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Gastro protecting influence of Topiramate in ethanol produced gastric ulcers in rats

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ABSTRACT

Background: Topiramate (TPM), an antiepileptic drug, is also effective against alcohol dependency, a crucial factor in forming gastric ulcers. There is an increased possibility of patients with compromised gastric conditions getting exposed to TPM, but its effect on gastric ulcers is unknown. This study investigates the implication of acute TPM in ethanol-produced gastric ulceration in rats.

Material and methods: The effect of TPM studied in male 200−225 g Sprague Dawley rats against ethanol-induced gastric ulcers and for gastric secretion and acidity. The factors assessed include gastric secretion and acidity, gastric ulcer score, biochemical and histological changes, NF-kB, and p53 expression. The analysis of data performed by using the Kruskal Wallis test and Dunnett's multiple comparison tests.

Results: TPM pretreatment showed gastroprotective effects. It significantly reduced ethanol-induced increased gastric secretion, acidity, and gastric ulcer index and prevented gastric mucus depletion. The ethanol-induced inflammation and apoptosis were also significantly decreased by reducing the increased gastric myeloperoxidase activity and the expression of NF-kB and p53. TPM pretreatment also reduced the ethanol-induced damage to the gastric histology in rats.

Conclusion: TPM exerted a gastro-protective effect against ethanol-induced gastric ulcers mediated by reducing the gastric ulcer index, preventing a decrease of the mucus levels, reduction in inflammation, damage to gastric histology, and a decrease in the enhanced expression of NF-kB and TPM. Further detailed investigations are essential to understand the chronic influence of TPM on gastric ulcers.

1. Introduction

Gastric ulcer formation is a significant cause of morbidity and a burden on health care in almost all countries [1]. Consumption of fast foods and alcoholic beverages are a few of the crucial causes attributed to the formation of gastric ulcers. Regular alcohol use damages gastric mucosa and is associated with gastric inflammation, ulceration, and even carcinoma of the gastric tissue [2]. Alcohol causes gastric damage through different mechanisms such as increased gastric secretion, decreased mucosal protection, the release of pro-inflammatory cytokines [3–6], and invasion of activated neutrophils, apoptosis, and oxidative stress [7,8]. On the other hand, different drugs, such as TPM, are effective against alcohol abuse and dependency. However, these drugs' effects on alcohol-induced compromised gastric conditions, including gastric ulcers, have not received due importance.

TPM (2,3:4,5-Bis-O-(1-methylethylidene)-beta-D-fructo-pyranose sulfamate) is a commonly used antiepileptic drug. In addition to its antiepileptic activity, it helps manage other disorders [9]. TPM also acts as an antioxidant [10], protects against free radical damage, loss of pericytes, and learning in mice [11]. It reduces the expression of pro-inflammatory markers and increases the expression of anti-inflammatory pointers [12]. TPM is also used to treat alcohol use disorders and is vital for alcoholism [13,14]. Therefore, people with acute and chronic gastritis and gastric ulcers have a high possibility of its use. However, the effect of TPM in gastric ulcers is not known. This investigation studied the effect of TPM in ethanol-produced gastric

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ulcers in rats.

2. Material and methods

The Ethics committee of the Scientific Research Center of the Medical Services Department approved this study (vide approval number 002/122018). All the experiments performed adhered to the institutional and international guidelines for the care and use of experimental animals. Male Sprague Dawley rats of 200–225 g maintained with optimum conditions segregated into different groups—each group with six animals used for the study. TPM in doses of 50 mg, 100 mg, and 200 mg/Kg body weight was administered orally. The doses of TPM were selected based on earlier studies [15–17].

2.1. Gastric secretion and acidity

Pylorus ligation, as described by Shay et al. [18], was performed in four groups. Animals in three groups were administered TPM in different doses (50 mg, 100 mg, and 200 mg/Kg) one hour before ligation. The control group animals received water in the same volume. The animals were killed 6 h after the pylorus ligation, stomachs isolated, and the gastric contents collected and measured as total gastric secretion. After centrifugation, the total acid output of the gastric secretion was calculated by titrating with 0.01 N NaOH.

2.2. Induction of gastric ulcers

Ethanol is used for inducing experimental gastric ulcers in rats either alone [19,20] or in combination with hydrochloric acid (HCL) [21,22]. Ethanol was used for the induction of gastric ulcers as we observed it to be highly effective in producing gastric ulcers in fasted rats [7], the ulceration was observed in all the animals administered ethanol.

Six groups, each comprising of six animals, were used for the induction of gastric ulcers. Rats were housed in individual cages with the required measures to avoid fighting and coprophagy. They had unlimited drinking water access but deprived of food for 24 h. The first two groups were the control and the drug (TPM 200 mg/Kg) alone. The animals in groups 3, 4, and 5 were administered TPM (50 mg, 100 mg, and 200 mg/Kg, respectively) by gavage. Group 6 was the ulcer alone group and received water in the same volume as the TPM-treated animals. Thirty minutes after administering the drug, the experimental gastric ulcer was induced in groups 3–6 by intra-gastric administration of 1 mL of absolute ethanol, as described earlier [7]. The control, ethanol alone, and TPM alone grouped animals received water.

Sixty minutes after the ethanol administration, the animals were killed under deep anesthesia. The stomachs were rapidly removed, opened, and cleaned with ice-cold buffered saline, and gastric mucosal damage was examined for the number and severity of gastric lesions (Schiantarelli et al. [23]). The observer was blind to the treatment protocol.

2.3. Assessment of histological and biochemical changes

The same protocol used for the generation of gastric ulcers and TPM dosage administration was followed to study ethanol and TPM's effects on histological and biochemical changes in the gastric tissue. The collected stomachs were used for measuring the gastric wall mucus and myeloperoxidase (MPO). Phosphate-buffered formaldehyde was used to preserve the stomachs for histological studies.

2.4. Measurement of Gastric wall mucus and Myeloperoxidase (MPO) activity

The method of Corne et al. [24], was used to measure the gastric wall mucus, and MPO activity was determined by following the protocol of Bradley et al. [25].

2.5. Histology of ethanol-induced gastric lesions

The rats' stomachs in the different groups were collected, opened, and cleaned with saline and preserved in 10 % neutral buffered formaldehyde for 24 h and processed for histological assessment. The histological changes were studied in hematoxylin and eosin-stained sections by a qualified specialist, unaware of the different groups under a light microscope.

2.6. NF-kB and p53 expression

Paraffin-embedded 5 μ m thick stomach tissue sections were processed for expression of NF-kB and p53 by immunohistochemistry. After deparaffinization, the sections were dehydrated and rehydrated and then heated in citrate buffer for antigen retrieval. The reaction was blocked with normal goat serum (ab138478) and followed by treatment with primary antibodies (anti-p53 antibody [PAb 240] dilution1:100 ab26 and anti-NF-kB p105/p50 (Abcam, ab131493), at four °C. The sections were then processed with the specific HRP (ABC) detection IHC kits and the immunoreactions observed with 3,3-diaminobenzidine. Hematoxylin was used for counterstaining the slides. Microscopic analysis was conducted blindly.

2.7. Statistical analysis

Data were analyzed by utilizing the SPSS software platform (Version 20) and applying the Kruskal Wallis H test and one-way analysis of variance (ANOVA) followed by Dunnett's multiple comparison tests. $P < 0.05$ was considered statistically significant.

3. Results

3.1. Topiramate treatment and ethanol-induced gastric ulcers

Fig. 1 depicts the macroscopic changes observed in ethanol and TPM pretreated rats in the gastric mucosa. Exposure of animals to ethanol resulted in gastric mucosal edema and extensive erosion, visible as elongated severe hemorrhagic lesions (Fig. 1B) compared to healthy animals (Fig. 1A). The severity of the ethanol-induced gastric lesions was reduced dose-dependently in TPM pretreated rats (Fig. 1 C–E).

Exposure to ethanol resulted in widespread gastric abrasions in the rats with an ulcer index score of 7.5 ± 0.22 (Fig. 2). TPM decreased the acute gastric abrasions produced by ethanol dose-dependently. All TPM doses significantly attenuated the development and severity of gastric injuries, as evident (Fig. 2) from the ulcer score reduction.

3.2. Topiramate treatment and gastric secretion and acidity

Our results showed TPM to possess intense anti-gastric secretory activity in pylorus-ligated rats (Fig. 3A). A total of 9.66 ± 0.33 mL of gastric secretion volume accumulated in untreated pylorus ligated animals. Pretreatment with TPM substantially reduced gastric secretion. The gastric secretion was significantly reduced in TPM pretreated animals (100 mg/Kg (5.863 ± 0.6 mL) and 200 mg/Kg (5.0 ± 0.52 mL) of TPM. Although gastric secretion decreased (8.0 ± 0.57 mL) in the animals treated with the low dose of TPM, the difference was statistically insignificant.

Pretreatment with TPM was also effective in reducing the gastric acidity in pylorus-ligated rats. The gastric acidity in untreated control (ethanol only) rats was 816.66 ± 111.26 mEq.

The gastric acidity declined dose dependently in TPM pretreated rats. (Fig. 3, B)

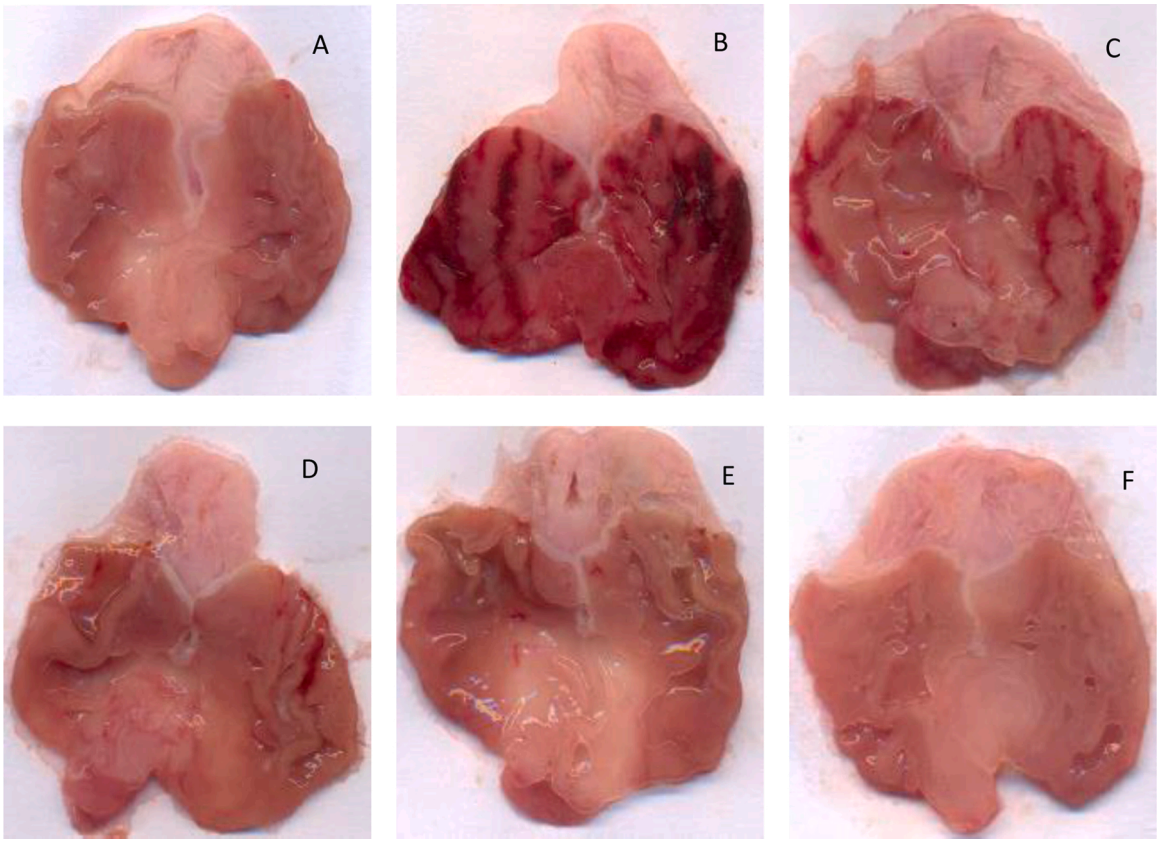

Fig. 1. Gross macroscopic appearance of the gastric mucosa of Control (A), Ethanol (B), Topiramate 50 mg/Kg (C), 100 mg/Kg (D), 200 mg/Kg (E), and Topiramate alone 200 mg/Kg (F) pretreated rats. Rats were pretreated with Topiramate 30 min earlier to ethanol exposure. Control, ethanol alone, and Topiramate alone grouped animals were given water instead of the drug.

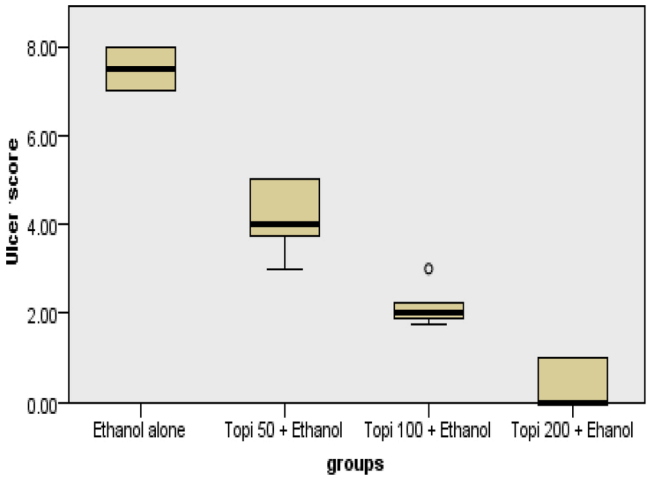

Fig. 2. Topiramate pretreatment effects on gastric ulcer scores in ethanol-induced ulcers in rats. Groups compared by Kruskal Wallis test. $F = 3 = 21.60$. $P < 0.0001$. Topi – Topiramate 50, 100, and 200 mg/Kg. Animals in the ethanol alone group received water instead of the drug.

3.3. Topiramate treatment and ethanol-produced changes in gastric wall mucus

Gastric mucus acts as a crucial defensive barrier against chemical or mechanical damage to the gastric mucosa. As compared to control animals, the Alcian blue binding capacity, a valuable indicator of mucus in the gastric mucosa, was significantly ($P < 0.001$) depleted in ethanol-treated rats (Fig. 4). While pretreatment with TPM at 100 mg/Kg and 200 mg/Kg significantly restored the depleted mucus levels of the gastric mucosa, suggesting an increase in mucus production and exerting a positive effect against ethanol-induced depletion of gastric mucus.

3.4. Topiramate treatment and ethanol-produced changes in the histopathology of stomach

Changes in the stomach's histological architecture shown in Fig. 5A, illustrates a typical gastric architecture in untreated healthy control animals. Treatment with ethanol initiated mucosal erosion and marked the hemorrhage's appearance, with inflammation in the sub-mucosal layer and infiltration of neutrophils resulting in gastric lesions' formation with loss of glandular cells and the detachment of the surface epithelium and a discontinuity in the mucosal lining (Fig. 5 B). Pretreatment with TPM substantially weakened the detrimental ethanol-produced gastric mucosal changes wielding a gastroprotective effect (Fig. 5 C–E). TPM pretreatment (100 mg/Kg and 200 mg /Kg) resulted in a nearly typical gastric mucosal structure, with minimum infiltration of inflammatory cells and a substantial improvement in the glandular structure and arrangement (Fig. 5 D & E).

3.5. Topiramate treatment and ethanol-produced variations in p53 and NF-kB expression

The immunohistochemical analysis results for the expression of p53 proteins and NF-kB in gastric tissue of rats also demonstrated a protective effect of TPM in ethanol-induced gastric ulcers. The results for p53 showed intense staining in ethanol-treated animals' gastric tissue. The intense staining indicates the immunoreactivity and overexpression of p53 protein. In contrast, the healthy control animals showed no immunoreactivity (Fig. 6 B & A). Pretreatment with TPM reduced the

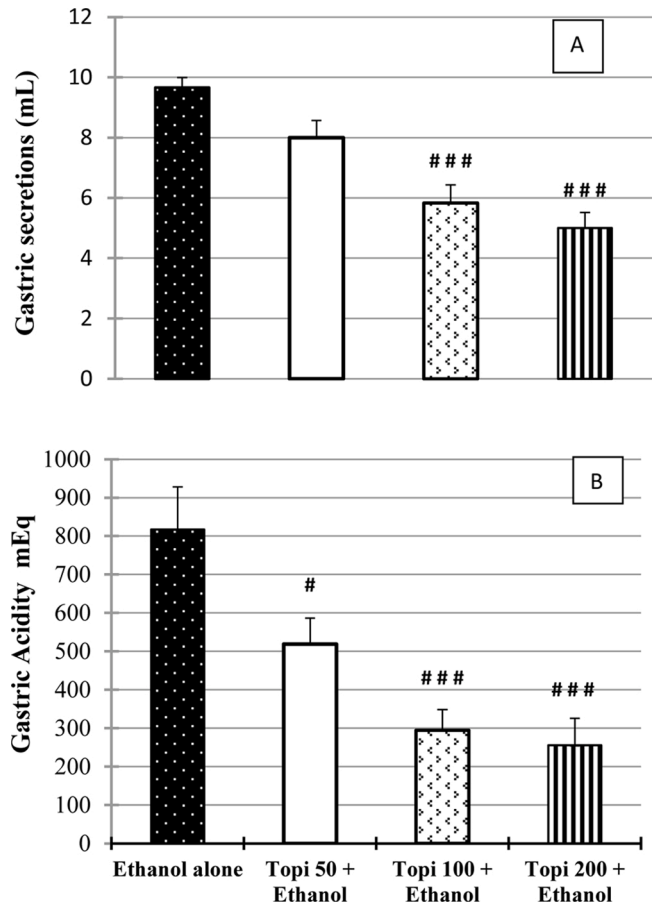

Fig. 3. Topiramate pretreatment effects on gastric secretion (A) and acidity (B) rats. # $P < 0.05$ and # # # $P < 0.0001$ as compared with control animals using ANOVA followed by post hoc comparison with Dunnett's test. Topi - Topiramate 50, 100 and 200 mg/Kg. Animals treated with only ethanol were given water instead of the drug.

overexpression of p53 protein (Fig. 6 C–E).

Compared to control animals, the ethanol-treated rats showed intense expression of NF-kB (Fig. 7 B). Pretreatment with TPM markedly down-regulated the ethanol-induced overexpression of NF-kB (Fig. 7 C–E).

3.6. Topiramate treatment and ethanol-produced changes in the gastric MPO activity

Pretreatment with TPM significantly protected against ethanol-induced gastric ulcers by decreasing the infiltration of activated neutrophils, as reflected in the results of the MPO activity in ethanol and TPM-treated animals. Ethanol-induced increased MPO activity was significantly reduced in TPM- treated rats (Fig. 8).

4. Discussion

Topiramate is a commonly used antiepileptic drug with potent antioxidant, anti-apoptotic, and anti-inflammatory properties. It is also effectively used for treating alcohol dependency. Since alcohol use is a significant cause of gastric ulcers, people with gastric ulcers are likely to get inadvertently exposed to TPM. However, the effect of TPM on gastric ulcers remains unexplored. This study explored the pretreatment effect of TPM on alcohol-produced gastric ulcers in rats.

Administration of ethanol produced gastric injury that manifests in deep ulceration, as seen in the macroscopic appearance and the ulcer scores (Figs. 1 and 2). TPM pretreatment attenuated ethanol-produced gastric hemorrhagic abrasions and ulcers dose-dependently. The high TPM dose almost wholly prevented gastric lesions (Figs. 1 and 2), which was also evident from the stomach's histological architecture changes. Ethanol-produced gastric lesions characterized by the interruption in the mucosal layer, necrosis, edema, and leucocytes" infiltration were significantly reversed by TPM pretreatment. Formation of the hemorrhagic lesions in the stomach involves diverse mechanisms, including enhanced gastric secretion and acidity, reduction in the protective mucosal barrier, disruption of micro-vessels, infiltration of activated neutrophils, oxidative stress, increased pro-inflammatory factors, and apoptosis [3–5,7,8]. A reduction in the severity of the hemorrhagic lesions in the TPM pretreated animals suggests an ameliorative influence of TPM on the hemorrhagic mechanisms.

TPM pretreatment significantly decreased both gastric secretion and acidity (Fig. 3.A & B). Gastric secretion and acidity play a vital role in forming gastric ulcers by unsettling the normal physiological process [26]. Different substances are involved in the stimulation of gastric secretion by parietal cells. These include the cholinergic transmitter acetylcholine, histamine and, carbonic anhydrases. Activation of the different isoforms of carbonic anhydrase plays a dynamic role in gastric secretion and ulcer formation. Both Helicobacter pylori infection and chemically induced gastric ulcers [27,28] activate the carbonic anhydrases.

Furthermore, cysteamine, a potent ulcerogenic compound, acts through direct activation of the carbonic anhydrases in the gastric mucosa parietal cells [29]. Calcium modulates the activation of carbonic anhydrases. Increased blood calcium levels are associated with increased carbonic anhydrase activity and a concomitant increase in gastric acid secretion. On the contrary, calcium channel blockers and carbonic anhydrase inhibitors decrease gastric secretion and heal gastric ulcers [30,31]. The reduction in gastric secretion and acidity in TPM pretreated rats is likely due to TPM's multiple action mechanisms. TPM is a carbonic anhydrase inhibitor, a calcium channel modulator, and an active anticholinergic agent [11,30,31]. Therefore, the decreased gastric secretion and the TPM's gastro-protective effect may be attributed to these modulating properties.

Ethanol-produced gastric ulceration also involves reducing gastric mucus and permeability, resulting in increased leakage of hydrogen ions from the lumen [32]. Mucus is one of the significant components of the mucosal barrier that acts as a defensive shield against noxious substances in the gastric tissue and facilitates its normal functioning. Mucus gel adhering to the mucous surface entraps bicarbonate secreted by the gastric epithelium facilitating neutralization of the gastric luminal acid [33,34]. Besides, the mucus acts as a barrier to the diffusion of low molecular weight solutes, microorganisms, and toxins [35]. Furthermore, mucus may also act as an antioxidant and prevent oxygen-free radical-mediated damage to the gastric mucosa [34,35]. This study's results, wherein TPM treatment significantly attenuated the ethanol-produced depletion of mucus levels (Fig. 4), suggest that TPM enhances the secretion of mucus. Our findings agree with earlier studies in which an increase in mucus secretion stimulated by different compounds attenuated experimental gastric lesions in rats [5,7].

p53 is an important transcription factor and tumor suppressor that plays a crucial role in coordinating many cellular signaling pathways that mediate cellular response to stress [36,37]. Helicobacter pylori-infected human gastric mucosa, and H. pylori-associated chronic gastritis [37], increasingly express p53. The expression of p53 is increased in gastric ulcers and carcinoma [38,39]. Our observation of increased expression of p53 in ethanol-treated rats (Fig. 6) may result from the gastric mucosa's immediate response to ethanol stimulation. A recent study reported a ten times higher expression of p53 in rats' stomachs administered a single dose of ethanol compared to healthy animals [8]. Other studies also show an association between gastric ulceration and increased expression of p53 and caspase3 activities in different models of gastric ulcers [40]. One of the critical functions of p53 is to activate the process of apoptosis. Induction of p53 alters the

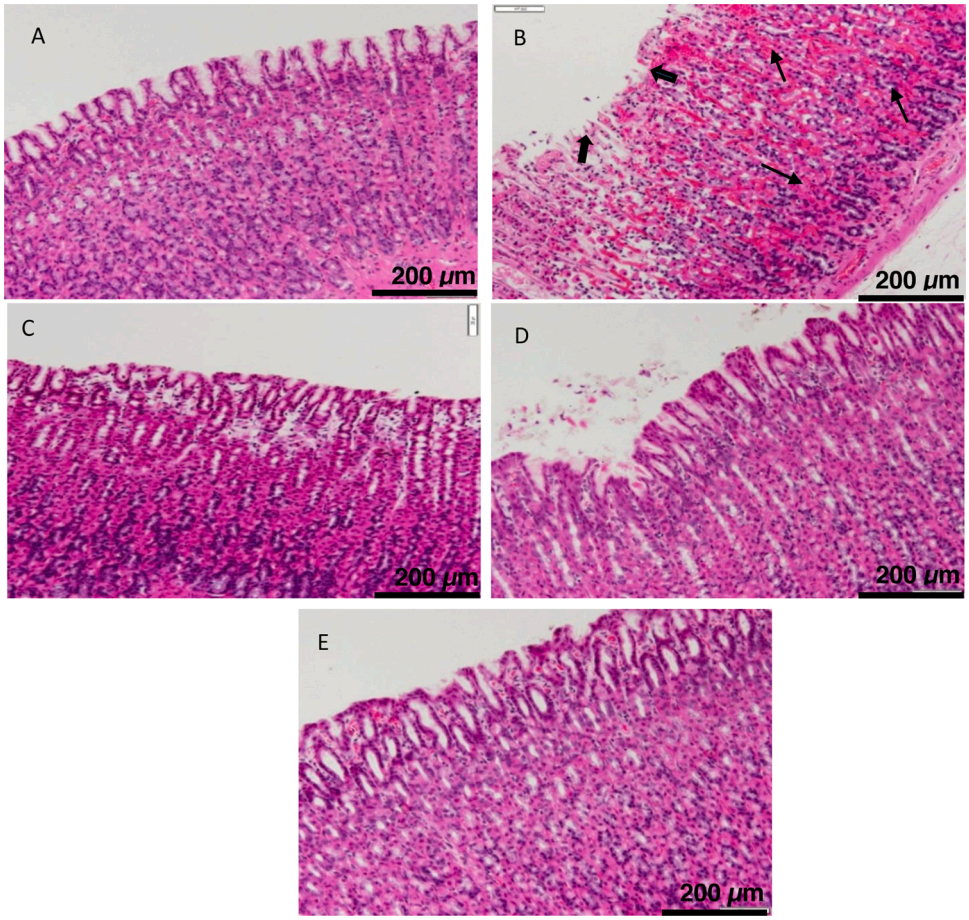

Fig. 4. Topiramate pretreatment effects on ethanol-produced changes in the gastric mucous levels of rats. * * $P < 0.001$ when related to normal control animals and # # $P < 0.001$ when related to animals treated with ethanol by using Dunnett's multiple comparison test. Topi - Topiramate 50, 100 and 200 mg/Kg. Control, ethanol alone, and Topiramate alone grouped animals were given water instead of the drug.

REDOX metabolism resulting in increased oxidative stress before apoptotic cell death onset [41].

On the other hand, p53 mediated apoptosis and cell death in ethanol-produced gastric injuries get reduced in an antioxidant's presence [8]. The intense antioxidant activity and anti-apoptotic effects [10,16] of TPM may be responsible for the decreased expression of p53 in TPM pretreated rats.

Alcohol damages the stomach through NF-kB expression [6,42], a transcription factor that regulates the expression of inflammation and cell injury-associated genes [6]. In healthy resting cells, NF-kB in the cytosol is in an inactive form bound with inhibitor – kB (I-kB). Inflammation and inflammatory stimuli enable I-kB's phosphorylation and its dissociation from NF-kB, which then is translocated into the nucleus. Activated NF-kB is detected only in ulcerated tissue and sustained until gastric ulcers [43]. It is a signal pathway that plays a vital role in gastric ulcers and gastric pathology through involvement in multitudes of actions. The activation of NF-kB results in the up-regulated expression of many mediators of inflammation [6,42]. The exposure of rats to ethanol in our study also resulted in overexpression of NF-kB compared to the control animals, while pretreatment with different TPM doses markedly down-regulated the overexpression of NF-kB (Fig. 7). The down-regulation of NF-kB and its downstream targets help in the amelioration of ethanol-produced gastric ulcers [6,44].

Another mechanism that plays a critical role in ethanol-produced damage is the infiltration of activated neutrophils. Infiltration of activated neutrophils into the gastric mucosa triggers an oxidative burst that stimulates gastric mucosal lesioning [45]. Myeloperoxidase (MPO), the marker enzyme for activation of neutrophils, is a valuable indicator of gastric ulcers' inflammatory activity [7,40]. Compounds that reduced the activation and infiltration of neutrophils and increased MPO activity protect against ethanol-produced gastric damage [6,7,40]. We also observed a significantly increased MPO activity in ethanol-treated rats. Pretreatment of rats with TPM significantly and dose-dependently reduced the alcohol-produced increase in MPO activity (Fig. 8). Therefore, suggesting that TPM's protective effect may also be due to its anti-inflammatory potential, as evidenced by the reduction in the ethanol-produced increase in MPO activity and NF-kB expression, valuable indicators of inflammation [6]. Furthermore, TPM has potent antioxidant and anti-inflammatory activity and suppresses lymphocytes' accumulation in ischemia-reperfusion injury [11,46].

5. Conclusion

In conclusion, this study shows that pretreatment with TPM attenuates ethanol-produced gastric ulcers in rats. The protective action of TPM was associated with the regulation of gastric secretion, strengthening of the mucosal barrier, inhibition of neutrophil infiltration, inflammation, and apoptosis.

Author contributions

Category 1

Conception and design of study: Saeed Kadasah, Ahmad Saleh AI Eid, Mohammed Arshaduddin, Ibrahim Elfaki.

Acquisition of data: Ibrahim Elfaki, Salem Saleh Alawad, Abdullah S AI Shahrani, Ahmed Salem Alruwahi.

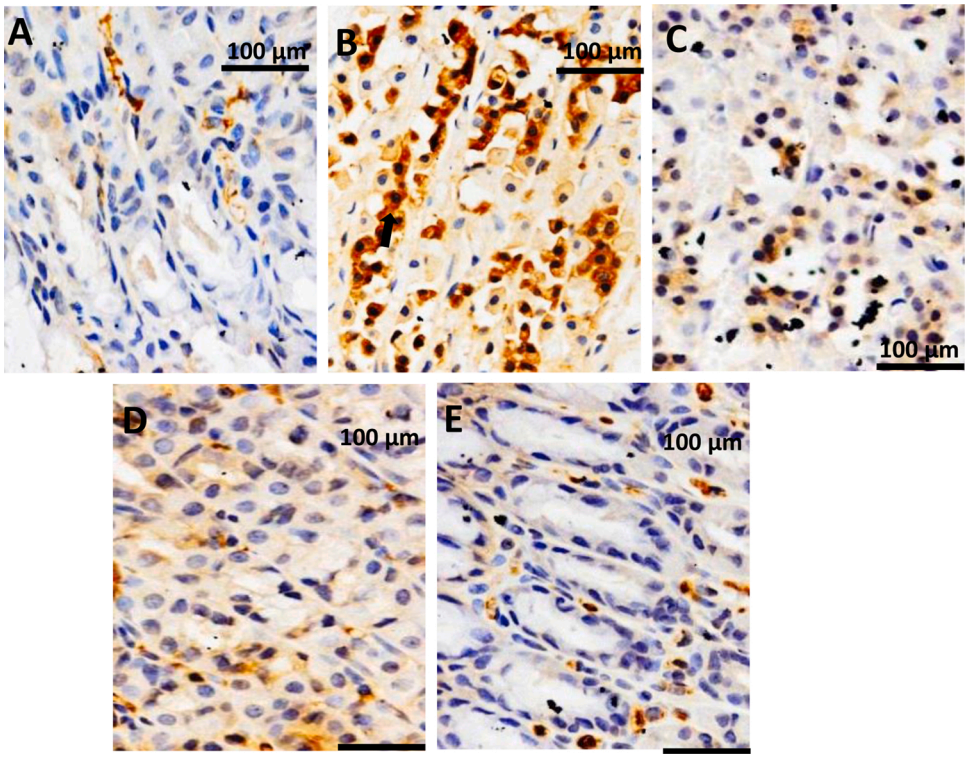

Fig. 5. Topiramate pretreatment effects on ethanol-produced changes in the histology of the rat's stomach. Figures A-E represent the light micrographs of the stomach of rats. A, - Normal rat Stomach. B, - Rat Stomach exposed to ethanol showing the damaged gastric mucosa and discontinuity in the mucosal lining (thick arrows). C – E, - Stomach of TPM pretreated rats (50 mg, 100 mg, and 200 mg/Kg of Topiramate + Ethanol, respectively). Animals in the control and the ethanol alone groups received water. Treatment with 100 mg/Kg and 200 mg/Kg of Topiramate showing almost complete normalcy in the histological architecture. Thick arrows show ethanol-induced gastric erosion, and the thin arrows show edema and hemorrhage.

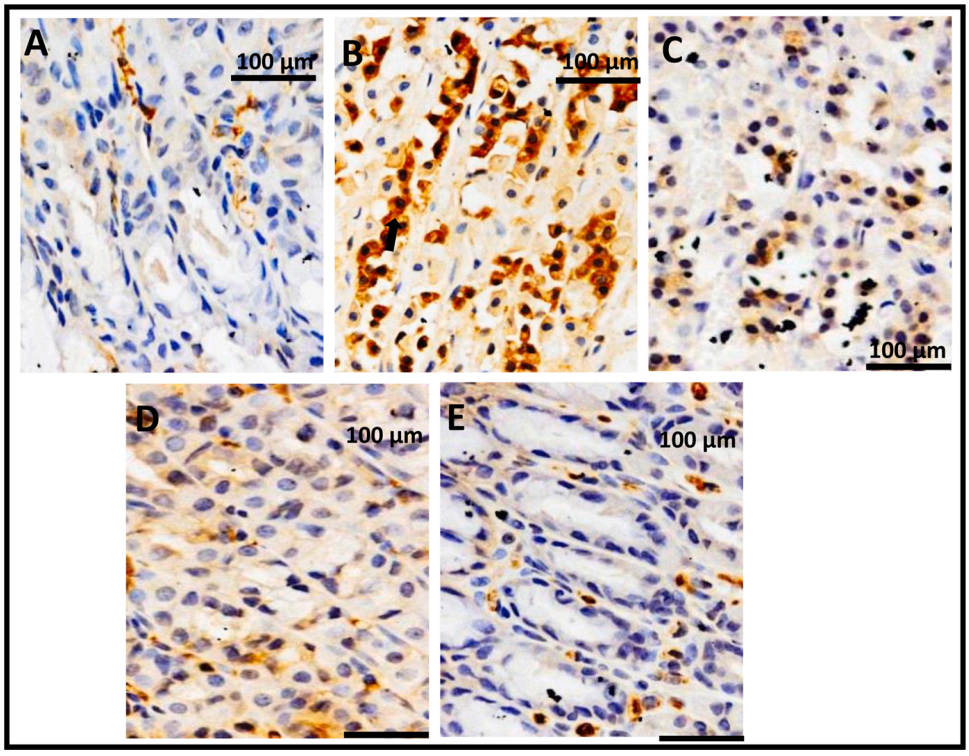

Fig. 6. Topiramate pretreatment effects on ethanol-produced changes in the immunohistochemical localization and expression of p53 in rat's stomach. (A) Control animals show no p53 expression. (B) Ethanol-exposed rats are displaying a strong expression of p53. (C–E) Topiramate-pretreated animals show comparatively more minor staining and expression of p53. Animals in the control and ethanol alone groups received water.

Analysis and/or interpretation of data: Mohammed Arshaduddin, Ibrahim Elfaki, Yaser AI Asmari.

Category 2

Drafting the manuscript: Saeed Kadasah, Ahmad Saleh AI Eid, Mohammed Arshaduddin, Ibrahim Elfaki.

Revising the manuscript critically for important intellectual content: All authors.

Category 3

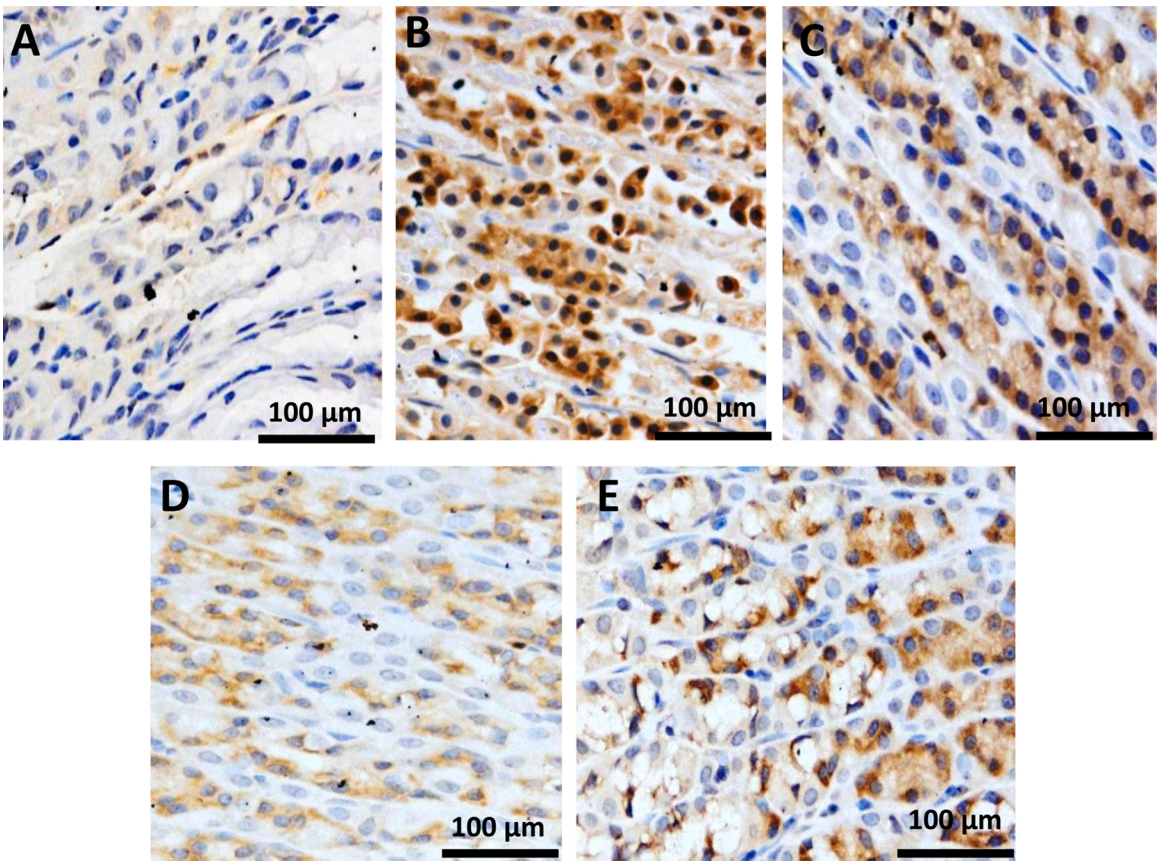

Fig. 7. Topiramate pretreatment effects on ethanol-produced changes in the immunohistochemical localization and expression of NF-kB in rat's stomachs. Photomicrographs showing immunohistochemical activation of NF-kB. (A) Control animals show no NF-kB expression. (B) Ethanol-exposed rats are displaying a strong expression of NF-kB. (C–E). Topiramate pretreated animals are showing comparatively more minor staining and expression of NF-kB. Animals in the control and ethanol alone groups received water.

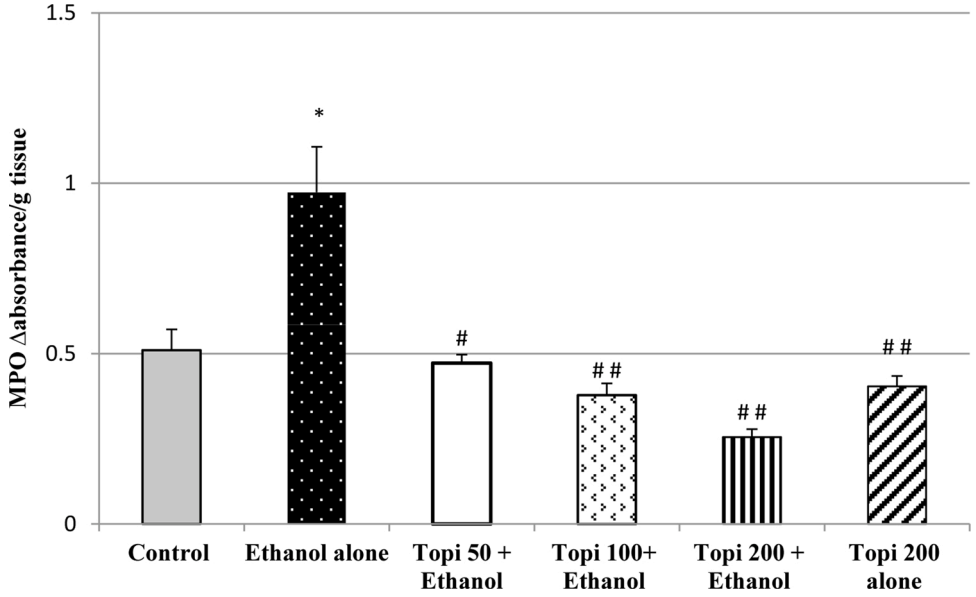

Fig. 8. Topiramate pretreatment effects on ethanol-produced changes in MPO activity of rats. * $P < 0.01$ related to control animals and # $P < 0.05$, # # $P < 0.001$ related with ethanol alone treated animals by using Dunnett's multiple comparison test. Topi - Topiramate 50, 100, and 200 mg/Kg Animals in the control, ethanol alone, and the Topiramate alone groups received water.

Approval of the version of the manuscript to be published (the name of all authors must be listed): Saeed Kadasah, Ahmad Saleh AI Eid, Salem Saleh Alawad, Abdullah S AI Shahrani, Ahmed Salem Alruwaihi, Yaser AI Asmari, Ibrahim Elfaki, Mohammed Arshaduddin.

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CRediT authorship contribution statement

Saeed Kadasah: Conceptualization, Methodology, Data curation, Writing - original draft, Supervision, Writing - review & editing. **Ahmad Saleh Al Eid:** Conceptualization, Methodology, Data curation, Writing - original draft, Writing - review & editing. **Salem Saleh Alawad:** Visualization, Investigation, Writing - review & editing. **Abdullah S. Al Shahrani:** Visualization, Investigation, Writing - review & editing. **Ahmed Salem Alruwaihi:** Visualization, Investigation, Writing - review & editing. **Ibrahim Elfaki:** Conceptualization, Methodology, Data curation, Writing - original draft, Visualization, Investigation, Writing - review & editing. **Mohammed Arshaduddin:** Conceptualization, Methodology, Data curation, Writing - original draft, Writing - review & editing.

Declaration of Competing Interest

The authors declare no conflict of interest.

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References

[1] H. Azhari, F. Underwood, J. King, et al., A36. The global incidence of peptic ulcer disease and its complications at the turn of the 21st century: a systematic review, J. Can. Assoc. Gastroenterol. 1 (suppl_2) (2018) 61–62, https://doi.org/10.1093/jcag/gwy009.036.

[2] G. Amin, M. Siegel, T. Naimi, National cancer societies and their public statements on alcohol consumption and cancer risk, Addiction (2018) 25, https://doi.org/10.1111/add.14254.

[3] C.Y. Li, M. Su, Y.Y. Yan, L. Zhou, L.Y. Ao, W.R. Fang, Y.M. Li, KFP-H008 blocks gastric acid secretion through inhibiting H+-K+-ATPase, Eur. J. Pharmacol. 5 (2017) 112–119, https://doi.org/10.1016/j.ejphar.2017.06.020.

[4] X. Zhao, Q. Cheng, Y. Qian, R. Yi, L. Gu, S. Wang, J.L. Song, Insect tea attenuates hydrochloric acid and ethanol-induced mice with an acute gastric injury, Exp. Ther. Med. 14 (2017) 5135–5142, https://doi.org/10.3892/etm.2017.5181.

[5] F. Tayeby, A.A.A. Salman, S. Kamran, S.L. Khaing, N.B. Salehen, G.M.A.D. Mohan, Ulcer prevention effect of 3, 4, 5-tihydroxy-n0-[(2-methyl-1h-indol-3yl) methylidene] benzo hydrazide in Hcl/ethanol-induced gastric mucosal damage in rats, Int. J. Med. Sci. 14 (2017) 1317–1326, https://doi.org/10.7150/ijms.20984.

[6] Su Mei, C.Y. Li, Lin Zhou, Y.Y. Yan, Lu-Yao Ao, G.J. Wang, W. Fang, C.Y. Li, Anti-ulcerogenic effect of KFP-H008 against ethanol-induced gastric ulcer: via p38 MAPK/NF-κB pathway, RSC Adv. 7 (2017) 49423–49435, https://doi.org/10.1039/C7RA07178G.

[7] A. Al Asmari, H. Al Shahrani, N. Al Masri, A. Al Faraidi, I. Elfaki, M. Arshaduddin, Vanillin abrogates ethanol-induced gastric injury in rats via modulation of gastric secretion, oxidative stress, and inflammation, Toxicol. Rep. 3 (2016) 105–113, https://doi.org/10.1016/j.toxrep.2015.11.001.

[8] S.R. Hamad, H.R. Hamad Mohamed, Amelioration of ethanol-induced apoptotic damage and ulcerative injuries in the mice gastric tissues by starch oral administration, Toxicol. Mech. Methods 28 (2018) 130–139, https://doi.org/10.1080/15376516.2017.1373879.

[9] B.R. Sommer, E.L. Mitchell, T.E. Wroolie, Topiramate: effects on cognition in patients with epilepsy, migraine headache, and obesity, Ther. Adv. Neurol. Disord. 6 (2013) 211–227, https://doi.org/10.1177/1756285613481257.

[10] N. Cárdenas-Rodríguez, E. Coballase-Urrutia, B. Huerta-Gertrudis, M. García-Cruz, J. Pedraza-Chaverri, R. Coria-Jiménez, et al., Antioxidant activity of Topiramate: an antiepileptic agent, Neurol. Sci. 34 (2013) 741–747, https://doi.org/10.1007/s10072-012-1127-5.

[11] T.O. Price, S.A. Farr, M.L. Niehoff, N. Ercal, J.E. Morley, G.N. Shah, Protective effect of Topiramate on hyperglycemia-induced cerebral oxidative stress, pericyte loss and learning behavior in diabetic mice, Int. Libr. Diabetes Metab. 1 (2015) 6–12.

[12] C.P. Jara, V.C.D. Bóbbo, R.S. Carraro, T.M.F. de Araujo, M.H.M. Lima, L.A. Velloso, E.P. Araújo, Effects of topical Topiramate in wound healing in mice, Arch. Dermatol. Res. 310 (2018) 363–373, https://doi.org/10.1038/sj.jid.5700701.

[13] H.R. Kranzler, M. Soyka, Diagnosis and pharmacotherapy of alcohol use disorder: a review, JAMA 320 (2018) 815–824, https://doi.org/10.1001/jama.2018.11406.

[14] M. Soyka, H.R. Kranzler, V. Hesselbrock, S. Kasper, J. Mutschler, H.J. Möller, WFSBP task force on treatment guidelines for substance use disorders. Guidelines for biological treatment of substance use and related disorders, part 1: alcoholism, first revision, World J. Biol. Psychiatry 18 (2017) 86–119, https://doi.org/10.1080/15622975.2016.1246752.

[15] A. Kurt, Y. Kalkan, H. Turut, M.C. Cure, L. Tumkaya, E. Cure, Topiramate reduces aortic cross clamping -induced lung injury in male rats, Acta Medica (Hradec Kralove) 61 (2018) 144–149, https://doi.org/10.14712/18059694.2018.133.

[16] M. Motaghinejad, M. Motevalian, F. Babalouei, M. Abdollahi, M. Heidari, Z. Madjd, Possible involvement of CREB/BDNF signaling pathway in neuroprotective effects of Topiramate against methylphenidate-induced apoptosis, oxidative stress and inflammation in the isolated hippocampus of rats: molecular, biochemical and histological evidence, Brain Res. Bull. 132 (2017) 82–98, https://doi.org/10.1016/j.brainresbull.2017.05.011.

[17] A.I. El Makawy, F.M. Ibrahim, D.M. Mabrouk, K.A. Ahmed, M. Fawzy Ramadan, Effect of antiepileptic drug (Topiramate) and cold pressed ginger oil on testicular genes expression, sexual hormones and histopathological alterations in mice, Biomed. Pharmacother. 110 (February) (2019) 409–419, https://doi.org/10.1016/j.biopha.2018.11.146.

[18] H. Shay, S.A. Komarov, S.S. Fels, D. Meranze, M. Grunstein, A. Siplet, A simple method for the uniform production of gastric ulceration in the rat, Gastroenterology 5 (1945) 43–61.

[19] F.A. Armah, I.T. Henneh, J. Alake, W. Ahlidja, B. Amoani, E.G. Ofori, B. Asante-Kyei, G.I. Temitayo, C.K. Adokoh, Allanblackia floribunda seed extract attenuates the ethanol-induced gastric ulcer in rats via the inhibition of TNF-α and INF-γ levels and modulation in the expression of Ki67 protein, Biomed Res. Int. 2021 (January) (2021) 6694572, https://doi.org/10.1155/2021/6694572. PMID: 33521129;.

[20] R.M. Aman, R.A. Zaghloul, M.S. El-Dahhan, Formulation, optimization and characterization of allantoin-loaded chitosan nanoparticles to alleviate ethanol-induced gastric ulcer: in-vitro and in-vivo studies, Sci. Rep. 11 (January (1)) (2021) 2216, https://doi.org/10.1038/s41598-021-81183-x. PMID: 33500454; PMCID: PMC7838192.

[21] E. Gugliandolo, M. Cordaro, R. Fusco, A.F. Peritore, R. Siracusa, T. Genovese, R. D'Amico, D. Impellizzeri, R. Di Paola, S. Cuzzocrea, R. Crupi, Protective effect of snail secretion filtrate against ethanol-induced gastric ulcer in mice, Sci. Rep. 11 (February (1)) (2021) 3638, https://doi.org/10.1038/s41598-021-83170-8. PMID: 33574472; PMCID: PMC7878904.

[22] N. Djebli, M.R. Mustafa, M. Keskin, S. Kolayli, Anti-ulcerogenic and cytoprotective effects of Saharian (Sidr) honey from Algeria, Comb. Chem. High Throughput Screen (November) (2020), https://doi.org/10.2174/1386207323999201117114008.

[23] P. Schiantarelli, S. Cadel, G.C. Folco, Gastroprotective effects of morniflumate, an esterified anti-inflammatory drug, Arzneimittelforschung 34 (1984) 885–890.

[24] S. Corne, S. Morrissey, R. Woods, Proceedings: a method for the quantitative estimation of gastric barrier mucus, J. Physiol. 242 (1974) 116–117.

[25] P.P. Bradley, D.A. Priebat, R.D. Christensen, G. Rothstein, Measurement of cutaneous inflammation: estimation of neutrophil content with an enzyme marker, J. Invest. Dermatol. 78 (1982) 206–209, 0022-202X/82/7803-0206$02.00/0.

[26] M.L. Schubert, D.A. Peura, Control of gastric acid secretion in health and disease, Gastroenterology 134 (2008) 1842–1860, https://doi.org/10.1053/j.gastro.2008.05.021.

[27] G.M. Buzás, C.T. Supuran, The history and rationale of using carbonic anhydrase inhibitors in the treatment of peptic ulcers. In memoriam Ioan Puşcaş (1932-2015), J. Enzyme Inhib. Med. Chem. 31 (2016) 527–533, https://doi.org/10.3109/14756366.2015.1051042.

[28] I. Puscas, M. Coltau, M. Baican, G. Domuta, A. Hecht, Calcium, carbonic anhydrase and gastric acid secretion, Physiol. Res. 50 (2001) 359–364.

[29] I. Puscas, M. Coltau, A. Maghiar, G. Domuta, Cysteamine, the most potent ulcerogenic drug known so far, powerfully activates carbonic anhydrase I, II and IV. In vitro and in vivo studies, Exp. Toxicol. Pathol. 52 (2000) 431–435, https://doi.org/10.1016/S0940-2993(00)80076-80077.

[30] R.P. Shank, V.L. Smith-Swintosky, B.E. Maryanoff, Carbonic anhydrase inhibition. Insight into the characteristics of Zonisamide, Topiramate and the sulfamide cognate of Topiramate, J. Enzyme Inhib. Med. Chem. 23 (2008) 271–276, https://doi.org/10.1080/14756360701507001.

[31] M.L. Chew, B.H. Mulsant, B.G. Pollock, M.E. Lehman, A. Greenspan, R. A. Mahmoud, et al., Anticholinergic activity of 107 medications commonly used by older adults, J. Am. Geriatr. Soc. 56 (7) (2008) 1333–1341, https://doi.org/10.1111/j.1532-5415.2008.01737.

[32] G.L. Kauffman Jr., The gastric mucosal barrier. Component control, Dig. Dis. Sci. 30 (1985), https://doi.org/10.1007/BF01309388, 69S-76.

[33] A. Allen, G. Flemström, Gastro duodenal mucus bicarbonate barrier: protection against acid and pepsin, Am. J. Physiol. Cell Physiol. 288 (2005) C1–19, https://doi.org/10.1152/ajpcell.00102.2004.

[34] J.L. Wallace, D.N. Grangers, The cellular and molecular basis of the gastric mucosal defense, FASEB J. 10 (1996) 731–740, https://doi.org/10.1096/fasebj.10.7.8635690.

[35] K. Seno, T. Joh, Y. Yokoyama, M. Itoh, Role of mucus in gastric mucosal injury induced by focal ischemia/reperfusion, J. Lab. Clin. Med. 126 (1995) 287–293.

[36] P.A. Lazo, Reverting p53 activation after recovery of cellular stress to resume with cell cycle progression, Cell. Signal. 33 (2017) 49–58, https://doi.org/10.1016/j.cellsig.2017.02.005.

[37] M. Kodama, K. Murakami, T. Okimoto, R. Sato, K. Watanabe, T. Fujioka, Expression of mutant type-p53 products in H. Pylori-associated chronic gastritis, World J. Gastroenterol. 13 (2007) 1541–1546, https://doi.org/10.3748/wjg.v13.i10.1541.

[38] M.F. Bellini, A.C. Cadamuro, M. Succi, M.A. Proença, A.E. Silva, Alterations of the TP53 gene in gastric and esophageal carcinogenesis, J. Biomed. Biotechnol. (2012) 891961, https://doi.org/10.1155/2012/891961.

[39] S.C.U. Patne, V.B. Abhilash, V.K. Dixit, R. Katiyar, S. Kumar, G.P. Singh, Immunohistochemical expression of human epidermal growth factor receptor 2 (HER2) and p53 in gastric adenocarcinoma: a pilot study from northern India, J. Clin. Diagn. Res. 11 (2017) EC43–45, https://doi.org/10.7860/JCDR/2017/25650.9921.

[40] H.H. Arab, S.A. Salama, H.A. Omar, el-S.A. Arafa, I.A. Maghrabi, Diosmin protects against ethanol-induced gastric injury in rats: novel anti-ulcer actions, PLoS One 10 (3) (2015), e0122417 doi: 1371/journal.pone.0122417.

[41] K. Polyak, Y. Xia, J.L. Zweier, K.W. Kinzler, B.A. Vogelstein, Model for p53-induced apoptosis, Nature 389 (1997) 300–305, https://doi.org/10.1038/38525.

[42] W.C. Zhao, Y.S. Xu, G. Chen, Y. Guo, D.Y. Wang, G.B. Meng, Veronicastrum axillare alleviates ethanol-induced injury on gastric epithelial cells via downregulation of the Nf-kB signaling pathway, Gastroenterol. Res. Pract. 2017 (2017), 7395032, https://doi.org/10.1155/2017/7395032.

[43] S. Takahashi, T. Fujita, A. Yamamoto, Role of nuclear factor-kB in gastric ulcer healing in rats, Am. J. Physiol. Gastrointest. Liver Physiol. 280 (2001) G1296–G1304, https://doi.org/10.1152/ajpgi.2001.280.6. G1296.

[44] R.G. Baker, M.S. Hayden, S. Ghosh, NF-κB, Inflammation, and metabolic disease, Cell Metab. 13 (2011) 11–22, https://doi.org/10.1016/j.cmet.2010.12.008.

[45] H. Chen, O.J. Olatunji, Y. Zhou, Anti-oxidative, anti-secretory and anti-inflammatory activities of the extract from the root bark of Lycium chinense (Cortex Lycii) against gastric ulcer in mice, J. Nat. Med. 70 (2016) 610–619, https://doi.org/10.1007/s11418-016-0984-2.

[46] E. Cure, M.C. Cure, L. Tumkaya, Y. Kalkan, I. Aydin, A. Kirbas, et al., Topiramate ameliorates abdominal aorta cross-clamping induced liver injury in rats, Saudi J. Gastroenterol. 20 (2014) 297–303, https://doi.org/10.4103/1319-3767.141690.