Original Article

Gastroprotective and antioxidant effects of fluvoxamine on stress-induced peptic ulcer in rats

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Abstract

Objectives: Stress-induced peptic ulcer disease (SPUD) refers to erosions in the mucosa of the upper gastrointestinal tract that are caused by stress. Some antidepressants are reported to have antioxidant and antiulcer effects. However, histopathological and biochemical evaluation of the anti-ulcer activity of a comparable antidepressant, fluvoxamine, has not been adequately investigated. This study aims to determine the anti-ulcer efficacy of fluvoxamine in reducing stress-induced histopathological and biochemical changes in the gastric mucosa.

Methods: Thirty adult male albino rats were divided into three groups of 10 rats each: the control groups, the SPUD group, and the fluvoxamine-pre-treated group, which received fluvoxamine for eight days before stress exposure. The cold-restraint stress method was used to induce stomach ulcers in the SPUD and fluvoxamine groups. Afterward, the stomachs of rats were removed, opened, and ulcer indices were calculated. Light microscopy was performed following haematoxylin and eosin staining, periodic acid Schiff’s, Masson’s trichrome staining, and proliferating cell nuclear antigen immunostaining. Gastric tissue levels of oxidative stress markers were measured and compared among groups.

Results: The stomachs of the fluvoxamine-treated rats showed a significantly lower number of ulcers with

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Introduction

Peptic ulcer disease (PUD) is a common disease worldwide. PUD occurs as a defect in the mucosa of the stomach or duodenum that exceeds the muscularis mucosa. PUD follows gastric mucosal injuries as a result of imbalance between the defensive and the aggressive factors affecting the mucosa. Many factors contribute to the development of PUD, of which environmental factors such as psychosocial conditions and stress are the most outstanding. Stress is an acute hazard/risk to homeostasis that excites an allostatic or adaptive response. Stress affects the function of the gastrointestinal tract either in short or long-term impacts. Studies revealed that stress contributes to the formation of PUD and is frequently used to produce PUD in experimental animal models.

Stress-induced peptic ulcer disease (SPUD) or stress-related gastric mucosal lesions occur as a typical stress-induced organ injury. SPUD incidence is increasing worldwide and is considered a significant cause of pain and distress, with an accompanying impairment of quality of life. The onset and modulation of SPUD may be caused by various types of stress, of which several types of major physiologic harms, including trauma, CNS injury, burn injury, major surgical procedures and critical illnesses are the most common. The pathogenesis of SPUD is not clearly discussed in previous research, but it differs from ordinary PUD in symptoms and risk factors. It has been suggested that in SPUD there is insufficient blood microcirculation, which results in accumulation of reactive oxygen species (ROS) with accompanying lipid peroxidation and subsequent loss of normal cellular functions.

Being a serious gastrointestinal disorder, PUD demands a well-targeted therapeutic approach. Numerous drugs are available for the treatment of PUD, involving anti-acids, H2 receptor antagonists, and proton pump inhibitors; however, clinical evaluation has revealed major side effects, drug interactions, and incidences of relapse from these drugs.

Tricyclic antidepressants have been reported to be used for their antioxidant effects. They were the first antidepressants used for the treatment of PUD. Although some selective serotonin reuptake inhibitor (SSRI) drugs have gastric side effects that might progress to gastrointestinal bleeding if used in combination with indomethacin, over time, other antidepressants have been shown to possess variable degrees of anti-ulcer action. Alternatively, novel anxiolytics have gastroprotective effects in experimental animals. Some drugs have shown other, more beneficial GIT effects, such as increasing gastric contractility and decreasing stomach and intestinal distension.

Fluvoxamine is an SSRI broadly prescribed for depression and is used for treating obsessive-compulsive disorder. This drug inhibits CYP1A2, an enzyme known to be involved in ROS generation. Unlike most SSRIs, which enhance upper GIT bleeding, fluvoxamine is postulated to be beneficial in the management of PUD.

The combined antioxidant and antidepressant effects of fluvoxamine favours its use in treatment of SPUD. However, the histopathological and biochemical changes associated with its anti-ulcer activity are not fully elucidated. Thus, the aims of this study is to examine the histopathological and biochemical changes in the gastric mucosa induced by stress, and to investigate the effects of fluvoxamine on stress-induced ulcers.

Materials and Methods

Thirty adult male eleven-week-old albino rats (130–150 g average body weight), obtained from the Mansoura Animal House were used in this study. Animals were housed in the Mansoura Faculty of Medicine Animal House under standard laboratory conditions. Commercial standard pellet diet was used for feeding, with free access to food and water. The animals were acclimatized to standard laboratory conditions. Commercial standard pellet diet (according to Mansour University IRB protocols); the temperature was 20 ± 1 °C, with a 12:12-h light–dark cycle for 10 days before the experiment. To prevent coprophagy, a grid floor was placed in each cage. The animals were randomly assigned to three groups of 10 animals each: Group I (the control group), Group II (the SPUD group), and Group III (the fluvoxamine-treated group). Groups I and II received sterile water, while Group III received fluvoxamine solution by an orogastric tube for 8 days before stress induction.

The fluvoxamine solution was prepared by dissolving 50 mg film-coated fluvoxamine tablets (Solvay, Cairo, Egypt) in sterile water. The solution was prepared just prior to dosing at a concentration of 50 mg/kg and administered daily to 12-h fasted rats by an orogastric tube as a pre-treatment (for 1 day) and repeated for 7 consecutive days.

Induction of SPUD in 12 h-fasted rats of Groups II and III using the cold immobilization restraint method as previously described. Rats were tied to a wooden plank and immersed individually in cold water (6 ± 0.6 °C) for 6 h. The same procedure was repeated daily for 7 days. At the assigned time, the animals were sacrificed under diethyl ether anaesthesia, the abdomens were opened at the midline and the stomachs were gently removed, washed with saline, opened at the greater curvature, and photographed with a digital camera (Canon 650D).

The total ulcer surface area was measured from the photographs after considering the drawing scale. Ulcer severity was scored by the sum of the total ulcer surface area

Conclusion: Fluvoxamine pre-treatment exerted a gastroprotective effect against ulcer development and promoted healing of the developed lesions.

Keywords: Fluvoxamine; Gastric ulcer; Peptic ulcer; Stress; Stress-induced peptic ulcer

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in the glandular portion of the stomach by a person blind to the experimental conditions. The gastric lesions were scored between 1 and 6 according to their severity. The calculation of the ulcer score was performed according to Palle et al.\(^{29}\) The index was calculated by multiplying the average number of ulcers per stomach by the ulcer severity score and the percentage of animals with ulcers.

The stomachs were divided into two equal halves (at the lesser curvature): one for microscopic examination and the other for biochemical assessment. For light microscopic examination, specimens were prefixed in 10% neutral buffered formalin and processed for staining with haematoxylin and eosin (H&E), Masson’s trichrome, and Periodic Acid Schiff’s (PAS) stains.\(^{30}\) Proliferating cell nuclear antigen (PCNA) immunohistochemical staining was performed (a three-step immunoperoxidase staining technique) using mouse monoclonal anti-PCNA/cyclin antibody (Dako, clone PC-10) purchased from Heliopolis, Cairo, Egypt, with haematoxylin counterstaining.\(^{31}\)

For biochemical assessments, the stomach halves were homogenized with 0.1 M phosphate saline buffer, filtered, centrifuged, and stored according to the standards.\(^{29}\) The supernatants were used for determination of oxidative enzymes (lipid peroxidation (LPO), catalase (CAT), superoxide dismutase (SOD)), and reduced glutathione (GSH) using commercially available kits (Sigma-Aldrich, Riyadh KSA) by the usual techniques.\(^{32,33}\)

Each experimental value was expressed as the mean ± SD. One-way analysis of variance (ANOVA) was performed to compare different groups. A mean difference was considered significant at \(P < 0.05\). The Bonferroni multiple range test was used as a post-hoc test.

**Results**

Photographs of the morphological examinations of the stomachs are shown in Figure 1. Group I stomachs showed apparently normal mucosa without signs of inflammation, haemorrhage or hyperaemia (Figure 1A). On the other hand, Group II showed marked severe injuries in the gastric mucosa in the form of severe haemorrhagic patches in both the fundic and corporeal regions of the stomachs and less marked patches in the antra. The ulcers appeared as dark reddish patches of variable forms and sizes with generalized hyperaemia in the gastric mucosa (Figure 1B). Group III stomachs showed fewer mucosa with less marked hyperaemia and moderate mucosal injuries. Ulcers appeared smaller, widely spaced, and discontinuous. Lesions in the gastric mucosa were limited to the corporeal region, while the fundus appeared normal (Figure 1C). None of the animals showed perforation lesions.

**Histological examination**

H&E staining of Group I samples revealed normal gastric mucosal layers resting on the submucosa. The mucosa is thrown into folds formed of columnar ciliated epithelium. The apparent normal lamina propria, with its contained gastric glands, and the muscularis mucosa was observed (Figure 2A). Group II samples showed areas of sloughing of the gastric mucosa. The gastric glands showed vacuolar degeneration and areas of necrosis, with dilated gastric pits with inflammatory cell infiltration into the submucosa. Areas of haemorrhage were evident in the submucosa, with congestion of the nearby blood vessels (Figure 2B and C). Group III samples showed nearly normal gastric mucosa, with signs of regeneration in the gastric glands, but inflammatory cell infiltration was still evident (Figure 2D and E).

Group I samples showed strong PAS staining of the mucosal cells of both the surface and the neck of the gastric glands (Figure 3A and B). Group II samples showed areas of mucosal shedding, and weaker PAS reactivity (Figure 3C). Group III samples had a continuous, nearly normal mucosal covering, with PAS-reactive mucosal cells apart from small areas where reactivity was absent (Figure 3D).

Immunohistochemical staining of the control group revealed weak expression of PCNA in the neck cells of the gastric glands (Figure 4A). The reactivity was moderate in the glandular epithelium of Group II samples (Figure 4B). In Group III samples, the reactivity was mild and limited to the gland neck cells (Figure 4C).

The effect of fluvoxamine pretreatment on SPUD ulcer index parameters \((n = 10, X ± SEM)\) significantly increased the ulcer index, score, and area in Group III samples \((6.21 ± 1.02, 1.93 ± 0.09\) and \(7.53 ± 0.63)\)
Figure 2: A) Photomicrograph of a section of the fundic region of a representative control group rat. The mucosa has an intact surface epithelial covering (arrows), gastric glands stuffed in the lamina propria (L), and the muscularis mucosa (M) appears normal (H&E X100). B) Group II rat fundus showing patches of sloughing of the gastric mucosal epithelium (arrows) with signs of lining cell desquamation and degeneration of the gastric glands, which appear vacuolated (Arrow heads). The submucosa has a distinct area of haemorrhage with congestion of the nearby blood vessels (V) (H&E X100). C) Higher magnification of the submucosa showing patches of sloughing of the gastric mucosal epithelium (arrows) with signs of lining cell desquamation and degeneration of the gastric glands, which appear vacuolated (Arrow heads), and infiltration of multiple mononuclear inflammatory cells (double-tailed arrows) (H&E X200). D) Group III rat fundic sections showing a more-or-less normal gastric mucosa with a small area of the surface epithelial atrophy still apparent (arrows) (H&E X100). E) Higher magnification showing a more-or-less normal gastric mucosa, with a small area of surface epithelial atrophy still apparent (arrows) and regenerating gastric glands (L) with fewer marked signs of cytoplasmic vacuolation (arrow heads). Mononuclear cell infiltration is still evident in the submucosa (double-tailed arrows) (H&E X400).
compared with those in Group II samples (20.01 ± 1.08, 4.69 ± 0.06 and 81.02 ± 9.21) (P < 0.05) (Table 1 and Diagrams 1 and 2).

Group II rats showed significantly higher levels of LPO (0.91 ± 0.07) and lower levels of SOD and CAT (12.62 ± 1.86 and 8.09 ± 1.41, respectively) than did rats from Groups I and III (P < 0.05). Conversely, fluvoxamine pretreatment significantly decreased LPO (0.65 ± 0.05) and increased the SOD and CAT levels (30.3 ± 0.59 and 17.71 ± 0.85, respectively). Their levels were closer to control values, as shown in Table 2. The GSH level of Group II was significantly lower than that of Group I (8.95 ± 0.31). Group III showed a low but significant level (17.01 ± 0.21) (P < 0.05) (Table 2 and Diagram 3).

**Diagram 1:** Ulcer area of the three groups in mm². I = Control group, II = Stress-induced peptic ulcer disease (SPUD) group, III = Fluvoxamine-treated group.

**Diagram 2:** Ulcer index and score of the three groups. I = Control group, II = Stress-induced ulcer (SPUD) group, III = Fluvoxamine treated group.

**Figure 3:** A) Control rat fundus showing strongly positive PAS reactivity in surface mucosal cells (a) and the neck regions of the gastric glands (b) (PAS X100). B) Higher magnification showing strong positive PAS reactivity in surface mucosal cells (a) and the neck regions of the gastric glands (b) (PAS X400). C) Group II rat fundus showing an area of interruption of the mucosa (arrow) with mucoid degeneration in some glands (arrow heads) and weak PAS reactivity in surface mucosal cells (a) and the neck regions of the gastric glands (b) (PAS X400). D) Group III rat fundus, showing positive PAS reactivity in surface mucosal cells (a) and the neck regions of the gastric glands (b) apart from small areas of non-reactivity (arrows) (PAS X100).
Discussion

Stress is known as a significant participant in ulcer pathogenesis. Older studies attributed SPUD to excessive histamine release, which enhances acid secretion and reduces mucus production. Other studies reported an increase in gastric motility, vagal overactivity, mast cell degranulation, and decreased prostaglandins release.

SPUD pathogenesis involves insufficient blood microcirculation with subsequent tissue hypoxemia and oxidative stress, with accumulation of ROS, which are known inducers of apoptosis. ROS disrupt the chemical structures of cell proteins, including DNA and lipids, and induce cell death in various ways. ROS also act as signalling molecules that control tissue responses to cell injury and inflammation.

The body defends against ROS by both enzymatic and non-enzymatic defence mechanisms. The non-enzymatic defence mechanisms are evaluated by histopathological examination, and enzymatic defence mechanisms by biochemical examination.

Our results showed that exposure of the animals to cold stress induced shedding of the gastric protective layer with vacuolar degeneration of the gastric glands. Similar results were reported by Guo et al. A clear demonstration of sloughing of the mucosal lining and submucosal haemorrhage was a characteristic of SPUD. This finding is in accordance with the study of Ahmad et al. They explained these tissue changes by the altered gastric mucosal microcirculation, with subsequent disturbances of

### Table 1: Morphometric measurements of the ulcer areas, indices, and score.

| Group   | Ulcer area (mm²) | Ulcer index | Ulcer score |
|---------|------------------|-------------|-------------|
| I       | 0                | 0           | 0           |
| II      | 81.02 ± 9.21     | 20.01 ± 1.08| 4.69 ± 0.06 |
| III     | 7.53 ± 0.63*     | 6.21 ± 1.02*| 1.93 ± 0.09*|

I = Control group, II = Stress-induced peptic ulcer disease group, III = Fluvoxamine treated group.

Data are represented as the mean ± standard deviation.

*P < 0.05 versus Group II.

![Diagram 3: Effect of fluvoxamine on stress-induced peptic ulcer disease biochemical parameters: lipid peroxidation (LPO), catalase (CAT), and superoxide dismutase (SOD). Data are represented as the mean ± standard deviation.](image)

![Figure 4: A) Control rat fundus showing weak PCNA expression in the neck cells of the gastric mucosa (arrow heads) (PCNA X100). B) Group II rat fundus showing marked expression of PCNA in the epithelia of the mucus glands (arrows) (PCNA X400). C) Group III rat fundus showing mild PCNA expression in the epithelia of the mucus glands at the neck region (arrows) (PCNA X400).](image)
The increased mucosal barrier, indicated by enhanced PAS activities of myeloperoxidase and NO synthase.48,49 Previous studies reported neutrophil infiltration into the gastric secretions42,43 and motility.44 ROS and leukotrienes were postulated to mediate the cascade of stress-induced mucosal injury.45 The resulting superoxides in the tissues lead to tissue damage by promoting lipid peroxidation.46,47

Conversely, fluvoxamine treated animals exhibited nearly normal gastric mucosa, with areas of epithelial atrophy and signs of gland regeneration. Persistent inflammatory cell infiltration detected in the submucosa can be explained by the fact that the healing processes of ulcers remains continuous and requires considerable time to be fully resolved.

Some researchers have attributed the anti-ulcerogenic activity of antidepressants by their ability to block leukotriene receptors or reduce histamine secretion from mast cells.45,50 However, in our study, pretreatment with fluvoxamine protected the mucosa from excessive sloughing and haemorrhagic patches. A reduction in the degree of damage of the stomach wall glandular tissue was noted. These findings were confirmed by our statistical analysis of the ulcerated areas, indices, and scores. It was clear that intact mucosa provides protection for the underlying tissues, including inner glandular and muscular layers.

Mucopolysaccharides in the gastric mucosa are visualised by PAS staining.51 The weak PAS reactivity revealed that the glycoprotein content of the gastric mucosa was reduced in Group II. Conversely, an upsurge in the glycoprotein was evident by the augmented level of PAS reactivity in Group III.

Ulcerative lesions in the stomach are always associated with weak PAS reactivity. Gastroprotective agent treatments are usually accompanied by increases in reactivity.52 Other researchers have reported increased PAS reactivity with increased size of mucous glands.53

PCNA is an important tissue proliferation marker. The immunohistochemical outcomes of Group II revealed down-regulation of PCNA compared with that in Group I or Group III. Polo et al.54 found similar results comparing acetic acid-induced PUD with cimetidine and essential oil-treated groups.

PCNA down-regulation in Group III indicates that fluvoxamine treatment promoted healing of gastric ulcers. The increased PCNA reactivity accompanied increases in cellular proliferation, which is a sign of ulcer re-epithelialisation.53

The increased mucosal barrier, indicated by enhanced PAS reactivity, and the increased cellular proliferation, indicated by enhanced PCNA staining, positively correlates with ulcer healing. Fluvoxamine not only maintained the gastric mucosa, but also promoted regeneration of the ulcerated regions. This effect is mostly produced by the cytoprotective effects of this drug in maintaining the integrity of the gastric mucosal microcirculation.

Biochemical identification of decreased SOD and CAT levels was reported to the formation of ROS.55 These enzymes are produced by the body as an enzymatic defence to facilitate the breakdown of free radicals.56 Our results showed that SPUD is accompanied by a significant decrease in the levels of both SOD and CAT. Conversely, fluvoxamine reversed these changes. The significant improvements in SOD and CAT levels strongly suggest that fluvoxamine acts against ROS.

As a marker of lipid peroxidation, LPO showed a significantly decreased level in the fluvoxamine-treated group. The inhibition of lipid peroxidation in the gastric mucosa is always associated with tissue protection. LPO levels decrease in accordance with the increased free radical scavenging enzymes (SOD and CAT).57

Gastric GSH is one of the most abundant antioxidant enzymes.58 A strong relationship between GSH levels and the levels of ulcer severity has been reported.57 GSH acts by trapping ROS. The decrease in GSH level is a sign of increased tissue oxidative stress.58 In our study fluvoxamine significantly increased GSH levels, although GSH remained lower than levels measured in the controls. A similar finding is reported as supporting evidence of efficacy for most drugs and natural products with antioxidant gastroprotective effects.59 Other studies showed that fluvoxamine inhibited the indomethacin-induced ulcers in rats60 by decreasing levels of oxidant parameters in stomach tissues, particularly gastric GSH.

The exact mechanism by which fluvoxamine suppresses oxidative stress is still unclear. However, fluvoxamine, being an SSRI drug, inhibits the enzyme CYP1A2, which is an inhibitor of ROS.56 The neuroprotective effect of fluvoxamine was attributed to its potent antioxidant and anti-inflammatory effects.61 This action was explained by its ability to inhibit NADPH oxidase and nitric oxide synthase.51 Recent studies revealed that it has the ability to modulate genes related to redox pathways, which in turn stimulates antioxidant elements.62 Other researchers demonstrated that fluvoxamine interacts with the mitochondrial lipid bilayer and affects electron transport, thereby inhibiting oxidative phosphorylation.63 It was also reported that fluvoxamine induces its antioxidant effect in nerves by increasing serotonin levels.64

### Table 2: Effect of fluvoxamine on stress-induced peptic ulcer disease biochemical parameters: lipid peroxidation (LPO), catalase (CAT), and superoxide dismutase (SOD).

| Group | LPO (nmol MDA/mg protein) | SOD (u/mg protein) | CAT (μmol H2O2/min/g protein) | GSH (μmol/g tissue) |
|-------|-------------------------|-------------------|-------------------------------|---------------------|
| I     | 0.50 ± 0.019            | 36.9 ± 0.22       | 18.22 ± 0.18                  | 27.33 ± 0.22        |
| II    | 0.91 ± 0.07*            | 12.62 ± 1.86*     | 8.09 ± 1.41*                  | 8.95 ± 0.31*        |
| III   | 0.65 ± 0.05**           | 30.3 ± 0.59**     | 17.71 ± 0.85**                | 17.01 ± 0.21**      |

I = Control group, II = Affected group, III = Treated group. Data are represented as the mean ± standard deviation. *P < 0.05 versus Group I. **P < 0.05 versus Group II.
The expected future increase in the coexistence of stress and SPUD adds to the importance of the use of antidepressants with SPUD healing properties.\textsuperscript{21,65} Other studies have shown that antidepressants\textsuperscript{65,66} and anxiolytics\textsuperscript{67,68} can significantly reduce stress-induced ulcer formation, sometimes with better results than the traditionally used anti-ulcer drugs such as H2 receptor antagonists and antacids.\textsuperscript{67} Our findings lend support to these studies. The combined findings of both non-enzymatic and enzymatic defence mechanisms demonstrate the gastroprotective activity of fluvoxamine through an antioxidant pathway.

Conclusion

Fluvoxamine exerts gastroprotective effects via reduction of mucosal atrophy, promotion of gland regeneration, and potentiation of mucous secretion through inhibition of gastric tissue oxidative stress. Our results show that fluvoxamine exerts both an indirect effect on ulcer development through inhibition of stress and direct effects on previously developed ulcers.

Recommendation

Fluvoxamine can be used as a pretreatment to suppress the development of SPUD.

Conflict of interest

The authors have no conflict of interest to declare.

Ethical approval

All animal handling procedures were in accordance to Mansoura University IRB protocols.

Authors’ contributions

WME conceived and designed the study, conducted research, provided research materials, and collected and organized data. AMA, BTA, GTR and RMT shared analyses and interpretations of data. All authors wrote initial and final drafts of the article and provided logistical support. All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

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