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The Gastroprotective Effects of *Cordia myxa* Leaf Extract Against Ethanol-Induced Gastric Ulcers In Rats

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ABSTRACT

In this study, the effect of Cordia myxaleaf extract on ethanol-induced gastric ulcers was investigated in rats. A methanolic extract of C. myxawas prepared via cold maceration. Gastric ulceration was induced by a single oral administration of 70% ethanol at a dose of 10 mL/kg. The animals were divided into five groups of six animals each. In each test, Groups I, II and III were administered normal saline, (10m/kg) of 70 % ethanol and (20 mg/kg) of omeprazole, respectively, and 200 mg/kg and 400 mg/kg of oral plant extract was also administered to Groups IV and V, respectively.Gastric juice acidity and gastric injury were examined directly. The administration of ethanol significantly increased the free and total acidity levels as well as the ulcer index in the experimental groups compared with the control group. However, pretreating the rats with a methanolic extract of C. myxa leaves prior to ethanol application had an inhibitory effect on free acidity, total acidity and ulcer index; this effect depended on the concentration, as the percent of inhibition was higherat 400 mg/kg than at 200 mg/kg concentrations. The results of the present study show that a methanolic extract of C. myxa leaves has gastroprotective effects on ethanol-induced ulcers.
Keywords: acidity, antioxidant, Cordia myxa, peptic ulcer

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INTRODUCTION

Peptic ulcer disease affects the digestive system and includes both duodenal and gastric ulcers. Evidence from recent studies indicates that the prevalence of peptic ulcers is approximately 4%; on average, 10% develop peptic ulcers in their lifetime in united states [1]. Previous studies have indicated that *Helicobacter pylori* infection is a major risk factor for peptic ulcers[2, 3]. According to a previous study on the aetiology of peptic ulcers, *H. pylori* is considered a major mechanism of pathogenesis that increases the development of these ulcers [2]. However, in approximately 20% of peptic ulcer cases, patients do not exhibit any evidence of *H. pylori*. Previous study have also revealed a strong association between peptic ulcers and both lifestyle and intake of non-organic materials. Lifestyle and non-organic factors are often associated with the onset, course and severity of a peptic ulcer [4].

The pathophysiological mechanism of peptic ulcers arises from an imbalance between the secretions of acid–pepsin, reactive oxygen species and protective factors, including cell regeneration, mucus secretion, blood flow and the epithelial barrier within the gastric mucosa. Reactive oxygen species play an essential role in the onset and development of pathologies related to stomach like peptic ulcerations, gastric adenocarcinoma and gastritis [5]. The multiple layers within the gastric mucosa are and effective barrier in counteracting the adverse effects of noxious agents through various defence mechanisms of endogenous antioxidants. Elevated oxidative damage is closely linked to the destruction of gastric mucosa, resulting in peptic ulcers. The destruction in gastric mucosa may affect the stomach and the small and large intestines [6-8].

Alcohol consumption has been cited as a significant aetiologic factor that is closely linked with peptic ulcers. For example, chronic alcohol consumption has been associated with chronic active gastritis [9, 10]. However, inflammatory changes within the mucosa are closely related to *H. pylori*. Evidence from recent studies also suggests a close relationship between gastric metaplasia and chronic alcoholism. Experimentally and clinically, a higher consumption of alcohol has been shown to impair the mucosal

barrier and mucosal histology. In this regard, the essential function of the gastric defence system is affected to a great extent by the ulcerogenic effects of alcohol[10].

Different pharmacological therapies are available for the treatment of peptic ulcers [11]; however, many of the medications currently used for the treatment of gastric ulcerations are associated with various side effects such as diarrhoea, osteomalacia and liver damage [12, 13]. As a result, recent pharmacological research in this discipline has focused on the best alternatives available. There has been increasing interest in alternative therapies and natural products, such as plant-based treatments [14, 15]. *Cordia myxa*, from the Boraginaceae family, is a medicinal plant that grows worldwide, including in the Kingdom of Saudi Arabia (KSA). Locally known as 'Bumber'[16], it is popularly used for its efficacy in chest and urinary infections; many other recent records attest to its antioxidant, anti-diabetic and hepatoprotective activities [17, 18].

C. myxa has received much attention in the literature because of evidence showing its inhibition efficacy against gastric ulceration in mice [19]. Pharmacological evidence from past studies has shown that *C. myxa* fruit extract exhibits significant gastrointestinal protective and anti-inflammatory effects [19, 20]. Due to its effectiveness and safety as a therapeutic and pharmacological agent as well as its chemical composition, *C. myxa* has been considered a promising herbal drug for the treatment of gastritis. Abdallah et al. suggested that *C. myxa* fruit offers protection against the gastric ulceration and inflammation induced by indomethacin because the plant extract has high mucin- and antioxidative-enhancing properties [19]. In addition, it has been reported that leaf extract of some species of *C. myxa*, including *C. francisci* and *C. serratifolia*, shows anti-inflammatory, anti-arthritic and analgesic effects in rats [21]. The aim of the present study is to investigate the gastroprotective effects of a methanolic extract of *C. myxa* leaves on ethanol-induced ulcers in rats.

MATERIALS AND METHODS

Plant material

*C. myxa*leaves were collected from Al-Hasa, which is in the eastern region of the KSA. The leaves were air-dried according to standard protocols. A voucher specimen was kept in the Department of Pharmaceutical Sciences, College of Clinical Pharmacy, King Faisal University, Al-Hasa, KSA (05-17-Apr-CM).

Preparation of extract

The powdered air-dried *C. myxa*leaves (500.0 gm) were exhaustively extracted twice at room temperature (for 5 days) using 3 L of 70% MeOH/H_2O. A cold maceration technique was applied at room temperature to protect the potential active ingredients from destruction. The solvent mixture was removed through distillation under vacuum using a rotary evaporator (Rotavapor®), and dried extracts were immediately freeze-dried to obtain the total methanol extract of leaves (43.0 g). This extract was kept at -20°C for the following steps [22].

Animals

The animals were obtained from Animal House, Faculty of Medicine, Assiut University (Assiut, Egypt) and were fed a standard diet with water ad libitum. During the rats were maintained at a 12-hr light: dark cycle. They were fasted for 24 hr before the experiments but had free access to drinking water [22]. Experimental protocols were approved by the scientific research practice committee at Al-Azhar University, Egypt.

Thirty Wistar albino rats of either sex weighing between 140 and 200 g were obtained from the animal house at the College of Clinical Pharmacy, King Faisal University. The animals were housed in polypropylene cages under standard laboratory conditions of temperature (25 ± 2°C) and relative humidity (55% ± 5%) with a 12:12 light-dark cycle. The animals were given a standard rat pellet diet and water ad libitum. They were fasted 24 hours prior to the experiments but had free access to drinking water. Experimental protocols were approved by the scientific research practice committee at King Faisal University, KSA.All procedures were carried out in accordance with institutional guidelines foranimal care and use.

Preparation of test samples for bioassay

Test samples were administered orally to the test animals after suspension in a 0.5% sodium carboxymethyl cellulose (Na-CMC) solution in distilled water.

Assessment of antiulcer activity

The animals were divided into five groups of six animals each. Group I served as a healthy control and received 0.5% Na-CMC solution in distilled water. As the disease group, rats in Group II were administered 70% ethanol orally [23]. Group III served as a standard and was administered 20 mg/kgof omeprazole orally. Groups IV and V were treated orally with 200 mg/kg and 400 mg/kg of a methanol extract of *C. myxa*, respectively. One hour after pretreatment in Groups III, IV and V, the rats were

administered orally with 70% ethanol (10 mL/kg) in order to induce gastric ulcers.After one hour, the rats were sacrificedunder an overdose of diethyl ether anaesthesia. The stomach of each animal was immediately and carefully excised, keeping the oesophagus closed; the gastric contents were collected and centrifugedat 3000 rpm for 10 min to remove any solid debris and the volume of the supernatant was measured [24].

The volume of the supernatant was measured and expressed as mL/100 g then examined for pH. Each stomach was opened along the greater curvature, the stomachs were washed with ice-cold saline and examined for macroscopical mucosal lesions.Ulcer index (UI) was calculated using an arbitrary scoring system. The ulcerative lesions were classified as follows: normal stomach = 0; spot ulceration = 1.0; haemorrhagic streaks = 1.5 and ulcer = 2 and above.

Percentage inhibition of ulceration

Percentage inhibition of ulceration was calculated as shown below:

$$\% \text{ Inhibition of Ulceration} = \frac{\text{UI Control - UI Test}}{\text{UI Control}} \times 100$$

Determination of total acidity

An aliquot of 1 mL of gastric juice diluted with 1 mL of distilled water was taken into a 50 mL conical flask, to which two drops of phenolphthalein indicator were added. The flask was titrated with 0.01 N NaOH until a permanent pink colour was observed. The volume of 0.01 N NaOH consumed was noted. The total acidity was expressed as mEq/L by the following formula

Acidity = Volume of NaOH × Normality × 100/0.1

Determination of free acidity

Instead of a phenolphthalein indicator, Topfer's reagent was used. An aliquot of gastric juices was titrated with 0.01 N NaOH until a canary yellow colour was observed. The volume of 0.01 N NaOH consumed was noted. The free acidity level was calculated by the same formula as that for the determination of total acidity.

Statistical analysis

All the results were expressed as mean ± standard error of the mean (SEM). The data were statistically analysed by one-way analysis of variance (ANOVA), and P values < 0.05 were considered significant.

RESULTS ANDDISCUSSION

The findings of the present study revealed an inhibition of gastric ulceration as in figure 1 a result of treatment with *C. myxa* leaf extract, as indicated by the fourth and the fifth samples. The percent inhibition of ulceration in the fifth sample was 72.88%, while in the fourth sample, it was 58.52%. This can be attributed to the varying dosage of *C. myxa*leafextract since the concentration was higher in the fifth sample (400 mg/kg) than in the fourth sample (200 mg/kg). These results further suggest that increasing the dosage of *C. myxa* leaf extract from 200 to 400 mg/kg results in increased inhibition of gastric ulcerations. This is further indicated by the low levels of both free and total acidity, as indicated in Table 1. For instance, for the 200 mg/kg dosage of *C. myxa*, there was gastric ulceration inhibition of 58.52%, 80.47% total acidity and 76.56% free acidity. In comparison, the higher dosage of 400 mg/kg of *C. myxa* extract had 72.88% gastric ulceration inhibition, 67.62% total acidity and 59.27% free acidity. Hence, the results indicate that *C. myxa* could be effective in the management of peptic ulcers disease. The inhibition of gastric ulceration is associated with reduced acidity, so there is reduced corrosion of the mucosal layers. The findings in this experiment are consistent with the results of previous studies in which researchers used fruit C.myxa. A study by Abdallah et al. examined the protective effects of *C. myxa*fruitextract against indomethacin-induced gastric ulcer in rats [19]. The results of their study showed a protective effect within the stomachs of rats administered with *C. myxa* fruit extracts. They further noted that this extract helps to protect against indomethacin-induced gastric ulceration because it has significant antioxidative and mucin-enhancing characteristics[19]. Another study by Ranjbar et al. investigated the effect of *C. myxa* fruit on formalin-induced nociception in mice and found that *C. myxa* fruit extract exhibited an anti-inflammatory effect [17]. These studies support the results of our experiment by indicating the potential effects of *C. myxa* extract as a protective agent against peptic ulcers [17-19].

Figure 1: Aprotective effect of *Cordia myxa* leaves on gastric mucosa lesions induced by ethanol in rats. A: Control group, B: Ethanol group (10 mL/kg), C: *C. myxa* leaves (200 mg/kg), D: *C. myxa* leaves (400 mg/kg).

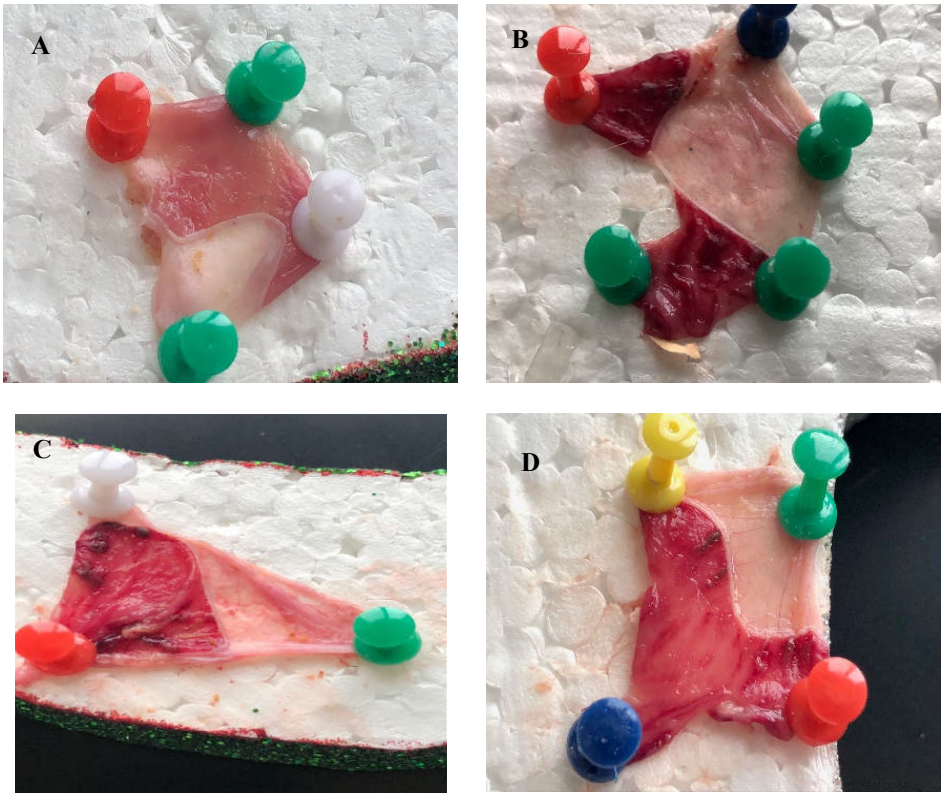

Table 1: Effect of omeprazole treatment in combination with two concentrations of *Cordia myxa* leaf pretreatment on free acidity, total acidity, ulcer index and percent of ulcer inhibition in rats with ethanol-induced ulcers.

Group	Treatment	Dose	Free acidity (mEq/L)	Total acidity (mEq/L)	Mean ulcer index	% of ulcer inhibition
I	Healthy control (Na-CMC)	10 mL/kg	110.14 ± 1.35	117 ± 1.68	----------	------
II	Disease group(70% ethanol)	10 mL/kg	234.61 ± 3.09	268 ± 2.37	10.03 ± 0.06	------
III	Standard drug (omeprazole)	20 mg/kg	34.80 ± 2.32	43.75 ± 3.94	1.21 ± 0.09	87.93
IV	Methanolic extract of *C. myxa*	200 mg/kg	76.56 ± 4.39	80.47 ± 7.06	4.16 ± 0.13	58.52
V	Methanolic extract of *C. myxa*	400 mg/kg	59.27 ± 3.61	67.62 ± 2.79	2.72 ± 0.27	72.88

Values are expressed as mean ± SEM (n = 6). P values < 0.05 were considered statistically significant when Groups IV and V were compared with Group III.

CONCLUSIONS

In conclusion, *C. myxa* extract has been demonstrated through various experiments to positively impact oxidative stress and reduce gastric acidity, thereby increasing the efficacy of gastric ulceration inhibition. Previous studies suggest that C*. myxa* extract could be used as an alternative therapy in the treatment and management of inflammatory conditions, such as peptic ulcers, due to its inhibition efficacy, at least from the results observed in mice. Moreover, this plant extract can be used as a complimentary therapy that allows patients to be treated at reduced doses of standard anti-gastric ulceration drugs, such as omeprazole, thus reducing the side effects of such drugs. However, further investigations need to be conducted to understand the principle of inhibition and the actual mechanism of action at the molecule

level, as well as to enhance our understanding of the chemical constituents of this plant extract that are responsible for this activity.

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