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RESEARCH ARTICLE

Therapeutic and prophylactic effect of *Andrographis paniculata* on aspirin-induced gastric ulcer

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ABSTRACT

Background: *Andrographis paniculata* is extensively used in the Southeast Asia in treating different kinds of diseases. **Aims and Objectives:** The study aimed to determine the chemical constituents of *A. paniculata* extract and its therapeutic and prophylactic effects on aspirin-induced gastric ulcer in male albino mice using histopathological analysis. **Materials and Methods:** Lyophilized filtered leaf extract of *A. paniculata* was administered to the experimental subjects at varying doses of 25%, 50%, and 75% concentrations once a day for 3 consecutive days in the prophylactic group followed by aspirin administration for another 3 days. For the therapeutic group, aspirin was administered first and after 3 days, plant extract was administered for 3 consecutive days. On the 7th day, longitudinal sections of the gastric tissue from the fundus of the mice were excised for histopathologic analysis using light microscopy to assess gastric mucosal lesions, presence of necrosis, and degree of inflammation. **Results:** Phytochemical tests on *A. paniculata* extract revealed the presence of tannins, glycosides, reducing substances, terpenoidal compounds, and flavones. Administration of 25%,50%, and 75% *A. paniculata* extract remarkably decreased the severity of ulceration, hastened regeneration and repair, and produced normal gastric mucosa, respectively. The prophylactic group showed similar results regardless of *A. paniculata* extract concentration in delaying gastric ulcer progression. **Conclusion:** Crude extract of *A. paniculata* plant has an ulcer-healing and prophylactic potential.

KEY WORDS: *Andrographis paniculata*; Aspirin; Sucralfate; Gastric Ulcer; Prophylaxis

INTRODUCTION

Gastric ulcer has been a major therapeutic target due to its prevalence and complications. It arises from the imbalance between the defensive factors typically found in the stomach and the aggressive factors including acids emitted by the stomach itself and those derived from the food ingested and drugs taken. Gastric ulcers have been correlated with the occurrence of *Helicobacter pylori* bacteria,[1] and the incessant use of nonsteroidal anti-inflammatory drugs (NSAIDs).[2] Symptoms of gastric ulcers are non-specific including melena, gastrointestinal bleeding, gastric obstruction, and hemorrhage,[3] and these symptoms can be worsened by NSAIDs approximately 3- to 10-fold.[4-6] Studies revealed that aspirin, one of the well-known NSAIDs used today, generates an acute mucosal damage in just an hour of administration visualized as an extensive intramucosal petechial hemorrhage with erosions.[7]

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In the medical management of ulcers, numerous drugs are available, but these have some adverse effects. For instance, sucralfate causes dizziness and constipation.[8] In lieu of this, scientists are now in search for new therapy which withdraws the side-effects posed by these available drugs. Prompted by the high cost of the available antiulcer medications, scientists are now in search for these nontoxic and inexpensive antiulcer formulations derived from medicinal plants.

Andrographis paniculata is an annual-branched plant easily cultivated because it grows in all soil types and abundant in tropic countries like the Philippines.[9] It is used to treat a variety of chronic and infectious diseases with a wide range of beneficial pharmacological benefits including analgesic, anti-inflammatory, antiperiodic, antithrombotic, cancerolytic, and cardioprotective properties among others.[10] Although many studies accounted for much of its benefits, still, its therapeutic and prophylactic effect on gastric ulcer has not been extensively reported. Hence, this study aimed to obtain more information regarding the chemical constituents, and the potential therapeutic and prophylactic benefits of *A. paniculata* on aspirin-induced gastric ulcer. Specifically, a comparative analysis was performed on the histopathological changes of gastric mucosal lesions in the presence of necrosis and inflammation on aspirin-induced gastric ulcers in male albino mice when given by *A. paniculata* extract. Moreover, comparison on the effectiveness of *A. paniculata* extract with sucralfate was also done. Findings of the research will offer a valuable contribution to the vast growing number of studies involving gastric ulcer and exploration on the prophylactic and therapeutic effects of *A. paniculata* on gastric ulcer as a possible cheaper alternative for the costly medicines provided in the market.

MATERIALS AND METHODS

About 45 a week old male albino mice weighing approximately 10 g were procured from the University of the Philippines Manila National Institutes of Health. The animals were acclimatized in steel cages with wood shavings under standard lighting and temperature conditions with food and water provided *ad-libitum*. The study protocol adhered to the guidelines set for the care and use of laboratory animals and was approved by the Institutional Ethics and Review Board. The subjects were randomly assigned to the 9 treatment groups. Group 1 consisted of subjects not exposed to aspirin (untreated group). Aspirin-induced subjects treated with sucralfate were in Group 2 (positive control), while untreated aspirin-induced mice were assigned in Group 3 (negative control). Aspirin-induced subjects receiving varying concentrations of plant extract were assigned to three more groups: Group 4 (25%), Group 5 (50%), and Group 6 (75%) for the curative effect. For the prophylactic effect, subjects administered with 25%, 50%, and 75% plant extract were assigned to Groups 7, 8 and 9, respectively.

About 10 kg of *A. paniculata* was obtained from Naos De Cavite Villa Canacao, Sta. Isabel, Kawit, Cavite and SEB Commercial Compound, Taytay, Rizal. The specimens were submitted to the National Library of the Philippines Ermita, Manila for specimen confirmation. The collected leaves were thoroughly washed with distilled water and air-dried at room temperature (25°C), subsequently homogenized using a blender (Oster® OSTERIZER Pulse Matic Blender 10 Speed). Five grams of dried powder was soaked in 500 ml double distilled water and refluxed for 5 h. The aqueous solution was filtered and concentrated to 100 ml.[11] The extracts were placed in sterile bottles, concentrated and stored in a laboratory freezer with a controlled temperature of 5°C.[12]

Using a 1ml tuberculin syringe (G 26 detachable needle, B. Braun Medical, Inc.), aspirin, sucralfate, and *A. paniculata* were administered orally. Aspirin (Bayer Aspirin® 100 mg tablets, Bayer) was given at a dose of 150 mg/kg, and sucralfate (Pfizer Sucralfate® 1 g tablets, Pfizer) was administered at a dose of 50 mg/kg. In this study, experimental doses of 25%, 50%, and 75% of *A. paniculata* were used. These were all defined by an experimental protocol selected based on its median lethal dose. The animals were monitored twice a day for any signs of discomfort. Treatments were administered once a day for 3 consecutive days. A. paniculata extract was administered to the prophylactic groups, whereas aspirin was given in the curative groups. After 3 d, administration was done in reversal for 3 consecutive days. Following administration, on the 7th day, the mice were fasted, but the water was given *ad-libitum* for 14 h before euthanasia. The longitudinal sections of the gastric tissue from the fundus of the mice were excised and fixed with 10% formalin and were brought to the Pathology Section, College of Medicine, University of the Philippines Manila for staining. Histopathologic analysis of gastric mucosal lesions was performed afterward using an Olympus Optical CH10 light microscope.

RESULTS

Phytochemical tests on *A. paniculata* extract revealed the presence of tannins, glycosides, reducing substances, terpenoidal compounds, and flavones (Table 1). Varying concentrations of *A. paniculata* extract were assessed on its therapeutic and prophylactic effects on aspirin-induced gastric ulcerations. The subjects not exposed to aspirin had an intact muscularis externa, submucosa, and gastric mucosa with an abundance of chief cells found just above the submucosa occupying one-fourth of the entire gastric mucosa (Figure 1a). A complete distortion of the gastric mucosa is observed due to the damage caused by aspirin with superficial erosions of gastric mucosa and destruction of the basal lamina (Figure 1b). One of the major complications of NSAIDs is observed where tissue necrosis has extended through the artery causing hemorrhage where several blood clots and perforations all over the gastric mucosa are visible

Table 1: Summary of phytochemical screening and constituents of *Andrographis paniculata* aqueous extract

Tests	Positive results	Actual results	Indications
pH paper	-	pH=7.0	Neutral
Tannins	Blue-black precipitate	Dark brown precipitate	Positive for tannins
Glycosides	Precipitation or turbidity	White precipitate	Positive for glycosides
Reducing Substances	Brick red precipitate	Brick red precipitate	Positive for reducing substances
Alkaloids			
Mayer's	Pale yellow flocculent precipitate	Light yellow solution	Negative for alkaloids
Valser's	White precipitate	Light yellow solution	-
Wagner's	Reddish brown precipitate	Light red solution	-
Dragendorff's	Orange red precipitate	Slight turbidity	-
Sonnenschein's	Precipitation	Slight turbidity	-
Picric acid	Precipitation	Slight turbidity	-
Tannic acid	Precipitation	Slight turbidity	-
Plant acids	Stable and dense froth	No stable froth	Negative for plant acids
Saponins			
Froth test	Honeycomb froth>3 cm after 30 min	No stable froth after 30 min	Negative for saponins
Steroidal compounds			
Liebermann-Burchard test	Blue, blue-green or green	Light brown solution	Negative for steroidal compounds
	Red, pink, purple, or violet	Light brown solution	Positive for terpenoidal compounds
Salkowski test	Cherry red color	Brown solution	Negative for unsaturated sterols
Flavonoids			
Mg-HCl test	Orange to red color	Light orange solution	May contain flavones
	Red to crimson color	-	-
Molisch test	Purple ring at the junction of the acid layer	No purple ring at the junction of the acid layer	Negative for sugars

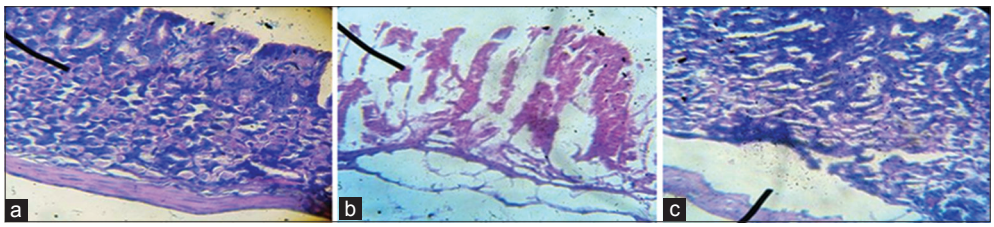

Figure 1: Histopathologic assessment, viewed under high power objective, of the gastric mucosa of, (a) untreated, (b) 6 h after aspirin administration, (c) treated with aspirin for 3 consecutive days and sacrificed 3 days after

(Figure 1b). When aspirin was removed after 3 days on induction, following 3 more days of water administration, tissues eventually emerged after the destruction (Figure 1c). In comparison with Figure 1b, which also comes from the same group but is sacrificed earlier, there is re-epithelialization and healing depicted from the histology of this group as epithelial cells start to regrow and occupy the damaged surfaces of the gastric mucosa (Figure 1c).

The gastric mucosal tissues of the *A. paniculata* treated groups (both curative and prophylactic) showed almost normal and continuous formation of the epithelial layer. The gastric mucosal treated with sucralfate after ulceration appears like the normal control with muscularis externa intact with the submucosa (Figures 2a and b). The chief cells also appear normal and occupy about a quadrant of the gastric mucosa. However, the parietal cells start to dilate, and the pyramidal shape of the cells is gradually deformed with nucleus starting to settle at the side, and with adipose tissues starting to replace these cells. The foveal region is not as intact as normal, and regeneration is starting to occur. Foveolar cells are severely dilated with regular dilation patterns. The control group treated with sucralfate shows comparable histologic findings with all treatment groups although with degenerating foveolar cells.

Progressive degree of healing with severe dilations and necrotic areas were noted in the 25% and 75% curative groups. The parietal and the foveolar cells are separated by large spaces (Figure 2f). The degree of regularity for the foveal is also increasing with the extract concentration. The fragments of dead cells are found all over the lumen

indicating continuous healing and repair when compared to the negative control (Figures 2d-f). There are visible slight dilations and regeneration of the foveal. Regardless of the extract concentration, curative effect was faster when compared to auto healing (Figures 2c-f).

The prophylactic groups revealed an apparently progressive protective effect against ulceration through the observed conditions of the gastric mucosa (Figures 2g-i). There is no foveoli and mucus degeneration observed, exemplified by the intact mucus surface cells in all the given concentrations. Although there is the evident effect of aspirin destruction due to slight dilations, these appear to be very minimal. The 75% prophylactic group shows a considerable significant result since it looks qualitatively similar with the untreated group (Figures 2a and i). The only difference is the slight decrease in parietal cells evident in other treated groups. Furthermore, in the untreated control group, the gastric mucosa is intact and no observed ulceration seen with foveolar, parietal, and chief cells in normal conditions (Figure 3a). There is a moderate to severe necrosis of the cells found at the periphery of ulceration in the negative control group (Figure 3b). The parietal cells are decreased, and the muscularis externa is affected by the ulcer. A mild to moderate dilations of the parietal and foveolar cells are observed, with regeneration and healing (Figure 3c). In the 25% curative group, *s*evere ulceration is observed in the gastric mucosa with no decrease in the parietal cells (Figure 3d). Elongated dilations and infiltration of foreign bodies are seen at the site of erosion. However, there are moderate to severe ulcerations seen in the 50% curative group with slight regeneration of the cells (Figure 3e). When compared to the 75% curative group, there are no severe ulcerations observed, but marked sites of ulcerations are still apparent (Figure 3f). The gastric mucosa is restored and almost normal in appearance. When *A. paniculata* was employed as a prophylaxis, in the 25% group, there are no ulcerations identified, but necrotic cells characterized by dilations are observed (Figure 3g). The dilations are moderate, and there is a regeneration of the gastric mucosa to replace the damaged cells. For the 50% group, there are no ulcerations detected but with some observable mild dilations with regular foveolar cells (Figure 3h) while no ulcerations observed with normal-appearing gastric mucosa in the 75% prophylactic group (Figure 3i).

DISCUSSION

The main active ingredient of *A. paniculata* is andrographolide which accounts for the bitter taste of the plant.[13] When consumed, it accumulates in organs throughout the viscera 48h post-ingestion with rapid absorption and excretion processes.[14] In this study, *A. paniculata* showed potential gastric ulcer-healing effects similar to *Piper betel*, which has a role in mucin protection and regeneration against anti-inflammatory drugs with efficiency comparable to misoprostol protecting the gastric mucosa from lipid peroxidation.[15]

Considering the pathogenesis of gastric ulceration, cyclooxygenase pathways have been implicated since once

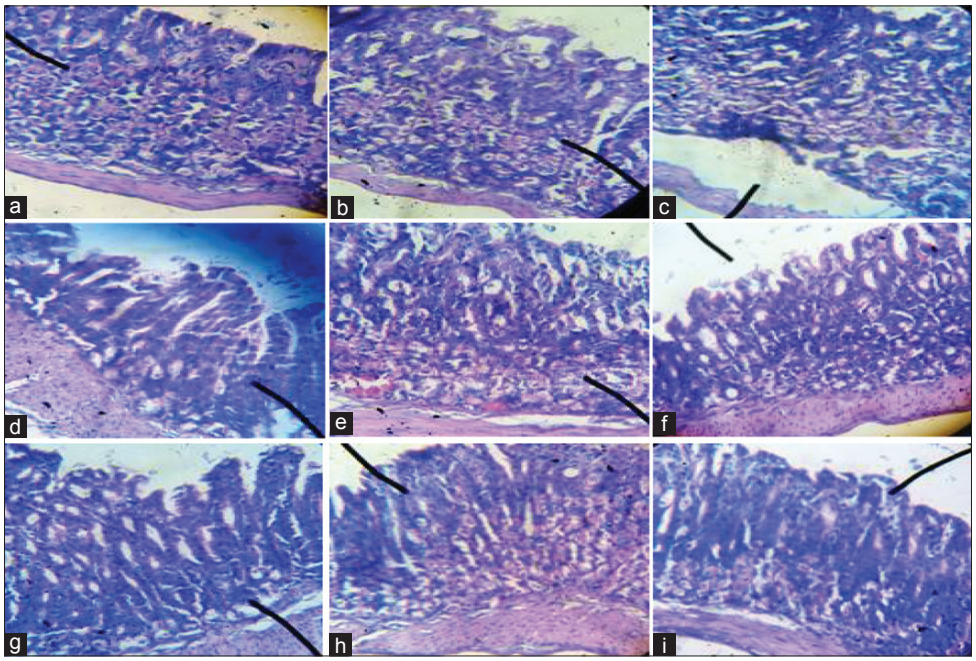

Figure 2: Histopathologic assessment, viewed under high power objective, of gastric mucosa obtained from, (a) untreated control group (normal), (b) aspirin-induced ulceration treated with sucralfate for 3 days (positive control), (c) aspirin-induced ulceration untreated 6 h after aspirin administration (negative control), (d) aspirin-induced ulceration treated with 25% extract for 3 days, (e) aspirin-induced ulceration treated with 50% extract for 3 days, (f) aspirin-induced ulceration treated with 75% extract for 3 days, (g) 25% extract prophylaxis before aspirin induction, (h) 50% extract prophylaxis before aspirin induction, (i) 75% extract prophylaxis before aspirin induction

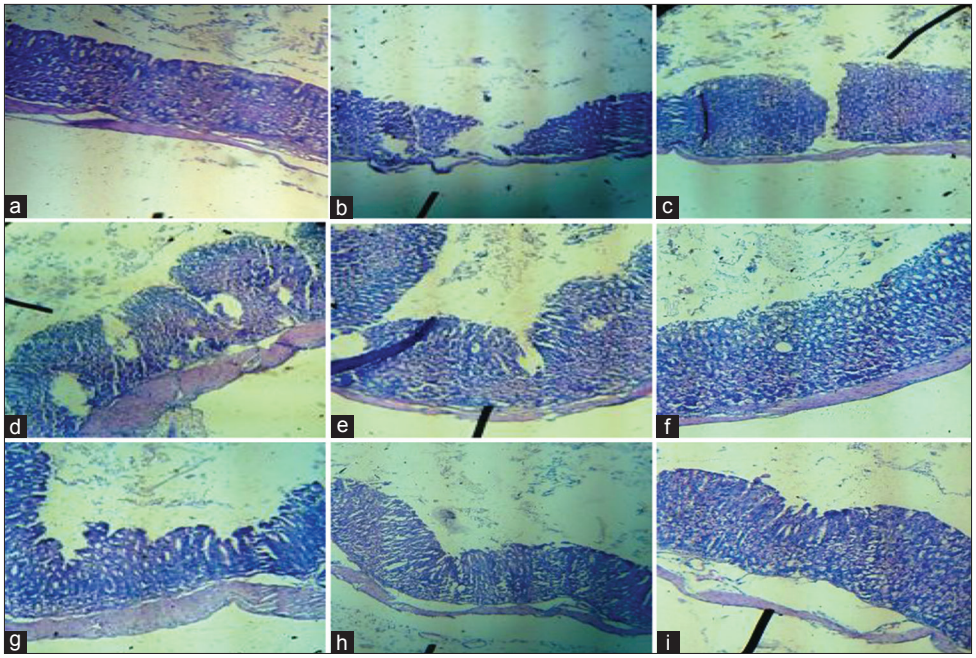

Figure 3: Histopathologic assessment, viewed under low-power objective, of gastric mucosa obtained from, (a) untreated control group (normal), (b) aspirin-induced ulceration untreated 6 days after aspirin administration (negative control), (c) aspirin-induced ulceration treated with sucralfate for 3 days (positive control), (d) aspirin-induced ulceration treated with 25% extract for 3 days, (e) aspirin-induced ulceration treated with 50% extract for 3 days, (f) aspirin-induced ulceration treated with 75% extract for 3 days, (g) 25% extract prophylaxis before aspirin induction, (h) 50% extract prophylaxis before aspirin induction, (i) 75% extract prophylaxis before aspirin induction

suppressed, gastric ulceration would preferentially occur.[16] One of the drugs providing superficial cytoprotection for the stomach is sucralfate for an ulcer in a week long duration.[17] In assessing gastric ulcers, cellular adaptations are visible microscopically, stemming from the normal growth and tissue development of an organ to the pathologically inclined condition due to environment changes. Normally, an intact muscularis externa, submucosa, and gastric mucosa will reflect the presence of chief cells found just above the submucosa occupying one-fourth of the entire gastric mucosa. These normal chief cells are usually distinguished by their condensed basal nuclei and basophilic granular cytoplasm because they contain numerous ribosomes, which contain large doses of proteins responsible for peptin secretion.[18] On the other hand, parietal cells are found just above the chief cells. They are the largest, pyramidal cells with extensive eosinophilic cytoplasm and a centrally located nucleus occupying more than half of the gastric mucosa.

Gastric mucosal condition is determined by the extent of either destruction or repair occurring naturally in the stomach. Once the destructive forces such as gastric juices and NSAIDs exceeded the natural capacity of the stomach to stand their presence and repair the cells for any damage, it begins to show signs of inflammation[19] with superficial erosions of gastric mucosa and destruction of the basal lamina.[20] In this study, one of the major complications of NSAIDs was observed, where tissue necrosis has extended through the artery causing hemorrhage with great number of blood clots and perforations all over the gastric mucosa. Fibrous tissue formations are found at different portions of the stomach as visible meshwork of interwoven fine strands acting as a physical barrier limiting the invasion of foreign microorganisms. When aspirin was removed after 3 days on induction, following 3 more days of water administration, tissues eventually emerged after the destruction suggesting autohealing.[21] The muscularis mucosa is still visible and quite intact, but its surface is starting to erode, the adipose tissues are starting to invade, the chief cells are degrading, and the parietal cells are redilating due to necrosis.

Necrosis is characterized by vacuolation which is a vast growing number of distinct, irregular spaces in between tissues. If degradation does not cease, the nucleus of parietal cells which are initially rounded and brightly stained will soon get smaller and fragment into minute particles. The decrease in parietal moiety suggests shrinkage in cell population and structure due to injury. The foveolar cells are highly vacuolated, characterized by the elongated dilations and the continuous replacement of adipose tissues. Epithelial cells start to re-grow and occupy the damaged surfaces of the gastric mucosa accounting for the disruption of the gastric mucosa with partial restoration after 6 days showing autohealing. Autohealing is characterized by the desquamation of the surface mucus cells into the lumen, with complete restoration of the population for about 3 days. The newly formed cells are displaced upward to replace the lost cells at the surface.[20] Mucus release promotes epithelial recovery by neutralizing luminal acid, protecting against pepsin, oxidants, and other

damaging agents[22] with hexosamine as the main constituent of gastric mucin.[23]

Administration of varying concentrations of *A. paniculata* has resulted to re-epithelialization and healing. When compared with the untreated group, the curative treatment groups showed less parietal cells. In the case of the negative control, parietal cells are apparently normal but the foveolar cells almost disappear. Gastric ulcerations are distinguishable by the breaks in gastric mucosa extending through the submucosa and the muscularis externa. The muscularis externa is thin and almost eroded with no visible capillaries and vessels. The positive control showed signs of regeneration and repair from ulceration, the gastric mucosa is thicker, and the parietal cells are slightly regenerated when compared with the negative control. The clumps of cells above the gastric mucosa are the cells replaced by new cells. The 25% *A. paniculata* curative treatment is showing slight regeneration of the mucosa. The central ulceration is regenerating upward to form normal mucosa. For the 50% *A. paniculata* curative treatment, no ulcerations are found, but slight dilations of the mucosa and erosions are still visible. As compared with the 25% *A. paniculata* curative treatment, slightly shallow erosions are found. The 75% *A. paniculata* curative treatment is showing seemingly normal gastric mucosa, although some circular formations are still present within the mucosa. These may be ulcerations or erosions formed earlier that significantly healed over time, or artifacts resulting from staining procedures. In comparison with the normal and positive control, the curative group shows better efficiency than sucralfate, since healing accompanied the curative group showing that at concentrations 50-75%, no ulcerations are visible. For the prophylactic group, no ulcerations were found as the 25% prophylactic treatment revealed oval and dilated cells with an intact gastric mucosa. The 50% prophylactic treatment displayed elongated dilations of parietal and foveolar cells with intact gastric mucosa when compared to the 25% prophylactic treatment. The 75% prophylactic treatment has regenerated normal population of cuboidal parietal cells occupying one-half of the gastric mucosa with slight dilations in the foveolar cells. Overall, the prophylactic group shows no typical ulcerations at the gastric mucosa suggesting the protective potential of *A. paniculata*.

CONCLUSION

Crude extract of *A. paniculata* plant has an ulcer curative and prophylactic effect. There is a remarkable decrease in the severity of ulceration noted at 25% extract concentration. Reduced ulceration, faster regeneration, and repair observed in the 50% extract concentration, while the 75% extract concentration produced histologically normal gastric mucosa in just 3 days of administration. The prophylactic group showed the same result when all the *A. paniculata* extract concentrations hindered progression of gastric ulceration.

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