The Protective Effect of Dapsone Against Ethanol, Stress, and Indomethacin-Induced Gastric Erosion in Rats

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Abstract- Several factors contribute to the development of gastric erosions, including corticosteroids and nonsteroidal anti-inflammatory drugs (NSAIDs), alcohol, and stress. These factors can cause or worsen gastrointestinal ulcers by activating inflammatory pathways or by altering gastric mucosal blood flow. Dapsone is an antimicrobial compound with anti-inflammatory properties. The aim of this study was to evaluate the protective effects of dapsone against gastric erosions induced by alcohol, stress, or indomethacin. Gastric damage was induced in male rats in three different experimental models: ethanol (5 ml/kg, p.o.)-, water-immersion stress-, and indomethacin (30 mg/kg, p.o.)- induced ulcer. Rats in each of these three experimental models were divided into five groups: Normal group, 2. Control group (gastric damage+vehicle), 3. Gastric damage+dapsone 1 mg/kg, 4. Gastric damage+dapsone 3 mg/kg, 5. Gastric damage+dapsone 10 mg/kg. In this study, the J- score ulcer index and histopathological assessment were performed. In addition, inflammatory cytokines levels, NF-κB expression, and MPO activity were determined. Dapsone reduced the tissue injuries and erosion area in all three experimental groups compared to the control group. In addition, serum levels of inflammatory cytokines, TNF-alpha, and IL-1β were reduced in the dapsone treatment groups. The expression of NF-κB and tissue concentration of myeloperoxidase (a marker of neutrophil activation) was also reduced in rats given dapsone. To conclude, dapsone exhibits significant protective effects against the development of experimental gastric erosions in rats, and these effects seem to be related to its anti-inflammatory and antioxidant properties.

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Keywords: Gastric erosion; Inflammation; Dapsone; Ethanol; Stress; Indomethacin

Introduction

Peptic ulcers are a major disorder in the digestive tract, which is associated with high mortality and morbidity (1,2). The major causes of gastric epithelial damage are *H. pylori* infection, stress, ethanol as well as medications such as corticosteroids and NSAIDs (3-5). Different mechanisms contribute to the development of gastric erosions. For example, inhibition of cyclooxygenase (COX), blockade of the production of prostaglandins, reduce the protective effects of prostaglandins on gastric mucosa, which causes submucosal erosion and gastrointestinal ulcer by NSAIDs (6,7). Prostaglandins are also involved in the protective and therapeutic effects of gastrointestinal hormones in the digestive system (8-10). Maintaining adequate blood flow in the gut is essential for the protection and healing of the mucous membrane (11). Mucosal ischemia following decreased gastric mucosal blood flow also plays a role in the pathogenesis of gastric mucosal damage induced by stress and ethanol (12,13) and reduction of gastric mucosal blood and subsequent ischemia-reperfusion by stress as well (14). In addition, inflammatory processes and oxidative stress play a role in these processes.

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Disruption of gastric mucosal defense mechanisms such as mucus and bicarbonate secretion, anti-inflammatory and antioxidant agents are further factors leading to the development of peptic ulcers (15-18).

Dapsone is an antimicrobial compound of the synthetic sulfone family used in the treatment of numerous systemic and dermatologic disorders. Similar to the sulphonamide drugs, dapsone acts by competing with para-aminobenzoic acid for the active site of the enzyme dihydropteroate synthetase and via inhibiting the synthesis of dihydrofolic acid (19). Dapsone has anti-inflammatory properties equivalent to NSAIDs (20,21). It appears that dapsone can reduce the level of inflammatory cytokines, adhesion molecules, lymphocyte activity, and leukotrienes. Dapsone inhibits chemoattractant-induced signal transduction followed by suppression of neutrophil adherence in skin dermatitis (22). Moreover, dapsone can inhibit the synthesis of both prostaglandins and leukotrienes by macrophages (23). Studies have also shown that dapsone has antioxidant properties and is able to reduce reactive oxygen species (ROS) formation (24). Besides, dapsone can reduce the number of myeloperoxidase enzymes leading to inhibition of HOCl formation (25).

Given the anti-inflammatory effect of dapsone, this study was designed to investigate the protective effects of dapsone in gastric erosions induced from ethanol, water-immersion stress, and NSAIDs in rats.

Materials and Methods

Animal preparations

Male Wistar rats weighing 250-300 g were used in this study. They were maintained under normal conditions such as free access to food and water, 23±2º C room temperature, 12 h light and 12 h dark cycles, and standard humidity. One day before the experiment, all rats were deprived of food but had free access to water. All experiments were carried out according to the National Institutes of Health guide for the care and use of laboratory animals (NIH Publications No. 8023, revised 1978). The Ethical Committee of Tehran University of Medical Sciences approved all experiment details and animal study. (IR.TUMS.VCR.REC.1398.225).

Drugs

Dapsone powder was a gift from Gilaranco Co, Tehran, Iran, and dissolved in normal saline. Absolute ethanol (Merck, Germany) was diluted 1:1 (vol/ vol) in water. Indomethacin (Sigma-Aldrich, United States) was suspended in 1% carboxymethyl cellulose solution.

Experimental procedures

120 male Wistar rats were used in this study and were randomly divided into three experimental models:

Model 1: Ethanol-induced gastric damage: Ethanol-induced ulcer was produced by administration of 5 ml/kg of ethanol (1:1 v/v) via oral gavage (26).

Model 2: Water immersion stress model: Stress ulcers were induced by immersing restrained rats in cold water (23º C) up to the level of animal necks for three and a half hours as described (27).

Model 3: Indomethacin-induced gastric damage; Indomethacin-induced ulcer was produced by oral administration of indomethacin at a single dose of 30 mg/kg by gavage (28).

Each of the three experimental models was divided into five groups of eight rats, which included 1. Normal group (rats without any intervention), 2. Control (peptic ulcer-induced group+vehicle), 3. Gastric ulcer+pretreated dapsone 1 mg/kg, 4. Gastric ulcer+pretreated dapsone 3 mg/kg, 5. Gastric ulcer + pretreated dapsone 10 mg/kg.

In group 1, animals received only intraperitoneal injection of normal saline without gastric damage. Treated groups in all three models received either 1, 3, or 10 mg/kg intraperitoneal injection of dapsone 30 minutes before gastric damage induction.

After 4 hours of indomethacin and 1 hour of ethanol ulcer administration, rats were anesthetized with ketamine (80 mg/kg; *i.p.*) and xylazine (8 mg/kg; *i.p.*), then the stomach was separated and observed for macroscopic evaluation. After that, their blood was collected for measurement of inflammatory factors such as TNF-α and IL1-betausingenzyme-linked immunosorbent assay (ELISA) method.

Finally, the gastric tissues were fixed in buffered formaldehyde for histopathological analysis or restored in -80° C for measurement of myeloperoxidase (MPO) activity.

Assessment of gastric erosions

Macroscopic assessment: The stomachs were washed with 1 ml of phosphate-buffered. The severity of the ulcer was examined according to the J-Scoring method, and the score of each group was determined as the ulcer index. Macroscopic

measurements were performed blindly. J- Score for each group was calculated by evaluating the erosions in size order: (0-1mm) in diameter=1; (1-2 mm)=2; greater than 2 mm in diameter=3. The sum of these measured areas in each animal was described as the ulcer index (29).

Microscopic assessment: Histological studies were

performed on the stomach by hematoxylin and eosin (H and E) staining method. In brief, tissues were fixed in 10% of buffered formalin solution for 24 hours, embedded in paraffin wax to form blocks, and produced sections into four μm thicknesses. These sections were hydrated and stained for evaluating morphological damages by a blinded histopathologist. The observation was performed under a light microscope.

Inflammatory cytokines measurement

Serum levels of TNF-α and IL-1β were measured by ELISA method using rat tumor necrosis factor α ELISA Kit (RAB0479, Sigma Aldrich, United States) and rat IL-1β ELISA Kit (RAB0277, Sigma Aldrich, United States). Serums were separated by centrifugation at 2500 (×g) for 10 min, and then samples were kept in aliquots at -80° C until the time of assay. Serum levels were assessed for TNF-α and IL-1β using (Bio-Tek Synergy HT, US) ELISA plate reader. The levels of TNF-α and IL-1β are presented in pg/ml.

Measurement of gastric myeloperoxidase (MPO) activity

Gastric tissues were used for the measurement of MPO activity. Tissues were homogenized by a mechanical homogenizer and centrifuged at 15,000 x g for 20 min. The supernatants were used for measurement of MPO activity analysis using a plate reader as described by the manufacturer's instruction (Sigma Aldrich, United States). Tissue MPO activities are presented as U/g tissue.

Immunohistochemical assessment of P-NF-κB

The primary and secondary antibodies used were rabbit polyclonal NF-κB p65 (phospho S536) antibody (at 1:100 dilution, Ab 86299, Cambridge, USA) and FITC Goat anti-Rabbit IgG (at 1:200 dilution, Ab 6717, Cambridge, USA), respectively. To evaluation of p-NF-κB protein localization in stomach tissue, 4-μm thick paraffin-embedded tissue pieces were deparaffinized in xylene. Slides were incubated sequentially overnight at 4◦ C with primary antibodies and in secondary antibody for 30 min at room temperature and then washed in PBS. The slides were stained by 4′, 6-diamidino-2-phenylindole (DAPI), and immunostained sections were examined using a fluorescence microscope for the staining intensity evaluation. Images were quantified using image j software.

Statistical analysis

One or two-way analysis of variance (ANOVA) was used, followed by Tukey's *post-hoc* comparisons for normally distributed data using GraphPad Prism5 software. The results were expressed as the mean±SEM, and the significance value was set at 0.05. Tests of homogeneity of variance were used to ensure the normal distribution of the data.

Results

Effect of dapsone on macroscopic damage in ethanol-induced peptic ulcer

As shown in (Figure 1a), hemorrhagic and necrotic areas were visible in the gastric mucosa following ethanol administration in control groups. A remarkable reduction in gastric mucosal damage was observed in the group that had received dapsone (10 mg/kg), as shown in (Figure 1b). The J-scores are represented in table 1which indicates a significantly higher J-score in the ethanol group (61.5±3.90) in comparison with the normal group (P<0.001). Pretreatment with 1 mg/kg dapsone didn't show any significant changes in the gastric erosion area, but in animals subjected to 3 and 10 mg/kg dapsone, a remarkable decrease in J-score was observed by the decrease the J-score to 42.3±3.27 (P<0.05 versus control) and 20.16±1.097 (P<0.001 versus control), respectively.

Effect of dapsone on macroscopic damage in stress-induced peptic ulcer

As shown in (Figure 1c), the water-immersion stress was associated with focal hemorrhagic lesions in the control group compared to normal, but administration of dapsone before stress, particularly at a dose of 10 mg/kg, markedly abolished the gastric lesions in comparison with control untreated group (Figure 1d).

As demonstrated in Table.1, the mean J-score index was 34.66±4.68 in stress untreated groups, and administration of 1 mg/kg dapsone failed to significantly affect the severity of erosions in comparison to control. However, dapsone (3 and 10 mg/kg) treated groups showed improvement in the J-score (P<0.01 and P<0.001, respectively).

Effect of dapsone on macroscopic damage in indomethacin-induced gastric damage

As shown in (Figure 1e), indomethacin led to the formation of multiple mucosal erosions in the control groups compared to the normal group. However, these lesions were significantly reduced with 10 mg/kg dapsone pretreatment when compared to the control group (Figure 1f).

According to Table 1, the J-score in control rats exposed to indomethacin reached 43.1±4.99, which is

markedly higher than rats that did not receive indomethacin. Pretreatment with 10 mg/kg dapsone was protective against indomethacin-induced gastric damage (J-score=15±2.06, P<0.01). Pretreatment with dapsone at doses of 1 and 3 mg/kg did not show significant protective effects on gastric lesions.

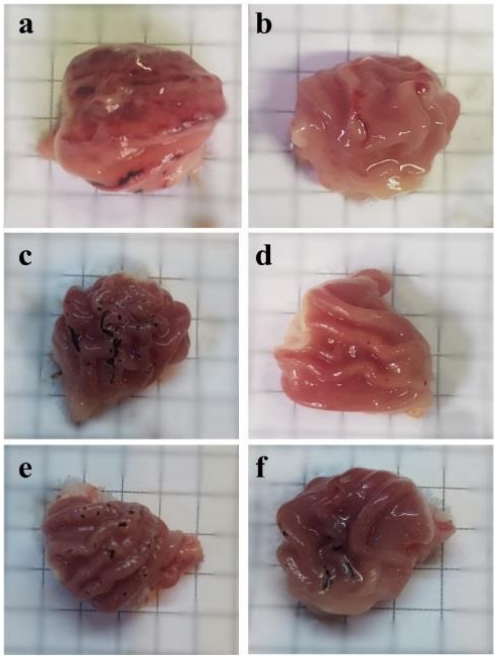

Figure 1. Macroscopic assessment of gastric mucosa of rats in control and 10 mg/kg dapsone treated groups. (a) Effect of ethanol, (c) stress, and (e) indomethacin on gastric tissues (control groups). (b) Treatment with dapsone (10 mg/kg) in ethanol-induced gastric ulcer group, (d) stress-induced gastric ulcer group, (f) Indomethacin -induced gastric ulcer group

Table 1. Comparison of J-Score between control and dapsone treated groups

GROUPS	ALCOHOL	INDOMETHACIN	STRESS
Control	61.5±3.90	43.1±4.99	34.66±4.68
Dapsone 1 mg/kg	56±5.46	36.16±5.62	29.16±3.71
Dapsone 3 mg/kg	42.3±3.27 *	29±5.20	18.83±2.01 **
Dapsone 10 mg/kg	20.16±1.097 ***	15±2.06 **	7.16±0.87 ***

Data are presented as Mean±SEM; Number of animals in each group: 8, *P< 0.05; **P< 0.01; ***P<0.001 compared to relative control group

Histopathological assessment of gastric tissue

(Figure 2a) shows the histological features of the gastric mucosa in a normal rat. Histological examination of the gastric tissues in all control rats in all three models showed severe chronic active gastritis with mucosal erosion (Figure 2b, d, and f) in comparison with the normal group (P<0.01). The results showed that treatment with dapsone (10 mg/kg) improved mucosal congestion in the body of the stomach (as shown in Figure 2c, g). Dapsone (10 mg/kg) treatment in ethanol and indomethacin-induced ulcerated rats showed mild submucosal erosions (about 1/3 and less than 1/4 of the mucosal thickness, respectively). In (Figure 2e), dapsone (10 mg/kg) treatment in stress-induced ulcerated rats showed normal histopathology without significant superficial mucosal epithelial degeneration.

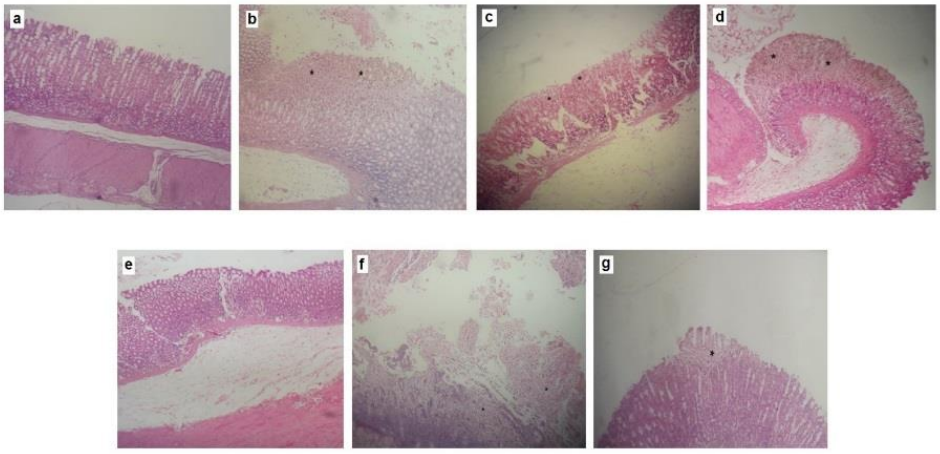

Figure 2. Effects of dapsone on histopathological lesions in the gastric injury of rats exposed to ethanol, stress, and indomethacin. Slices stained with H&E (20x). (a) Gastric mucosa of a normal rat. (b) Ethanol-induced ulcer tissues showed active gastritis with mucosal erosion (more than 1/2 of the mucosal thickness shown by *). (d) Stress-induced ulcer tissues showed severe mucosal erosion with intramucosal hemorrhage (more than 1/2 of the mucosal thickness shown by *). (f) The black star in the indomethacin received group showed deep mucosal erosion in the body of the stomach (more than 2/3 of the mucosal thickness). Pathological changes with 10 mg/kg dapsone treatment: (c) The ethanol /dapsone (10 mg/kg) group showed active gastritis with mucosal erosion (about 1/3 of the mucosal thickness shown by *). (e) The stress/dapsone (10 mg/kg) group showed normal histopathology without significant pathologic changes. (g) The black stars in the indomethacin/ dapsone (10 mg/kg) group showed mild active gastritis with superficial erosion (less than 1/4 of the mucosa thickness, shown by*)

Effect of dapsone on plasma inflammatory cytokines

In order to evaluate the inflammatory response, inflammatory factors such as TNF-α and IL-1β in serum were detected by ELISA. There was a high serum level of TNF-α and IL-1β in the ethanol-, stress-, and indomethacin- control groups as compared with normal groups (P<0.001). Among the tested doses, a high dose of dapsone (10 mg/kg, *i.p.*) showed a reduction in serum concentration of TNF-α and IL-1β in all three models.

As demonstrated in (Fig. 3a and b), TNF-α and IL-1β levels in the ethanol-induced ulcer group were significantly different in control rats in comparison with rats given dapsone (10 mg/kg; P<0.001 and P<0.05 respectively). But with lower doses of dapsone, there was no statistically significant improvement.

In water immersion stress groups (Figures 4a and b), a statistically significant decrease in serum concentration of TNF-α was observed in both higher doses of dapsone (3 and 10 mg/kg) as compared to the control group (P<0.01 and P<0.001 respectively). With regard to serum IL-1β concentration, dapsone could only reduce it at the highest dose 10 mg/kg used in this study (P<0.01).

In the indomethacin-induced erosion groups (Figure 5a, b), rats pretreated with both doses of 3 and 10 mg/kg of dapsone showed a remarkably lower serum concentration of TNF-α (P<0.05 and P<0.001). Only administration of 10mg/kg dapsone exhibited a significant reduction in serum level of IL-1β when compared to control (P<0.05).

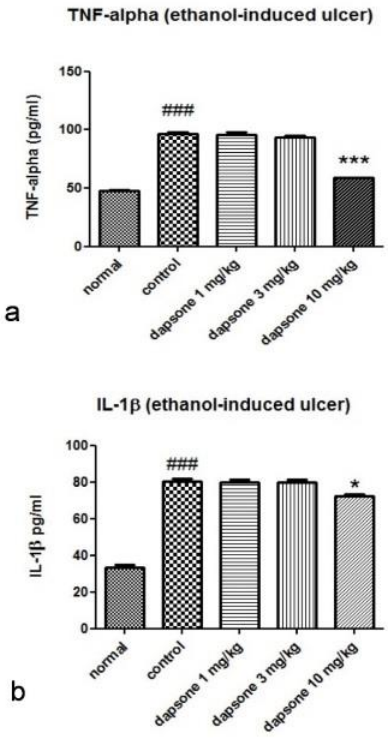

Figure 3. Serum levels of TNF-α (a) and IL-1β (b) in the ethanol-induced ulcer group. Results are expressed as mean±SEM; Number of animals in each group: 8, $^{###}P$<0.001, compared to the normal group; $^{*}P$<0.05, $^{***}P$<0.001, compared to control group

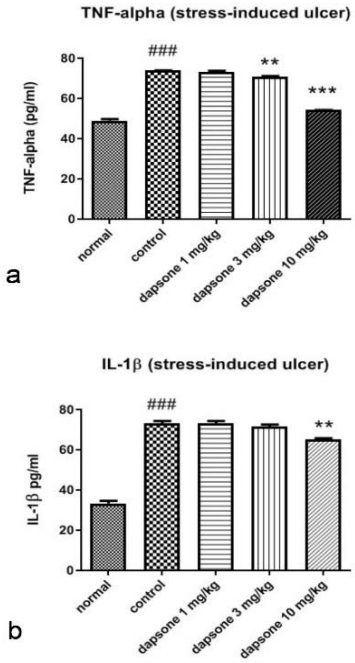

Figure 4. Serum levels of TNF-α (a) and IL-1β (b) in the stress-induced ulcer group. Results are expressed as mean±SEM; Number of animals in each group: 8, $^{###}P<0.001$, compared to the normal group; $^{**}P<0.01$, $^{***}P<0.001$, compared to control group

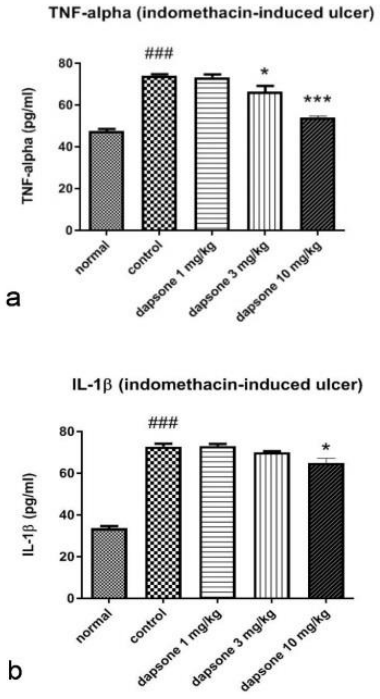

Figure 5. Serum levels of TNF-α (a) and IL-1β (b) in the indomethacin-induced ulcer group. Results are expressed as mean±SEM; Number of animal in each group: 8, $^{###}P< 0.001$, control compared to normal group; $^{*}P< 0.05$, $^{***}P< 0.001$, compared to control group

Effect of dapsone on MPO activity

In both ethanol and indomethacin-induced ulcer groups, a significant reduction in gastric MPO activity was observed in dapsone-treated groups (3 and 10 mg/kg) in comparison with the control group (P<0.05, P<0.01, respectively). However, the level of MPO in stress-induced gastric ulcer groups was slightly decreased (P<0.05) compared with ethanol and indomethacin-induced gastritis groups (P<0.01) following dapsone 10 mg/kg treatment. (Figure 6) indicates that treatment with dapsone (10 mg/kg) led to a more significant decrease in gastric MPO level of all three models. On the other hand, the result revealed an inhibitory effect of dapsone (especially at a dose of 10 mg/kg) on MPO activity as a marker of neutrophil infiltration.

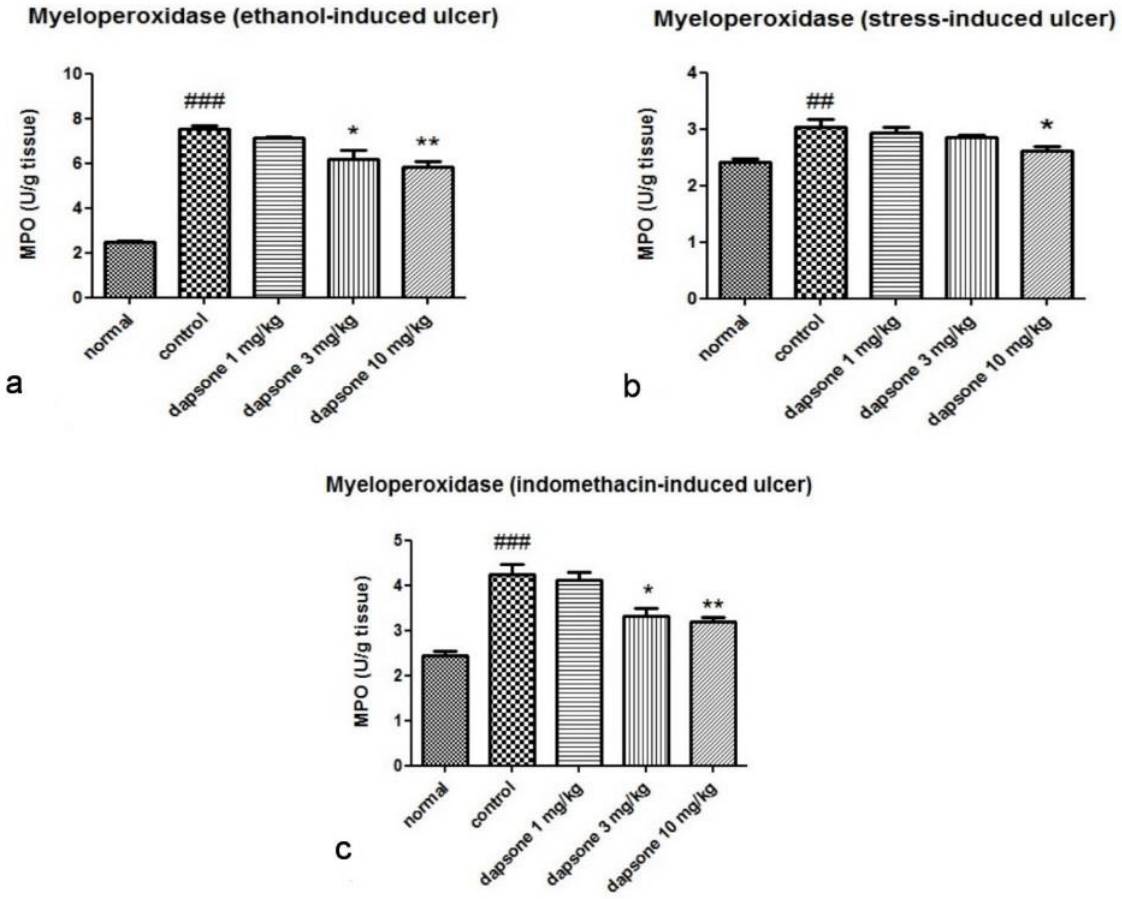

Figure 6. Tissue levels of MPO in ethanol-induced ulcer group (a); stress-induced ulcer group (b); indomethacin-induced ulcer group (c). Results are expressed as mean±SEM; Number of animals in each group: 8, $^{###}P$<0.001, compared to the normal group; $^{*}P$<0.05, $^{**}P$<0.01, compared to control group

Effect of dapsone on NF-κB expression

We performed immunohistochemistry in order to determine the expression level of NF-κB protein in all three peptic ulcer models (Figure 7). In the ethanol-induced peptic ulcer model based on results achieved from the IHC staining method, the expression of this protein was dramatically decreased in the dapsone 10 mg/kg treated group in comparison with the control (ethanol-induced) group (P<0.001). In the same manner, pretreatment with 10 mg/kg dapsone revealed a significant decrease in NF-κB expression compared to the control group in stress-induced peptic ulcer (Figure 8) (P<0.001). According to (Figure 9), similar to the previous two models, in the indomethacin-induced peptic ulcer model remarkable reduction of NF-κB expression in the dapsone 10 mg/kg treated group was detected (P<0.001).

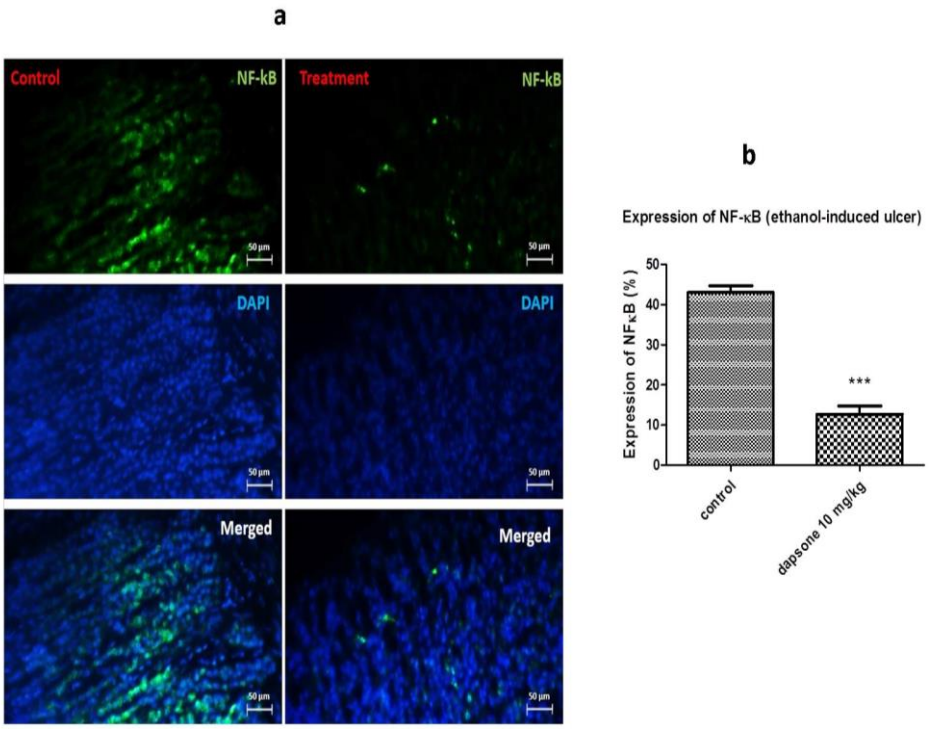

Figure 7. Immunohistochemical staining of NF-κB p65 expression in the gastric tissue of rats in ethanol-induced ulcer model (×40), stained with DAPI (blue), through immunofluorescence via an antibody bound to fluorescein isothiocyanate (FITC) (green) (a). Immunohistochemical analysis of gastric tissue sections for NF-κB expression in ethanol-induced ulcer model (b). Results are expressed as mean±SEM. Number of animals in each group: 8. ****P*<0.001 compared to the control group

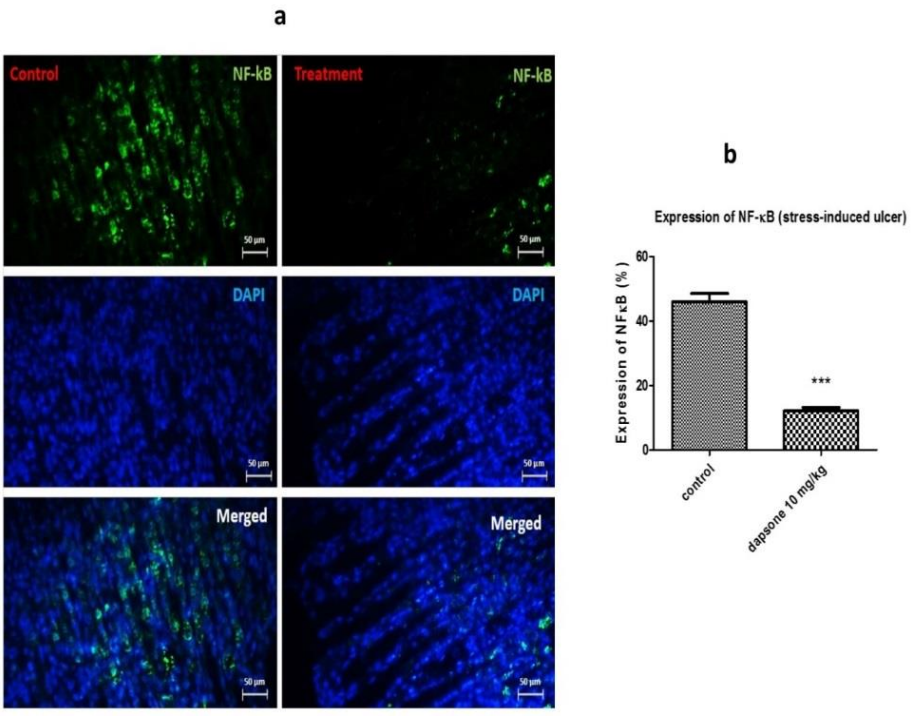

Figure 8. Immunohistochemical staining of NF-κB p65 expression in the gastric tissue of rats in stress-induced ulcer model (×40), stained with DAPI (blue), through immunofluorescence via an antibody bound to fluorescein isothiocyanate (FITC) (green) (a). Immunohistochemical analysis of gastric tissue sections for NF-κB expression in stress-induced ulcer model (b). Results are expressed as mean±SEM. Number of animals in each group: 8. ****P*<0.001 compared to the control group

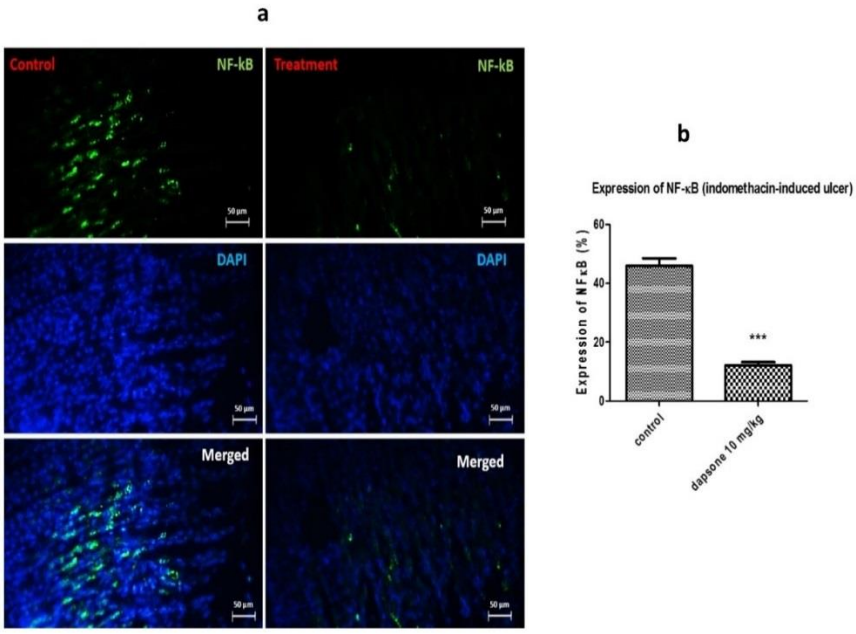

Figure 9. Immunohistochemical staining of NF-κB p65 expression in the gastric tissue of rats in indomethacin-induced ulcer model (×40), stained with DAPI (blue), through immunofluorescence via an antibody bound to fluorescein isothiocyanate (FITC) (green) (a). Immunohistochemical analysis of gastric tissue sections for NF-κB expression in indomethacin-induced ulcer model (b). Results are expressed as mean±SEM. Number of animals in each group: 8. ****P*<0.001 compared to the control group

Discussion

In the present study, anti-inflammatory and protective effects of dapsone in different rat models of peptic erosion were demonstrated. Three different doses of dapsone (1, 3, and 10 mg/kg) were administered intraperitoneally before ulcer induction. According to the results of this research, dapsone at a dose of 1 mg/kg showed no significant protective effect in all three experimental models, but at the doses of 3 mg/kg and especially 10 mg/kg, the effects of dapsone on reduction of mucosal erosions (J score), histopathology, as well as inflammatory factors were evident.

First, we induced gastric ulcers using oral gavage of ethanol. Studies have shown that ethanol can indirectly induce destructive effects in submucosal venules through leukotriene C4 (LTC4) overproduction (13). Also, it was reported that dapsone could inhibit the synthesis of leukotrienes (23); therefore, it may suppress the following inflammation. Various reports have proved that free radical formation and oxidative stress pathways play a critical role in the process of inflammation and can accelerate gastric injury following ethanol administration (30). Reactive oxygen species (ROS), which are produced by inflammatory cells such as active neutrophils, enhance the severity of damages and cause a concomitant increase in MPO activity which is considered as an indicator of neutrophil infiltration (31). In agreement with previous reports, our study showed that the level of gastric MPO was increased remarkably after 1 hour of oral ethanol gavage in the control group and pretreatment with 10 mg/kg dapsone resulted in a significant decrease in MPO activity. NF-κB is a transcription factor that facilitates the essential inflammatory process in ethanol-induced gastric injury, including the expression of several proinflammatory factors such as TNF-α and IL-8 (32). NFκB contains p65 and p50 subunits, although the NFκB-p65 subunit has been considered as an indicator for NFκB activation (33). In recent studies, compounds that decreased the expression of NF-κB have been observed to be useful in the attenuation of gastric erosion (34). Besides, ethanol administration can provoke a great number of proinflammatory cytokines generation such as IL-1β and TNF-α (35,36). IL-1β induces macrophage infiltration and ICAM-1 overexpression (37). Moreover, TNF-α can suppress gastric microcirculation and upregulate NF-κB expression (38), as well as adhesion molecules production (32). We observed an increasing amount of NF-κB protein expression as well as IL-1β and TNF-α serum levels following ethanol gavage in accordance with previous studies. Data of this study demonstrated that dapsone only at a dose of 10 mg/kg

showed a significant decrease in these inflammatory markers.

For the second model, animals were immersed in cold water under controlled conditions. In the pathophysiology of stress-induced ulcer, oxidative damage and excessive generation of ROS (39), production of proinflammatory cytokines (such as TNF-α, IL-1β, and IL-6) and infiltration of neutrophils (40) are involved following local hypoxia and ischemia. Recent studies have shown that TNF-α, IL-1β can lead to delayed healing of gastric ulcers (41). Most of these inflammatory cytokines are downstream mediators of the NF-κB pathway, and the p65 subunit of NF-κB plays a critical role in response to stress by stimulating the expression of specific genes (42). In this study, water immersion restraint enhanced TNF-α, IL-1β, and NF-κB activity. In addition, it has been found that dapsone has anti-inflammatory properties through down-regulation of the NF-kB pathway in a rat model of colitis (43). The present study demonstrated that dapsone reduced mucosal injury of the stomach tissue and J score mean in a dose-dependent manner in stress ulcers. Although this should be taken into consideration that in microscopic study and J score evaluation, gastric damage resulted from stress showed lower intensity. In addition, we found that dapsone attenuates stress-induced ulcers by suppressing inflammatory cascades mediators. Furthermore, in this study, dapsone only reduced the gastric mucosal level of MPO at the highest dose (10 mg/kg). Our data are consistent with a study that report dapsone can inhibit human leukocyte enzyme MPO production, and this inhibition depends on various factors such as dapsone concentration (44).

In the last step, the gastric ulcer was induced in rats by oral gavage of indomethacin. As mentioned in previous studies, NSAIDs have inhibitory effects on cyclooxygenase enzymes and subsequently prevent the synthesis of protective mucosal prostaglandins. PGE2 could reduce TNF-α and IL-1 release from macrophages and leukotriene B4 (45). Accumulated evidence shows the ability of indomethacin to stimulate NF-κB expression and subsequently up-regulation of its promoting downstream cytokines such as TNF-α and IL-1β (46-48). Furthermore, an increase in gastric MPO level indicates neutrophil infiltration during indomethacin-induced gastric injury (49). Increased gastric mucosal permeability following disruption in mucosal barriers leads to microbial invasion, neutrophil chemotaxis, and inflammation (50). Pretreatment with 10 mg/kg dapsone resulted in a significant decrease in the level of MPO, TNF-α, and IL-1β as compared to control groups. In addition, dapsone prevented NF-κB expression and the formation of gastric erosions in this model.

Since inflammatory pathways are highly involved in causing and advancing gastric ulcers (15), compounds with antioxidant and anti-inflammatory properties may represent protective roles in the development of gastric injuries and erosions. A vast majority of anti-inflammatory drugs such as corticosteroids or NSAIDs have been shown to breed gastric destruction (3,4), whereas dapsone showed gastro-protective effects via inhibition of inflammatory cascades in this study. This protection may be related to different anti-inflammatory properties of dapsone compared to mentioned drugs.

In summary, dapsone exhibits gastro-protective effects against three different causes of gastric mucosal damage, namely ethanol, water-immersion stress, and indomethacin. According to the present study, the effects of dapsone seem to be associated with a decrease in proinflammatory cytokines (TNF-α and IL-1β) and gastric leukocyte infiltration, which might be related to the anti-inflammatory effects of dapsone. Nevertheless, further research is needed to distinguish the exact protective mechanisms of dapsone.

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