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Research Article
Ameliorative Effect of Ginger Extract in Acetic Acid Induced Ulcerative Colitis in Rats

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Abstract
The present study was conducted to examine the anti-inflammatory effect of ethanolic extract of ginger in acetic acid induced ulcerative colitis in rats. Forty eight Wistar rats were randomly divided into 4 equal groups; (1) Normal control group, (2) Acetic acid treated group, (3) An ethanol extract of ginger-treated group and (4) Dexamethasone-treated group. Rats were fasted for 24 h and colitis was induced in groups 2, 3 and 4 by intra-colonic administration of 4% acetic acid (2 mL). Post colitis induction, treatment was started in group 3 with ginger extract (700 mg kg^{-1} per day, orally) and group 4 with dexamethasone (2 mg kg^{-1}, intraperitoneal) for 14 days. At the end of the experiment, colon samples were estimated for superoxide dismutase (SOD), catalase (CAT), reduced glutathione (GSH) and glutathione peroxidase (GPx), thiobarbituric acid reacting substance (TBARS) and Protein Carbonyls (PC). Inflammatory and anti-inflammatory cytokines viz., Tumor necrosis factor-alpha (TNF-α), interleukin-1β (IL-1β) and interleukin-10 (IL-10) and prostaglandins E_2 level (PGE_2) was estimated in the colon and a portion of colon samples were snap-frozen for histopathological studies. Results revealed that treatment groups significantly ($p<0.05$) attenuated the increased colonic TBARS, PC, TNF-α, IL-1β and PGE_2 levels and significantly ($p<0.05$) increased the SOD, CAT, GSH, GPx and IL-10 levels. Histopathological examinations revealed reduced haemorrhage and oedema of the colon in the treatment groups. The study suggests that ginger extract significantly attenuated the acetic acid induced inflammation and histopathological changes may be through its scavenging effect on oxygen-derived free radicals.

Key words: Acetic acid, cytokines, ginger, dexamethasone, ulcerative colitis

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Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Ulcerative Colitis (UC) is a chronic inflammatory bowel disease related to the disruption of the immune homeostasis of the intestinal epithelium with unknown etiology (Coskun, 2014; Baumgart and Sandborn, 2012). The commonly used medical treatments for UC include Non-Steroidal Anti-inflammatory Drugs (NSAIDs), glucocorticoids, immuno-modulators, selective Cyclooxygenase-2 (COX-2) inhibitors and Phytotherapy. Phytogenic agents have traditionally been used by herbalists for the treatment of ulcers (Borrelli and Izzo, 2000). Gingerone, phytogenic agent in ginger rhizome shows better anti-inflammatory effects by inhibiting arachidonic acid metabolism in both COX and lipoxygenase (LOX) pathways (Rahmani *et al*., 2014). Dexamethasone, an NSAID drug, shows a significant decrease in ulcer formation in trinitrobenzensulphonic acid-control group and decrease in activity of pro-inflammatory cytokines like tumour necrosis factor-α and interleukins-1β in colitis conditions (Motavallian *et al*., 2013). The study was designed and conducted to determine the anti-inflammatory effect of ginger extract in acetic acid induced colitis in Wistar rats.

MATERIALS AND METHODS

Preparation of the extract: The shade dried and finely powdered ginger rhizome (150 g) was macerated with 600 mL of ethanol (70%) for 12 h at 70°C in the water bath. The mixture mass was filtered and evaporated in a rotatory evaporator under reduced pressure until dryness (Minaiyan *et al*., 2006). The final extracts were kept in a tight closed container and stored at 4°C.

Drugs and chemicals: All chemicals were obtained from Qualigens Pvt. Ltd., Mumbai and SRL Pvt. Ltd., Mumbai and dexamethasone from Virbac Animal Health, Mumbai (India).

Experimental design: Forty eight adult male Wistar rats weighing 200±50 g were obtained from Teena Biolabs, Hyderabad. They were divided into four groups with 12 animals in each (N = 12):

- **Group 1:** Normal control group received the normal saline (2 mL kg^{-1} b.wt., orally) for 14 days
- **Group 2:** Colitis group received the acetic acid intraperiteonally and subjected to the colitis induction procedure
- **Group 3:** Acetic acid induced colitic rats treated with ginger extract (700 mg kg^{-1} b.wt., orally) for 14 days
- **Group 4:** Acetic acid induced colitic rats treated with dexamethasone (2 mg kg^{-1} b.wt., intraperitoneal) for 14 days

Colitis was induced in rats by intra-colonic administration of 4% acetic acid (2 mL) through a lubricated catheter under low-dose ether anaesthesia (Millar *et al*., 1996) and treatment was started post-colitis induction. The instillation site was about 8 cm from the anal verge into the rectum. Rats were maintained in trendelenburg position for 30 sec to prevent the leakage of the acid. Control group rats received the saline intraperitoneally. Rats were acclimatized to laboratory conditions for 7 days before the start of experimental procedures and maintained in a well ventilated cage under standard protocols. The study was conducted with the approval from the Institutional Animal Ethics Committee (Approval No. CPCSEA 4/7/2012). On the 14th day, animals were sacrificed and colon samples were collected and stored at -80°C for the estimation of the anti-oxidant parameters, viz., superoxide dismutase, catalase, reduced glutathione and glutathione peroxide.

Estimation of antioxidant markers of colon homogenates: The colon samples were homogenized in 1mL of 10 mmol L^{-1} Tris-HCl buffer of pH 7.1 using a glass-Teflon Homogenizer for 5 min at 5000 RPM and the homogenate was used for the estimation of superoxide dismutase (Madesh and Balasubramanian, 1998), catalase (Sinha, 1972), reduced glutathione (Moron *et al*., 1979) and glutathione peroxide (Paglia and Valentine, 1967).

Estimation ofperoxidation markers of colon homogenates: Malondialdehyde, a lipid peroxidation product was estimated by reaction with Thiobarbituric Acid Reacting Substances (TBARS) (Balasubramanian *et al*., 1988). Protein carbonyls (PC) were estimated based on the reaction of amino carbonyls with 2, 4-dinitrophenyl hydrazine to form hydrazones, which can be detected spectrophotometrically at 372 nm (Levine *et al*., 1990). Total protein in the colon was quantified as per Lowry *et al*. (1951).

Estimation of Myeloperoxidase activity of colon homogenates: Myeloperoxidase (MPO) activity was measured spectrophotometrically with the colon homogenates with the maximum absorbance at 460 nm as previously described method of Krawisz *et al*. (1984).

Determination of inflammatory mediators of colon homogenates: The concentration of Tumour Necrosis Factor-α (TNF-α), Interleukins-1β (IL-1β), Interleukins-10 (IL-10) and Prostaglandins (PGE_2) (pg mg^{-1} tissue) in the colon homogenate measured using a commercially available ELISA kit according to the manufacturer's instructions.

Histopathology: At the end of the experiment, colonic specimens were immediately fixed in 10% formalin, cleared in xylene, embedded in paraffin blocks and cut into fine microscopic sections. The sections were stained with hematoxylin and eosin and examined for mucosal damage assessment under a light microscope (Singh and Sulochana, 1997).

Statistical analysis: Statistical analysis was performed by one-way ANOVA using SPSS® 20.0 (IBM, USA) and the results were expressed as Mean±SD. Group differences were determined by Duncan's multiple comparison test ($p<0.05$).

RESULTS

Effect of ginger and dexamethasone on antioxidant and peroxidation markers of inflammed colon: In acetic acid treated group, the concentration of SOD, CAT, GSH and Gpx were significantly ($p<0.05$) reduced while, the concentration of TBARS, MPO and PC were significantly ($p<0.05$) increased in the control group. Administration of dexamethasone and ginger significantly ($p<0.05$) reversed the above values as compared to acetic acid treated group (Table 1 and 2).

Effect of ginger and dexamethasone on cytokines and PGE_2 level of inflammed colon: Levels of TNF-α and IL-1β were significantly ($p<0.05$) elevated in the colon samples of animals treated with acetic acid. Tissue levels of these cytokines were significantly ($p<0.05$) reduced in rats treated with dexamethasone and ginger. No significant increase in these cytokines was observed in specimens of control rats (Table 3).

IL-10 levels were significantly ($p<0.05$) down regulated in the colon samples of animals treated with acetic acid. Administration of dexamethasone and ginger to acetic acid treated rats ameliorated the decrease in IL-10 levels significantly ($p<0.05$) as compared to acetic acid treated group (Table 3).

Similarly, PGE_2 concentration was significantly ($p<0.05$) up-regulated in acetic acid treated group as compared to control. Treatment with dexamethasone and ginger ameliorated the increase in PGE_2 concentration significantly ($p<0.05$) as compared to acetic acid treated group (Table 3).

Table 1: Effect of ginger and dexamethasone on anti-oxidant and peroxidation parameters of acetic acid induced colitis in colon of different group of rats

Groups	GSH (n mol mg^{-1} protein)	Gpx (U mg^{-1} protein)	SOD (U mg^{-1} protein)	Catalase (U mg^{-1} protein)
Control	140.42±10.14^{A}	695.42±10.17^{A}	12.81±0.43^{A}	25.42±1.20^{A}
Acetic acid control	36.38±3.78^{B}	198.35±10.3^{D}	3.76±0.09^{C}	13.06±0.29^{C}
Ginger extract	127.72±4.23^{A}	520.32±11.4^{C}	10.34±0.20^{B}	19.32±0.50^{B}
Dexamethasone	130.94±8.20^{A}	474.23±10.2^{B}	11.71±0.44^{B}	18.30±0.72^{B}

GSH: Reduced glutathione, Gpx: Glutathione peroxidase, SOD: Superoxide dismutase, values are expressed as Mean±SEM (n=12) and analyzed using analysis of variance followed by Duncan *post hoc* test, means with different superscript letters differ significantly at *$p<0.05$ as compared to control group

Table 2: Effect of ginger and dexamethasone on peroxidation parameters of acetic acid induced colitis in colon of different group of rats

Groups	TBARS (n mol of MDA released mg^{-1} protein)	Protein Carbonyls (n mol carbonyl mg^{-1} protein)	Myeloperoxidase (U g^{-1} tissue)
Control	8.51±0.41^{C}	2.40±0.14^{C}	3.52±0.14^{D}
Acetic acid control	35.95±1.71^{A}	5.84±0.15^{A}	16.30±0.49^{A}
Ginger extract	14.33±1.11^{B}	2.27±0.09^{BC}	7.50±0.57^{B}
Dexamethasone	15.05±0.73^{B}	3.08±0.14^{BC}	8.16±0.44^{C}

Values are expressed as Mean±SEM (n=12) and analyzed using analysis of variance followed by Duncan *post hoc* test, means with different superscript letters differ significantly at *$p<0.05$ as compared to control group, TBARS: Thiobarbituric acid reacting substance

Table 3: Effect of ginger and dexamethasone on cytokine and PGE_2 level of acetic acid induced colitis in colon of different group of rats

	TNF-α	IL-1β	IL-10	PGE_2
Groups	(pg mg^{-1} tissue)			
Control	87.27±2.30^{D}	1.03±0.01^{C}	3.74±0.11^{A}	0.84±0.01^{C}
Acetic acid control	192.04±5.08^{A}	1.29±0.02^{A}	1.22±0.03^{C}	1.51±0.02^{A}
Ginger extract	109.40±3.41^{C}	1.07±0.00^{BC}	3.19±0.11^{B}	1.01±0.03^{B}
Dexamethasone	125.96±3.95^{B}	1.09±0.00^{B}	2.91±0.07^{B}	1.01±0.03^{B}

Values are expressed as Mean±SEM (n=12) and analyzed using analysis of variance followed by Duncan *post hoc* test, means with different superscript letters differ significantly at *$p<0.05$ as compared to control group, TNF-α: Tumour necrosis factor-alpha, IL-1β: 1β, Interleukin, IL-10: Interleukin 10, PGE_2: Prostaglandins E_2

Effect of ginger and dexamethasone on histopathology of inflammed colon: Normal colon showed intact mucosal layer and normal intestinal epithelial lining (Fig. 1). Acetic acid instillation into the colon induced erosion of surface epithelium, haemorrhage, edema and acute inflammation of the wall of the colon (Fig. 2). Treatment with ginger extract revealed absence of acute inflammation, crypt damage and surface epithelial loss (Fig. 3). Treatment with dexamethasone revealed mild neutrophilic infiltration, increase in the number of goblet cell and a slight disruption of the epithelium lining (Fig. 4).

DISCUSSION

Ulcerative colitis is a chronic recurrent inflammatory bowel disease characterized by up-regulated pro-inflammatory mediators and dysregulated immune responses resulting in tissue damage (Xu *et al*., 2014). Oxidative stress has been implicated in the pathogenesis of ulcerative colitis in experimental animals (Rana *et al*., 2014) and infiltration of neutrophils, macrophages, lymphocytes and mast cells eventually contribute to the intestinal injury (Jin *et al*., 2010).

Superoxide dismutase, levels are reduced in inflammed intestinal tissues as free radicals affect the intestinal epithelium (Kandhare *et al*., 2013). Oxidative damage of the colitis imbalances the catalytic activity resulting in inflammation and oxidative damage to the colonic mucosa (Circu and Aw, 2012). SOD activity is significantly increased in the ginger extract group may be attributed to control the ROS accumulation as reported by Mukherjee *et al*. (2015).

Ginger extract with its free radical scavenging capability effectively increased the GSH and GPx level through restoration of GSH level and tissue detoxification in colitic rats

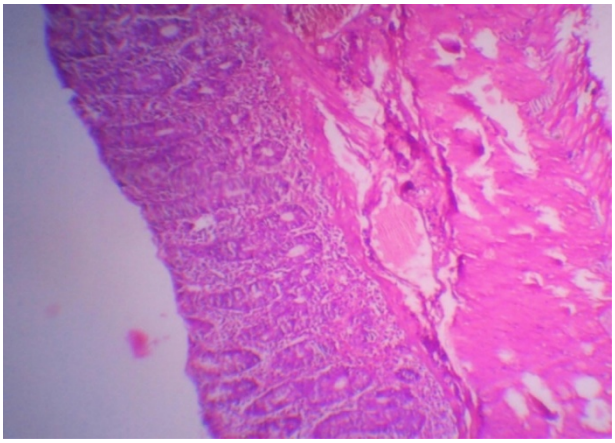

Fig. 1: Photomicrograph of colon showing no lesions of pathological significance (Group 1)

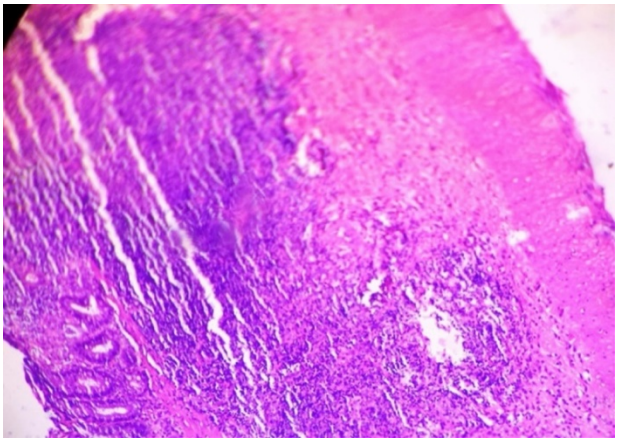

Fig. 2: Photomicrograph showing erosion of surface epithelium, edema and acute inflammation of the colon (Group 2)

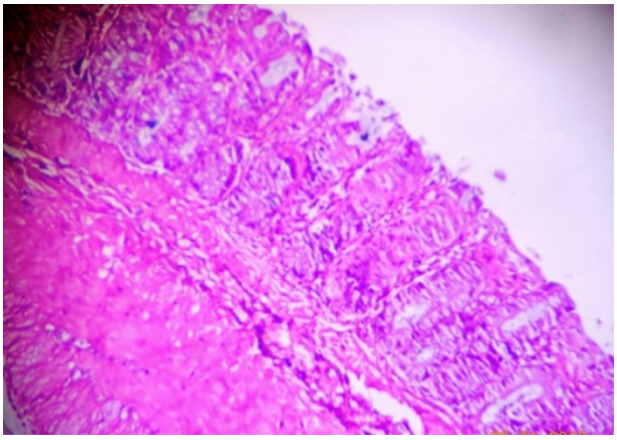

Fig. 3: Photomicrograph of colon showing absence of acute inflammation, crypt damage and surface epithelial loss (Group 3)

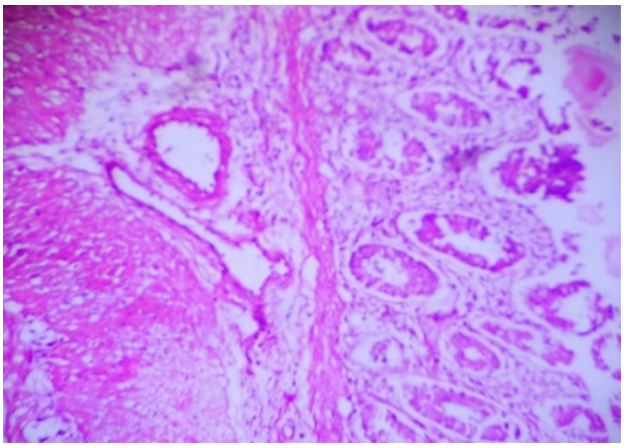

Fig. 4: Photomicrograph of colon showing mild neutrophilic infiltration, increase in number of goblet cell, slight disruption of epithelium lining (Group 4)

(Attia *et al*., 2013). Earlier workers reported that administration of dexamethasone compensates for deficits in anti-oxidant defense system such as GSH, CAT, SOD and also suppresses lipid peroxidation in intrauterine ischemia in the fetal rat brain (Hasturk *et al*., 2013) and inhibit pro-inflammatory cytokine production (Zeng *et al*., 2015).

In this study, the phyto-active principles in ginger inhibit the production of prostaglandins and leukotrienes through the reduced inflammatory COX-2 expression, which in turn decreases inflammation (Tjendraputra *et al*., 2001). Similarly, the action of dexamethasone on COX-2 suppression is well documented by Lim *et al*. (2014). The elevated MPO activity in treated groups was markedly decreased by the anti-inflammatory effects of ginger extract and dexamethasone resulting in mitigation of the histopathologic indices. Our finding is in agreement with El-Abhar *et al*. (2008) for ginger and Huang *et al*. (2014) for dexamethasone.

The TNF-α, IL-1β and PGE_2 concentration was up-regulated in acetic acid induced colitis group as compared to control. The elevation of IL-1β levels in the inflammed intestine can adversely contribute to the tissue damage in the course of inflammatory bowel disease (Saniabadi *et al*., 2014). Treatment with dexamethasone and ginger extract significantly ameliorated the increase as compared to acetic acid treated group. The TNF-α is abundantly expressed in the inflammed colon due to enhanced production of PGE_2 (Otani *et al*., 2006). The effect of ginger on reducing levels of TNF-α may be attributed by blocking of production and activation of pro-inflammatory mediators (Justo *et al*., 2015). Inhibition of PGE_2 may result from the ability of

ginger extract (Al-Nahain *et al*., 2014) and dexamethasone (Baghaei *et al*., 2010) to inhibit cyclooxygenase enzymes.

Treatment with ginger and dexamethasone ameliorated the rise in IL-10 level, which relates to the suppression of the inflammation was evidenced by El-Boshy *et al*., (2015) in lead intoxicated rats for ginger and Hegazy (2011) for dexamethasone. Severe hemorrhage and ulceration of the intestine in colitic group confirms the biological evidence of oxidative stress induced by acetic acid. Treatment with ginger extract revealed regeneration of epithelium, mild neutrophilic infiltration and these results are in accordance with Minaiyan *et al*. (2008), who stated that ginger ameliorate the altered microscopic lesions to normal when given at high dose. Similarly, dexamethasone group rats recovered from the inflammation.

CONCLUSION

In conclusion, the present study showed the protective effect of ginger extract on acetic acid induced colitis by improving anti-oxidant, inflammatory and anti-inflammatory cytokines. The out comes of the present study may encourage future clinical trials of the ginger extract or its bio active compounds as natural, safe and effective treatments for patients with ulcerative colitis.

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