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Histopathological Study of N-acetyl-para-aminophenol-Induced Gastric Alterations and Ascorbic Acid Administration in Albino Rats

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ABSTRACT

N-acetyl-para-aminophenol (NAPA) is widely used as an analgesic and antipyretic drug; however, prolonged administration or high doses may adversely affect the gastrointestinal tract. The present study aimed to investigate the histopathological alterations induced by NAPA in gastric tissues and to evaluate the effects of ascorbic acid (AA) administration in albino rats. Thirty-five adult male albino rats were randomly allocated into five experimental groups: control, AA-treated, NAPA-treated, co-treated (AA + NAPA), and AA pre-treated groups. NAPA was administered orally at a dose of 500 mg/kg body weight for two weeks, while AA was administered at the same dose either alone, concurrently with NAPA, or before NAPA exposure. Histological examination of gastric tissues from NAPA-treated rats revealed pronounced pathological alterations, including epithelial disruption, mucosal necrosis, inflammatory cell penetration, vascular dilation, and submucosal oedema. Co-administration of AA with NAPA resulted in partial modulation of these histopathological changes; however, erosive and necrotic lesions remained evident. In contrast, AA pre-treatment did not confer a significant protective effect, as gastric tissues continued to exhibit marked pathological changes. In conclusion, NAPA induces significant gastric tissue injury in albino rats, and AA provides limited protection depending on the mode of administration. These findings may provide a basis for further studies exploring potential strategies to mitigate NAPA-induced gastric injury in humans.

1. INTRODUCTION

N-acetyl-para-aminophenol (NAPA), also known as acetaminophen, is one of the most widely used analgesic and antipyretic agents globally, available both by prescription and over-the-counter, due to its efficacy and generally favorable safety profile at therapeutic doses (Prescott, 2000; Ayoub, 2021). Despite its widespread use, accumulating experimental and clinical evidence indicates that prolonged or high-dose administration of NAPA can induce toxicity in multiple organs, including the liver (Ramachandran & Jaeschke, 2019; Alshailabi et al., 2021), kidneys (Abdallah et al., 2016; El-Dduob et al., 2023), and gastrointestinal tract, particularly the stomach (Laine, 2004; González-Pérez & García Rodríguez, 2006). The gastric mucosa is especially vulnerable to drug-induced damage because of its direct exposure to orally ingested compounds and their reactive metabolites (Bordin et al., 2023). NAPA has been shown to compromise mucosal defense mechanisms via oxidative stress (OS), mitochondrial dysfunction, and depletion of endogenous antioxidants, leading to epithelial deterioration, inflammatory penetration, and mucosal erosion (Ramachandran et al., 2018; El-Dduob et al., 2023). Additionally, OS has been recognized as a central mechanism underlying NAPA-induced tissue injury (Jin & Park, 2012), where the excessive production of reactive oxygen species (ROS) initiates lipid peroxidation (LPO), protein oxidation, and nucleic acid damage, ultimately resulting in cellular necrosis and impaired tissue function (D'Oria et al., 2020; Asrafiel et al., 2024). Such findings have prompted increasing interest in the use of antioxidants as protective agents capable of mitigating the adverse effects of NAPA and other OS-inducing compounds (Deavall et al., 2012; Alshailabi et al., 2021; Gulcin, 2025). Antioxidants constitute a broad class of compounds that protect tissues against oxidative damage by scavenging free radicals, enhancing endogenous antioxidant defense systems, and maintaining redox homeostasis, where both enzymatic antioxidants (e.g., superoxide dismutase, catalase, glutathione peroxidase) and non-enzymatic antioxidants (e.g., vitamins C and E, flavonoids, polyphenols) have demonstrated the ability to reduce cellular injury in various experimental models of drug-induced toxicity (Pandey & Rizvi, 2009; Forman & Zhang, 2021) By neutralizing ROS and limiting LPO, antioxidants help preserve cell membrane integrity, maintain protein function, and prevent inflammation-induced tissue damage (Lobo et al., 2010; El-Dduob et al., 2023). Ascorbic acid (AA), a water-soluble vitamin and potent antioxidant, has been extensively studied for its protective properties against OS-related tissue injury (Pullar et al., 2017). Beyond its systemic antioxidant activity, AA has been shown to exert specific gastroprotective effects, including stabilization of gastric mucosal membranes, attenuation of inflammatory responses, and promotion of tissue repair following chemically induced gastric injury (Becker et al., 2003; Koc et al., 2008). Experimental studies have suggested that AA can restore depleted antioxidant levels, reduce ROS generation, and suppress pathways involved in cellular apoptosis and necrosis, thereby limiting tissue damage (Adeneye & Olagunju, 2008; Shati et al., 2022; Zheng et al., 2024). Despite these findings, understanding these effects is important because it could provide a practical strategy to prevent or reduce gastrointestinal toxicity associated with high-dose or prolonged NAPA administration. Therefore, the present study was designed to evaluate the histopathological alterations induced by NAPA in gastric tissues and to examine the effects of AA administration under different treatment regimens in albino rats.

2. METHOD

Experimental Animals

Thirty-five adult male albino rats (*Rattus norvegicus*), weighing between 200 and 250 g, were used in this study. The animals were obtained from the Central Animal House, College of Veterinary Medicine, University of Omar Al-Mokhtar, El-Beyda, Libya, and were housed under standard laboratory conditions (22–25 °C, 12-hour light/dark cycle) with free access to food and water. All experimental procedures were carried out in accordance with institutional and international ethical guidelines for animal research. The experimental protocol was adapted from our previously validated histological procedures applied to hepatic tissues (Alshailabi et al., 2021), with modifications for gastric tissue assessment.

Experimental Design

The rats were randomly assigned to five groups (n = 7 per group) as follows:

- Control group: Received distilled water orally for two weeks.
- AA group: Received AA at 500 mg/kg body weight orally (Adeneye and Olagunju, 2008) for two weeks.
- NAPA group: Received NAPA at 500 mg/kg body weight orally (Modo et al., 2015) for two weeks.
- AA + NAPA group (co-treated): Received AA and NAPA concurrently at the same doses (500 mg/kg each) for two weeks.
- AA per-treated group: Received AA (500 mg/kg) orally for one week, followed by NAPA (500 mg/kg) for an additional one week.

Tissue Sampling

At the conclusion of the experimental period, all animals were euthanized under anesthesia. The stomachs were carefully excised, rinsed in normal saline, and fixed in 10% neutral buffered formalin for histological processing (Lillie, 1954).

Histopathological Examination

Fixed gastric tissues were processed using standard histological techniques, embedded in paraffin, and sectioned at a thickness of 4–5 µm. Sections were stained with hematoxylin and eosin (H&E) for microscopic evaluation (Lillie, 1954). Histopathological assessment focused on the integrity of the mucosa, epithelial alterations, inflammatory cell penetration, vascular congestion, and necrotic changes. For each animal, at least three tissue sections were examined, and a minimum of ten randomly selected microscopic fields per section were analyzed to ensure representative sampling (Haghighat et al., 2022). Gastric lesions were semi-quantitatively scored as absent (–), mild (+), moderate (++), or severe (+++) according to Moshaie-Nezhad et al. (2021) & Alshailabi et al. (2023).

Data Presentation

For each experimental group, mean semi-quantitative scores for all histopathological parameters were calculated and expressed as mean ± standard deviation (SD). Results were summarized in tables and illustrated graphically using bar charts to facilitate comparison of lesion severity among groups (Papparella et al., 2022). Semi-quantitative histopathological scores (– = 0, + = 1, ++ = 2, +++ = 3) were analyzed statistically. Comparisons among groups were performed using the Kruskal-Wallis test, followed by Mann-Whitney post-hoc tests for pairwise comparisons. A p-value < 0.05 was considered statistically significant. All analyses were conducted using SPSS version 20.

3. ETHICAL APPROVAL

Ethical approval for all animal experiments was obtained from the Al-Mukhtar Bioethics Committee, the Libyan National Committee for Biosafety and Bioethics, the Libyan Authority for Scientific Research, and the University of Omar Al-Mukhtar, El-Beyda, Libya (NBC: 007.A.26.67).

4. RESULT

Histopathological Results

Histological examination of gastric tissues from control rats revealed a typical histoarchitectural organization of the stomach wall. The mucosa exhibited an intact epithelial lining with well-defined gastric pits and regularly arranged gastric glands. All layers of the stomach, including the mucosa, muscularis mucosae, submucosa, muscularis externa, and serosa, appeared structurally preserved, with no evidence of cellular deterioration, inflammatory penetration, or vascular abnormalities (Figs. 1, 2). Similarly, gastric sections obtained from rats treated with AA alone demonstrated regular histological features comparable to those observed in the control group. The mucosal epithelium remained intact, gastric pits and glands were regularly organized, and no pathological alterations were detected, indicating that AA administration alone did not adversely affect gastric tissues (Figs. 3, 4). In contrast, marked histopathological alterations were observed in gastric tissues from rats treated with NAPA. These alterations were characterized by disruption of the luminal surface epithelium, damage to gastric pit cells, and the presence of deep gastric ulcerations associated with extensive necrosis involving the mucosal layer. Necrotic areas were frequently accompanied by vascular dilation and submucosal oedema (Fig. 5). Examination revealed necrotic foci between gastric glands, aggregation of inflammatory cells, dilated blood vessels, and persistent oedematous changes within the submucosa, reflecting severe gastric injury induced by NAPA administration (Fig. 6).

On the other hand, gastric tissues from rats receiving concurrent administration of AA and NAPA also exhibited pronounced pathological changes. The mucosa showed multiple erosions and deeper ulcerative lesions, often appearing as cup-shaped necrotic areas extending within the mucosal layer. Inflammatory cell penetration was evident. Exfoliation of necrotic epithelial cells into the gastric lumen and mild submucosal oedema were also observed (Fig. 7). Increased vascular dilation and mild congestion were observed, indicating that concurrent AA administration did not fully prevent NAPA-induced gastric injury (Fig. 8). Likewise, gastric sections from rats pre-treated with AA before NAPA exposure revealed persistent histopathological damage. The gastric mucosa exhibited surface epithelial disruption, focal and deep necrotic lesions, and areas of tissue deterioration accompanied by dilated blood vessels and submucosal oedema (Fig. 9). Moreover, demonstrated focal epithelial necrosis with disrupted cellular membranes, inflammatory cell infiltration, and oedematous changes (Fig. 10). In addition, haemorrhagic lesions were observed in some sections within the mucosa of the glandular stomach, together with inflammatory penetration and vascular dilation (Fig. 11). These findings indicate that AA pre-treatment did not confer a significant protective effect against NAPA-induced gastric damage under the present experimental conditions.

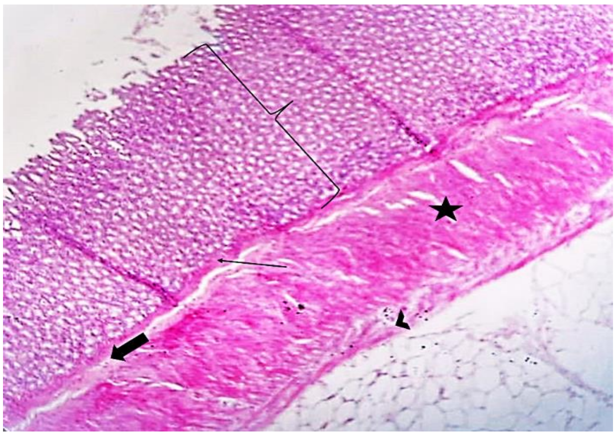

Fig. 1: The gastric tissue from control rats showing typical histological organization of the stomach wall, including intact mucosa (⫞), muscularis mucosae (long arrow), submucosa (thick arrow), muscularis externa (star), and serosa (head arrow). Well-defined gastric pits and glands are evident. (H&E stain, ×100)

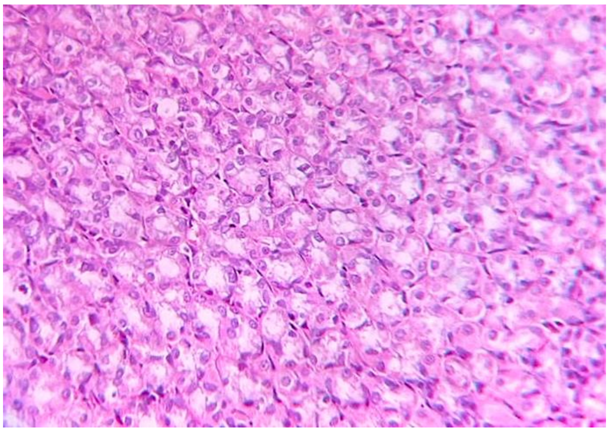

Fig. 2: The gastric tissue from control rats demonstrates typical gastric epithelial cells and regularly arranged gastric glands without detectable histopathological alterations. (H&E stain, ×400)

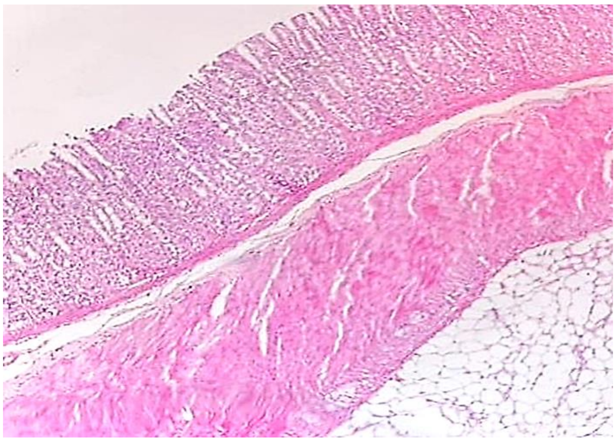

Fig. 3: gastric tissue from rats treated with AA alone showing preserved histological architecture of all gastric layers with intact epithelial lining, normal gastric pits, and well-organized glands. (H&E stain, ×100)

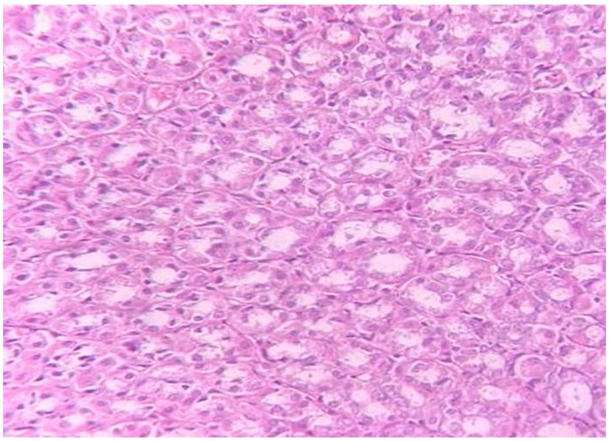

Fig. 4: The gastric tissue from AA-treated rats illustrates the typical morphology of gastric epithelial cells and glands comparable to those observed in the control group. (H&E stain, ×400)

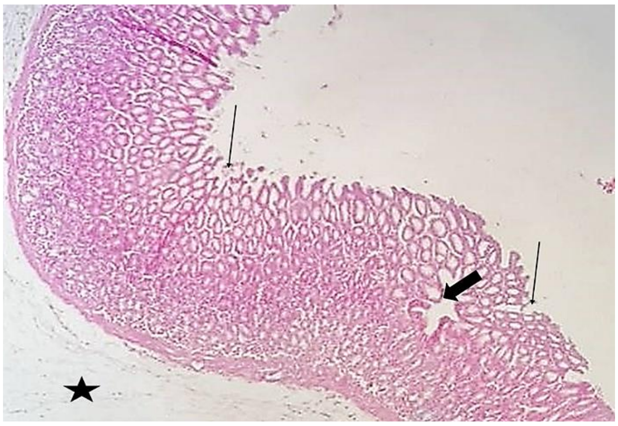

Fig. 5: The gastric tissue from NAPA-treated rats showing disruption of the luminal surface epithelium and gastric pits, accompanied by deep gastric ulceration and extensive necrosis involving the mucosal layer (arrows). Necrosis involving the mucosal layer (thick arrow), and submucosal oedema are also observed (star). (H&E stain, ×100)

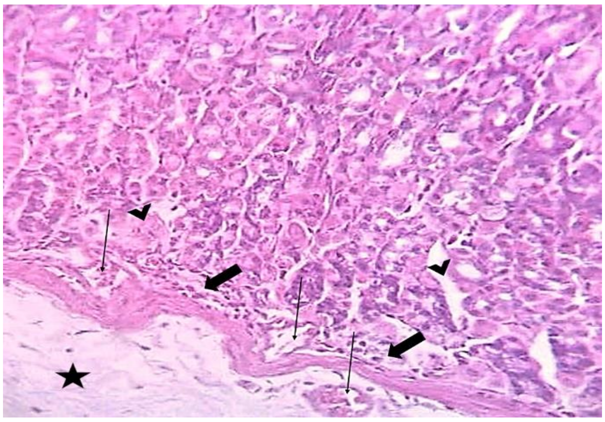

Fig. 6: The gastric tissue from NAPA-treated rats illustrating necrotic foci between gastric glands (head arrows), dilated blood vessels (thin arrows), aggregation of inflammatory cells (thick arrows), and mild submucosal oedema (star). (H&E stain, ×400)

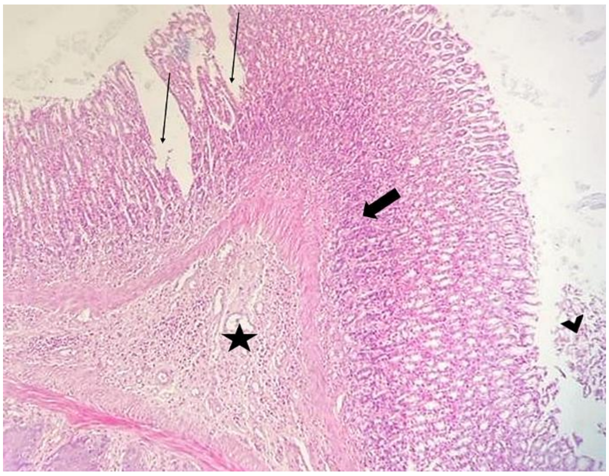

Fig. 7: The gastric tissue from the co-treated group showing multiple mucosal erosions and deeper ulcerative lesions appearing as cup-shaped necrotic areas within the mucosa (arrows). Inflammatory cell penetration (thick arrow), exfoliated necrotic cells within the gastric lumen (head arrow), and mild submucosal oedema (star) are also evident. (H&E stain, ×100)

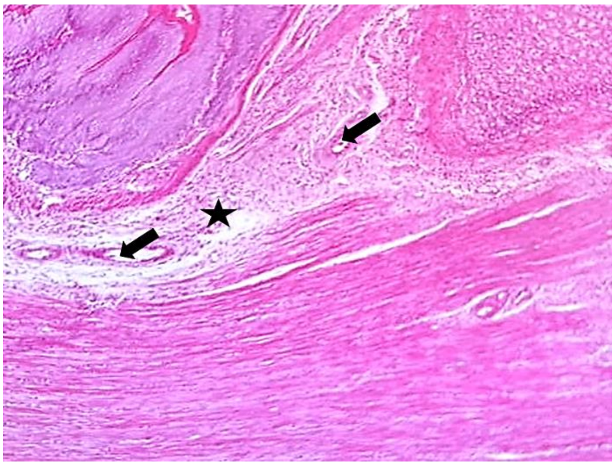

Fig. 8: The gastric tissue from the co-treated group demonstrating vascular dilation (thick arrows) with mild vascular congestion and associated submucosal oedema (star). (H&E stain, ×400)

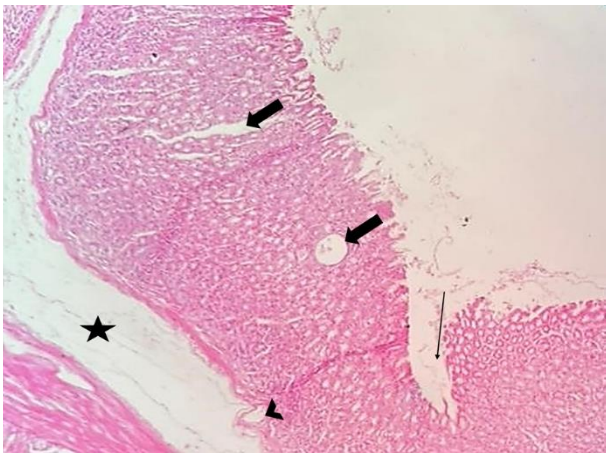

Fig. 9: The gastric tissue from AA pre-treated rats showing disruption of the surface epithelium, focal mucosal necrosis (arrow), necrotic areas (thick arrow), dilated blood vessels (head arrow), and mild submucosal oedema (star). (H&E stain, ×100)

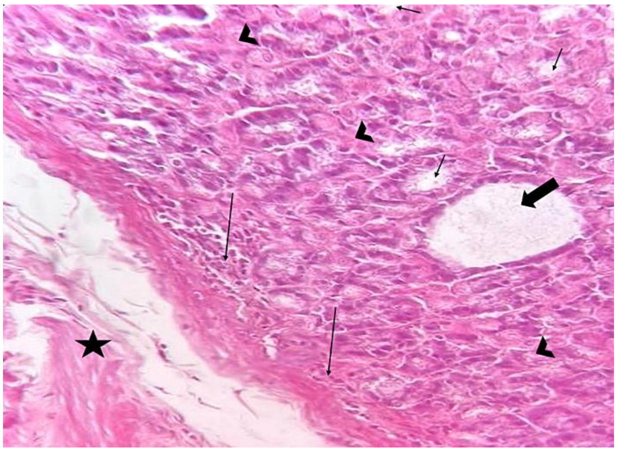

Fig. 10: The gastric tissue from AA pre-treated rats illustrating focal epithelial necrosis (small arrows) with necrosis involving the mucosal layer (thick arrow), disrupted cell membranes (head arrows), inflammatory cell penetration (thin arrows), and mild submucosal oedema (star). (H&E stain, ×400)

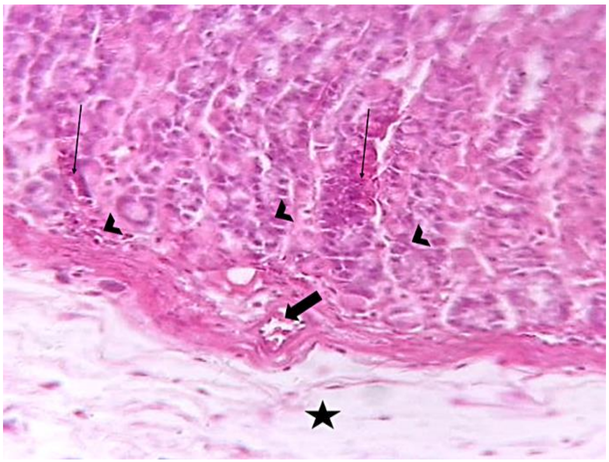

Fig. 11: The gastric tissue from AA pre-treated rats showing haemorrhagic lesions within the mucosa of the glandular stomach (thin arrows), accompanied by inflammatory cell penetration (head arrows), vascular dilation (thick arrow), and mild submucosal oedema (star). (H&E stain, ×400)

Semi-Quantitative Histopathological Scoring of Gastric Tissues

Control and AA-treated groups exhibited normal gastric architecture, with all histopathological parameters scored as absent (–). Moreover, NAPA administration induced marked gastric injury, with severe mucosal disruption, epithelial alterations, necrotic changes, moderate inflammatory penetration, and mild vascular congestion. Scores in the NAPA group were significantly higher than Control and AA groups for mucosal integrity, epithelial alteration, and necrotic changes ($p < 0.001$, Table 1, Fig. 12). While, co-treatment with AA (AA + NAPA) partially reduced lesion severity, with significant improvement in mucosal integrity and necrotic changes compared to NAPA alone ($p < 0.05$), although inflammatory penetration and vascular congestion showed no significant difference ($p > 0.05$). Pre-treatment with AA (AA Pre-treated) did not significantly reduce lesion severity compared to NAPA ($p > 0.05$).

These results indicate that NAPA causes pronounced gastric damage, co-administration of AA provides limited protection, and pre-treatment with AA is ineffective under the current experimental conditions.

Table 1: Semi-quantitative histopathological scoring of gastric tissues across experimental groups

Group	Mucosal integrity	Epithelial alteration	Inflammatory cell penetration	Vascular congestion	Necrotic changes
Control	–	–	–	–	–
AA	–	–	–	–	–
NAPA	+++	+++	++	+	+++
AA + NAPA (co-treated)	++	++	+	+	++
AA pre-treated	++	++	++	+	++

Scoring system: Absent/ normal (–), Mild (+), Moderate (++), Severe (+++)

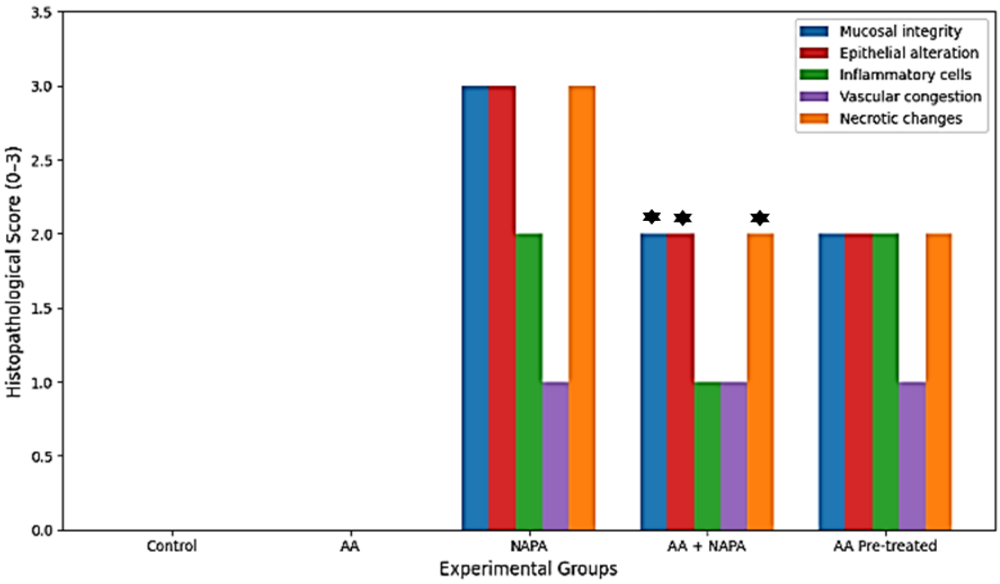

Fig. 12: Semi-quantitative histopathological scoring of gastric tissues in experimental groups.
"*p < 0.05 vs NAPA group (Mann-Whitney test)"

5. DISCUSSION

In the present study, histopathological analysis revealed that administration of NAPA induced marked gastric injury in albino rats. The observed alterations, including epithelial disruption, necrosis of the mucosal layer, inflammatory cell penetration, vascular dilation, and submucosal oedema, are consistent with the known toxic effects of NAPA on gastrointestinal tissues. These findings support previous reports indicating that high doses or prolonged use of NAPA can compromise gastric mucosal integrity through mechanisms involving OS, mitochondrial dysfunction, and depletion of endogenous antioxidant defenses (Cho & Ogle, 1990; Nakamoto et al., 1997). Moreover, OS appears to play a central role in the pathogenesis of NAPA-induced gastric injury. Excessive generation of ROS can initiate LPO, protein oxidation, and nucleic acid damage, leading to cellular necrosis and impaired tissue function.

In this context, the histopathological observations of necrosis, inflammatory penetration, and submucosal oedema likely reflect the direct consequences of ROS-mediated tissue damage (Cho & Ogle, 1990; González-Pérez & García Rodríguez, 2006; Jaeschke et al., 2012). The disruption of gastric epithelial cells and deterioration of gastric glands observed in NAPA-treated rats are in line with prior experimental studies highlighting the susceptibility of the gastric mucosa to oxidative injury (Jaeschke et al., 2012; Asrafiel et al., 2024).

Furthermore, concurrent administration of AA with NAPA produced moderate modulation of gastric injury. Sections from the co-treated group demonstrated erosive and necrotic lesions similar to those observed in NAPA-treated rats, although vascular congestion and submucosal oedema appeared slightly less pronounced. These findings suggest that AA, when administered simultaneously with NAPA, may partially interact with the oxidative processes induced by the drug, potentially mitigating, but not fully preventing, gastric damage. The observed partial attenuation is consistent with the known antioxidant properties of AA, which include ROS scavenging, restoration of endogenous antioxidant levels, and stabilization of cellular membranes (Becker et al., 2003; Koc et al., 2008; Pullar et al., 2017).

Interestingly, pre-treatment with AA before NAPA exposure did not confer a clear protective effect. Histopathological alterations in this group, including mucosal necrosis, inflammatory penetration, haemorrhagic lesions, and submucosal oedema, were comparable in severity to those observed in rats treated with NAPA alone. This outcome may reflect several factors: the high dose of NAPA used in the current study may have overwhelmed the antioxidant capacity provided by AA, the duration of pre-treatment may have been insufficient to accumulate protective concentrations in gastric tissues, or AA alone may not be adequate to counteract the complex mechanisms underlying NAPA-induced gastric injury. Similar observations have been reported in other studies where antioxidant pre-treatment failed to fully prevent tissue damage under conditions of severe OS (Lobo et al., 2010; Halliwell & Gutteridge, 2015; Zheng et al., 2024).

Furthermore, the semi-quantitative histopathological scoring supported the qualitative microscopic observations and confirmed the severity of gastric injury induced by NAPA administration. The elevated scores recorded for mucosal disruption, epithelial damage, and necrosis indicate extensive tissue injury, consistent with previous studies reporting that NAPA-induced toxicity is closely associated with OS-mediated mechanisms leading to gastric mucosal damage (Jaeschke et al., 2012; Du et al., 2016; Alshailabi et al., 2021). Besides, the moderate reduction in histopathological scores observed in the co-treated group suggests a limited modulatory influence of AA when administered concurrently with NAPA. However, the persistence of necrotic and inflammatory alterations indicates that this effect was insufficient to fully prevent NAPA-induced gastric injury, particularly under conditions of sustained or severe toxic exposure (González-Pérez & García Rodríguez, 2006; Jaeschke et al., 2012). Notably, the absence of a marked reduction in histopathological scores in the AA pre-treated group further demonstrates that pre-treatment alone did not confer effective protection against NAPA-induced gastric damage. This lack of efficacy may be attributed to the overwhelming oxidative burden induced by NAPA or the involvement of additional non-oxidative pathways that contribute to tissue injury (Halliwell & Gutteridge, 2015).

The findings of this study underscore the complexity of NAPA-induced gastric toxicity and highlight the limitations of antioxidant supplementation in mitigating such effects. While AA possesses well-documented systemic and gastroprotective antioxidant properties, its efficacy appears to be context-dependent, influenced by factors such as drug dosage, timing of administration, and the severity of oxidative insult. Future studies could explore dose optimization, combination therapy with other antioxidants, or longer pre-treatment periods to determine whether the protective potential of AA can be enhanced under experimental conditions.

6. CONCLUSION

The present study demonstrated that NAPA administration induced pronounced histopathological alterations in the gastric tissues of albino rats, characterized by epithelial disruption, mucosal necrosis, inflammatory penetration, vascular congestion, and submucosal oedema. Concurrent administration of AA with NAPA resulted in limited modulation of gastric injury. In contrast, pre-treatment with AA failed to confer a clear protective or prophylactic effect against NAPA-induced gastric damage. These findings indicate that, under the experimental conditions applied, AA was insufficient to prevent or markedly attenuate gastric histopathological alterations induced by NAPA. Further studies are warranted to explore alternative dosing regimens or combined antioxidant strategies for mitigating drug-induced gastric toxicity. While these results are based on an experimental rat model, they may provide a preliminary indication that antioxidant supplementation alone may be insufficient to prevent NAPA-related gastric injury, warranting further investigation in clinically relevant models.

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