

Full Length Research Paper

Anti-ulcerogenic properties of *Albuca setosa*

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Albuca setosa is a medicinal plant used by Xhosa tribe in the rural area of South Africa for the treatment of wounds, articulation problems, rheumatoid arthritis and digestive disorders. This study aimed to evaluate the healing effect of *A. setosa* on experimental induced gastric ulcer. The anti-ulcerogenic effects of *A. setosa* were investigated in male Wistar rats. Gastric ulcer was induced *per os* using indomethacin (50 mg/kg) and ethanol (2 ml/animal). The ulceration lesion index was calculated for each one of the ulcerated stomach; the macroscopic and histomorphology evaluation were made. In indomethacin-induced gastric ulcers, oral administration of *A. setosa* significantly inhibited ($P < 0.01$) gastric ulcer formation by 82 and 83% at the dose of 100 and 200 mg/kg, respectively. In ethanol-induced gastric ulcers, *A. setosa* significantly inhibited ($P < 0.05$) gastric ulcer formation by 39 and 35% at the dose of 100 and 200 mg/kg, respectively. Macroscopic evaluation of ulcerated stomachs of *A. setosa* treated groups showed a reduced area of gastric lesion, with moderate disruption of the gastric epithelium as well as the mucosa stromal cell. The results obtained in this study suggest that the *A. setosa* possesses some anti-ulcerogenic properties, which may support evidence for its traditional use.

Key words: Gastric ulcer, indomethacin, ethanol, *Albuca setosa*, inflammation.

INTRODUCTION

Albuca setosa, also known as “*inqwebeba*” by Xhosa people living in the Eastern Cape province of South Africa is widely distributed from Namaqualand, the Southwest Cape, Eastern Cape province of South Africa to the Kingdom of Swaziland. The plant is found on rocky grounds, flats and mountain slopes. Xhosa tribes use *A. setosa* for cultural purposes such as ritual wash, an emetic and facial and body steam treatment to protect against bad luck and sorcery. In addition, the plant in this region is used for ritual purification such as body wash, and therapeutically as a purgative, spraying and fumigating (Cocks, 2006). *A. setosa* leaves are used for treatment of wounds, articulation problems, rheumatoid arthritis, and gastric ulceration and could also be used as an anthelmintic, lotion for washing wounds in animals and to treat venereal diseases (Hutchings et al., 1996). *A.*

setosa is often available through commercial trade at around US\$ 3.5 /kg, depending on the availability of the plant and the season. Very few studies have reported the healing properties of the plant; the anti-inflammatory properties and the suggested mechanism of action of *A. setosa* were reported by Ndebia et al. (2011). Subsequent work by the authors revealed that an *A. setosa* possesses some membrane stabilization properties, which could limit the process of protein denaturation and decrease white blood cell migration during acute inflammation (Umapathy et al., 2010). However, it is important to understand the bio-cellular function of the plant since it is commonly used for digestive disorders and inflammation. The aim of this study was to investigate the anti-ulceration properties of *A. setosa* in experiment gastric ulcer induced by indomethacin and alcohol.

MATERIALS AND METHODS

Plant

The plant materials of *A. setosa* were collected from its natural environment at approximately 5 km South West of Flagstaff in the OR Tambo municipality, Eastern Cape Province of South Africa. The identification and authentication of the plant was done at the Kei Herbarium at Walter Sisulu University in Mthatha. Leaf sample of the *A. setosa* was chopped, air dried and grounded to powder (pulverised). The resulted dried powder weighed 40 g was macerated in distilled water. The mixture was shaken for 72 h on an orbital shaker and taken into a Buchner funnel and Watman No.1 filter paper and then concentrated to dryness using freeze dryer (Freeze dryer Modulyo, EDWARDS) where a resulted 5 g brown powder was obtained. A preliminary screening of the plant's toxicity and activity suggested the choice of the minimum effective dosage between 100 and 200 mg/kg which were used in the study (Data not shown).

Animals

Albino male Wistar rats weighing 150 to 200 g were provided by South African Vaccine Producers (SAVP). The animals were put in plastic cages and housed at the Walter Sisulu University's (WSU) animal house, they were fed with a standard pellet diet (Epol) and water *ad libitum*. The animals were kept into eight groups of six animals each in standard cages at room temperature in 12 h dark and 12 h light control. The experiments were performed in accordance with the recommendations of the declaration and guiding principles laid down by Animal Welfare Organization and the Society for the Prevention of Cruelty to Animals (SPCA). Ethics clearance no. 0023/009 was obtained from the Faculty of Health Sciences Ethics Committee, Walter Sisulu University.

Phytochemical screening

The extract of *A. Setosa* was routinely screened for various constituents (alkaloids, saponins, tannins, flavonoids, anthrocyanosides, reducing sugars) using an established method (Ikhir et al., 1992).

Indomethacin induced gastric ulcer

Male adult Wistar rats were used for the experiment; the animals were randomly divided into four groups of six rats each. Food was withdrawn 24 h and water 2 h before the commencement of experiment. Group 1 (control) received distilled water (10 ml/kg), Groups 2 and 3 were pre-treated with *A. Setosa* aqueous extract (100 and 200 mg/kg p.o. respectively) and Group 4 received omeprazole (20 mg/kg p.o. dissolved in 5% Tween 80), a standard anti-ulcer drug which action decreases the secretion of gastric HCl. One hour later, animals in all the groups (1 to 4) were administered with indomethacin (Fluka, 50 mg/kg p.o.). Four hour following indomethacin administration, animals were killed by high dose of anaesthesia (diethyl ether, ACE). The stomachs were removed and opened along the greater curvature before the tissues were fixed with 10% formaldehyde in saline. Macroscopic examination of the ulcerated stomachs was carried out with a hand lens (Kyowa optical, Japan) and the presence of ulcer lesions was scored. The ulcerative lesion index (ULI) of each animal was calculated using the methodology described by Pariera et al. (2005) and as summarized in Table 1. The formula used for the calculation of the percentage of ulceration inhibition in the groups is as follows:

Ulceration inhibition (%) = $\frac{[ULI(\text{control}) - (ULI(\text{treated})/ULI(\text{control}))] \times 100}{}$

Table 1. Ulcerative Lesion Index (ULI) determination on a ulcerated rat stomach.

Loss of normal morphology	1 point
Discoloring of mucous membrane	1 point
Mucous edema	1 point
Hemorrhages	1 point
Petechial points	(until 9) 2 points
Petechial points	(> 10) 3 points
Ulcers up to 1 mm	*n × 2 points
Ulcers > 1 mm	*n × 3 points

*Number of ulcers found.

where ULI is ulcerative lesion index.

Absolute ethanol induced gastric ulcer

The animals received similar treatment as described earlier in the indomethacin induced gastric ulcer with a slight difference. Male adult Wistar rats were used for the experiment. Animals were randomly divided into four groups of six rats each. Food was withdrawn 24 h and water 2 h before the commencement of experiment. Group 1 (control) received distilled water (10 ml/kg), Groups 2 and 3 were pre-treated with *A. Setosa* aqueous extract (100 and 200 mg/kg p.o., respectively) and Group 4 received omeprazole (20 mg/kg p.o. dissolved in 5% Tween 80). One hour later, animals in all the groups (1 to 4) were administered with 2 ml of absolute ethanol. One hour after alcohol administration, animals were killed by high dose of anaesthesia (diethyl ether, ACE). The stomachs were removed and opened along the greater curvature before the tissues were fixed with 10% formaldehyde in saline. Macroscopic examination of the ulcerated stomachs was carried out with a hand lens (Kyowa optical, Japan) and the presence of ulcer lesions was scored. The ulcerative lesion index of each animal was calculated using the same formulation as described previously with indomethacin induced ulcer.

Histomorphological studies of ulcerated stomach

Stomachs obtained from each rats were fixed in 10% buffered formalin and were routinely processed for histology using an auto processor. Glandular portions of the stomach were trimmed and embedded in paraffin wax. Tissue sections were cut at a thickness of 5 µm and stained with Haematoxylin and Eosin for evaluation. The sections were analyzed using a light microscope at ×200 magnification.

Statistical analysis

All data obtained were reported as mean ± standard error mean (SEM) and were carried into the statistical software Graphpad Instat version 3.06 and analyzed using the analysis of variance (ANOVA), followed by the Dunnett's test. The level of protection between rats treated with 100 and 200 mg/kg of *A. setosa* aqueous extract and the control group was calculated by considering the difference in ulcerative lesion index (ULI). A 100% protection indicated that there was complete inhibition on the gastric mucosa due to the effect of the plant's extract, while a 0% protection indicated there was no inhibition of gastric lesions. P value less than 0.05 (P<0.05) were considered statistically significant.

Table 2. Phytochemical analysis of the *A. setosa*.

Alkaloids	+
Tannins	-
Saponins	+
Flavonoids	+
Anthrocyanosides	-
Reducing sugars	-

Present (+), not present (-).

RESULTS

Phytochemical analysis

Phytochemical analysis summarized in Table 2 revealed the presence of alkaloids, saponins and flavonoids in the plant.

Indomethacin-induced gastric ulceration

The extract (p.o.) pre-treatment with indomethacin-induced gastric ulceration showed a decrease in ulcer indices in treated groups relative to control. This decrease was statistically significant ($P < 0.01$) when compared with the control group (Table 3). The effect was comparable to that of the standard drug, omeprazole.

Ethanol-induced gastric ulceration

The extract (p.o.) pre-treatment with ethanol-induced gastric ulceration showed a decrease in ulcer indices in treated groups as compared to control group. The reduction was statistically significant ($P < 0.05$) with both dosage compared to control (Table 4). The effect was comparable to that of the standard drug, omeprazole.

Gross evaluation of gastric lesion

Macroscopic evaluation of anti-ulcerogenic activity of *A. Setosa* in indomethacin or ethanol-induced gastric lesion is as shown in Figures 1 and 2. Results showed that rats pre-treated with *A. Setosa* (Figure 1b and c) and omeprazole (Figure 1D) had significantly reduced areas of gastric lesions as compared to the control (Figure 1A).

Histomorphology evaluation of gastric ulcer

Control group

The histological study of the ulcerated distilled water pre-treated stomach showed a disruption to the surface epithelium, with an extensive ulceration of the epithelial cells, due to the effects of indomethacin or ethanol. There

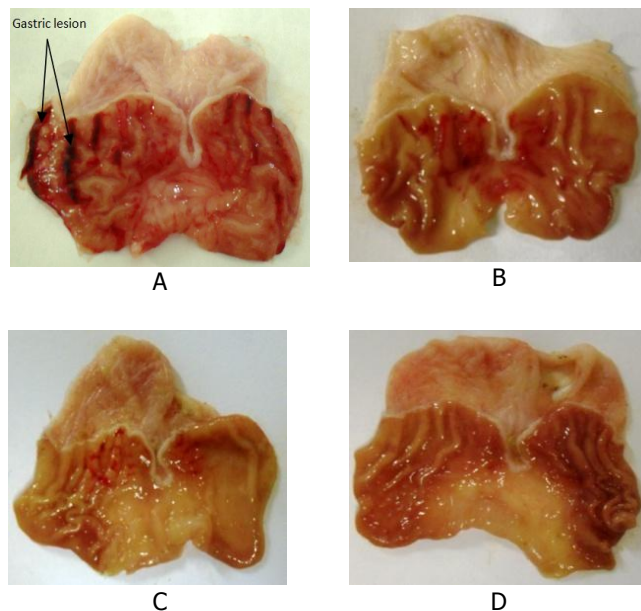


Figure 1. Gross appearance of the gastric mucosa in an indomethacin-induced gastric lesion. Severe ischemic injuries are seen on the entire surface area of the gastric mucosa in the control group, with the presence of prominent lesions (A: Control group); Moderate to reduced ischemic injuries are seen on gastric mucosa in the treated groups, with no apparent gross gastric lesion (B: ASEA 100 mg/kg; C: ASEA 200 mg/kg; D: Omeprazole). ASEA: *A. Setosa* aqueous extract.

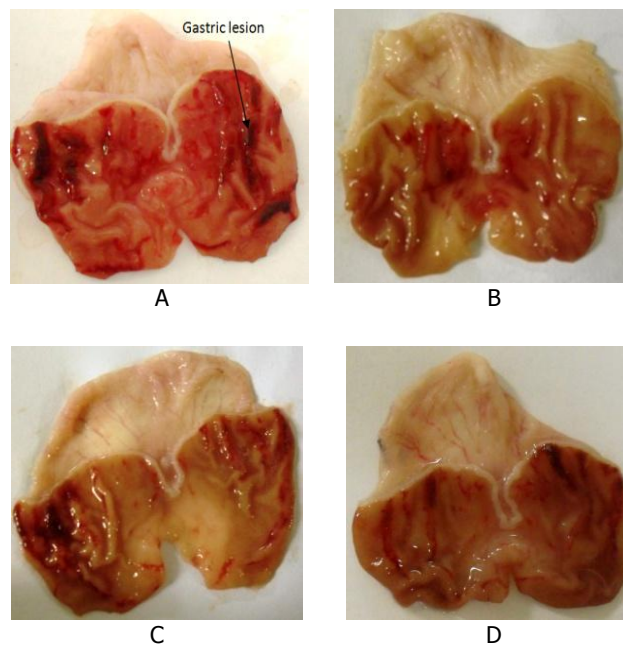


Figure 2. Gross appearance of the gastric mucosa in an Ethanol-induced gastric lesion. Severe ischemic injuries are seen on the gastric mucosa in the control group (A: Control group), with numerous sites of gastric lesions/ulceration; a reduced ischemia is observable in the treated group (B: ASEA 100 mg/kg; C: ASEA 200 mg/kg; D: Omeprazole), but gastric lesions are persistent. ASEA: *A. Setosa* aqueous extract.

Table 3. Effect of oral administration of aqueous extract of *A. setosa* on indomethacin-induced gastric ulcer.

Treatment	Dosage (mg/kg)	Ulcerative lesion index (ULI)	Ulceration inhibition (%)
Control	-	23.0 ± 2.5	-
ASAE	100	4.2 ± 0.8**	82
ASAE	200	4.0 ± 2.1**	83
Omeprazole	20	3.6 ± 0.7**	84

Values are mean ± SEM (n = 6). Variation compared to the control animals ** (P<0.01) ANOVA followed by Dunnett's test. ASAE: *Albuca setosa* aqueous extract.

Table 4. Effect of oral administration of aqueous extract of *A setosa* on ethanol induced gastric ulcer.

Treatment	Dosage (mg/kg)	Ulcerative lesion index (ULI)	Ulceration inhibition (%)
Control	-	43.7 ± 3.7	-
ASAE	100	26.5 ± 5.9*	39
ASAE	200	28.2 ± 7.6*	35
Omeprazole	20	27.2 ± 4.3*	38

Values are mean ± SEM (n = 6). Variation compared to the control animals, *(P<0.05), ANOVA followed by Dunnett's test. ASAE: *Albuca setosa* aqueous extract.

was a significant disruption of the glandular pits, associated with vascular injuries. Extensive scarification of the connective tissue stromal cells was observable; the glandular cells were necrotic, with no evidence of mucous secretions (Figure 3A).

ASAE 100 mg/kg group

Stomachs pre-treated with ASAE 100 mg/kg showed a net recovery of the surface epithelium with no ulceration. The gastric pits were well defined as compared to the control (Figure 3A), with numerous mucinogens (mucous secreting cells) exhibiting mucous secretions at luminal surface and within gastric pits. Mild scarifications of the epithelial underlying connective tissues were also seen in this group; although no cellular necroses glandular cells were apparent. There was also a mild lymphocytic infiltrates seen in the lamina propria (Figure 3B).

ASAE 200 mg/kg group

There was a mild disruption of the surface epithelium in the stomachs pre-treated with ASAE 200 mg/kg. However, the gastric pits were delineated in this group as compared to the control group (Figure 3A); but there were little or no mucous secretions observed. Extensive scarifications very present similar to the control group, however, there were some invasive lymphocytic infiltrates seen in the lamina propria. Most glandular cells lost their detachment to the basement membrane; and the underlying myocytes were flattened exhibiting the necrotic appearance seen in the control group (Figure 3C).

Omeprazole 20 mg/kg

Omeprazole pre-treated stomachs showed a level of recovery of the surface epithelium. The gastric pits were clearly delineated, with a number of mucous secretions observable and comparable to ASA100. There was less evidence of lymphocytic infiltration as compared to ASA200 (Figure 3C). Most goblets cells were well defined and at various mitotic stages; however, there were few scarifications as seen in the control group (Figure 3A).

DISCUSSION

Drug induced damage to the stomach due the increased use of alcohol and a known non-steroidal anti-inflammatory drug (NSAID) is a worldwide phenomenon. Gastric ulcers are caused when the aggressive factors of acid and pepsin overpower the defensive mechanisms of mucus, bicarbonate, mucosal turnover leading to deterioration of the mucosal barrier and disturbance of blood supply (Piper and Stiel, 1986). The resulted ulceration could be well managed by decreasing the aggressive factors and/or by a natural substance enhancing the protective factors of the stomach. *A. setosa* is a plant that has been used in the management and treatment of inflammation, painful conditions and digestive disorders in the Eastern Cape province of South Africa. The anti-inflammatory properties and its suggested action mechanisms were reported by Ndebia et al. (2011). Previous studies have shown the stabilization properties of *A. setosa*, which could limit a process of protein and decrease white blood cell migration that is seen in acute inflammation (Umapathy et al., 2010). In the present study,

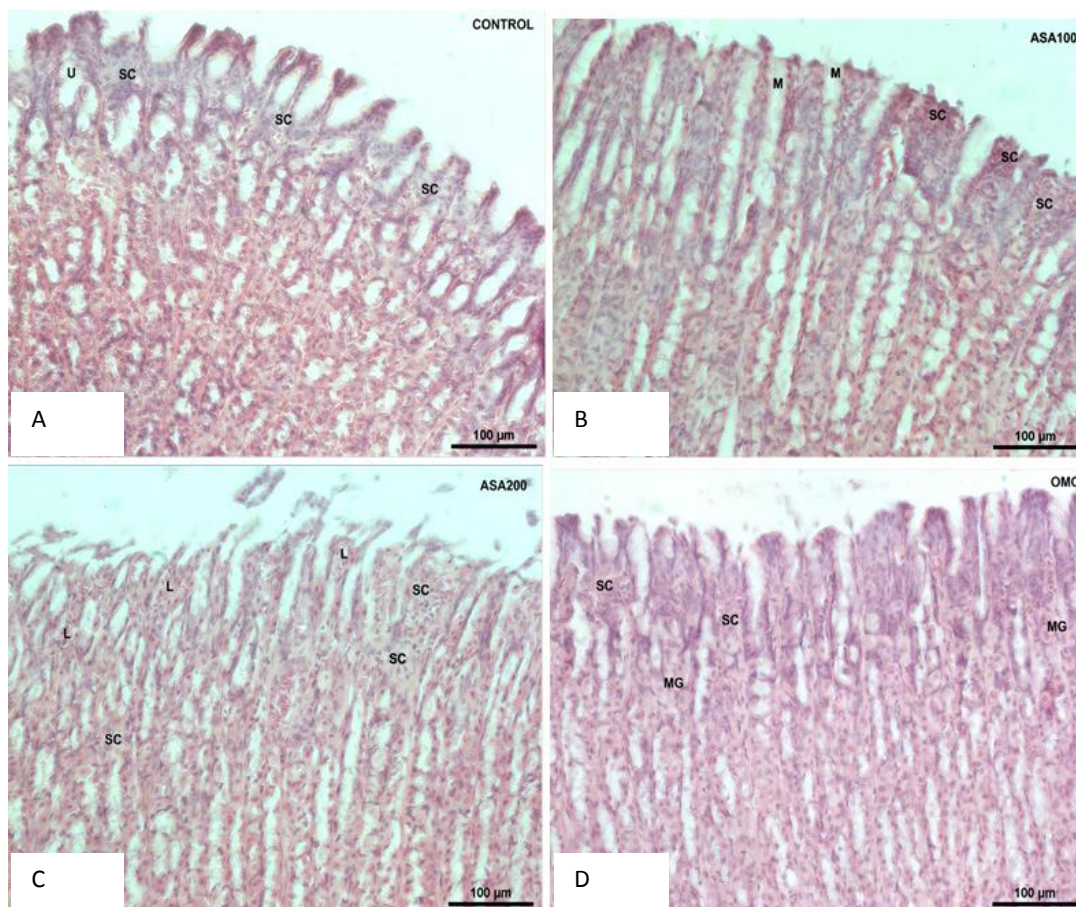


Figure 3. Histomorphological observation of gastric mucosae in indomethacin or ethanol induced gastric lesion. Treatment with distilled water (A) shows ulceration (u) of the surface epithelium; the underlying tissue exhibits scarification (SC), with highly distorted gastric pits. ASAE 100 mg/kg (B) shows scarification underlying recovering surface epithelial cells. There are numerous goblet cells exhibiting mucous secretions (M). C and D show stomachs treated with ASAE 200 mg/kg and Omeprazole, respectively; while C shows high lymphocytic infiltrations with little or no mucous secretion, Fig 3d exhibits moderate epithelial repaired with high levels of mitotic goblet cells (MG), and very little mucinogens. U: Ulceration, ASAE: A. *Setosa* aqueous extract, SC: scare formation, L: lymphocyte infiltrates, M: Mucous secretion, MG: mitotic goblet cells, Magnification X200.

the effect of the plant on gastric ulcer protection was evaluated; the extract demonstrated a potent efficiency against gastric ulcer induced with indomethacin and ethanol, respectively.

Indomethacin, a known ulcerogenic drug, induces ulcer mostly on the glandular (mucosal) part of the stomach by inhibiting prostaglandin synthetase (Okokon et al., 2009). The main physiological role of prostaglandins in the stomach is to increase bicarbonate and mucus secretion (Hiruma-Lima et al., 2006); therefore, the suppression of prostaglandins synthesis by indomethacin lead to an increased susceptibility of stomach to mucosal injury and gastro-duodenal ulceration. Indomethacin led to the blockade of the Cyclo-oxygenase (COX) pathway, thus shifting the arachidonic acid metabolism to the 5-Lipo-oxygenase (5 LO) pathway which in turn led to enhanced production of leukotrienes (LTC₄ and LTD₄), leading to

glandular disruption, excessive ulceration, and bleeding (Rainsford, 1987) as seen on the macroscopic observation of our ulcerated stomach sample. *A. setosa* aqueous extract (ASAE) was observed to significantly reduce mucosal damage in the indomethacin-induced ulcer model, suggesting the plausible extract mobilization and the involvement of prostaglandin in the anti-ulcer effect of the plant's extract.

Absolute ethanol produces linear hemorrhagic lesions, extensive submucosal edema, mucosal friability and necrosis of the gastric mucosa by its direct toxic effects, thereby reducing the secretion of bicarbonates and production of mucus (Franke et al., 2005). Chronic alcohol misuse is associated with significantly reduced capacity for prostaglandin synthesis in gastric mucosa (Zhao et al., 2009). Ethanol however, produces exogenous and endogenous active oxygen and free radicals

leading to gastric lesions giving an appearance of multiple-hemorrhagic red bands of different sizes along the glandular stomach as observed in the macroscopic evaluation of our ulcerated stomach sample. This oxidative damage is produced as a result of lipid peroxidation mediated by the interaction of hydroxyl radicals with the cell membrane, subsequently producing lipid-derivative free radicals such as conjugated dyes and lipid hydro-peroxides (Pereira et al., 2005), that release hydroxyl radicals “steal” electrons thus damaging the gastric mucosa. Absolute alcohol has extensively damaged the gastric mucosa allowing an increased neutrophil infiltration into the gastric mucosa leading to the ulceration of the epithelium with highly distorted glandular pit as seen on the histomorphological assessment of our ulcerated sample. Actions of neutrophils are known to mediate lipid oxidation through the production of superoxide anions (Kobayashi et al., 2001); the resulting oxygen-free radicals favor the inhibitory effects of the healing process in gastric ulceration in the rat (Alrashdi et al., 2012). A study attempting to suppress the infiltration of neutrophils during the inflammatory process has resulted in an enhanced gastric healing (Tsukimi et al., 1996). This finding is further supported by the mild lymphocytic infiltration of neutrophils in the lamina propria of the stomach rats treated with ASAE in this study. This is a clear indication that ASAE might be blocking one of the steps of acute inflammation leading to the decrease of the gastric lesions, hence its anti-ulcer properties. The white blood cell anti-migration effects of ASAE have been demonstrated in their study by Umapathy et al. (2010); further studies by Ndebia et al. (2011) also confirmed their anti-inflammatory activity of the plant's extract.

Flavonoids protective function on gastric mucosa is known to increase mucosal prostaglandin content and inhibit histamine secretion from mast cells (Borelli and Izzo, 2000). It was also proven that flavonoids such as quercetin prevent gastric mucosal lesions in various experimental models by increasing the amount of neutral glycoproteins (Zayachkivska et al., 2005). Furthermore, flavonoids (Singh et al., 2007, Lakshmi et al., 2010) and tannins (Eswaran et al., 2010) have also been shown to be efficient in preventing gastric damage induced by the oral administration of absolute ethanol in rats. The protective effect of saponins against anti-ulcer induced with ethanol- and/or indomethacin-induced gastric lesions in rats was also reported (Pongpiriyadacha et al., 2003; Matsuda et al., 2002). Alkaloid was also proven to increase free mucus and prostaglandin in the gastric mucosa, with a decreased exfoliation of the superficial cells, haemorrhage and blood cell infiltration that could all be mediated by increase in gastrin secretion, hence demonstrating a protective effect of mucus secretion against gastric ulcer (Toma et al., 2004). Taking this into consideration, the anti-ulcerogenic properties of ASAE could be due to the presence of alkaloids, flavonoids and saponins as demonstrated in the phytochemical study of the plant.

Conclusion

Conclusively, this study confirmed that *A. setosa* aqueous extract possesses some anti ulcerogenic properties, which may provide evidence for its folkloric use and further exploitation. The action mechanism of the plant is suggested to be due to the flavonoids, alkaloids and saponins that possess both anti-inflammatory and anti-ulcerogenic activities. Nevertheless, the action mechanism of the plant on the ulcer healing process needs further investigations.

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