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Original article

Gastric Mucosal Protective Effect of Cinnamon Oil on Induced Indomethacin Peptic Ulcer

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Abstract
Peptic ulcer disease is a gastrointestinal disorder defined by an imbalance between the protective mechanisms (mucus-bicarbonate layer, prostaglandins, and blood flow) and aggressive factors (*H.pylori*, increased acid secretion, bile salts, and some medications). To evaluate the possible protective effects of *oleum cinnamomi* on indomethacin-induced gastric ulcer. The present work was conducted on 24 male albino rats. Animals were randomly divided into 3 groups; Group I (8 rats) served as the plain control group; they received 5 ml/kg body weight of 2% gum acacia orally daily for 7 days. Group II (8 rats) served as the indomethacin-induced gastric ulcer group; Group III (8 rats) served as the oleum cinnamomi – pretreated indomethacin – induced gastric ulcer group. Indomethacin administration produced a gastric mucosal lesion in comparison to the plain control group. Indomethacin produced a significant decrease in gastric mucosal superoxide dismutase (SOD) activity in comparison to the control group. Also, it produced a significant increase in gastric Malondialdehyde (MDA) and an increase in gastric Nuclear E2_related factor2 content (Nrf2) content in comparison to the plain control group. *Oleum Cinnamomi* treatment (III) resulted in a significant reduction in the ulcer score ($P < 0.001$) in comparison to the indomethacin group. A reduction in Malondialdehyde content ($P < 0.001$) and Nuclear E2-related factor 2 content ($P < 0.001$) in comparison to the indomethacin group, respectively; and an elevation in Superoxide dismutase and glutathione peroxidase (GPx) activities in comparison to the indomethacin group. Pretreatment for seven days with *cinnamon oleum* resulted in improvement in ulcer score and gastric mucosal protection in rats with gastric ulcer induced by indomethacin. This was associated with improvement in antioxidant parameters.
Keywords. Peptic Ulcer, Indomethacin, Oxidative Stress, Cinnamon Oleum.

Introduction

Peptic ulcer disease is a multifactorial health problem affecting almost all populations worldwide and has had a tremendous effect on morbidity and mortality until the last decades of the 20th century, when epidemiological trends started to point to an impressive fall in its incidence. Two important developments are associated with the decrease in rates of peptic ulcer disease: the discovery of effective and potent acid suppressants, and targeting Helicobacter pylori. Despite substantial advances, this disease remains an important clinical problem, largely because of the increasingly widespread use of non-steroidal anti-inflammatory drugs (NSAIDs) and low-dose aspirin [1]. Indomethacin is a widely used analgesic in humans, but in many studies, it showed pro-oxidant activity and led to the production of ROS. Thus, leading to the onset of lipid peroxidation and the confrontation of the mucosal cells with antioxidant systems [2]. Especially, ROS such as hydrogen peroxide (H2O2) can be seen as the cause of many illnesses, especially gastric damage [3]. So researchers have concentrated more on oxygen-derived free radicals in recent years.

ROS attacks unsaturated fatty acids, destroys the structure of membrane lipids, and initiates lipid peroxidation. The enzyme activity, permeability, and cell activation are reduced in the damaged membrane proteins. Therefore, antioxidant defense systems are important to prevent the toxic effects of free radicals, which cause many diseases. Oxygen-handling cells contain antioxidant enzymes, both enzymatic and non-enzymatic, that can protect them against oxidative stress. These antioxidants, such as glutathione (GSH), vitamin A and C, α-tocopherol, and β-carotene, also play an important role in the prevention of gastric damage [4,5]. There are several drugs available for the treatment of gastric ulcers. 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. Plants have been used all over the world for hundreds of years to improve the taste and aroma of foods, eliminate unwanted odor in food, and, most importantly, for therapeutic reasons [6].

Cinnamon is a traditional herb used for many diseases, and it also has effects as an antioxidant, anti-inflammatory, antispasmodic, and anti-ulcerative [7]. The current study assessed the gastroprotective effects of (*oleum cinnamomi*) on indomethacin ulcer, was concern to clarify and evaluate 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).

Materials and Methods

Study Design

It is an experimental study, and 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, eight rats for the indomethacin-induced ulcer. The

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rats received a single dose of indomethacin (100mg/kg for each rat orally for 7 days). Group III (8 rats), oleum cinnamomi – pretreated with indomethacin (Oleum cinnamon 2.5 ml/kg orally daily for 7 days) before induction of indomethacin ulcer.

Experimental animals

The present study was conducted on 24 male albino rats of body weight ranging from 160-180 gm. Animals were housed in animal cages in groups of 8 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.

Drugs and chemicals

Indomethacin powder (Euro OTC Pharma), *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 peroxidase (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 the 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 [8]. Then the mucosa was scraped 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 × g for 15 minutes at 4 Co. The supernatant was removed and frozen at -20 Co for assessment of the following parameters:

- Superoxide dismutase [9].
- Malondialdehyde [10].
- Glutathione peroxidase [11].
- Nuclear factor erythroid related factor (Nrf2) [12].

Statistical methods

Data analysis was performed using the Statistical Package of Social Science (SPSS version 20 software package. For 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 oleum cinnamomi on indomethacin-induced gastric ulcer in rats

Indomethacin produced gastric lesions with a mean ulcer score of mean±SE 13±1.02. Indomethacin produced a significant increase in MDA and Nrf2 contents, and a decrease in the activity of SOD as compared to the control group, but no changes in GPx activity. *Oleum Cinnamomi* produced a prominent decrease in MDA gastric content.

Table 1. Effect of oleum cinnamomi on indomethacin-induced gastric ulcer in rats

	Control Group	**Indomethacin Group**	**Indomethacin with Cinnamon**
Ulcer Score	--	13±1.02	7±0.93$^{\#@\blacklozenge}$
		P<0.001	
SOD activity	5.07±0.15	3.06±0.62$^{\$}$	4.72±0.43$^{\$\#}$
		F=9.745 p<0.001	
MDA content	321.25±12.02	388±27.22$^{\$}$	217.66±12.21$^{\#}$
		F=18.343 P<0.001	
GPx activity	14.13±0.04	16.35±1.01	45.81±3.63$^{\$\#}$
		P<0.001	
NrF_2 content	92.95±9.16	206.13±11.49$^{\$}$	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 oleum cinnamomi group.

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Discussion

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 the lower oesophagus. The need for new or adjuvant drugs led to the present study, which studied the effect of *oleum cinnamomi* in two models of PUD in rats, namely an indomethacin-induced ulcer. In the present study, indomethacin-induced mucosal injury has been associated with increased MDA and Nrf2 levels and reduced 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 [13]. Many other studies, together with these results, indicate that oxidative stress-induced lipid peroxidation, DNA damage, and neutrophil-dependent microvascular injuries that lead to cell death can explain indomethacin-induced gastric ulceration [14-16]. The reduction in SOD activity observed in the indomethacin group can be explained by the generation of OH radicals, which decreases the activity of SOD [17].

Besides, a previous study has also shown that indomethacin induced, time-dependently, mitochondrial perturbations which led to loss of antioxidant enzymes [18]. Another 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 NSAID-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 [19]. GPX activity in this study was not significantly changed in the indomethacin group as compared to the 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 [20]. 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 [21,15].

Indomethacin-induced ulcer was associated with increased gastric mucosal Nrf2 level, which is in agreement with another previous study [15]. Again, this probably occurs as a defense mechanism under the effect of ROS through dissociating Nrf2 from Keap1 in the cytoplasm [22]. In the present study, *oleum cinnamomi* significantly decreased gastric mucosal lesion score. Previous studies also showed that pretreatment with cinnamon extract significantly protected rats against gastric ulceration produced by ethanol, HCl, or oral aspirin [23,24]. Another study demonstrated that eugenol (a major constituent of cinnamon leaf oil) reduced gastric lesions induced by either ethanol or indomethacin. The gastroprotective effect was related to factors that increase mucus production and barrier resistance [25,26]. Previous studies demonstrated that polyphenolic compounds, as present in cinnamon oil, exhibit several biological activities in the gastroprotective area, including anti-secretory, cytoprotective, and antioxidant actions [27]. 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 the indomethacin and ethanol control groups. This was associated with increased GPx activity, which was statistically significant in the *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 [28]. Another study also showed that *oleum cinnamomi* increased the activity of GPX and demonstrated significant free radical scavenging activity in a testicular rat model [29] and in the liver of diabetic mice [30]. Another study revealed that cinnamon contained high levels of phenolic groups that inhibited the chain reaction of lipid peroxidation in rat hepatocytes, resulting in decreased MDA content and elevated SOD activity [31]. 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 [32]. Moreover, the phenolic compounds 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 [33,34]. The present study showed a significant decrease in the Nrf2 content of gastric mucosa in both pretreated cinnamon oil groups as compared to the indomethacin and ethanol control groups. This also reflects improvement in oxidative stress in both groups in view of considering that Nrf2 is a marker of increased oxidative stress.

Conclusion

Oleum cinnamomi produced a prominent reduction in MDA mucosal content in an indomethacin-induced ulcer. It can be, thus, *Oleum cinnamomi* is advised to be added as a food supplement in patients with a history of PUD.

Approval Ethics

The study was conducted after acceptance by the ethical committee of Alexandria Faculty of Medicine.

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