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Gastroprotective, Hepatoprotective, and Nephroprotective Effects of α-Lipoic Acid Against Aspirin-Induced Toxicity in Rats

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Abstract

Peptic ulcer disease continues to be a significant global health challenge, especially because of the nearly ubiquitous use of nonsteroidal anti-inflammatory drugs such as aspirin, which may cause gastric, liver and kidney toxicity. ObjectiveThis research was in order to study the gastroprotective, hepatoprotective and nephroprotective effects of α-lipoic acid (ALA) on acute aspirin-induced toxicity in rats compared to omeprazole. Four groups of 24 male albino rats were randomly assigned to create the normal control, the aspirin-treated negative control, and the omeprazole- or supplementary ALA-treated group. The treatments were given orally for 28 d. The levels of gastric acidity, pH, ulcer index, prostaglandin E_2 (PGE_2), liver enzymes and renal function markers as well as histopathological changes were evaluated. Gastric volume, acidity, ulcer area and ulcer index were significantly increased in the aspirin groups whereas gastric pH and mucosal PGE_2 levels were significantly decreased compared to control values ($p < 0.01$). High levels of serum and liver histopathological damage. Serum ALT, AST, ALP, creatinine and urea levels all peaked significantly higher than with no exposure or control animals (groups 1 and 2) indicating that both hepatic and renal function are impaired. A significant increase of gastric acidity and ulcer index, as well as PGE_2 levels was observed in aspirin-treated group when compared with ALA treated rats; inversely liver and kidney dysfunction marker were significantly ($p < 0.05$) well be decreased after ALA treatment compared with the aspirin-treated group. Histopathological analysis confirmed the protection effects of ALA evidenced by the preservation of tissue architecture and reduced inflammatory and degenerative changes. Though the protection provided by omeprazole was slightly better. These results suggest that alpha lipoic acid has important protective effects for the stomach, liver, kidneys of rats probably due to its beneficial action on the antioxidant system in varied rat tissues.

Keywords: α-lipoic acid, aspirin, gastroprotective, hepatoprotective, nephroprotective, PG E2

1. INTRODUCTION

Peptic ulcer disease is still a major worldwide health issue resulting in serious complications (gastrointestinal bleeding, perforation) which may lead to severe morbidity and mortality. Gastric acidity is a central determinant in ulcer formation, although peptic ulcers have a multifactorial pathogenesis. Risk factors such as smoking, drinking, psychological stress, spicy food and long-time use of NSAIDs may destroy the protective effects of stomach. These include the mucus barrier, bicarbonate secretion, prostaglandins and gastric hormones, all of these defenses usually preserve the integrity of the mucous membrane and prevent infection [1–3].

NSAIDs are the most widely used medications globally, but their benefits also have well-documented gastrointestinal risks. They are also associated with the emergence of new gastric mucosal erosions, ulcers, hemorrhages and even perforations. In patients with peptic ulcer disease, NSAIDs significantly increase the risk of serious complication [2–4]. The majority of these medicines act as an inhibitor for cyclooxygenase (COX) enzymes that are actively involved in the synthesis of prostaglandins which have a major role in pain and inflammation, but also responsible for gastric mucosal protection [1].

In addition to inhibiting prostaglandins, NSAIDs also contribute to the oxidative stress, which have a crucial role in gastric ulcer [5, 6]. The inflammatory processes triggered by NSAIDs generate large amounts of reactive oxygen species (ROS), such as hydrogen peroxide (H_2O_2) and superoxide radicals (O_2^-). These molecules are harmful to cellular structures and are involved in several pathological conditions, including gastric injury, atherosclerosis, neurodegeneration, renal damage, hepatic damage and arthritis. Their damaging effects include lipid peroxidation, cell apoptosis, neutrophil infiltration, and further suppression of prostaglandin synthesis [7].

It is also known that NSAIDs have a toxic effect on the kidneys, as they can cause two main types of acute kidney injury (AKI): hemodynamically mediated injury—such as decreased renal blood flow, immune-mediated and tubular necrosis_ injury, including acute interstitial nephritis [5, 6]. The underlying mechanism involves mitochondrial dysfunction in kidney cells, which leads to ROS overproduction and oxidative stress Additionally, inhibition of renal prostaglandins reduces the dilation of afferent arterioles, increasing vascular resistance and decreasing glomerular filtration rate (GFR), which ultimately contributes to kidney injury [7–10]. Although aspirin liver toxicity is considered to be dose-dependent, rheumatic patients maybe predisposed and even low-dose aspirins taken regularly might put the patient into higher risk of liver damage [9, 11, 12]. Histologic features in the liver include focal nonspecific necrosis with hepatocellular degeneration and hydropic changes [7, 10–13].

At present, proton pump inhibitors are regarded as some of the most powerful medications available for treatment of peptic ulcer disease. They predominantly act through irreversible blockade of proton pump (H^+/K^+-ATPase) in the parietal cell of stomach , which leads to inhibition of the final step in gastric acid secretion. PPIs markedly suppress acid production, leading to a less acidic gastric environment that allows for healing (two) of the injured gastric and duodenal mucosa. Decreased acid secretion does not solely relieve epigastric pain and discomfort-related symptoms, it also protects ulcerated mucosal surfaces from damage caused by excessive acid. This kind of friendly setting provides the optimal substrate for tissue regeneration and ultimately buena conduct for ulcer healing. In addition, PPIs are preventative on recurrence of the disease and reduce complications associated with ulcers such as bleeding and perforation particularly in patients taking NSAIDs or large group of treatment conditions like acid related GI diseases. PPIs remain the cornerstone of treatment and management for peptic ulcer disease due to their excellent antisecretory effect, duration of action [14].

Alpha-lipoic acid (ALA), also known as Thioctic acid is a naturally occurring compound with strong antioxidant properties [10]. Chemically known as 1,2-dithiolane-3-pentanoic acid ($C_8H_{14}O_2S_2$) [15]. Alpha-lipoic acid (ALA) has gained a huge attention for its ability to protect against damage associated with oxidative stress in various tissues. Recent studies suggest that ALA can effectively reduce colistin-induced nephrotoxicity. Functioning both Moreover, it has been shown to act as a potent antioxidant agent and co-factor in mitochondrial energy metabolism. ALA acts in both lipid and aqueous environments, scavenging reactive oxygen and nitrogen species such as hydrogen peroxide, hydroxyl radicals, peroxynitrite [10, 12]. It also possesses metal-chelating capabilities and rejuvenates endogenous antioxidants such as vitamins C and E, enhancing the body's intrinsic defense against oxidative damage [16]. Cellular and molecular protective mechanisms against NSAID hepatorenal toxicity via ALA has been shown in many studies [17], Various researches has been done on the combination of α-lipoic acid with other medications for the purpose of increasing therapeutic effects and a synergistic effect like Antioxidant Effects of Thioctic Acid, Metformin, Sitagliptin and Rosuvastatin in Diabetıc Rats [18]. α-Lipoic acid in an experimental gouty arthritis model: evaluation of xanthine oxidase inhibitory, antihyperuriceamic, antiinflammatory and analgesic effects [19], The Therapeutic Efficacy of α-Lipoic Acid and Gabapentin in Patients with Burning Mouth Syndrome: A Randomized Controlled Clinical Trial Write to the Author [20]. This paper will discuss the effect of hepatic, nephron-gastro protective in rats with use of acetyl salicylic acid drug. Investigating the potential protective effects of alpha lipoic acid in stomach, liver and kidneys against uses of non-steroidal anti-inflammatory drugs (NSAIDs) agents (aspirin) to long time.

2. MATERIALS AND METHODS

Animals and housing conditions. Twenty-four male albino rats weighing 170–200 g were obtained from the College of Veterinary Medicine, University of Basrah. The animals were housed in the animal care unit of the College of Pharmacy, University of Basrah, and allowed to acclimatize for three weeks under controlled laboratory conditions at $25 \pm 2\,^{\circ}\mathrm{C}$. Throughout the acclimatization period, the rats had unrestricted access to standard pelleted feed and clean drinking water to ensure appropriate adaptation and stabilization of body weight.

Experimental design and treatments. Following acclimatization, the animals were randomly allocated to four groups, with six rats in each group ($n = 6$):

- *Group A (normal control):* Rats received the vehicle only, consisting of 1% carboxymethyl cellulose (CMC) in distilled water.
- *Group B (negative control):* Rats received acetylsalicylic acid (aspirin) at a dose of $200\,\mathrm{mg\,kg^{-1}}$.
- *Group C (omeprazole-treated group):* Rats received omeprazole at a dose of $20\,\mathrm{mg\,kg^{-1}}$.
- *Group D (α-lipoic acid-treated group):* Rats received α-lipoic acid at a dose of $100\,\mathrm{mg\,kg^{-1}}$.

All treatments were prepared in a 1% CMC solution and administered orally by gavage once daily for 28 consecutive days. Animals in Groups C and D received aspirin one hour after the administration of omeprazole and α-lipoic acid, respectively.

Following the final treatment, the rats were anesthetized with chloroform, and the abdominal cavity was opened. Blood samples were collected by cardiac puncture and transferred into gel-containing tubes. The samples were centrifuged at $3500 \times g$ for 10 minutes, after which the serum was separated and stored at $-20\,^{\circ}\mathrm{C}$ until biochemical analysis. The stomach, liver, and kidneys were carefully excised, rinsed with normal saline, and prepared for gross and histopathological examination. Serum samples were used to assess biochemical markers of hepatic and renal function, including urea, creatinine, liver enzymes, and prostaglandin levels.

Gross evaluation of gastric lesions. The stomachs were excised after ligation of the esophageal and pyloric ends. Gastric contents were collected, and the stomach tissues were rinsed with normal saline. Gastric mucosal damage was quantified using ImageJ, a Java-based image-processing application. The ulcer index was calculated, and mucosal damage was expressed as a percentage of the total surface area of the glandular stomach, measured in square millimeters [21]. The ulcer index was calculated as

$$\mathrm{UI} = \frac{\text{ulcerated area } (\mathrm{mm^2})}{\text{total gastric area } (\mathrm{mm^2})} \times 100. \tag{1}$$

The percentage of ulcer inhibition was calculated as

$$\text{Ulcer inhibition } (\%) = \frac{\mathrm{UI}_{\text{negative control}} - \mathrm{UI}_{\text{treated}}}{\mathrm{UI}_{\text{negative control}}} \times 100. \tag{2}$$

Measurement of gastric volume and acidity. The gastric contents were aspirated and transferred to a graduated cylinder for volume measurement. The samples were centrifuged at $4000\,\mathrm{rpm}$ for 10 minutes, and the resulting supernatant was used for pH determination with a digital pH meter. For acidity measurement, $1\,\mathrm{mL}$ of gastric juice was mixed with $1\,\mathrm{mL}$ of distilled water. Two drops of phenolphthalein indicator were added, and the mixture was titrated with $0.01\,\mathrm{N}$ NaOH until a persistent pink color appeared [22]. Total acidity was calculated using

$$\text{Acidity} = \frac{V_{\mathrm{NaOH}} \times N_{\mathrm{NaOH}} \times 100}{0.1}\ \mathrm{mEq\,L^{-1}}, \tag{3}$$

where V_{NaOH} is the volume of NaOH used and N_{NaOH} is its normality.

Measurement of prostaglandin $\mathbf{E_2}$. Following blood collection, the serum was separated, and prostaglandin $\mathrm{E_2}$ ($\mathrm{PGE_2}$) levels were measured using an enzyme-linked immunosorbent assay kit supplied by Reed Biotech, USA. The $\mathrm{PGE_2}$ levels in the omeprazole- and α-lipoic acid-treated groups were compared with those in the aspirin-treated group.

Assessment of liver and kidney function. Serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (ALP) activities were determined using commercially available colorimetric assay kits supplied by Elabscience Biotechnology. These enzymes were measured as indicators of hepatocellular injury and hepatic functional status [24].

Serum creatinine concentration was measured using a commercial colorimetric assay kit supplied by Elabscience Biotechnology, USA. Serum urea concentration was determined using a blood urea nitrogen (BUN) colorimetric assay kit

based on the urease enzymatic method. Serum urea and creatinine levels were evaluated as indicators of renal functional status [23]. All biochemical parameters were quantified spectrophotometrically according to the standard operating procedures provided by the manufacturer to ensure the accuracy, reproducibility, and reliability of the analyses.

Histopathological examination. Samples of the stomach, liver, and kidneys were collected and fixed in 10% neutral-buffered formalin before routine histopathological processing. Tissue sections were stained with hematoxylin and eosin (H&E) and examined under a light microscope to assess tissue injury and associated inflammatory changes.

Statistical analysis. Statistical analyses were performed using GraphPad Prism version 8 (GraphPad Software, San Diego, CA, USA). Data were expressed as the mean $\pm$ standard deviation. Differences among the experimental groups were evaluated using one-way analysis of variance (ANOVA). Each treatment group was subsequently compared with the aspirin-treated group using an unpaired t-test. Differences were considered statistically significant at $P < 0.05$.

3. RESULT AND DISCUSSION

3.1. GASTRIC FLUID VOLUME, ACIDITY AND PH

The results of the present work revealed a high significant increase (p <0.001) in gastric volume content in the animals of negative group compared to normal control. Rats treated with α-Lipoic acid had significantly (p <0.001) lower gastric volumes compared to the negative control group. On the other hand, the gastric fluid volume in rats treated with omeprazole (positive group) dropped significantly (p <0.001) compared to that in the negative control group as shown in (Table 1, Figure 1-2).

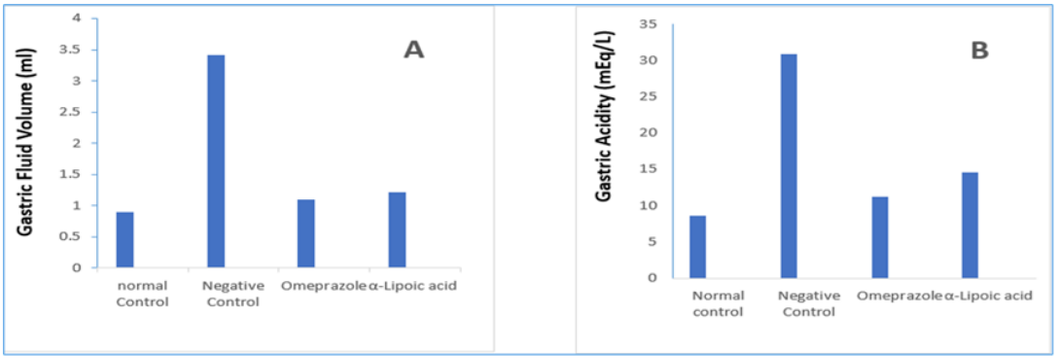

Figure 1. *Effect of α-Lipoic acid and Omeprazole on (A) the gastric fluid volume, and (B) gastric total acidity*

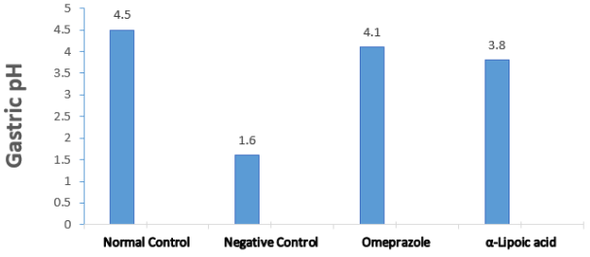

Figure 2. *Effect of α-Lipoic acid and Omeprazole on gastric pH*

The study showed significant changes in the gastric acidity and pH between the animal groups (P-value > 0.05). The negative control revealed a significant increase (p <0.001) in the gastric acidity and pH as compared with rats of normal control. The α-Lipoic acid and omeprazole (positive control) groups showed a significant decrease (p <0.001) in both of gastric acidity and pH compared to the negative control group as shown in (Table 1).

The present findings showed that the ulcer-induced group exhibited significant increases in gastric fluid volume and acidity, along with a marked decrease in gastric pH, indicating excessive acid secretion and gastric mucosal damage. Treatment with α-lipoic acid significantly reduced gastric volume and acidity while improving pH compared with the negative control group, suggesting a gastroprotective effect that may be related to its antioxidant activity and mucosal protective properties [12, 13, 24]. Omeprazole exerted a somewhat stronger activity because of its direct inhibition of gastric acid secretion. Collectively, these findings provide further evidence for the protective role of α-lipoic acid against gastric injury and hyperacidity.

Table 1. *Effect of α-Lipoic acid and Omeprazole on Gastric fluid volume, Gastric acidity and pH*

Group	Gastric Fluid Volume (ml)	Gastric Acidity (mEq/L)	pH
Normal control	0.95 ± 0.28	8.55 ± 1.25	4.5 ± 0.4
Negative control	3.42 ± 0.44 †††	30.86 ± 2.85 †††	1.6 ± 0.8 †††
Omeprazole	1.10 ± 0.34 ***	11.24 ± 1.84 ***	4.1 ± 0.6 ***
α-Lipoic acid	1.21 ± 0.25 ***	14.50 ± 2.45 ***	3.8 ± 0.7 ***

Data expressed as Mean ± SD., † p <0.05; †† p <0.01; ††† p <0.001 compared to normal control; * p <0.05; ** p <0.01; *** p <0.001 compared to negative control.

3.2. GASTRIC ULCER AREA, ULCER INDEX, AND LESION INHIBITION

There was a highly significant increase (p <0.001) in the gastric lesion areas in the stomachs of negative control group when compared to normal control group, while these areas were significantly decreased (p <0.001) with each of α-lipoic acid and omeprazole treatments compared with negative group. The ulcer index in the α-lipoic acid and omeprazole groups were also significantly lower than those in the negative control group. With respect to the percentage of ulcer inhibition; the use of positive drug (omeprazole) and α-lipoic acid resulted in (78.4 %) and (70.2 %) respectively, as shown in Table 2, Figure 3).

Results showed that negative control group demonstrated extensive gastric mucosal injury as indicated by the significantly (p < 0.001) increased ulcerated area and ulcer index compared to the normal control group. α-lipoic acid treatments produced a statistically significant (P<0.0001) decrease compared to the untreated groups in both ulcer area and ulcer index, demonstrating a protective effect for gastric mucosal damage. This might be due to its antioxidant and cytoprotective potential as it protects mucosal integrity and lessens tissue injury. Omeprazole was more effective than alpha lipoic acid in preventing the formation of lesions (by virtue of its potent anti-secretory action) [14]. However, the considerable inhibition produced by α-lipoic acid (70.2%) suggests that it has promising anti-ulcer activity and may contribute to gastric mucosal protection [12].

Table 2. *Effect of α-Lipoic acid and Omeprazole on Gastric Ulcer Area, Gastric Ulcer Index, and Percentage of Lesion Inhibition*

Group	Total Gastric Area (mm2)	Ulcerated Area (mm2)	Ulcer Index	% Inhibition
Normal control	460 ± 40	-	-	-
Negative control	480 ± 28	158 ± 10 †††	32.9 †††	-
Omeprazole	510 ± 46	36 ± 6 ***	7.1 ***	78.4 ***
α-Lipoic acid	490 ± 36	48 ± 8 ***	9.8 ***	70.2 ***

Data expressed as Mean ± SD., † p <0.05; †† p <0.01; ††† p <0.001 compared to normal control; * p <0.05; ** p <0.01; *** p <0.001 compared to negative control.

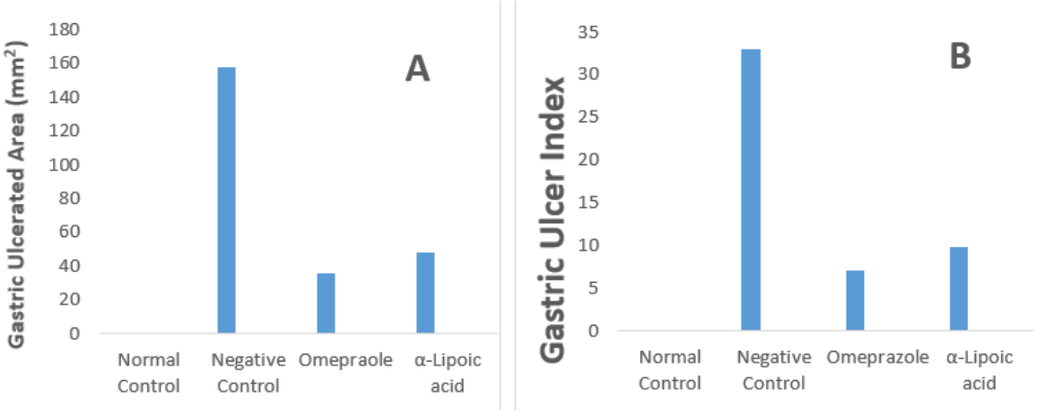

Figure 3. *Effect of α-Lipoic acid and Omeprazole on (A) gastric ulcerated area and (B) gastric ulcer index*

3.3. GROSS EVALUATION OF GASTRIC LESIONS

Macroscopic analysis shows that omeprazole and α-lipoic acid have gastroprotective effects (78.4% and 70.2%, respectively). The pictures of the 4 treatment groups are shown in Figure 4A–D. In comparison with the negative group (Figure 4B), the antiulcer efficacy of omeprazole (Figure 4C) and α-lipoic acid (Figure 4D) was similar and easily visible. Macroscopic examination showed obvious gastric lesions in the negative control group but omeprazole and α-lipoic acid treatment significantly reduced macroscopic mucosal damage. Both treatments displayed significant gastroprotective effects indicated by less ulceration and a better gastric appearance than the untreated group. Omeprazole was slightly more

protective although [8]. There was also a significant reduction of lesions produced by α-lipoic acid, which supports its possible beneficial action on the gastric mucosa to support protection from ulcerative dysregulation.

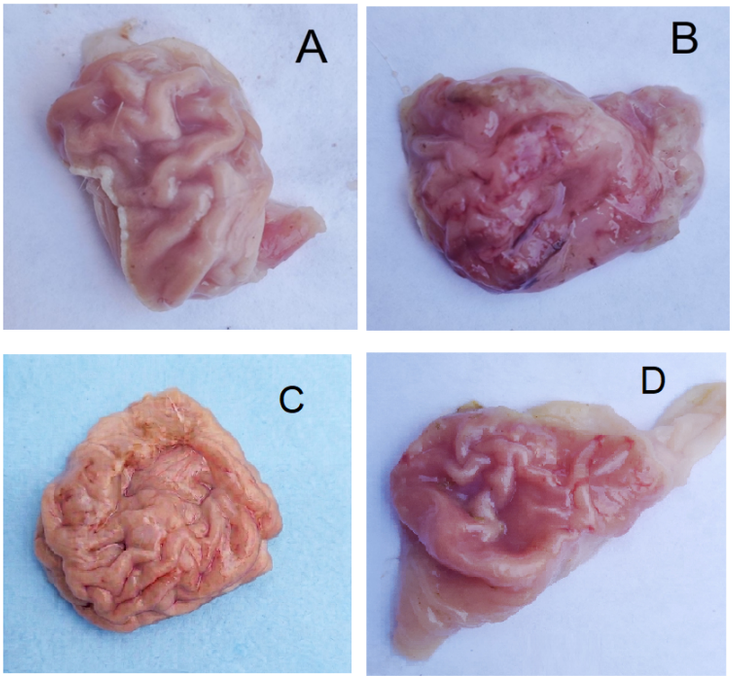

Figure 4. *Representative images of stomachs from experimental groups: (A) normal control (B) negative control (C) omeprazole (20 mg/kg), (D) α-Lipoic acid (100 mg/kg)*

3.4. PROSTAGLANDIN E_2 (PG E_2)

Quantification of prostaglandin E2 (PG E2) was performed using an ELISA method (Reed Biotech), this sensitive and reliable assay supports the validity and accuracy of findings obtained in this work.

Results shown in (Table 3, Figure 5) show that aspirin, omeprazole and α-lipoic acid significantly modulating of gastric levels of prostaglandin E2 a mediator involved in maintaining gastric mucosal integrity.

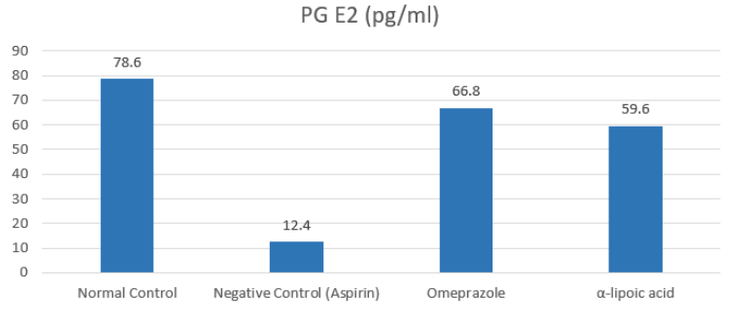

Figure 5. *Effect of alpha lipoic acid and omeprazole on prostaglandin (PG E2)*

PG E2 levels were high (78.6 pg/ml) in the normal control group, indicating a physiological condition where this prostaglandin is involved in mucosal defense through stimulation of mucins, mucus and bicarbonate secretion as well as adequate blood flow. However, administration of aspirin (200 mg/kg) for the negative control animals caused a significant decrease in PG E2 levels from 12.4 pg/ml($p<0.001$) compared with normal control. This decrease in prostaglandin is in accordance with the previously described inhibition of cyclooxygenase (COX) enzymes by aspirin, resulting in inhibition of prostaglandin production and increasing susceptibility of gastric mucosal injury—this also reiterates our findings mentioned within the introduction to this study [1].

After treating the rats with Omeprazole (20 mg/kg), PG E2 levels were significantly restored (66.8 pg/ml; $p<0.001$) when compared to negative control group. Although best known as an acid-suppressive agent, this observation indicates that omeprazole might also enhance mucosal defenses indirectly via prostaglandin sparing. Administration of α-Lipoic acid (100 mg) also caused a significant increase of PG E2 levels (59.6 pg/ml compared to negative control $p < 0.001$) though still lower than changes in the Omeprazole group. This effect can be because of its powerful antioxidant activity, which

could ameliorate oxidative damage, protect COX enzyme activity, and consequently facilitate prostaglandin synthesis as already discussed [12].

Overall, these results suggest that α-lipoic acid has a protective effect on aspirin-induced gastric ulceration, partially through restoration of PG E2 levels. It is somewhat less potent than omeprazole, but is nevertheless quite effective and provides a rationale for possible use as an adjunct therapeutic agent.

Table 3. *Effects of α-lipoic acid on PG E_2 in aspirin-induced ulcer rats*

Group	Dose	PG E2 (pg/ml)
Normal Control	-	78.6
Negative Control (Aspirin)	200 mg/kg	12.4 †††
Omeprazole	20 mg/kg	66.8 ***
α-lipoic acid	100 mg	59.6 ***

Data expressed as Mean ± SD., † p <0.05; †† p <0.01; ††† p <0.001 compared to normal control; * p <0.05; ** p <0.01; *** p <0.001 compared to negative control.

3.5. LIVER AND RENAL FUNCTION TESTS:

The biochemical results (Table 4, Figure 6-7) demonstrate a clear trend towards hepatic and renal impairment after aspirin treatment with the ability of α-lipoic acid to provide striking protection.

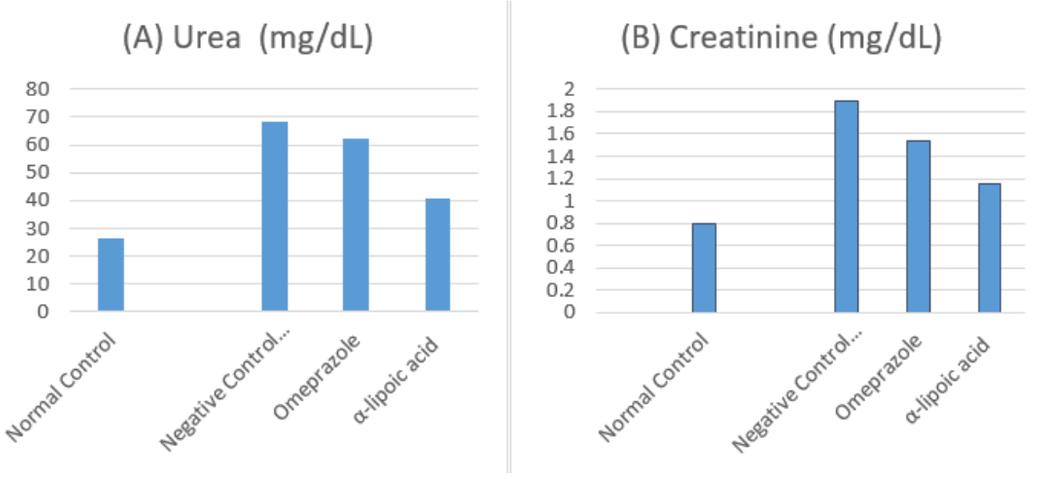

Figure 6. *Effects of omeprazole and alpha lipoic acid on urea (A) and creatinine (B)*

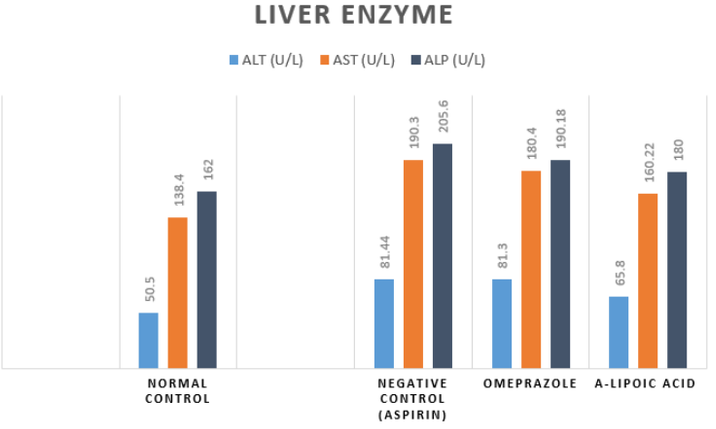

Figure 7. *Effects of alpha lipoic acid and omeprazole on liver enzyme*

Compared to the normal control, Alanine aminotransferase (ALT), Aspartate aminotransferase (AST) and Alkaline phosphatase (ALP) demonstrated a nearly significant increase in liver enzymes in the negative control group (p <0.001). Such an increase suggests hepatocellular injury and/or disruption of membrane integrity with leakage of such enzymes into the circulation. At the same time, it is known that renal function markers i.e. Creatinine and Urea also increased remarkably (p<0.001), suggesting an impaired renal function. These changes are consistent with the established systemic

toxicities of aspirin, which are predominantly mediated by oxidative stress and mitochondrial damage [4].These indicators were slightly improved with omeprazole therapy. All groups received a significant reduction ($p < 0.05$) in the levels of ALT, AST and ALP compared to the negative control group, approaching even the values recorded in the normal group. In a similar trait, creatinine levels were also having significant reduction ($p < 0.05$) while the decline in urea reading was not quite significant which shows some kind of recovery are seen in kidney functions [7–10].

Table 4. *Effects of α-lipoic acid on the serum levels of ALT, AST, ALP, Creatinine and Urea in aspirin-treated rats*

Group	ALT (U/L)	AST (U/L)	ALP (U/L)	Creatinine (mg/dL)	Urea (mg/dL)
Normal Control	46.26 ± 8.46	132.42 ± 10.82	154.6 ± 11.25	0.78 ± 0.11	24.84 ± 3.36
Negative Control (Aspirin)	86.44 ± 7.25 †††	188.36 ± 12.32 †††	196.46 ± 14.26 †††	1.82 ± 0.18 †††	64.88 ± 6.24 †††
Omeprazole	78.36 ± 6.86 *	176.24 ± 8.76 *	181.18 ± 10.16 *	1.54 ± 0.08 *	60.32 ± 4.32
α-lipoic acid	60.84 ± 8.28 ***	152.22 ± 11.26 **	171.24 ± 28 **	1.16 ± 0.16 ***	38.82 ± 5.21 ***

Data expressed as Mean ± SD., † p <0.05; †† p <0.01; ††† p <0.001 compared to normal control; * p <0.05; ** p <0.01; *** p <0.001 compared to negative control.

Oral supplementation of α-lipoic acid showed very significant improvement in all hepatic and renal markers. These probenecid-induced reductions in serum levels of ALT, AST, and ALP were significantly lower than those of the negative group (p <0.001–0.01). There was a notable significant reduction for creatinine and urea level. The potent protective effect of α-lipoic acid, due most likely to its strong antioxidant capacity, notably scavenging reactive oxygen species and preserving [25] the integrity of liver and kidney tissues are indicated in these data [17]. Overall, our data show that aspirin caused significant liver and kidney dysfunction, whereas α-lipoic acid alleviated these adverse effects. While omeprazole appears more effective than α-lipoic acid in restoring biochemical parameters towards normal, the latter seems to play a significant protective role and may be useful as an adjunct for reducing organ toxicity induced by aspirin.

3.6. HISTOPATHOLOGICAL EXAMINATION OF RENAL

Histopathological assessment of renal tissues exhibited distinct differences between the experimental groups and mirrored the effects of administered treatments on kidney architecture and cellular integrity.

When looking into the control group (Figure 8), the renal tissue appears with normal histological features. Glomeruli were of normal size and shape with intact Bowman's capsules and preserved basement membranes. Also, the proximal and distal convoluted tubules were normal without evidence of degeneration, necrosis or infiltrate inflammatory. These results confirm the lack of pathological changes in untreated animals and indicate healthy renal architecture.

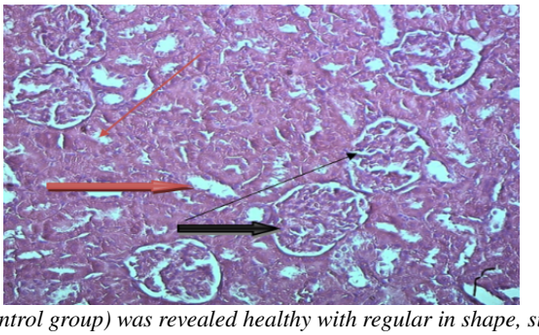

Figure 8. *Microscopic of renal rats (control group) was revealed healthy with regular in shape, size, space, vascular pole and basement membrane of glomeruli surrounded by Bowman's capsule (black arrow), normal proximal and distal convoluted tubules were observed (red arrow).H&E:20X*

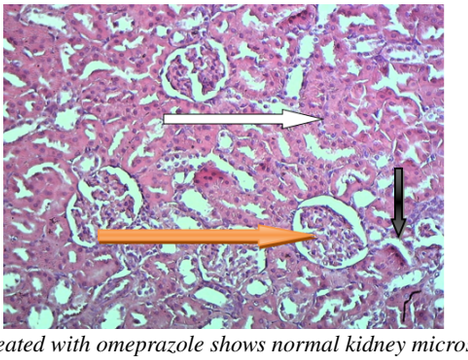

Figure 9. *Photomicrographs of rat kidneys treated with omeprazole shows normal kidney microscopic respectively, glomeruli surrounded by Bowman's capsule (red arrow), renal tubules (white arrow), thickness with proliferating epithelial cells afferent arteriole (black arrow). H&E:20X*

Likewise, renal histology in the omeprazole-treated group (Figure 9) was nearly normal. The glomeruli were normal in organization and associated with intact Bowman's capsules, whereas the renal tubules appeared structurally preserved. Histopathological Findings: We observed mild epithelial proliferation and slight thickening in the afferent arteriole which could indicate an adaptive or protective response (fig. Conclusions: Omeprazole was not associated with significant renal injury in this study. For renal tissue was consisted of the normal microscopic structure in group of rats treated with α-lipoic acid (Figure 10). Renal filtration structures were preserved as glomeruli retained normal morphology and size. Mild renal tubular thickening was observed while there was no gross necrosis, edema or severe degenerative changes. These findings confirm the protective and antioxidant role of α-lipoic acid [16]. which likely play a role in preserving renal cellular architecture and preventing trauma from oxidative stress.

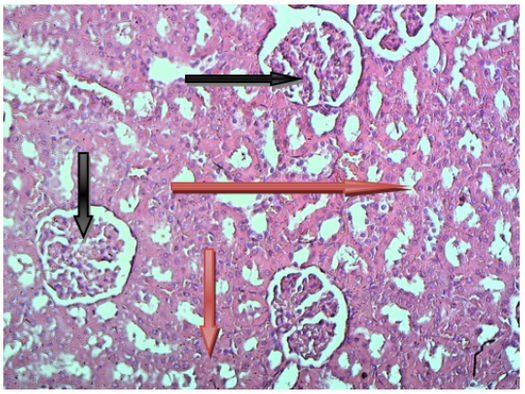

Figure 10. *Microscopic of renal treated with alpha lipoic acid showed normal glomeruli structured with normal size (black arrow). Thickness of renal tubules was appeared (red arrow). H&E:20X*

In contrast, histopathological changes showing renal injury were observed in the acetylsalicylic acid-treated group (Figure 11). The glomeruli were hypercellular with some thickening of the basement membranes with varying size and shape which is typical of damage / inflammatory change (Figure 3).

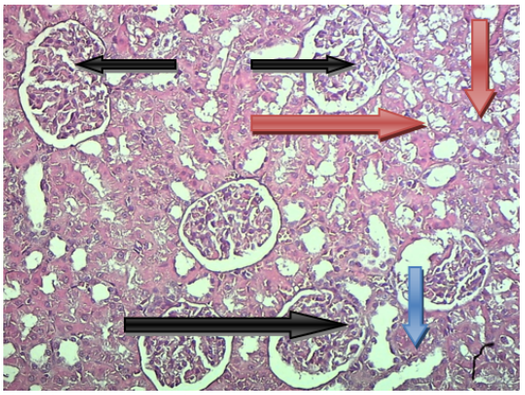

Figure 11. *Microscopic of renal treated with acetyl salicylic acid showed hyper cellular with thickness of basement membranes (black arrow) with different in size and ship observed; all proximal convoluted tubules are necrotic changes with thickness (red, green arrow), the proximal and distal tubules are edematous with dilated (blue arrow).H&E:20X*

Moreover, the proximal convoluted tubules showed extensive necrotic changes and tubular dilatation, while both proximal and distal tubules had edema and dilation. These pathological findings reveal major nephrotoxicity due to administration of acetylsalicylic acid. The tubules changes and edema are possibly due to oxidative stress, decelerated renal blood flow that can be induced by NSAID treatment [4–6].

In summary, the histopathological observation reveals that acetylsalicylic acid produced conspicuous renal structural damage [7–10], while α-lipoic acid and omeprazole retained normal renal architecture with only small changes. Antioxidants and free radical scavengers are known to prevent cellular injury not just by inhibiting oxidative stress but also by maintaining tissue integrity and thereby hold nephroprotective properties, which might be the reason behind α-lipoic acid exhibiting nephroprotection [10–12].

3.7. HISTOPATHOLOGICAL EXAMINATION LIVER OF RATS

Histopathological examination of liver tissues verified the apparent differences Histopathological examination of liver tissues confirmed the clear differences between experimental groups. The normal hepatic architecture along with the intact

hepatocytes and central veins and sinusoids in the liver (Figure 12) confirms the healthy tissue from the control group. In contrast, the acetyl salicylic acid–treated induced group (Figure 13) showed marked hepatic injury such as hepatocyte swelling, nuclear necrosis, sinusoids lose and inflammatory cell infiltration that indicate severe oxidative and inflammatory damage [7, 10–13].

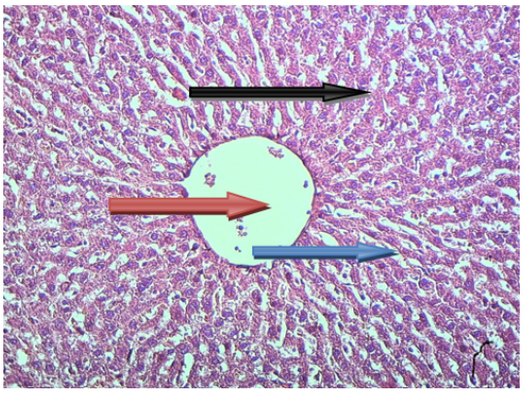

Figure 12. *Micrograph of liver of control group rats with normal hepatocyte architecture (black arrow), normal central vein (red arrow) and normal sinusoid (blue arrow) with in normal limit (WNL). H&E:20X*

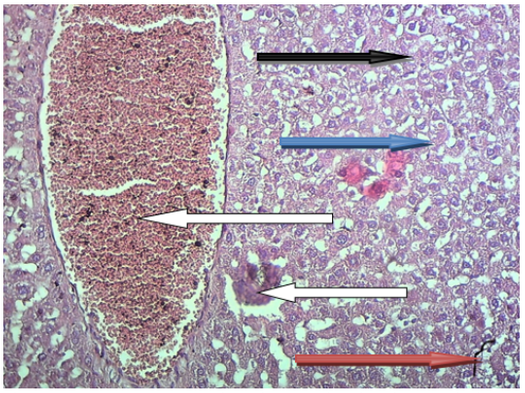

Figure 13. *Micrograph of liver of induced rat group post treated with acetyl salicylic acid showed hypertrophied hepatocyte (black arrow) with pyknotic and necrotic of some nuclei of hepatic cells (blue arrow), pale appearance narrow or complete cancellation of sinusoids and congested hepatic vein (white arrow) and focal area of hepatic necrosis were infiltrated by leucocytic cells (red arrow). H&E:20X*

Partial histological improvement was achieved with treatment α-lipoic acid (Figure 14) due to the fact that some of the hepatocytes maintain an almost normal morphology but mild changes at cellular level were observed [10, 12, 17]. This protective effect might be linked to the antioxidant role of α-lipoic acid. On the other hand, the omeprazole treated group (Figure 15) showed an almost normal liver architecture with significant improvement in pathological appearance which reflect more potent hepatoprotective activity.

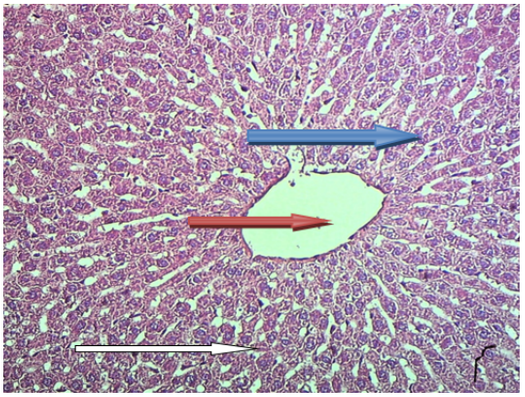

Figure 14. *Micrograph of liver rat treated with a lipoic acid alpha, clearly the hepatic vein (red arrow) that is normal and hepatocytes adjacent to the vein appear normal (blue arrow) and not in direct contact with blood vessels increase without apoptosis characterized by nuclei that shrink or pyknotic nuclei (black arrow). H&E: 20X*

In summary, the histological data corroborate the biochemical results thereby indicating that both α-lipoic acid and

omeprazole ameliorate hepatic injury with beneficial effects seen to be greater for omeprazole under present experimental conditions.

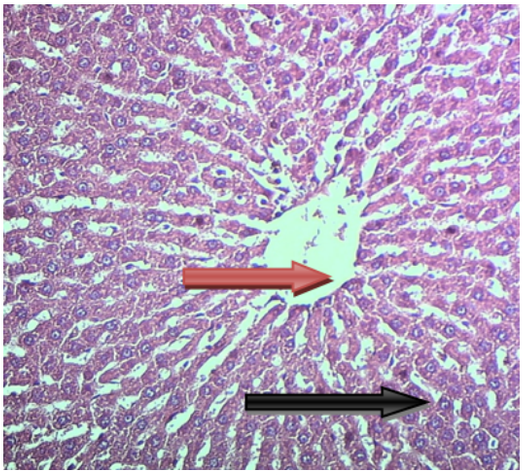

Figure 15. *In the present study, the liver section treated with omeprazole have normal hepatocyte (red arrow) and central vein (black arrow) was appeared compared with induced group. H&E:20X*

4. STUDY LIMITATIONS

The present study has several limitations that should be considered when interpreting its findings. First, the experiment included a relatively small number of animals, with six male rats assigned to each group. The exclusive use of male rats also limits the extent to which the findings can be generalized across sexes. Second, only one dose of aspirin, omeprazole, and α-lipoic acid was evaluated over a single treatment period. Consequently, the study does not establish dose–response relationships or determine whether the protective effects vary with treatment duration.

The study also did not include a group treated with α-lipoic acid alone. Therefore, its effects under normal physiological conditions could not be distinguished from its protective effects against aspirin-induced toxicity. In addition, the proposed antioxidant mechanism was not directly evaluated using oxidative-stress biomarkers such as malondialdehyde, reduced glutathione, superoxide dismutase, or catalase. The antioxidant explanation is therefore based primarily on the established properties of α-lipoic acid and the observed biochemical and histopathological improvements.

Histopathological findings were primarily described qualitatively, and no standardized injury-scoring system or blinded assessment procedure was reported. Future studies should include larger sample sizes, both sexes, multiple dose levels, quantitative histopathological scoring, oxidative and inflammatory biomarkers, and longer follow-up periods to confirm the protective mechanisms and therapeutic potential of α-lipoic acid.

5. CONCLUSION

Repeated aspirin administration produced substantial gastric, hepatic, and renal toxicity in rats. These effects were demonstrated by increased gastric fluid volume and acidity, reduced gastric pH, increased ulcerated area and ulcer index, depletion of prostaglandin E_2, elevation of hepatic and renal biochemical markers, and marked histopathological alterations in the stomach, liver, and kidneys.

Treatment with α-lipoic acid significantly reduced aspirin-induced gastric mucosal injury, decreased gastric acidity and ulcer formation, restored prostaglandin E_2 levels, and improved biochemical indicators of hepatic and renal function. The histopathological findings further demonstrated that α-lipoic acid preserved tissue architecture and reduced inflammatory, degenerative, and necrotic changes.

Omeprazole produced slightly greater protection against gastric ulceration and restored gastric defensive parameters more effectively. However, α-lipoic acid produced considerable gastroprotective effects and pronounced improvements in hepatic and renal markers, indicating broader systemic protection against aspirin-induced toxicity. These findings suggest that α-lipoic acid may have potential as an adjunctive protective agent during prolonged aspirin exposure. Further experimental and clinical investigations are required before its routine therapeutic use can be recommended.

ETHICS APPROVAL

All procedures involving animals were conducted in accordance with applicable institutional and national guidelines for the care and use of laboratory animals. The experimental protocol was reviewed and approved by the appropriate animal research ethics committee of the University of Basrah.

AUTHOR CONTRIBUTIONS

All authors contributed to the conception and design of the study, experimental procedures, acquisition and interpretation of the data, and preparation of the manuscript. All authors critically reviewed the manuscript, approved its final version, and agreed to be accountable for the integrity and accuracy of the work.

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CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest related to this study.

DATA AVAILABILITY

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

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