The Possible Protective Role of Zingerone on Ethanol Induced Entrotoxicity of Jejunum in Adult Albino Rats: Light and Scanning Electron Microscopic Study

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Abstract

Introduction: Zingerone is a nontoxic important extract of dry ginger plant. It is reported that zingerone has an anticancer property, strong anti-inflammatory and antimicrobial properties. **Aim of the Work:** is to evaluate the possible protective effects of zingerone on ethanol-induced lesions on the jejunum of adult male albino rats. **Materials and Methods:** twenty four adult male albino rats were used, divided into 3 groups; A control group (I); consisted of 8 rats, ethanol group (II); contained 8 rats and each rat given 50% v/v alcohol at a dose of 4 g/kg.bw orally for 15 days. Ethanol zingerone group (III); consisted of 8 rats, each received zingerone at a dose of 50 mg/kg and alcohol at the same previous dose daily and orally for 15 days. At the appropriate time, the specimens were taken and prepared for light and electron microscope study. **Results:** Histological examination of jejunum sections of ethanol group (II) showed massive jejunal villi ulcerations with shedding of their surface epithelium, loss of the villous architecture and loss of the microvilli covering some enterocytes. Examination of ethanol zingerone group (III) showed evidence of improvement in the form of nearly normal architecture of the jejunal villi with few areas of ulcerations on the top of some villi and increased cells with mitotic activity. **Conclusion:** Accordingly, we can conclude that zingerone administration can remarkably ameliorate ethanol-induced enterotoxiciy and jejunal ulcerations in rats by its anti-inflammatory properties and by suppressing oxidative stress.

Keywords: Ethanol, jejunum, rats, zingerone

INTRODUCTION

Disorders of the gastrointestinal (GIT) tract in the form of inflammations, ulcers, or motility affection are very common. They produce a major suffering problem for humans. These disorders are due to increase in the damaging factors within the gut more than the protective mechanisms. Nowadays, there is a great use of plant source medications trying to avoid the occurrence of such disorders with fewer side effects if compared with the conventional drugs. One of the most common causes of GIT upset is the orally administrated ethanol (EtOH).[1]

Ethanol intake is a common habit among people, and it may produce severe adverse effects on several organs like the GIT, liver and the nervous system. Alcohol can damage the motility of the intestine, affects the capacity of gut absorption and can produce damage of the mucosa and even carcinogenesis.

According to the reports of World Health Organization, alcoholism was considered to cause nearly 6% of all cases of death every year. Ethanol is soluble in aqueous and lipid environment due to the presence of a hydroxyl group; so, it passes easily from body fluids into cells and absorbed from the mucosa of GIT, especially the stomach and intestine passing to the blood then to the liver where it is metabolized and then eliminated from the body.[2-4]

Nearly 11% of medications in this century are extracted mainly from plant origin. Ginger is one of these herbs whose extracts have many reported health benefits either for ameliorating inflammations, decreasing cancer rates, and preventing some

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GIT disorders.[5] Ginger has been planted since thousands of years and has been used as spices in beverages, in food, and for pharmacological purposes. It has several types like white ginger variety (*Zingiber Officinale* Roscoe) which is first implanted in South-East Asia and is one of the most commonly used food flavoring agents, while other types like red ginger and bitter ginger which are less used. Several experimental studies have reported that ginger has gastroprotective effects on the gastric ulcer rat models.[6,7]

Zingerone (ZO) is a nontoxic important extract of dry ginger plant (*Z. Officinale* Roscoe, family: *Zingiberaceae*) with various medical effects. It has a basic phenolic ring with a methoxy group attached to benzene ring (4-(4-hydroxy-3-methoxyphenyl)-2-butanone). ZO is present in a significant amount of about 9.25% in ginger; it cannot be found in fresh ginger while cooking or heating of ginger transforms gingerol to ZO. It is reported that ZO has an anticancer property, strong anti-inflammatory, and antimicrobial properties. Other studies also reported the antioxidant function of ZO.[8,9]

According to these previous reports about zingerone, this study aimed to evaluate the possible protective effects of zingerone on ethanol-induced lesions on the jejunum of adult male albino rats.

MATERIALS AND METHODS

In this study, 24 adult male albino rats were used weighing about 150–200 g. The animals were kept in clean appropriate cages with good ventilation and given *ad libitum* access to a rodent pellet diet and purified water. The protocol of this experiment was approved by the Local Ethics Committee of Tanta University, Faculty of Medicine, Egypt. The animals were randomly allocated into the following groups:

Group I (control group)
It included 8 rats; animals of this group were equally divided into two subgroups:
- Subgroup Ia (negative control): It consisted 4 rats received no medication and sacrificed after 15 days
- Subgroup Ib (ZO control group): It consisted of 4 rats, each received ZO at a dose of 50 mg/kg purchased from Sigma Chemical Co. (St. Louis, MO, USA). A crystalline form with ≥96% purity dissolved in distilled water. It was given once daily by orogastric tube for 15 days.[8]

Group II (ethanol group)
It included 8 rats; each rat was given 50% v/v (volume/volume) alcohol at a dose of 4 g/kg/bw given by orogastric tube once daily for 15 days.[4]

Group III (zingerone and ethanol group)
It included 8 rats; each rat received ZO and alcohol once daily at the same doses and concentrations of the previous groups for 15 days.

At the end of the experiment, all animals were sacrificed using an appropriate dose of ether. The abdomen of each animal was opened through a midline incision and the small intestine of each rat was gently removed. The jejunum (upper intestine) was taken; then, the intestinal lumen for each segment was washed and perfused with cold saline solution for 2 min to remove debris.

For light microscopic examination
Specimens were fixed in 10% buffered formalin, then washed, dehydrated in alcohol and finally embedded in paraffin then sectioned at 5 μm thicknesses. Sections of 5 μm thickness were stained with hematoxylin and eosin stains (H and E).[10]

For scanning electron microscopic examination
The jejunal segments were cut longitudinally and pinned flat on a board of paraffin wax with the mucosal surface facing upward and gently cleaned with a cold saline solution. These tissue samples then were fixed in 2% glutaraldehyde in 0.1M sodium cacodylate buffer pH 7.2 for 1 h, rinsed in buffer three times and then fixed in 1% osmium tetroxide for 1 h. Following washing in double-distilled water, the samples were dehydrated in ascending concentrations of acetone. After drying, the specimens were coated with gold and viewed in a JEOL JSM scanning electron microscope in the Electron Microscopy Unit of Faculty of Science, Alexandria University.[10]

RESULTS

Rats of the experimental groups have tolerated both ethanol and ZO treatments, and all of them survived till the end of the experiment.

Light microscopic study
Light microscopic examination of H and E-stained sections from both the negative and ZO control groups were the same and showed the normal histological architecture of the jejunum formed of four layers (mucosa, submucosa, musculosa, and serosa). The musculosa formed of outer longitudinal and inner circular layers, the mucosa and submucosa were thrown into villi towards the lumen, and they were finger shaped in appearance [Figure 1a]. Each intestinal villous was covered with a single layer of simple columnar epithelium (enterocytes or absorptive cells) and its center is invaded with the lamina propria. The enterocytes were tall columnar cells with oval basal basophilic nuclei and acidophilic cytoplasm and in between them scattered the goblet cells (mucous secreting cells) [Figure 1a and b]. The lamina propria and submucosa were formed of connective tissue contained free cells, some lymphocytes, macrophages, and spindle-shaped muscle cells with blood and lymph vessels. The jejunal crypts or glands are tubular canals extend from the bottom of the villi, lined with clusters of cells with oxyphilic granules (Paneth cells) located at the fundus of each crypt [Figure 1a and b].

After administration of alcohol in Group II, light microscopic examination revealed massive villous ulcerations with shedding of their surface epithelium, necrosis of the lamina propria, loss of the villous architecture, and loss of the microvilli covering some enterocytes. Some villi showed complete distortion and
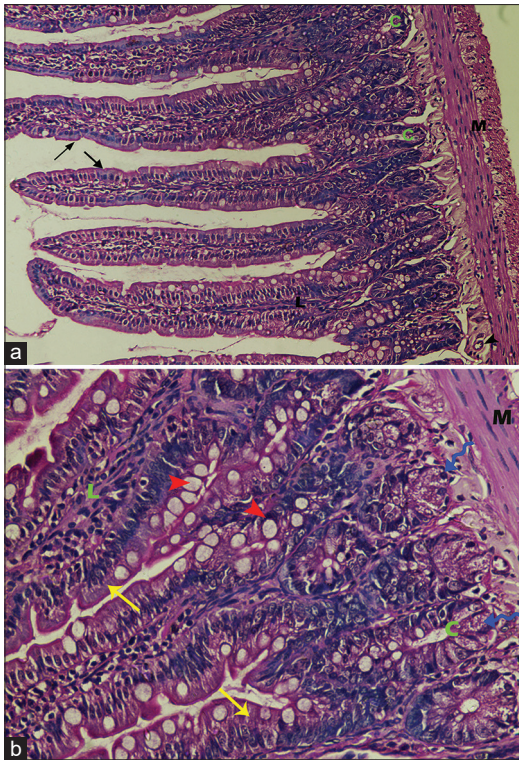
Figure 1: Photomicrographs of sections of the control group showing: (a) The jejunum consisting of four layers; mucosa, submucosa, musculosa (M) and serosa. The mucosa showing finger like villi (arrows), tubular crypts (C), submucosa or lamina propria (L), and a blood vessel can be seen (arrow head) (H and E, ×200). (b) The intestinal villi covered with columnar epithelial cells (arrows) (with oval basal nuclei and acidophilic cytoplasm) covered with microvilli (brush border), goblet cells (red arrow heads) in-between enterocytes and showing the intestinal crypts (C) lined by the characteristic Paneth cells (blue curved arrows) (H and E, ×400)

Figure 2: Photomicrographs of sections of Group II showing: (a) Jejunal villi with ulceration and shedding of the surface epithelium (arrows), loss of the villous architecture (stars) with necrosis of lamina propria (H and E, ×200). (b) The villi showed detachment of the submucosa (star) from the musculosa, distorted intestinal villi (V), and few cells show pyknotic nuclei (arrows) (H and E, ×400). (c) The distorted villi with increased and enlarged goblet cells (arrows), distorted intestinal crypts (C), dilated, congested blood vessels (V) with areas of hemorrhage (H) (H and E, ×400). (d) The jejunal mucosa with mononuclear inflammatory cellular infiltration (F) in the lamina propria and areas of ulceration of the villi (arrows) loss of the microvilli covering some enterocytes (H and E, ×400)

detachment of the submucosa from the underling muscle layer, and few enterocytes showed pyknotic nuclei [Figure 2a and b]. Some intestinal villi showed enlarged goblet cells, distorted intestinal crypts, dilated and congested blood vessels with areas of hemorrhage. Mononuclear inflammatory cellular infiltrate in the lamina propria were detected with loss of the microvilli covering some enterocytes [Figure 2c and d].

Light microscopic examination of the jejunum of Group III (ZO and Ethanol group) showed evidence of improvement as compared to Group II in the form of nearly normal architecture of the jejunal villi with few areas of ulcerations on the top of some villi. Nearly normal intestinal crypts and Paneth cells were seen, while spaces between the submucosa and the musculosa were still present and increased cells with mitotic activity could be detected [Figure 3a and b].

Scanning electron microscopic study
Scanning electron microscopic (SEM) examination of both subgroups (Ia, Ib) of the control group showed the same results. They revealed groups of finger or tongue shaped villi, Each villous was well constructed, distinct from each other and had a broad base with tapering and blunt points. The surface of each villous showed corrugated surface with clefts and some areas
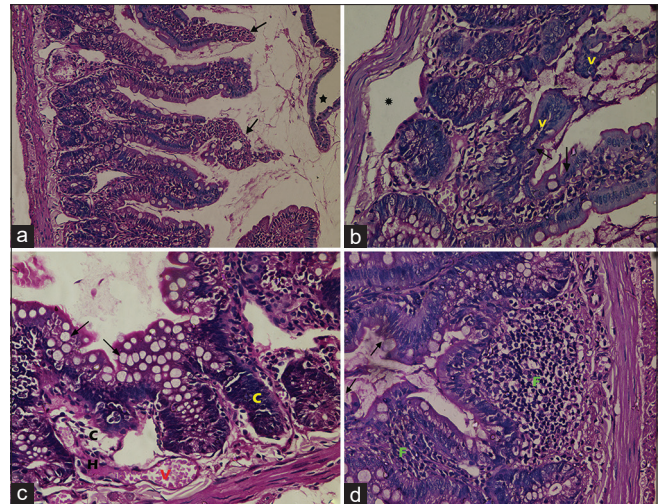
were covered with irregular blobs of mucous extruded from goblet cells. Circular or oval holes (openings of goblet cells) were seen and some of them were closed with mucous blobs. Higher magnification exhibited the hexagonal arrangement of enterocytes in the honey comb appearance with microvilli covering their surface (brush border) [Figure 4a-c].

SEM examination of sections of Group II showed groups of villi with ulcerations of their mucous membrane, shedding of their apical parts, and exposure of the underling connective tissue. Some villi appeared with loss of the microvilli covering some enterocytes and others with complete loss of the covering surface epithelium [Figure 5a-d].

In Group III (ZO and ethanol group), SEM examination confirmed the light microscopic findings revealing groups of villi with almost normal finger and tongue like architecture, while few areas showed epithelial ulcerations and increased mucous covering the villous surface. Most enterocytes exhibited a nearly normal picture with the characteristic honey comb appearance, except few enterocytes which showed loss of their covering microvilli [Figure 6a and b].

DISCUSSION
Alcohol use disorder (AUD) is considered as a major untreated epidemic health problem in modern societies. It has been proved nowadays that chronic alcohol consumption leads to multiorgan damage like, kidney, liver, and the GIT which is considered the first organ to be affected by alcohol ingestion
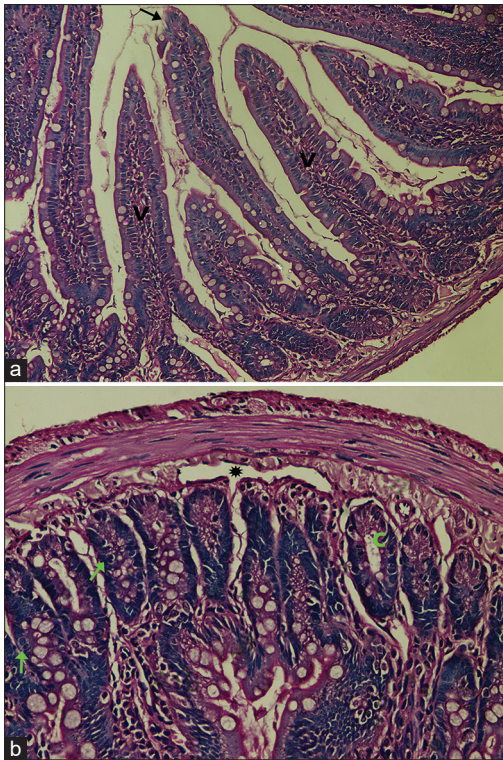
Figure 3: Photomicrographs of sections of Group III showing: (a) Jejunal villi (V) with nearly normal architecture of the jejunal villi with few areas of ulceration of the top of some villi (arrow) (H and E, ×200). (b) Jejunal mucosa showing almost normal intestinal crypts (C) with presence of spaces (star) between the submucosa and the musculosa and increased cells with mitotic activity (arrows) (H and E, ×400)

Figure 4: Scanning electron micrographs of the control group showing: (a) Groups of villi (V) with finger like appearance with some areas covered with irregular blobs of mucous extruded from goblet cells (arrows) (SEM, ×350). (b) Surface of a villous with surface corrugations (arrows) and goblet cells openings (arrow heads) (SEM, ×1500). (c) A higher magnification showing the hexagonal arrangement of enterocytes (E) in the honey comb appearance with microvilli on their surface. Corrugations of villi (arrow), goblet cell openings (arrow heads), and mucous (M) droplets can be seen (SEM, ×5000)

due to the high propensity of the GIT epithelium toward EtOH. Some pharmacotherapy trials have been proposed trying to treat AUD or decreasing its hazardous effects on human health; however, the efficacy of these medications remained controversial.[11]

This study was performed to investigate the associations between alcohol consumption and the histopathological deleterious effects on jejunum with evaluating the possible protective effect of ZO on it.

Several researchers had reported the hazardous effects of EtOH on different organs, especially on the stomach; they reported its gastrotoxic effects on the stomach and gastric mucosa causing damage of the surface epithelium, submucosal edema, inflammatory cellular infiltration and gastric hyperemia even hemorrhagic damage and necrosis.[3,12] In this study, ethanol administration resulted in several histological changes on the jejunum of the experimental rats producing ulceration and shedding of the surface epithelium of the jejunal mucosa with necrosis of the lamina propria; these results agreed with the previous reports of alcohol damaging effects on the gastric mucosa.

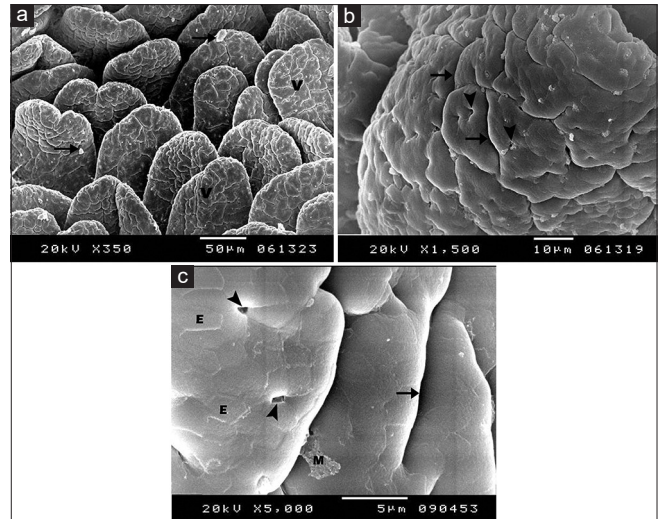It has been demonstrated that alcohol exhibited functional GIT disorders, like functional constipation, diarrhea and dyspeptic symptoms. Ohlsson[13] confirmed this and attributed these disorders to smoking and alcohol consumption. Also it is reported that alcohol inhibits the absorption of essential nutrients by the intestinal epithelial absorptive cells[14,15] These reports agree with our histopathological findings produced by alcohol administration which detected ulceration and necrosis of the jejunal mucosa with degenerative changes occurring to the enterocytes and destruction of their absorptive brush border.

In the present research, distorted villi with enlarged goblet cells, distorted intestinal crypts, dilated, and congested blood vessels with areas of hemorrhage were reported, and these findings were in agree with Boule et al.[16] who reported that alcohol/septic mice had increased apoptosis of intestinal epithelial cells, decreased crypt proliferation, decreased the villous length and persistent inflammatory environment with vascular congestion and also contributed in disruption of the intestinal tight junctions and increasing their permeability.

Alcohol intake produces acute inflammatory reactions which occur usually as a part of the natural defense mechanisms of the body against tissue damage, resulting in an imbalance between inflammatory and anti-inflammatory cytokines with persistence of the inflammatory reaction, and consequent overproduction of NO producing more tissue injury and hindering gastric ulcer healing.[17] These facts coincide with the findings of this research in the form of invasion of the lamina propria of the jejunal mucosa with mononuclear inflammatory cellular infiltrate and the detected blood vessels congestion with areas of hemorrhage.

Several mechanisms were suggested to explain the damaging effect of ethanol administration, which may be due to its direct
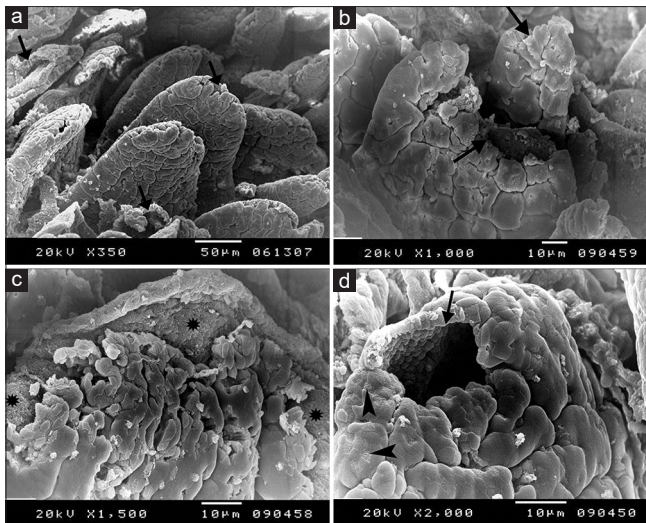
Figure 5: Scanning electron micrographs of Group II showing: (a) Groups of villi with ulcerations and shedding of their mucous membrane (arrows) (SEM, ×350). (b) villi with shedding of their apical parts (arrows) and exposure of the underling connective tissue (SEM, ×1000). (c) villi with complete loss of the covering epithelium and exposure of the underlying connective tissue (stars) (SEM, ×1500). (d) A villous with ulcerated apical part (arrow) and loss of the microvilli covering some enterocytes (arrow heads) (SEM, ×2000)

Figure 6: Scanning electron micrographs of Group III showing: (a) Groups of villi almost normal finger like architecture with few areas showing ulcerations (arrows) and increased mucous (arrow heads) (SEM, ×500). (b) Villous surface showing few enterocytes with loss of their covering microvilli (arrows) and increased mucous patches (arrow heads) (SEM, ×3500)

effects on tissues or may be due to release of inflammatory and vasoactive ingredients, producing ischemia and mucosal damage.[15] Capurso and Lahner[18] suggested that ethanol is metabolized by catalase enzymes to acetaldehyde which in turn causes DNA damage in the GIT mucosa and apoptosis, while Guzmán-Gómez et al.[3] noted that the liberation of reactive oxygen species (ROS) and subsequent oxidative stress is considered an important mechanism in the pathogenesis of gastric ulcers caused by ethanol. The injury of the mucosa is performed when there is an imbalance between apoptosis and regeneration of the cells; so, reepithelialization of the gastrointestinal mucosa is essential for the recovery of the gastric mucosa on ulceration.[19]

Several preventive trials were established trying to decrease the chance of GIT mucosa ulcerations or to enhance re-epithelialization of the lesions to facilitate their recovery.[20] In the present research, we administered ZO in accompany with alcohol intake to investigate its preventive effect on the mucosa of rat jejunum. The results were promising, where nearly normal jejunal architecture were detected in ZO alcohol group with slight affection of the jejunal mucosa in the form of few areas of ulceration of the top of some villi and few enterocytes showed loss of their covering brush microvillous border. These findings were in agree with Sistani et al.,[8] who stated that oral pretreatment with ZO had decreased the number and the length of ethanol induced gastric ulcers.

The improvement achieved in the histopathological picture of the jejunal mucosa with ZO administration in this research can be explained by several mechanisms, as the chemical composition of ZO containing the methoxy group and a
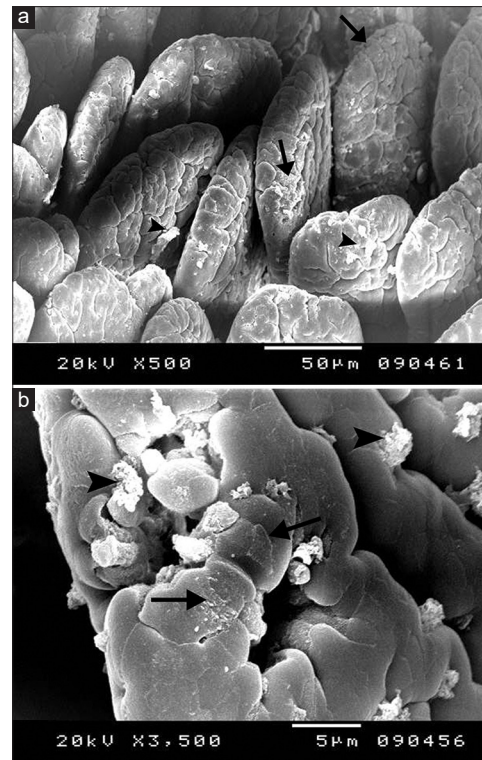
long-chain ethyl methyl ketone group, which help greatly in scavenging the o_2 free radicals generated with ethanol intake and help in elimination of ROS with suppression of oxidative stress.[21,22] In this study, we found lesser inflammatory infiltrates in the jejunal mucosa with ZO administration, these findings may be due to its anti-inflammatory effect on the intestinal mucosa, and these results were in agreement with Lee et al.[23] who reported the anti-inflammatory role of ZO on the liver tissues through its probable immune-modulatory effects.

Ghareib et al.[24] stated that ZO has anti-apoptotic activity over body cells specially muscle cells and antilipid peroxidative potency, while Kandemir et al.[25] proved the efficacy of ZO in the treatment of vancomycin-induced cellular apoptosis, inflammation, and oxidative stress in the rat kidney. These effects may be through decreasing nitric oxide liberation which is a crucial factor in producing oxidative stress and apoptosis. Xie et al.[26] stated that ZO attenuates lipopolysaccharide-induced acute pulmonary histopathologic injury, by diminishing the inflammatory cytokines and decreasing neutrophil infiltration in lungs. While other researchers stated that ZO has antigenotoxic and antiapoptotic effects against radiation-induced lymphocytic damage.[27]

In the present work, we noticed an increase in the size of goblet cells in rat jejunal mucosa of both alcohol and ZO alcohol

groups; these may be explained as a defense mechanism of the intestinal mucosa against the irritating or damaging factors as a trial for protection of the lining jejunal epithelium. Also, in this work, we detected and increase in cells with mitotic activity, this explains the nearly normal appearance of the jejunal mucosa with ZO, as it may stimulate regeneration of cells to enhance recovery of intestinal lesions.

Conclusion

Accordingly, considering the results in the present research and the relevant informations available from the previous literatures, we can conclude that zingerone can remarkably ameliorate ethanol-induced enterotoxicity and jejunal ulcerations in rats by its anti-inflammatory properties and by suppressing oxidative stress. We recommend more histopathological studies on ZO and its ulceroprotective role on the intestinal mucosa, which needs to be more investigated in the future researches.

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Conflicts of interest
There are no conflicts of interest.

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