (0-4) as outlined by Dalayeli *et al*. (21).

Evaluation of MPO activity

Frozen tissue samples were first thawed and homogenized in 10 mM potassium phosphate buffer (PBS, pH 7) containing HTAB (0.5%) using a homogenizer. The homogenate was centrifuged at 20,000 *g* for 10 min at 4 °C. The supernatant was then collected, and a reaction mixture containing H_2O_2 (0.1 mM) and ODZ (1.6 mM) was added. The absorbance of the resulting solution was measured at 450 nm to determine MPO activity (21).

Determination of MDA content

MDA, a lipid peroxidation marker, was determined by incorporating 1 mL of 1.15% w/v KCl into 10 mg of isolated colon tissue. The homogenized mixture underwent centrifugation at 7500 rpm for 10 min, and its absorbance was measured at 532 nm. The studies were conducted utilizing the analytical kit (Navand-Salamat, Iran) in accordance with the company's instructions (21).

Antioxidant power assay within the colon tissue

For this purpose, the ferric reducing antioxidant power (FRAP) assay was employed, following a previously validated method. This method evaluates antioxidant capacity by measuring the reduction of ferric ions (Fe^{3+}) to ferrous ions (Fe^{2+}) in the presence

of antioxidants within the sample. In this study, the FRAP assay kit (Navand-Salamat, Naxifer™, Iran) was used to ensure accuracy and reproducibility. $FeSO_4$ solutions at concentrations ranging from 100 to 1,000 µM were prepared as the standard curve for the assay. Colon samples and standards were incubated with the FRAP reagent for 30 min at 37 °C. The absorbance of each reaction was then measured spectrophotometrically at 593 nm. The power of antioxidant capacity of each colon sample was then calculated by interpolating its absorbance value on the standard curve (22).

Statistical analysis

The data are presented as mean ± SEM or SD and were analyzed using one-way ANOVA followed by Tukey's post hoc test. Paired Student's t-test was used to compare weight changes. Scoring data, which was displayed as the median (range), was analyzed by the Mann-Whitney U-test. All statistical analyses were performed using Graphpad Prism software (Version 8 GraphPad Software, USA). *P* values < 0.05 were considered statistically different.

RESULTS

Animals' body weight changes

A significant weight reduction was observed in the control group following disease induction. Intervention by lacosamide at different doses, both oral and rectal, caused the cessation of weight loss, although only the oral dose of 10 mg could significantly increase the body weight of the animal. Dexamethasone administration also resulted in weight loss in a significant manner, while mesalazine administration led to weight gain; however, this effect was not statistically significant (Table 1).

Colon weight changes

Disease induction significantly increased the colon weight in the control group compared to the normal group. Intervention with lacosamide at all applied doses caused a significant decrease in colon weight compared to the control group. Colon weight in the mesalazine and dexamethasone groups was significantly reduced compared to the control group. There was no statistically significant difference in colon weight reduction activity among lacosamide-treated groups (Fig. 1).

Changes in ulcer index

The effects of various treatments on the ulcer index in acetic acid-induced colitis in rats are depicted in Fig. 2. The induction of colitis led to a significant increase in the ulcer index (ulcer score plus ulcer area) in the control versus the normal group. All treatment groups, including dexamethasone, mesalazine, and different doses of lacosamide (10, 20, and 40 mg/kg p.o., and 10 mg/kg *via* enema), demonstrated a marked reduction in this parameter compared to the control group. Various degrees of edema, thickness, erythema, erosion, and even necrosis were evident in treated colitis tissues (Fig. 3).

Table 1. The rat's body weight changes before and after the treatment. Data are presented as mean ± SD.

Group/dose (mg/kg)	Body weight			*P* value*
	Before treatment (g)	After treatment (g)	Change (%)	
Normal	194.3 ± 5.8	202.0 ± 6.8	0.03	< 0.05
Control	196.8 ± 4.7	171.3 ± 4.7	-12.9	< 0.001
Lacosamide 10	199.1 ± 6.9	210.8 ± 7.6	5.6	< 0.05
Lacosamide 20	196.6 ± 5.7	202.3± 7.6	2.8	> 0.05
Lacosamide 40	199.7 ± 6.1	195.3 ± 5.1	-2.2	> 0.05
Lacosamide enema 10	201.8 ± 6.6	206.7 ± 8.2	2.4	> 0.05
Mesalazine 100	195.8 ± 5.7	200.8 ± 5.7	2.5	> 0.05
Dexamethasone 1	194.8 ± 4.8	187.8 ± 5.5	-3.72	< 0.05

**P* values < 0.05 indicate significant differences in each group before and after treatment using the Paired Student's t-test

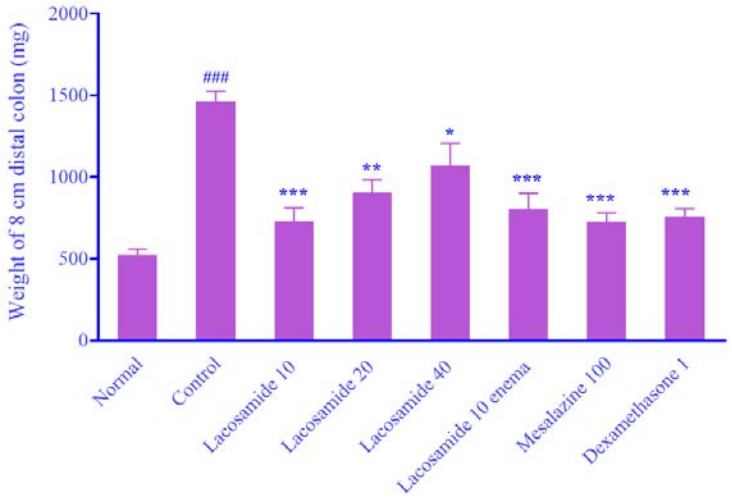

Fig. 1. Effects of lacosamide on the colon weight of rats. Data are presented as mean ± SEM $^{###}P < 0.001$ indicates significant differences in comparison with the normal group, $*P < 0.05$, $**P < 0.01$, and $***P < 0.001$ versus the control group.

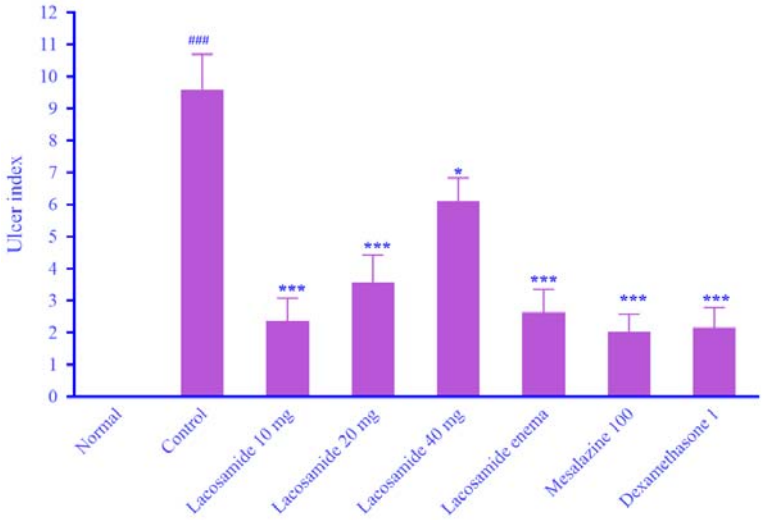

Fig. 2. Effects of lacosamide on ulcer index of colitis in rats. Data are presented as mean ± SEM. $^{###}P < 0.001$ indicates significant differences in comparison with the normal group, $*P < 0.05$, $**P < 0.01$, and $***P < 0.001$ versus the control group.

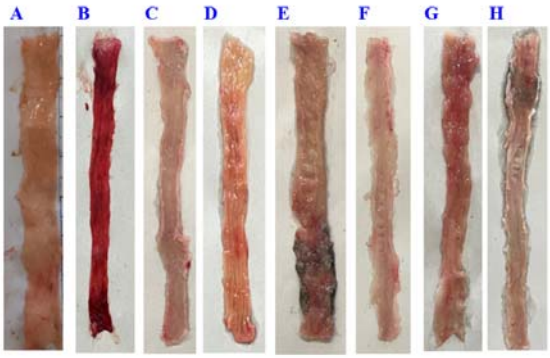

Fig. 3. Macroscopic presentation of colitis in rats. (A) Normal group, (B) control colitis group (edema, erythema, thickening, erosion, ulcer and even tissue necrosis are evident), (C-F) lacosamide-treated group (10, 20, 40 mg/kg and 10 mg/kg *via* enema, respectively), (G) mesalazine-treated group (100 mg/kg), (H) dexamethasone-treated group (1 mg/kg).

Changes in histopathologic features

In the normal group, there was no sign of tissue damage, so the inflammation severity, extent of inflammation, leukocyte infiltration, and crypt damage scores were all recorded as zero. In contrast, the control group, serving as the reference for disease induction, exhibited the most severe pathological alterations, including the highest levels of edema, inflammation, and crypt loss, and the lowest tissue regeneration scores (Table 2 and Fig. 4). The lacosamide 10 mg/kg group, both orally and *via* enema, and at the dose of 20 mg/kg demonstrated remarkable improvements across all histopathologic parameters. The lacosamide 40 mg/kg group caused a slight improvement in histological parameters, although it was not significant overall ($P > 0.05$). Dexamethasone and mesalazine accelerated the regeneration of damaged colon tissue and, as expected, significantly improved histopathological lesions (Table 2 and Fig. 4).

Effect of lacosamide on MDA content

The amount of MDA in the control group significantly increased due to tissue damage caused by acetic acid in comparison with the normal group. MDA level as an oxidative stress marker was significantly reduced compared to the control group in all lacosamide treatment groups except for the group that received 40 mg/kg lacosamide p.o. ($P > 0.05$). The groups treated with reference drugs (especially mesalazine) showed the highest MDA drop (Fig. 5).

Table 2. Effects of lacosamide on pathological parameters of acetic acid-induced colitis in rats. Data are expressed as median (range).

Groups/dose (mg/kg)	Inflammation Severity (0-3)	Inflammation Extent (0-3)	Leukocyte Infiltration (0-3)	Crypt damage (0-4)	Total colitis index (0-13)
Normal	0.0 (0-0)	0.0 (0-0)	0.0 (0-0)	0.0 (0-0)	0.0 (0-0)
Control	3.0 (3-3)$^{###}$	3.0 (3-3)$^{###}$	3.0 (2-3)$^{###}$	3.5 (3-4)$^{###}$	12.5 (11-13)$^{###}$
Lacosamide 10	1.0 (1-2)**	1.0 (0-2)**	1.5 (1-2)**	1.5 (0-1)***	5.0 (2-6)**
Lacosamide 20	1.5 (1-2)**	1.0 (1-2)***	1.5 (1-3)*	2.5 (1-3)	6.5 (4-10)*
Lacosamide 40	1.5 (2-3)	2.5 (1-3)	1.5 (1-3)*	2.0 (1-4)	7.5 (5-13)
Lacosamide enema 10	1.0 (0-2)***	1.0 (1-2)***	1.0 (0-2)***	1.0 (0-2)***	4.0 (1-8)***
Mesalazine 100	1.0 (1-2)***	1.0 (0-2)***	0.5 (0-2)***	1.5 (1-2)***	4.0 (2-8)***
Dexamethasone 1	0.5 (0-1)***	0.5 (0-1)***	0.5 (0-2)***	1.0 (1-2)***	2.5 (1-6)***

$^{###}P < 0.001$ indicates significant differences in comparison with the normal group, $*P < 0.05$, $**P < 0.01$, and $***P < 0.001$ versus the control group.

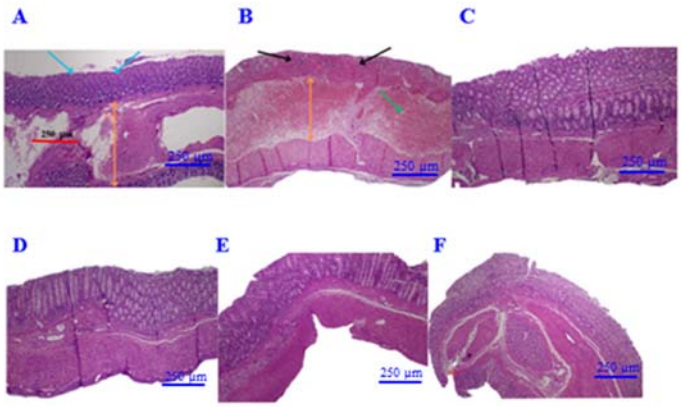

Fig. 4. Histological presentation of colitis in rats stained by hematoxylin and eosin. (A) Normal colon (mucosal, submucosa and crypts (blue arrow) and intact, (B) control colitis colon (mucosal layer, and crypts have destroyed while inflammation of sub-mucosal layer (black arrow) and leucocyte infiltration (green arrow) are evident, orange arrow shows mucosal and sub-mucosal thickness, (C) lacosamide-treated group (10 mg/kg), (D) lacosamide-treated group (10 mg/kg *via* enema), (E) mesalazine-treated group (100 mg/kg), (F) dexamethasone-treated group (1 mg/kg). Magnification: × 40.

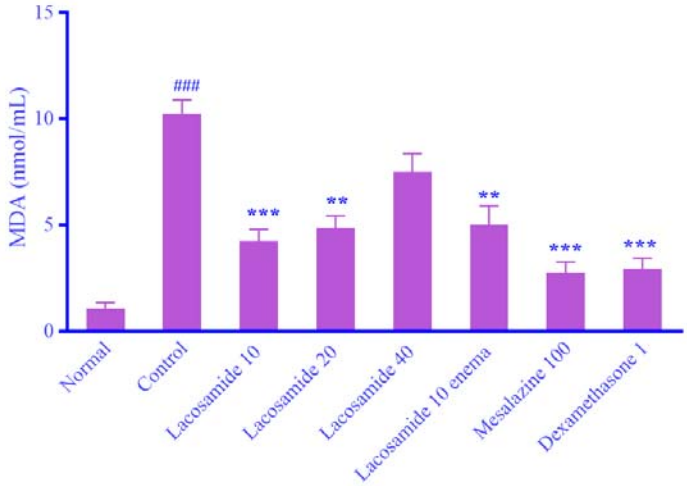

Fig. 5. Effects of lacosamide on MDA levels of colitis tissue in rats. Data are presented as mean ± SEM. $^{###}P < 0.001$ indicates significant differences in comparison with the normal group, $^{**}P < 0.01$, and $^{***}P < 0.001$ versus the control group.

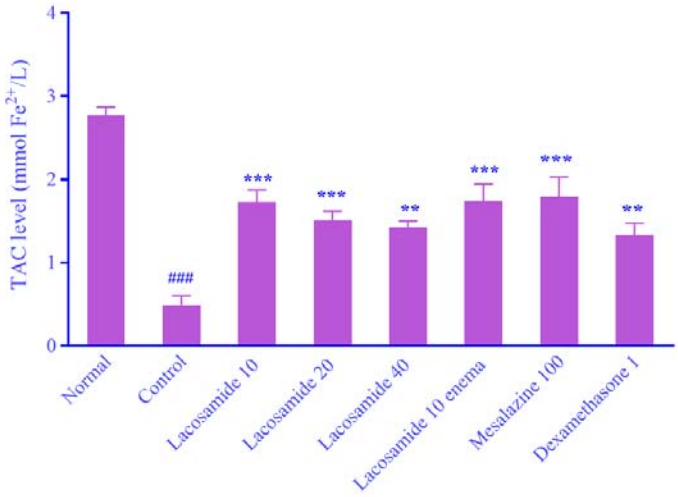

Fig. 6. Effects of lacosamide on TAC (total antioxidant capacity) levels of colitis tissue in rats. Data are presented as mean ± SEM. $^{###}P < 0.001$ indicates significant differences in comparison with the normal group, $^{**}P < 0.01$, and $^{***}P < 0.001$ versus the control group.

Effect of lacosamide on MDA content

The amount of MDA in the control group significantly increased due to tissue damage caused by acetic acid in comparison with the normal group. MDA level as an oxidative stress marker was significantly reduced compared to the control group in all lacosamide treatment groups except for the group that received 40 mg/kg lacosamide p.o. ($P > 0.05$). The groups treated with reference drugs (especially mesalazine) showed the highest MDA drop (Fig. 5).

Effect of lacosamide on FRAP level

As shown in Fig. 6, the normal group exhibited the highest antioxidant capacity (FRAP) levels. The colitis control group demonstrated a significantly lower antioxidant capacity compared to the normal group. The lacosamide groups at various doses (10-40 mg/kg p.o. and 10 mg/kg enema), as well as the mesalazine and dexamethasone groups, showed higher antioxidant capacity levels compared to the control group in a significant manner (Fig. 6).

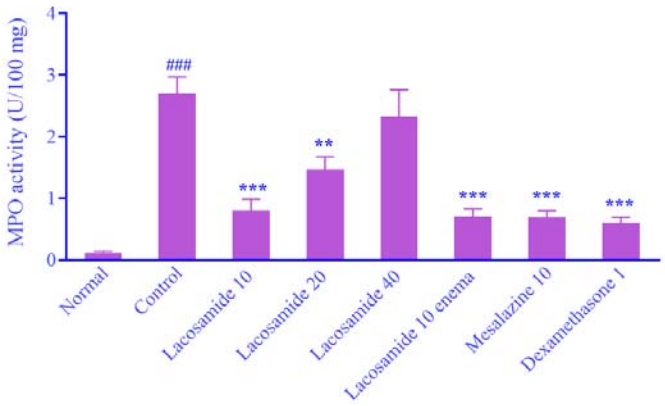

Fig. 7. Effects of lacosamide on MPO activity of colitis tissue in rats. Data are presented as mean ± SEM. $^{###}P < 0.001$ indicates significant differences in comparison with the normal group, $^{**}P < 0.01$ and $^{***}P < 0.001$ versus the control group. MPO, Myeloperoxidase.

Effect of lacosamide on MPO activity

The normal group displayed the lowest MPO levels because no tissue damage was developed (Fig. 7). The colitis control group clearly showed the highest MPO amounts versus the normal group. Lacosamide-treated groups at two doses (10 and 20 mg/kg, p.o. and *via* rectum 10 mg/kg) caused a significant decline in MPO versus the control group. Similarly, the mesalazine and especially dexamethasone exhibited a significant dip in MPO levels relative to the control group (Fig. 7).

DISCUSSION

This study explored the anti-inflammatory and anti-ulcerative effects of lacosamide on acetic acid-induced colitis in rats. Observations in the control group, such as weight changes, elevated MPO and MDA levels, and decreased antioxidant capacity, confirmed the successful induction of experimental colitis (23). Furthermore, significant weight loss in the control group aligns with systemic symptoms observed in human colitis, often due to anorexia, malnutrition, and malabsorption (24). This study demonstrated that lacosamide alleviated all manifestations and parameters of colitis at least in two applied smaller doses (10 and 20 mg/kg p.o. and 10 mg/kg enema). Indeed, histological evaluation revealed remarkable reductions in edema, congestion, inflammation extent, and severity, alongside improved tissue regeneration in groups treated with lacosamide through oral or rectal administration. The success of the lacosamide in the form of an enema showed that the topical form of this drug also had adequate tissue availability and effectiveness in this investigation (25). Pharmacokinetic investigations with varying doses *via* the enema route could provide a more comprehensive understanding of its bioavailability and therapeutic potential. On the other hand, the dose of 40 mg/kg of lacosamide was more effective on the macroscopic parameters of colitis; however, it couldn't significantly improve the pathological signs of the colon tissue. Besides, the findings indicated that while all doses of lacosamide demonstrated ulcer-healing effects in the treatment of colitis, the increase in dosage did not yield markedly greater benefits or additional significant advantages compared to lower doses. It means that probably an inverse relationship between the dose of lacosamide and therapeutic effectiveness might be supposed, but greater doses should be tried. Lacosamide in higher doses may cause some complications (*e.g.*, diarrhea, spasm, and anorexia) in the digestive system, which counteract its beneficial effects. These complications have previously been reported in human subjects as lacosamide's common adverse effects (26,27). In this research, dexamethasone and mesalazine, as commonly used medications for colitis, had beneficial effects on the acetic acid model of colitis. Both drugs significantly improved all aspects of colon tissue damage; however, dexamethasone did not stop disease-induced

weight loss. This effect, which has already been reported in similar studies, can be due to the catabolic properties of this potent corticosteroid and the breakdown of muscle tissue (28).

In this research, lacosamide was initially selected based on evidence highlighting the potential benefits of anticonvulsants in treating ulcerative colitis, likely due to their anti-inflammatory, neuroprotective, and tissue-preserving properties (29). In this regard, we can refer to the studies that have been done on topiramate, pregabalin, gabapentin, levetiracetam, and sodium valproate, which have had promising effects on laboratory colitis models (7-11). All of these drugs were able to improve the tissue damage caused by colitis and reduce the severity of inflammation and ulceration; meanwhile, the level of oxidative stress and inflammatory cytokines in the target tissue dramatically decreased. In this regard, a study conducted by Varzandeh *et al*. demonstrated that topiramate (100 mg/kg/day) not only reduces MDA levels but also exerts significant protective effects against acetic acid-induced colitis by inhibiting lipid peroxidation and enhancing the activity of antioxidant enzymes like catalase, superoxide dismutase, and glutathione peroxidase (30). These findings are particularly aligned with the current study, which indicates a reduction in MDA levels and an improvement in total antioxidant capacity (FRAP) in the groups treated with lacosamide. In another related study, Motavallian *et al.* investigated the anti-inflammatory effects of pregabalin on colitis caused by acetic acid (11). Their research demonstrated that pregabalin, at doses of 15-100 mg/kg/day, significantly reduced macroscopic and microscopic signs of colonic damage, including ulceration, necrosis, and overall inflammation. This was accompanied by remarkable decreases in MPO activity and pro-inflammatory cytokines such as TNF-α, IL-6, and IL-1β. They suggested that pregabalin, traditionally used for neuropathic pain, might have a new role in reducing inflammation in colitis, potentially expanding its therapeutic applications. Najafi *et al*. provided further insight into the potential of anticonvulsants by assessing the effects of sodium valproate (50-300 mg/kg, i.p.) on a similar (acetic acid-induced) method of colitis induction (7). Their findings indicated that sodium valproate at a greater dose (300 mg/kg) significantly improved several parameters of colitis, including weight loss, ulcer area, and hematocrit levels, while decreasing levels of inflammatory markers like MPO and cytokines (IL-1β, IL-6, and TNF-α). Indeed, MPO activity reflecting leucocyte infiltration, especially neutrophils in damaged tissue which is directly related to inflammation extent and severity. The results of the current study indicated that this marker was reduced across nearly all lacosamide-treated groups (with the exception of 40 mg/kg/day) relative to the control, indicating diminished inflammation and extravasation in the damaged tissue (31).

Furthermore, lacosamide has shown significant anti-inflammatory effects in various inflammation and pain evaluation models. For instance, Agarwal *et al*. demonstrated that lacosamide could alleviate kynurenine pathway-related seizure comorbid with neuronal inflammation and depression in C57BL/6 mice (32). Lacosamide showed promising effects on neuro-inflammation-mediated seizure by reducing hippocampal kynurenine levels as well as inflammatory cytokines and oxidative markers. In another study by Corvace *et al*., lacosamide inhibited microglial activation in astrocyte-microglia cell co-cultures under inflammatory conditions (33). They concluded that the anti-inflammatory features of lacosamide, through inhibition of microglial activation under inflammatory conditions, support its beneficial role in disease conditions associated with neuroinflammation. Indeed, reduced inflammatory markers in septic neuropathy models and providing analgesic effects in chronic inflammatory pain models like osteoarthritis, neuropathic pain, and fibromyalgia support lacosamide's utility in managing neuroinflammation and colic-like pain related to IBD (16,18,34).

Taken together, this study underscores the potential utility of lacosamide as an ulcer-healing and anti-inflammatory agent in managing ulcerative colitis, particularly when conventional therapies are insufficient. The observed reductions in MPO activity and MDA level, as well as enhanced antioxidant capacity (FRAP) in affected tissue, suggest that this drug can modulate the inflammatory response in colitis.

CONCLUSION

This study demonstrated the effectiveness of lacosamide in a common model of laboratory induction of colitis. The findings suggest that lacosamide, like many drugs with anti-seizure activity, holds promise for managing IBD, especially when the greater potency of this drug is taken into consideration. Additionally, the effectiveness of lacosamide in the form of an enema and at the lowest experimental dose showed that this drug could be promising in a topical form. However, further research is required to validate its therapeutic properties for potential clinical applications and in a human setting.

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Conflict of interest statements

The authors declared no conflict of interest in this study.

Authors' contributions

M. Minaiyan presented the idea of the study, supervised all stages of the work, actively participated in the preparation, writing, analysis of the results, and replies to the referees' comments; N. Mottaghi carried out all the implementations of the study and extracting the results, as well as analyzing the data with statistical software and drawing graphs and tables, and participated in writing the initial manuscript and all later stages of publishing the article. Both authors have read and approved the finalized article. Each author has fulfilled the authorship criteria and affirmed that this article represents honest and original work.

AI declaration

The authors did not use any AI-assisted technologies in the preparation of this manuscript.

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