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Research Article
Bupropion Inhibits Oxidant Status and Inflammation in Ethanol-Induced Chronic Gastritis in Rats

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Abstract

Background and Objective: Chronic gastritis, today, is a significant disorder amongst chronic gastritis digestive system diseases manifesting itself as anorexia and stomach ache. Despite it is known that dopamine antagonists induce ulcers and dopamine agonists to help to treat ulcers the protective effects of bupropion on ethanol-induced gastritis were not clarified completely. This study was conducted to assess the potential protective activity of bupropion on ethanol-induced chronic gastritis. **Materials and Methods:** Chronic gastritis model was established by administering 56% ethanol to rats for four weeks. Bupropion (30 and 60 mg kg^{-1}) was orally administered for seven days to assess the healing effect. **Results:** At the end of the study, the changes in biochemical, histopathologic and proinflammatory cytokines showed that bupropion healed ethanol-induced gastritis. **Conclusion:** The study findings showed that bupropion suppressed lipid peroxidation and inflammatory response, on the other hand, relieves chronic gastritis effectively by increasing activation of the antioxidant system.

Key words: Bupropion, ethanol, inflammation, oxidant status, chronic gastritis

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Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Alcohol consumption and use of nonsteroidal anti-inflammatory medicines increase bleeding risk in the upper parts of the digestive system[1,2]. Gastritis and gastric ulcers usually appear as a result of unbalancing between gastric mucosal protective factors and abrasive-aggressive factors mucus encountered. Gastric Hydrochloric Acid (HCL) secretion, reactive oxygen radicals, mucosal hypoperfusion and alcohol consumption may be given as samples amongst aggressive factors[3]. Amongst them, alcohol consumption is the most essential factor that contributes to gastric ulcer formation and excessive alcohol consumption increases the risk of gastric mucosal damage[4]. Alcohol intake intervenes in the secretion of cyclooxygenase (COX) in stomach mucus, cytokines and free radicals derived from oxygen and hence this damages stomach mucus directly and indirectly. For this reason, ethanol-induced gastric mucosal damage models is a model frequently used to investigate factors causing human gastric ulceration and materials having anti-ulcer activity[5].

Antidepressant medications are used to treat various non-psychological disorders since the 1950s as well as psychiatric diseases[6,7]. Most antidepressant medications (fluoxetine, doxepin, maprotiline, mianserin, trimipramine, idazoxan, monoamine oxidase b inhibitors etc) has been shown experimentally to prevent ulcer in various ulcer models[8-10]. In addition, not only experimentally but also clinically antidepressant medications have been shown to prevent ulcers successfully[11,12]. Result of literature reviews tricyclic antidepressants opipramol, amitriptyline, imipramine has been reported to help to prevent ulcer. It has been reported that the medications included in the selective serotonin reuptake inhibitors group generally inflaming ulcer, fluvoxamine and fluoxetine to suppress ulcer exceptionally, moclobemide one of monoamine oxidase inhibitors and one type of antidepressant called tianeptine and mirtazapine having effects to help to heal and preventing ulcer. In light of this information, it has been reported that care should be taken on the selection of this group of medications other than especially fluoxetine and fluvoxamine in depression patients with ulcer, tricyclic antidepressant medications may be used safer. It has been emphasized to prefer mirtazapine and tianeptine that of atypical antidepressants in depression with ulcer incidences on suitable occasions[13].

Bupropion is a reuptake inhibitor of selective dopamine and noradrenaline medications. It is a medication proven to suppress withdrawal symptoms stop-smoking induced despite effective in the treatment of depression and is a pharmacological agent other than nicotine validated to use for this purpose[14]. In the studies, despite dopamine antagonists induce ulcers, dopamine antagonists like bupropion, bromocriptine has been shown to help to heal the number of controls related to bupropion is limited[15]. Especially, a study that shows the effect of bupropion on gastritis was not found. For this reason, it was aimed to determine the effect on preventing stomach damage in bupropion administered rats with gastritis induced by alcohol.

MATERIALS AND METHODS

Study area: The study was carried out at the laboratories of Veterinary Faculty, Afyon Kocatepe University, Turkey, from February-May, 2021.

Chemicals: Bupropion HCl, omeprazole and 98% high purity ethanol used in the study were purchased from GlaxoSmithKline (Istanbul, Turkey), Sandoz Drug Industry (Istanbul, Turkey) and Sigma-Aldrich (MO, USA), respectively. Other chemicals to be used to determine parameters of analysis were purchased from commercial companies at high purity.

Animals and experimental design: In this study, 2 months (180-200 g) 36 Sprague Dawley type male rats were obtained from Afyon Kocatepe University Experimental Animal Application and Research Center. During the experiment, practices applied to animals were conducted in accordance with universal ethical principles and by the approval of Afyon Kocatepe University Experimental Animal Local Ethics Committee (Ethical number: 49533702/16). Care and feeding of the rats were conducted at 22±2°C room temperature, 55-60 humidity and with a photoperiod of 12:12 hrs. The rats in the working group were fed with standard rodent and fresh drinking water ad libitum. In addition, animals were kept without food before 24 hrs of alcohol treatment.

Ethanol[16] and bupropion[17-19] doses to be used in an experimental phase were identified following the study done as before. Animals were divided randomly into 5 groups each consisting of 6 male rats. These are the normal group, alcohol group (ethanol-induced gastritis model), group treated with moderate-dose bupropion (30 mg kg^{-1}), group treated with high dose bupropion (60 mg kg^{-1}) and omeprazole group (20 mg kg^{-1}). The gastritis model was created with 56% ethanol. After 12 hrs fasting, rats were administered orally with 56% (8 g kg^{-1}) ethanol two times a week. Normal and model groups were also orally administered with physiological saline following the same protocol. After four weeks, the chronic gastritis model was developed completely. All therapeutics

were administered once a day for seven days and after 2 hrs of last administration the animals were taken under general anaesthesia (isoflurane inhalation anaesthesia 5% in air) and necessary tissue and blood samples were collected. To obtain serum from blood samples, blood was centrifuged at 600 g for 15 min. In addition, for homogenization of stomach tissues, the tissues were homogenized in 0.15 M Tris-HCL buffer (pH 7.4). Then, tissues were centrifuged at 4°C, 2500 rpm for 10 min. After centrifuge supernatants obtained were stored until they were analyzed at -20°C.

Determination of gastric damage

Macroscopic investigation of the stomach: After stomach tissue was extracted it was opened by cutting along the curvature line and was macroscopically displayed after rinsed in physiologic saline. Gastric lesions were assessed by blinded observers and scoring was (0, no lesion; 1-2 small lesions; 3-4 small ulcer; 5-6 big ulcer; 7 full ulcers)[16,20].

Determination of gastric mucosa: The methods of Rujjanawate *et al.*[21] and Ribeiro *et al.*[22] were taken as the basis for the determination of gastric mucosa. For this purpose, some part of the stomach was immersed into the solution (pH 5.8) including 10 mL 0.02% Alcian blue and 0.16 M sucrose /0.05 M sodium acetate and was incubated at 25°C for 24 hrs and thereafter was centrifuged for 10 min at 3000 g and 4°C. The absorbance of supernatant taken was identified at 620 mm with a spectrophotometer and free mucus in the stomach content was calculated according to binding quantity (mg g^{-1} tissue) of Alcian blue.

Biochemical analysis: In the stomach tissue taken, malondialdehyde (MDA)[23], reduced glutathione (GSH)[24] levels, superoxide dismutase (SOD)[25] and catalase (CAT)[26] and protein[27] levels were measured with Spectrophotometrically by Shimadzu 1601-UV spectrophotometer (Tokyo, Japan). In addition, in stomach homogeneous to identify PGE2 and NO the commercial BT-LAB (Shanghai, China) and Cayman (Michigan, USA) ELISA kits were used, respectively.

mRNA expressions of proinflammatory cytokines: Total RNA of the gastric was extracted and reversed transcribed using A.B.T.™ Blood/Tissue RNA Purification Kit (Atlas Biotechnology, Ankara, Turkey), respectively following the manufacturer's protocols. Expression levels of nuclear factor (NFκB), cyclooxygenase-2 (Cox-2), inducible nitric oxide synthase (iNOS), tumour necrosis factor-α (TNF-α), interleukin 1β (IL1-β) and interleukin-6 (IL-6) mRNA inside the prepared gastric tissues were determined by real-time PCR (StepOnePlus, Applied Biosystems). Primers were ordered from Sentegen Biotechnology (Ankara, Turkey) and shown in Table 1. Each sample was analyzed in triplicate. Also, normalization was performed according to the housekeeping gene β-actin expression level. The results are stated as relative gene expression using the delta-delta CT method[28].

Table 1: Description of polymerase chain reaction primers (NF-κβ, Cox-2, iNOS, TNF-α, IL1-β, IL-6 and β-actin) and product size

Genes	Primers	Product size (bp)
NF-κβ	F: TGGACGATCTGTTTCCCCTC	
	R: CCCTCGCACTTGTAACGGAA	126
Cox-2	F: AAGGCGTTCAACTGAGCTGT	
	R: CAACACAGGAATCTTCACAAATGGA	122
iNOS	F: ATTGGCACCATCTAACGCACT	
	R: TGGGGATTTTGTTCTGGGCAT	101
TNF-α	F: CATCCGTTCTCTACCCAGCC	
	R: AATTCTGAGCCCGGAGTTGG	134
IL1-β	F: AGGCTGACAGACCCCAAAAG	
	R: CTCCACGGGCAAGACATAGG	115
IL-6	F: TCTGGTCTTCTGGAGTTCCGT	
	R: GGAAGTTGGGGTAGGAAGGAC	144
β-actin	F: ACAACCTTCTTGCAGCTCCTC	
	R: CTGACCCATACCCACCATCAC	154

Histopathological examination: Collected stomach tissues were fixed in 10% (v/v) solution and embedded in paraffin. Paraffin blocks were sectioned at 5 µm thickness using a microtome (RM-2125 RT; Leica, Nussloch, Germany). Tissue damage was investigated under the microscope (Nikon DS Fİ3, microscopic digital camera systems, Tokyo, Japan)by staining haematoxylin and eosin (H and E).

Statistical analysis: Statistical analyses of data were performed using the SPSS software version 22.0 (SPSS Inc., Chicago, IL, USA) and data are expressed as mean±standard deviation (n: 6 per group). Data were analyzed by one-way analysis of variance (ANOVA) followed by *post hoc* Duncan's multiple range test. The p-values less than 0.05 were considered significant. Significant differences were pointed with different alphabetical letters.

RESULTS

Changes in gastric mucosa: In the stomach mucosa of the rats exposed to ethanol treatment in Fig. 1b hemorrhagic areas were found while no macroscopic changes were observed in the stomach mucosa of the rats in control groups in Fig. 1a. When gastric mucosa of the group treated with omeprazole was investigated it was determined that the medicine had a protective effect for the alcohol-induced gastric damage in

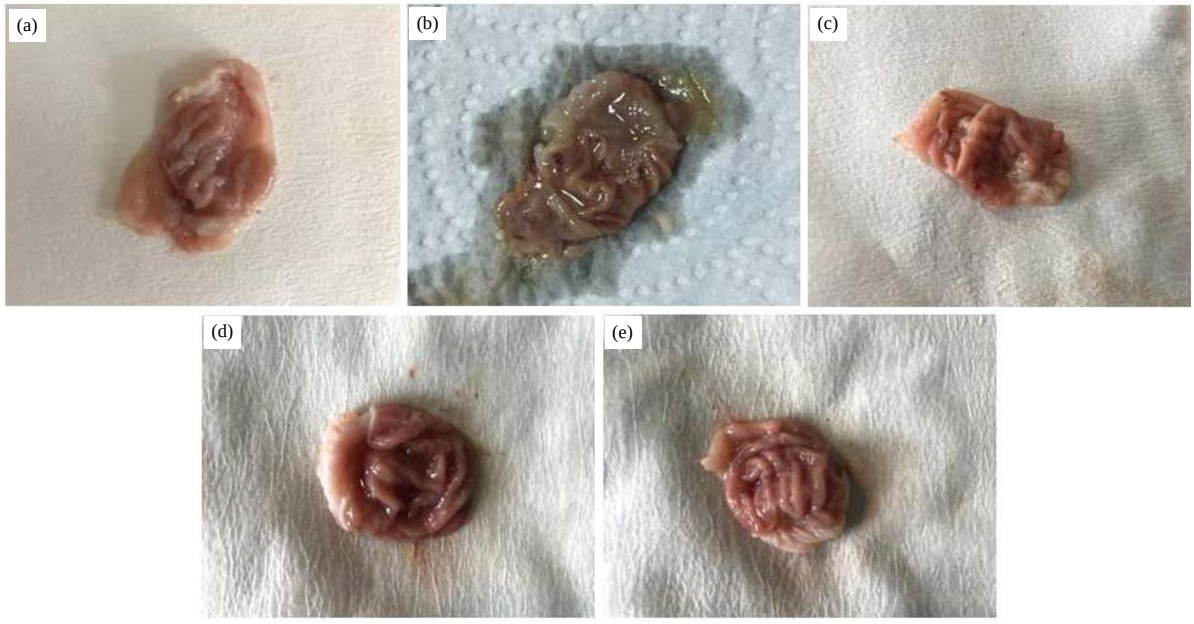


Fig. 1(a-e): Macroscopic evaluation of the effect of bupropion on ethanol-induced gastritis in rats
(a) Rats were treated with physiologic saline (p.o.), (b) 2 hrs before of the administration of 56% ethanol (8 g kg^{-1}; p.o.), (c) Omeprazole (20 mg kg^{-1}; p.o.), (d) 30 and (e) 60 mg kg^{-1} bupropion (p.o.)

Fig. 1c. However, gastric damage in rats administered with bupropion in the dose of 30 mg kg^{-1} Fig. 1d and with bupropion in the dose of 60 mg kg^{-1} in Fig. 1e was significantly decreased compared to the alcohol group. By scoring the Fig. 2a it was found that gastric mucosal damage in the alcohol group (4.66±0.8 mm^2) were more compared to the normal control group (0.16±0.4 mm^2), however, the oral administration of bupropion in doses of 30 (3.83±0.9 mm^2) and 60 (2.33±0.5 mm^2) mg kg^{-1} decreased the gastric mucosal damage when comparing with alcohol group ($p<0.001$). Also, omeprazole as a positive control decreased mucosal damage (1.50±0.5 mm^2). When comparing mucosal context in Fig. 2b to normal control rats (3.77±0.4 mg g^{-1} tissue) it was observed that gastric mucosal content of the alcohol group (0.48±0.2 mg kg^{-1} tissue) was significantly decreased ($p<0.001$); but gastric mucosal content for the groups administered with bupropion in doses of 30 mg kg^{-1} (1.16±0.4 mg kg^{-1} tissue) and 60 mg kg^{-1} (2.37±0.6 mg kg^{-1} tissue) was higher than alcohol group ($p<0.001$). Also, mucosal content was found to be a high level (3.37±0.4 mg kg^{-1} tissue) in the omeprazole group.

Changes in biochemical parameters: It was found that the alcohol treatment increased MDA levels (7.76±1.0 nmol g^{-1} tissue) in Fig. 3a in gastric tissue compared with the control group (3.32±0.4 nmol g^{-1} tissue; $p<0.001$). In addition, moderate (5.92±0.7 nmol g^{-1} tissue) and high dose (4.96±0.4 nmol g^{-1} tissue) of bupropion and omeprazole (3.71±0.4 nmol g^{-1} tissue) treatments decreased the MDA levels compared with the alcohol group ($p<0.001$). On the other hand, it was found that the alcohol treatment decreased (5.06±1.5 nmol g^{-1} tissue; $p<0.001$) GSH levels in gastric tissue in Fig. 3b when compared with the control group (12.48±1.7 nmol g^{-1} tissue), nevertheless the 30 (7.76±1.3 nmol g^{-1} tissue) and 60 (9.42±0.4 nmol g^{-1} tissue) mg kg^{-1} bupropion and omeprazole (10.07±0.5 nmol g^{-1} tissue) treatments increased the GSH levels ($p<0.001$) when compared to an alcohol group. In addition of these, in Fig. 3c; the alcohol treatment decreased SOD activity (7.20±1.1 U μg^{-1} protein) in gastric tissue when compared with the control group (30.42±2.8 U μg^{-1} protein; $p<0.001$); the 30 (13.59±1.3 U μg^{-1} protein) and 60 (16.80±2.3 U μg^{-1} protein) mg kg^{-1} bupropion and omeprazole (21.38±2.7 U μg^{-1} protein) treatments improved SOD activity when compared with alcohol group ($p<0.001$). Also, it was observed that in Fig. 3d the alcohol treatment decreased CAT (24.41±2.9 U μg^{-1} protein) activities in gastric tissue when compared with control group (57.05±4.0 U μg^{-1} protein; $p<0.001$); the 30 (37.03±4.6 U μg^{-1} protein) and 60 (43.43±7.5 U μg^{-1} protein) mg kg^{-1} bupropion and omeprazole (47.03±3.0 U μg^{-1} protein) treatments improved CAT activities when compared with alcohol group ($p<0.001$). It was found that alcohol treatment decreased gastric PGE2 in Fig. 3e levels (4.47±0.8 ng g^{-1} protein) when compared with

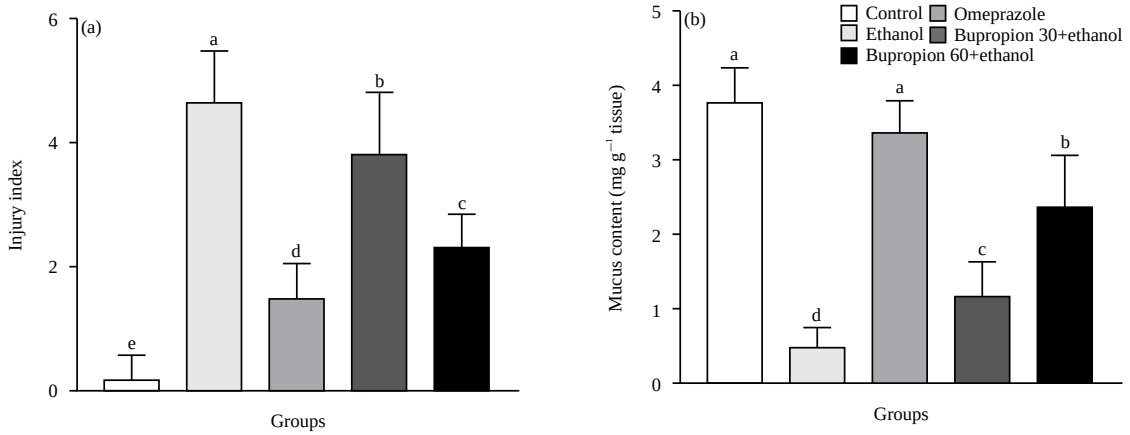


Fig. 2(a-b): (a) Effect of bupropion on gastric injury score and (b) Mucus content against ethanol-induced gastritis in rats
Rats were treated with physiologic saline, 30 and 60 mg kg^{-1} bupropion; p.o., or omeprazole (20 mg kg^{-1}; p.o.) 2 hrs before the administration of 56% ethanol (8 g kg^{-1}; p.o.). The results are presented as the Mean±SD 6 rats per group. Letters (a, b, c, d and e) show statistically significant differences between all groups and the control group (p<0.001)

control (10.29±1.3 ng g^{-1} protein; p<0.001) but, the bupropion treatments at doses of 30 (5.75±1.1 ng g^{-1} protein) and 60 (6.87±1.1 ng g^{-1} protein) mg kg^{-1} treatments increased PGE2 levels when compared with alcohol (p<0.001). In addition, it was observed that omeprazole (8.51±0.9 ng g^{-1} protein) treatment when compared with control returned these parameters to control. It was found that alcohol treatment (4.09±0.8 μmol g^{-1} protein) decreased gastric NO in Fig. 3f level when compared with control (13.34±1.6 μmol g^{-1} protein; p<0.001) but, the 30 (7.26±1.4 μmol g^{-1} protein) and 60 (8.14±0.6 μmol g^{-1} protein) mg kg^{-1} bupropion treatment increased NO levels when compared with alcohol (p<0.001). In addition, it was observed that omeprazole treatment (9.84±1.9 μmol g^{-1} protein) when compared with control returned these parameters to control.

mRNA expression levels in gastric tissue: When gastric mRNA expression fold increases were investigated; NF-κβ in Fig. 4a, Cox-2 in Fig. 4b, iNOS in Fig. 4c, TNF-α in Fig. 4d, IL1-β in Fig. 4e and IL-6 in Fig. 4f mRNA expression levels were found at 4.7, 3.5, 3.3, 3.2, 2.2 and 4.1as nearly increased fold changes in alcohol group compared to normal control groups (p<0.001), respectively. However, it was found that mRNA expressions of these genes in groups administered with bupropion in doses of 30 (3.9, 2.6, 2.5, 2.4, 1.6 and 3.4 as nearly increased fold changes, respectively) and 60 (3.6, 2.2, 2.2, 2.0, 1.4 and 2.5 as nearly increased fold changes, respectively) mg kg^{-1} were decreased compared to alcohol group (p<0.001). In addition, in the group administered with omeprazole (2.1, 1.4, 1.6, 1.4, 1.1 and 2.0 as nearly increased fold changes, respectively)the fold increases of these genes were found to be returned to control.

Histopathological changes: Ethanol/HCl treatment caused chronic surface epithelial damage in gastric mucosa, bleeding, mononuclear cell infiltration and significant changes in the mucosa in Fig. 5b (p<0.001) compared to the control group in Fig. 5a. Oedema and bleeding in gastric tissue mucosa of alcohol group rats were followed distinctively. On the other hand, the gastric surface mucosal layer of rats in groups administered with 30 and 60 mg kg^{-1} bupropion and omeprazole in Fig. 5d, e and c respectively, was healthy and oedema in the mucosa was lesser. In addition, it was determined by the statistical method that, damages in groups administered with omeprazole and bupropion (30 and 60 mg kg^{-1}) were significantly decreased (p<0.001).

DISCUSSION

Chronic gastritis is a disease showing clinical effects of anorexia, loss in weight, stomachache and diarrhoea as well as a specific effect like a damage in stomach mucosa depending on long term alcohol intake[29]. On the other hand, current treatments applied to alcohol-induced chronic gastritis accompany side effects clinically[30,31]. For this purpose, researchers are studying new approaches to reveal and improve the mechanisms of ethanol-induced chronic gastritis. Bupropion is known as with another name as amfebutamone is a typical type of anti-depressant medicine and indicates its

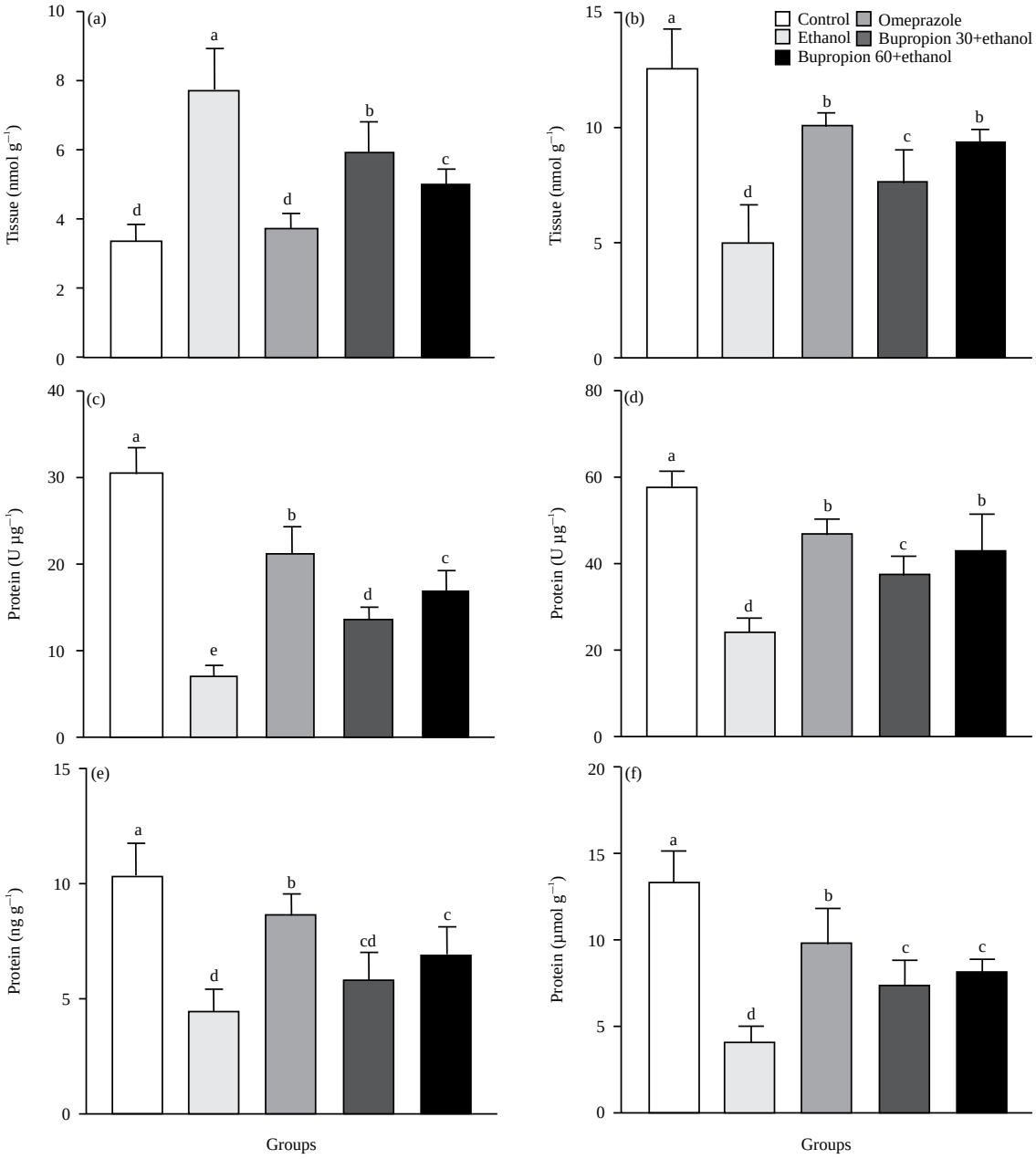


Fig. 3(a-f): Effect of bupropion on, (a) Malondialdehyde (MDA), (b) Reduced glutathione (GSH), (c) Superoxide dismutase (SOD), (d) Catalase (CAT), (e) Prostaglandin E2 (PGE2) and (f) Nitric oxide (NO) levels against ethanol-induced gastritis in rats

Rats were treated with physiologic saline, 30 and 60 mg kg^{-1} bupropion; p.o., or omeprazole (20 mg kg^{-1}; p.o.) 2 hrs before the administration of 56% ethanol (8 g kg^{-1}; p.o.). The results are presented as the Mean±SD 6 rats per group. Letters (a, b, c, d and e) show statistically significant differences between all groups and the control group ($p<0.001$)

effect by providing norepinephrine and dopamine neuronal reuptake inhibition[32]. Studies were reported that bupropion decreased the levels of inflammatory cytokines like TNF-α and interferon-gamma (INF-γ)[33-35]. In another study, it was reported that bupropion relieved inflammation by decreasing expressions of Toll-like receptors (TLR3 and TLR4) in patients with major depressive disorders[36]. For this reason, in our study, it was significant that bupropion showed significant therapeutic effects on ethanol-induced gastritis. But the mechanisms playing role in ulcer protective activity of bupropion were not illuminated before. For this reason, the current study for the first time clarified the potential gastroprotective activity of bupropion in rats against ethanol-induced gastritis.

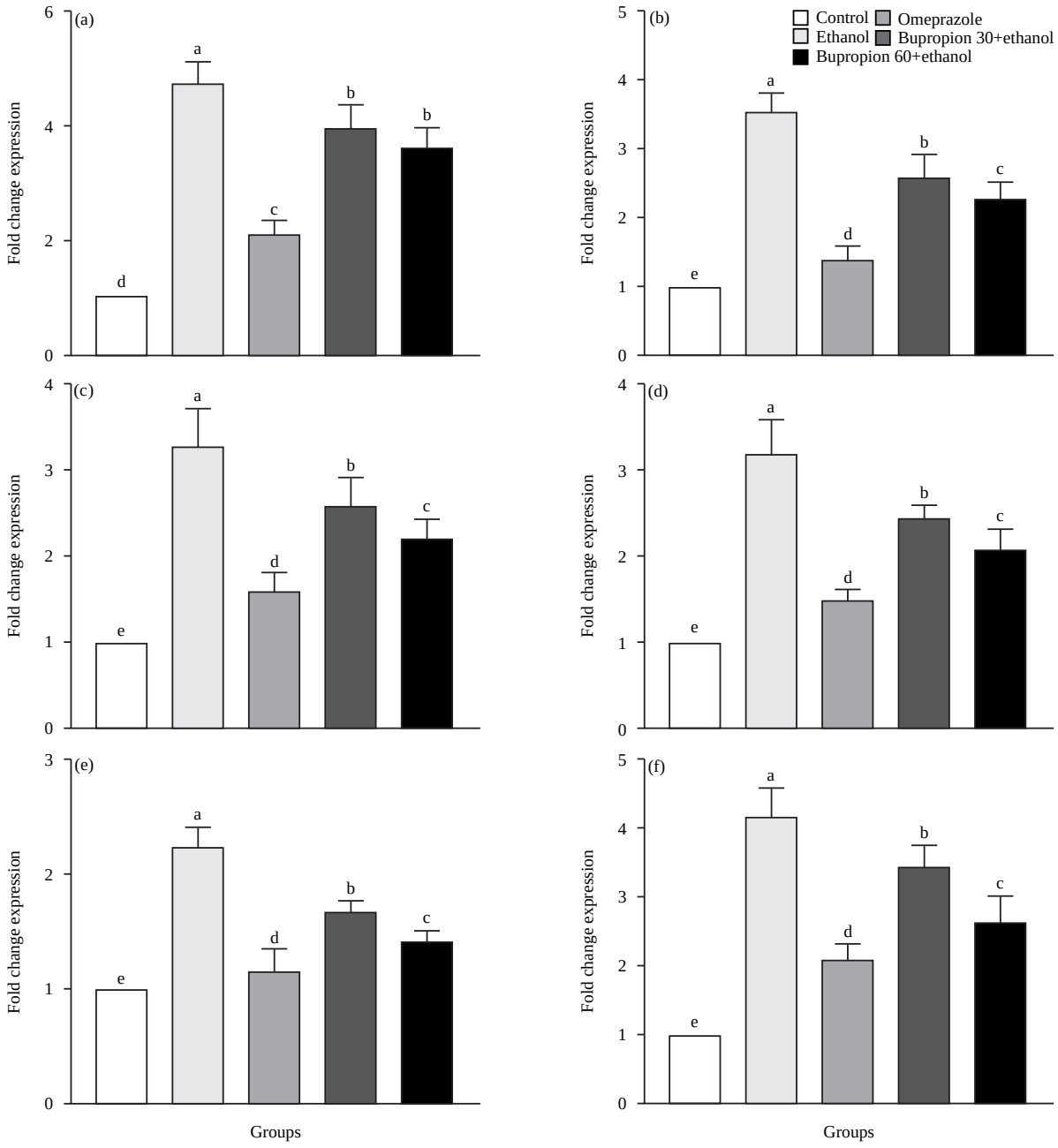
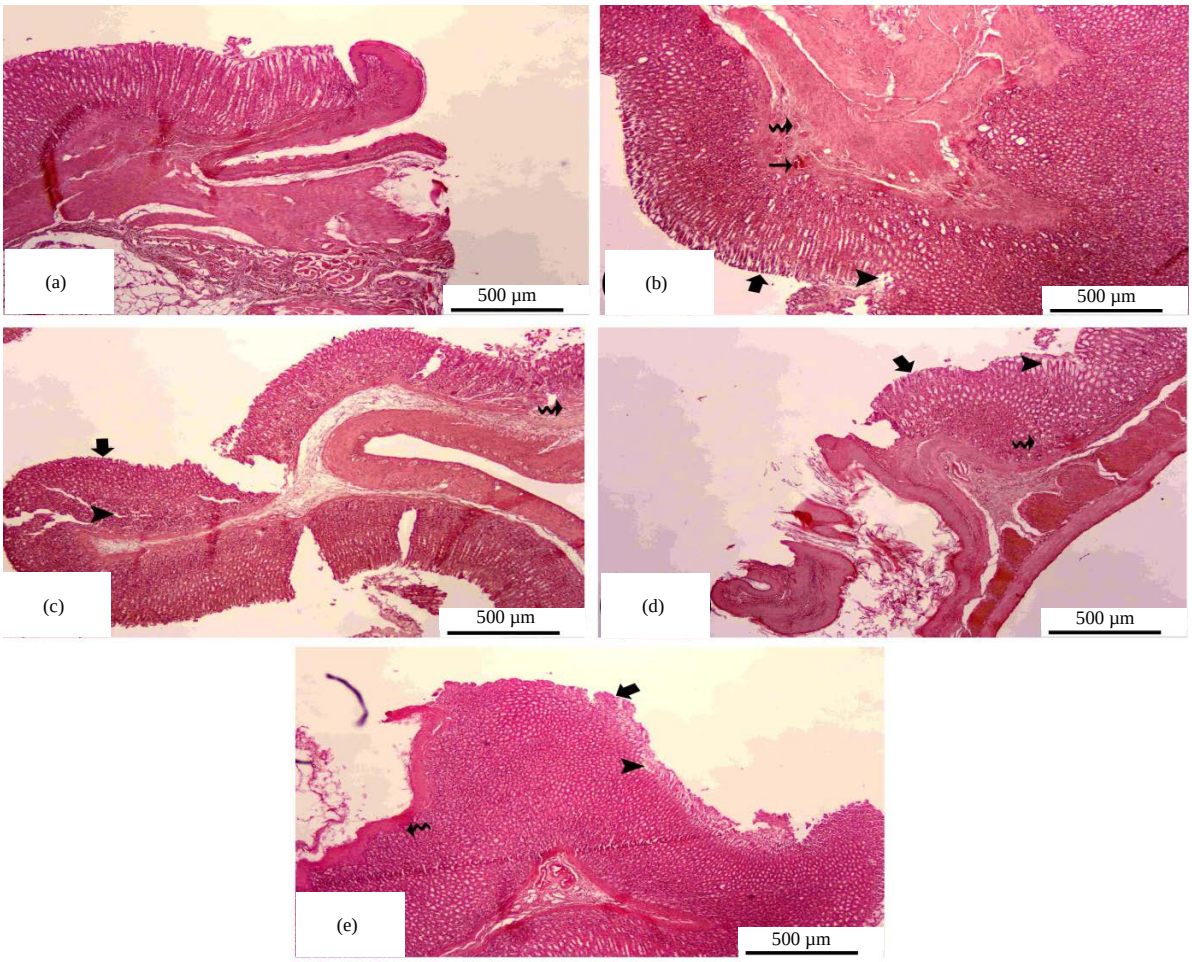


Fig. 4(a-f): Effect of bupropion on, (a) mRNA expression levels of NF-κβ, (b) Cox-2, (c) iNOS, (d) TNF-α, (e) IL1-β and (f) IL-6 against ethanol-induced gastritis in rats

Rats were treated with physiologic saline, 30 and 60 mg kg^{-1} bupropion; p.o., or omeprazole (20 mg kg^{-1}; p.o.) 2 hrs before the administration of 56% ethanol (8 g kg^{-1}; p.o.). The results are presented as the Mean±SD 6 rats per group. Letters (a, b, c, d and e) show statistically significant differences between all groups and the control group ($p<0.001$)

The stomach mucosa layer is the first defensive line for protecting the stomach mucosa. Studies conducted showed that excessive alcohol intake may decrease significantly the thickness of the stomach mucosal layer and hence the protective effect of the stomach mucosa may be decreased[37,38]. The results of this study presented similarly showed that excessive alcohol intake may decrease the content of mucosa and in the end may cause stomach mucosal damage.

It was determined that the long-term alcohol treatment causes free radicals to be produced in gastric tissue, together with increasing lipid peroxidation products the GSH levels



Tissue	Histopathological changes	Control	Ethanol	Omeprazole	Bupropion 30+Ethanol	Bupropion 60+Ethanol
Fundus	Epithelial loss	0.00±0.00^{c}	2.10±0.02^{a}	0.16±0.04^{c}	1.06±0.93^{b}	0.70±1.08^{bc}
	Hemorrhage	0.00±0.00^{c}	2.26±0.41^{a}	0.33±0.05^{bc}	1.05±1.15^{b}	0.88±1.03^{bc}
	Mononuclear cell infiltration	0.00±0.00^{c}	1.75±0.85^{a}	0.16±0.04^{c}	1.23±1.03^{ab}	0.70±1.08^{bc}
	Edema	0.00±0.00^{c}	2.10±0.01^{a}	0.16±0.04^{bc}	1.06+0.93^{b}	1.05±1.15^{b}

Fig. 5(a-e): Histopathological and statistical evaluation of the effect of bupropion on ethanol-induced gastritis in rats

(a) Rats were treated with physiologic saline (p.o.), (b) 2 hrs before of the administration of 56% ethanol (8 g kg^{-1}; p.o.), © Omeprazole (20 mg kg^{-1}; p.o.), (d) 30 and (e) 60 mg kg^{-1} bupropion; p.o. Representative figures were stained with hematoxylin and eosin. The original magnification was ×4 and the scale bars represent 500 µm. Bold, thin and curved arrows and arrowheads indicate epithelial loss, haemorrhage, areas of mononuclear cell infiltration and oedema, respectively

known as protective effects against damages induced by oxidative stress and antioxidants like SOD and CAT were decreased[39-41]. Similarly, in the current study, it was found that MDA was increased in the rats administered with alcohol nevertheless GSH level and SOD and CAT activities were inhibited. But it was observed that the bupropion treatment improved increased lipid peroxidation induced by alcohol and decreased antioxidant effect. These results show that bupropion suppresses antioxidant enzymes and prevent oxidative damage. It is known that PGE2 increases mucosal blood flow by inducing gastric mucosal secretion, protects mucosal cells against ulcers and speeds up mucosal healing[42,43]. On the other hand, ethanol treatment decreases gastric mucosal PGE2 content[44]. In addition, it was reported that bupropion increases inflammation and TNF-α level in psoriasis and atopic dermatitis, hepatitis B, Crohn and decreases inflammation in some diseases like chronic lymphocytic leukaemia and multiple myeloma[30]. In this study, bupropion treatment improved alcohol-induced effects in PGE2 levels. These results indicate that bupropion increases

PGE2 quantity and has protective effects against gastritis. It was reported that NO can protect the mucous layer by increasing the secretion of mucous and bicarbonate in gastrointestinal mucus, improving gastric blood flow and circulation and decreasing neutrophil infiltration[39]. In the study conducted in line with other studies[39-40] related to NO levels in gastric tissues, it was found that NO levels were decreased significantly by the alcohol treatment. On the other hand, NO level was increased significantly in the rats administered with bupropion. These results show that bupropion treatment can increase NO level by improving the antioxidant defence system and by modulating dopaminergic and L-arginine-nitric oxide-cyclic guanosine monophosphate signal pathway.

Depending on long term or excessive alcohol intake, it was reported that immune responses were shaped and proinflammatory cytokine levels were increased[16]. NF-κβ activation is shaped in mucosal inflammation induced by gastritis. NF-κβ activation in the presence of itself, induces Cox-2, IL-1β, IL-6, TNF-α and iNOS expressions and causes inflammatory reactions to occur[16,45]. On the other hand, it was reported that in the acetic acid-induced rat colitis model, 40, 80 and 160 mg kg^{-1}/p.o bupropion treatment for 5 days inhibited TLR4 and NF-κβ signal pathway, hence activation of inflammatory cytokines (such as IL-1, IL-6, IL-8, IL-27 and TNF-α) was decreased[46]. Again, in a study where the effects of bupropion were investigated on femoral bones; it was emphasized that in ovariectomized rats administered orally with bupropion (30 and 60 mg kg^{-1}/day) for six weeks decreased serum TNF-α, IL-1β and IL-6 levels[17]. In the current study, it was found that gastric NF-κβ, Cox2, IL-1β, IL-6, TNF-α and iNOS mRNA expression levels were increased significantly in rats exposed to alcohol. On the other hand, it was found that in the groups administered with bupropion there were significant downstream regulations in gastric NF-κβ, Cox2, IL-1β, IL-6, TNF-α and iNOS mRNA expression levels compared with the alcohol group. Current results show that bupropion treatment may have an anti-inflammatory effect by modulating the NF-κβ signal pathway.

In line with other studies[16,45], after ethanol treatment, it was found histopathologically acute surface epithelium damage, bleeding, mononuclear cell infiltration in the fundus and oedema in the mucosa. Contrary to this, it was found that alcohol-induced microscopic lesions were decreased distinctively by the bupropion treatment. These results describe that bupropion has a protective effect against an alcohol-induced gastric ulcer in the rat model.

CONCLUSION

As a result, it was determined that bupropion has a therapeutic effect in gastritis by balancing oxidant status and by regulating downstream NF-κβ mediated cytokine production against chronic gastritis developed depending on alcohol intake.

SIGNIFICANCE STATEMENT

This study revealed that bupropion blocking dopamine and noradrenaline reuptake and having a non-competitive antagonistic effect to central nicotinic acetylcholine receptors had a healing effect on gastritis. Through this study's findings, it may be possible to approach that bupropion may have potential use as a gastroprotective agent as well as antidepressant effect and other effects.

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