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ANTIDIABETIC AND ANTIULCER EFFECTS OF EXTRACT OF *EUGENIA JAMBOLANA* SEED IN MILD DIABETIC RATS: STUDY ON GASTRIC MUCOSAL OFFENSIVE ACID-PEPSIN SECRETION

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Abstract : Diabetes has been reported to increase propensity to peptic ulceration through its effect both on offensive and defensive mucosal factors. Seeds of *Eugenia jambolana* (EJ) have been reported to have both antidiabetic as well as ulcer protective effects. The present study evaluates the antidiabetic effects of ethanolic extract of dried seed kernel *of Eugenia jambolana* (EJE) and its comparative effect on gastric ulceration and acid-pepsin secretion with standard antisecretory FL-blocker. Ranitidine and antidiabetic glibenclamide with a premise that *Eugenia jambolana* may show better ulcer healing effects by promoting defensive or reducing offensive mucosal factors in mild diabetes (MD) rats. MD was produced in adult rats by administration of streptozotocin (45 mg/kg, ip). EJE was given orally in the doses of 100–400 mg/kg for 10 days and in the dose of 200 mg/kg for 30 days respectively to study its dose- and time-dependent effects on various diabetic parameters like blood glucose, serum cholesterol and triglycerides, insulin level and glycosylated hemoglobin. For ulcer protective and gastric secretion studies, EJE (200 mg/kg) was given orally for 10 days against 2 h cold restraint stress (CRS)-, 4 h pylorus ligation (PL), aspirin (ASP, 200 mg/kg, 4 h) – and 95% ethanol (EtOH, 1 ml/200 g, 1 h)-induced gastric ulcers and offensive acid-pepsin secretion after 4 h PL with co-occurring MD in rats. EJE showed dose-dependent decrease in blood glucose level in MD rats. Blood glucose level remained stable in mild diabetic rats from 3rd day onwards after streptozotocin administration (taken as 1st day for treatment) and EJE (200 mg/kg) showed anti-hyperglycemic effect on 10th day of its administration. Further, EJE in the above dose also decreased cholesterol level with little or no effect on triglycerides level and reversed the decrease and increase in insulin and glycosylated hemoglobin level

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near to the normal level as observed alter 30 days treatment in MD rats. MD rats exhibited an increased propensity to gastric ulceration induced by CRS, ASP, EtOH and PL and caused increase in acid-pepsin secretion. EJE was not only effective in reversing the increased propensity to ulceration in diabetic rats but also decreased the acid-pepsin output better than glibenclamide. The ulcer protective effect of *Eugenia Jambolana* seems to be due to its antidiabetic and gastric antisecretory effects.

Key words : *Eugenia jambolana* mild diabetes anti-hyperglycemic gastric ulceration acid-pepsin secretion

INTRODUCTION

Diabetes mellitus (DM) affects more than 100 million people worldwide (6% of the population) and in the next 10 years it may affect about five times more people than it does now (1). The prevalence rate of diabetes is estimated to be 1–5% in India (2). There are clinical reports suggesting increased healing time and mortality rate in gastric ulcer patients also suffering from diabetes mellitus (3). Several reports also indicated that diabetes mellitus increased the mucosal susceptibility to ulcerogenic stimuli and predisposition to gastric ulceration (4, 5). Although incidences of gastric ulcer in diabetes may be infrequent, gastric bleeding is often fatal in diabetes (6). In such conditions of co-occurring diabetes and gastric ulcers, it would be better to manage with drugs that have both anti-diabetic and anti-ulcer activities. This would be cost-effective as well as incidences of adverse effects can be minimized. Recently we reported that *Pterocarpus marsupium* (vijaysar) and *Azadirachta indica* (neem) decreased blood glucose level with concomitant ulcer protective effects in type 2 Diabetes mellitus rats (7–9).

Eugenia jambolana (EJ) popularly known as Jamun or Indian blackberry has been indicated in Ayurveda, an ancient system of Indian medicine, for use in DM (10). In accordance to its claimed anti-diabetic effect in traditional medicine, EJ has been reported to have hypoglycemic effects both in experimental models and clinical studies (11–13). EJ seed apart from hypoglycemic activity has been reported to have anti-inflammatory (14), neuropsycho-pharmacological (15), anti-bacterial (16), anti-HIV (17) and anti-diarrhoeal (18) effects. EJ seed kernel decreased the oxidative stress in diabetic rats, which in turn may be due to its hypoglycemic property (19). We recently reported the ulcer protective effect of ethanolic extract of E. jambolana seeds (EJE) and the effect seemed to be due to its predominant action on mucosal defensive factor and antioxidant effect (20). However, there are no reports pertaining to the anti-ulcer activity of *Eugenia jambolana* against experimental gastric ulcers with co-occurring DM in rats so the present work pertains to the study of EJE on experimental gastric ulcers with co-occurring diabetes in rats.

MATERIALS AND METHODS

Animals

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 hrs respectively. Animals were provided with standard rodent pellet diet (Pashu Aahar Vihar, Varanasi) and the food was withdrawn 18 hours before the experiment through 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* (Hyderabad Colony, Banaras Hindu University Campus) were collected 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 amounts 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 dried powdered seed kernel of *Eugenia jambolana* (EJ) was 12.5 g/100 g. Ulcer protective H_2-blocker drug ranitidine (RAN, 2.5 mg/kg) and antidiabetic drug glibenclamide (GLC, 0.6 mg/kg) were taken as standard drugs.

Induction of mild diabetes in rats

Mild diabetes was induced by intraperitoneal injection of streptozotocin in citrate buffer (STZ, 45 mg/kg, i.p., pH 4.5) to adult rats. Control rats received citrate buffer alone. 72 hours after injection of STZ, the rats were checked for fasting glucose level and those with blood glucose greater than 140 mg/dL but less than 200 mg/dL were considered as mild diabetic rats (21) and used for further studies. Blood glucose was then estimated at Days 3rd, 7th, 13th, 23rd and 33rd days after streptozotocin to assess the onset and duration of diabetes in rats. Further the test drug, EJE and standard drug, glibenclamide was also given from 3rd day onward till 33rd day to assess the onset and duration of anti-hyperglycemic effect of the above drugs in mild diabetic rats.

Drug treatment

Ethanolic extract of *Eugenia jambolana* (EJE) suspended in 1% Carboxymethylcellulose (CMC) in distilled water (1 ml/100 g body weight) was administered orally once daily in the doses of 100, 200 and 400 mg/kg for 10 days for dose-dependent effect in mild diabetic rats. An optimal dose of 200 mg/kg was then selected on the basis of our preliminary observations on the anti-hyperglycemic activity of EJE as mentioned in the results and given at 3rd Day (1st day test drug treatment) to 33rd Day (30th day test drug treatment) after streptozotocin administration, daily continuously to study the onset of its anti-hyperglycemic effect. The test drugs were either given for 10 or 30 days, the last dose being given 1 h prior to the experiment 18 h fasted rats depending upon the type of experiment. The results were compared with standard antidiabetic, glibenclamide (GLC, 0.6 mg/kg) and antisecretory, H_2-blocker ranitidine (RAN, 2.5 mg/kg) while, control group rats received suspension of CMC (1%) in distilled water.

Estimation of blood parameters

Blood samples were collected form the retro-orbital plexus of the rat and the blood glucose level was estimated by the GOD-POD method, Total cholesterol levels were estimated by CHOD-PAP method and Triglycerides level was estimated by GPO-ESPAS method using Ranbaxy Diagnostic Kits, New Delhi following the kit's procedure. Serum insulin levels were estimated by radioimmunoassay method by using R.I.A. Kit (Bhaba Atomic Research Center, Bombay, India). The results are expressed as µU of insulin/ml.

Hemoglobin and glycosylated Hb (HbA_1C)

Hemoglobin was estimated by the method of Drabkin and Austin, 1932 (22). Glycosylated hemoglobin (HbA_1C) was estimated by following the method of Sudhakar Nayak and Pattabiraman, 1982 (23). Briefly, Saline washed red cells were treated with water/CCL_4 for lysis and incubated at 37°C for 15 min, and oxalate/HCl solution was then added and mixed. The filtrate was heated in a boiling water bath for 4 h, cooled with ice-cold water, treated with 40% TCA, and again centrifuged at 1000 g for 10 min. The supernatant obtained was then heated with 80% phenol and H_2SO_4 and the color developed using thiobarbituric acid was read at 480 nm after 30 min.

Antiulcer study

Gastric ulcers in rats were produced on 11th day of experiment in 18 h fasted normal (NR) and EJE-untreated and EJE-treated mild diabetic (MD) rats following physical (2 h cold restraint- and 4 h pylorus ligation-induced) and chemical (aspirin-and ethanol-induced) methods. Cold restraint stress (CRS) (24) gastric ulcer (GU) was induced by strapping on a wooden plank and keeping them for 2 h at 4–6°C. The animals were then sacrificed by cervical dislocation after 2 h of CRS. 4 h pylorus ligation (PL) GU was induced by ligating the pyloric end of the stomach without causing any damage to the blood supply under pentobarbitone (35 mg/kg i.p.) anesthesia while aspirin (ASP)-induced GU was produced by administering ASP in the dose of 200 mg/kg (20 mg/ml) (25). The animals were then sacrificed by overdose of ether after 4 h in both PL- and ASP-induced GU. The stomach was taken out and cut open along the greater curvature and ulcers were scored by a person unaware of the experimental protocol in the glandular portion of the stomach. The ulcer index was calculated by adding the total number of ulcers per stomach and the total severity of ulcer as +1 per stomach as described earlier (26). Ethanol (EtOH)-induced GU was induced by administering EtOH (95%, 1 ml/200 g). The animals were sacrificed by cervical dislocation after one hour of EtOH administration. The ulcer index was scored based upon the product of the length and width of the ulcers present in the glandular protein of the stomach (mm^2/rat) (27).

On day 11th of the experiment in an 18 h fasted animals and after 1 h of the test drugs administration, the rats were anesthetized using pentobarbitone (35 mg/kg, i.p.). The abdomen was opened and pylorus ligation was done without causing any damage to its blood supply. The stomach was replaced carefully and the abdomen was closed in two layers. The animals were deprived of water during the postoperative period and were sacrificed with an overdose of ether after 4 h. Stomach was dissected out and the gastric juice was collected and

centrifuged for 5 min at 2000 rpm. The volume of the supernatant was expressed as ml/100 g body weight. Total acid output was determined by titrating with 0.01 *N* NaOH, using phenolphthalein as the indicator and was expressed as µEq/4 h. Peptic activity was determined using haemoglobin as substrate and was expressed as µmol of tyrosine/4 h (28).

RESULTS

Effect on blood glucose level

STZ induced mild diabetic rats showed an increase in blood glucose level by 137.6% compared to normal rats (NR Blood glucose level: 73.4±3.9 mg/dl). EJE (100, 200 and 400 mg/kg) showed dose-dependent decreasing effect (% decrease: –13.1%, –27.5% and –31.5% respectively; P<0.05) on blood glucose level in mild diabetic rats (MD blood glucose level- 174.4±6.8 mg/dl). The optimal dose of 200 mg/kg of EJE was then selected for further studies. STZ showed mild hyperglycemic effect from 3rd day onwards which was maintained more or less to the same level till 33rd of experiment. EJE 200 mg/kg showed anti-hyperglycemic effect after 10th day onwards while GLC (0.6) showed the above effect after 4th day onwards of their administration in mild diabetic rats (Table I). Further EJE 200 mg/kg caused reduction in triglyceride (TG) and showed significant decrease in total cholesterol (TC) and raised insulin levels. EGE's above mentioned effects were comparable with GLC (Table II). Glycosylated Hb level in mild diabetic rats was decreased significantly after

TABLE I: Effect of EJE and GLC on blood glucose level after 3rd, 7th, 13th, 23rd and 33rd days of streptozotocin (45 mg/kg, ip, stat) administration.

Oral treatment (mg/kg)	*Blood glucose level (mg/dL)*				
	3rd day	*7th day*	*13th day*	*23rd day*	*33rd day*
NRC (1% CMC)	70.6±2.8	71.5±4.9	72.3±3.8	70.6±3.1	74.7±4.2
MDC (1% CMC)	178.7±3.4*	179.6±7.6*	180.5±4.4*	173.0±3.6*	168.2±4.8*
MD + EJE 200	168.2±4.8	160.0±8.3	129.6±8.9[a]	126.2±5.8[a]	121.4±5.4[a]
MD + GLC 0.6	168.9±3.7	142.5±4.7[a]	126.7±2.6[a]	124.3±3.8[a]	119.6±5.3[a]

Results are Mean±SEM of 6 rats in each group.

One-way ANOVA followed by Dunnett's multiple comparisons test was applied for comparing with the NRC and MDC groups. P values: *<0.05 compared to respective NRC group and [a]<0.05 compared to respective MDC group.

TABLE II: Effect of EJE and GLC on blood glucose level (BGL), total cholesterol (TC), triglycerides (TG), insulin, hemoglobin and glycosylated hemoglobin levels in diabetic rats.

Oral treatment (mg/kg)	*10 days oral treatment group*			*30 days oral treatment group*		
	Blood glucose level (mg/dL)	*Total cholesterol (mg/dL)*	*Triglycerides (mg/dL)*	*Insulin (µU/ml)*	*% Hemoglobin (g)*	*Glycosylated Hb/gHb*
Control (1% CMC)	72.3±3.8	71.5±3.1	67.6±4.2	33.2±2.7	13.1±1.1	0.223±0.014
MDC (1% CMC)	180.5±4.4*	87.3±4.4*	79.9±4.0	25.9±1.3*	9.7±0.61	0.405±0.020*
MD + EJE 200	120.8±6.9[a]	69.1±3.3[a]	69.6±3.5	32.6±2.1[a]	13.0±0.37	0.290±0.009[a]
MD + GLC 0.6	130.3±9.2[a]	66.5±4.7[a]	71.1±3.6	35.5±2.9[a]	11.9±0.7	0.270±0.021[a]

Results are Mean±SEM of 6 rats in each group.

One-way ANOVA followed by Dunnett's multiple comparisons test was applied for comparing with the NRC and MDC groups. P values: *<0.05 compared to respective normal rats and [a]<0.05 compared to respective diabetic control.

treatment with EJE for 30 days (Table II).

Ulcer protective effects

Mild diabetic rats showed increased propensity to ulceration in all models of gastric ulcers. EJE and RAN showed ulcer protective effects in both normal and mild diabetic rats while, GLC showed ulcer protective effect only in diabetic rats (Figs. 1 and 2).

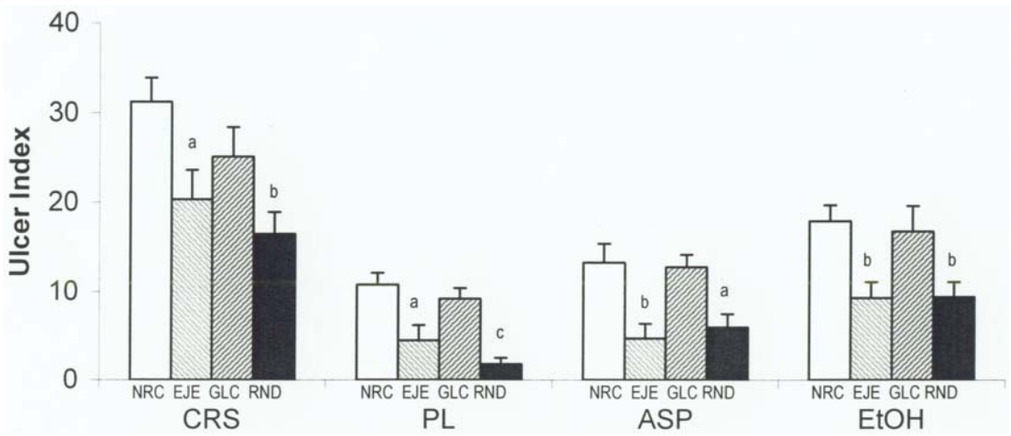

Fig. 1 : Effect of EJE, GLC and RND on gastric ulcers induced by CRS, PL, ASP and EtOH in normal rats. Results are Mean±SEM of 6 rats in each group.
P values: *<0.05, **<0.001 compared to respective NR control group [a]<0.05, [b]<0.01, [c]<0.001 compared to their respective NR and MD control groups.
Normal control rat ulcer index (mm^2/rat): CRS (31.2±2.7); PL (10.8±1.3); ASP (13.3±2.1), EtOH (17.9±1.8).

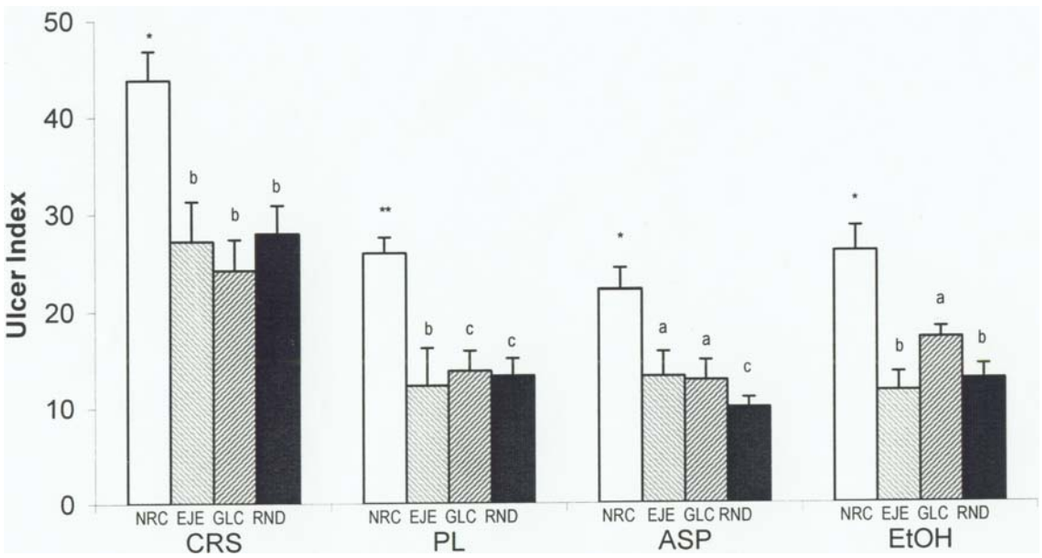

Fig. 2 : Effect of EJE, GLC and RND on gastric ulcers induced by CRS, PL, ASP and EtOH in diabetic rats. Results are Mean±SEM of 6 rats in each group.
P values: *<0.05, **<0.001 compared to respective NR control group [a]<0.05, [b]<0.01, [c]<0.001 compared to their respective NR and MD control groups.
Diabetic control rat ulcer index (mm^2/rat): CRS (43.8±3.0); PL (26.0±1.6); ASP (22.2±2.2), EtOH (26.1±2.6).

Effect of acid pepsin secretion

Mild diabetic rats showed significant increase in acid and pepsin secretion as observed by their increase effect on respective outputs. EJE treatment in mild diabetic rats decreased the increased output of acid and pepsin output near to the normal level. RND was more effective while, GLC was less effective in reversing acid and pepsin output compared to EJE (Table III).

TABLE III: Effect of EJE (200 mg/kg, po), GLC (0.6 mg/kg, po) and RND (2.5 mg/kg, po) on gastric juice parameters in mild diabetic rats.

Juice parameters	*NR*	*DR*	*DR+EJE*	*DR+GLC*	*DR+RND*
Volume (ml/100 g)	1.74±0.17	2.57±0.37	1.95±0.17	2.03±0.16	1.62±0.12[a]
Acid output (μEq/4 h)	135.8±13.5	213.0±19.1*	147.3±12.6[a]	156.8±22.1[a]	81.4±5.14[a]
Peptic output (μEq/4 h)	465.3±67.7	659.5±52.1*	456.2±58.7[a]	547.5±33.2	276.8±26.7[a]

Results are Mean±SEM of 6 rats in each group.

One-way ANOVA followed by Dunnett's multiple comparisons test was applied for comparing with the NRC and MDC groups. P values: *<0.05 compared to respective normal rats and [a]<0.05 compared to respective diabetic control.

DISCUSSION

Hypoglycemic effect of EJ is well documented (12, 29–32). Our present result with EJE also showed a dose-dependent antihyperglycemic effect in diabetic rats. EJE was also found to decrease cholesterol, triglyceride and glycosylated hemoglobin levels which are also raised in diabetes (29, 30). EJ has been reported to show significant antihyperglycemic activity in mild diabetes rats which have functioning pancreatic β cells indicating that it may modulate insulin release which we have observed with an increase in insulin level with EJ treatment. Our result is in concordance with earlier reports where EJ was found to increase insulin secretion (30). Further it was reported that EJ could have insulinomimitic action and might not necessarily require functioning β cells for hypoglycemic action (29). EJ has been reported to work as antidiabetic by enhancing cathepsin B activity thereby increasing the proteolytic conversion of proinsulin to insulin (31) and inhibits insulinase activity of liver and kidney (33). The antihyperglycemic effect of this plant has also been dependent upon the dose of diabetogenic agent and therefore on the degree of β-cell destruction. EJ is thus reported to exert a dual effect, namely a combination of action of sulfonylurea and biguanides (12). Chronic diabetes has been reported to enhance glycosylated hemoglobin level due to prolonged high blood level of glucose which leads to glycosylation of Hb. Padma and Krishnaswamy, 1980 (32) have reported a significant correlation between the fasting blood sugar level and glycosylated Hb-A level in diabetic patients. They also reported an increase in glycosylated Hb level in diabetic rats. In our present study, EJE when administered for prolonged period (30 days) was effective in reducing glycosylated Hb level in diabetic rats indicating its effectiveness in correcting the deleterious effect of diabetes.

Our present study indicated that EJE had significant antidiabetic and anti-ulcer activity in mild diabetes with co-occurring gastric ulcers in rats. Both clinical and experimental diabetes have shown an increase vulnerability of gastric mucosa towards ulceration (34, 35, 36). Recently we reported the anti-ulcer activity of *Eugenia jambolana* against both physical (4 h pylorus ligation and 2 h cold restraint stress)-and chemical (aspirin and alcohol)-induced gastric ulcers in rats where it was reported to show ulcer protective effects mainly through promotion of mucosal defensive factors and antioxidant status and decreasing lipid peroxidation (20). EJE thus showed significant decrease in the ulcer index of both normal and mild diabetic rats giving it an edge over the other drugs which have either only antiulcer (ranitidine) or antidiabetic (glibenclamide) effects. Peptic ulcer occurs due to imbalance between enhanced acid-pepsin secretions versus impaired mucosal resistance. Experimental mild diabetes has shown to increase the propensity to gastric ulceration with an increase in offensive factors namely acid-pepsin secretion and lipid peroxidation and decrease in antioxidant status, mucin secretion and mucosal cell shedding, glycoproteins without any effect on cell proliferation (7, 9, 36, 37). Hence, in mild diabetes increase in offensive acid and pepsin secretion plays an important role in increased propensity to gastric ulceration and this may be one of the reasons for ranitidine to be effective in gastric ulceration in mild diabetic rats. EJE significantly decreased acid and pepsin output in 4 h PE diabetic rats. This effect was almost similar to the reference antiulcer drug raniditine. Hence, the antiulcer effect of EJE in mild diabetic rats could be due to decrease in acid-pepsin secretion. However, the anti-diabetic drug GLC reduced acid but not pepsin out put. GLC was earlier reported not to have antiulcer effect against 4 h pylorus ligation-, 2 h cold restraint stress-, aspirin- and alcohol-induced gastric ulcerations in normal rats (9, 36, 37). GLC therefore, showed decrease in propensity to ulceration only in diabetic rats in mild diabetic rats by correcting blood sugar level and reversing the enhanced acid secretion near to normal level.

EJE thus, showed significant antiulcer activity in mild diabetic rats. Hence, *Eugenia jambolana* could be more effective and economical in diabetes with co-occurring gastric ulcers due to its direct actions both on gastric mucosal offensive and defensive factors or on enhanced acid-pepsin secretion induced by diabetes compared to ranitidine or glibenclamide which are either decreasing acid-pepsin secretion or correcting diabetic parameters only and thus, showing indirect effect on deranged offensive and/or defensive mucosal factors in diabetes. Further studies on any derangement in the status of mucosal defensive factors like mucin secretion, cell shedding, mucosal glycoproteins, oxidative defensive mechanism and tissue damage due to enhanced lipid peroxidation in mild diabetes may throw more light on the mechanism of action of EJE. Thus, the observed beneficial effects of EJE in diabetic rats with co-occurring gastric ulcer could be due to its both antidiabetic (reversing the noxious effect of diabetes on gastric mucosa) and direct promoting effect on the gastric mucosal defense.

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