Protective Effect of Ginger and Cinnamon Aqueous Extracts Against Aspirin-Induced Peptic Ulcer

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Abstract: The present study was carried out to investigate the gastro-protective effect of aqueous extracts of ginger, cinnamon and their combination, on gastric acid secretion and healing of acute gastric ulcer induced by aspirin in male rats in doses of 100 and 200mg/kg after 2 weeks of prevention on oxidative stress markers and biomarkers of gastric ulcer (gastric ulcer index, gastric juice acidity, gastric juice volume). As well as histopathological examination of stomach was also performed. Fifty six adult male Wister rats were divided into seven equal groups as follows: Group 1: negative control group, Group 2: positive control group, Groups 3, 4, 5 and 6 were orally given ginger and cinnamon aqueous extracts in doses of 100 and 200 mg/kg b.wt, respectively, Group 7: orally given the combination of ginger and cinnamon in a dose of 200 mg/kg b.wt. At the end of the experimental period all groups were given aspirin 200 mg/kg b. wt., to induce peptic ulcer, except group 1. The results showed that oral administration of ginger, cinnamon aqueous extracts and their combination for 2 weeks significantly improved gastric juice volume, decreased the gastric juice acidity and gastric ulcer index in depended manner, oxidative stress markers were significantly improved as compared to the control positive group. Histopathological examination of the stomach showed alleviation of histological degeneration changes caused by aspirin. It could be concluded that oral administration of ginger and cinnamon aqueous extracts and their combination may be useful in the management of gastric ulcer. The study recommended that, intake of ginger and cinnamon aqueous extracts and their combination may be beneficial for patients suffering from acute gastric ulcer.

Key words: Ginger - Cinnamon - Gastric ulcer - Aspirin - Antioxidant enzymes - Rats

INTRODUCTION

Peptic ulcer disease (PUD) as "a group of disorders characterized by the presence of ulcers in any portion of the gastrointestinal tract exposed to acid in sufficient and concentration"[1]. The ulcer relapses and inflames a precise definition that defines the endoscopic characteristics and criteria could not be accurate for the ulcer relapse, healing and remission [2]. Peptic ulcer affects approximately 5-10% of the people during their life [3]. Chronic gastritis is likely to underlie H. pylori-related diseases. The main common reason for most ulcers is recognized infection of H. pylori bacteria [4]. The second basic reason of ulcers is the long-term uses of anti-inflammatory drugs (non-steroidal) such as aspirin [4]. There are other factors such as some types of food that consumed by the patient can have influence in peptic ulcer such as spicy food, fatty food, or food containing caffeine which stimulated acid secretion in the stomach [5] and also stress and smoking play an important role in the incidence of peptic ulcer [6]. Aspirin is a potent non-steroidal anti-inflammatory drug NSAID that is used for the treatment of some diseases such as rheumatoid arthritis as well as the prevention of cardiovascular diseases. The use of aspirin is a major problem for peptic ulcer disease because it increases gastric acid and pepsin secretions, gastric microcirculation and prostaglandin E2, PGE2 content [7]. The usage of herbal drugs for the prevention and treatment of various diseases is constantly developing throughout the world. Ginger, the rhizome of Zingiber officinale has a long history of medicinal use dating back 2500 years [8]. Ginger is also used as a home remedy and is of immense value in treating various gastric ailments like constipation, dyspepsia, belching, bloating, gastritis, epigastric discomfort, gastric ulcerations, indigestion, nausea and
vomiting and scientific studies have validated the ethnomedical uses [9]. There are three main active ingredients in ginger that gives ginger its unique properties. These chemical constituents are gingerol, shogaol and zingerone [10]. Cinnamon is an ancient and important spice with wide applications in flavoring, perfumery, beverages and medicines [11]. Cinnamon used for many diseases and it has also effects as an antioxidant, anti-inflammatory, antispasmodic and anti-ulcerative [12]. Therefore, this study was designed to investigate the effect of ginger and cinnamon against aspirin-induced gastric ulcer in male rats.

MATERIALS AND METHODS

Material

Plant Material: Ginger (Zingiber officinale Roscoe) and cinnamon (Cinnamomum zeylanicum Nees; Lauracea) were purchased as crude dried materials from a local market from Jeddah, Saudi Arabia.

Aspirin (Acetyl salicylic acid, Aspegic): Aspirin (aspirin adult tab 500 mg) was purchased from local pharmacy (Jeddah, Saudi Arabia) manufacture by (Bayer Schering Pharma AG, Germany).

Solvent and Chemical Reagent: Distilled water was supplied from (distilled unit, PURELAB Ultra, USA); Saline solution was purchased (Pharmaceutical Solutions Industry, Jeddah); Carboxy methylcellulose (1%), Diethyl ether and Neutral buffered formalin (10%) were obtained from (Sigma-Aldrich, Poole, UK).

Kits for Biochemical Analysis: Assay kits were required for estimating Glutathione Peroxidase (GPx 703102), Superoxide Dismutase (SOD 706002), Catalase (CAT 707002), TBARS-TCA Method (MDA700870). Parameters used in the study, were supplied by Cayman Chemicals and Bio Vision Incorporated, USA.

Methods

Determination of Antioxidant Activity of Ginger and Cinnamon

Free Radical Scavenging Activity: The free radical scavenging activity of extracts was measured by 1, 1-diphenyl-2-picryl-hydrazil DPPH using the method of Shimada et al.[13]. All plant extracts were screened at 100 µg/ml, while the most potent active extracts (gave more 90 %) were assayed at 25-75µg/ml. Briefly, 0.1mM solution of DPPH in methanol was prepared. Then, 1 ml of this solution was added to 3 ml of extract solution at different concentrations (25-75µg/ml). The mixture was shaken vigorously and allowed to stand at room temperature for 30 min. Then the absorbance was measured at 517 nm in assays micro plate reader. Lower absorbance of the reaction mixture indicated higher free radical scavenging activity:

\[
\text{DPPH scavenging effect (\%) = 100 - \frac{(A0-A1)}{A0} \times 100}
\]

Where: A0 was the absorbance of the control reaction and A1 was the absorbance in the presence of the sample [14].

Determination of the Phenolic Compounds of Ginger and Cinnamon: Total phenolics concentration was analyzed using the method described by Singleton and Rossi [15] with modifications. The acetone extract or standard (0.1 ml) was mixed with 1ml of DDW and 0.1 ml of Fc reagent. After allowing the solution to react for approximately 6 min, 0.8 ml of 75gl Na2CO3 was added. The solution was placed in the dark for 90 min at room temperature to allow for colour development, then the absorbance at 760 nm was read against the reagent blank. Gallic acid was used as a standard at 0-300 mg ml⁻¹ [15].

Determination of Total Flavonoids of Ginger and Cinnamon: Total flavonoids concentration was quantified using the spectrophotometric method described by Jia et al. [16]. Acetone extract (0.25 ml), 1 ml of distilled deionized water (DDW) and 0.075 ml of 50 gl NaNO2 were combined and vortexed for 5 min. Next, 0.15 ml of 100 gl AlCl3 was added to the solution. The solution was left to stand for 6 min, after which 0.5 ml of 1 mol L⁻¹ NaOH and 0.5 ml of DDW were added. The solution was centrifuged (3220 g for 5 min at room temperature) to void the precipitate and the absorbance at 510 nm was measured against the reagent blank. Each sample and standard was run in duplicate. Total flavonoid concentration was expressed as mg catechin equivalent (CE)g⁻¹ sample. Catechin was used as a standard at 5-250 mg ml⁻¹ to produce a calibration curve (average R²=0.9996).

Preparation of Aqueous Extract: The aqueous extracts of ginger and cinnamon were prepared by using (10 g) of dried material dissolved in (100 ml) distilled water then vortex for (2 min) and boiled for (5 min) at (100°C). The extracts were filtrated by gauze, then by filter paper (20im-25 mm). The extracts were used freshly every three
days and stored at (-15°C) [17]. Rotary evaporator was used to concentration the extracts at temperature (50°C) under pressure.

**Experimental Animals:** A total of n (56) Wistar male rats (8 weeks) old, weighing between (175-185g), were purchased from the Experimental Animal Unit of King Fahd Medical Research Center, King Abdulaziz University, Jeddah, Saudi Arabia.

**Feeding of Rats:** All rats were fed on commercial rat pellets obtained from Grain Silos and Flour Mills Organization, Jeddah, KSA. These pellets consisted of crude protein (20 %), fat (4%), crude fibers (3.5%), ash (0.6%), calcium (1%), phosphorus (0.6%), other salts (0.5%), vitamin A (20 IU/g), vitamin D (2.2 IU/g) and vitamin E (70 IU/g). These constituents were thoroughly mixed and commercially manufactured in the form of pellets.

**Experimental Design:** Fifty six rats, 8 weeks old weighing between 175-185 g. Rats will be kept in a temperature-controlled room at 24±1°C, 50% humidity and 12hrs /12 hrs light/dark cycle. Rats will be adapted to the environment for one week prior to the start of experiment. Animals will be fed on rat pellets and water will be provided *ad libitum* during experimental period (4 weeks). After acclimatization period, rats will be divided into seven groups of equal weight and number (8 rats each):

- **Group (1):** will be kept as negative control group.
- **Group (2):** service as positive control group. These two groups will be fed on the rat pellets and given orally saline at volume of 1.0 ml/100 g b. wt.
- **Groups (3 and 4):** will be fed on rat pellets and given orally ginger aqueous extract by tube feeding for 30 days at doses of 100 and 200 mg/kg b. wt., respectively.
- **Groups (5 and 6):** will be fed on the rat pellets and given orally cinnamon aqueous extract by tube feeding for 30 days at doses of 100 and 200 mg/kg b. wt., respectively.
- **Group (7):** will be fed on rat pellets and orally given ginger and cinnamon combined extracts in a dose of 200 mg/kg b. wt/day each.

At the last day of experimental period (28 days), all rats were starved of food but not of water for 12 hours. Animals of Groups (2), (3), (4), (5), (6) and (7) will be orally given aspirin at a dose of 200 mg/kg b. wt. for induction of acute gastric ulcer according to the method described by Agrawal et al. [18]. Blood will be collected from the retro orbital plexus with capillary tubes for biochemical analysis and then all rats will be sacrificed after 4 hours of administrated aspirin.

**Blood Sample Collection:** At the end of the experimental period (16 day). Blood samples were collected from the retro orbital plexus with capillary tubes, after having the dose of aspirin serum will be separated by centrifuge at (3000 rpm) for (15 min) and serum aliquots will be stored at (–80°C) until biochemical analysis. After (4 hours) of administrated aspirin, all rats were sacrificed after using an overdose of diethyl ether. Stomachs were removed and washed with cold saline solution for histopathological examination.

**Determination of Antioxidant Enzyme Activity:** Activities of antioxidant enzymes such as:

**Glutathione Peroxidase:** Glutathione peroxidase (GPx) catalyzes the reduction of hydroperoxides, including hydrogen peroxides, by reducing glutathione and functions to protect the cell from oxidative damage. The enzyme uses glutathione as the ultimate electron donor to regenerate the reduced form of the selenocysteine [19].

**Superoxide Dismutase:** The assay Kit of SOD used to measure the activity from plasma, serum, tissue homogenates and cell lysates. SOD activity is assessed by measuring the dismutation of superoxide radicals generated by xanthine oxidase and hypoxanthine in a convenient 96 well format [19].

**Catalase:** This enzyme catalyzes the conversion of two molecules of H2O2 to molecular oxygen and two molecules of water (catalytic activity). Catalase Assay Kit utilizes the peroxidatic function of CAT for determination of enzyme activity. The method is based on the reaction of the enzyme with methanol in the presence of an optimal concentration of H2O2. The formaldehyde produced is measured spectrophotometrically with 4-amino-3-hydrazino-5-mercaptop-1, 2, 4-triazole (Purpald) as the chromogen. Oxidation changes from colorless to a purple color [19].

**Malondialdehyde Level:** MDA can be quantified through a controlled reaction with thiobarbituric acid, generating 'Thiobarbituric Acid Reactive Substances' (TBARS). The MDA-TBA adduct formed by the reaction of MDA and
TBA under high temperature (90-100°C) and acidic conditions can be measured either colorimetrically at (530-540 nm) or with much higher sensitivity fluorometrically at an excitation wavelength of (530 nm) and an emission wavelength of (550 nm) [19].

**Biomarkers of Gastric Ulcer:** Determination both of gastric juice acidity and volume, then stomachs open to measure gastric ulcer index.

**Gastric Ulcer Index:** The method described by Agrawal *et al.* [18] was employed in the present study. In brief, after 4 hours of administrated aspirin, all rats were sacrificed after using an overdose of diethyl ether and their stomachs removed and washed with saline. The gastric juice was collected in a 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 lesion areas for each animal was measured and served as the ulcer index. The curative ratio was calculated for each group using the following equation:

$$\text{Curative ratio (CR)} = (\text{LC} - \text{LT}) / \text{LC} \times 100$$

Where:
LC: The length of gastric ulcer in positive group.
LT: The length of gastric ulcer in treated group

**Determination of Gastric Juice Acidity:** The total acidity was determined according to the method described in A.O.A.C. [20]. Percentages of the decrease in total acidity of gastric juice of the treated group compared to the positive (C+Ve) control group were calculated using the following equation:

$$\text{Percentage of the decrease} = \frac{\text{TAC} - \text{TAT}}{\text{TAC}} \times 100$$

Where:
TAC = Total acidity of gastric juice of the positive control group.
TAT = Total acidity of gastric juice of the treated group.

**Determination of Gastric Juice Volume:** Gastric juices from all groups were collected in test tubes, centrifuged at 5000 rpm for 10 minutes and their volume of were measured by a graduated cylinder. Percentages of the decrease in volume of the gastric juice of the treated groups compared to the positive(C+Ve) control group were calculated according to the method described by Agrawal *et al.* [18] using the following equation:

$$\% \text{ Percentage of the decrease} = \frac{\text{VJC} - \text{VJT}}{\text{VJC}} \times 100$$

Where:
VJC = Volume of gastric juice of the positive control group.
VJT = Volume of gastric juice of the treated group.

**Histopathological Examination:** Stomach of the rats will be fixed at 10% neutral formalin solution. The fixed specimens were then trimmed, washed and dehydrated in ascending grades of alcohol. These specimens were then colored in xylene, embedded in paraffin, sectioned at 4-6 microns thickness and stained with hematoxylen and eosin (H&E), then examined microscopically according to Carleton [21].

**Statistical Analysis:** All data obtained will be analyzed using Statistical Package for the Social Sciences (SPSS) for Windows, version 20 (SPSS Inc., Chicago, IL, USA). Collected data will be presented as a mean ± standard deviation (SD). Analysis of Variance (ANOVA) test will be used for determining the significances among different groups according to Armitage and Berry [22]. All differences will consider significant if *P*-values were < 0.05.

**RESULTS**

**Determination of Total Antioxidants Activity, Total Phenols and Flavonoids in Aqueous Extract, of Ginger and Cinnamon:** Data presented in Table 1 indicated that aqueous extract of cinnamon contain higher concentration of antioxidant activity, total phenol and total flavonoids than aqueous extract of ginger.

**Effect of Oral Administration of Aqueous Extracts of Ginger (AGE), Cinnamon (ACE) and their Combination on Gastric Ulcer Index in Aspirin-Induced Peptic Ulcer in Rats:** Data presented in Table 2 showed that the mean value of gastric ulcer index in positive control rats was 4.72±1.19 mm compared to zero (no ulcer) in the negative control group (normal rats). Oral administration of AEG 200 mg/kg b. wt., AEC100 and 200 mg/kg b. wt. and their combination (AEG 100 mg/kg b. wt. + AEC100 mg/kg b. wt.), resulted in a significant decrease in gastric ulcer index and an increase in the curative ratio compared to
positive control group. Oral administration of AEG 100 mg/kg b. wt., showed no significant changes in gastric ulcer index when compared with the positive control group. The curative ratios from ulcer were 16, 65, 53.2, 69.7 and 81.4% by using AEG 100 mg/kg b. wt., AEG 200 mg/kg b. wt., AEC 200 mg/kg b. wt. and their combination (AEG 100 mg/kg b. wt., + AEC100 mg/kg b. wt.), respectively.

**Effect of Oral Administration Aqueous Extracts of Ginger (AGE), Cinnamon (ACE) and their Combination on the Volume of Gastric Juice in Aspirin Induced Peptic Ulcer in Rats:** Aqueous extracts of ginger AEG 200 mg/kg b. wt., cinnamon AEC 100 mg/kg b. wt., and the combination of AEG 100 mg/kg b. wt. + AEC100 mg/kg b. wt when orally given to rats with gastric ulcer significantly (P<0.001) decreased the volume of gastric juice by 34%, 58.2%, 67.7% and 74.7%, respectively compared to the positive control group. The highest reduction in TTA of gastric juice was found in the group of rats orally given combined of aqueous extracts of both ginger and cinnamon by 43% compared to positive control group.

**Table 1: Determination of total antioxidant activity, total phenols and total flavonoids in aqueous extract, of ginger and cinnamon.**

<table>
<thead>
<tr>
<th>Sample code</th>
<th>Antioxidant activity test (%)</th>
<th>DPPH scavenging activity</th>
<th>IC₅₀ (µg/ml)</th>
<th>IC₉₀ (µg/ml)</th>
<th>Total phenols (%)</th>
<th>Total flavonoids (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aqueous extract of ginger</td>
<td>23.2% at 100 µg/ml</td>
<td>23.2% at 100 µg/ml</td>
<td>120</td>
<td>86.13</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aqueous extract of cinnamon</td>
<td>60.1% at 100 µg/ml</td>
<td>60.1% at 100 µg/ml</td>
<td>263.6</td>
<td>172.80</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Table 2: Effect of oral administration of aqueous extracts of ginger (AGE), cinnamon (ACE) and their combination on gastric ulcer index in Aspirin-Induced Peptic Ulcer in rats. (n = 8 male rats).**

<table>
<thead>
<tr>
<th>Groups</th>
<th>Index stomach ulcers (mm)</th>
<th>Curative ratio %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1 (Negative control)</td>
<td>0.00±0.00</td>
<td>100</td>
</tr>
<tr>
<td>Group 2 (Positive control)</td>
<td>4.72±1.19</td>
<td>0</td>
</tr>
<tr>
<td>Group 3 (100 mg/kg b. wt/day ginger)</td>
<td>3.96±1.07</td>
<td>16</td>
</tr>
<tr>
<td>Group 4 (200 mg/kg b. wt./day ginger)</td>
<td>1.65±0.65</td>
<td>65</td>
</tr>
<tr>
<td>Group 5 (100 mg/kg b. wt./day cinnamon)</td>
<td>2.21±0.95</td>
<td>53.2</td>
</tr>
<tr>
<td>Group 6 (200 mg/kg b. wt./day cinnamon)</td>
<td>1.43±0.24</td>
<td>69.7</td>
</tr>
<tr>
<td>Group 7 (100 mg/kg b. wt./day ginger + 100 mg/kg b. wt./day cinnamon)</td>
<td>0.88±0.52</td>
<td>81.4</td>
</tr>
</tbody>
</table>

Data are presented as means ± standard deviation, (n = 8 for each group).

Values with different superscripts within the column are significantly different at P< 0.05.

Values with similar or partially similar superscripts are non-significant.
Table 3: Effect of oral administration aqueous extracts of ginger (AGE), cinnamon (ACE) and their combination on the volume of gastric juice in Aspirin Induced Peptic Ulcer in rats. (n= 8 male rats).

<table>
<thead>
<tr>
<th>Groups</th>
<th>Volume of gastric juice (ml)</th>
<th>Decrease %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1 (Negative control)</td>
<td>1.07±0.05^c</td>
<td>0</td>
</tr>
<tr>
<td>Group 2 (Positive control)</td>
<td>3.68±0.45^a</td>
<td>0</td>
</tr>
<tr>
<td>Group 3 (100 mg/kg b. wt./day ginger)</td>
<td>3.16±0.98^a</td>
<td>14.1</td>
</tr>
<tr>
<td>Group 4 (200 mg/kg b. wt. /day ginger)</td>
<td>1.54±0.54^a</td>
<td>58.2</td>
</tr>
<tr>
<td>Group 5 (100 mg/kg b. wt./day cinnamon)</td>
<td>2.43±0.44^a</td>
<td>34</td>
</tr>
<tr>
<td>Group 6 (200 mg/kg b. wt./day cinnamon)</td>
<td>1.19±0.42^a</td>
<td>67.7</td>
</tr>
<tr>
<td>Group 7 (100 mg/kg b. wt./day ginger + 100 mg/kg b. wt./day cinnamon)</td>
<td>0.93±0.27^c</td>
<td>74.7</td>
</tr>
</tbody>
</table>

Data are presented as means ± standard deviation, (n = 8 for each group).

Values with different superscripts within the column are significantly different at P< 0.05.

Values with similar or partially similar superscripts are non-significant.

Table 4: Effect of oral administration of aqueous extracts of ginger (AGE), cinnamon (ACE) and their combination on total acidity of the gastric juice in Aspirin-Induced Peptic Ulcer in rats. (n= 8 male rats).

<table>
<thead>
<tr>
<th>Groups</th>
<th>Total acidity of gastric juice (meq/L)</th>
<th>Decrease %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1 (Negative control)</td>
<td>1.66 ± 0.12^c</td>
<td>0</td>
</tr>
<tr>
<td>Group 2 (Positive control)</td>
<td>2.88 ± 0.06^c</td>
<td>0</td>
</tr>
<tr>
<td>Group 3 (100 mg/kg b. wt/day ginger)</td>
<td>2.62±0.67^a</td>
<td>9</td>
</tr>
<tr>
<td>Group 4 (200 mg/kg b. wt. /day ginger)</td>
<td>1.98±0.55^a</td>
<td>31.3</td>
</tr>
<tr>
<td>Group 5 (100 mg/kg b. wt/day cinnamon)</td>
<td>2.06 ±0.35^b</td>
<td>28.5</td>
</tr>
<tr>
<td>Group 6 (200 mg/kg b. wt/day cinnamon)</td>
<td>1.73±0.56^a</td>
<td>40</td>
</tr>
<tr>
<td>Group 7 (100 mg/kg b. wt/day ginger + 100 mg/kg b. wt/day cinnamon)</td>
<td>1.64±0.76^c</td>
<td>43</td>
</tr>
</tbody>
</table>

Data are presented as means ± standard deviation, (n = 8 for each group).

Values with different superscripts within the column are significantly different at P< 0.05.

Values with similar or partially similar superscripts are non-significant.

Table 5: Effect of oral administration of aqueous extracts of ginger (AGE), cinnamon (ACE) and their combination on antioxidant enzymes activities and malondialdehyde (MDA) in Aspirin-Induced Peptic Ulcer in rats.

<table>
<thead>
<tr>
<th>Groups</th>
<th>GPx (u/ml)</th>
<th>SOD (u/ml)</th>
<th>CAT (u/ml)</th>
<th>MDA (nmol/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1 (Negative control)</td>
<td>179.45±0.76^a</td>
<td>5.64±0.32^a</td>
<td>8.27±0.22^a</td>
<td>16.04±1.73^a</td>
</tr>
<tr>
<td>Group 2 (Positive control)</td>
<td>107.44±1.20^a</td>
<td>2.3±0.26^d</td>
<td>5.93±0.60^d</td>
<td>34.43±3.29^a</td>
</tr>
<tr>
<td>Group 3 (100 mg/kg b. wt/day ginger)</td>
<td>119.56±1.12^a</td>
<td>2.97±0.12^a</td>
<td>6.17±0.15^a</td>
<td>25.18±1.38^b</td>
</tr>
<tr>
<td>Group 4 (200 mg/kg b. wt. /day ginger)</td>
<td>163.46±1.43^b</td>
<td>4.40±0.32^a</td>
<td>7.46±0.21^b</td>
<td>17.46±1.09^c</td>
</tr>
<tr>
<td>Group 5 (100 mg/kg b. wt/day cinnamon)</td>
<td>143.64±0.82^a</td>
<td>3.95±0.13^a</td>
<td>6.73±0.26^a</td>
<td>18.19±1.81^c</td>
</tr>
<tr>
<td>Group 6 (200 mg/kg b. wt/day cinnamon)</td>
<td>166.25±0.95^b</td>
<td>4.83±0.09^a</td>
<td>7.96±0.21^a</td>
<td>17.06±2.21^c</td>
</tr>
<tr>
<td>Group 7 (100 mg/kg b. wt/day ginger + 100 mg/kg b. wt/day cinnamon)</td>
<td>170.36±1.12^a</td>
<td>5.44±0.32^a</td>
<td>8.04±0.22^a</td>
<td>15.91±1.61^c</td>
</tr>
</tbody>
</table>

Data are presented as means ± standard deviation, (n = 8 for each group).

Values with different superscripts within the column are significantly different at P< 0.05.

Values with similar or partially similar superscripts are non-significant.

their combination to male rats orally given aspirin to induce gastric ulcer with mean value 7.46±0.21, 6.73±0.26, 7.96±0.21 and 8.04±0.22, respectively when compared with the positive control group as shown in Table 5. Rats orally given AEG 100 mg/kg b. wt., showed no significant changes in activities of GPx, SOD and CAT enzymes when compared with the negative control group as shown in Table 5. Tabulated data showed that serum levels of malondialdehyde of rats orally given AEG 100 and 200 mg/kg b.wt., AEC100 and 200 mg/kg b.wt and their combination (AEG 100 mg/kg b.wt., + AEC100 mg/kg b.wt.,) caused a significant (P<0.001) reduction in malondialdehyde levels with mean value 25.18±1.38, 17.46±1.09, 18.19±1.81, 17.06±2.21 and 15.91±1.61 %, respectively as compared to the positive control group.

Histopathological Examination of the Stomach:
Microscopically, stomachs of rats from the negative control group (Group 1) revealed normal gastric mucosa (Fig. 1). Meanwhile, stomach of rats orally given Aspirin...
Fig. 1: Stomach of rat from (Group 1) negative control showing normal gastric layers (mucosa, submucosa, musculosa and serosa) (H & E x 100).

Fig. 2: Stomach of rat from (Group 2) positive control showing focal necrosis of gastric mucosa (H & E x 100).

Fig. 3: Stomach of rat from (Group 2) positive control showing congestion of mucosal blood vessels and submucosal inflammatory cells infiltration (H & E x 100).
Fig. 4: Stomach of rat from (Group 3) 100 mg/kg b. wt. /day extract of ginger showing congestion of mucosal blood vessels (H & E x 100).

Fig. 5: Stomach of rat from (Group 4) 200 mg/kg b. wt. /day extract of ginger showing no histopathological changes (H & E x 100).

Fig. 6: Stomach of rat from (Group 5) 100 mg/kg b. wt. /day extract of cinnamon showing slight submucosal oedema (H & E x 100).
Fig. 7: Stomach of rat from (group 6) 200 mg/kg b. wt./day extract of cinnamon showing no histopathological changes (H & E x 100).

Fig. 8: Stomach of rat from (Group 7) 100 mg/kg b. wt./day extract of ginger + 100 mg/kg b. wt./day extract of cinnamon showing apparent normal mucosa (H & E x 100).

to induce Peptic Ulcer without treatment (Positive control group) (Group 2) showed focal necrosis of gastric mucosa (Fig. 2) and congestion of mucosal blood vessels and submucosal inflammatory cells infiltration (Fig. 3). Examined stomachs of rats treated with ginger at a dose of 100 mg/kg of b.wt., (Group 3) revealed congestion of mucosal blood vessels as shown in Fig. 4. No histopathological changes were observed in stomachs of rats orally given 200 mg/kg b.wt/day extract of ginger (Group 4) (Fig 5). Moreover, stomachs of rats orally given cinnamon in a dose of 100 mg/kg b.wt/day (Group 5) showed slight submucosal oedema (Fig. 6). No histopathological changes were observed in stomach of rats orally given 100 mg/kg b.wt/day extract of ginger +100 mg/kg b.wt/day extract of cinnamon (Group 7) (Figs 7 and 8, respectively).

DISCUSSION

Our finding showed that ginger and cinnamon aqueous extracts at the different tested doses (100, 200 mg/kg of b.wt) and their combination had gastroprotective effects on acute experimental gastric ulcer in rats during the experimental period (4 weeks). Results obtained in this study showed that there was a significant increase in gastric volume, total acidity of values of the gastric juice and ulcer index values as a result of giving aspirin to the animals compared to negative control group. These
Results of this study revealed that aqueous extract of ginger and cinnamon contain total antioxidant activity, total phenols and flavonoids. This phytochemical composition could explain the antiulcer activity produced by herbs extract which was detected in our study. Moreover, the gastro-protective effect of flavonoids has been previously reported by Sakr et al. [26], who indicated that ginger is a powerful antioxidant plant that protects the blood of rats against the adverse harmful effects of cadmium chloride exposure as well as cadmium chloride-induced oxidative stress. Akinola et al., [27] reported that the plant, Z. officinale, was able to reduce oedema volume, the levels of lipid peroxidation and increased the activity of the enzyme, SOD, after induction of inflammation. As well as, in treated groups of animals with aqueous extract of ginger, results showed a significant reduction in ulcer index values, curative ratio percentage, volume and total acidity of gastric juice compared to the ulcerated group. These results could be supported by the findings of Khushart et al. [28], who indicated that ginger oil has a protective action against gastric ulcers induced by aspirin plus pylorus ligation in Wistar rats. Similar finding was recorded by Yoshikawa et al. [29].

Data of the present study showed a significant reduction in serum level of malondialdehyde, while increasing total antioxidants capacity level of serum. These results were confirmed by Kamel et al.[30], who showed that ginger and fenugreek oils have a promising antioxidant effect represented by increasing catalase CAT and super oxide dismutase SOD activities and decreased malondialdehyde MDA values. In the present study the antiulcer properties of ginger is in agreement with those obtained by Anosike and Ossai [31], who found that methanol extract of Zingiber officinale (MEZO) possesses potent anti-ulcer genic and hepatoprotective properties and can be used as herbal remedy for the treatment of gastro-intestinal ulcers and liver damage. These results were also confirmed by Wang et al.[32], who demonstrated that ginger powder prevents the aspirin induced gastric ulcer formation by reducing mucosal inducible form of NO synthase iNOS activity and the plasma levels of inflammatory cytokines but does not affect gastric juice or acid production or mucosal prostaglandin PGE<sub>2</sub> content. This protective effect of ginger powder against gastric ulcers may be attributable to both gingerol and shogaol.

Recent research revealed that aqueous extract of ginger, singly or combined with other plants have antiulcerogenic activity [33]. Ginger extract and polaprezinc both show anti-oxidation that consequently alleviates gastric mucosal damage and promotes ulcer healing, which together serve as effective mucosal protective agents. Furthermore, El-Metwally [34] revealed that, the treatment with the ginger, clove and castor oils possess antiulcer potential due to its antioxidant and anti-inflammatory. The healing activity may be due to its cytoprotective effect coupled with anti-secretory activity. Similar finding was recorded by Stoilova et al. [35]. Cinnamon bark is an important component of some Japanese herbal compounds, which have been reported to possess an antiulcer activity [36]. In the present study the antiulcer properties of cinnamon is due to its high concentration of total antioxidant activity, total phenols and flavonoids; this is in agreement with those obtained by Akira et al.[37], who reported that CIAE inhibits gastric secretion and promotes gastric mucosal blood flow. Hence, the enhanced gastric nonprotein sulphydryl groups (NP-SH) and mucus levels may contribute to the cinnamon antiulcer activity by its antioxidant potential [38]. In treated groups of animals with aqueous extract of cinnamon, results showed a significant reduction in ulcer index values, curative ratio percentage, volume and total acidity of gastric juice compared to the ulcerated group. These results could be supported by the findings of Mohammed[39], who reported that the Cinnamomum zeylanicum (100 mg kg<sup>-1</sup>, p.o.) produced an increase in healing of gastric ulcers and prevented the development of duodenal ulcers in rats indicating that it possess both gastric cytoprotective and anti-secretory effects. Similar finding was recorded by Saleh[40], who demonstrated that the gastro-protection of cinnamon is attributed to its effect through inhibition of basal gastric secretion (attenuation of aggressive factors) and stimulation mucus secretion (potentiation of defensive factors); and increase in nonprotein-sulphhydryl concentration which probably due to prostaglandin-inducing abilities mediated through its antioxidant property. Concerning serum level of malondialdehyde of treated groups the results showed that there was a
reduction in serum level of malondialdehyde, while there was an increasing in total antioxidant capacity level; these results are in agreement with those reported by Tankam et al. [41]. Earlier, some studies also suggested that cinnamon possesses strong free radical scavenging capacity [42]. The previous results were confirmed by the histopathological examination of stomach. Histopathological results revealed that rats orally given aqueous extract of ginger, cinnamon and their combination ameliorate lesion in stomach compared to ulcerated rats by aspirin. These results are in accordance with those reported by El-Metwally [34]. In conclusion, combined aqueous extract of ginger and cinnamon showed more intense increase in all parameters compare to ginger and cinnamon alone. Hence, the combined ginger and cinnamon have significant beneficial effects on rats with aspirin induced gastric ulcer produces antisecretory, cytoprotective and gastric ulcer healing activities. The major goal for treating patients with peptic ulcer disease is to avoid the extreme elevation of gastric acid secretion and the direct irritation of gastric mucosa. Therefore, this study recommends conducting this experiment on patients suffering from gastric ulcer disease.

CONCLUSION

The present study concluded that oral administration of water extracts of ginger and cinnamon had potential antulcer effect, the presence of polyphenol and flavonoids might be responsible for these pharmacological actions. Aqueous extract of cinnamon contain higher concentration of antioxidant activity, total phenols and flavonoids than aqueous extract of ginger. These phyto -constituents provide protection against gastric mucosal damage induced by aspirin. The antulcer curative ratios were dose dependent, the most dose effects was 200 mg/kg p.w. for ginger and cinnamon and his combination, with no adverse effects. Therefore, the current study recommends that consuming water extracts of ginger and cinnamon may be beneficial for patients who suffer from peptic ulcer.

REFERENCES


