Anti-ulcer Effect of Cinnamon and Chamomile Aqueous Extracts in Rat Models

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Abstract: Peptic ulcer disease is a problem of the gastrointestinal tract. Nowadays, drugs are expensive and have many side effects during treatment of any disorders. Therefore, our study aimed to investigate and compare antiulcer effect of cinnamon and chamomile aqueous extracts at doses of 100, 200, 300, 400mg/kg of body weight (b.wt) with antiulcer drug (Zantac ™ Ranitidine). Fifty male rats weighing 160±5g were distributed into ten groups. Group I serves as a positive group. Group II serves as control group (treated with drug). Groups III, IV, V and VI were administered orally the different doses of cinnamon aqueous extract (CIAE). Groups VII, VIII, IX and X were administered orally the different doses of chamomile aqueous extract (CHAE). Values of pH and volume of gastric juice, ulcer area and curative ratio were estimated as well as histopathological examination of stomach. Results revealed that treatment with Zantac and CIAE or CHAE was associated with significant increase in pH values compared to the respective value of the positive group. CHAE was superior to that of CIAE. Oral administration of CIAE or CHAE was associated with significant reduction in the volume of gastric juice compared to positive and control groups. A curative ratio of gastric ulcer was better in rats given CIAE or CHAE over those given Zantac. Furthermore, CHAE was superior over CIAE in its curative ratios of gastric ulcer. Histological study showed necrosis of gastric mucosa associated with congestion of submucosal blood vessels, submucosal edema and hemorrhage in the stomachs of positive rats. The stomachs of group receiving Zantac showed necrosis of gastric mucosa associated with hemorrhage. Whereas, higher dosages of CIAE (300 or 400 mg/kg of b. wt and CHAE dosages i.e., 200, 300 or 400 mg/kg of b.wt were efficient to arrest histopathological changes in the stomachs. In conclusion: results revealed that CHAE and CHAE had potential antiulcer effect, which was superior to the respective effect observed with Zantac. Chamomile extracts were more superior to cinnamon in its protection of the stomach. The antiulcer effect was dose dependent with no adverse effects. [Journal of American Science. 2010;6(12):209-216]. (ISSN: 1545-1003).

Keywords: Chamomile- Cinnamon-Peptic ulcer.

1- Introduction

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 generally, it occurs in the lower esophagus, the distal duodenum, or the jejunum, as in unopposed hypersecretory states such as Zollinger-Ellison syndrome, in hiatus hernias, or in ectopic gastric mucosa (Kalyanakrishnan and Robert, 2007). Some of the causes of these disorders are stress, smoking, nutritional deficiencies and ingestion of non-steroidal anti-inflammatory drugs (Nash et al., 1994; Basil and Howard, 1995). The pathogenesis of gastroduodenal ulcers are influenced by various aggressive and defensive factors, such as acid-pepsin secretion, mucosal barrier, mucus secretion, blood flow, cellular regeneration and endogenous protective agents (prostaglandins and epidermal growth factor) (Salas, 1990).

Nowadays, drugs are expensive and have many side effects during treatment of any disorders. Therefore, the potential of the health promoting and disease preventing properties of plant-derived compounds has received increased attention from researchers in recent years. Plants that have medicinal properties are used to improve symptoms or prevent diseases such as diarrhea, stomach disorder, asthma, hypertension, coughs and other respiratory ailments and urinary tract infections etc.

Cinnamon is a native of Southern Asia and South America. Now it is cultivated in many tropical countries such as China, India, Brazil, Madagascar, Mexico and the Caribbean. Cinnamon (*Cinnamomum cassia*) of the family *Lauracease* is a favorite spice around the world because of its health benefits, flavors and preserves food (Chaudhry and Tariq, 2006). The most favorite chemical constituents of cinnamon are volatile oil (cinnamaldehyde, eugenol, cinnamic acid, and weitherhin), mucilage, diterpenes and proanthocyanidins (Jayaprakasha et al., 2002). Cinnamon possess chemopreventive, antispasmodic, sedative, hypothermic, choleretic, antibacterial, antifungal, antipyretic, antiviral, antiplatelet properties, antiseptic, lipolytic, anesthetic, cytotoxic, anodyne, hypolipidemic, and also stimulate immune system that may be useful adjuncts in helping to reduce the risk of cardiovascular disease and cancer (Cralg, 1999). Medicinally, it is used in the treatment of colic, colds, low vitality, poor appetite, rheumatism, kidney weakness and coldness, fevers,

arthritic angina, and palpitations. It is also used in stimulate of the circulatory system and capillary circulation, spasms, vomiting, controls infections and digestive or stomach complaints related to cold and chills. Cinnamon bark have a potentiating effect on insulin (Khan et al., 1990) and can be useful in the treatment of type 2 diabetes; as well as lowering triglyceride levels and serum cholesterol (Onderoglu et al., 1999; Broadhurst et al., 2000; Khan et al., 2003). Water-based extracts of cinnamon bark might bind endotoxin, thereby protecting against endotoxin-induced organ damage (Azumi et al., 1997), has anti-bacterial effects, clinical trials against *Helicobacter pylori*, associated with gastric ulcer (Martin and Ernst, 2003) and improve symptoms associated with the metabolic syndrome in rodents and humans metabolism and lipid profile (Khan et al., 2003; Kannappan et al., 2006).

Chamomile is one of the most widely used as medicinal plants. It has been included in the pharmacopoeia of 26 countries. Amino acids, polysaccharides, fatty acids, essential oils, mineral elements, flavonoids, and other phenolic compounds are the main constituents of chamomile (McKay and Blumberg, 2006). Chamomile used in modern medicine primarily for their spasmolytic, antiphlogistic, antibacterial properties, and as a multipurpose digestive to treat gastrointestinal disturbances including flatulence, indigestion, diarrhea, anorexia, motion sickness, nausea, and vomiting (Shikov et al., 2008). German chamomile (*Matricaria chamomilla*) is also used to healing wound (Glowania et al., 1997), treat various diseases including diarrhea (de la Motte et al., 1997), and inflammation, cancer (Hernández-Ceruelos et al., 2002). Its extract blocks aggregation of *Helicobacter pylori* and various strains of *Escherichia coli* (Annuk et al., 1999). Chamazulene, alpha-bisabolol, flavonoids, and umbelliferone display antifungal properties against *Trichophyton mentagrophytes* and *Trichophyton rubrum* (Turi et al., 1997). Apigenin, alpha-bisabolol, and the cisspiroethers appear to provide the most significant antispasmodic effects. Other flavonoids and coumarins contribute to smooth muscle relaxation (Achterrath-Tuckermann et al., 1980). The aim of the present study was to investigate and compare the gastroprotective effect of different doses (100, 200, 300 and 400mg/kg of body weight (b.wt.) of cinnamon or chamomile aqueous extracts with antiulcer drug. pH and volume of gastric juice, ulcer area and curative ratio were estimated and a reliable parameter was presented for comparing the data. Histopathological examination of gastric ulcer was achieved.

2. Materials and Methods

2.1 Materials

2.1.1 Herbs

Cinnamon and chamomile were purchased as crude dried material from a local Company for Medicinal Plants and Herbs, Cairo, Egypt.

2.1.2 Animals

Fifty male albino rats, Sprague Dawley strain weighing 160±5g, were obtained from the Laboratory Animal Colony, Helwan, Egypt.

2.1.3 Drugs

Anti-ulcer agent (Zantac ™ (Ranitidine) was obtained in the form of ampoules from Glaxo Smithkline S.A.E., El-Salam City, Egypt.

2.2 Methods:

2.2.1 Preparation of aqueous extract

The aqueous extracts of cinnamon and chamomile were prepared using 10g dried material/100 ml distilled water and boiling for 5 min at 100°C. Then they were filtrated, concentrated at 50 °C under reduced pressure using a Rota vapor. The extracts were kept at -15 °C until it was used in the experiment (Kassi et al., 2004).

2.2.2 Preparation of basal diet

The basal diet (AIN-93M) (Reeves et al., 1993) was formulated to meet recommended nutrients levels for rats as shown in Table (1).

Table (1): Composition of the modified AIN-93M diet.

Ingredient	Content (g/kg)
Casein	140.0
Corn starch	620.69
Sucrose	100.00
Soybean oil	40.0
Fibers	50.0
Mineral mix.	35.0
Vitamin mix.	10.0
L-Cystine	1·8
Choline chloride	2.5
Tert-Butylhydroquinone	0.008

2.2.3 Experimental design

All Animals were fed on the basal diet and water *ad libitum* and they were maintained under healthy conditions of humidity, temperature (20-25°C) and light (12-h light: 12-h dark cycle) for one week before starting the experimental to acclimatization. After acclimatization period, rats were divided into ten groups of equal weight and number (5 rats each). Group (I): kept as positive group and Group (II): service as control group. These two groups fed on the basal diet and given orally saline at volume of 1.0 ml / 100 g b. wt). Groups (III, IV, V and VI) fed on the basal diet and given orally cinnamon aqueous extract (CIAE) by tube feeding for seven days at a dose of 100, 200, 300 and 400 mg/kg b. wt, respectively. Groups (VII, VIII, IX and X): fed on the basal diet and given orally chamomile aqueous extract (CHAE) by tube feeding for seven days at a dose of 100, 200, 300 and 400 mg/kg b. wt, respectively.

At the last day of experimental period (7 days), all rats were starved of food but not of water for 12

hours according to ethanol-induced gastric ulcer protocols. After fasting period, group II (control group) was given (I/P) intraperioteneally Zantac (ranitidine) at a dose 6 mg/100 of body weight, 60 min prior administered ethanol. Groups (I and II) were given orally saline and the other eight groups were given CIAE or CHAE, 120 min prior administered ethanol (Jafri et al., 2001). Then ethanol was administered orally to all groups at 0.5 ml/100g (Hollander et al., 1985).

2.2.4 Gastric ulcer index

The method described by Agrawal et al., (2000) was employed in the present study. In briefly, after 4 hours of administrated ethanol, all rats were sacrificed after using an overdose of diethyl ether and their stomachs removed and washed by saline. The gastric juice was collected in test tube. Then stomachs opened along the greater curvature, washed with saline and examined under dissecting microscope for gastric ulcers. The sum of length for all lesions area for each animal was measured and served as the ulcer index. The curative ratio was calculated for each group using following equation:

Curative ratio (CR) = (LC-LT/LC) x100

LC: The length of gastric ulcer in positive group.

LT: The length of gastric ulcer in treated group.

2.2.5 Determination of gastric juice acidity

Acidity degree (pH) of gastric juice was determined by using pH meter apparatus (HI 9021).

2.2.6 Determination of gastric juice volume

Gastric juices were centrifuged at 500 rpm for 5 minutes, then separated and measured volume by graduated cylinder.

2.2.7 Histopathological examination

The stomachs of the scarified rats were taken and immersed in 10% formalin solution. The fixed specimens were then trimmed, washed and dehydrated in ascending grades of alcohol. Specimens were then cleared in xylol, embedded in paraffin, sectioned at 4-6 microns thickness and stained with Heamtoxylin and Eosin stain for examination of the stomach as described by Carleton, (1979).

2.2.8 Statistical analysis

The obtained results were expressed as Mean ± SE. Data were evaluated statistically using one-way analysis of variance (ANOVA). Significant difference between means was estimated at $p<0.05$ (STATSOFT, 2006).

3. Results

3. 1 pH of gastric juice

Values of pH in rats treated with antiulcer drug and oral administration of CIAE and CHAE at different doses is recorded in Table (2). Results demonstrated that control group given I/P antiulcer drug and groups given orally different doses of CIAE or CHAE (100, 200, 300 or 400mg/kg b.wt) had significant increase in pH value of gastric juice at $p<0.05$ as compared to positive group.

In rats given orally CIAE at doses of 200, 300 and 400mg/kg b.wt, pH values of gastric juice as mean±SE were 7.90±0.19, 8.40±0.37 and 8.60±0.19, respectively and showed significant increase as compared to control group and those given orally 100mg/kg of b. wt CIAE (5.80±0.46 and 6.50±0.45 respectively). In contrast, groups given orally the different doses (100, 200, 300 and 400mg/kg of b.wt.) of CHAE had significant increase in pH values of gastric juice (7.80±0.26, 8.20±0.12, 8.40±0.25 and 8.66±0.19, respectively) compared to control group given I/P anti ulcer drug (5.80±0.46).

The increase in pH values of gastric juice of treated rats with extract was more detectable with increasing the dose. Results revealed that different doses of CHAE caused increase in mean ± SE of pH values than that the similar doses of CIAE.

Table (2): Effect of antiulcer drug and oral administration of CIAE and CHAE on pH value of gastric juice in rats.

Groups		Parameter as Mean ± SE pH of gastric juice	
		Cinnamon	Chamomile
Positive group		c 4.70±0.26	c 4.70±0.26
Control group		b 5.80±0.46	b 5.80±0.46
Treated groups with aqueous extracts at a doses of:	100mg/kg b. wt	b 6.50±0.45	a 7.80±0.26
	200mg/kg b. wt	a 7.90±0.19	a 8.20±0.12
	300mg/kg b. wt	a 8.40±0.37	a 8.40±0.25
	400mg/kg b. wt	a 8.60±0.19	a 8.66±0.19

Different superscript letters in the same column denotes significant differences at $p<0.05$.

3.2 Volume of gastric juice

Volume of gastric juice (cm^3) in rats treated antiulcer drug and oral administration of CIAE and CHAE at different doses is shown in Table (3). Data was obvious that volume of gastric juice (cm^3) as mean±SE of group given I/P antiulcer drug (control group) was not significant decrease (4.30±0.37) at $p<0.05$ as compared to positive group (4.60±0.52). Rats given orally different doses of CIAE or CHAE had significant decrease in volume of gastric juice compared to positive and control rats. Rats given orally CIAE at a dose of 100mg/kg of b.wt. had a significant increase in volume of gastric juice as compared to rats given extracts at doses of 200, 300 and 400mg/kg of b.wt.

Aqueous extract of chamomile at a dose of 400 mg/kg of b.wt caused significant decrease in volume of gastric juice as compared to a dose of 100 mg/kg of b.wt, and there was not significant decrease as compared to treated groups with doses of 200 and 300mg/kg of b.wt. There were not significant differences in volume of gastric juice among groups treated with CHAE at doses of 100, 200 and 300 mg/kg of b.wt.

Tabulated data showed that groups treated with CHAE had the lower volume of gastric juice as mean ± SE (cm^3) compared to those treated with CIAE.

Table (3): Effect of antiulcer drug and oral administration of CIAE and CHAE on the volume of gastric juice (cm^3) in rats.

Groups		Parameter as Mean ± SE	
		Volume of gastric juice (cm^3)	
		Cinnamon	Chamomile
Positive group		a 4.60±0.52	a 4.60±0.52
Control group		a 4.30±0.37	a 4.30±0.37
Treated groups with aqueous extracts at a doses of:	100mg/kg b. wt	b 2.90±0.19	b 2.50±0.16
	200mg/kg b. wt	c 2.00±0.16	bc 1.90±0.19
	300mg/kg b. wt	c 1.70±0.20	bc 1.70±0.12
	400mg/kg b. wt	c 1.60±0.19	c 1.50±0.16

Different superscript letters in the same column denotes significant differences at $p<0.05$.

3.3 Length of gastric ulcer

The length of gastric ulcer (mm) in rats as result of antiulcer drug and oral administration of CIAE or CHAE effect is recorded in Table (4). Tabulated results revealed that the length of gastric ulcer (mm) as mean±SE of treated group with antiulcer drug (control group) was significant decrease (5.90±0.60) at $p<0.05$ compared to untreated group (positive group) (7.40±0.87). Groups given orally different doses of CIAE or CHAE (100, 200, 300 and 400 mg/kg of b.wt) had significant decrease in the length of gastric ulcer at $p<0.05$ as compared to positive and control groups.

Aqueous extract of cinnamon at a dose of 400 mg/kg of b.wt caused significant decrease in the length of gastric ulcer as compared to a dose of 100 mg/kg of b.wt, while there was not significant decrease as compared to doses of 200 and 300 mg/kg of b.wt.

The differences in the length of gastric ulcer in rats given orally CHAE were not significant.

Groups given orally CHAE at different doses had the lower mean±SE values in length of gastric ulcer (mm) as compared to those given orally similar doses of CIAE. The decreases in the length of gastric ulcer (mm) were more detectable with increased doses of CIAE and CHAE.

Table (4): Effect of antiulcer drug and oral administration of CIAE and CHAE on the length of gastric ulcer (mm) in rats.

Groups		Parameter as Mean ± SE	
		Length of gastric ulcer (mm)	
		Cinnamon	Chamomile
Positive group		a 7.40±0.87	a 7.40±0.87
Control group		b 5.90±0.60	b 5.90±0.60
Treated groups with aqueous extracts at a doses of:	100mg/kg b. wt	c 3.20±0.54	c 1.80±0.52
	200mg/kg b. wt	d 1.50±0.16	c 0.88±0.20
	300mg/kg b. wt	d 0.92±0.12	c 0.52±0.01
	400mg/kg b. wt	d 0.70±0.12	c 0.42±0.14

Different superscript letters in the same column denotes significant differences at $p<0.05$.

3.4 Curative ratio

Effect of antiulcer drug and oral administration of CIAE and CHAE at different doses on curative ratio of peptic ulcer in rats is showed in Figure (1). Mean of curative ratio of groups given orally different doses of CIAE or CHAE was higher than that of treated groups with antiulcer drug. Groups treated with CHAE at doses of 100, 200, 300 and 400mg/kg of b.wt had higher mean values of curative ratio (75.68, 88.11, 92.97 and 94.32, respectively) compared to those given orally similar doses of CIAE (56.76, 79.73, 87.57 and 90.54, respectively).

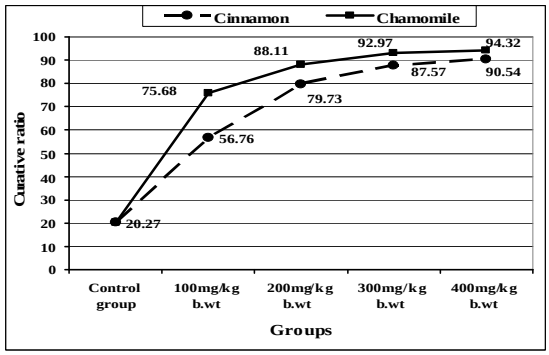

Figure (1): Effect of antiulcer drug and oral administration of CIAE and CHAE on curative ratio of gastric ulcer in rats.

3.5 Histopathological results

Microscopically, stomachs of rats from the positive group showed necrosis of gastric mucosa associated with congestion of submucosal blood

vesselsm, submucosal edema and hemorrhage (Figure 2). Examined stomachs of rats from control group (treated with anti-ulcer drug) revealed necrosis of gastric mucosa associated with hemorrhage as showed in Figure (3).

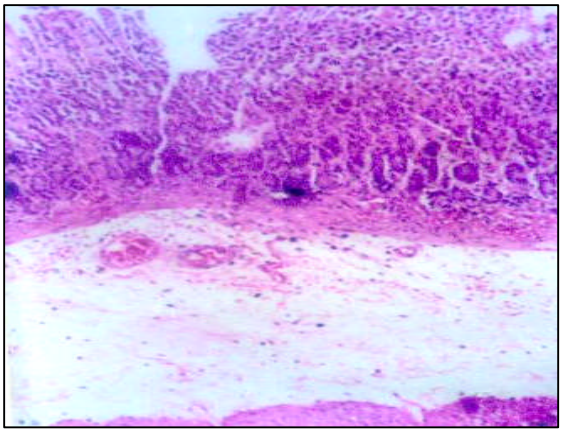

Figure (2): Stomach of positive rat showing necrosis of gastric mucosa, congestion of submucosal blood vessels associated with submucosal edema and hemorrhage (H and E x 100).

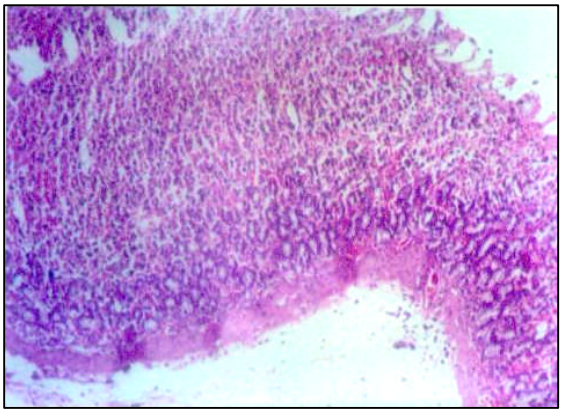

Figure (3): Stomach of control rats showing marked necrosis of gastric mucosa associated with hemorrhage (H and E x 100).

Examined stomachs of rats treated with CIAE at a dose of 100mg/kg of b.wt revealed atrophy of gastric mucosa associated with submucosal edema as showed in Figure (4). Moreover, stomachs of rats from given orally 200mg/kg of b.wt of CIAE showed congestion of submucosal blood vessels associated with edema (Figure 5). Meanwhile, stomachs of rats treated with extract at doses of 300 and 400mg/kg of b.wt showed no histopathological changes (Figure 6).

With regard to the effect of CHAE, histopathological results showed that rats treated with of extract at a dose of 100mg/kg of b.wt showed submucosal leucocytic cells infiltration (Figure 7). Examined sections from treated groups with extracts at doses of 200, 300 and 400mg/kg of b.wt revealed no histopathological changes as showed in Figure (8).

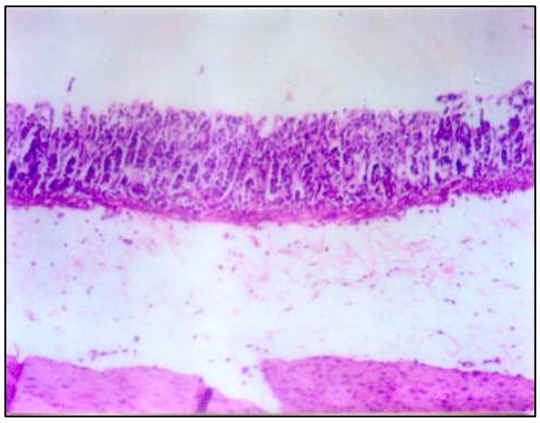

Figure (4): Stomach of rats given orally CIAE at a dose of 100mg/kg of b.wt showing atrophy of gastric mucosa associated with submucosal edema (H and E x 100).

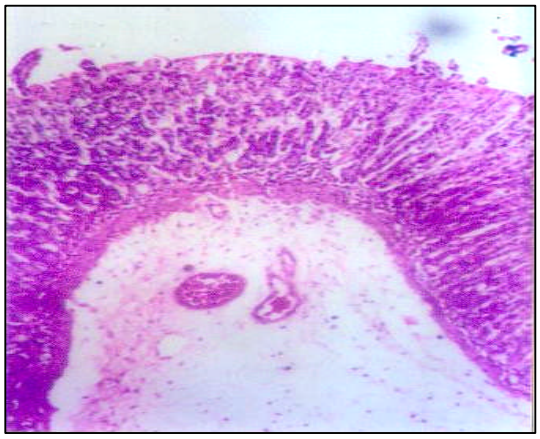

Figure (5): Stomach of rats given orally CIAE a dose of 200mg/kg of b.wt showing congestion of submucosal blood vessels associated with edema (H and E x 100).

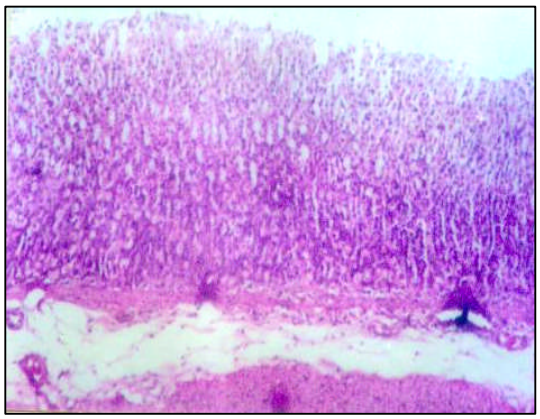

Figure (6): Stomach of rats given orally CIAE at doses of 300 and 400mg/kg of b.wt showing no histological changes (H and E x 100).

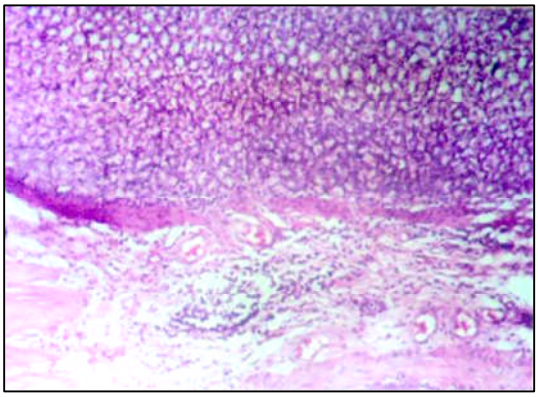

Figure (7): Stomach of rats given orally CHAE at a dose of 100 mg/kg of b.wt showing submucosal leucocytic cells infiltration (H and E x 100).

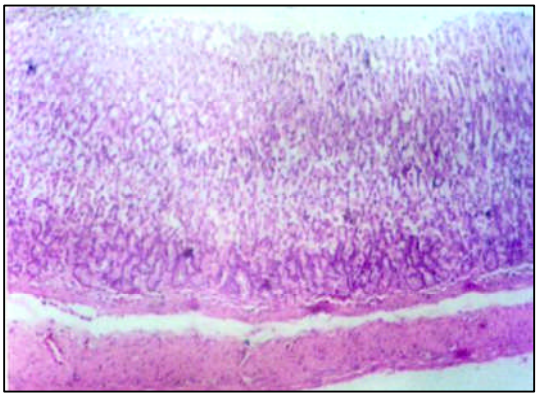

Figure (8): Stomach of rat given orally CHAE at doses of 200, 300 and 400mg/kg of b.wt showing no histological changes (H and E x 100).

4. Discussion

The aim of the present study was to investigate the antiulcer effect of cinnamon and chamomile aqueous extracts and compare them with antiulcer drug as a reference of antiulcer. Our finding showed that cinnamon and chamomile aqueous extracts at the different tested doses (100, 200, 300 and 400 mg/kg of b.wt) had gastroprotective effects on acute experimental gastric ulcer in rats. Antiulcer effect of cinnamon and chamomile aqueous extracts was higher than that of antiulcer drug. Aqueous extract chamomile had much more favorable antiulcer effect, compared to aqueous extract of cinnamon.

Peptic ulcer disease is a problem of the gastrointestinal tract characterized by mucosal damage secondary to pepsin and gastric acid secretion (Kalyanakrishnan and Robert, 2007). Therefore, the major mechanism action of cinnamon or chamomile aqueous extracts as anti-ulcer appears may be due to its effect in the decrease of acid-pepsin secretion and volume of gastric juice, and the promotion of mucosal protection by gastric mucin activity.

In the present study the antiulcer properties of cinnamon, agreed with Akira et al., (1986) who reported that CIAE inhibits gastric secretion and promotes gastric mucosal blood flow. These results confirmed by Tanaka et al., (1989) who demonstrated that cinnamon extract had 3-(2-hydroxyphenyl)-propanoic acid and its O-glucoside that prevent serotonin-induced ulcerogenesis in rats. It inhibits gastric ulcers induced by the ulcerogens such as ethanol, phenylbutazone, and water immersion stress, although it failed to prevent indomethacin-induced ulcers. 3-(2-hydroxyphenyl)-propanoic acid inhibits the secretion of gastric acid and promoted the gastric blood flow. Therefore, the antiulcerogenic effect of this compound is due to the potentiation of defensive factors through the improvement of the circulatory disorder and gastric cytoprotection. Zhu et al., (1993) revealed that water and ether extract of cinnamon had antiulcer effect on four types of experimental gastric ulcer. Aguilar, (1999); Cralg, (1999) also, reported that cinnamon used in the medicine for the treatment of gastric ulcer and digestive or stomach complaints. Recent research demonstrated that cinnamon extract decreased the level of prostaglandin that is associated with gastric ulcers (Jonathan et al., 2008).

On the other hand, the anti-spasmodic and anti-peptic actions of chamomile extract may be due to chamomile flavonoid constituents, apigenin (Achterrath-Tuckermann et al., 1980). In addition to, similar results were observed with alpha-bisabolol and the cis-spiroethers and the small amount of coumarins contribute to smooth muscle relaxation (Holzl et al., 1986). The antiulcer effect of chamomile extract agreed with Mann and Staba, (1986) who reported that chamomile had anti-inflammatory and spasmolytic effects on the stomach and duodenum. Therefore, it is thought to heal ulcers. Previous study reported that chamomile flower extract has a complex effect on the luminal and mucosal environment of the stomach and duodenum. Some of these actions are important in healing the ulcers and others are important in preventing subsequent ulcer relapse. Chamomile flower extract has a direct effect on acid secretion, and increases mucosal resistance against damaging agents such as ethanol and aspirin (Rees, 1992). Recent research revealed that CHAE, singly or combined with other plants have antiulcerogenic activity (Khayyal et al., 2001). Ramos-e-Silva et al., (2006) reported that CHAE had analgesic effect in oral aphtus ulcer.

The anti ulcer action of CHAE may be related to a variety of mineral elements including manganese and magnesium and 1-2% volatile oils including α-bisabolol, α- bisabolol oxides A and B, matricine presented in the chamomile flowers (McKay and Blumberg, 2006). Hwang et al., (2008) demonstrated that chamomilla extract contains many components that may exert antiulcer effects. Phenolic and flavonoids compounds, apigenin, quercetin,

patuletin, luteolin and their glycosides are the major flavonoids present in the flower. The presence of large amounts of cinnamic acid derivatives, frolic and caffeic acid and all of the constituents, may have therapeutic effects. Polysaccharides, amino acids and fatty acids are some of its constituents. Recently, Karbalay-Doust and Noorafshan, (2009) revealed that oral administration of chamomile extract at 400 mg/kg can be effective in preventing gastric ulceration in mice and does not produce toxic effects in doses up to 5000 mg/kg confirmed these results.

5. Conclusion

The present finding concluded that water extracts of cinnamon and chamomile had potential antiulcer effect, which was superior to the respective effect observed with Zantac. Chamomile extracts were more superior to cinnamon in its protection of the stomach. The antiulcer curative ratios were dose dependent with no adverse effects.

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