Therapeutic Potential of Sweet Orange Juice in Ethanol-Induced Gastric Ulcers: Timing and Mechanisms of Protection.

Abstract

Background: Gastric ulcer (GU) is a prevalent gastrointestinal disorder caused by an imbalance between aggressive and protective factors in the gastric mucosa. The effectiveness of conventional treatments such as proton pump inhibitors and antibiotics have been limited by their adverse effects and high costs. Citrus fruits have demonstrated antimicrobial, antioxidative, and anti-inflammatory properties, and could therefore be useful for gastric ulcer management. This study investigates the gastroprotective effects of *Citrus sinensis* (sweet orange) juice in an ethanol-induced gastric ulcer model in Wistar rats.

Methods: Thirty male Wistar rats (150 ± 20 g) were randomly assigned into six groups (n = 5). Rats were fasted for 24 hours and gastric ulceration was induced via oral administration of 96% ethanol (5 mL/kg). Sweet orange juice (5 mL/kg) was administered at different time points for seven days. Rats were sacrificed and stomach tissue were harvested for histological and biochemical analysis. Data were analyzed using one-way ANOVA followed by Tukey's post-hoc test, with significance set at $p<0.05$.

Results: Ethanol-induced gastric ulcers led to increased ulcer scores and ulcer index, with a significant reduction in % ulcer inhibition. Sweet orange juice administration from the fifth day post-ulcer induction (PUI) significantly reduced ulcer severity. Inflammatory marker analysis showed that NF-κB and MPO levels were significantly elevated in the ulcer group compared to the control but were markedly reduced following orange juice treatment. Histological findings demonstrated substantial gastric mucosal restoration in groups treated with sweet orange juice, particularly in those receiving treatment from the fifth day post-ulcer induction.

Conclusion: Sweet orange juice exhibits gastroprotective effects against ethanol-induced gastric ulcers, potentially via anti-inflammatory mechanisms. The most significant protective effect was observed when treatment was initiated five days after ulcer induction.

Keywords: Gastric Ulcer, Citrus Sinensis, Sweet Orange Juice, Ethanol-Induced Ulcer

A. Introduction

Gastric ulcer (GU) is a common clinical presentation associated with deep mucosal tissue defect of the gastric mucosa. It is stimulated by pepsin and gastric acid which eat deep into the muscularis mucosa. Long-term healing failure or deep damage may extend into the intrinsic muscle layer, causing duodenal ulcer (Heda et al., 2023). Hence, duodenal ulcer and gastric ulcer are collectively referred to as the peptic ulcer.

There are different causes of gastric ulcers, however, the most common etiologies are bacteria infection with *Helicobacter pylori* and long-term use of non-steroidal anti-inflammatory medications. *H. pylori* triggers a chronic inflammatory response leading to the release of pro-inflammatory cytokines and production of reactive oxygen species (ROS), which cause oxidative damage to gastric epithelial cells (Ige et al., 2021a; Butcher et al., 2017). Other etiologies of gastric ulcers are viral infections, heavy alcohol consumption, chemotherapy, Crohn disease, and cigarette smoking (Woolf et al., 2023; Ige et al., 2021b). These factors enhance a breakdown in the mucosal barrier, making the gastric mucosa more susceptible to the corrosive effects of gastric acid (Woolf et al., 2023). The development of gastric ulcer is however more complex and multifactorial, arising from the imbalance between mucous invasive forces and protective forces (Périco et al., 2020).

Epidemiological studies estimate that approximately 5-10% of the adult population will develop a peptic ulcer at some point in their lives, with gastric ulcers accounting for about one-third of these cases (Abbasi-Kangevari et al., 2022; Tarasconi et al., 2020). In developed countries, the prevalence of H. pylori infection has declined, leading to a decrease in ulcer incidence. However, in developing countries, the prevalence of Helicobacter pylori (H. pylori) infection remains high, hence, gastric ulcer remains a public health issue (Che et al., 2023).

The economic burden of gastric ulcers is substantial and multifaceted, impacting both individuals and healthcare systems globally. There are direct medical costs including expenses related to the diagnosis, treatment, and management of gastric ulcers and indirect costs encompassing the broader economic impacts beyond direct medical expenses such as impact on

the quality of life and loss of productivity. The objective of treating and managing gastric ulcers is to elevate gastric pH, facilitating the healing of the stomach mucosa, achievable through the use of proton pump inhibitors (Woolf et al., 2023). Other medications prescribed for the treatment of gastric ulcer are antibiotics, Histamine-2 Receptor Antagonists, and antacids.

While treatments for gastric ulcers are generally effective, they do come with potential downsides and side effects. For example, overuse of antibiotics can lead to the development of resistant strains of H. pylori, making future infections harder to treat (Stollman, 2016) while prolonged use of proton pump inhibitors has been associated with an increased risk of bone fractures, kidney disease, and nutrient deficiencies (Kommer et al., 2024). The economic burden of these medications can be high, especially on patients living in developing countries. Hence, developing cost effective treatment strategies are important for this population. In addition, ulcer may recur after discontinuation of the medications that inhibit gastric acid secretion (Kim, 2015). Furthermore, complete healing of submucous tissue structure means that single-target drugs may not effectively heal GU.

Traditional medicine has been used to treat or manage diseases in Asian and African cultures (Ayilara & Owoyele, 2024). Traditional medicine is more accessible and affordable for the majority of the population. Given the high cost of pharmaceuticals and hospital care, many people rely on herbal remedies and traditional healing practices as a cost-effective alternative. Many studies exploring the mechanisms and targets of such natural medications on gastric ulcer have been carried out (Gong et al., 2024; Chen et al., 2023). Citrus fruits are economically important fruit crop in the world mostly consumed because of its high vitamin C content, rich flavor, and balanced sweetness and sourness. Multiple scholarly articles have found that eating citrus fruits can reduce the risk of cancer, inflammation, heart disease, and ulcers (Hurtado-Barroso et al., 2020; Bigoniya & Singh, 2014). Given its antimicrobial, oxidative, anti-apopotic, and inflammatory effects (Abou Baker et al., 2022; Khan et al., 2020), we propose that citrus *citrus sinensis* juice can prevent or reduce the severity of gastric ulcer in ethanol-induced gastric ulcer in rats.

B. Materials and Methods

A total of thirty (30) male Wistar rats, with an average weight of 150 ± 20 g, were utilized for this study. The animals were housed in a well-ventilated cage within the animal facility of the Department of Physiology, Ladoke Akintola University of Technology, under controlled conditions at a temperature of 37 ± 2°C. Prior to the commencement of the experiment, the animals underwent a 28-day acclimatization period, during which they received appropriate care. They were provided with standard laboratory crumble feed and water ad libitum throughout the acclimatization period. All experimental procedures were conducted in compliance with the principles of Laboratory Animal Care of the National Medical Research Council and the guidelines for the care and use of laboratory animals established by the National Academy of Sciences (National Institute of Health Publication, 1978).

The animals were randomly assigned into six groups (n = 5 per group) as follows:

Group 1 (Control): Received standard laboratory feed and distilled water only.

Group 2 (Ulcer group): Served as the untreated ulcer model.

Group 3 (Ulcer + J 1 hr B4 M): Induced ulcer, treated with sweet orange juice one hour before meals from the day of ulcer induction for five days.

Group 4 (Ulcer + J 1 hr Aft. M): Induced ulcer, treated with sweet orange juice one hour after meals from the day of ulcer induction for five days.

Group 5 (Ulcer + J 1 hr B4 M 5thPUI): Induced ulcer, treated with sweet orange juice one hour before meals, starting from the fifth day post-ulcer induction (PUI), for five days.

Group 6 (Ulcer + J 1 hr B4 M 5thPUI): Induced ulcer, treated with sweet orange juice one hour after meals, starting from the fifth day post-ulcer induction (PUI), for five days.

Gastric ulceration was induced in the experimental groups through the administration of 96% ethanol (5 mL/kg, p.o.). Prior to ulcer induction, all animals were weighed and subjected to a 24-hour fasting period. Sweet orange juice was freshly prepared from oranges obtained from the local market in Ogbomosho, Oyo State. The oranges were cut in half, and the juice was manually extracted by hand squeezing into a clean bowl. The collected juice was subsequently strained through a fine mesh strainer to remove pulp and seeds. Animals in Groups 3 to 6 received a standardized dosage of 5 mL/kg of sweet orange juice for seven days.

On the eighth day of the experiment, all rats were euthanized via cervical dislocation. A gastrectomy was performed, and the stomachs were excised, cut along the greater curvature, and gently rinsed to remove residual gastric contents. Any blood stains and adhering tissues around the excised stomachs were carefully cleaned.

Biochemical Analysis

For biochemical analysis, brain tissues were homogenized in ice-cold phosphate-buffered saline (PBS), and the homogenates were centrifuged at 5000 rpm for 10 minutes at 4°C. The resulting supernatants were collected for further biochemical assays. Inflammatory and oxidative markers were determined using enzyme-linked immunosorbent assays (ELISA) kits. The kits were procured from Elabscience Biotech. Texas, USA and manufacturer's protocols were followed strictly.

Histological analysis

Tissues designated for histological analysis were fixed in 10% neutral buffered formalin. The tissues were processed into paraffin wax blocks, sectioned at 6 μm using a microtome, and stained with hematoxylin and eosin (H&E) and cresyl violet dyes. Photomicrographs of the stomach tissues were captured using a digital camera (Amscope MU900) mounted on an Olympus C2X microscope.

The stomach tissue is examined for ulcers, and the number, size, and severity of ulcers are recorded. Ulcer Index (UI) is calculated using the following formula:

$$\text{Ulcer Index} = \frac{\text{Sum of ulcer scores for all animals in the group}}{\text{Total number of animals in the group}}$$

Ulcer severity was be graded using the following scoring system:

- **0** = No visible lesions
- **1** = Superficial ulcers (small lesions)
- **2** = Deep ulcers (larger lesions)
- **3** = Perforated ulcers

The percentage ulcer inhibition (% UI) is a measure of the effectiveness of a treatment or compound in reducing the severity of gastric ulcers in experimental animals. % U was calculated using the following formula:

$$\% \text{ Ulcer Inhibition} = \frac{\text{Ulcer index of control group} - \text{Ulcer index of treated group}}{\text{Ulcer index of control group}} \times 100$$

Statistical Analysis

Statistical analysis was conducted using GraphPad Prism 10. Data which was presented as mean ± SEM were analysed using one-way ANOVA followed by Tukey's post-hoc test multiple comparison between groups. α was set 0.05.

C. Results

1. Effect of orange juice on ulcer score, ulcer index, and %ulcer inhibition in ethanol-induced gastric ulcer

The results showed that there is a statistically significant increase in the ulcer scores of the ulcer group and ULCER + J 1hr Aft. M group when compared to the control group (figure 1A). In comparison with the ulcer group, the ULCER + J 1hr Aft. 5th PUI group has a significantly lower ulcer score. However, the remaining treatment groups had nonsignificant decrease in the ulcer score when compared to the ulcer group. In addition, there was significant increase ($p<0.05$) in ulcer index across all groups compared with the control (figure 1B). Figure 1C shows an increase in the %ulcer inhibition across the treatment groups. However, only ULCER + J 1hr Aft. M 5th PUI group has a statistically significant increase ($p<0.05$) in %ulcer inhibition when compared to the control and ulcer groups.

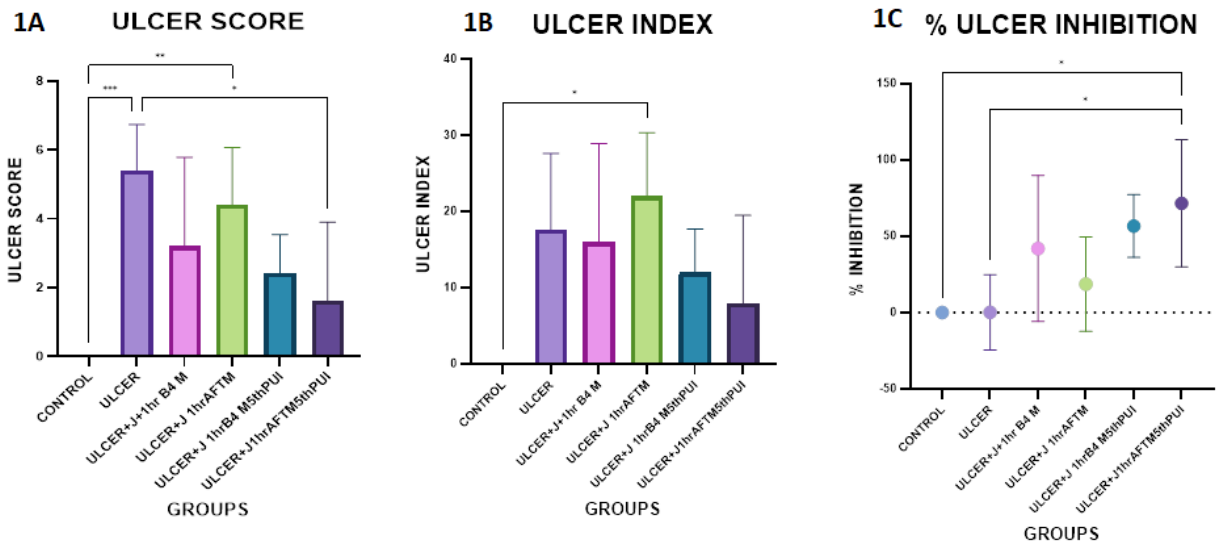

Figure 1: Effect of orange juice on ulcer score, ulcer index, and %ulcer inhibition in ethanol-induced gastric ulcer

2. Effect of orange juice on Tumor Necrosis Factor alpha (TNF-α), Prostaglandin E_2 (PGE2), Nuclear Factor kappa B (NF-kB), and Myeloperoxidase (MPO) in ethanol-induced gastric ulcer

Figure 2 shows the effects of orange juice administration on inflammatory markers in ethanol-induced gastric ulcer. Figure 2A shows that there is no significant difference between the groups when compared to the control. However, there is a significant increase ($p<0.05$) in the TNF-α levels of ULCER + J 1hr B4 M when compared with ulcer and ULCER + J 1hr Aft. M 5th PUI group. Furthermore, the results indicate that there is no significant difference in the PGE2 levels (figure 2B). ULCER + J 1hr Aft. M 5th PUI group had increased level of PGE2 while other treatment groups had lower PGE2 levels when compared against the control and ulcer group. Our study also found that the NFKB level of the ulcer group is increased significantly ($p<0.05$) when compared to the control while the other treatment groups had no significant difference when compared with the control (figure 2C). However, when compared with the ulcer group, the treatment groups had significantly decreased NFKB levels. In figure 2D, our results showed that there is a statistically significant increase ($p<0.05$) in MPO level of the ulcer group when compared to the control while there is no significant difference in MPO levels between the treatment groups in comparison to the control group. However, the treatment groups had significantly decreased ($p<0.05$) MPO levels when compared to the ulcer group.

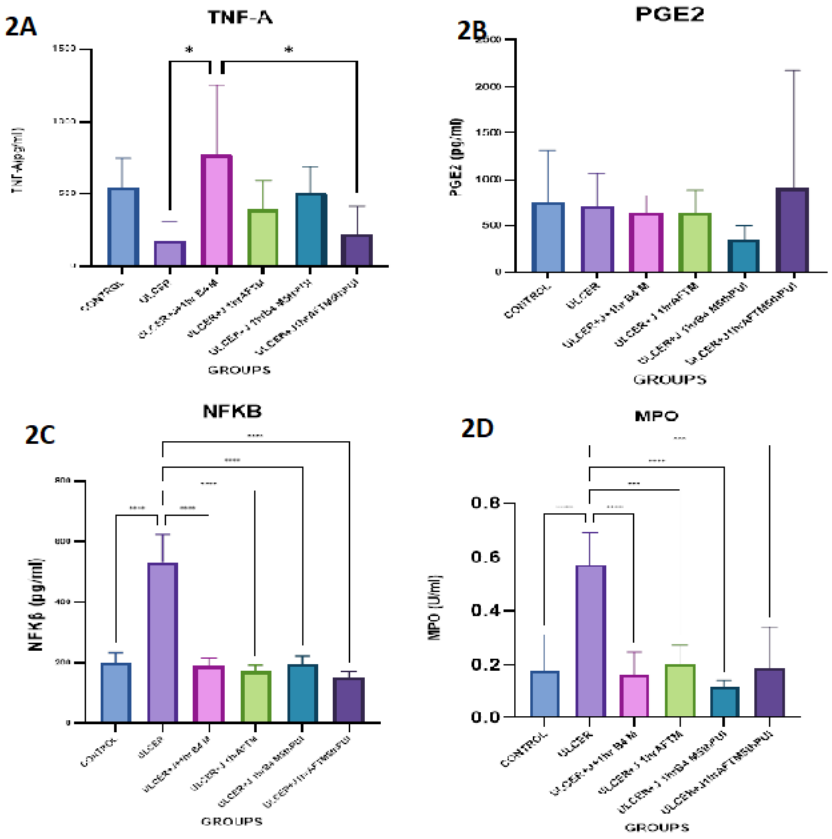

Figure 2: Effect of orange juice on Tumor Necrosis Factor alpha (TNF-α), Prostaglandin E_2 (PGE2), Nuclear Factor kappa B (NF-kB), and Myeloperoxidase (MPO) in ethanol-induced gastric ulcer

3. Effect of orange juice on Malondialdehyde (MDA), Catalase, 8-hydroxy-2'-deoxyguanosine (8-OHdG), and Nitric Oxide (NO) in ethanol-induced gastric ulcer

Our results show that there is no statistically significant difference in the MDA mean levels between the groups (figure 3A). Likewise, there is no significant difference in catalase levels between the groups. The control and ulcer groups have slightly similar catalase activity (figure 3B). However, figure 3C shows there is a statistically significant difference ($p<0.05$) between the control and ULCER + J 1hr B4 M 5thPUI groups while all the other groups had nonsignificant decrease in 8-OHDG levels when compared to the control. Similarly, there is a statistically significant difference ($p<0.05$) in the levels of NO concentration between the control and ULCER + J 1hr Aft. M group (figure 3D). However, all the other groups had nonsignificant decrease in NO concentration levels when compared to the control.

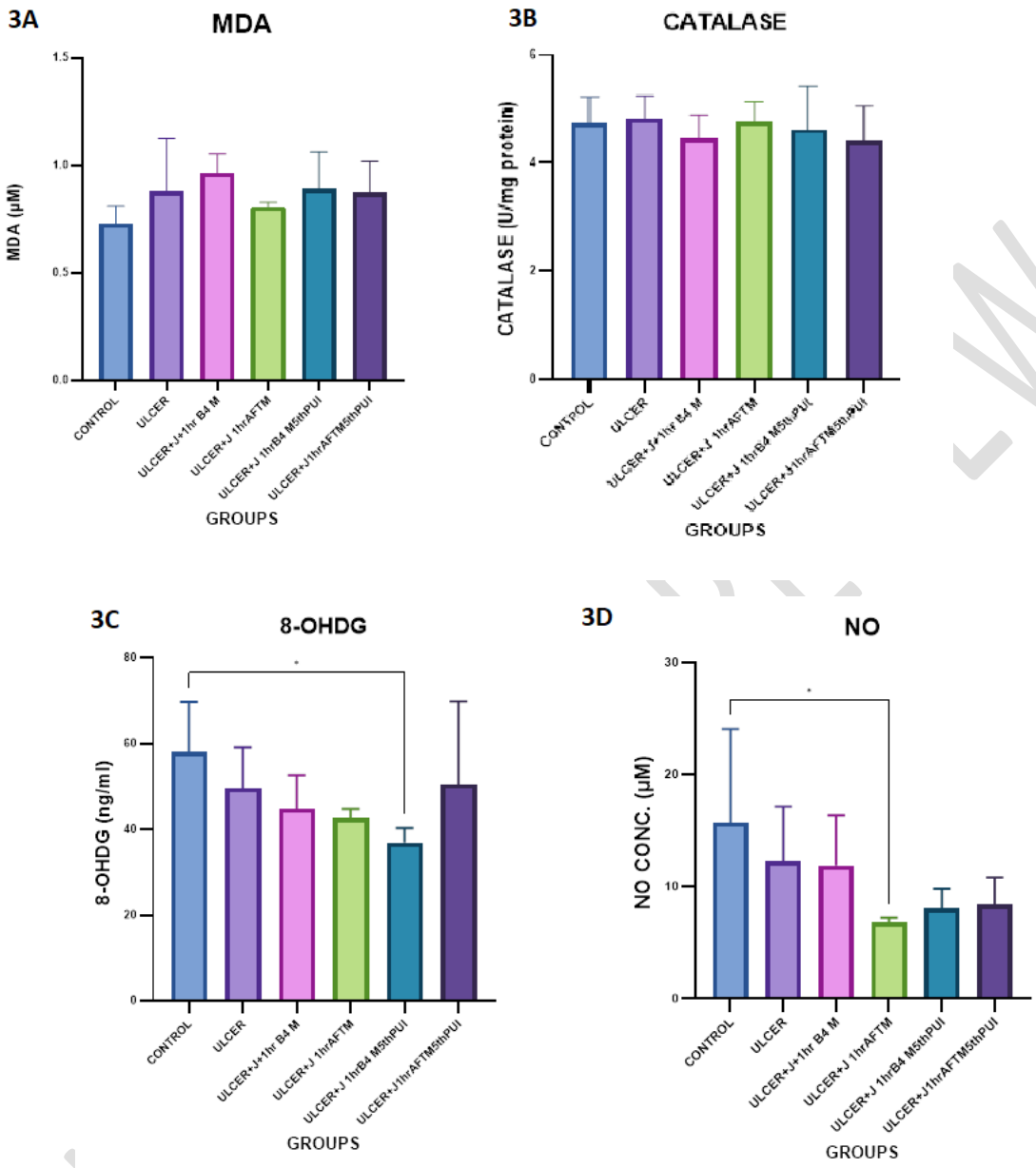

Figure 3: Effect of orange juice on Malondialdehyde (MDA), Catalase, 8-hydroxy-2'-deoxyguanosine (8-OHdG), and Nitric Oxide (NO) in ethanol-induced gastric ulcer

4. Effect of orange juice on stomach tissue in ethanol-induced gastric ulcer

Figure 4 shows the tissue histology. In the ulcer group, there was expansion of submucosa and inflammatory cells extending to the submucosa from mucosa. Administration of sweet orange juice, either before or after meal, restored the stomach tissue histology.

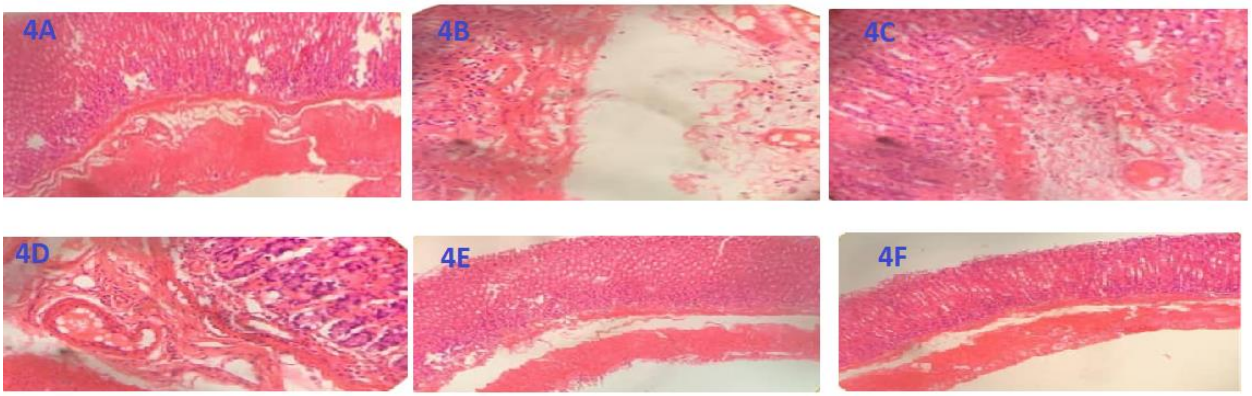

Figure 4: Representative photomicrographs of the effect of sweet orange juice on ethanol-induced gastric ulcer. A. Control group shows no abnormality. B. Ulcer group, shows expansion of submucosa and inflammatory cells extending to the submucosa from mucosa. C. Ulcer + J 1 hr B4 M, shows intact mucosa but extension of inflammatory cells from mucosa to submucosa. D. Ulcer + J 1 hr Aft. M, showing intact mucosa and submucosa. E. Ulcer + J 1 hr B4 M 5th PUI, no abnormality seen. F. Ulcer + J 1 hr Aft. M 5th PUI, no abnormality seen.

Discussion

The current study investigated the effects of sweet orange juice on ethanol-induced gastric ulcers, focusing on ulcer severity, inflammatory response, oxidative stress, and histological recovery. This study found that ethanol induced ulcer by increase ulcer score, ulcer index, and reducing % ulcer inhibition. The ulcer group and the *Ulcer + J 1 hr Aft. M* group had significantly higher ulcer scores than the control. Administration of sweet orange juice 5th day after ulcer induction significantly reduced ulcer score. Also, the *Ulcer + J 1 hr Aft. M 5th PUI* group showed a significant increase in % ulcer inhibition. This shows that orange juice is most effective in reversing ulcer 5th day after ulcer occurrence.

Our result established the role of inflammation in gastric ulcer. Although no significant differences in PGE2 levels were found in all groups, NF-kB levels were significantly higher in

the ulcer group compared to the control, while treatment groups showed significant reductions. Furthermore, MPO levels were significantly elevated in the ulcer group compared to the control, but treatment groups significantly reduced MPO levels. This shows that sweet orange exhibited its effect through anti-inflammatory mechanism.

We further assessed certain oxidative stress markers in our study. However, we found that ethanol-induced gastric ulcer had little effect on oxidative stress as no significant differences in MDA or catalase levels across groups were found. However, sweet orange juice demonstrated its anti-oxidative effects by significantly reducing NO and 8-OHdG levels in the *Ulcer + J 1 hr B4 M 5th PUI* group.

Histological analysis revealed that ulcer group displayed expansion of the submucosa with inflammatory cell infiltration. Treatment with sweet orange juice before or after meals partially restored stomach tissue integrity. Initiating treatment from the 5^{th} day of ulcer induction completely restore histology of the stomach as evident in the *Ulcer + J 1 hr B4 M 5th PUI* and *Ulcer + J 1 hr Aft. M 5th PUI* groups.

Previous studies have demonstrated the gastroprotective effects of citrus, being mediated by its high flavonoids and vitamin C content (Zhang et al., 2020; Mahmoud et al., 2019). Our results align with this, showing that orange juice administration, particularly in the *5th PUI* groups, significantly reduced ulcer severity and increased ulcer inhibition. However, unlike studies such as Selmi et al. (2017), our data suggest that a delayed intervention is needed for optimal ulcer healing. However, this interpretation must be approached with caution, as postponing treatment could increase the risk of ulcer complications, such as perforation, which constitutes a medical emergency. Nonetheless, given that many patients with gastric ulcers remain asymptomatic and may not seek medical attention promptly, our results indicate that orange juice could play a beneficial role in facilitating recovery in such cases.

The significant decrease in NF-kB and MPO levels in treatment groups relative to the ulcer group suggests that orange juice might modulate inflammatory signaling, as observed in studies on flavonoid-rich extracts (Zhang et al., 2020). However, we found an unexpected increase in TNF-α levels in the *Ulcer + J 1 hr B4 M* group differs. This observation is different from

previous studies where citrus flavonoids typically reduced pro-inflammatory cytokines (Khan et al., 2020). This discrepancy may be due to variations in flavonoid composition or perhaps a temporary inflammatory response necessary for tissue repair. Furthermore, our study found that orange juice primarily exerts its effects via anti-inflammatory and antioxidant pathways rather than through PGE2-mediated gastric mucosal protection previously reported (Moraes et al., 2009).

The lack of significant changes in MDA and catalase levels is in contrast to previous research, where citrus flavonoids significantly reduced lipid peroxidation and enhanced antioxidant enzyme activity (Moraes et al., 2009). This may suggest that the protective effect of sweet orange juice is not primarily due to modulation of lipid peroxidation but rather its role in inflammation and tissue repair. However, we observed significant reduction in 8-OHdG in the *Ulcer + J 1 hr B4 M 5th PUI* group, suggesting that citrus flavonoids reduce DNA damage induced by oxidative stress. Indeed, studies have showed that citrus flavonoids could reduce DNA damage caused by oxidative stress (Zahra et al., 2024).

The observed restoration of gastric mucosa with sweet orange juice treatment is consistent with past studies. It has been demonstrated by Zulkefli et al. (2023) and da Silva et al. (2019) that citrus flavonoids promote mucosal healing through angiogenesis and epithelial regeneration. The absence of abnormalities in the *5th PUI* groups further supports the hypothesis that a delayed intervention enhances tissue recovery more effectively than immediate intervention. However, as stated earlier, this requires careful application and further investigation.

Conclusion

Our study confirms the gastroprotective role of sweet orange juice, particularly when administered five days post-ulcer induction. This effect is majorly mediated by the anti-inflammatory property of the sweet orange juice. While previous research has highlighted the role of citrus flavonoids in reducing oxidative stress and inflammation, our findings suggest that timing of administration significantly influences the efficacy. Further studies are needed to explore the molecular mechanisms underlying this delayed effect.

Ethical Approval

The animal caring procedure was examined and approved by the ethical committee, Faculty of Basic Medical Sciences, LAUTECH, Ogbomoso, Oyo State, Nigeria. Principles of laboratory animal care (NIH publication No. 8523, revised 1985) were also followed.

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