ULCER HEALING PROPERTIES OF ETHANOLIC EXTRACT OF *EUGENIA JAMBOLANA* SEED IN DIABETIC RATS : STUDY ON GASTRIC MUCOSAL DEFENSIVE FACTORS

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Abstract : Diabetes has been reported to cause an increase in offensive and decrease in defensive gastric mucosal factors, the imbalance of which can cause ulceration and delay the ulcer healing. *Eugenia jambolana* has been documented to have both antidiabetic and antiulcer activities. The present study evaluates the effects of ethanolic extract of *E. jambolana* on gastric ulcer healing and on rat gastric mucosal defensive factors in gastric ulcer with co-occurring diabetes. *E. jambolana* extract was administered orally in the dose of 200 mg/kg once daily for 10 days. *E. jambolana* extract increased mucin secretion, mucosal glycoprotein and glutathione levels and decreased the lipid peroxidation in gastric mucosa of diabetic rats. Its treatment also reversed the decrease in life span of gastric mucosal cells as indicated by decreased cell shedding in the gastric juice but found to have no effect on cell proliferation, indicating enhanced defensive status. *E. jambolana* extract was effective in reversing the delayed healing of gastric ulcer in diabetic rats near to the normal level. *E. jambolana* showed better ulcer healing effect than glibenclamide, because of its both antihyperglycemic and mucosal defensive actions. It could thus, be a better choice for treating gastric ulcers co-occurring with diabetes.

Key words : ulcer healing   gastric mucosal defensive factors
              antioxidant   lipid peroxidation

INTRODUCTION

Diabetes increases the mucosal susceptibility to ulcerogenic stimuli and predisposition to gastric ulceration (1, 2). Experimental studies indicate that prolonged diabetic conditions have deleterious influences on various functions in the

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gastrointestinal tract (3). Recent studies have shown aggravation of gastric mucosal ulcerogenic responses to starvation and stress in insulin dependent diabetic rats (1, 4), and impaired healing of gastric lesions in streptozotocin (STZ)-induced insulin dependent diabetes rats (5). There are clinical reports suggesting increased healing time and mortality rate in gastric ulcer patients suffering from diabetes mellitus (6). Earlier, we reported the antiulcer and ulcer healing effects of extracts of *Pteocarpus marsupium* (vijaysar) (7), *Bacopa monniera, Azadirachta indica* (8) and plantain banana (*Musa sapientum* var. *paradisiaca*) (9, 10) which were due to correction of either blood sugar level or promotion of mucosal defensive factors affected in diabetes.

Eugenia jambolana (EJ) popularly known as *Jamun* or Indian blackberry has been indicated in Ayurveda, an ancient system of Indian medicine for use in diabetes (11). EJ has been reported to have hypoglycemic effects both in experimental and clinical studies (12-14). EJ seeds apart from hypoglycemic activity have been reported to have anti-inflammatory (15), neuropsycho-pharmacological (16), anti-bacterial (17), anti HIV (18) and anti-diarrhoeal (19) effects. EJ seed kernel decreased the oxidative stress in diabetic rats, which in turn may be due to its hypoglycemic property (14). We reported earlier the ulcer protective effects of EJ against both physically and chemically induced gastric ulcers in normal rats mainly by promoting the mucosal defensive factors and antioxidant status and decreasing lipid peroxidation (20).

Peptic ulcer occurs due to imbalance between offensive acid pepsin secretion versus impaired mucosal resistance which includes mucin bicarbonate secretion, life span of cells, cell proliferation, mucosal blood flow etc. (21). The present work was undertaken with the hypothesis that diabetes being a chronic disease would further compromise, if any, (i) the mucosal defensive factors with concomitant delay in chronic ulcer healing; and (ii) the change induced by diabetes mellitus can be prevented or cured after using known antidiabetic and ulcer protective drugs which correct the blood glucose levels, promote the mucosal defensive factors or both. Hence, we selected *E. jambolana* seed to evaluate its effects on the susceptibility of diabetic rat's gastroduodenal mucosa to gastric ulcer healing in acetic acid-induced ulcers. The results were also compared with standard oral hypoglycemic drug glibenclamide and anti ulcer/ulcer protective drug like ranitidine, on mucosal defensive factors and ulcer healing in gastric ulcer co-occurring with diabetes.

MATERIAL AND METHODS

Animals

Inbred Charles Foster (CF) albino rats (130–180 g) of either sex, obtained from the Central Animal House of the Institute of Medical Sciences, Banaras Hindu University, Varanasi, were kept in the departmental animal house at 26±2°C and relative humidity 44–56% light and dark cycles of 10 and 14 h respectively. Animals were provided with standard rodent pellet diet (Pashu Aahar Kendra, Varanasi) and the food was withdrawn 18 h before the experiment though water was allowed *ad libitum*. Principles of laboratory animal care guidelines

were followed and prior permission was sought from the Institute Animal Ethics Committee for conducting the study.

Plant   material

Fruits of *Eugenia jambolana* were collected locally in the month of June/July. Dried coverings of the seeds were peeled off and the seed kernel was dried at room temperature and grounded in an electric grinder to have coarse powder. Extraction of the seed powder was done with adequate amounts of ethanol for 7 days and the extract so obtained was filtered. The procedure was again repeated twice using adequate volume of ethanol for 3 days. The extract was again filtered and mixed with previous lot. It was then vacuum dried and stored in refrigerator at −20°C until further use. The yield of the ethanolic extract of the seeds of *Eugenia jambolana* (EJE) was 12.5 g/100 g of dried powdered seed kernel.

Drug   Treatment

The test drugs were administered 72 hours after induction of diabetes (blood glucose greater than 140 mg/dL). They were suspended in 1% carboxymethylcellulose in distilled water and given orally, once daily for 10 days (1 ml/100g body weight). Animals received EJE (200 mg/kg) (20), standard antidiabetic; glibenclamide (0.6 mg/kg) and H_2-blocker; ranitidine (2.5 mg/kg) while control group animals received suspension of 1% carboxymethylcellulose in distilled water (8).

Induction   of   diabetes

Diabetes was induced by intraperitoneal injection of streptozotocin in citrate buffer (STZ, 45 mg/kg i.p.) to adult rats (22). Control rats received citrate buffer alone. 72 hours after injection of STZ, the rats were checked for fasting glucose level and those with fasting blood glucose level greater than 140 mg/dL were considered as diabetic rats and used for further studies.

Ulcer   healing   study

Acetic acid induced ulcer

Rats were anaesthetized with pentobarbitone (35 mg/kg, ip). The abdomen was opened and the stomach was visualized. A cylindrical glass tube (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. 50% acetic acid (0.06 ml/animal) was instilled into the tube and allowed to remain for 60 sec on the gastric wall (23). After removal of acid solution, the abdomen was closed in two layers and animals were caged and fed normally. EJE (200 mg/kg) was given on day one, orally, twice daily, 4 h after the application of acetic acid and continued up to 9 days after induction of ulcer. The animals were then sacrificed after 18 h of the last dose of drug on 10th day 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.

Study on mucosal defensive factors

A.   Gastric   secretion   study

Mucoprotein and cell shedding: The gastric juice was collected 4 h after pyloric

ligation and centrifuged for 5 min at $224 \times g$. Dissolved mucosubstances were estimated in 90% alcoholic precipitate of the gastric juice. The precipitate thus obtained was either dissolved in 1 ml of 0.1 N NaOH or 1 ml of 0.1 N H_2SO_4. The former was used for the estimation of protein (24), total hexoses, hexosamine and fucose, while the latter was used for the estimation of sialic acid (25). The ratio of total carbohydrates (sum of total hexoses, hexosamine, fucose and sialic acid) to protein has been taken as the index of mucin activity (25). DNA content was estimated and expressed as µg/ml gastric juice following the method as described earlier (26).

B. Gastric mucosal study

Glycoproteins: Sample of gastric mucosal scraping were homogenized in distilled water and treated with 90% ethanol. The carbohydrates and the proteins in the samples were estimated using the methods as described above for gastric juice contents.

Cell Proliferation: DNA and protein were estimated in the gastric mucosal homogenate following the method described earlier (24, 27). The concentration of DNA was expressed as µg DNA/ mg protein which is a reliable index of cell proliferation as reported earlier (27).

C. Free radical and antioxidant study

Estimation of free radical (Lipid peroxidase, LPO): EJE was given orally for 9 days and on day 10, 1 h prior to subjecting the animals to 2 h cold restraint stress. The animals were sacrificed after 2 h and fundal mucosa of the stomach was homogenized and was used for the estimation of lipid peroxidase expressed as n mol of malondialdehyde/g wet tissue (9, 28).

Estimation of antioxidant activity (Glutathione level, GSH): Glutathione levels were estimated in ethanol-induced gastric ulcer model. Reduced glutathione was estimated in the gastric mucosal homogenate scrap following the standard procedure (29). The result was expressed as µmol/g wet tissue and was calculated from the standard curve prepared by using standard glutathione.

Statistical analysis

One way analysis of variance (ANOVA) followed by Dunnett's test was done for multiple comparisons. The difference was considered to be significant when P<0.05.

RESULTS

Ulcer healing effect

Diabetes significantly delayed healing of acetic acid-induced chronic gastric ulcer as shown by an increase in ulcer index. EJE, glibenclamide and ranitidine were all effective in facilitating gastric ulcer healing as shown by decrease in ulcer index in diabetic rats. However EJE showed better effect compared to glibenclamide (Fig. 1).

Effect on gastric juice and mucosal parameters

Diabetic rats showed decrease in mucin secretion in the gastric juice and glycoprotein content of the gastric
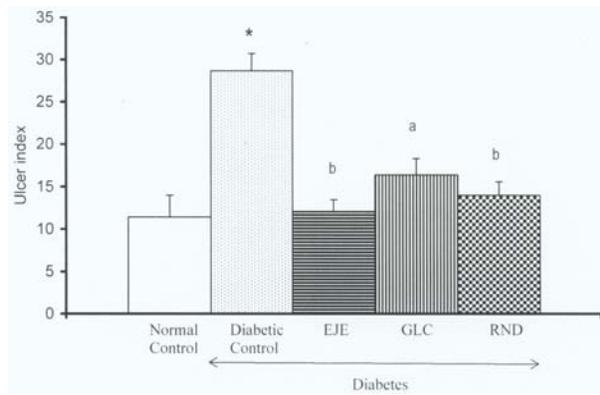
Fig. 1 : Ulcer healing effect of ethanolic extract of
seeds of *E. jambolana* (EJE), Glibenclamide
(GLC) and Ranitidine (RND) on acetic acid-
induced chronic gastric ulcer in diabetic rats.
Results are mean±SEM of 6 rats.
*P<0.001, compared with Normal Control
group; [a]P<0.01 and [b]P<0.001 as compared
with Diabetic Control group.

mucosa as indicated by decreased Total carbohydrates: Protein ratio (Tables I, II). Diabetic rats also showed increase in gastric mucosal shedding as shown by an increase in DNA content of gastric juice indicating decreased mucosal cell life span (Table I) though it did not show any effect on cell proliferation in terms of µg DNA per mg protein, a reliable index for cell proliferation (Table II). EJE caused increase in mucin secretion, mucosal glycoprotein content and the life span of gastric mucosal cells near to the normal level better than glibenclamide or ranitidine without any effect on cell proliferation which was also not affected in diabetic rats (Tables I, II).

TABLE I : Effect of orally administered ethanolic extract of seed kernel of *Eugenia jambolana* (200 mg
kg×10 days), glibenclamide (0.6 mg/kg×10 days) and ranitidine (2.5 mg/kg×10 days) on
mucin secretion and cell shedding in 4 h pylorus ligated normal and diabetic rats.

Gastric juice	I	II	III	I V	V
A. Gastric juice mucoprotein (µg/ml)					
Total Carbohydrates (TC)	553.4±15.9	440.1±18.8*	599.4±32.3[a]	499.1±17.9	486.7±27.3
Protein (P)	603.8±44.5	606.5±48.4	611.2±56.8	614.2±6.2	661.2±11.9
TC:P	0.96±0.07	0.73±0.07*	1.02±0.09[a]	0.82±0.05	0.73±0.04
B. Gastric juice cell shedding (µg/ml)					
DNA	129.0±17.6	223.6±20.6*	101.3±5.9[a]	178.3±11.4	148.8±8.2[a]

I-Normal Control, II-Diabetic Control, III-Diabetic + EJE, IV-Diabetic + Glibenclamide, V-Diabetic + Ranitidine.
The values are mean±SEM of 6 rats in each group. One-way ANOVA followed by Dunnett's test for
multiple comparisons for comparing the Diabetic control with Normal control groups and Diabetic + Test
drugs treated groups with respective Diabetic control groups. The difference was considered to be
significant when * indicates P<0.05 compared to respective Normal control group and a indicates P <0.05
compared to respective Diabetic control group.

TABLE II : Effect of orally administered EJE (200 mg/kg×10 days), Glibenclamide (0.6 mg/kg×10 days)
and Ranitidine (2.5 mg/kg×10 days) on gastric mucosal parameters in Normal and Diabetic rats.

Gastric mucosa	I	II	III	I V	V
A. Gastric mucosal glycoprotein (µg/100 mg wet tissue)					
Total Carbohydrates (TC)	4120±161	3674±90	4487±132[a]	3970±66	3747±112
Protein (P)	5247±227	6192±494	5458±251	5373±232	5636±164
TC:P	0.79±0.03	0.62±0.05*	0.83±0.04[a]	0.74±0.04	0.67±0.03
B. Gastric mucosal cell proliferation (µg DNA/mg protein)					
µg DNA/mg protein	106.7±3.2	100.9±3.3	105.6±2.9	105.1±4.7	100.3±2.0

I-Normal Control, II-Diabetic Control, III-Diabetic + EJE, IV-Diabetic + Glibenclamide, V-Diabetic +
Ranitidine. The values are mean±SEM of 6 rats in each group. One-way ANOVA followed by Dunnett's
test for multiple comparisons for comparing the Diabetic control with Normal control groups and
Diabetic + Test drugs treated groups with respective Diabetic control groups. The difference was
considered to be significant when *P<0.05 compared to respective Normal control group and [a]P<0.05
compared to respective Diabetic control group.

Effect on gastric mucosal Lipid peroxidation and Reduced Glutathione

Cold restraint stress caused a significant increase in gastric mucosal lipid peroxidation in normal rats which was further increased in diabetic rats. EJE, glibenclamide and ranitidine significantly reversed the raised lipid peroxidation level in diabetic gastric ulcerated rats near to the control stress level (Table III). Ethanol ingestion in normal rats significantly decreased reduced glutathione level which was further decreased in diabetic rats. Reduced glutathione level was significantly augmented by EJE, glibenclamide and ranitidine near to the control ethanol level (Table III).

TABLE III : Effect of EJE, Glibenclamide (GLC) and Ranitidine (RND) on gastric mucosal Lipid peroxidation in Cold restraint stress (CRS)-induced gastric ulcer and reduced glutathione (GSH) in ethanol (EtOH) induced gastric ulcer in normal and diabetic rats.

Treatment (mg/kg, od, po×10 days)	LPO (n mol/g wet tissue)	GSH (µ mol/g wet tissue)
Normal Control	189.5±17.4	367±15
Cold Restraint Stress/Ethanol	295.3±16.0*	295±13*
Diabetes + CRS/EtOH	410.2±21.6[a]	223±23[a]
Diabetes + CRS/EtOH + EJE-200	315.0±19.3[b]	310±13[b]
Diabetes + CRS/EtOH + GLC-0.6	329.5±17.7	297±12
Diabetes + CRS/EtOH + RND-2.5	315.2±15.7[b]	326±15[b]

Results are mean±SEM of 6 rats in each group. One-way ANOVA followed by Dunnett's test for multiple comparisons was applied for comparing the CRS/EtOH with Normal control group and Diabetic + CRS/EtOH group with respective CRS/EtOH-control groups and Diabetic + Test drugs + CRS/EtOH with Diabetic + CRS/EtOH group. The difference was considered to be significant when *$P<0.05$ compared to respective Normal control group and [a]$P<0.05$ compared to respective CRS/EtOH-control group and [b]$P<0.05$ compared to respective Diabetic + CRS/EtOH group.

DISCUSSION

Our earlier studies showed that acetic acid-induced chronic gastric ulcer healing was delayed in STZ-induced diabetic rats (30). Our present result with EJE indicated significant healing of gastric ulcers in diabetic rats. Acetic acid-induced ulcer model better resembles clinical ulcers in location, chronicity and severity and serves as the most reliable model to study healing process. Although specific mechanisms remain controversial, increase in acid output and subsequent pyloric obstruction may be the cause for ulceration due to acetic acid (31).

Diabetic rats were reported to show an increase in offensive acid-pepsin secretion and decrease in defensive mucin secretion, mucosal glycoproteins and life span of mucosal cells (1, 7, 9, 10), the net imbalance of them, is thought to be the detrimental factor in ulcerogenesis and ulcer healing (21). The decreased mucin secretion and mucosal glycoprotein content in diabetic rats indicate the decreased ability of the mucosal membrane to protect the mucosa as evidenced by an increase in DNA content of the gastric juice (26). The rapid proliferation of the gastric mucosa plays an important role in mucosal protection during normal state and following mucosal damage. However, there was no change in cell proliferation in the gastric mucosa of normal, diabetic or test drugs treatment in diabetic rats. Treatment with both glibenclamide and EJE either tended to reverse or reversed the diabetic-induced acute adverse effect on the above parameters thus indicating the deleterious effects of diabetes and its reversal by antihyperglycemic agents. Ranitidine on the other hand exhibits its antiulcer and

ulcer healing effects by virtue of its predominant inhibitory action on acid-pepsin secretion (32).

Stress causes both sympathetic and parasympathetic stimulation of stomach leading to local hypoxia (near or actual "ischemia"). The ischemic condition caused an increase in the levels H_2O_2 which in conjugation with O_2 generates OH^- ions which oxidized various cellular constituents such as proteins, membrane lipids and depletes glutathione. Lipid peroxidation causes loss of membrane fluidity and loss of cellular function (33). The lipid peroxidation level was significantly increased in cold restraint stress as well as in cold restraint stress-diabetic rat gastric mucosa. Treatment with EJE significantly decreased the lipid peroxidase levels of gastric mucosa against cold restraint stress and cold restraint stress plus diabetic induced lipid peroxidase changes in rat gastric mucosa. The role of free radicals and antioxidants; enzymes (superoxide dismutase, catalase and glutathione peroxidase) as well as reduced glutathione in gastric ulceration are well documented (21). Reduced glutathione in conjugation with glutathione peroxidase and glutathione S transferase (GST) plays a central role in the defense against free radicals. Thiols such as glutathione are able to bind to reactive free radicals and may influence the physical properties of mucous since its subunits are joined by disulphide bridges. Diethyl malate markedly depletes gastric glutathione and causes severe gastric ulceration indicating the defensive role played by glutathione in ulcer formation. Glutathione level in gastric mucosa has been reported to decrease in both ethanol induced gastric ulcer in normal rats as well as in diabetic rats (9). The

decrease in glutathione level after ethanol ingestion in diabetic rats in the present work was increased by EJE treatment indicating an enhanced antioxidant status and ulcer protection by EJE. Thus, EJE significantly decreased lipid peroxidase and augmented reduced glutathione levels in diabetic gastric ulcer rats. As lipid peroxidation and reduced glutathione are known determinants for etiology of gastric ulcer and diabetes (21), anti oxidant effect of EJE may be one of the important factors for its ulcer healing effect in diabetic rats.

Flavonoids diglycosides (34) (Quercetin and Myricetin), hydrolysable tannins (1-0-galloyl castalagin and casuarinin) (35) and a triterpene, oleanolic acid (36) were isolated from seeds of *E. jambolana*. The gastric ulcer healing activity of EJE in both normal and diabetic rats may be due to the presence of flavonoids as they have been reported to possess both antiulcer and anti-inflammatory activities (37, 38). Flavonoids have been reported to affect arachidonate metabolism where cyclo-oxygenase products like PGE and PGI_2 protect gastric mucosa against damage (21, 38, 39).

Ranitidine was found to be less effective than EJE in case of experimental ulcer healing in diabetic rats. It might be due to its partial ability to change the adverse effect of diabetes on the gastric mucosa. Standard oral hypoglycemic drug glibenclamide had no antiulcer activity in normal rats (20) but it reversed the impaired ulcer healing in diabetic rats near to normal values. EJE by virtue of its both *per se* effect (20) as well as reducing the deleterious effects of diabetes on mucosal defensive factors could be a better choice in the treatment of gastric ulcer

with concomitant diabetes.

In conclusion, the present results suggested that the diabetic conditions increased the vulnerability of gastric mucosa to ulceration and delayed the healing process as compared to normal mucosa. Ethanolic extract of *E. jambolana* possessed both antiulcer and healing promoting activities in normal and diabetic rats. Hence, *E. jambolana* may be potentially useful in diabetes with co-occurring gastric ulcers. However, further studies on other defensive mechanisms may provide more insight on the etiopathogenesis of ulceration and healing in diabetes mellitus and ulcer protective activity of ethanolic extract of seeds of *Eugenia jambolana*.

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