Gastric Antiulcer Activity of *Syngonanthus arthrotrichus* Silveira

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Syngonanthus arthrotrichus Silveira, **popularly known as "sempre-vivas mini-saia," is found in mountains of the Espinhaço range in the Brazilian states of Bahia and Minas Gerais. Extracts of this species contain several constituents, including flavonoids which may have antiulcerogenic activity. An ethanolic extract (EEOH), and flavonoid-rich (FRF) and flavonoid-deficient (FDF) fractions obtained from the scapes of *S. arthrotrichus* were investigated for their ability to prevent ulceration of the gastric mucosa in mice and rats. In the ethanol/HCl-induced ulcer model, lansoprazole (30 mg/kg), EEOH (50, 100, 250 mg/kg) given orally protected the gastric mucosal against injury in mice by 79%, 78%, 73%, and 64% respectively. In the ethanol-induced gastric ulcer model in rats, the lansoprazole (30 mg/kg), FRF and FDF (100 mg/kg) significantly protected the gastric mucosal of rats by 65%, 38% and 25% respectively when compared with the negative control group. In indomethacin/bethanechol-induced gastric ulcers, cimetidine (100 mg/kg) and the EEOH (100, 250 mg/kg) inhibited gastric ulcer formation by 73%, 55% and 32% respectively. In this exactly model other treatments as cimetidine, FRF and FDF (100 mg/kg) each caused 54%, 36% and 45% inhibition, respectively. In the stress-induced gastric ulcer model, cimetidine (100 mg/kg) and the EEOH (50, 100, 250 mg/kg), inhibited gastric ulcer formation by 63%, 73%, 68% and 69% respectively. In the same model, cimetidine, FRF and FDF (100 mg/kg) significantly protected the gastric mucosal of the mice by 60%, 51% and 47% when compared to the control group. In pylorus-ligated mice, cimetidine (positive control) and FRF significantly decreased gastric acid secretion, increased gastric pH and reduced the acid output when compared to the negative control. FDF had no significant effect on these parameters. The protection provided by FRF probably involved an antisecretory mechanism mediated by flavonoids which were absent in FDF. The amount of adherent mucous in the stomach contents was also evaluated with the treatments carbenoxolone (200 mg/kg), FRF and FDF (100 mg/kg) treatment. Each treatments significantly increased the amount of adherent mucous in the gastric juice (8.67±1.73, 3.35±1.59, 2.1±0.41 mg/g of wet tissue, respectively) compared to the control group, indicating a cytoprotective action on the gastric mucosa. Treatment with FRF plus indomethacin and FDF plus indomethacin reduced the prostaglandin biosyntesis (13.6±6.5, 27±5.5 pg/well) by the mucosa, indicating that the cytoprotective action on the gastric mucosa was not related to the level of prostaglandins. Only FDF (38±17 pg/well) maintained the level of prostaglandins and guaranteed the integrity of the mucosa. The results indicate that the EEOH, FRF and FDF have antisecretory and cytoprotective actions, that may be related to the presence of luteoline in the extract and active fractions.**

Key words   *Syngonanthus arthrotrichus*; antisecretory; cytoprotective; ulcer; flavonoid

Syngonanthus arthrotrichus Silveira (Eriocaulaceae) popularly know as "sempre-vivas mini-saia" is found chiefly in the Espinhaço mountain range in the Brazilian states of Bahia and Minas Gerais where it grows in rocky or sandy soil in areas of open vegetation.[1]

The family Eriocaulaceae is complex and includes diverse herbaceous, monocotyledonous species which have miniature flowers grouped in clusters. These plants have inflorescences and scapes that retain the appearance of living structures when dried.[2] Species of the genus *Syngonanthus* are of economic importance since they are exported as ornamental plants to various countries.

Little is known about the ethnopharmacology of *Syngonanthus* species. Phytochemical studies have detected a variety of chemical constituents,[3,4] including flavonoids which have antiulcerogenic, antioxidant,[5] and immunostimulant actions.[6]

Gastric and duodenal ulcers affect a large proportion of the world population and are induced by several factors, including stress, smoking, nutritional deficiencies, and ingestion of nonsteroidal anti-inflammatory drugs.[7,8]

Protection of the gastric mucosa involves the factors such as acid-pepsin secretion, parietal cell activity, mucosal barrier, mucus secretion, blood flow, cell regeneration, and the release of endogenous protective agents, especially prostaglandins and epidermal growth factors.[9]

Numerous approaches have been used to combat gastric ulcers, including the control of acid secretion, *Helicobacter pylori* level, and H^+/K^+-ATPase activity, in an attempt to reverse mucosal damage and inflammation.[10] In this context, extracts and active principles from plants could serve as leads for the development of new drugs.[11] Flavonoids such as catechin, hypoletin, apigenin, luteolin, rugin, and genistein have antiulcer activity.[12—15]

The objective of this study was to investigate the antiulcerogenic action of extracts from *Syngonanthus arthrotrichus* in ulcers induced by different agents in mice and rats and to examine the action mechanisms involved.

MATERIALS AND METHODS

Drugs   Lansoprazole (30 mg/kg *p.o.*), cimetidine (100 mg/kg v.o.), indomethacin (30 mg/kg s.c.) and bethanechol chloride (5 mg/kg i.p.) were obtained from Sigma Chemical

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Co., St. Louis, Mo, (U.S.A.). An ethanolic extract (EEOH), as well as flavonoid-rich (FRF) and flavonoid-deficient (FDF) fractions were obtained from the scapes of *S. arthrotrichus*, and were dissolved in 0.9% of saline (w/v). The EEOH was administered at doses of 50, 100, 250 mg/kg and the FRF and FDF at a dose of 100 mg/kg. Drugs such as cimetidine or lansoprazole, plant extract and fractions were administered intraduodenally or orally by gavage.

Animals Male Swiss albino mice (30—40 g) and male Wistar rats (180—250 g) obtained from the breending of the State University of Campinas (CEMIB/UNICAMP) were used. The animals were fed a certified Nuvilab CR-diet, with free access to tap water, and were housed on a 12 h light/dark cycle at $60 \pm 1\%$ humidity and a temperature of $21.5 \pm 2\,°C$. The experimental protocols were approved by the Institutional Committee for Ethics in Animal Experimentation (CEEA/UNICAMP).

Plant Material *Syngonanthus arthrotrichus* was collected in the Serra do Cipó mountain range in the state of Minas Gerais, Brazil. A voucher specimen was deposited in the Herbarium of the Departament of Botany of the Institute of Biosciences, University of São Paulo, Brazil.

Ethanolic Extracts and Active Fraction Scapes (500 g) of *S. arthrotrichus* collected in the Serra do Cipó, Minas Gerais, were dried in an oven at 60 °C for 4 d and then powdered. The resulting material was macerated sequentially at room temperature in methylene chloride, EEOH and 70% EEOH for one week with each solvent. The extracts were filtered and concentrated under vacuum.

Phytochemical Analysis The EEOH and 70% EEOH extracts were analyzed by TLC on silica gel plates using *n*-BuOH/HOAc/H_2O (6 : 1 : 2, v/v/v). The TLC spots were detected using UV light and NP/PEG reagent which yields yellow or orange spots characteristic of flavonoids. Since these extracts contained material with similar retention factors (*Rf*), they were combined and weighed.

A sample (3.5 g) of the ethanolic extract was dissolved in 10 ml of MeOH and fractionated on a Sephadex LH-20 CC column (100×3 cm). The extract was eluted in MeOH at a flow rate of 0.5 ml/min and 3 ml fractions were collected. The fractions were combined based on their migration in the TLC system described above. Fractions 1—22 were deficient in flavonoids, fractions 23—47 were intermediate fractions and fractions 58—64 were rich in flavonoids. Analysis by HPLC-ES-MS with UV detection showed that luteoline was present in the extract and fractions.

Antiulcerogenic Activity The antiulcerogenic activity of the ethanolic extract (EEOH), and of the FRF and FDF fractions of *S. arthrotrichus* was investigated in several experimental ulcer models.

HCl/Ethanol-Induced Gastric Lesions These lesions were produced as described by Mizui and Doteuchi (1983)[16] with some modifications. Mice were fasted for 24 h and then given an oral dose of saline (10 ml/kg), lansoprazole (30 mg/kg), EEOH (50, 100, 250 mg/kg), and FRF or FDF (100 mg/kg). After 50 min, all groups were treated orally with 0.2 ml of a 0.3 M HCl/60% ethanol solution (HCl/ethanol) to induce gastric ulcers. The mice were sacrificed 1 h after the administration of HCl/ethanol and the stomachs were excised after the injection of 2 ml of 0.9% saline. The results were expressed as an ulcerative index (UI) as described by Szelenyi and Thiemer.[17]

Ethanol-Induced Gastric Lesions Ethanol-induced ulcers were produced in rats according to the method of Morimoto (1991).[18] Twenty-eight rats were randomly divided into four groups and fasted for 24 h before the experiment, but had free access to water. One milliliter of 99.5% ethanol was administered orally to rats treated 1 h previously with FRF or FDF (100 mg/kg), lansoprazole (30 mg/kg) or saline (10 ml/kg). One hour after the administration of ethanol, the rats were killed and the stomachs were removed for examination. The results were expressed as an ulcerative index (UI) as described above.

Indomethacin/Bethanechol-Induced Gastric Lesions This experiment was performed by the method of Rainsford (1978).[19] Gastric lesions were induced with indomethacin (30 mg/kg, s.c.) and bethanechol (5 mg/kg, i.p.) administered to mice after a 24 h fast. EEOH (50, 100, 250 mg/kg), FRF and FDF (100 mg/kg), cimetidine (100 mg/kg) or saline (10 ml/kg) was administered orally 30 min before the induction of gastric lesions. The animals were killed by cervical dislocation 4 h after treatment with the ulcerogenic agents. The stomachs were removed and the gastric damage was assessed as described above.

Hypothermic Restrain Stress-Induced Gastric Lesions The method of Levine (1971)[20] was used with some modifications. Mice were divided into groups of seven animals each. After a 24 h of fast, the animals received an oral dose of saline (10 ml/kg), cimetidine (100 mg/kg), EEOH (50, 100, 250 mg/kg) or FRF and FDF (100 mg/kg). One hour after treatment, gastric ulceration was induced by immobilizing the animals in a closed cylindrical cage maintained at 4 °C. After 4 h, the animal were sacrificed and the stomachs removed and opened along the great curvature. The results were expressed as ulcerative index (UI) as described above.

Determination of Gastric Secretion Gastric secretion was assessed by the method of Shay (1945)[21] with some modifications. The mice were fasted for 24 h, with free access to water. After ligation of the pylorus, FRF or FDF (100 mg/kg), cimetidine (100 mg/kg) or saline (10 ml/kg) was administered intraduodenally. The mice were killed by cervical dislocation 4 h later, the abdomen was opened, and another ligature was placed around the esophagus close to the diaphragm. The stomachs were removed and the volume of gastric juice (ml) and pH were determined. Distilled water (5 ml) was added and the solution was centrifuged at 3000 rpm for 10 min. The total acid in the gastric secretion was determined in the supernatant volume by titration to pH 7.0 with 0.01 N NaOH.

Determination of Mucus in Gastric Content This assay was done as described by Corne (1974)[22] with some modifications. Rats were fasted for 24 h and, under anesthesia, the abdomen was incised and the pylorus ligated. Saline (10 ml/kg), carbenoxolone (200 mg/kg), FRF and FDF (100 mg/kg) was then administered intraduodenally after ligation of the pylorus. The animals were killed by cervical dislocation 4 h after ligation and the glandular segments of the stomachs were removed and weighed. Each glandular segment was immediately immersed in 10 ml of the 0.1% alcian blue solution (0.16 M sucrose/0.05 M sodium acetate, pH 5.8). After immersion for 2 h, excess dye was removed by two successive rinses with 10 ml of 0.25 M sucrose, first for 15 min

and then for 45 min. The stomach was all sequentially transferred to 0.5 M magnesium chloride and shaken for 2 h. Four milliliters of the blue extract was then shaken vigorously with an equal volume of ether. The resulting emulsion was centrifuged at 3600 rpm and the absorbance of the aqueous layer was read at 580 nm. The amount of alcian blue extracted per gram of wet glandular tissue was then calculated.

Determination of Prostaglandin Synthesis This experiment was done according to the method of Curtis (1995) in rats.[23] The animals were killed by cervical dislocation 30 min after treatment with saline (10 ml/kg), or saline (10 ml/kg) plus indomethacin (20 mg/kg, s.c.) or FRF or FDF (100 mg/kg v.o.), or FRF or FDF (100 mg/kg v.o.) plus indomethacin (20 mg/kg, s.c.). The abdomen of these animals were opened, samples of the corpus (full thickness) were excised, weighed and suspended in 1 ml of 10 mM sodium phosphate buffer, pH 7.4. The tissue was minced finely with scissors and incubated at 37 °C for 20 min. The prostaglandin content of the buffer was measured using an enzyme immunoassay (RPN222, Amersham).

Statistical Analysis The results are expressed as the mean±S.D. Statistical significance between groups was assessed by one-way analysis of variance (ANOVA) followed by Dunnett's test with the level of significance $p < 0.05$.

RESULTS AND DISCUSSION

Plants contain a large variety of natural products with diverse biological activities, including antiulcerogenic actions.[24] In this work, we examined the antiulcerogenic effect of an ethanolic extract (EEOH), and flavonoid-rich (FRF) and flavonoid-deficient (FDF) fractions obtained from the scapes of *S. arthrotrichus* in mice and rats using different experimental models of gastric ulcers.

Although in most cases the etiology of ulcers in unknown, it is generally accepted that they result from an imbalance between factors such as acid and pepsin production and the maintenance of mucosal integrity through endogenous defense mechanisms.[25]

Oral treatment with ethanol causes focal hyperemia, edema, necrosis, and submucosal hemorrhage, as well as circulatory disturbances.[26] The extent of ethanol-induced gastric mucosal damage in rats correlates with the number of degranulating mast cells[26,27] since these cells are a source of several neuropeptides and inflammatory mediators, including histamine and leukotrienes.[28] The formation of gastric mucosal lesions by necrotic agents such as HCl and ethanol involves several gastric mechanisms[29] which reduce the gastric blood flow, thereby contributing to the development of hemorrhage and necrosis,[30] and to the solubilization of mucus constituents in the stomach. These actions result in an increased flux of Na^+ and K^+, increased pepsin secretion, and a loss of H^+ ions and histamine into the lumen.[31]

As shown in Table 1, both lansoprazole (30 mg/kg, positive control) and the ethanolic extract (50, 100, 250 mg/kg) significantly protected against ethanol/HCl-induced ulcers in mice. Similarly, the FRF and FDF (100 mg/kg) also significantly protected the gastric mucosa of rats against ethanol-induced ulcers (Table 2). This protection could reflect the inhibition of gastric secretion or an increase in the release of protective substances by the mucosa. Agents that enhance mu-

Table 1. Effects of Lanzoprazol and an Ethanolic Extract (EEOH) of *Syngonanthus arthrotrichus* on HCl/Ethanol-Induced Gastric Ulcers in Mice

Treatment	Dose (mg/kg)	UI	Inhibition (%)
Saline	—	17±8.3	—
Lansoprazole	30	3.4±1.0**	79
EEOH	50	3.7±1.2**	78
	100	4.5±2.3**	73
	250	6.0±2.6**	64

The results (UI) are the mean±S.D. ANOVA $F_{(4,27)} = 12.3$ followed by Dunnett's test ** $p < 0.001$ compared to saline control.

Table 2. Effects of Flavonoid-Rich (FRF) and Flavonoid-Deficient (FDF) Fractions Obtained from *Syngonanthus arthrotrichus* and of Lanzoprazol on Ethanol-Induced Gastric Ulcers in Rats

Treatment	Dose (mg/kg)	IU	Inhibition (%)
Saline	—	77±13	—
Lansoprazole	30	27±6.8**	65
FRF	100	48±13.2**	38
FDF	100	58±7.4*	25

The results (UI=ulcerative index) are the mean±S.D. ANOVA $F_{(3,24)} = 31$ followed by Dunnett's test. * $p < 0.05$ and ** $p < 0.001$ compared to saline control.

Table 3. Effects of Cimetidine, and Ethanolic Extract (EEOH), Flavonoid-Rich (FRF) and Flavonoid-Deficient (FDF) Fractions Obtained from *Syngonanthus arthrotrichus* on Stress-Induced Ulcers in Mice

Treatment	Dose (mg/kg)	UI	Inhibition (%)
Saline	—	24±5.9	—
Cimetidine	100	9.1±1.8**	63
EEOH	50	6.5±2.1**	73
	100	7.7±2.7**	68
	250	7.6±2.9**	69
Saline	—	25±9.0	—
Cimetidine	100	10±3.3**	60
FRF	100	12±3.6**	51
FDF	100	13±5.3*	47

ANOVA: $F_{(4,28)} = 31$ for EEOH; $F_{(3,28)} = 10.4$ for FRF and FDF, respectively; $p < 0.05$. Dunnett's test: * $p < 0.05$ and ** $p < 0.001$ compared to saline control.

cosal defense factors, such as prostaglandins, protect the gastric mucosa against HCl-induced injury.[18] The generation of stress-induced mucosal damage results from an imbalance between aggressive and defensive mucosal factors.[32] Stress-induced ulcers are probably mediated by histamine release, with an enhancement of acid secretion and a reduction in mucous production.[33]

In humans and animals, exposure to stress increases gastric motility,[34] vagal activity[35] and mast cell degranulation,[36] and decreases gastric mucosal blood flow[37] and prostaglandin levels,[32] this leading to ulcer generation. Ulcer induction by hypothermic restraint stress has been widely used to evaluate antiulcerogenic activity in mice. Pretreatment of mice with cimetidine (100 mg/kg), EEOH (50, 100, 250 mg/kg) or FRF and FDF (100 mg/kg) significantly protected the gastric mucosa of mice when compared to the control group (Table 3). Antisecretory mechanisms, such as reduced histamine secretion and increased mucous synthesis, are re-

sponsible for this protection.[33]

Enzyme systems are involved in the responses to stress. Superoxide dismutase inactivates peroxides involved in the accumulation of H_2O_2 and the more reactive OH. Stress may also significantly decrease prostaglandin synthetase activity and make the gastric mucosa more susceptible to oxidative damage during ulcer generation.[38]

In the stomach, prostaglandins have a vital protective role, where they stimulate the secretion of bicarbonate and mucus, maintain mucosal blood flow, and regulate mucosal cell turnover and repair.[39] The suppression of prostaglandin synthesis by nonsteroidal antiinflammatory drugs (NSAIDS), such as indomethacin, results in increased susceptibility to mucosal injury and gastroduodenal ulceration.[40] Cholinomimetic agent (bethanechol) administered in association with NSAIDS have a synergistic effect on the gastric injury induced by increased secretion of acid and pepsin in the stomach.[19,41] In the indomethacin/bethanechol-induced ulcer model, cimetidine (100 mg/kg), EEOH (50, 100, 250 mg/kg), FRF and FDF (100 mg/kg) significantly protected the gastric mucous against ulcer formation (Table 4), probably by a mechanism involving increased mucous production.

We also examined the biochemical parameters of gastric juice, as well as mucous production and prostaglandin synthesis following ligation of the pylorus, and intraduodenal treatment with FRF, FDF and cimetidine (100 mg/kg each) in mice. As shown in Table 5, cimetidine (positive control) and FRF significantly decreased gastric acid secretion, increased gastric pH, and reduced the acid output when compared to the negative control. FDF had no significant effect on the parameters evaluated. The protection produced for the FRF probably involves the antisecretory mechanism mediated by the flavonoids, what it does not hoppen with the FDF.

The gastric epithelium is covered by a continuous mucous layer which adheres to the mucosal surface.[42] This adherent mucus gel, together with bicarbonate secreted by the epithelium, serves as an unstirred buffering barrier against luminal acid.[43] Endogenous PGE_2 plays an important role in maintaining gastric mucus synthesis[44,45] and secretion.[46]

As shown in Fig. 1, pretreatment with carbenoxolone (200 mg/kg) and FRF (100 mg/kg) significantly increased the adherent mucous in the gastric juice when compared to the control group. This increase probably contributed to the cytoprotection of these substances in the mucosal barrier. FDF (100 mg/kg) caused no significant increase in adherent mucus.

Exposure to irritating agents[47] increases prostaglandin production by the gastric mucosa as a consequence of a reduction in the gastric lumen pH[48] probably through the stimulation of acid secretion.[49] The protective action of prostaglandins is mediated by increased production of mucus and bicarbonate secretion,[50] modulation of gastric acid secretion,[51] inhibition of the release of inflammatory mediators by mast cells,[52] and the maintenance of gastric blood flow during exposure.[30]

Figure 2 shows that FRF plus indomethacin and FDF plus indomethacin reduced prostaglandin biosynthesis in the mucosa, suggesting that the cytoprotective action on the gastric

Table 4. Effects of Cimetidine, and an Ethanolic Extract (EEOH) and Flavonoid-Rich (FRF) and Flavonoid-Deficient (FDF) Fractions Obtained from *Syngonanthus arthrotrichus* on Indomethacin/Bethanechol-Induced Gastric Ulcers in Mice

Treatment	Dose (mg/kg)	UI	Inhibition (%)
Saline	—	17 ± 3.3	—
Cimetidine	100	4.5 ± 1.4**	73
EEOH	50	16 ± 3.3	6
	100	18 ± 10**	55
	250	12 ± 3.0*	32
Saline	—	17 ± 6.0	—
Cimetidine	100	7.8 ± 4.8**	54
FRF	100	11 ± 3.0*	36
FDF	100	9.4 ± 3.2*	45

ANOVA: $F_{(4,27)} = 28$ for EEOH; $F_{(3,27)} = 3.8$ for FRF and FDF ($p < 0.05$). Dunnett's test *$p < 0.05$ and **$p < 0.001$ compared to saline control.

Table 5. Effects of Intraduodenal Cimetidine and Flavonoid-Rich (FRF) and Flavonoid-Deficient (FDF) Fractions Obtained from *Syngonanthus arthrotrichus* on the Biochemical Parameters of Gastric Juice from Pylorus-Ligated Mice

Treatment	Dose (mg/kg)	pH (units)	Gastric juice (mg)	Acid output (mEq/ml/4 h)
Saline	—	2.3 ± 0.48	284 ± 50	11.7 ± 4.4
Cimetidine	100	4 ± 0.82**	179 ± 49**	6.3 ± 1.34**
FRF	100	3.5 ± 0.53**	184 ± 32*	6.5 ± 1.95**
FDF	100	2.14 ± 0.38	249 ± 77	10.7 ± 3.5

The data are the mean $\pm$ S.D. ANOVA: $F_{(3,31)} = 21$ for pH, $F_{(3,31)} = 7.58$ for gastric juice and $F_{(3,31)} = 8.89$ for acid output followed by Dunnett's test. *$p < 0.05$ and **$p < 0.001$ compared to saline control.
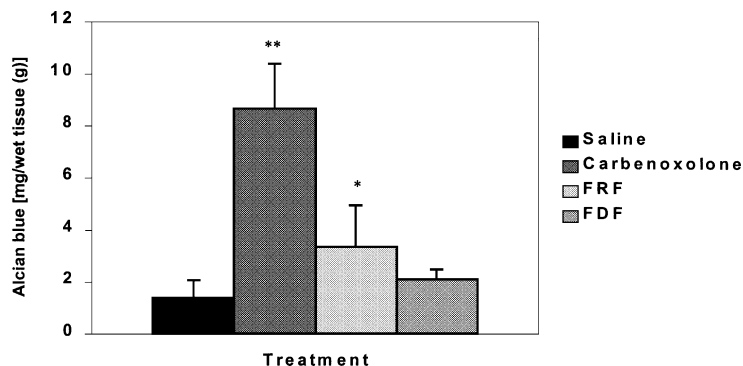

Fig. 1. Effects of Intraduodenal Carbenoxolone and Flavonoid-Rich (FRF) and Flavonoid-Deficient (FDF) Fractions Obtained from *S. arthrotrichus* on Adherent Gastric Mucous (Measured as the Amount of Alcian Blue Bound) in Pylorus-Ligated Rats

Columms are the mean $\pm$ S.D. of rats. ANOVA: $F_{(3,21)} = 45$ for FRF and FDF ($p < 0.05$). *$p < 0.05$ and **$p < 0.001$ compared to the saline group (Dunnet's test).
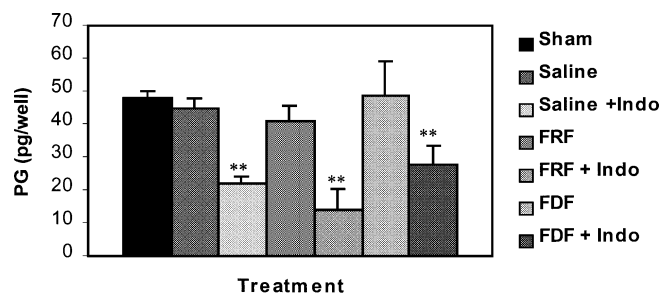
Fig. 2. Effects of Oral Administration of Flavonoid-Rich (FRF) and Flavonoid-Deficient (FDF) Fractions from *S. arthrotrichus* and Subcutaneous Indomethacin (Indo) on Gastric Prostaglandin Synthesis in Rats

Columns are the mean±S.D. of rats. ANOVA: $F_{(6,42)}=41$ for FRF and FDF $p<0.05$ followed by Dunnett's test ∗∗ $p<0.001$ compared to control group.

mucosa may not be related specifically to the level of prostaglandins.

Phytochemical and pharmacological studies have suggested that the flavonoids present in the ethanolic extract and fractions of *S. arthrotrichus* are responsible for the antisecretory and cytoprotective action of this plant. Although the mechanism underlying the antiulcerogenic effect seen here remain unknown, it may be related to the flavonoid derivatives from luteolin present in the extract and in the active fractions.

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