Effect of Cow's Milk and Glutathione as a Protective Factor on Physiological and Histological Parameters in Male Rats with Gastric Ulcers

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Abstract Gastrointestinal ulcer is one of the common diseases, affecting more than 10% of the world's population. Aim of the study: The present study aimed to assess C-reactive protein (CRP), white blood cell (WBC), malonaldehyde (MDA), glutathione (GSH), alanine aminotransferase (ALT), and aspartate aminotransferase (AST) in gastrointestinal ulcer rats after being treated with cow milk and glutathione. This study was conducted in the laboratories of the Department of Food Sciences at the College of Agriculture, Tikrit University; the Animal House at the College of Veterinary Medicine, Tikrit University; and the Central Laboratory at the Presidency of Tikrit University. The research was conducted from September 2024 to January 2025. A sample of 20 sexually mature male animals was used, randomly distributed into 4 groups of similar animals as follows: M1 (healthy control group, n = 5), M2 (infected with a gastrointestinal ulcer after being orally dosed with ethanol as a control group, n = 5), and M3 (the group of animals infected with a gastrointestinal ulcer and treated after being orally dosed with cow's milk at a concentration of 5 ml, n = 5). Finally, M4 for animals infected with a gastrointestinal ulcer and treated after being orally dosed with glutathione (n = 5). The present study showed increased CRP and WBC in rats infected with gastrointestinal ulcer M2 that were 12.9±1.3 mg/l and 7.82±0.18 ×109/mm3, as compared with control group M1, which was 7.5±0.7 mg/l and 5.58±0.04×109± 0.04×109/mm3, while decreased in M3(p<0.05). Furthermore, there are no differences in the level of M4 and M2. In addition, increased MDA in rats infected with gastrointestinal ulcer M2 (3.12±0.511 nmol/l), as compared with control groups M1 (1.24±0.317 nmol/l), while decreased in M3 and M4, (p<0.05). Furthermore, decreased GSH in M2 as compared with M1 (0.35±0.022 ng/l and 0.93±0.047 ng/l, respectively), while increased GSH in M3 and M4(p<0.05). Histopathologically, the small intestinal wall has lengthy, branched mucous villi with distal degeneration and epithelial cell sloughing. The primary sheet had many densely packed intestinal glands and white blood cells in the interstitial tissue. Mucus-secreting goblet cells extended into tufts between the villi. treated with cow milk, less improved intestinal ulcer. This study found that there was a protective effect of cow's milk against gastrointestinal ulcers in rats by significantly reducing CRP, WBC, ALT, AST, and MDA.

Key Words Cow milk, Glutathione, Gastric ulcers, Rats

INTRODUCTION

Peptic ulcer disease (PUD) is a major global health concern, defined by mucosal damage in the stomach or duodenum due to an imbalance between protective systems and harmful causes [1]. The gastrointestinal mucosa is typically safeguarded by a multilayered defensive mechanism, comprising mucus and bicarbonate secretion, tight epithelial junctions, prostaglandin production, mucosal blood circulation, and endogenous antioxidants like glutathione (GSH). Ulceration occurs when this balance is disrupted by excessive secretion of stomach acid and pepsin, oxidative stress, or compromise of mucosal integrity [2].

Experimental ulcer models, especially those generated by ethanol, are extensively utilized to replicate the biochemical and histological processes of human stomach ulceration [3]. Ethanol-induced ulceration causes direct mucosal necrosis, lipid peroxidation, and inflammatory infiltration, whereas acetic-acid ulcers mimic chronic gastrointestinal lesions characterized by delayed healing and fibrotic repair. These models are crucial for assessing gastroprotective drugs and examining oxidative and inflammatory responses in gastrointestinal tissue [4].

Recently, bioactive constituents of dairy products have garnered heightened interest as potential natural gastroprotective

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agents. Milk and its protein components—namely casein, whey protein, and lactoferrin—exhibit buffering, cytoprotective, and antioxidant characteristics [5]. In ethanol-induced ulcer models, lactoferrin, a principal iron-binding glycoprotein found in milk, significantly mitigated mucosal damage, reduced malondialdehyde (MDA) levels, and increased reduced glutathione (GSH) concentrations, partially via the modulation of the Nrf2/ROS signaling pathway [6]. Cow milk exhibited significant gastroprotective and anti-inflammatory properties in indomethacin- and ethanol-induced ulcers in rats, owing to their elevated whey-to-casein ratios, antioxidant vitamins, and bioactive peptides that facilitate epithelial regeneration and mitigate oxidative damage [7].

These findings support the concept that dairy-derived proteins provide dual protective effects—mechanical and biochemical. Milk proteins mechanically create a thin layer on the gastrointestinal mucosa, offering a temporary buffer against acid and pepsin. Their peptides and minerals, especially calcium and phosphorus, biochemically increase mucus secretion, regulate acid production, and enhance mucosal healing. Additionally, some proteins like lactoferrin and β-lactoglobulin demonstrate radical-scavenging properties and can enhance the expression of natural antioxidant enzymes [8].

Alongside milk proteins, glutathione (GSH) serves as an essential element of the mucosal defense system. It functions as a cellular redox regulator by neutralizing reactive oxygen species (ROS), inhibiting lipid peroxidation, and preserving mitochondrial stability. Studies on ethanol-induced ulcer models demonstrate that a decrease in mucosal GSH correlates with heightened ulcer severity, whereas GSH supplementation restores mucosal integrity and reduces necrotic lesions. Consequently, GSH functions as both a biomarker and a therapeutic target in the healing of stomach ulcers [9].

By synthesizing both findings, it is plausible to postulate that concurrent administration of cow milk and GSH may yield synergistic effects in combating ulceration. Milk offers nutritional and physical safeguarding for the mucosa, while GSH bolsters cellular antioxidant defenses and mitigates inflammatory pathways. Thus, concomitant treatment is anticipated to diminish blood CRP and WBC levels (showing reduced systemic inflammation), lower stomach MDA concentrations (signifying decreased lipid peroxidation), and elevating mucosal GSH levels (representing improved antioxidant capacity).

This work seeks to analyze the possible gastroprotective effects of cow milk and glutathione in an experimentally produced gastrointestinal ulcer model, utilizing integrated biochemical and histological evaluations.

METHODS

Study site
This study was conducted in the laboratories of the Department of Food Sciences at the College of Agriculture, Tikrit University; the Animal House at the College of Veterinary Medicine, Tikrit University; and the Central Laboratory at the Presidency of Tikrit University. The research was conducted from September 2024 to January 2025.

Animals and Housing
Laboratory rats of the albino type were obtained at the age of 2 months and weighed between 190 and 200 g. In this study, before starting the experiment, the animals were observed and evaluated for 5 days in order to adapt and verify their ideal health status. Before using them in the experiment, the animals underwent a comprehensive examination by the specialized veterinarian at the center to ensure their safety and freedom from diseases and disabilities. A sample of 20 sexually mature male animals was used, randomly distributed into 4 groups of similar weights. The animals were housed in plastic cages with a floor covered with sawdust, which were changed four times a week. The animals were fed regularly with ready-made feed, as the light period was 12 hours, and the darkness period was also 12 hours. The temperature was maintained at 24±2 degrees Celsius, and a number was assigned to each cage. The animals had continuous access to water and were fed the diet assigned to each treatment during the 30-day trial period after confirmation of infection.

Ulcer Induction
Five rats were isolated for control treatment (without infection), and the remaining rats were dosed orally with ethanol, and the animals were dosed at a concentration of 1 ml/kg of body weight. After confirming the presence of intestinal ulcers by examining blood images (CBC) and withdrawing a blood sample by cardiac puncture, the amount of blood withdrawn ranged from 0.5 to 5 ml, using a 5 ml injector, and was injected into test tubes containing EDTA to prevent clotting. The blood images included white blood cells (WBCs) and an evaluation of C-reactive protein (CRP). A decrease in the amount of food consumed by the animals and loss of appetite were also noted, along with blood in the stool due to internal bleeding.

Interventions
Pasteurized cow's milk was collected between October 2023 and February 2024 from the Uwainat and Al-Alam areas in the Tikrit district, Salah Al-Din Governorate. Samples were stored in tightly sealed and sterilized containers at a temperature of 4-5°C for no more than 3-6 hours before starting the experiment. Reduced glutathione (L-GSH; Sigma-Aldrich, USA) was freshly prepared in sterile saline and administered intraperitoneally at a dose of 6.42 mg/kg BW once daily [10].

Experimental Design
After confirming that the animals were infected with gastrointestinal ulcers through blood analysis and stool analysis, they were distributed into 5 plastic cages with metal mesh covers, each cage with dimensions of 60, 30, and 30 cm, and were distributed as follows:

- **M1:** The ideal healthy control group (untreated and provided only with water and food throughout the experiment period)
- **M2:** The infected control group (infected with a gastrointestinal ulcer after being orally dosed with ethanol while continuing to give them food and water throughout the experiment period)
- **M3:** The group of animals infected with a gastrointestinal ulcer and treated after being orally dosed with cow's milk at a concentration of 5 ml in two doses, morning and evening
- **M4:** The group of animals infected with a gastrointestinal ulcer and treated after being orally dosed with glutathione (642 mg/kg BW)

Biochemical Assays

Measurement of C-reactive concentration (mg/L) in the Mindray BC-5390 system (Shenzhen, China), ALT (U/L), and AST (U/L) measured by using manuscript Biolab kits. While GSH (ng/L) and MDA (nmol/ml) were assessed by using an ELISA kit (Sunnlong).

Histology

Intestinal tissues were fixed in 10% neutral buffered formalin for 48 h, dehydrated in graded ethanol, cleared in xylene, and embedded in paraffin. Sections of 5 μm were stained with hematoxylin and eosin (H&E) for general architecture and examined under a light microscope at ×40 magnification (Olympus BX43). The ulcer index and mucosal damage scores were determined by a blinded histopathologist using a 0–4 scale based on epithelial disruption, edema, and inflammatory infiltration.

Outcomes and Timing

Primary outcomes included ulcer index, MDA, GSH, CRP, and WBC levels. Secondary outcomes included histopathological healing and mucosal regeneration. Treatment continued for 7 days post-ulcer induction, after which animals were euthanized, and samples collected for analysis.

Statistical Analysis

Data was analyzed using the Statistical Analysis System (SAS, 2018). Differences among groups were assessed by one-way ANOVA, followed by Tukey's post-hoc test for multiple comparisons. Data normality and homogeneity were verified using the Shapiro–Wilk and Levene's tests, respectively. Results are expressed as mean±SE, with $p < 0.05$ considered statistically significant.

RESULTS AND DISCUSSION

The present study showed an increase in CRP and WBC in rats infected with gastrointestinal ulcer M2 that were 12.9±1.3 mg/l and 7.82±0.18×10⁹/mm3, as compared with control group M1, which was 7.5±0.7 mg/l and 5.58±0.04×109± 0.04×10⁹/mm3, while M3 decreased, ($p < 0.05$). Furthermore, there are no differences in the level of M4 and M2, as shown in Table 1.

Table 1: Protective effect of cow milk, and glutathione, on CRP and WBC rats infected with gastrointestinal ulcer

WBC (×10⁹/mm³)	CRP (mg/l)	Groups
5.58±0.04c	7.5±0.7c	M1(n = 5)
7.82±0.18a	12.9±1.3a	M2(n = 5)
6.55 ±0.21b	9.1±0.5b	M3(n = 5)
6.86±0.05a	12.3±0.9a	M4(n = 5)
0.05	0.02	P value

Note: Values are expressed as mean±SD. Different superscript letters (a–c) indicate significant differences (p<0.05) among groups based on one-way ANOVA (95% CI shown in supplementary data).

Table 2: Protective effect of cow milk, and glutathione, on liver function test rats infected with gastrointestinal ulcer

Groups	ALT (U/L)	AST (U/L)
M1(n = 5)	60.64±0.82c	35.32±0.52b
M2(n = 5)	82.72±0.24a	62.11±0.11a
M3(n = 5)	74.56±0.37b	45.33±0.47b
M4(n = 5)	81.08±0.42a	59.65±0.08a
P value	0.04	0.02

Note: Values are expressed as mean±SD. Different superscript letters (a–c) indicate significant differences (p<0.05) among groups based on one-way ANOVA (95% CI shown in supplementary data).

Table 3: Protective effect of cow milk, and glutathione, on antioxidant and oxidative stress in rats infected with gastrointestinal ulcer

Groups	GSH (ng/ml)	MDA (nmol/ml)
M1(n = 5)	0.93±0.047 a	1.24±0.317 b
M2(n = 5)	0.35±0.022 b	3.12±0.511 a
M3(n = 5)	0.6± 0.13 ab	2.4±0.32ab
M4(n = 5)	0.8± 0.016 a	2.5±0.57ab
P value	0.05	0.03

Note: Values are expressed as mean±SD. Different superscript letters (a–c) indicate significant differences (p<0.05) among groups based on one-way ANOVA (95% CI shown in supplementary data).

The present study showed an increase in ALT and AST in rats infected with gastrointestinal ulcer M2 that were 82.72±0.24 U/L and 62.11±0.11 U/L, as compared with control group M1, which was 60.64±0.82 U/L and 35.32±0.52 U/L (p<0.05), while there was a decrease in M3 and no differences with M4, as shown in Table 2.

The present study showed an increase in MDA in rats infected with gastrointestinal ulcer M2 (3.12±0.511 nmol/ml), as compared with control group M1 (1.24±0.3l7 nmol/ml), while there was a decrease in M3 and M4. Furthermore, decrease GSH in M2 as compared with M1 (0.35±0.022 ng/ml and 0.93±0.047 ng/ml, respectively), while increasing GSH in M3 and M4 (p<0.05), as shown in Table 3.

The wall of the small intestine contains a mucosal layer containing long finger-shaped villi lined with simple columnar cells. The core of the villi contains loose connective tissue containing numbers of white blood cells. The basal layer beneath the villi contains large numbers of intestinal glands secreting yeast and mucus and continuous with the surface of the intestinal cavity at the base of the villi as in Figure 1.

The wall of the small intestine contained long, branched mucous villi with degeneration at the ends of the villi and sloughing of some of their epithelial cells. Mucus-secreting goblet cells were found extending into tufts between the villi, which were continuous with the intestinal glands in the primary sheet, in which large numbers of densely packed
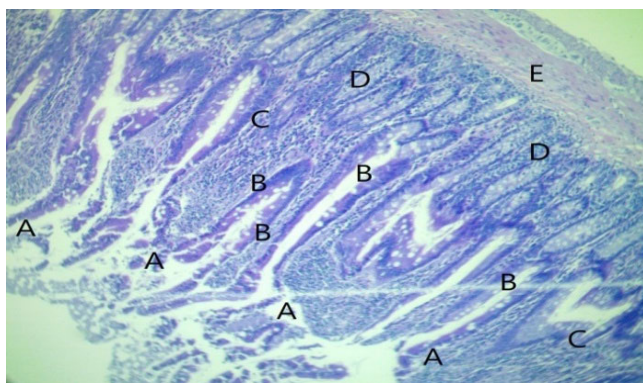
Figure 1: A cross-section showing the tissues of the small intestine stained with H&E of male, healthy control treatment (M1), showing intestinal villi (A), simple columnar epithelium (B), villi core and leukocyte tissue (C), intestinal glands in the basal layer (D), muscular layer (E) CH2E (10X)
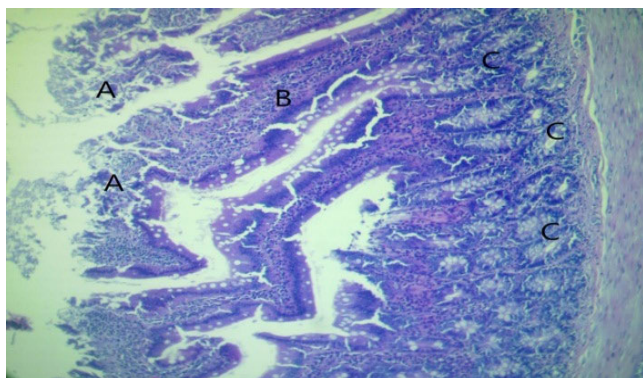

Figure 2: A cross-section of the wall of the small intestine stained with H&E of male rats treated (M2) with ulcers, showing the intestinal villi of the small intestine and degeneration at the ends of the villi (A), the core of the villi and white blood cells (B), and the intestinal glands on the main page (C). CH2E (10X)
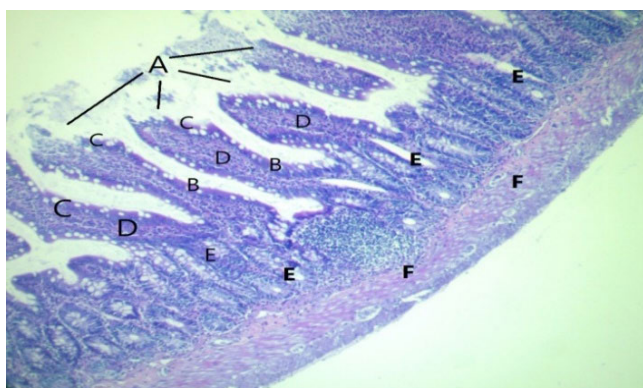

Figure 3: A cross-section of the wall of the small intestine stained with H&E of male rats treated with infected and cow milk (M3) showing the finger villi (A), columnar lining epithelial cells (B), goblet cells (C), the core of the villi containing white blood cells (D), the intestinal glands in the basal layer (E), and the smooth muscle layer (F). CH2E (10X)
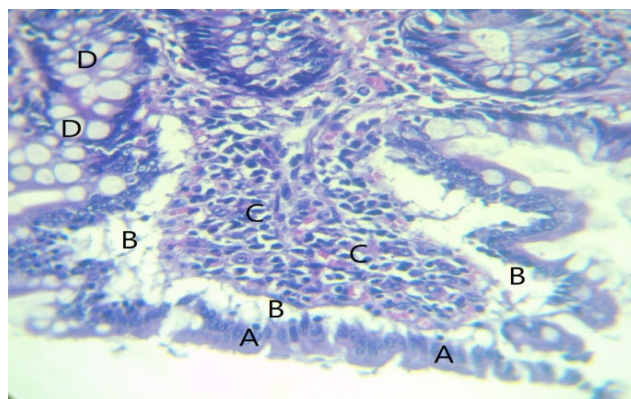

Figure 4: A cross-section of the wall of the small intestine stained with H&E of male rats treated (M4) with intestinal ulcers and treated with glutathione, showing simple columnar epithelial cells (A), shrinkage of the villi (B), infiltration of white blood cells and macrophages in the villi (C), and intestinal glands with mucus droplets (D). CH2E (40X)

intestinal glands were spread, and around them were white blood cells in the interstitial tissue of the primary sheet, Figure 2.

The wall of the small intestine is damaged by its mucosal layer containing finger-shaped intestinal villi extending into the intestinal lumen, and some villi were found shorter than others extended. All villi were lined with simple columnar cells, and between these cells appeared a limited number of mucus-secreting goblet cells. The core of the villi was filled with white blood cells spread in the basal layer under the villi and between the intestinal mucosal glands secreting yeasts. The submucosal layer contained some blood vessels and loose connective tissue, surrounded from the outside by a smooth muscle layer arranged in rows inward and outward longitudinally, Figure 3. There were a disintegration of the intestinal villi and a degeneration of a number of epithelial cells lining the intestinal mucosa wall and a shrinkage in the core of the villi containing white blood cells and those cells extending to the basal layer where the intestinal glands are located filled with mucus droplets, Figure 4.

The immune system relies on white blood cells (WBCs) to protect the body from pathogens and other harmful chemicals [8]. The present investigation found that total leukocyte count was reduced in ulcer-induced rats when cow milk was administered to them. This decline might be due to the reduction of systemic inflammatory responses brought about by the modulatory actions of bioactive milk components on the activity of immune cells. Previous research has shown that white blood cell (WBC) levels decrease after milk delivery, which is in line with our current results [9]. Antioxidant vitamins, especially vitamins C and E, found in milk, prevent oxidative damage to cell membranes and lymphocyte DNA [10].

A major acute-phase protein produced by hepatocytes in response to pro-inflammatory cytokines like IL-6, C-reactive protein (CRP) was considerably reduced in the ulcer model when cow milk was administered prior to ulcer formation [11].

Based on the observed reduction in CRP, it appears that milk could potentially reduce inflammation linked to stomach damage caused by ethanol. Glutathione supplementation, on the other hand, had no discernible effect on white blood cell or C-reactive protein levels in this animal, suggesting that it may have a more targeted function in modulating local oxidative stress rather than systemic inflammatory indicators.

We also looked at ALT and AST, which are markers of liver function. A sign of hepatocyte injury, ALT is unique to the liver, while AST can increase in diseases affecting other organs [12]. The results showed that neither ethanol-induced stomach damage nor glutathione treatment significantly changed ALT or AST levels, which is in line with the fact that the ulcer model is localized [13-13]. Based on these findings, it appears that the oxidative damage that was seen was mostly limited to the stomach tissues and did not cause any harm to the liver systemically.

The cellular redox equilibrium is affected by glutathione depletion during oxidative stress, which can hinder physiological responses [16]. Lipids, proteins, and DNA are all vulnerable to oxidative damage when exposed to ethanol, which produces reactive oxygen species (ROS) [17-20]. Biomarkers of oxidative stress intensity often include lipid peroxidation products, such as malondialdehyde (MDA) [18]. Pretreatment with cow's milk considerably decreased MDA levels, indicating efficient attenuation of lipid peroxidation [19], in contrast to the present study's finding that ethanol delivery raised gastric MDA content.

Milk protected stomach tissue from ethanol-induced damage, according to histopathological investigation. Rats given milk prior to surgery showed a significant improvement in gastric gland lesions compared to controls, including desquamation, bleeding, inflammatory infiltration, and severe localized epithelial damage. It appears from these results that milk has a dual effect on the stomach mucosal barrier, reducing oxidative stress and maybe improving it through enhanced mucin synthesis and epithelial integrity maintenance [21, 22].

Taken together, these findings demonstrate that cow's milk may protect the gastrointestinal tract from ulcers caused by ethanol. Instead of systemic changes in liver enzymes or leukocyte counts, the process seems to include lowering lipid peroxidation, maintaining epithelial integrity, and regulating local oxidative stress. To ensure translational relevance, future research should examine the effects of dairy proteins and glutathione in rats using various ulcer models, paying special attention to dose-dependent effects and molecular pathways.

CONCLUSIONS

This study found that there was a protective effect of cow's milk against gastrointestinal ulcers in rats by significantly reducing CRP, WBC, ALT, AST, and MDA. Alternatively, treatment with glutathione resulted in a considerable decrease in malondialdehyde (MDA) and an increase in tissue glutathione (GSH) levels, but no changes were observed in C-reactive protein (CRP), white blood cell (WBC), acid hydroxide (ALT), or aspartate aminotransferase (AST). This finding suggests that glutathione action is more of a targeted antioxidant than a systemic anti-inflammatory. The results show that glutathione has an antioxidant impact in experimental ulcer models and that cow's milk may have a gastroprotective function. To validate and expand upon these findings, additional research with larger samples, blind study designs, pasteurized milk, and dose-response assessments is necessary.

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