International Journal of Pharmacy Research **Vol. 1, No. 2, 2010**
0976-2167

Anti-ulcerogenic and ulcer healing effects of *Zingiber officinale*(L.) on experimental ulcer models: possible mechanism for the inhibition of acid formation

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Research Article

ABSTRACT

Gastroprotective effect of 50% ethanolic extract of *Zingiber officinale* (ZOE) Zingiberaceae rhizome have assessed in different gastric ulcer models in rats. ZOE (50, 100 and 200 mg/kg body weight) was administered orally, twice daily for 5 days for prevention from ethanol (EtOH) and 10 days for prevention of acetic acid induced ulcers. ZOE showed dose dependent inhibition of ulcer index in ethanol and acetic acid–induced ulcers. ZOE prevents the oxidative damage of gastric mucosa by blocking lipid peroxidation and by significant decrease in superoxide dismutase, and increase in catalase activity. When animals were pre-treated with ZOE (50 -200 mg/kg) for five days in ethanol induced and ten days in acetic acid induced model showed reduced in U.I. 15.23 ± 0.62 to 5.08 ± 0.80 & 11.88 ±0.85 to 3.93 ± 0.55 as compared to standard 3.75 ± 0.53 &2.18 ± 0.25. in ethanol induced animals there was significant reduced the LPO, SOD, 0.50 ± 0.02 to 0.25 ± 0.02 & 217.4 ±6.86 to 170.1 ± 5.21and increase in CAT level by 19.08 ± 1.43 to 35.55 ± 2.91 as compared to standard (50 mg/kg) the level of LPO, SOD, & CAT is 0.42 ± 0.02, 143.65 ±6.22 and 30.83 ± 2.20. while in acetic acid induced animals there was also significant reduced the LPO, SOD,0.53 ± 0.03 to 0.25 ± 0.02 & 220 ± 5.41 to 158.13 ± 5.31 and increase in the level of CAT 19.41 ± 1.61 to 37.51 ±3.16 in standard treated animals the level of LPO, SOD, & CAT is 0.47 ± 0.03, 147.6 ± 6.22& 32.68 ± 2.04. Our results show that ZOE possesses significant gastro-protective activity which might be due to gastric defence factors and gingerol might be the main constituents responsible for this activity.

Key words: *Zingiber officinale, Anti-ulcer, Antioxidant, Gastroprotective, Lipid peroxidation*

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Article Info: Date received: 19 March 2010 **Date accepted : 15 July 2010**

INTRODUCTION

Gastric hyperacidity and ulcer are very common causing human suffering today. It is an imbalance between damaging factors within the lumen and protective mechanisms

within the gastro duodenal mucosa. Although prolonged anxiety, emotional stress, hemorrhagic surgical shock, burns and trauma are known to cause severe gastric irritation, the mechanism is still very poorly understood [1]. Oxygen derived free radicals have been implicated in the pathogenesis of a wide variety of clinical disorders and gastric damage is caused by physical, chemical and psychological factors that leads to gastric ulceration in human and experimental animals Most of the available drugs are thought to act on the offensive factors which neutralize acid secretion like antacids, H_2 receptor blockers like ranitidine, famotidine, anticholinergics like pirenzepin, telezipine, proton pump blockers like omeprazole, lansoprazole, etc. which interfere with acid secretion [2].

To regain the balance, different therapeutic agents including plant extracts are used. *Zingiber officinale* Rosc. rhizomes extract is one such herbal drug currently undertaken in the present study. It is a member of the tropical and sub-tropical Zingiberaceae, has been cultivated for thousands of years as a spice and for medicinal purposes. Rhizomes are aromatic, thick lobed and pale yellowish. It is a sweet, pungent, heating appetizer, an aphrodisiac and carminative. It is used extensively in Traditional Chinese medicine to treat headaches, nausea and colds and in Ayurvedic and Western herbal medicinal practice for the treatment of arthritis, rheumatic disorders and muscular discomfort. This species contains biologically active constituents including the main pungent principles, the gingerols and shogaol [3]. (6)-Gingerol-1 has been found to possess various pharmacological and physiological effects including anti-inflammatory, analgesic, antipyretic, gastroprotective, cardiotonic, and anti-hepatotoxic activities [4, 5].The medicinal value of ginger is due to pharmacologically active compounds, such as the anti-inflammatory gingerols, that the plant produces and stores in its rhizomes. To date, more than 100 chemical constituents from ginger have been isolated or detected [5,6,7,]. In Ayurveda, ginger is considered as valuable medicine because of its action as rubefacient, antiasthmatic and stimulant to the gastrointestinal tract .It is currently cultivated commercially in India, China, South East Asia, West Indies, Mexico, Africa, Fiji and Australia [8]. Ginger has a long history of medicinal use dating back 2500 years.

MATERIALS AND METHODS

Plant material

The fresh rhizomes of ZOE were locally purchased from the local market and identified with the existed voucher specimen of NBRI, Lucknow. Rhizome of ZOE (1kg) were cut into small pieces and completely dried in shed up to 3-4 days. Powder is obtained with the help of mixer, then extraction is done using 50 % ethanol (v/v). The homogenate was concentrated on rotavapour. The residue was designated as ethanol extract (11.5 g). The extract was pre- solubilised in distilled water for the *in vivo* studies.

Test animals

Sprague–Dawley rats (140–180 g) were procured from the animal house of Central Drug Research Institute, Lucknow. They were kept in the departmental animal house at 26±2 °c and relative humidity 44–56%, light and dark cycles of 10 and 14 hrs, respectively for

1 week before and during the experiments. Animals were provided with standard rodent pellet diet (Amrut, India) and the food was withdrawn 18–24 hrs before the experiment though water was allowed ad libitum. All experiments were performed in the morning according to current guidelines for the care of laboratory animals and the ethical guidelines for investigations of experimental pain in conscious animals.

Phytochemical screening

Preliminary qualitative photochemical screening of ZOE extract gave the positive test for steroids, alkaloids, terpenoids, saponins, and tannins.

Experimental procedure

ZOE, suspended in 1% carboxy methyl cellulose (CMC) in distilled water in doses of 50, 100 and 200 mg/kg and Omeprazole, (the reference drug) in the dose of 50 mg/kg were administered orally twice daily at 10:00 and 16:00 hrs, respectively, for 5 days for ulcer protective studies. Further the effective dose of ZOE 50 mg/kg, b.d for 5 days was used for secretion and mucosal studies, and up to 10 days for ulcer healing study. Control group of animals received suspension of 1% CMC in distilled water.

Anti-ulcer study

The following experimental models were used.

Ethanol (EtOH)-induced ulcers

The gastric ulcers were induced in rats by administering EtOH (1 ml/200 g/1 hr) [9] and the animals were sacrificed by cervical dislocation and stomach was incised along the greater curvature and examined for ulcers. The ulcer index was scored by a person unaware of the experimental protocol, based upon the product of length and width of the ulcers present in the glandular portion of the stomach (mm^2/ rat).

Acetic acid-induced ulcers

The rats were anaesthetized with pentobarbitone (35 mg/kg, i.p.). The abdomen was opened and the stomach was visualized. A cylindrical glass tube of 6 mm in diameter was tightly placed upon the anterior serosal surface of the glandular portion of stomach 1 cm away from the pyloric end. A total of 50% acetic acid (0.06 ml/ animal) was instilled into the tube and allowed to remain 60 sec. on the gastric wall. After removal of the acid solution, the abdomen was closed in two layers and animals were caged and fed normally. ZOE was given in the dose of 20 mg/kg on day 1, orally, twice daily, 4 hrs after the application of acetic acid and continued either up to 5 or 10 days after induction of the ulcer. The animals were then sacrificed after 18 hrs of the last dose of drug either on day 6 or day 11 of experiment to assess the ulcer size and healing. Ulcer index was calculated based upon the product of length and width (mm^2/rat) of ulcers [10]. Statistical significance was calculated using unpaired Student's t -test.

Determination of gastric wall mucus

Gastric wall mucus was determined according to the method of Corne et al. (1974). The glandular segments from

stomachs were removed, weighed and incubated in tubes containing 1% Alcian blue solution (0.16 M sucrose in 0.05 M sodium acetate, pH 5.8) for 2 hr. The alcian blue binding extract was centrifuged at 3000 rpm for 10 min and the absorbency of supernatant was measured at 498 nm. The quantity of alcian blue extracted (gm/gm of glandular tissue) was then calculated.

Lipid peroxidase (LPO) activity

LPO product malondialdehyde (MDA) was estimated using 1,1,3,3-tetraethoxypropane as the standard and is expressed as nmol/mg protein [11].

Superoxide dismutase (SOD) activity

SOD was estimated by following the procedure of [12]. The inhibition of reduction of nitro blue tetrazolium (NBT) to blue colored formozanin presence of phenazine metha sulphate (PMS) and NADH was measured at 560 nm using n-butanol as blank. One unit (U) of enzyme activity was defined as the amount of enzyme that inhibits rate of reaction by 50% in 1 min under the defined assay conditions.

Catalase (CAT) activity

Decomposition of H_2O_2 in presence of catalase was followed at 240 nm [13]. One unit of (U) CAT was defined as the amount of enzyme required to decompose 1 mmol of H_2O_2/min, at 25.8 o_C and pH 7.0. Results are expressed as U of CAT activity/mg Protein.

Statistical analysis

Values were represented as mean±S.E.M. for six rats. Analysis of variance (ANOVA) test was followed by individual comparison by Newmann Keuls test for the determination of level of significance.

RESULTS

Antiulcer and ulcer healing effects Ethanol-induced depletion of gastric wall mucus has been significantly prevented by ZOE. As secretion of acid is decreased with increasing dose of (ZOE 50-200 mg/kg) and a copious amount of gastric mucus is secreted during superficial mucosal damage and provides a favourable microenvironment in repair by restitution. The topical action of the ethanolic extract of ZOE in accelerating ulcer healing has been explained by several mechanisms, such as stimulating the contraction of the ulcer and increasing the formation of epithelisation.

After five & ten days of treatment, the rats treated with ethanol & acetic acid showed loss of gland architecture with erosion of the epithelial layer and evident oedema and infiltration by inflammatory cell. ZOE (100 mg/kg) treated rats showed no ulceration but intactness of gastric epithelium was not completely restored. Minimal oedema and infiltration was seen in the lower half of the mucosa. ZOE (200mg/kg) treated rats showed no ulceration in the mucosa. Glands are regular with complete restoration of gastric epithelium. Minimal oedema and infiltration were seen in one area. Omeprazole treated groups showed no ulceration in gastric mucosa, glands were regular and no inflammation was observed.

Ethanolic extract of ZOE 50–200 mg/kg, given orally, twice daily for 5 days, showed dose-dependent protective effect against gastric ulcers induced by ethanol (Table 1) and healed acetic acid-induced chronic ulcers after 10 days of treatment (Table3). In ethanol induced animals ZOE showed decrease in (U.I.) by15.23 ± 0.62 to 5.08 ± 0.80 (P<0.001) compared to standard 3.75±0.53, control animals showed UI 18.43±0.53. ZOE50-200 mg/kg significantly decrease ulcers index induced by 50 % acetic acid after 5 and 10 days of treatment by 18.97 ± 0.605 to 12.13 ±0.94 (P< 0.001) &11.88 ± 0.85 to 3.93 ± 0.55 (P< 0.001) as compared to control 22.28± 0.81, &13.88 ± 0.81, and standard 11.68 ± 0.59,& 2.18 ± 0.25.

Effect on gastric wall mucous contents

Secretion of mucus and bicarbonate by surface epithelial constitute a mucus–bicarbonate barrier, which is regarded as first line of defence against potential ulcerogens. In chronic ulcers induced by 50% acetic acid, ZOE 50- 200 mg/kg tended to increased the concentration of individual carbohydrates and total carbohydrates (TC) in the alcoholic precipitate of gastric juice with significant decrease in protein (P) content leading to significant increase in TC:P ratio. However, it increased the defensive mucin (P< 0.001) secretion. ZOE showed again similar effect on mucosal glycol-proteins content of the mucosa as observed by an increase in TC: P ratio.

In vivo antioxidant potential

Ginger extract contains chemical constituents such as gingerol, shogaol, phenolic1, 3-diketones, zingerone, have been shown to protect against lipid peroxidation, a significant scavenging effect of oxygen radicals. when ethanol induced animals were pre-treated with ZOE (50 -200 mg/kg) for five days there was significant reduced in the LPO, SOD, 0.50 ± 0.02 to 0.25 ± 0.02 & 217.4 ± 6.86 to 170.1 ± 5.21and increase in CAT level by 19.08 ± 1.43 to 35.55 ± 2.91 as compared to standard (50 mg/kg) the level of LPO, SOD, & CAT is 0.42 ± 0.02, 143.65 ± 6.22 and 30.83 ± 2.20.in control animals the level of LPO, SOD, and CAT is 0.40±0.046, 106.78±5.06, & 30.88±2.20. While in acetic acid induced animals show significant reduction in the LPO, SOD,0.53 ± 0.03 to 0.25 ± 0.02 & 220 ± 5.41 to 158.13 ± 5.31 and increase in the level of CAT 19.41 ±1.61 to 37.51 ±3.16 in standard animals the level of LPO, SOD, & CAT is 0.47 ± 0.03, 147.6 ± 6.22 & 32.68 ± 2.04.control animals showed the LPO, SOD & CAT is 0.45±0.05, 106.15±5.88 & 38.6±2.97.

Effects of test drugs on ulcer healing

Oral treatment with Omeprazole (Twice daily) 50 mg/kg for 10 days markedly accelerated the healing of gastric ulcers, and decreased the U.I. by 3.75 ± 0.53 & 2.18 ± 0.25 in ethanol and acetic acid induced animals respectively and decreased the defective area in the ulcerated region rats.

DISCUSSION

Gastric ulcer is often a chronic disease and it may persist for 10–20 years characterized by repeated episodes of healing and re-exacerbations. Ethanol- induced gastric ulcers have been widely used for the evaluation of gastro protective activity. Ethanol is

metabolised in the body and releases superoxide anion and hydro-peroxy free radicals. It has been found that oxygen-derived free radicals are implicated in the mechanism of acute and chronic ulceration in the gastric mucosa [14] and scavenging these free radicals can play an appreciable role in healing these ulcers [15]. Ulcers caused by ethanol are due to superficial damage to mucosal cells [16]. Mucosal blood flow has been attributed to be an important factor in the damage caused by alcohol and is modulated by prostaglandins [17]. The ethanol-induced ulcers is predominant in the glandular part of stomach was reported to stimulate the formation of leukotriene C4 (LTC_4), mast cell secretary products [18], and reactive oxygen oxygen species resulting in the damage of rat gastric mucosa [19].

Acetic acid-induced chronic ulcer model was chosen because it produces gastric lesion, which is similar to human chronic ulcers. In this model, acid cause mucosal injury, which was confined to the glandular stomach [20]. The ulcer produced by acetic acid is due to the release of histamine, which increases the capillary permeability and back diffusion of HCl [21], and increase in acidic gastric juice [22].

The chronic ulcers induced by acetic acid in rats are known to resemble the human peptic ulcer both grossly and histologically. It is due to increase in volume of acid output leading to subsequent pyloric obstruction and mucosal necrosis [22]. Even though the causative factors for ulcerogenesis may be different. It is well established that superficial injury is promptly healed through migration from underlying cells of the gastric pit. Mucus is secreted by the mucus neck cells and covers the gastric mucosa thereby preventing physical damage and back diffusion of hydrogen ions [23]. Increase in synthesis of mucus and decrease in total acid output is the important contributing factors for ulcer protective role of ZOE. The ability of ZOE to protect the stomach against ulcerogens without influencing acid secretion or neutralising intra- gastric acidity can as well lead it to be classified as a cytoprotective agent. The pathogenesis of lesions during stress is still unclear. The role of free radicals in gastric ulcerations is well documented. ZOE significantly reduced lipid peroxidation, SOD and its accumulation due to decreased CAT level in rat gastric mucosa. SOD scavenges the super oxide radical O_2-, one of the reactive oxygen species (ROS) responsible for lipid peroxidation. This reaction leads to increase in generation of peroxyl radical H_2O_2-, which is also capable of producing more oxidative damage. ZOE cause decrease in acid secretion by affecting the final step.

Prostaglandins have long been known to afford protection to the gastric mucosa. They do so by inhibiting acid secretion and increasing mucosal defences. PGs are reported to restore mucosal defense, and thereby prevent damage by several irritants and influence repair of gastric ulcers. PGs are reported to act through endogenous prostaglandin (EP) receptors and the subtype EP-3 in the stomach and duodenum has been reported to be responsible for bicarbonate secretion [24]. Hence decrease in CAT levels has led to increase in accumulation of these reactive products and thus, has caused increased lipid peroxidation and tissue damage [25]. Omiprazole has been reported to protect

against ethanol-induced damage by increased accumulation of PGs rather than reduction of acid secretion.

The results of our study prove that the crude extract of ZOE possess antiulcer activity against experimentally induced acute and chronic gastric ulcer .Hence, it can be suggested that the antiulcer activity of the extract may be attributed to its antisecretory and antioxidant activities.

The present study reveals that (ZOE 50-200 mg/kg) treated groups showed a significant ($P < 0.001$) increase in gastric juice pH, reduces the gastric volume, free acidity and total acidity when compared to control. This effect was similar to omeprazole treated group.

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Table 1: Effect of *Zingiber officnale* Linn. (ZOE) Rhizomes extract (twice daily for five days) on ethanol-induced gastric ulcer.

Group	Treatment	Dose (mg/kg)	Ulcer index (mm^2/rat)	Percent protection
I	Ethanol	-	18.43 ± 0.53	-
II	ZOE	50	15.77 ± 0.83[c]	14.43
III	ZOE	100	14.55 ± 1.20[b]	21.05
IV	ZOE	200	5.08 ± 0.80[a]	72.43
V	Standard	50	3.75 ± 0.53[a]	79.65

Values are mean ± SEM for 6 rats. [a]P< 0.001 compared to respective EtOH group.
[b]P < 0.01 compared to respective EtOH group. [c]p < 0.05 compared to respective EtOH group.

Table 2: Effect of *Zingiber officnale* Linn. (ZOE) Rhizomes extract (twice daily for five days) on lipid peroxidation (LPO), superoxide dismutase (SOD), and catalase (CAT) in ethanol-induced gastric ulcer

Group	Treatment	Dose (mg/kg)	LPO	SOD	CAT
I	Control	-	0.40 ± 0.04	106.8 ± 5.06	30.88 ± 1.93
II	Ethanol	-	0.50 ± 0.02	217.41 ± 6.86	19.08 ± 1.43
III	ZOE	50	0.37 ± 0.03	193.73 ± 6.47	22.05 ± 1.36
IV	ZOE	100	0.28 ± 0.02	172.4 ± 5.91[y]	34.15 ± 2.90
V	ZOE	200	0.25 ± 0.02[y]	153.15 ± 5.21[x]	35.55 ± 2.91[x]
VI	Omeprazole	50	0.42 ± 0.02[x]	143.65 ± 6.22[x]	30.83 ± 2.20[y]

Values are mean ± SEM for 6 rats. [x]P< 0.001 compared to respective control group.
[y]P <0.001 compared to respective control group.

Table 3: Effect of *Zingiber officnale* Linn. Rhizomes extract (twice daily for five days) on acetic acid-induced gastric ulcer

Group	Treatment and Dose (mg/kg)	5 days treated Ulcer index	% incident of perforation	10 days treated Ulcer index	% incident of perforation
I	Control	22.28±0.81	--	13.88±0.81	--
II	ZOE, 50	20.35±0.62	8.66%	11.88±0.85	14.41%
III	ZOE, 100	17.98±0.70[b]	19.30%	8.91±0.87[b]	35.81%
IV	ZOE, 200	12.13±0.94[a]	45.56%	3.93±0.55[a]	71.68%
V	Omeprazole,50	11.68 ± 0.59[a]	47.58%	2.18±0.25[a]	84.29%

Values are mean ± SEM for 6 rats.
[a]P< 0.001 compared to respective control group. [b]P < 0.01 compared to respective control group.

Table 4: Effect of *Zingiber officnale* Linn. Rhizomes extract (twice daily for five days) on lipid peroxidation (LPO), superoxide dismutase (SOD), and catalase (CAT) in acetic acid-induced gastric ulcer

Group	Treatment	Dose (mg/kg)	LPO	SOD	CAT
I	Control	-	0.45 ± 0.05	106.15 ± 5.88	38.6 ± 2.98
II	Acetic acid	-	0.53 ± 0.03	219.9 ± 5.41	19.47 ± 1.61
III	ZOE. extract	50	0.38 ± 0.02	197.01 ± 7.10	24.55 ± 1.56
IV	ZOE. Extract	100	0.29 ± 0.03	175.23 ± 7.33[y]	35.83 ± 3.73
V	ZOE. extract	200	0.25 ± 0.02[x]	158.13 ± 5.31	37.51 ±3.16[x]
VI	Omeprazole	50	0.47 ± 0.03[x]	147.6 ± 6.22[x]	32.68 ± 2.04[x]

Values are mean ± SEM for 6 rats.
[x]P< 0.001 compared to respective control group. [y]P <0.001 compared to respective control group.