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Original article

Possible Protective Effects of Rebamipide, Tianeptine, Oleum Cinnamomi on Ethanol-Induced and Indomethacin-Induced Gastric Ulcer in Rats

Shahrazad Gazeti*[1], Doaa Abdelmonsif[2], Amr Okda[3]

[1]*Department of Pharmacology, Faculty of Medicine, University of Zawia, Libya*
[2]*Department of Medical Biochemistry, Faculty of Medicine, University of Alexandria, Egypt*
[3]*Department of Clinical Pharmacology, Faculty of Medicine, University of Alexandria, Egypt*

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Corresponding Email. *s.gazeti@zu.edu.ly*
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ABSTRACT

Background and objectives. *Peptic ulcer disease is a problem of the gastrointestinal tract characterized by mucosal damage secondary to pepsin and gastric acid secretion. It usually occurs in the stomach and proximal duodenum; less commonly it occurs in lower esophagus. The prominent causes are infection with Helicobacter pylori and the use of nonsteroidal anti-inflammatory drugs. This study was aimed to evaluate the possible protective effects of rebamipide, tianeptine, oleum cinnamomi on ethanol- and indomethacin-induced gastric ulcer.* ***Methods****. The present work was conducted on 72 male albino rats. Animals were randomly divided into 3 groups; Group I (8 rats), served as plain control group, they received 5 ml/kg body weight of 2% gum acacia orally daily for 7 days. Group II (32 rats), served as ethanol-induced gastric ulcer group. Group III (32 rats), served as indomethacin-induced gastric ulcer group.* ***Results****. In ethanol group; rebamipide treatment (II-b) resulted in a significant reduction in the ulcer score (P <0.001), Malondialdehyde content (P < 0.001) and Nuclear E2_releated factor2 content (P< 0.001). On the other hand, rebamipide produced an elevation of glutathione peroxidase activity (P<0.001), in ethanol control group. Tianeptine treatment (II-c) resulted in significant reduction in ulcer score P (<0.001), Malondialdehyde content (P < 0.001), Nuclear E2_releated factor2 content (P< 0.001), and an elevation of glutathione peroxidase activity with (P < 0.001) in ethanol group. Whereas, the Oleum Cinnamomi treatment resulted in significant reductions in ulcer score (P < 0.001), Malondialdehde content (P < 0.001), Nuclear E2_related E2 content (P< 0.001), and elevation in Superoxide dismutase activity content (P < 0.001) in ethanol control group. In indomethacin group; Rebamipide treatment (III-b) resulted in significant reductions in the ulcer score (P < 0.001) and Nuclear E2_related factor2 content (P < 0.001) in indomethacin control group respectively, while caused elevation in Superoxide dismutase, glutathione peroxides in indomethacin group respectively. Tianeptine treatment (III-c) resulted in significant reduction in the ulcer score (P < 0.001), Malondialdehyde content (P < 0.001) and Nuclear E2_ related factor content (P < 0.001) in indomethacin control group respectively; and an elevation in Superoxide dismutase, glutathione peroxidase activities in indomethacin control group respectively. Oleum Cinnamomi treatment (III-c) resulted in significant reduction in the ulcer score (P < 0.001), Malondialdehyde content (P < 0.001) and Nuclear E2_related factor2 content (P < 0.001) in indomethacin control group respectively; and an elevation in Superoxide dismutase, glutathione peroxidase activities in indomethacin control group respectively.* ***Conclusion****. Pretreatment for seven days with rebamipide, tianeptine, and cinnamon oleum, resulted in improvement in ulcer score, and gastric mucosal protection in rats with gastric ulcer induced by either in ethanol or indomethacin. This was associated with improvement in antioxidant parameters. Rebamipide produced the most prominent effect in ulcer score reduction.*

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INTRODUCTION

Peptic ulcer disease is a gastrointestinal disorder defined by imbalance between the protective mechanisms (mucus-bicarbonate layer, prostaglandins, and blood flow) and aggressive factors (H pylori, increased acid secretion, bile salts, and some medication) [1].

Moreover, mucosal damage is usually associated with generation of oxygen free radicals [2]. The mechanism of damage involves lipid peroxidation, which destroys cell membranes with the release of intracellular components, such as lysosomal enzymes, leading to further tissue damage. These free radicals also promote mucosal damage by causing degradation of the epithelial basement membrane components, complete alteration of the cell metabolism and DNA damage [3].
There are several drugs available for treatment of gastric ulcer. However, they are frequently incompletely sufficient for controlling ulcer manifestations. Moreover, many of them are expensive and could have adverse effects not tolerated by all patients. Rebamipide, 2-(4-chlorobenzoylamino)-3-[2(1H)-quinolion-4-yl] propionic acid, is a new drug acting as an antioxidant by inhibiting lipid perioxidation in the gastric mucosa [4]. Many herbs and plant extracts have been shown to impart antioxidant effects, the active principles are phenolics. Cinnamon is one of such traditional herbs that possess potent antioxidant, anti-inflammatory, anti-mutagenic, anti-carcinogenic, and anti-tumour activities. Such chemoprotective properties of cinnamon appear helpful in gastric ulcer disease [5]. Moreover; many antidepressant drug therapy benefits patients with ulcers; a study has shown that imipramine and amitriptyline dose dependently prevent gastric ulcer in different models [6]. Tianeptine was shown to exert a direct gastroprotective effect via the alpha 2 adrenoreceptors in rats, [7] and prevent the reduction of glutathione (GSH) content that occurs in the indomethacin-damaged stomach tissue in rats [8].
Knowing that they could act by different mechanisms, it was concern to elucidate their possible protective action on gastric mucosa through improving malondialdehyde (MDA) and nuclear factor-erythroid 2-related factor 2 (Nrf2) contents of gastric mucosa, preserving enzymatic activity of superoxide dismutase (SOD) and glutathione peroxidase (GPx). The main aim of this study was to evaluate the possible protective effects of rebamipide, tianeptine, oleum cinnamomi on ethanol- and indomethacin-induced gastric ulcer.

METHODS

Animals

This was an experimental study conducted on 72 male albino rats of body weight ranging from 160-180 gm. Animals were housed in animal cages in groups of 4 rats each, and were kept under standard conditions of light and temperature, with free access to food and water ad libitum for one week before the start of the experiment as an acclimatization period.
Animals were randomly divided into 3 main groups: Group I, Normal control 8 rats received 5 ml/kg body weight of 2% gum acacia orally daily for 7 days. Group II, four subgroups each of eight rats for the ethanol induced ulcer (IIa, IIb, IIc, IId). The ethanol induced ulcer group (IIa) received a single dose of ethanol (1ml of 70% for each rat orally), [9] while subgroups IIb, IIc, IId were pretreated with rebamipide 60 mg/kg, Tianeptin 12 mg/kg, Oleum cinnamon 2.5 ml/kg orally daily for 7 days before induction of ethanol ulcer. Group III, four subgroups each of eight rats for the indomethacin induced ulcer (IIIa, IIIb, IIIc, IIId). The ethanol induced ulcer group (IIIa) received a single dose of indomethacin (100mg/kg for each rat orally), while subgroups IIIb, IIIc, IIId received the above-mentioned drugs in group II in the same dose and for the same duration before induction of indomethacin ulcer.

Drugs and chemicals

Indomethacin powder (Euro OTC Pharma), Ethanol (Sigma-Chemical Co.), Tianeptine (Stablon) tablet (Servier Eygpt Industries), Rebamipide (Mucosta) tablet (Egypt Otuska Pharmaceuticals Co.), Cinnamon Oleum (Sigma-Chemical Co), Gum acacia (Arabic Laboratory Equipment Co.), Colorimetric kit for Superoxide dismutase assay (Newtest chemical Co), Colorimetric kit for malondialdehyde assay (Newtest chemical Co), Colorimetric kit for glutathione perioxidase (Newtest chemical Co), Nuclear factor erythroid related factor(Nrf2) elisa kit (Newtest chemical Co), Protease inhibitor cocktail (Newtest chemical Co).

Experimental procedures

By the end of experimentation period, four hours after drug treatment, animals were sacrificed under ether anesthesia. The whole stomach was gently separated from the surrounding organs and tissues. Each stomach was dipped in a beaker filled with ice cold physiological saline, then carefully dried. The stomach was opened along the greater curvature, the ulcer index and protective ratio were assessed on the basis of lesion diameter according to Abou Zeit Har [10]. Then the mucosa was scrapped by using a glass slide and homogenized in 5 ml cold buffer [50 mM (Tris base: hydroxymethyl, aminomethane {C4H11No3}), 20 mM EDTA, 0.2 mM sucrose] per gram tissue. Then it was centrifuged at 100,000 Xg for 15 minutes at 4 Co. The supernatant was removed and frozen at -20 Co for assessment of the following parameters: Superoxide dismutase, Malondialdehyde, Glutathione peroxidase, and nuclear factor erythroid related factor (Nrf2) [11-14].

Statistical methods

Data analysis was performed using the Statistical Package of Social Science, SPSS version 20 software package. For the SOD, and MDA, the test was ANOVA. For GP, Nrf2 and ulcer score the test was Kruskal-Wallis; and for comparison of multiple groups, SOD and MDA the test was t-test and for GP, Nrf2 and ulcer score it was the Mann-Whitney. All results were expressed as mean ± standard error (SE).

RESULTS

Effect of rebamipide, tianeptine and oleum cinnamomi on ethanol-induced gastric ulcer in rats: (table I).

Ethanol produced gastric lesion with a mean ulcer score of mean±SE 26.88±2.29. Ethanol produced a significant increase in gastric content of MDA and Nrf2, and decrease the activity of SOD as compared to the control group, and no changes in GP activity.

Rebamipide, tianeptine and oleum cinnamomi, protected gastric mucosa against ulceration by indomethacin; the protective ratios were 72%, 48% and 60% respectively.

Rebamipide and tianeptine, produced significant increases in GP activity with no significant effect on SOD activity as compared to ethanol group. Oleum cinnamomi produced no changes in GP activity; but produced a prominent increase in SOD activity as compared to ethanol control group and other treated groups. All of the three drugs decreased MDA and Nrf2 contents of gastric mucosa as compared to ethanol control group.

Table 1. Effect of rebamipide, tianeptine, oleum cinnamomi on ethanol induced gastric ulcer in rats.

Parameters	Control Group	Ethanol Group	Ethanol with Rebamipide	Ethanol with Tianeptine	Ethanol with Cinnamon
Ulcer Score	--	26.88±2.29	7.75±0.65$^{\#}$	13.50±0.98$^{\#@}$	10.75±1$^{\#@}$
	P<0.001*				
SOD activity	5.07±0.15	2.69±0.73$^{\$}$	3±0.37$^{\$\&}$	2.49±0.32$^{\$\&}$	6.63±0.94$^{\#}$
	F=8.921 P<0.001*				
MDA content	321.25±12.02	383.25±18.23$^{\$}$	143.63±7.84$^{\$\#}$	163.75±9.01$^{\$\#}$	183.91±37.56$^{\$\#}$
	F=27.937 P<0.001*				
GPx activity	14.13±0.04	18.49±2.76	75.69±4.48$^{\$\#\&}$	65.66±5.32$^{\$\#\&}$	15.64±1.29
	P<0.001*				
NrF$_2$ content	92.95±9.16	165.55±11.11$^{\$}$	70.13±6.43$^{\#\&}$	74.59±3.31$^{\#\&}$	93.46±3.1$^{\#}$
	P<0.001*				

$ Significant as compared to the control group. # Significant as compared to the Ethanol group. @ Significant as compared to the Ethanol with rebamipide group. & Significant as compared to the Ethanol with oleum cinnamomi group.

Effect of rebamipide, tianeptine and oleum cinnamomi on indomethacin-induced gastric ulcer in rats.

As shown in table 2, indomethacin produced gastric lesion with a mean ulcer score of mean±SE 13±1.02. Indomethacin produced a significant increase in MDA and Nrf2 contents, and decrease in the activity of SOD as compared to the control group, but no changes in GPx activity.

Rebamipide, tianeptine and oleum cinnamomi protected gastric mucosa against indomethacin-induced ulceration; the protective ratios were 74%, 25% and 46% respectively.

Rebamipide, tianeptine, and oleum cinnamomi produced significant increases in the SOD and GP activities as compared to indomethacin control group, and also decreased Nrf2 content of gastric mucosa as compared to indomethacin control group. MDA gastric content was also decreased in tianepine and oleum cinnamomi treated groups.

Rebamipide produced the most prominent reduction in ulcer score as compared to other treated groups and in both ethanol- and indomethacin-induced ulcer groups. Oleum Cinnamomi produced the most prominent increase in SOD activity in ethanol group and the most prominent decrease in MDA gastric content in indomethacin group.

Table 2. Effect of rebamipide, tianeptine, oleum cinnamomi on indomethacin induced gastric ulcer in rats.

Parameters	Control Group	Indomethacin Group	Indomethacin with Rebamipide	Indomethacin with Tianeptine	Indomethacin with Cinnamon
Ulcer Score	--	13±1.02	3.5±0.71$^{\#\blacklozenge}$	9.88±0.64$^{\#@}$	7±0.93$^{\#@\blacklozenge}$
	P<0.001*				
SOD activity	5.07±0.15	3.06±0.62$^{\$}$	5.96±0.27$^{\$\#\&}$	5.65±0.23$^{\#}$	4.72±0.43$^{\$\#}$
	F= 9.745 P <0.001*				
MDA content	321.25±12.02	388±27.22$^{\$}$	328.50±29.73$^{\&}$	283.38±21.71$^{\#\&}$	217.66±12.21$^{\#}$
	F=18.343 P<0.001*				
GPx activity	14.13±0.04	16.35±1.01	66.75±5.95$^{\$\#\&}$	51.63±2.89$^{\$\#}$	45.81±3.63$^{\$\#}$
	P<0.001*				
NrF_2 content	92.95±9.16	206.13±11.49$^{\$}$	126.58±10.96$^{\$\#}$	117.5±4.82$^{\#}$	112.54±11.19$^{\#}$
	P<0.001*				

$ Significant as compared to the control group. # Significant as compared to the indomethacin group. @ Significant as compared to the Indomethacin with rebamipide group. ♦ Significant as compared to the Indomethacin with tianeptine group. & Significant as compared to the Indomethacin with oleum cinnamomi group.

DISCUSSION

Peptic ulcer disease is a multifactorial health problem affecting almost all populations worldwide, and is still a problem not completely controlled by available drugs. The need for new or adjuvant drugs was behind undergoing the present study, which studied the effect of rebamipide, tianeptine, oleum cinnamomi in two models of PUD in rats, namely indomethacin- and ethanol- induced ulcer.

In the present study ethanol-induced mucosal injury was associated with elevation of gastric mucosal MDA as compared to control group. Lipid peroxidation is a major outcome of free-radical-mediated injury, and MDA is a final product of lipid peroxidation. Many studies coincide with this result [15-17]. A previous study showed that ethanol toxicity in the liver was associated with elevation of MDA. Similar results were observed in the brain tissue and serum after ethanol administration.

In the present study ethanol-induced gastric injury was associated with reduction of SOD activity in gastric mucosa. Low level of SOD activity indicates high risk of cell injury. A previous study also showed that ethanol decreases the activity of SOD [18]. It has been suggested that reduction is likely to be due to the high utilization of SOD in the decomposition of superoxide anion generated by lipid peroxidation [19].

Another biomarker of oxidative stress is GPx activity; however, in the present study no significant changes were observed with ethanol as compared to the control group. The effect of ROS generation on GPX activity is multifactorial. While it can upregulate this antioxidant enzyme through Nrf2, overproduction of ROS can directly decrease the activity of this antioxidant enzyme [20]. In the present study, gastric mucosal Nrf2 was significantly increased in association with ethanol-induced gastric injury. A previous study indicated that ROS generated from mitochondria by oxidative stress dissociates binding of Nrf2 protein from keap 1 in cytoplasm, increasing its free concentration. Therefore, Nrf2 could be considered as an indicator of oxidative stress. It is supposed that increasing Nrf2 level is a defense mechanism since it acts to upregulate several antioxidant enzymes [21].

In the indomethacin group; the injured mucosa has also been associated with increased MDA and Nrf2 levels and reduced in SOD activity as compared to the control group, with no changes in GPx activity. This can be explained by the same mechanisms related to increased lipid peroxidation due to ROS generation by indomethacin [22]. Many studies coincide with these results, indicating that oxidative stress-induced lipid peroxidation, DNA damage and neutrophil-dependent microvascular injuries that lead to cell death can explain indomethacin-induced gastric ulceration [23-25]. The reduced SOD activity observed in indomethacin group can be explained by generation of OH radical which decreases the activity of SOD.26 Besides, a previous study has also shown that indomethacin induced, time-dependently, mitochondrial perturbations which led to cell losses of antioxidant enzymes [27].

An additional mechanism for indomethacin-induced mucosal injury includes a depletion of endogenous PGs by inhibiting cyclooxygenase (COX) activity. It is considered that deficiency of PGs plays a key role in NSAIDs- induced gastrointestinal side effects. The identification of cyclooxygenase-2 (COX-2), which predominates at sites of inflammation, led to suggestions that inhibition of COX-2 accounts for the therapeutic benefit of NSAIDs whereas inhibition of cyclooxygenase-1 (COX-1) underlies the NSAID-induced toxicity, particularly in the gastrointestinal tract [28].

In the present study GPX activity was not significantly changed in indomethacin group as compared to control group. This result is in accordance with another study which indicated that indomethacin-induced ulcer was not associated with any significant effect on GPx activity [29]. This can be explained by multifactorial affection of GPx activity under oxidative stress as explained herein before. However; in some other studies, indomethacin administration was followed by reduction of GPx activity. This difference might be attributed to different timing of measurement of GPx activity after indomethacin administration or to measuring only the mitochondrial fraction of this enzyme [30,24].

In the present study, indomethacin-induced ulcer was associated with increased gastric mucosal Nrf2 level, which is in agreement with another previous study [24]. Again, this probably occurs as a defense mechanism under the effect of ROS through dissociating Nrf2 from keap1 in the cytoplasm [31]. The present study showed a significant decrease in gastric mucosal lesion score in rebamipide pretreated rats in both ethanol and indomethacin models. These results are in agreement with other studies in humans and experimental rat models.32-34In a rat model administration of 5mM sodium taurocholate (TCA) induced gastritis, in that study rebamipide dose-dependently reduced the total length of the gastric erosion, normalized the mucosal thickness and increased the number of parietal and total cells, and tended to reduce interstitial infiltration of inflammatory cells and proliferation of collagenous fibers, and increased the PAS-positive mucus in the cell [35].

The gastroprotective effect of rebamipide can be explained by different mechanisms. It has been demonstrated that rebamipide induces prostaglandin synthesis, especially the gastroprotective PGE2, via expression of COX2 enzyme. It could also induce the expression of PG receptor [36,37]. It was also shown that rebamipide exhibit cytoprotective and anti-inflammatory effects through inhibition of cytokines produced from leukocytes [36]. It was demonstrated that neutrophil-mediated inflammation is involved in the development of indomethacin-induced injury. Several chemokine-related genes were upregulated 24 hours after indomethacin administration and were downregulated by rebamipide treatment. The anti-inflammatory effect of rebamipide was attributed to downregulation of certain chemokines in gastric epithelial cells [38]. An additional mechanism is increased blood flow and improvement of mucosal microcirculation [39].

It has also been determined that rebamipide exerts cytoprotective effects against indomethacin-induced cell death by inhibiting apoptosis-related genes [40]. Moreover; it was reported that rebamipide has a free radical scavenging activity, [36] which also explains its antioxidant effect in the present work. The present study showed that rebamipide pretreatment produced a decrease in mucosal MDA content together with increased GPx activity in both models. It also significantly increased SOD activity in indomethacin group.

The antioxidant properties of rebamipide have been demonstrated in several previous studies. A study showed that rebamipide scavenges the hydroxyl radicals in cell free system in both animal models and human.41 In a rat model of indomethacin insults, pretreatment with rebamipide significantly decreased the signal intensity of superoxide anion from the Mitochondria, and attenuated lipid peroxidation by increasing the expression of MnSOD protein and decreasing superoxide anion leakage from mitochondria [42]. It has been demonstrated the ROS and the generation of hydroxyl radicals cause reduction in SOD activity, thus rebamipide by scavenging the radicals, and inhibiting the production of ROS could increase SOD activity [43]. Moreover, it was found that rebamipide prevents the impairment of GPx under conditions of oxidative stress [44,43].

The present study showed decreased Nrf2 level in rebamipide pretreated groups as compared to imdomethacin and ethanol groups. This can be explained by the antioxidane activity of rebamipide which eliminates ROS that responsible for inducing Nrf2. The present study also showed a significant decrease in gastric mucosal lesion score in tianeptine pretreated rats in both ethanol and indomethacin models. This result is consistent with previous works indicating gastroprotective effects of several antidepressant [45]. Studies on tianeptine demonstrated an antiulcer effect in a dose-dependent manner on rat stomach tissue [46]. The mechanism of tianeptine antiulcer effect is thought to be through stimulation of α2 adrenoreceptors. The stimulation of α2 adrenoreceptors inhibits the gastric acid secretion and motility.46 Another postulated mechanism involves an antioxidant effect of tianeptine [47].

In the present study, tianeptine decreased gastric mucosal MDA content as compared to indomethacin and ethanol control groups. This was associated with a significant increase in SOD activity in tianeptine pretreated indomethacin group and significant increases in GPx activity in both tianeptine pretreated groups. This is constituent with previous reports indicating

antioxidant activity of tianeptine [46,47]. A previous study on a different model also showed that tianeptine increased glutathione peroxidase activity in spontaneous and Ca2+ stimulated contracted uteri [48]. The current study showed also a decrease in Nrf2 gastric mucosal content in tianeptine pretreated groups as compared to both indomethacin and ethanol groups. This can be also explained by the antioxidant activity of tianeptine which eliminates ROS that responsible for inducing Nrf2.

In the present study oleum cinnamomi significantly decreased gastric mucosal lesion score in both ethanol and indomethacin models. Previous studies also showed that pretreatment with cinnamon extract significantly protected rats against gastric ulceration produced by ethanol, HCL or oral aspirin [49,50]. Another study demonstrated that eugenol (a major constituent of cinnamon leaf oil) reduced gastric lesion induced by either ethanol or indomethacin. The gastroprotective effect was related to factors that increase mucus production and barrier resistance [51,52].

The gastroprotective effect of eugenol and cinnamaldehyde could be related to the anti-inflammatory effect which was demonstrated in vitro, where they reduced the production tumor necrotic factor (TNF) [53]. Additional mechanisms might include antiradical effect which was shown against fructose-induced oxidative stress in rat liver [54]. Another study has elucidated the protection against ulcer and gastritis by cinnamic acid; it demonstrated potent antioxidant activity, acid-neutralizing capacity, and cytotoxicity against Helicobacter pylori. In that study cinnamic acid (100 mg/kg) significantly inhibited HCl/ethanol-induced gastric lesions and increased mucus content in rats [55].

Previous studies demonstrated that polyphenolic compounds; as there in cinnamon oil exhibit several biological activities in the gastroprotective area, including anti-secretory, cytoprotective, and antioxidant actions [56]. These polyphenolic compounds protected the gastrointestinal mucosa in various experimental ulcer models against different necrotic agents. Therefore, our obtained data about cinnamon oil as an antiulcer and gastroprotective agent strongly go hand in hand with other studies [57].

The present study showed a significant decrease in mucosal MDA content and an increase in SOD activity in both pretreated cinnamon oil groups as compared to indomethacin and ethanol control groups. This was associated with increased GPx activity which was statistically significant in oleum cinnamomi pretreated indomethacin group. A previous study also showed similar antioxidant effects for oleum cinnamomi, where it reduced MDA production and increased the activity of SOD [58]. Other study also showed that oleum cinnamomi increased the activity of GPX and demonstrated a significant free radical scavenging activity in testicular rat model, and in liver of diabetic mice [59,60]. It was also reported that cinnamon essential oil was able to reduce lipid peroxidation in the β-carotene-linoleic acid system. It exhibited a protective capacity against irradiation-induced lipid peroxidation in liposomes, and quenched hydroxyl radicals and hydrogen peroxide [61,62]. Another study revealed that cinnamon contained high level of phenolic groups that inhibited the chain reaction of lipid peroxidation in rat hepatocyte resulting in decreased MDA content and elevated in SOD activity.63 The active components of cinnamon could act as an electron donor, which can react with free radicals such as hydroxyl and superoxide radicals to form more stable products and thereby, terminate the radical chain reaction.54 Moreover, the phenolic compound in cinnamon essential oil were found to increase the activity of antioxidant enzymes which in turn detoxify hydrogen peroxide and convert lipid hydroperoxides to nontoxic substances [64,65].

The present study showed a significant decrease in the Nrf2 content of gastric mucosa in both pretreated cinnamon oil groups as compared to indomethacin and ethanol control groups. This also reflects improvement in oxidative stress in both groups in view of considering that Nrf2 as a marker of increased oxidative stress.

CONCLUSION

In conclusion the rebamipide exhibited the most prominent reduction in ulcer score in both indomethacin- and ethanol-induced ulcer groups. Oleum cinnamomi produced the most prominent reduction in MDA mucosal content in indomethacin group and the most prominent increase in SOD activity in ethanol group. The prominent anti-ulcer activity of rebamipide, exhibiting the highest protection ratio among other drugs in the present study, indicates that this agent produces such an effect through multiple mechanisms; not only via antioxidant effects. Oleum cinnamomi produced the most prominent antioxidant effect among other drugs; however, rebamipide was more effective as a gastroprotective against ulceration. It can be, thus, recommended that rebamipide is a good choice to be given concurrently with ulcerogenic drugs like NSAIDs to guard against gastric insults. Oleum cinnamomi is advised to be added as a food supplement in patients with history of PUD. Tianeptine could be a good choice particularly for PUD patients who are under stress.

Ethical approval
The study was conducted after acceptance of ethical committee of Alexandria, Faculty of medicine.

Disclaimer
The article has not been previously presented or published, and is not part of a thesis project.

Conflict of Interest
There are no financial, personal, or professional conflicts of interest to declare.

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