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Study of *Chlorophytum arundinaceum* Against Experimental Gastric Ulcer

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Abstract

The current study was designed to investigate the effect of a 50% alcohol extract of *Chlorophytum arundinaceum* Baker (CAE) against ethanol-induced pylorus ligation and cold stress–induced experimental gastric ulcer. The CAE was given at the dose of 100 mg/kg, p.o., in all the models, and results of those were compared with that of animals treated with omeprazole 20 mg/kg, p.o. (reference standard). Ulcer index was a common evaluating parameter in all the models. In the pylorus ligation model, acid secretory parameters (total acid, pepsin activity, and total acid output) and mucoprotective parameters (total carbohydrate, total protein, and mucin activity) were studied. In addition, lipid peroxidation and antioxidant activity were specifically studied in cold stress–induced gastric ulcer model. Effects on vascular permeability as well as gastric emptying were also studied. CAE has shown significant protection in gastric ulceration as evident from reduction ($p < 0.05$) in ulcer index in all the models. In the pylorus ligation model, CAE showed significant increase in mucin activity, but no significant change was observed on acid secretory parameters. Besides, CAE has shown antioxidant activity in gastric mucosal homogenate where it reversed the increased level of malondialdehyde (MDA) content and the decreased level of catalase content. Further, CAE has shown reduction in vascular permeability and gastric emptying. Hence, it is suggested that *Chlorophytum arundinaceum* possesses significant antiulcer activity. The mechanism of its activity is associated with strengthening of the gastric mucosal barrier.

Keywords: Antioxidant activity, *Chlorophytum arundinaceum*, cold stress, ethanol, gastric ulcer, pylorus ligation.

Introduction

Peptic ulcer is a recurrent disease, which includes ulceration at any site in the gastrointestinal tract where mucosal cells (parietal cells) secrete hydrochloric acid. The disease affects large populations in all geographical regions. A rational therapy for peptic ulcer still remains elusive, and search for safer potential drugs are still needed. Use of natural drugs in gastric ulcers is well documented (Sanyal et al., 1982; Dahanukar et al., 1983; Goel et al., 1986).

Chlorophytum arundinaceum Baker (Hindi-Safed Musli), belonging to the Liliacae family, a creeping perennial plant, is mentioned in Ayurveda for treatment of arthritis, rheumatism, and as an aphrodisiac agent (Kirtikar & Basu, 1994). Phytochemical reviews reveal the presence of steroidal saponins like tokorogenin, neogetogenin, stigastrol, and glycosides like arundinoside-A and arundinoside-B (Tandon & Shukla, 1992). Other plants containing similar constituents possess antiulcer action, for example, *Glycyrrhiza glabra* Linn. which contains tri-terpenoidal saponins (Saraswathi, 1986); *Asparagus racemosus* Willd. is known to contain steroidal glycosides (Dahanukar et al., 1983).

Hence, the current experimental work has been undertaken to study the effects of 50% alcohol extract of *Chlorophytum arundinaceum* on different models of gastric ulcer in rats and its possible effects on offensive and defensive mucosal factors.

Materials and Methods

Animals

Sprague-Dawley rats of either sex weighing between 220 and 250 g were procured from the Zydus Research Centre

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(Ahmedabad, India) and housed in well ventilated colony cages in the departmental animal house at 25 ± 1°C and 55 ± 10% RH, 10:14 h light/dark cycles throughout the experimental periods. The animals were fed standard chow diet and water *ad libitum*. Placing the animals in cages with grating on the floor prevented coprophagy. These experiments complied with the guidelines of our animal ethics committee.

Collection of plant

The dried root of *Chlorophytum arundinaceum* (CAE) was obtained during the month of March 2002 from Rachana Farm House near Rajkot, India, and was identified by the Department of Pharmacognosy, L.M. College of Pharmacy (Ahmedabad). The dried roots (250 g) were then crushed, finely powdered, and sifted from #40 sieve. The powder was defatted with petroleum ether (60–80°C, 500 ml × 4 times) and then extracted with 50% alcohol (500 ml × 6 times) by reflux distillation and evaporated under reduced pressure. The yield of product was 12.5%, which was stored in a refrigerator at 4°C in a glass container throughout the study.

Drugs

Drugs used included omeprazole (B.R. Chemicals, Ahmedabad, India), ranitidine HCL (Unique Pharmaceuticals, Ankleshwar, India), silymarin (Ranbaxy, Delhi, India).

Experimental design

The animals were divided into 3 groups of 6 animals each. Fresh drug solutions were prepared in distilled water at the time of administration.

Group 1: Control group received only vehicle before the ulcerogenic procedure.
Group 2: Animals received CAE (100 mg/kg, p.o.) 1 h before the ulcerogenic procedure.
Group 3: Animals received omeprazole (20 mg/kg, p.o.)/ silymarin (100 mg/kg, p.o.) 1 h before the ulcerogenic procedure.

Ethanol-induced gastric mucosal damage

Acute gastric ulceration was induced by absolute ethanol (ETOH) (Robert et al., 1979). For this, animals were fasted for 24 h before the experiment. The gastric ulcers were induced in rats by administration of 1 ml of ethanol p.o. Two hours after ethanol administration, animals were sacrificed and stomachs were removed and opened along the greater curvature and subjected to the measurement of ulcer index (Goswami et al., 1997).

Determination of vascular permeability

Animals were divided randomly into the groups of two containing 6 animals in each (see Szabo et al., 1985). One group received CAE (100 mg/kg, p.o.) 1 h before the ulcerogenic exposure. The second group served as a control group. One milliliter of ethanol was administered in both the groups and 45 min after the ethanol administration, Evan's blue (10 mg/kg) was given intravenously. Then 15 min after the administration of dye, animals were sacrificed by overdosage of ether. The stomachs were dissected out, the glandular portion was separated, weighed, and homogenized with saline (1 ml). To this homogenate HCl (32%, 2.5 ml) was added, mixed, and allowed to stand at room temperature for 2 h. Chloroform (2.5 ml) was then added, and the dye was extracted into the chloroform layer. The chloroform layer was separated, and the optical density was measured in a UV spectrophotometer at 610 nm.

Pylorus ligation model

Rats fasted for 24 h were subjected to pyloric ligation (PL; Shay et al., 1945). Under ether anesthesia, the abdomen was opened by a small midline incision below the xiphoid process, the pyloric portion of the stomach was slightly lifted out and ligated, avoiding traction to the pylorus or damage to its blood supply. The stomach was replaced carefully and the abdominal wall closed by interrupted sutures. The drugs were given orally immediately after pyloric ligation. Nineteen hours after pyloric ligation, the animals were sacrificed by giving an overdose of ether. The stomachs were dissected out; the contents were drained into graduated tubes, measured, centrifuged, and subjected to biochemical analysis.

The stomachs were cut open along the greater curvature and the inner surface was examined for ulceration, and the ulcer index was calculated (Goswami et al., 1997).

Gastric contents were assayed for total acidity by titration against 0.01 N NaOH to pH 8.0 using phenolphthalein as an indicator. The amount of HCl was calculated and expressed as mEq/l (Hawk, 1965). The volume of gastric content was measured (Hawk, 1965), and the total acid output was estimated (Goel et al., 1985). Pepsin activity of the gastric juice was determined as per the method of Debnath et al. (1974) and expressed in terms of micrograms of tyrosine per milliliter of gastric juice liberated during a 19 h period. Other biochemical parameters measured included total carbohydrate content (TC) (Nair, 1976), protein content (PR) (Lowry et al., 1951), and the mucin activity in terms of total carbohydrate to protein (TC/PR) ratio.

Cold restraint stress–induced ulcers

Animals were deprived of food for 12 h, then were immobilized in stress cages and placed in a cold room (4–6°C)

for 3 h (see Vincent et al., 1977). The drug was administered 1 h before immobilization. During the cold restraint stress (CRS) procedure, silymarin (100 mg/kg, p.o.) was used as standard instead of omeprazole. The animals were sacrificed by cervical dislocation and scored for intensity, and ulcer indices were calculated as per the method of Szabo (1978). Further, the glandular parts of the stomachs were subjected to estimation of free radicals as given below.

Estimation of free-radical generation

The fundic mucosal portion of the stomach was washed with ice-chilled sucrose solution (0.25 M) and then homogenized in ice-cold 50 mM phosphate buffer (pH 7.2) with a Remi homogenizer (Bombay, India) for 30 s. The homogenate was then centrifuged at $800 \times g$ for 10 min followed by centrifugation of the supernatant at $12{,}000 \times g$ for 15 min, and the obtained mitochondrial fraction was used for the following estimations (Das & Banerjee, 1993).

Measurement of lipid peroxidation

Lipid peroxidation (LPO) product malondialdehyde (MDA) was estimated according to the method of Kiso et al. (1984). Briefly, 0.2 ml of 5% homogenate was mixed with 0.2 ml 8% w/v sodium dodecylsulfate, 1.5 ml freshly prepared thiobarbituric acid (1% w/v), 1.5 ml of 20% acetic acid, and 0.6 ml of distilled water. The reaction mixture was heated in a water bath for 45 min at 95°C and then cooled. To 2 ml of this reaction mixture an equal volume of 10% TCA was added, and the reaction mixture was centrifuged at $400 \times g$ for 5 min. The optical density was determined with Shimadzu (Australia) UV spectrophotometer set at 532 nm against blank prepared similarly using a phosphate buffer solution (50 mM, pH 7.2).

Superoxide dismutase

Superoxide dismutase (SOD) was estimated as per the method of Misra and Fridovich (1972). A sample of gastric homogenate (0.1 ml) was mixed with 0.1 ml of EDTA (1×10^{-4} M), 0.5 ml of carbonate buffer (pH 9.7), and 1 ml of epinephrine (3×10^{-3} M). The optical density of formed adrenochrome was measured at 480 nm for 3 min at an interval of 30 s. The results were expressed as the mean difference of absorbance.

Catalase

Decomposition of H_2O_2 in the presence of catalase (CAT) was studied at 240 nm (Aebi, 1974). A 50 µM sample was added to buffered substrate (50 mM phosphate buffer, pH 7 containing 30 mM H_2O_2) to make total volume 3 ml, and decrease in the absorbance was monitored at 37°C for 2.5 min at an interval of 15 s. Results were expressed as the mean difference in absorbance.

Measurement of gastric emptying

Rats fasted for 24 h were orally administered the reagent (1.5 ml/rat), prepared by mixing 50 mg phenol red in 100 ml aqueous methyl cellulose (1.5%) (Scarpignato & Calpovilla, 1980). The drug solution was given 30 min prior to the administration of phenol red. All animals were sacrificed after 60 min of phenol red administration. The stomachs were dissected out carefully, and viscera and contents were homogenized in 5 ml of 0.1 N NaOH and centrifuged (2000 rpm for 5 min). The colorimetric assay of phenol red was performed at 560 nm after protein precipitation (20% trichloroacetic acid) and realklinization of the supernant (borate buffer, pH 10). For standard curve, phenol red at different concentrations was prepared and assayed similarly. Absorbance was measured against blank prepared simultaneously. The concentration of phenol red in treatment group was determined and compared with that of control group.

Statistical analysis

The results were expressed in terms of mean ± SEM. Significance was determined by one-way analysis of variance followed by the Tukey's multiple range test (Bolton, 1997); p values less than 0.05 were considered as indicative of significance.

Results

Ethanol-induced gastric mucosal damage

Ethanol produced linear hemorrhagic gastric lesions in the glandular portion of the stomach mucosa. CAE treatment reduced gastric erosion, as evident from the reduced ulcer index when compared with the control group (Table 1). Omeprazole also showed a significant reduction in ulcer index.

Effect on vascular permeability

The concentration of Evan's blue extracted with chloroform was higher in the control group. CAE showed reduced vascular permeability that was evident from the reduction in concentration of Evan's blue in chloroform layer (Table 2).

Pylorus ligation model

Circular hemorrhagic localized lesions were observed in the glandular portions of the stomach in pylorus ligation rats. However, linear lesions were also observed in

Table 1. Effect of 50% alcohol extract of *Chlorophytum arundinaceum* on ulcer index in ethanol-induced gastric ulcer model.

Groups	Ulcer index	%Protection
Control	1.53 ± 0.09	—
Alcohol extract (100 mg/kg)	0.31 ± 0.07*	79.74%
Omeprazole (20 mg/kg)	0.58 ± 0.05*	62.09%

All values represent mean ± SEM; n = 6.
*$p < 0.05$ when compared with the control group (ANOVA, followed by Tukey's multiple range test).

Table 2. Effect of 50% alcohol extract of *Chlorophytum arundinaceum* on vascular permeability in rats.

Groups	Concentration of Evan's blue (μg/ml)
Control	8.20 ± 1.14
Alcohol extract (100 mg/kg)	2.03 ± 0.64*

All values represent mean ± SEM; n = 6.
*$p < 0.05$ when compared with the control group (ANOVA, followed by Tukey's multiple range test).

several animals. The parameters studied in this model include ulcer index, volume of gastric secretion, total acidity, total acid output, pepsin activity, total carbohydrates, protein content, and total carbohydrates to protein (TC/PR) ratio.

CAE caused significant reduction in ulcer index and pepsin activity as evident from the data provided in the Table 3. However, volume of gastric secretion, total acidity, and total acid output were not significantly altered. Omeprazole showed significant reduction in ulcer index, total acidity, and pepsin content.

In case of mucoprotective parameters, CAE did not significantly alter the total carbohydrates, but there was a significant reduction in total protein content in the drug-treated group when compared with the control group (Table 4). Based on the results of TC and PR content of gastric juice, TC/PR ratio was derived. CAE showed significant increase in mucin activity (i.e., TC/PR ratio). Omeprazole did not change TC/PR ratio significantly.

Cold restraint stress–induced gastric ulcer model

The CRS model produced significant increase in ulcer index with increase in lipid peroxidation as observed from increase in MDA contents with a concomitant increase in SOD and decrease in CAT levels (Tables 4 and 5).

Pretreatment with CAE showed significant decrease in ulcer index and MDA contents along with increase in the CAT levels. However, no significant effect was found on SOD levels. Similar kinds of results were seen with the animals treated with silymarine.

Effect on gastric emptying

The concentration of phenol red in the control group was significantly lower, as shown in the Table 7. Treatment with CAE showed a significant increase in the concentration of phenol red in the stomach, indicating reduced gastric emptying rate. Similarly, omeprazole also showed reduction in gastric emptying.

Table 3. Effect of 50% alcohol extract of *Chlorophytum arundinaceum* on various acid secretary parameters against pylorus-ligated gastric ulcer model.

Parameters/groups	Control	Alcohol extract	Omeprazole
Ulcer index	0.79 ± 0.08	0.35 ± 0.04*	0.18 ± 0.02*
Volume of gastric secretion (ml/100 g b.w.)	1.64 ± 0.52	2.35 ± 0.38	2.70 ± 0.42
Total acidity (mEq/l)	7.25 ± 1.20	7.93 ± 1.40	2.49 ± 0.33*
Total acid output (μEq/100 g b.w.)	9.80 ± 2.70	15.19 ± 3.73	6.14 ± 0.73
Pepsin activity (μg/ml)	94.17 ± 5.24	49.17 ± 5.45*	60.50 ± 3.30*

All values represent mean ± SEM; n = 6.
*$p < 0.05$ when compared with the control group (ANOVA, followed by Tukey's multiple range test).

Table 4. Effect of 50% alcohol extract of *Chlorophytum arundinaceum* on various mucoprotective parameters against pylorus-ligated gastric ulcer model.

Parameters/groups	Control	Alcohol extract	Omeprazole
Total carbohydrates (mg/ml)	0.85 ± 0.13	0.85 ± 0.16	0.59 ± 0.10
Protein content (mg/ml)	1.64 ± 0.14	0.22 ± 0.05*	0.84 ± 0.06*
TC:PR ratio	0.55 ± 0.10	1.35 ± 0.21*	0.72 ± 0.13

TC/PR, total carbohydrates/protein ratio.
All values represent mean ± SEM; n = 6.
*$p < 0.05$ when compared with control group (ANOVA, followed by Tukey's multiple range test).

Table 5. Effect of 50% alcohal extract of *Chlorophytum arundinaceum* on ulcer index and score for intensity in cold stress–induced gastric ulcer model.

Groups	Ulcer index	Score for intensity
Control	1.39 ± 0.19	2.67 ± 0.21
Alcohol extract (100 mg/kg)	0.50 ± 0.07*	1.17 ± 0.17*
Silymarin (100 mg/kg)	0.72 ± 0.09*	1.50 ± 0.22*

All values represent mean ± SEM; n = 6.
*$p < 0.05$ when compared with the control group (ANOVA, followed by Tukey's multiple range test).

Table 6. Effect of 50% alcohol extract of *Chlorophytum arundinaceum* on MDA content, CAT level, and SOD level in CRS model.

Groups/parameters	MDA content	CAT level	SOD level
Normal	0.087 ± 0.004	0.0096 ± 0.0016	0.0352 ± 0.001
Stress control	0.120 ± 0.002**	0.0020 ± 0.0005**	0.0244 ± 0.002**
Alcohol extract (100 mg/kg)	0.046 ± 0.007*	0.0124 ± 0.0011*	0.0189 ± 0.001
Silymarin (100 mg/kg)	0.050 ± 0.003*	0.0125 ± 0.0007*	0.0452 ± 0.001*

All values represent mean ± SEM; n = 6.
MDA, malondialdehyde; CAT, catalase; SOD, superoxide dismutase; CRS, cold restraint stress.
*$p < 0.05$ when compared with the stress control group (ANOVA, followed by Tukey's multiple range test).
**$p < 0.05$ when compared with the normal group.

Table 7. Effect of 50% alcohol extract of *Chlorophytum arundinaceum* on gastric emptying.

Groups	Concentration of phenol red (μg/ml)
Control	1.9 ± 0.208
50% alcohol extract (100 mg/kg)	5.23 ± 0.348*
Omeprazole (20 mg/kg)	5.07 ± 0.318*

All values represent mean ± SEM; n = 6.
*$p < 0.05$ when compared with control group (ANOVA, followed by Tukey's multiple range test).

Discussion

The 50% alcohol extract of *Chlorphytum arundinaceum* showed significant antiulcer activity against ethanol-, CRS-, and PL-induced gastric ulcers in rats.

Ethanol and several nonsteroidal anti-inflammatory drugs (NSAIDs) such as aspirin irritate the gastrointestinal mucosa in both human and animals and may therefore cause the injury and bleeding. Ulcers caused by chemical inducers like ethanol is due to a number of contributing factors, which include effects on mucosal blood flow, platelet thrombi, damage to capillary endothelium, and release of arachidonate metabolites LTC4/D4 and PAF (Goel & Bhattacharya, 1991). Involvement of free radicals is also reported for gastric ulceration caused by ethanol (Mizui & Doteuchi, 1988). The protection afforded by CAE in ethanol model can be correlated to a decrease in vascular permeability, thereby

preventing damage to the capillary endothelium and release of arachidonate metabolites.

PL-induced ulcers are thought to be caused due to an increased presence of acid and pepsin in the stomach (Goel & Bhattacharya, 1991). Increased synthesis of nucleic acids, increased metabolism of carbohydrates, and other compensatory mechanisms could be responsible for ulceration due to pylorus ligation (Mozsik et al., 1969). The protection afforded by CAE against gastric ulcers induced by pylorus ligation appears to be produced by the suppression of pepsin levels and a corresponding increase in protein levels and thereby increased mucin activity.

Stress-induced ulcers are caused by a number of factors both physical and psychological (Miller, 1987). Increases in gastric motility (Garrick et al., 1986), vagal overactivity (Cho et al., 1976), mast cell degranulation (Cho & Ogle, 1979), decreased mucosal blood flow (Hase & Moss, 1973), and decreased Prostaglandin (PG) synthesis are reported to be involved in the genesis of stress-induced ulcers. Free radicals are also involved in gastric ulceration caused by stress (Das & Banerjee, 1993).

In stress-induced gastric ulceration, LPO and SOD levels were significantly increased with concomitant decreases in CAT concentrations as reported earlier (Das & Banerjee, 1993). Increases in LPO levels indicate an increase of reactive oxygen species (ROS), the major radicals being superoxide anion, H_2O_2, and hydroxy radical. These induce cell degranulation by increasing peroxidation of cell membrane lipids, causing loss of structural and functional integrity of cell membranes. Increases in SOD levels is in the response of increased tissue $O_2^{\cdot}$, speeding up their dismutation and reverting it immediately into H_2O_2 (Fridovich, 1985). Accumulation of H_2O_2 occurs in the mitochondria and cytosol if not scavenged by CAT (Das et al., 1997) and thus leads to increased generation of $OH^{\cdot}$ radical. As CAT levels are decreased, H_2O_2 is not effectively scavenged, resulting in increased lipid peroxidation (Michiels et al., 1994).

In the current study, CAE treatment reverted the stress-induced changes in LPO and CAT, whereas changes in SOD activites were insignificant. Reduction in MDA levels suggest decreased lipid peroxidation and free radical–induced damage. Increases in CAT levels were associated with decreases in H_2O_2 levels. No remarkable changes in SOD levels indicated that the free radicals were generated as such and rapidly converted into H_2O_2 that was scavenged immidiately by higher levels of CAT. Hence, the antioxidant activity of CAE might be one of the important defensive factors.

Another contributing factor in genesis of ulceration in cold stress–induced ulcer is gastric motility (Garrick et al., 1986). Treatment with CAE caused significant increase in phenol red concentration in the stomach, representing decreased gastric motility as evident from the decrease in gastric emptying rate, and this finding was comparable with that of omeprazole group. An increase in peristaltic activity of rat stomach leads to a reduction in blood flow that is particularly profound in the antral area (Livingstone et al., 1991). Thus, it is possible that CAE confers gastroprotection either through inhibition of gastric smooth muscle activity or through improvement of mucosal blood flow by reducing the motility.

Thus, the current study reports the antiulcerogenic effect of CAE. The mechanism of its antiulcer activity may be due to the augmentation of defensive factors as well as an antioxidant mechanism coupled with a decrease in gastric motility.

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