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Effect of plantain banana on gastric ulceration in NIDDM rats: Role of gastric mucosal glycoproteins, cell proliferation, antioxidants and free radicals

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Methanolic extract of *Musa sapientum* var. *Paradisiaca* (MSE, 100 mg/kg) was studied for its antiulcer and mucosal defensive factors in normal and non-insulin dependent diabetes mellitus (NIDDM) rats. NIDDM was induced by administering streptozotocin (STZ, 70 mg/kg, ip) to 5 days old rat pups. The animals showing blood glucose level >140mg/dL after 12 weeks of STZ administration were considered as NIDDM positive. Effects of MSE were compared with known ulcer protective drug, sucralfate (SFT, 500 mg/kg) and anti-diabetic drug glibenclamide (GLC, 0.6 mg/kg) when administered orally, once daily for 6 days against gastric ulcers (GU) induced by cold-restraint stress (CRS) and ethanol and subsequent changes in gastric mucosal glycoproteins, cell proliferation, free radicals (lipid peroxidation and nitric oxide) and anti-oxidants enzymes (super oxide dismutase and catalase) and glutathione (GSH) levels. MSE showed better ulcer protective effect in NIDDM rats compared with SFT and GLC in CRS-induced GU. NIDDM caused a significant decrease in gastric mucosal glycoprotein level without having any effect on cell proliferation. However, all the test drugs reversed the decrease in glycoprotein level in NIDDM rats, but cell proliferation was enhanced in case of MSE alone. Both CRS or NIDDM as such enhanced gastric mucosal LPO, NO and SOD, but decreased CAT levels while CRS plus NIDDM rats caused further increase in LPO and NO level without causing any further changes in SOD and CAT level. MSE pretreatment showed reversal in the levels of all the above parameters better than GLC. Ethanol caused a decrease in glutathione level which was further reduced in NIDDM-ethanol rats. MSE reversed the above changes significantly in both normal as well as in NIDDM rats, while GLC reversed it only in NIDDM rats. However, SFT was ineffective in reversing the changes induced by CRS or ethanol or when given in NIDDM-CRS or NIDDM-ethanol rats. The results indicated that the ulcer protective effect of MSE could be due to its predominant effect on mucosal glycoprotein, cell proliferation, free radicals and antioxidant systems.

Keywords: Antioxidants, Cell proliferation, Free radicals, Glycoproteins, *Musa sapientum*, NIDDM

Oxidative stress is believed to initiate and aggravate many diseases including peptic ulcers and diabetes mellitus (DM)[1,2]. Persistent hyperglycemic status in diabetes causes increased oxidative stress. Mechanisms that contribute to increased oxidative stress in diabetes may include not only increased non-enzymatic and oxidative glycosylation (glycation) but also due to change in energy metabolism, alteration in sorbitol pathway activity and the status of antioxidant defense system and localized tissue damage resulting from hypoxia and ischemic reperfusion injury[2]. Marked increase in oxidative stress in DM is indicated by elevated concentrations of lipid peroxidation products[3]. Transient changes in activities of antioxidant enzymes like superoxide dismutase, catalase and glutathione peroxidase have been found in conjunction with increases in plasma glucose levels in case where control of diabetes is poor[4]. The superoxide dismutase (SOD) activity and glutathione (GSH) levels have been reported to decrease in various organs of diabetic animals, such as kidney, intestine and stomach[5]. These reports are indicative that the increase in reactive oxygen species may have a role in the aggravation of gastric mucosal damage in diabetes.

Plantain banana (*Musa sapientum* var. *paradisiaca*, MS) was reported to possess ulcer protective and healing activity through its predominant action on mucosal defensive factors[6,7]. Methanolic extract of MS has shown antioxidant activity in gastric mucosal homogenates, where it reverses the increase in lipid peroxidation (LPO) and SOD induced by stress in normal rats[8]. A natural flavonoid, leucocyanidin isolated from MS has been reported to have anti-ulcer

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activity[9]. Further, derivatives of leucocyanidin isolated from *ficus bengalensis* have been reported to possess anti-diabetic and anti-oxidant activity[10,11].

We have earlier reported the increased susceptibility of gastric mucosa to gastric ulceration by cold restraint stress (CRS) and ethanol (EtOH) method in non-insulin dependent diabetes (NIDDM) rats[12]. Recently, we have communicated the ulcer protective effects of MSE in NIDDM rats by its predominant effects on mucin secretion and life span of mucosal cells rather than on acid-pepsin secretion. The present work includes the study of effect of MSE on gastric mucosal glycoprotein, cell proliferation, antioxidants and lipid peroxidation both in normal and diabetic rats. The result have been compared with standard anti-diabetic drug, glibenclamide (GLC) and ulcer protective drug, sucralfate (SFT) on the above parameters in both normal and NIDDM rats.

Materials and Methods

Animals

Charles-Foster strain albino rats of either sex weighing between 140-180 g were obtained from the Central Animal House of the Institute. They were kept in the departmental animal house at 26°±2° C, RH 44-56%, 10/14 light/dark cycles. Animals were provided with standard rodent pellet diet (Hind liver). They were kept in the animal cages for mating. Five days old pups, thus obtained, were either allowed to grow normal or used for induction of NIDDM. Food was withdrawn 18-24 h before the experiment, though water was allowed *ad libitum*. 'Principles of laboratory animal care' (NIH publication no. 82-23, revised 1985) guidelines were followed. Approval of the Institutional Ethics Committee was sought prior to the start of the work.

Extraction of *Musa sapientum* (MSE)

Methanolic extract was prepared from the dried powder of pulp of big sized, unripe, green plantain banana fruit (*Musa sapientum* Linn. var. *paradisiaca*) collected between the months of September to March from local market using standard procedure[8]. It was dried under vacuum and stored at -20°C until further use. The yield was 1.16%.

Drug treatment

MSE (100 mg/kg)[8] and standard anti-diabetic drug glibenclamide (0.6 mg/kg)[12] and standard anti-ulcer drug sucralfate (500 mg/kg) were suspended in 1% carboxymethyl cellulose (CMC) in distilled water. They were administered orally once daily for six days in both normal and NIDDM rats. Control group of animals received suspension of 1% CMC in distilled water.

Glycaemic study

To induce NIDDM, an intraperitoneal injection of streptozotocin (STZ, 70 mg/kg) dissolved in saline was given to 5 day old rat pups[12]. The control pups received saline alone. The pups were weaned till one month. Twelve weeks after injection of STZ, animals were checked for fasting glucose level and those showing glucose level greater than 140 mg/dL were considered as NIDDM rats. Blood was collected from the retro-orbital plexus of the rat and the blood glucose level was estimated by glucose GOD-POD method (Ranbaxy diagnostic kits).

Anti-ulcer study

Acute gastric ulcers were produced in 18 h fasted rats by subjecting them to 2 h cold restraint stress (CRS) and by administering ethanol (EtOH; 1 ml/200 g; 1 h) orally following the methods as reported earlier[13]. The animals were then sacrificed by cervical dislocation and ulcers were scored on the dissected stomachs. In case of CRS rats, ulcer index was calculated by adding the total number of ulcers per stomach and the total severity of ulcers per stomach, while in EtOH it was scored based upon the product of length and width of the ulcers present in the glandular portion of the stomach (mm^2/rat).

Estimation of mucosal glycoproteins

Samples of gastric mucosal scraping were homogenized in distilled water and treated with 90% ethanol and the mixture was kept for 10 minutes before it was centrifuged. 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[14], total hexoses, hexosamine and fucose, while the latter was used for the estimation of sialic acid[15]. The results are expressed in µg/ml. The ratio of total carbohydrate (TC; sum of total hexoses, hexosamine, fucose and sialic acid) to protein (P) has been taken as the index of mucin activity[15].

Cell proliferation

Mucosal scraping was homogenized in 2.5 ml of ice cooled 0.6 N perchloric acid (PCA). DNA[7] and protein[14] were then estimated. Cell proliferation was expressed as µg DNA/mg protein.

Estimation of free radicals and antioxidants generation

The fundic part of the stomach was homogenized (5%) in ice cold 0.9% saline with a Potter-Elvehjem glass homogenizer for 30 sec. The homogenate was used for the estimations of free radicals (LPO[13] and nitric oxide, NO[16]) and antioxidants enzymes (SOD[13] and catalase, CAT[13]) and non-enzyme glutathione (GSH[17]) following the methods in detail as described earlier[13].

Statistical analysis

One-way analysis of variance (ANOVA) followed by Dunnett's multiple comparisons test was applied in the same test groups of either normal or diabetic rats. Differences were considered to be significant when $*P<0.05$ compared to respective control. Unpaired Student's *t* test was also applied and mentioned in Tables.

Results

Effect of *Musa sapientum*

Effect on blood glucose — *Musa sapientum* (MSE, 100 mg/kg), glibenclamide (GLC, 0.6 mg/kg) and sucralfate (SFT, 500 mg/kg) were given orally, once daily, for six days. MSE showed a tendency to decrease while SFT showed little or no effect on blood glucose level both in normal (control- 97.5±4.9 mg/dL; MSE 88.1±3.1 mg/dL; SFT-98.7±5.3 mg/dL) and NIDDM (NIDDM control-181.2±7.4 mg/dL, MSE 165.8±7.8 mg/dL; SFT-179.7±8.1 mg/dL) rats. GLC on the other hand showed a significant decrease in blood glucose level both in normal (72.1 ±3.2mg/dL) and NIDDM (110.3±10.9mg/dL) rats. The percentage decrease of blood glucose level in GLC was 26.6% in normal and 42.7% in NIDDM rats (Fig. 1).

Ulcer protective effects—NIDDM rats showed increase in propensity to ulceration in both the gastric ulcer models in rats. Per cent increase of ulceration in NIDDM rats in cold restraint stress (CRS) was 56%, while in ethanol (EtOH)-induced model it was 87%, when compared to the respective normal control rats. MSE (100 mg/kg) showed a significant ulcer protective activity in normal and NIDDM rats of both the gastric ulcer models. The percentage ulcer protection against CRS was 55.4% in normal and 54.3% in NIDDM rats, while in EtOH model it was 13.8% in normal and 21.4% in NIDDM rats. The ulcer protective effect of MSE was better than the standard oral hypoglycemic drug GLC (per cent ulcer protection CRS: normal-17.9%, NIDDM-34.4%; EtOH: normal-5.1%, NIDDM-21.1%). Ulcer protective drug, SFT showed significant ulcer protection in both the ulcer models studied (percent ulcer protection CRS: normal- 67.2%, NIDDM- 40.9%; EtOH: normal-64.6%, NIDDM- 41.9%; Table 1).

Effect on gastric mucosal parameters — NIDDM rats showed a tendency to decrease in individual carbohydrate, total carbohydrate and TC:P, ratio but tended to increase protein content of gastric mucosa. MSE and GLC as well as SFT reversed the above changes significantly near to the control values indicating an increase in the mucosal glycoproteins (Table 2).

Effect on cell proliferation — NIDDM rats showed a tendency to decrease in cell proliferation in terms of DNA μg/mg protein compared to normal control rats. MSE, but not GLC and SFT, showed a significant increase in DNA μg/mg protein indicating increased cell proliferation by MSE (Table 2).

Effect on free radicals—Oxidative free radicals LPO and NO levels were increased significantly both in CRS and NIDDM rats. Both LPO and NO tended to increase in NIDDM-CRS rats when compared to CRS/NIDDM rats. Both MSE and GLC tended to reverse these enhanced free radicals in NIDDM-CRS rats. SFT did not show any effect on free radicals level (Table 3).

Effect on anti-oxidant enzymes—SOD level increased, but CAT level decreased in NR-CRS rats. However, SOD and CAT significantly decreased in NIDDM rats compared to NR group. The decreased level of both SOD and CAT in NIDDM rats was not

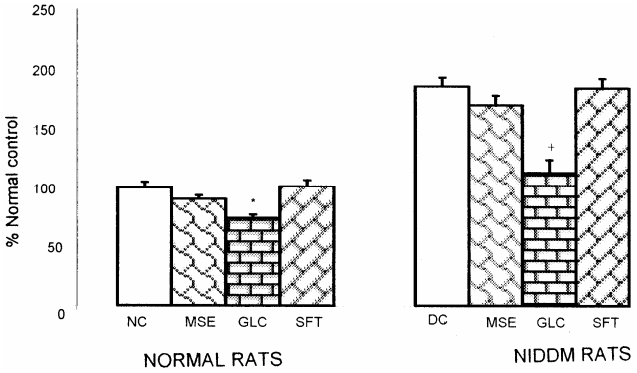

Fig. 1—Effect of *Musa sapientum* (MSE, 100 mg/kg), glibenclamide (GLC, 0.6 mg/kg) and sucralfate (SFT, 500 mg/kg) on blood glucose levels of normal and NIDDM rats. Statistical analysis amongst the control and treated groups were done by ANOVA (Significant at $P<0.001$) and multiple comparisons versus control group by Dunnett's test. [*indicates significantly different from normal control (NC) and $^{+}$indicates significantly different from NIDDM control (DC) group ($P<0.05$)].

affected by CRS. However, both MSE and GLC treatments significantly reversed SOD and CAT levels in NIDDM-CRS rats, while SFT did not show any effect (Table 3).

Effect on glutathione level—It decreased significantly both in EtOH- and NIDDM-control rats and further decreased in NIDDM-EtOH rats, when compared to NIDDM or EtOH rats. Both MSE and GLC tended to increase or increased the glutathione levels in normal- and NIDDM-EtOH rats. SFT did not show any effect on glutathione levels (Table 4).

Discussion

Data of the present study indicated an antiulcerogenic effect of plantain banana against cold restraint stress- and ethanol-induced gastric ulcers in rats. It has been suggested earlier that ulcer protection afforded by plantain banana could be due to its predominant effect on mucosal defensive factors like increase in mucin secretion, life span of mucosal cells, mucosal glycoproteins and cell proliferation in normal rats. Recently, we have observed a decrease in mucin secretion and enhanced cell shedding (indica-

Table 1 —Effect of orally administered MSE, GLC and SFT on cold restraint stress (CRS)- and ethanol (EtOH)-induced gastric ulcers in normal and NIDDM rats

[Values are mean±SEM of 8 rats in each group]

Oral treatment (mg/kg, po, od × 6 days)	Normal rats		NIDDM rats	
	Ulcer index	Decrease (%)	Ulcer index	Decrease (%)
		CRS-induced ulcers		
Control (DW)	29.6±2.9	-	46.2±5.8	-
MSE 100	13.2±3.1*	55.4	21.1±4.2*	54.3
GLC 0.6	24.3±2.7	17.9	30.3 ±2.3*	34.4
SFT 500	9.7±1.3*	67.2	27.3±3.8*	40.9
		EtOH-induced ulcers		
Control (DW)	19.5±3.8	-	36.5±3.1	-
MSE 100	16.8±2.9	13.8	28.7±2.6	21.4
GLC 0.6	18.5±2.8	5.1	28.8±3.3	21.1
SFT 500	6.9±1.6*	64.6	21.2±3.4*	41.9

P values: * <0.05 compared to respective NR and NIDDM control groups (ANOVA followed by Dunnett's test), DW-Distilled water

Table 2 —Effect of MSE, GLC and SFT on mucosal glycoprotein and cell proliferation in NIDDM rats

[Values are mean±SEM of 8 rats in each group]

Mucosal parameters	Normal control	NIDDM control	NIDDM + MSE	NIDDM+ GLC	NIDDM+ SFT
Glycoproteins (µg/ml)					
Total hexoses	2810±181	2276±129	2885±103*	2729±123	2714±97*
Hexosamine	1648±88	1546±53	1714±73	1604±33	1778±81*
Fucose	288±29	208±17	294±17*	290±17*	311±21*
Sialic acid	106±9	68±11[a]	106±9*	88±7	99±9*
Total carbohydrates (TC)	4852±270	4098±219[a]	4999±193	4711±129	4902±201*
Protein (P)	6240±476	7280±489	6549±573	6518±12	6728±413
TC:P	0.78±0.06	0.56±0.06[a]	0.76±0.07*	0.72±0.05*	0.73±0.05*
Cell proliferation					
Proteins (µg)	6996±562	7173±671	6889±593	7143±593	6658±497
DNA (µg)	756.7±31.7	726.3±21.3	881.3±39.3*	761±34	703.1±31.7
(µg DNA/mg protein)	108.2±9.2	101.3±4.7	127.9±7.3*	107±4.0	105.6±6.1

P values: [a]<0.05 compared to respective NR control (unpaired Student's *t* test) and *<0.05 when compared with NIDDM control group (ANOVA followed by Dunnett's test)

Table 3 —Effect of MSE, GLC and SFT on gastric mucosal free radicals (LPO, NO) and antioxidant enzymes (SOD and CAT) levels in NR, NIDDM and CRS rats

[Values are mean±SEM of 8 rats in each group]

Treatment (mg/kg, od, po×6 days)	LPO (nmol/g wet tissue)	NO (µmol/g wet tissue)	SOD (Units/g wet tissue)	CAT (Units/g wet tissue)
NR	242.8±17.0	241.3±6.3	93.1±9.1	25.3±2.5
NR-CRS	333.7±15.7***	283.2±8.2**	126.4±10.4*	19.0±3.0
NIDDM	315.0±14.3***	305.0±8.9***	56.4±4.2**	14.8±1.8**
NIDDM+CRS	452.1±36.3^{b,m}	330.1±12.2^{b}	52.1±4.8^{c}	13.4±1.9
NIDDM+CRS+MSE 100	262.7±16.4^{z}	268.3±8.5^{z}	73.6±7.6^{x}	21.7±2.4^{x}
NIDDM+CRS+GLC 0.6	391.5±40.3	285.7±9.4^{x}	91.0±4.2^{x}	22.4±2.0^{y}
NIDDM+CRS+SFT 500	456.3±40.1	308.3±15.5	53.0±3.2	14.2±1.2

P values: *<0.05, **<0.01, ***<0.001 compared to respective NR group; ^{b}< 0.01 compared to NR+CRS group; ^{m}< 0.01 compared to NIDDM group and ^{x}<0.05, ^{y}<0.01, ^{z}< 0.001 compared to NIDDM+ CRS group.

Table 4 —Effect of MSE, GLC and SFT on ethanol (EtOH)-induced changes in gastric mucosal glutathione (GSH) levels in NR and NIDDM rats.

[Values are mean±SEM of 8 rats in each group]

Oral treatment (mg/kg, od, po×6 days)	Glutathione level	
	Normal rats	NIDDM rats
Treatment		
Normal control	2.38±0.12	1.41±0.10*
EtOH control	1.26±0.11*	0.67±0.09^{a,n}
MSE 100 + EtOH	2.13±0.13^{x}	1.10±0.12^{x}
GLC 0.6 + EtOH	1.29±0.11	1.06±0.07^{x}
SFT 500 + EtOH	1.31±0.14	0.78±0.09

P values: ^{x}<0.05 compared to respective control EtOH group in normal and NIDDM rats (ANOVA followed by Dunnett's test). *<0.001 compared to normal control group; ^{a}<0.001 compared to NIDDM control and ^{n}<0.001 compared to the normal EtOH control group (unpaired Student's *t* test).

tive of decrease life span of mucosal cells) with increased propensity to ulceration in NIDDM rats[18]. The present work included the effect of NIDDM on cell proliferation and mucosal glycoproteins which were tended to decrease or decreased respectively. Both GLC and SFT reversed the decrease in mucosal glycoproteins in NIDDM rats, but cell proliferation tended to come near to the control values with them. However, MSE increased the cell proliferation significantly indicating better healing of ulcer by plantain banana in NIDDM rats. Further, it has been reported that banana contain leucocynadin, a flavonoid[9]. Leucocynadin together with its derivatives have been reported to possess antiulcer, antidiabetic and antioxidant properties which could be helpful in correcting the deleterious effects of diabetes on gastric ulceration because of its dual action both on diabetes (lowering blood glucose level) and peptic ulceration (promoting mucosal defense)[9-11].

Role of free radicals and oxidative stress in diabetes mellitus and gastric ulcerations is well documented[1,2]. Increased oxidative stress may result from overproduction of precursors to reactive oxygen radicals and/or decreased efficiency of inhibitory and scavenger system. Oxidative free radicals (OFRs) are cytotoxic and promote tissue damage. Among these are superoxide anion and hydroxyl radicals. These radicals damage cellular membranes releasing intracellular components, e.g. lysosomal enzymes, which lead to further tissue damage[19,20]. In addition the radicals, particularly hydroxyl causes degeneration of hyaluronic acid, the principal component of the epithelial basement membrane, and thus promote mucosal damage[21,22]. These radicals promote lipid peroxidation and membrane damage by cross-linking proteins, lipids and nucleic acids[20, 21].

However, biological systems have evolved an array of enzymatic and non-enzymatic antioxidant defense mechanism to combat the deleterious effects of OFRs. Superoxide dismutase (SOD) and catalase (CAT) play an important role in the detoxification of superoxide anion and H_2O_2, respectively, thereby protecting the cells against OFRs-induced damage[23]. Hydrogen peroxide may be reduced by enzymes glutathione peroxidase, but alternatively may react again with superoxide anion to form free hydroxyl radicals, which have a greater toxicity and a longer half life than superoxide anion[20,21]. Reduced glutathione (GSH) in conjunction with glutathione peroxidase (GPx) and glutathione-S-transferase (GST) may play a central role in the defense against free radicals, peroxides and a wide range of xenobiotics and

carcinogens. Oxidative stress arises when there is an imbalance between OFRs formation and scavenging by antioxidants.

Oxidative stress may be a common pathway linking diverse mechanisms for the pathogenesis of complications in diabetes. Mechanisms that contribute to increased oxidative glycosylation (glycation) but also due to change in energy metabolism, alteration in sorbitol pathway activity and status of antioxidant defense system and localized tissue damage resulting from hypoxia and ischemic reperfusion injury[2]. There is a marked increase in oxidative stress in DM as indicated by elevated concentrations of lipid peroxidation products such as thiobarbituric acid reactive substances in plasma[3]. Transient changes in activities of antioxidant enzymes like superoxide dismutase, catalase and glutathione peroxidase have been found in conjunction with increase in plasma glucose levels in case where control of diabetes is poor[4]. SOD activity and GSH levels have been reported to decrease in various organs of diabetic animals, such as kidney, intestine and stomach[5].

Nitric oxide plays an important role in regulation of various cellular functions in cardiovascular, neuronal and immune systems[24]. In the stomach, NO produced by constitutive NOS (cNOS) is considered to be beneficial in maintaining the mucosal integrity[25]. However, recent studies indicate the involvement of inducible NOS (iNOS) in the process of intestinal inflammatory disorders such as ulcerative colitis or intestinal lesions caused by NSAIDs and suggest that NO produced by iNOS may play a detrimental role in such diseases[26-28].

In our present study, both CRS-GU and NIDDM rats showed significant increase in oxidative free radicals, LPO and NO in the rat gastric mucosal homogenates compared to normal rats. When NIDDM rats were subjected to CRS-GU, they showed a further increase in LPO and NO compared to CRS-GU or NIDDM group. Antioxidant enzymes SOD and CAT were decreased in NIDDM rat mucosal homogenate indicating the dysfunction in antioxidant defensive system in diabetes mellitus. Further, CRS increased the SOD levels and decreased the CAT levels in normal rats, whereas NIDDM rats did not show further change in their levels. These changes indicated that normal conditions when the rats were subjected to CRS, due to the normal body defense mechanism caused an increase SOD level to compensate the increased oxidative stress as evidenced by increase in LPO level. Gastric mucosal LPO has been reported to increase in CRS-induced gastric ulcers[13,29]. The increase in SOD may be due to increased ROS generation during mucosal damage. This led to increased generation of H_2O_2 and its accumulation due to decreased CAT level. Inactivation of gastric peroximes during stress may also aggravate the mucosal damage[30]. However in chronic diseases like NIDDM, the decrease in SOD level may be due to depressed antioxidant system[5]. Lipid peroxidation is one of the major causative factors in cell injury produced by the free radicals process[31]. Since mucus is known to have a property of scavenging free radicals[32], it is possible that decreased mucus secretion in diabetic animals enhances accumulation of oxygen free radicals in mucosa.

Treatments with MSE and GLC however, significantly reduced both CRS plus NIDDM-induced increase in LPO and NO levels in rat gastric mucosal homogenate. MSE has been reported to possess significant antioxidant properties in gastric mucosal homogenate in CRS-induced gastric ulcers[8]. MSE has corrected the impairment in antioxidant enzymes SOD and CAT in normal[8] and NIDDM rats co-occurring with CRS whereas GLC reversed the decreased anti-oxidant enzymes levels in NIDDM rats.

Decrease LPO level with MSE and GLC treatment may be due to increase in free radical scavenging enzymes SOD and CAT in the gastric mucosa of NIDDM rats. SOD scavenges the super oxide radical O_2^-, one of the reactive oxygen species (ROS) responsible for lipid peroxidation[19]. This reaction leads to increase in generation of peroxyl radical $H_2O_2^-$, which is also capable of producing more oxidative damage[33]. CAT and other peroxidases further reduce $H_2O_2^-$. MSE but not GLC effectively alleviated stress-induced ulcers with marked decrease in LPO, suggesting decrease in oxidative damage. This was mostly due to increased balance between SOD and CAT levels, effectively counteracting the free radicals generated by cascade of reactions as described earlier. Thus, the anti-ulcerogenic activity MSE both in normal and NIDDM rats may be due to its gastric antioxidant effects and antidiabetic activity due to the presence of flavonoid like leucocyanidin. Flavonoids have been reported to possess both anti-ulcer and anti-inflammatory activities[34,35]. Flavonoids by virtue of their high chemical reactivity endogenous phospholipids metabolism leading to either stimu-

lation or inhibition of PGs[34,36], leukotrienes (LTs) and platelets activation factor (PAF) synthesis[37]. It is well known that the products of arachidonate metabolism play an important role in gastrointestinal mucosal damage; cyclooxygenase products like PGE and PGI_2 protect the gastric mucosa against damage while, LTC_4, a 5-lipoxygenase product and PAF, mediate damage and induce gastric and colonic ulceration[37]. Flavonoids possess antiulcer, anti-diabetic, anti-inflammatory[38] and antioxidant[39] activities. Flavonoids scavenge oxygen free radicals and inhibit the enzyme xanthine oxidase, lipid peroxidation and inflammation producing enzymes (cyclooxygenase and lipoxygenase)[39,40].

Anti-ulcerogenic effect of GLC could be seen in case of NIDDM rats by virtue of its blood glucose lowering effect. There is also evidence that elevation in glucose concentration may depress natural antioxidant defense such as vitamin C and glutathione (GSH)[41]. Glutathione, a polypeptide present in all the cells is an important antioxidant[42]. Decreased GSH levels in diabetes have been considered to be an indicator of increased oxidative stress[43]. In the present study, ethanol ingestion was found to decrease the level of GSH in normal rats. GSH level was significantly decreased in NIDDM rats and was further reduced when ethanol was given to them. Decrease in GSH level in normal and NIDDM rats by ethanol ingestion, however, was increased by MSE, while GLC increased the GSH level only in NIDDM rats indicating that the mucosal protective effect of antidiabetic drug GLC could be due to reversal of the diabetes-induced changes in oxidative free radicals and antioxidants. Thiols such as reduced glutathione (GSH) are able to bind reactive free radicals and may influence the physical properties of mucus, since its subunits are joined by disulfide bridges. Diethyl malate, an agent that markedly depletes gastric glutathione, causes severe gastric ulceration, suggesting a possible modulatory role for glutathione in ulcerogenesis[44]. Increase in GSH levels by MSE in the gastric mucosa of ethanol ingested normal and NIDDM rats indicated that their anti-ulcerogenic activity could be due to their effects on non-protein sulfhydryls.

Thus, the ulcer protective activity of plantain banana may be due to its effects on mucosal resistance factors like enhanced cell proliferation and mucosal glycoproteins. It has also been found to decrease lipid peroxidation and enhanced antioxidant status both in normal as observed earlier and diabetic rats with concomitant gastric ulceration.

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