Study of Anti-ulcer Activity of *Coriandrum sativum* Linn. in Aspirin Induced Gastric Ulcer in Albino Rats

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Abstract

Fruits of *Coriandrum sativum* Linn have been described in Unani literature to possess anti-gastritis, anti-ulcer, sedative, hypnotic, anti-anxiety and anti-stress activity. It has been studied scientifically for anti-ulcer activity on some of the parameters but no study has been conducted so far, for its role in aspirin induced gastric ulcer. The present study was designed to investigate the anti ulcer activity of hydro alcoholic extract of coriander against aspirin induced gastric ulcer in Wistar rats of either sex, weighing 150-200 gm. The animals were divided into 8 groups of 8 animals each. Different groups represented plain control (vehicle), negative control (ulcer induced), standard control (pre and post-treated with ranitidine) and four test groups, two each for preventive (pre-treated with 160 mg/kg and 273 mg/kg of extract) and curative (post-treated with 160 mg/kg and 273 mg/kg of extract) studies. Animals were treated for five days before or after the ulcer induction and sacrificed thereafter. Their stomach was dissected out and observed for lesions. The scoring of lesions was done to calculate the ulcer index and ulcer score. Histopathological studies were also carried out.

A significant decrease in ulcer index and ulcer score and remarkable changes in histopathological slides in curative group suggested that coriander possesses significant anti ulcer activity.

Keywords: *Coriandrum sativum*, Anti-ulcer, Aspirin, Unani Medicine

Introduction

Peptic ulcer disease (PUD) is one of the most common gastrointestinal disorders, which causes a high rate of morbidity (Andreoli *et al.,* 2001), while the most common causes of peptic ulcer include *H. pylori* infection and excessive use of Non-Steroidal Anti-Inflammatory Drugs (NSAID) such as aspirin, ibuprofen, indomethacin and diclofenac sodium etc. The incidence of ulcer disease increases with age, due to excessive use of NSAIDs and the reduction in tissue prostaglandins (Andreoli *et al.,* 1993). Being one of the most commonly prescribed drugs worldwide NSAIDs always remain a threat to the health of gastric mucosa. The therapy of peptic ulcer involves decreasing the secretion of acid with H_2-receptor antagonist or proton pump inhibitor, neutralizing the secreted acid with antacids and enhancing the mucosal protection mechanism by cytoprotective agents. The later one is being appreciated and taken up as equally important measure to that of anti-

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secretory agents in the management of peptic ulcer (Horn, 2000). Although these drugs have brought about remarkable success in the field of ulcer therapy but their efficacy and safety are still debatable because there are incidences of relapses, adverse effects and danger of drug interactions during ulcer therapy (Dharmani and Palit, 2006; Goel and Sairam, 2002). A number of plant drugs in recent years have been shown to possess significant anti ulcer effect. Most of the herbal drugs used in the management of peptic ulcer have been reported to reduce the offensive factors, they have been proved to be safe and effective and showed better patient tolerance. Therefore the use of natural drugs alone or in combination with other drugs is being seriously considered to manage the PUD (Goel and Sairam, 2002).The first drug reported effective against ulcer was carbenoxolone, discovered as a result of research on a commonly used indigenous plant, *Glycyrrhiza glabra* (Singh and Majumdar, 1999).

Coriandrum sativum Linn (coriander) which is considered both a herb and a spice, as both its leaves and seeds are used as a seasoning condiment is an important drug of Unani medicine (Saeed and Tariq, 2007). Its seed is used as carminative, stomachic, refrigerant, sedative; anti secretory and anti gastritic etc (Chaudhry and Tariq, 2006). It is an important ingredient of a number of pharmacopoeal and non pharmacopoeal preparation used to treat gastric disorders including gastritis and ulcer. In some of the studies it has been shown to produce anti ulcer effect in experimental models where the ulcers were induced with alcohol and stress etc. However, it was not studied against NSAIDs which are among the most commonly used therapeutic agents but are liable to induce gastric ulcer. Therefore the present study was designed to study the anti ulcer effect of seeds of *Coriandrum sativum* in aspirin-induced gastric ulcer in albino rats.

Materials and Methods

Plant Material

Seeds of coriander were purchased from the local market of Bangalore, Karnataka. An authorized committee of National Institute of Unani Medicine (NIUM), Bangalore, comprising of pharmacognosists, Unani experts and medicinal chemists confirmed the identity and the quality of the drug sample.

The drug was dried in shade and powdered coarsely in an electric grinder. The powder was then extracted in hydroalcoholic solution (50%+50%) in the ratio of 1:5, (100 gm of powdered drug was taken into 500 ml of hydroalcoholic

solution) with the help of a Soxhlet apparatus for 8 hrs. The liquid extract was then filtered and concentrated on water bath. The concentrated extract was weighed and the yield percentage was calculated with reference to the weight of crude drug. The yield was found to be 19.48% w/w.

Dosage of the test drug

The human therapeutic dose of coriander described in Unani literature, is 5-7 gm (Anonymous, 2007; Ghani, ynm). Its dose for albino rats was calculated by multiplying the higher dose of 7 gm by the conversion factor of 7 (Freirich *et al.,* 1966) and found to be 820 mg/kg body weight for rats. To study the dose dependent effect of the test drug, a second dose calculated by the method of Miller and Tainter (1944) and found to be 1400 mg/kg, was also used. The dose of extract corresponding to the dose of crude drug i.e. 160 mg/kg and 273 mg/kg respectively was used. The standard drug ranitidine (50 mg/kg) was purchased from Ranbaxy Laboratories Limited, Hyderabad (India) while the aspirin (200 mg/kg), used as ulcerogenic agent was of analytical grade, in the form of crystalline acetyl salicylic acid, supplied by Sigma Aldrich, Germany.

Drugs were administered by oral route with the help of a gastric cannula. The dosage forms were prepared freshly every day before the administration by suspending the drug in 1ml of 0.4% carboxymethyl cellulose (CMC).

Experimental animals

The study was carried out on Wistar rats of either sex, weighing 150-200 gm. They were procured from central animal house facility, National Institute of Mental Health and Neurosciences (NIMHANS), Bangalore. The rats were housed in polypropylene cages, under controlled conditions of light (12/24 hour) and temperature ($23 \pm 2\ ^0C$) and provided standard commercial food pellets (Hindustan Lever Ltd.) and tap water *ad libitum*, under strict hygienic conditions.

The experimental protocol was approved by the Institutional Animal Ethics Committee (IAEC), National Institute of Unani Medicine, Bangalore, Karnataka, India vide Reg. No. 953/C/06/CPCSEA, dated 28th August 08.

Aspirin-induced gastric ulcer

This test was carried out by the method of Goel *et al.* (1985), using albino rats divided into 8 groups of 8 animals each. The animals in Group I were treated with 1 ml of 0.4% CMC while those in Group II were administered 200 mg/kg

of aspirin (suspended in 1 ml of 1% CMC), and served as Plain control and Negative control, respectively. The animals in Group III and IV were treated with hydroalcoholic extract of the test drug in the dose of 160 mg/kg and 273 mg/kg (suspended in 1 ml of 0.4% CMC) daily for 5 days and served as Pre-treated test group A and B, respectively. Group V was treated with ranitidine 50 mg/kg daily for 5 days (suspended in 1 ml of 0.4% CMC) and served as Pre-treated standard group. From 6th day onwards aspirin (200 mg/kg) was given to all the animals except those in Plain and Negative control groups, orally for the next 5 days. After the administration of aspirin, food was withdrawn for a period of 2 hours (animals had free access to food and water thereafter). On 11th day after 5 days administration of aspirin, 12 hour fasted rats were sacrificed under thiopentone anaesthesia (40 mg/kg IP). While the animals in Negative control group were sacrificed on 6th day after 5 days of aspirin treatment and Plain control animals were sacrificed on 11th day.

The animals in Group VI, VII and VIII, were treated with aspirin (200 mg/kg) once daily for first five days and the food was withdrawn for two hours after each administration. From 6th day hydroalcoholic extract of test drug was given orally to Group VI and VII in the dose of 160 mg/kg and 273 mg/kg by oral route once daily for next five days. These two groups served as Post-treated test group A and B, respectively, whereas Group VIII received standard drug ranitidine 50 mg/kg orally, once daily for 5 days and served as Post-treated standard group. On 10th day after the administration of test and standard drugs the animals were kept on fasting with water *ad libitum*. Coprophagy was prevented during fasting by putting the animals in cages with grating on the floor. On 11th day after 24 hours of fasting, the animals were sacrificed.

In Aspirin-induced ulceration, gastric mucosa was examined for ulceration by the following method:

Abdomen of the anaesthetized animals was opened by the midline incision; stomach was dissected out carefully and opened along the greater curvature. The mucosa of stomach was washed with tap water and spread over a cardboard with the mucus surface upwards. The mucosal surface was examined for ulceration with the help of magnifying lens (10 fold magnification). The stomach of 2 rats from each group was preserved immediately in 10% formalin and sent for histopathological examination.

Determination of the degree of ulceration

The degree of ulceration was determined by the method of Adami *et al.,* (1964).

0.0 – Absence of any detectable lesion

0.5 – Small haemorrhagic effusion

1.0 – Haemorrhagic effusion

1.5 – Mucosal ulceration of limited diffusion involving not more than 1/3rd of whole surface of stomach

2.0 – Mucosal ulceration of limited diffusion involving not more than 2/3rd of whole surface of stomach

2.5 – Mucosal ulceration of generalized diffusion

3.0 – Deep ulceration of limited diffusion

3.5 – Deep ulcerations of generalized diffusion

4.0 – Perforated ulcer

The average degree of single ulceration (ADU) for each group was determined by adding together the degree of single ulceration (DSU) and dividing it by the number of animals. On the basis of the percentage of rats with ulceration (% RU), the ulcer index was calculated by the following formula (Srimal, 1984)

$$\text{Ulcer Index} = \frac{(\text{ADU})\ (\%\ \text{RU})}{100}$$

ADU – Average degree of single ulceration
% RU – Percentage of rats with ulceration

The observations in various groups were expressed as median with range. The ulcer scores of various groups were compared with Negative control group. The group comparison was analyzed using Kruskal-Wallis post hoc Dunn's multiple pair comparison test. The difference of median was considered significant at $p<0.05$.

Results

Median 'ulcer score' in Negative control group was found to be 2.5(1.5, 3.0). While the median score in Pre-treated test group A was found to be 1.5 (1, 2) showing non-significant result. Similarly, in Pre-treated test group B, the ulcer score was found non-significant with median score of 1.25 (1, 2). But in Pre-treated standard group where (ranitidine treated) the median score was 1 (0.5, 1.5), a significant ($p<0.01$) reduction was observed. The Post-treated group A showed non-significant result as the median score was found to be

1.25 (1, 2), whereas the median score of Group B and that of the standard group was found to be highly significant ($p<0.001$) with median score of 0.75 (0.5, 1.5) and 0.5 (0.5, 1.0), respectively.

The 'ulcer index' was found to be 2.25 in Negative Control group and 1.5 and 1.4 in Pre-treated test group A & B, respectively. In Pre-treated standard group, the ulcer index was found to be 0.94 whereas in Post-treated test group A it was found to be 1.31. In Post-treated test group B and standard group more reduction in ulcer index was found i.e. 0.81 and 0.68, respectively (Table 1 & 2; Fig. 1 & 2).

Histopathological findings

Ulceration and necrosis was seen in the gastric mucosa of the animals of Negative control. The submucosa showed severe oedema. Few engorged blood vessels and areas of necrosis were also seen (Slide 1, Table 3).

In Pre-treated test group A, section from the biopsy revealed atrophy of the mucosa (Slide 2, Table 3). Gastric mucosa of Pre-treated test group B, showed eosinophilic gastritis with increased number of paneth cells (Slide 3, Table 3). Section from the biopsy of Post-treated test group A revealed features of gastritis with increased number of paneth cells and eosinophils (Slide 4, Table 3), while Post-treated group B showed features of gastritis only (Slide 5, Table 3).

Table 1 : Effect of the extract of *Coriandrum sativum* Linn seeds on median ulcer score in Aspirin induced-gastric ulcer

Groups	Treatment	Median ulcer score
Group I Plain control	1 ml of 0.4% Carboxymethyl cellulose	0 (0, 0)
Group II Negative control	Aspirin (200 mg/kg)	2.5 (1.5, 3.0)
Group III Pre-treated test group	Coriander (160 mg/kg) + Aspirin (200 mg/kg)	1.5 (1.0, 2.0)
Group IV Pre-treated test group B	Coriander (273 mg/kg) + Aspirin (200 mg/kg)	1.25 (1.0, 2.0)

Groups	Treatment	Median ulcer score
Group V Pre-treated standard group	Ranitidine (50 mg/kg) + Aspirin (200 mg/kg)	1 (0.5, 1.5)
Group VI Post-treated test group A	Aspirin (200 mg/kg) + Coriander (160 mg/kg)	1.25 (1.0, 2.0)
Group VII Post-treated test group B	Aspirin (200 mg/kg) + Coriander (273 mg/kg)	0.75 (0.5, 1.5)
Group VIII Post-treated standard group	Aspirin (200 mg/kg) + Ranitidine (50 mg/kg)	0.5 (0.5, 1.0)

**p<0.01, ***p<0.001 with respect to Negative control, N = 8 in each group.

Table 2 : Effect of the extract of *Coriandrum sativum* Linn seeds on ulcer index in Aspirin-induced gastric ulcer

Groups	Ulcer incidence		Ulcer index
	No.	%	
Group I Plain control	0/8	0%	0
Group II Negative control	8/8	100%	2.25
Group III Pre-treated test group A	8/8	100%	1.5
Group IV Pre-treated test group B	8/8	100%	1.4
Group V Pre-treated standard group	8/8	100%	0.94
Group VI Post-treated test group A	8/8	100%	1.31
Group VII Post-treated test group B	8/8	100%	0.81
Group VIII Post-treated standard group	8/8	100%	0.68

N = 8 in each group.

Table 3 : Histopathological Summary of Aspirin induced-gastric ulcer Model

Groups	Congestion	Haemorrhage	Oedema	Necrosis	Inflamm. Changes	Erosion	Ulceration
Group I	-	-	-	-	-	-	-
Group II	+++	++	+	+	++	+	++
Group III	+++	++	+	-	+++	+	+
Group IV	++	+	+	-	++	+	-
Group V	+	+	-	-	+	-	-
Group VI	++	++	++	-	+	+	-
Group VII	+	+	-	-	+	-	-
GroupVIII	+	-	-	-	-	-	-

Normal: (-), Moderate: (+), Severe: (++), Intensely severe: (+++)

Effect of hydroalcoholic extract of *Coriandrum sativum* Linn. on "Aspirin induced-gastric ulcer"

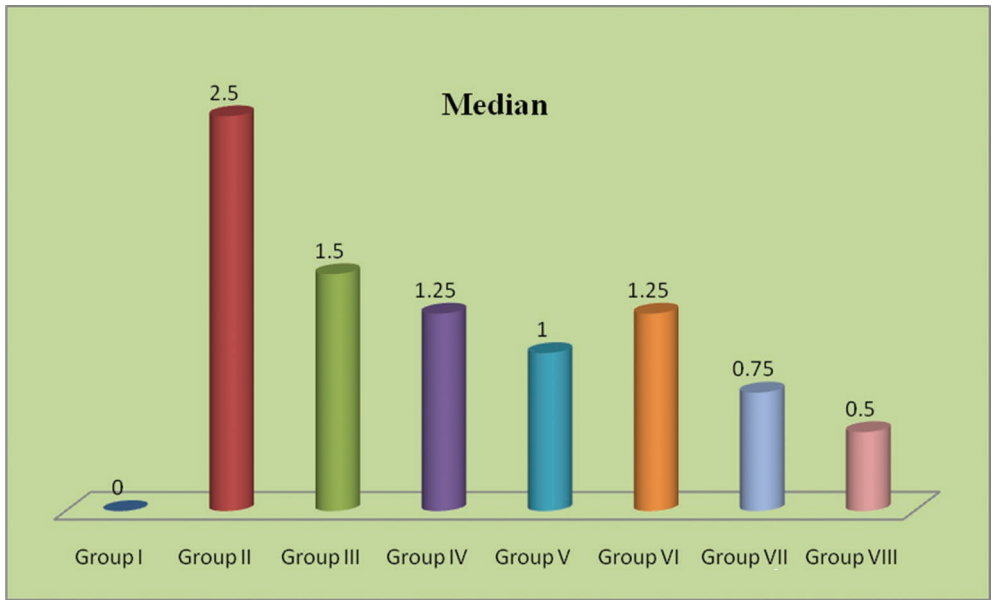


Fig. 1 : Showing ulcer score

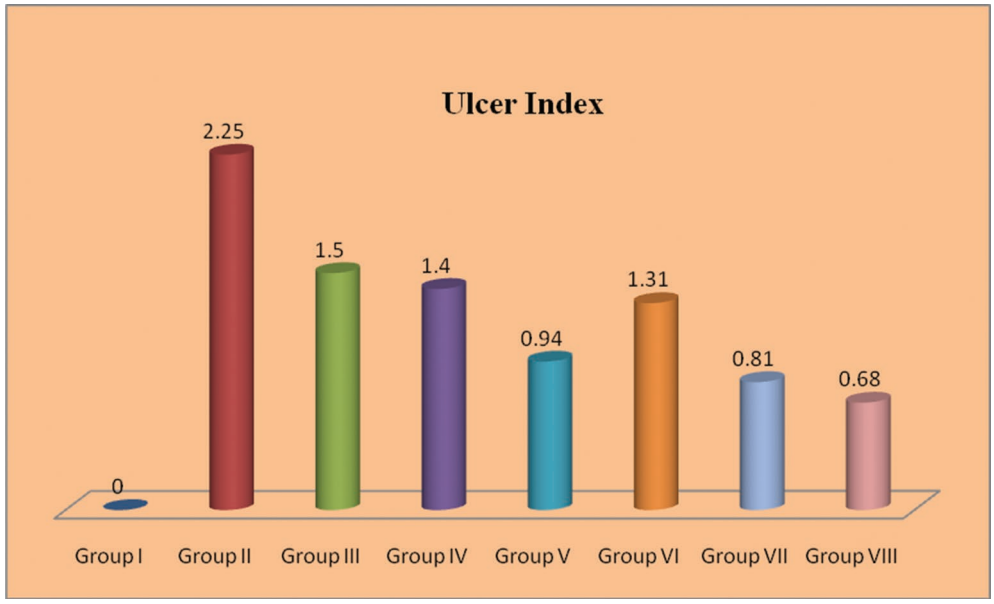
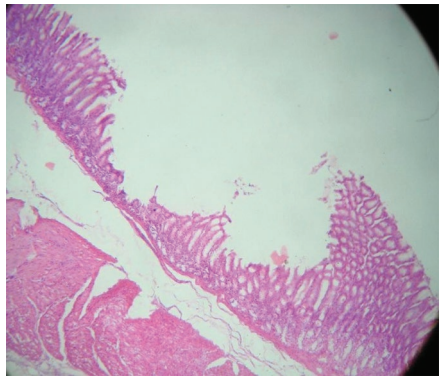
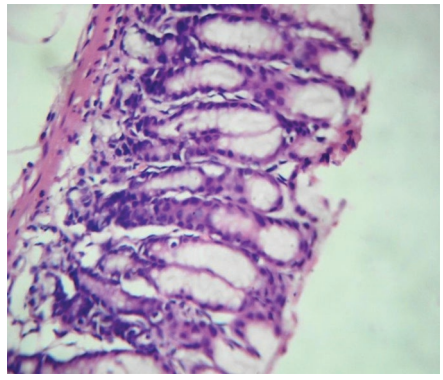


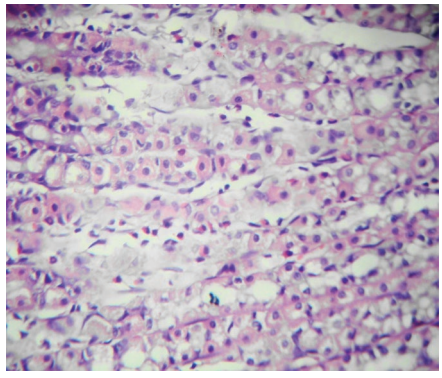
Fig. 2: Showing ulcer index



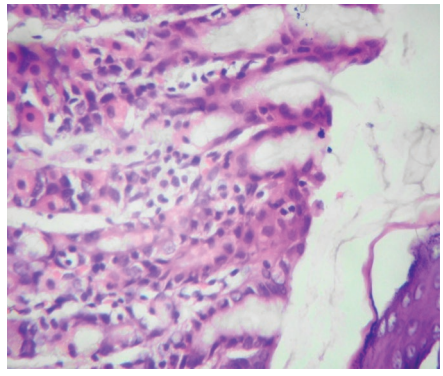
Slide No. 1 : Negative Control



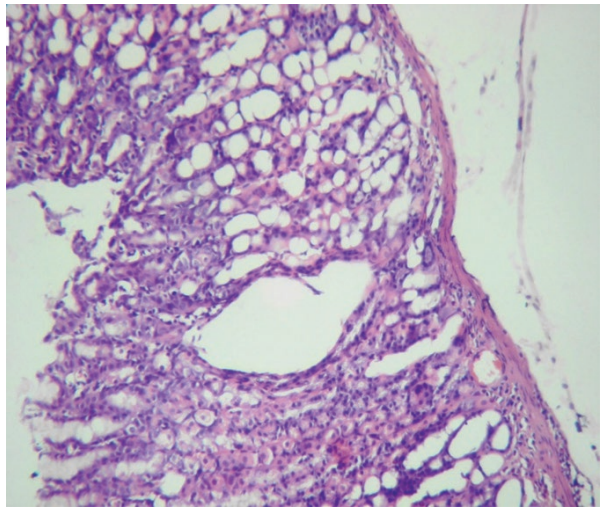
Slide No. 2 : Pre-treated group A



Slide No. 3 : Pre-treted group B



Slide No. 4 : Post treated group A



Slide No. 5 : Post treated group B

Discussion

The findings of the study demonstrated that the pre-treatment of test drug at low and high doses did not produce significant results. Similarly, the effect of low dose in post treated group was also found non-significant. However, the high dose in post-treated group produced significant reduction in ulcer score and ulcer index suggesting that the test drug at high dose possesses significant anti ulcer activity ($p<0.001$).

The results of the study clearly indicated that the test drug at low dose does not have the healing effective in experimentally induced gastric ulcer as it failed to reduce both the ulcer score and ulcer index. But it was found effective at higher dose and the efficacy was observed only in curative group. It signifies that the test drug has healing effect at higher dose level and only as a curative agent. It means the drug cannot be used as a prophylactic measure but can be used in treating the ulcers when they are formed. The result is in conformity with the other reports suggesting that Unani drugs frequently fail to induce the desirable response at the lower doses that have been recommended in Unani literature. However when the dose is increased the desirable response is achieved (Amin, 1998). It suggests that the dose of test drug should be increased to treat the PUD.

Non-steroidal anti-inflammatory drugs (NSAIDs) like aspirin are known to induce gastric ulceration, the reason being attributed principally to the inhibition of biosynthesis of cytoprotective prostaglandins, resulting in overproduction of leukotrienes and other products of 5-lipoxygenase pathway (Ranisford, 1987). It has been proposed that aspirin induces gastric ulcers by disrupting

the gastric mucosal barrier resulting in the back-diffusion of acid (Davenport, 1967). It is a potent irreversible prostaglandin biosynthesis inhibitor and causes a dose dependent reduction in mucosal prostaglandins (PGE_2 and PGI_2) biosynthesis accompanied by an increase in the areas of gastric mucosal damage. Further, the injury following the aspirin administration has been associated with the formation of reactive oxygen species that has been reported to accumulate in gastric mucosa and cause oxidative DNA damage (Kang *et al.,* 2007). Gastric mucosal damage caused by aspirin-like drugs has been reported to evolve certain other mechanisms such as the topical irritant effect on epithelium, impairment of mucosal barrier function, reduction of gastric mucosal blood flow and interference with the repair of the superficial injury. It appears therefore that the test drug probably evolved more than one mechanism to produce anti ulcer effect against aspirin induced mucosal damage. However, since it was found to be effective as curative agent and did not show any response as a protective agent, therefore it is likely that the anti ulcer effect was mediated through the curative mechanisms. Since the constituents found in coriander have been demonstrated to possess anti-oxidant property (Ammar *et al.,* 1997) therefore its effectiveness may at least partially be associated with its anti-oxidant activity. Secondly, in Unani literature it has been described to possess healing effect (Hakeem, 2002) therefore the improvement in ulcer is also likely to be associated with healing property of the test drug. Cytoprotection is mainly induced by the release of prostaglandins. Coriander has a number of fatty acids and flavonoids, which are the sources of prostaglandins thus the cytoprotective role of the test drug is also likely. Other studies on coriander demonstrating cytoprotective and anti-oxidant effect in it (Satyanarayana *et al.,* 2003) further strengthen our proposition regarding the cytoprotective effect of the test drug. The overall effect of the test drug is in consonance with another report that demonstrated that the oral administration of the coriander powder produced dose dependant effect against the ulcers induced by the ethanol and pylorus ligation (Al-Mofleh *et al.,* 2006).

In Unani literature the causes of gastric ulcer have been described to be *khilte haad* (hot and irritant humour), *fuzlat* (waste products), intake of hot and spicy foods, excessive use of alcohol, stress and strain, chronic gastritis and indigestion (Arzani, 2003; Ibn Hubal, 2004;Ibn Sina, 2007). The temperament of coriander is cold and dry in second degree (Ghani, ynm) so it is quite possible that it helps neutralize the *khilte haad* which has opposite temperament and the cold temperament may have arrested the secretion of corrosive *fuzlat*. Coriander has also been mentioned to possess *qabiz* (astringent), *musakkin* (sedative), *munawwim* (hypnotic), *muhallil* (resolvent)

and *munaqqi* (cathartic) properties (Ibn Sina, 2007; Ibn Baitar, 2003; Ibn Hubal, 2004). These effects may have a role in improving the gastric lesions either through the mediation of nervous system or by producing local effect of neutralization, healing and cytoprotection. Unani scholars have also mentioned it to be useful in various gastric disorders like *sue mizaj meda* (altered temperament of stomach), *wajae meda* (gastralgia), *zofe hazam* (oligopepsia), *sue hazam* (indigestion), *tukhma* (food poisoning) and *qurooh wa busoor meda* (gastric ulcers); all these conditions are associated with making the mucosal defense system weak (Arzani, 2003; Ibn Sina, 2007). Therefore, it may be assumed that coriander plays important role in improving the mucosal defense system. Some important constituents found in coriander have been reported to produce pharmacological effects that are responsible to improve the gastric lesions. The findings of the present study and the reports available on coriander and its various constituents suggest that it produces effect by evolving diverse mechanisms such as by reducing the stress, inducing cytoprotection, minimizing or neutralizing the acid secretion and by healing and anti-oxidant activity.

On the basis of above findings and discussion it can be concluded that coriander possesses significant anti-ulcer activity against aspirin induced gastric ulcers.

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