ANTIULCER ACTIVITY OF *CITHAREXYLUM QUADRANGULAR* JACQ LEAVES (ETHANOLIC EXTRACT) ON EXPERIMENTALLY INDUCED GASTRIC ULCERATION IN RATS

Ahlam H. Mahmoud*, Ebtehal M. Farrag and Dalia B. Fayed

Therapeutic Chemistry Department, National Research Center, Dokki, Egypt.

ABSTRACT

The use of medicinal plants in treating several diseases is growing in last decades. *Citharexylum quadrangular* Jacq (CQJ) leaves extract has been previously used as anti inflammatory source. The present study was directed to evaluate its antiulcer activity in gastric ulcerated rats. The number of lesions as well as the ulcer score were decreased in pre and post treated animals with the plant extract when compared with control groups. Similar improvement was recorded in gastric juice volume and total acidity. Nitric oxide, glutathione and lipid peroxidation as well as biomarkers (TNFα and VEGF) also indicated that CQJ has a Gastroprotective activity.

KEYWORDS: *Citharexylum quadrangular*, TNFα,VEGF and Gastric ulcer.

INTRODUCTION

Throughout history, man used various natural materials as a remedy for various diseases. In the past few decades, most natural products were replaced with synthetic drugs that were based on modern chemistry and biotechnology. However, we are recently witnessing a vastly growing and renewed interest in natural medicines. In particular, the herbal medicine market has exploded and became prosperous in pharmacies and many stores. With this increasing interest in natural medicine, more individuals will explore the possibility of using natural medicines to complement conventional therapy for many diseases. Peptic ulcers, which are characterized by the presence of mucosal damage, are predominantly caused by infection with *Helicobacter pylori*, antiplatelet agents such as acetylsalicylic acid (Yeomans et al., 2009), non-steroidal anti-inflammatory drugs (NSAIDs) such as oral bisphosphonates,
potassium chloride, immunosuppressive medications (Yuan et al., 2010), serotonin reuptake inhibitors (Itatsu et al., 2011) alcohol consumption and cigarette smoking (Soberg et al., 2010). Ranitidine is a competitive reversible H$_2$ receptor antagonist, commonly used to treat peptic ulcer, gastroesophageal reflux disease, Zollinger-Ellison syndrome and related disorders. Both oral and intravenous infusion of ranitidine has been associated with severe allergic reactions such as bronchospastic reaction, toxic epidermal necrolysis, ultraviolet B, photosensitivity and exanthematous pustulosis (Martinez et al., 2006). From the literature available, it is evident that both immunological and non-immunological mechanisms are involved in immediate type of reactions to ranitidine. Anaphylaxis caused by Ranitidine is a clinical syndrome that affects multiple organ systems and is characterized by rapid onset of life-threatening respiratory and cardiovascular symptoms as the first recognized signs in most severe cases (Antonicelli et al., 2012; Koh et al., 2006; Sripriya et al., 2013 and Aouam et al., 2012). One way to prevent such adverse reaction is by evading the administration of drugs to which the patient is allergic. Accordingly finding another drug for gastric ulcer treatment is a must.

Researchers have reported a large number of medicinal plants with antiulcer properties (Abdulla et al., 2010 and Wasman et al., 2011). The plant Citharexylum quadrangular Jacq (CQJ) that belongs to family Verbenaceae is a tree – type ornamental plant widely distributed in many gardens in Egypt (Worsdell, 1941). Terpenoids (monoterpenes and triterpenes) and phenolic compounds (mostly flavonoids) have been found in C. quadrangular. (El Nagar, 2007). The biological screening of 70% aqueous ethanolic extract revealed a significant antiinflammatory, antihypertensive and a hepato-proactive effect (Khalifa et al., 2002; Kadry et al., 2013 and Farrag et al., 2015). Reactive oxygen species (ROS) are the final products generated from a normal cellular metabolic process (Salga et al., 2011). Oxidative stress results from the accumulation of ROS and the inability of the antioxidant system to overcome them. Thus, in this situation, excessive production of ROS affects cell integrity (Kurose et al., 1997) such as in gastric tissue where oxidative stress was reported earlier to contribute in the gastrointestinal mucosal lesion formation (Nanjundaiah, 2011). The present study was conducted to evaluate the effect of CQJ total ethanolic leaf extract on gastric ulcer in rats orally injected with ethanol. For tracing the plant extract's effect some parameters were measured. The degree of ulcer formation was followed by the gastric juice volume, the titrated acidity as well as the number of lesions and their severity. Nitric oxide, glutathione and lipid peroxidation levels were measured in tissue homogenates of the stomach for
determining the ability of the plant extract to scavenge the produced reactive oxygen species. As a biomarker for inflammation we measured the proinflammatory cytokine TNF-α and the vascodilator growth factor VEGF.

MATERIAL AND METHODS

Drugs and Chemicals

All chemicals used in the present study were of high analytical grade, products of Sigma (USA), Merck (Germany), Fluka (Switzerland) and El-Nasr chemicals Co. Egypt.

Plant Collection and Extraction of C. quadrangular Jacq Leaves

Family: Verbenaceae were collected (April, 2014) from the Zoo, Giza, Egypt. It was identified by Mr. Mahmoud Yosery, General Manager and Head of Specialists of Plant Taxonomy, Giza Zoo, Egypt. The dried powdered leaves were extracted by 70% ethanol. After complete extraction, the ethanol solvent was evaporated to dryness under vacuum at 40° C yielding semisolid free ethanol extract residue.

Animals and Toxicity of Tested Plant Extract

Disease free Sprague-Dawley male rats (150-200gm) and their standard commercial feed pletes were purchased from the experimental animal house, National Research Center (NRC), Cairo, Egypt. Mice were kept in a controlled environment of air and temperature with access to diet and water ad libitum. Thirty six mice were divided into 6 groups (6 rats each) for determination of ethanol extract of C. quadrangular leaves safety. Six doses (500-5000 mg/Kg) were suspended in distilled water and orally administrated to rats. 24 hours post oral administration, the numbers of dead animals were counted and the mortality rate was calculated. No dead mice were recorded up to 5000 mg/kg body weight (B.wt) revealing extract safety.

Ethics

All experiments were carried out according to recommendation of the ethical conditions approved by the Ethics Committee of NRC of Experimental Animals, which is matched with international ethics for handling experimental animals (approval no. 13163).

Doses and route of administration

For ulcer induction, rats were fasted for 24 h before starting the experiments. Rats received a single dose of absolute ethanol (5 ml/kg) by oral gavage (Moustafa et al., 2013). Ranitidine
(100 mg/kg/day) (Mard et al., 2008) and *C. quadrangular* extract (500 mg/Kg B.wt /day) were orally administrated for one week either before or after ulceration for prophylactic and treated groups respectively.

**Experimental design**

The rats were divided into 7 groups each of 8 animals to study the prophylactic and the treatment effect of the plant comparing it with the effect of the reference drug ranitidine. Three controls were used in this study, a negative control (Group 1), a prophylactic positive control in which non supplemented rats were subjected to ulcer induction 2 hrs before scarification (Group 2), and a third control served as positive control for the treatment groups, in which the rats were ulcerated with ethanol and kept one week before scarification (Group 3). Groups 4 and 6 served for prophylactic study of the reference drug ranitidine and the plant extract respectively in which the animals were orally supplemented with either ranitidine or the plant extract using the mentioned doses daily for one week prior to ulcer induction and then scarified two hours after ethanol injection. Groups 5 and 7 were used for post treatment evaluation of ranitidine and the plant extract respectively. In these two groups the animals were subjected first to ulcer then treated for one week before the end of the experiment with either ranitidine or plant extract.

**Measurement of gastric secretion**

Rats were anesthetized, the abdomen was dissected and the esophagus nearest to the cardia and the distended stomach on the pyloric sphincter was immediately tied in a knot using a string to avoid leakage of the gastric contents (Shu et al., 2013). Then the stomach contents were collected, measured, centrifuged, and subjected to analysis for titratable acidity against 0.01 N NaOH to pH 7 (Shay, 1945 and Guedes et al., 2008).

**Quantification of Ulceration**

The glandular portion comprising of the fundic and corpus region of each stomach was opened longitudinally along the greater curvature and examined macroscopically using a magnifying lens. The number and score of lesions in the glandular mucosa were scored from 0 to 5 according to the method of Clementi et al. (1998).
Biochemical Analysis
Blood samples were taken from the retro-orbital venous plexus. Sera were separated from the clotted blood samples by centrifugation at 3000 rpm for 5 min and then, aliquotted and freezeed at −80°C till the time of the analyses.

1- Oxidative stress markers in tissue homogenate.
GSH level of gastric tissue was determined by Ellman's reaction using 5′5′-dithio-bis-2-nitrobenzoic acid (DTNB) as described by Faure and Lafond (1995). The intensity of the yellow colour was read at 412 nm. Malondialdehyde was determined as an indicator of lipid peroxidation (MDA) according to Buege and Aust (1978).

Tumor necrosis factor-α was determined using a commercially available ELISA Kit (Biosource, Camarillo, CA, USA) following the instructions of the manufacturer. TNF-α was expressed as pg/ml.

3. Determination of VEGF in serum
Serum (S) VEGF level was estimated using commercially available ELISA kits (Cayman Chemical, Ann Arbor, MI). VEGF was expressed as pg/ml.

Statistical analysis
The results were presented as mean ± standard error (S.E.). Results were analyzed statistically by one way analysis of variance (ANOVA) using SPSS (Statistical Package for the Social Sciences, version 9) software. P < 0.05 was considered statistically significant.

RESULTS
Evaluation of gastric juice volume, acidity and lesions.
The antiulcer activity of C. quadrangular Jacq leaf extract in ethanol-induced gastric lesion model is shown in table 1. Results indicate that protection with plant extract showed a significant reduction in the volume of the gastric juice as well as their acidity and number of lesions compared with ulcer control group. The significant inhibition of gastric ulcer in rats pretreated with C. quadrangular Jacq extract (500 mg/Kg B.wt /day) was compared to those pretreated with ranitidine (Table 1). Ranitidine failed to reduce the gastric volume as the plant extract did but it induced a similar effect on both the acidity level and the number of lesions. Post administration of either ranitidine or the plant extract induced amelioration in all
parameters represented in table 1 when compared with their corresponding untreated control group.

**Evaluation of antioxidant biomarkers**

NO was reduced in non treated ulcerated groups, however the pre and post- treatment with either ranitidine or the plant extract improved the pronounced decrease in NO level with a respect to their positive control groups (Table 2). Also the increase in LPO and the decrease in GSH were corrected in all treated groups when compared to their control non treated ones (Table 2). There is no great difference between ranitidine and the plant extract in almost all parameters presented in table (2).

**Table 1: Effect C. quadrangular extract on gastric ulcer indices**

<table>
<thead>
<tr>
<th>Group name</th>
<th>Parameter</th>
<th>Gastric juice volume</th>
<th>Total Acidity</th>
<th>Number of lesions</th>
<th>Ulcer Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clean control</td>
<td></td>
<td>160±9.13^b</td>
<td>14.5±0.84</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-treated control</td>
<td></td>
<td>1655±133.01^a</td>
<td>97.5±4.79</td>
<td>14.75±2.81</td>
<td>10.25±1.32</td>
</tr>
<tr>
<td>Ranitidine Pre-treated</td>
<td></td>
<td>1309±179.7^ab</td>
<td>63.75±6.25</td>
<td>11.6±1.71</td>
<td>5.75±1.44</td>
</tr>
<tr>
<td>C. quadrangular Pre-treated</td>
<td></td>
<td>237.5±23.94^ab</td>
<td>35±4.46ab</td>
<td>6.5±0.18</td>
<td>2.5±0.96</td>
</tr>
<tr>
<td>Pre-treated Control</td>
<td></td>
<td>625±179.7^a</td>
<td>43.75±6.2</td>
<td>5.3±0.91</td>
<td>2.9±0.33</td>
</tr>
<tr>
<td>Ranitidine Post-treated</td>
<td></td>
<td>153.88±12.09^c</td>
<td>18.65±2.71</td>
<td>3.1±0.63</td>
<td>1.7±0.15</td>
</tr>
<tr>
<td>C. quadrangular Post-treated</td>
<td></td>
<td>143.75±8.98^c</td>
<td>16.25±2.39</td>
<td>5.25±0.27</td>
<td>2.01±0.38</td>
</tr>
</tbody>
</table>

Data are means ± SE of six rats in each group; gastric volume is expressed in µl, total acidity as molar equivalent (mEq)/L, ^a^ P < 0.05 compared to clean control group and ^b^ P < 0.05 compared to ulcer group(prophylactic) and ^c^ P < 0.05 compared to ulcer group (post treated).

**Table 2: Effect C. quadrangular extract on oxidative stress markers in tissue**

<table>
<thead>
<tr>
<th>Group name</th>
<th>Parameter</th>
<th>NO (µM/g tissue)</th>
<th>Glutathione (mg/g tissue)</th>
<th>Malondialdehyde (nMole/mg tissue)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clean control</td>
<td></td>
<td>1195.25±29.89^bc</td>
<td>28.91±0.66</td>
<td>17.14±0.32</td>
</tr>
<tr>
<td>Pre-treated control</td>
<td></td>
<td>97.89±18.99^a</td>
<td>15.23±0.55</td>
<td>31.72±0.81</td>
</tr>
<tr>
<td>Ranitidine Pre-treated</td>
<td></td>
<td>736.58±43.79^ab</td>
<td>21.84±1.17</td>
<td>21.68±0.49</td>
</tr>
<tr>
<td>C. quadrangular Pre-treated</td>
<td></td>
<td>684.32±39.16^ab</td>
<td>20.95±0.8</td>
<td>23.74±0.94</td>
</tr>
<tr>
<td>Post- treated Control</td>
<td></td>
<td>554.51±67.94^a</td>
<td>19.39±052</td>
<td>28.21±0.44</td>
</tr>
<tr>
<td>Ranitidine Post-treated</td>
<td></td>
<td>768.04±47.28^ac</td>
<td>23.68±097</td>
<td>17.59±0.47</td>
</tr>
<tr>
<td>C. quadrangular Post-treated</td>
<td></td>
<td>755.35±23.79^ac</td>
<td>23.79±0.84</td>
<td>17.3±054</td>
</tr>
</tbody>
</table>

Data are means ± SE of six rats in each group; data are expressed as µg/g tissue for glutathione, nmol/g tissue for malondialdehyde and µmol/g tissue for Nitric oxide, ^a^ P < 0.05 compared to clean control group, ^b^ P < 0.05 compared to ulcer group(prophylactic) and ^c^ P < 0.05 compared to ulcer group (post treated).
Evaluation of cytokines.
A high significant increase in TNF-α in the pre and post non treated positive control was recorded (Table 3). All treated animals either with ranitidine or plant extract showed an intermediate level between the two positive control groups and the negative control. However this correction did not reach the normal value. Ulcer decreased the VEGF levels. Pre-treated plant extract was more effective than post treated plant one (Table 3) in improving the VEGF level. Ranitidine showed a better effect on both cytokines than the plant extract.

Table 3: Effect of C. quadrangular on TNF-α and VEGF

<table>
<thead>
<tr>
<th>Group name</th>
<th>Parameter</th>
<th>TNF-α (Pg/ml)</th>
<th>VEGF (Pg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clean control</td>
<td></td>
<td>52.54 ± 3.31bc</td>
<td>191.56±5.4bc</td>
</tr>
<tr>
<td>Pre-treated control</td>
<td></td>
<td>135.51 ±1.88a</td>
<td>125.53±2.51a</td>
</tr>
<tr>
<td>Ranitidine Pre-treated</td>
<td></td>
<td>72.6 ±5.09ab</td>
<td>176.99±1.97b</td>
</tr>
<tr>
<td>C. quadrangular Pre-treated</td>
<td></td>
<td>97.33±2.52ab</td>
<td>159.75±0.79bc</td>
</tr>
<tr>
<td>Post- treated Control</td>
<td></td>
<td>128.07 ± 1.02a</td>
<td>142.89±2.51a</td>
</tr>
<tr>
<td>Ranitidine Post-treated</td>
<td></td>
<td>85.74 ± 1.6ab</td>
<td>168.14±1.62bc</td>
</tr>
<tr>
<td>C. quadrangular Post-treated</td>
<td></td>
<td>115.09±2.41ac</td>
<td>157.3±1.82a</td>
</tr>
</tbody>
</table>

Data are means ± SE of six rats in each group; data are expressed as pg/ml serum for both tumor necrosis factor α (TNFα) and vascular endothelial growth factor (VEGF) (TNFα a P < 0.05 compared to clean control group and b P < 0.05 compared to ulcer group(prophylactic) and c P < 0.05 compared to ulcer group (post treated).

DISCUSSION
As chemical synthetic drugs have many adverse effects, vigorous studies are being conducted. However, as natural products consist of thousands of elements at least, it is hard to illuminate the specific mode of action of any of these plant's extracts. For this reason the only evaluation of the efficacy of any of them is to study several parameters in a model representing the concerned disease.

Acute toxicity study demonstrated that rats treated with the C. quadrangular Jacq (up to 5 g/kg) manifested no abnormal signs. The ethanol model is widely used to evaluate gastro protective activity, since ethanol is found to penetrate easily and rapidly into the gastric mucosa, causing membrane damage, exfoliation of cells and erosion. This subsequently increases mucosal permeability together with the release of vasoactive products, which result in gastric lesions and gastric ulcer formation (Szabo and Brown, 1987).
The volume of secreted gastric juice is an important measure in the formation of ulcer due to the exposure of the unprotected lumen of the stomach to the accumulating acid. The present data showed a high increase in the gastric juice volume in both post and pre none treated control groups when compared to non ulcer control group. A very high increase was measured in the prophylactic control and in the ranitidine prophylactic one. This high elevation can be attributed to the time duration after ulcer induction. Two hours after ethanol injection was not enough for any adaptive cytoprotection. However the plant extract was able to protect the stomach from the irritant ethanol in the pre treated group. The correction in the volume increase was measured in all post treated groups, even the control post non treated one compared to pre non treated control group which is an indication that adaptive cytoprotection increases with time when the erosion decreases. The adaptive cytoprotection was discussed by Brzozowski et al. (2005) in view of the role of prostaglandin in cytoprotection and gastric adaptation. It became evident that one of the important forms of cytoprotection is "adaptive cytoprotection", the term that was introduced originally by Robert and his associates (Robert et al., 1983).

Gastric ulcer as documented by almost all researchers is always accompanied with elevation in stomach acidity in another word the multifactorial pathogenesis of peptic ulcers is secretion of gastric acid. Accordingly, if the test drug is to be effective against the gastric ulcer it should have acidity decreasing effect. Acidity can be decreased by either anti-secretory effect that is to reduce the gastric juice secretion or the drug should neutralize the gastric acidity. Inhibition of acid may enhance healing of ulcers due to anti-secretory effect.

The marked decrease in both the gastric juice and the acidity in pre or post treatment with the plant extract with respect to ulcer untreated group contribute to anti-ulcer activity of C. quadrangular Jacq extract.

The number of lesion in the stomach is a further indication of ulcer degree; however the severity of these lesions may be more valuable for determining the effect of the different treatments. A reduction in both the number of lesions and their severity in the rats protected with plant extract was compared to their prophylactic control number. Accordingly to the ulcer indices we may say that therapeutic effect of C QJ is greater than the protective effect.

The phyto-constituents like flavonoids, tannins, terpenoids, and saponin have been reported in several anti-ulcer literatures as possible gastro protective agents (Pandian et al., 2002). The
presence of these compounds in *CQJ* extract explains its protective activity. More over the plant constituents play an important role as ROS scavenger.

Depletion in GSH level and an increase in lipid peroxidation were detected in untreated ulcerated control, which is parallel to many published works. Rozza et al. (2011) mentioned that ethanol exerts its allergenic effect on gastric tissue by increasing lipid peroxidation. It was also observed that the aggressive effect of ethanol on gastric mucosa is associated with reduced GSH level (Victor et al., 1991).

Lipid peroxidation was found to be an important pathophysiological event in a variety of diseases including gastric ulcer (Bandyopadhyay et al., 2001). It is well known that MDA from lipid peroxidation reacts with DNA bases and induces mutagenic lesions (Benamira et al., 1995). Pratibha et al. (2006) showed that the activated oxygen species can, in turn, induce cellular events such as enzyme inactivation, DNA strands cleavage and also membrane lipid peroxidation. In the present study antioxidant markers were significantly improved in all ranitidine or plant extract pre or post-treatments. The fact that the plant extract is reach in phenolic and flavonoids compounds can be attributed to play a role as an antioxidant.

One of the important factors for the slow flow of gastric blood, which leads to the development of hemorrhagic lesions and subsequent solubilization of gastric mucus contents, was found to be a reduction in the level of NO. This leads to an elevation in the flow of K+, Na+, and pepsin secretion (Pan et al., 2005). The protective barrier produced by NO, through the suppression of neutrophil infiltration, inhibits gastric damage from ethanol (Tuchinda et al., 2002). Through an inhibitory effect on neutrophil infiltration, NO also attenuates the secretion of inflammatory mediators (Kobayashi et al., 2001) and reduces the production of free radicals that ultimately result in gastric ulcer. Therefore, antiulcer agents with the ability to promote NO production can provide a more protective effect against gastric lesions. Several workers reported depletion in NO in ulcerated animals (Jian-Wen et al., 2012). The high depletion in NO in the ulcerated non-treated group, as reported in our findings, was corrected, with various degrees, in all treated groups. This explains the share of *C. quadrangular* Jacq extract in preventing the formation of free radicals, which in turn secretes mucus to prevent ulcer formation. A study by Sidahmed et al. (2013) reported similar increase in NO levels after the administration of a-mangostin from the *Cratoxylum arborescens* (Vahl) Blume species. Several workers (Montoro et al., 2005 and Balan et al., 2015), considered flavonoids among the majority of identified sources that have frequently
been implicated as antiulcer agents. Also, according to a study by Junaidi et al.(2013) the active principle of antiulcer activity in plant extracts are flavonoids, terpenoids and tannins. Therefore, data related to the present study are able to provide guidance on the use of C. quadrangular as gastroprotective agents due to the presence of phenolic compounds and flavenoids.

Proinflammatory cytokines exist to cause changes that allow the immune system to gain access to tissues. Because the cells of the immune system are usually trapped in the circulation, proinflammatory cytokines help these immune cells escape the blood circulation and get to the tissues where they are needed, either by causing the blood vessels to get leaky or by helping white blood cells to leave the blood vessels (Goldszmid and Trinchieri, 2012) The highest increase in serum TNF-α found in ulcerated non treated group, 2 hours after ulcer induction, supports the other data measured in this study. Senol et al. (2011) detected an increase in tissue TNF-α concentration in the gastric mucosa 3 h after aspirin administration. No great difference in TNF-α in pre or post treatment groups was detected.

VEGF is one of the major factors that initiate and regulate angiogenesis. VEGF promotes endothelial cell migration, proliferation, differentiation, and survival both in vitro and in vivo (Ferrara, 1999 and Ferrara et al., 2003), which are all critical for angiogenesis. The critical event of ulcer healing is tissue formation, which requires the concerted interaction of various growth factors and cellular systems, such as epidermal growth factor (EGF), vascular endothelial growth factor (VEGF) and nitric oxide (NO) (Konturk et al., 1993 and Takahashi et al., 1997).

The present data shows that the increase in ulcer parameters, gastric volume, acidity and number of lesions, is accompanied by a decrease in VEGF due to the nicrotic effect formed by ethanol. The pre and post treatment with the plant extract exhibited a moderate recovery level of this marker. So we can say that all the parameters measured are in harmony with each other. There is evidence to suggest that decreased levels of GSH may initiate vascular damage and vascular permeability (Ali a&b, 1995). At the same time, increase in GSH due to using extract helps to increase VEGF to repair the tissue damage and decreased the inflammatory effect. This finding coincides with the present data of GSH and VEGF changes.
CONCLUSION
Although the present study showed that Ranitidine improved some parameters more than the plant extract, but *C. quadrangular* Jacq is a natural treatment and exhibits no side effect up to our studies and knowledge. The results obtained in this study showed the safety of *C. quadrangular* Jacq in rats, even at the highest dose of 5 g/kg. However, further chronic toxicity testing should be conducted to confirm its safe usage. In vivo study in rats demonstrated the promising antiulcer effect of *C. quadrangular* Jacq against gastric mucosal injury induced by ethanol. *C. quadrangular* Jacq mediated its antiulcer potential probably through its ROS-scavenging activity and protective effect against stomach damage. Although some studies has been done to investigate the major active compound in *C. quadrangular* but more is still required, to fully illustrate the antiulcer potential of *C. quadrangular* Jacq leaves.

REFERENCES


