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ANTI-COLITIC ACTION OF METHANOL EXTRACT OF *MUSA SAPIENTUM* (BANANA) PEELS ON ACETIC ACID INDUCED COLITIS IN DIABETIC RATS

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ABSTRACT

Diabetes mellitus and ulcerative colitis are frequent comorbid condition. Management of colitis can be very challenging in diabetic patients because of the need to control blood glucose levels. It is therefore thoughtful, that an agent with both anti-inflammatory and hypoglycaemic properties may be helpful. *Musa sapientum* has demonstrated both anti-inflammatory and hypoglycaemic potentials. In this study, the effect of methanolic extract of *Musa sapientum* peel (MEMSP) was investigated in acetic acid induced colitis in diabetic rats. A total of 50 male Wistar rats were divided into 5 groups (n=10). Group I served as colitis control with no diabetes. Animals in group II-V were induced with diabetes by the administration of streptozotocin (70mg/kg) and 72 hours later were induced with colitis by intrarectal instillation of 2ml, 6% (v/v) acetic acid. Groups I and II received distilled water, groups III and IV received MEMSP at a dose of 100 and 200 mg/kg respectively, while group V received sulfasalazine (50 mg/kg). Treatments commenced 24 hours following colitis induction. Fasting blood sugar level, relative colon weight, macroscopic and microscopic score of colon mucosa were

accessed at 7- and 14- days post colitis induction to determine disease severity. Relative colon weight, Macroscopic and microscopic sores were significantly increased in dia+colitis group compared to colitis alone group, while both concentrations of MEMS peel and sulfasalazine significantly reduced these variables compared to dia+col group. The results suggest that MEMS peel and sulfasalazine may be effective in the treatment of ulcerative colitis in diabetic condition.

KEYWORDS: Comorbidity, Ulcerative colitis, Diabetes, Musa sapientum, Strecptozotocin, Acetic acid.

INTRODUCTION

Inflammatory bowel disease (IBD) and diabetes mellitus (DM) are becoming major global public health problem owing to their rapidly increasing prevalence,[1,2] and frequent comorbidity.[3] Ulcerative colitis (UC) being a type of IBD is an idiopathic disease that diffusely affects the colonic mucosa and is characterized by periods of relapse and reoccurrence.[2,4] It is caused by multiple factors involving an interaction between genetic and environmental factors that give rise to an inappropriate immunological response.[5] Diabetes mellitus on the other hand is a metabolic disorder characterized by hyperglycaemia, depletion of antioxidants and alteration in lipid metabolism of which insulin deficiency is a major cause of the disease condition.[6,7] The association of DM with UC has epidemiological, pathogenetic, clinical and therapeutic implications.[3] Both diseases have been reported to have genetic association as Wang e*t al*.[8] identified 1 diabetes mellitus locus (TNFAIP3) that confers UC risk and 2 UC loci (HERC2 and IL26) that confer type-1 diabetes mellitus risk. A major challenging problem in diabetic patients with ulcerative colitis is in the treatment as corticosteroids which are the treatment of choice of active ulcerative colitis may be associated with the onset of glucose intolerance, diabetes and with difficult control of blood glucose levels and complications in diabetic patients.[3,9,10] Medicinal plants have been useful in the treatment and management of various diseases their benefits have come with little or no side effects.[11,12]

Musa sapientum (banana) is a large herb with succulent and very juicy stem belonging to the *Musaceae* family.[13] It is well known that *Musa sapientum* (MS) pulp is edible and highly nutritious,[14,15,16] the peel has also been reported to be consumed in the south-western part of Nigeria and known to ameliorate gastric disorder.[17] *Musa sapientum* peel is used in Indian folk medicine for the treatment of diabetes mellitus and in Thai traditional medicine for the

treatment of diarrhea, constipation, allergy and foot wounds.[18] The anti-allergic property, anti-inflammatory and antioxidant effects have been reported.[18,19,20] Various fractions of *Musa sapientum* peel extract have been reported to ameliorate acetic acid-induced ulcerative colitis in rats.[21] Likewise, its hypolipidemic and hypoglycaemic properties has also been reported.[13] This study therefore, seeks to understand the possible potential of *Musa sapientum* peel in the management and treatment of ulcerative colitis in diabetic comorbidity.

MATERIALS AND METHODS

Chemicals

Streptozotocin and chloralhydrate were purchased from sigma, USA.

Plant Collection and Extract Preparation

Fresh peels (1.5kg) of *Musa sapientum* (banana) was collected authenticated at Forestry Research Institute, Nigeria (FRIN) Ibadan, Nigeria, where the voucher specimen number 109540 was given. The peels were air dried at room temperature during harmattan, milled into powder form and weighed. The powdered peels were cold extracted with 80% methanol over a period of 72 hrs. It was then sieved using whatman no 1 filter paper, and the filtrate was collected and then concentrated in a rotary vacuum evaporator at 45^0c and finally, air-dried at room temperature till all methanol was totally removed.

Experimental design

A total number 50 male Wistar rats weighing between 150 – 200g were used for this study. All protocols in this study were carried out in accordance with the guidelines of the National Institute of Health for Laboratory animal care and use. Animals were divided into 5 groups of 10 each which are stated as follows;

Group 1: No diabetes but was induced with colitis (Col alone).

Group 2: Were induced with diabetes and thereafter ulcerative colitis (Dia+Col) and were untreated.

Group 3: Were induced with diabetes, followed by ulcerative colitis and were treated with 100 mg/kg bw methanolic extract of *musa sapientum* (MEMS) peels (Dia+Col+100 mg/kgMEMS).

Group 4: Were induced with diabetes, followed by ulcerative colitis and were treated with 200 mg/kg bw methanolic extract of *musa sapientum* (MEMS) peel (Dia+Col+200 mg/kgMEMS).

Group 5: Were induced with diabetes, followed by ulcerative colitis and were treated with a

standard drug-Sulfasalazine (Dia+Col+sulf).

Induction of Diabetes

The rats were fasted overnight and diabetes mellitus was induced thereafter, by a single intraperitoneal administration of streptozotocin 70mg/kg.[22] Colitis was induced subsequently following induction of diabetes.

Determination of fasting blood sugar level

Blood samples were obtained from small cuts at the tip of the tail unto a glucometer test strip and analysed using a glucometer. Hyperglycaemia was confirmed 48 hours after streptozotocin injection by a sustained blood glucose level between 140 and 240 mg/dl.[23]

Induction of Colitis

Under light anaesthesia, an improvised Teflon Cannula (a flexible plastic catheter) was inserted rectally into the colon 8cm proximal to the anus, colitis was then induced by administering 1ml/200g, 6% acetic acid as reported by Omayone *et al*.[12]

Determination of relative colon weight

The colon was excised and the inside carefully turned out. It was then rinsed in ice-cold phosphate buffer saline to remove luminal contents and thereafter weighed with an electronic weighing balance, model DT 1000 with capacity of 0.01 to 100 g.

Macroscopic assessment

The distal 8 cm of the colon was excised, rinsed in ice-cold phosphate buffer saline and thereafter scored macroscopically using the grading scale of Morris *et al*.,[24] No damage (score 0), localized hyperemia but no ulcer (score 1), linear ulcers with no significant inflammation (score 2), linear ulcer with inflammation at one site (score 3), two or more sites of ulceration and inflammation (score 4), two or more sites of ulceration and inflammation or one major site of inflammation and ulceration extending >1 cm along the length of the colon (score 5), damage extending >2cm along the length of colon, where the score is increased by 1 for each additional 1cm (6-10).

Histological assessment

A section from the colon tissue was immediately fixed in 10% Formalin, dehydrated in gradual ethanol (50-100%), cleared in xylazine and embedded in paraffin. Sections were prepared and stained with Haematoxylin and Eosin (H&E) for microscopic observations and

scoring. Microscopic scoring was done according to the method of Harputluoglu *et al.*,[25] Each colon tissue was examined for the following:

Depth of necrosis: none=0; mucosal = 1; mucosal and submucosal =2; mucosal, submucosal, and muscularis propria = 3' full thickness = 4.

Extent of necrosis: none = 0; small area = 1; moderate area = 2; large area = 3; extensive = 4.

Degree of inflammation: none = 0; minimal = 1; mild = 2; moderate = 3; severe = 4.

Extent of inflammation: none = 0; mucosal = 1; mucosal and submucosal = 2; mucosal, submucosal, and muscularis propria = 3; full thickness = 4.

The scores for each category examined were calculated for each specimen in the different groups. These were then added to obtain the total score, which was then divided by the number of at colons examined in each group to obtain the average histological score of induced colitis for the group.

Statistics

The results were expressed as Mean±SEM and evaluated using ANOVA for parametric variables, while non-parametric variables were evaluated using Kruskal Wallis followed by appropriate post-hoc test. $P < 0.05$ value was considered significant. Graph Pad Prism, version 6.00 was adopted for this study.

RESULTS

Effect of MEMS on fasting blood sugar level. The administration of streptozotocin resulted in an increase in blood sugar level in groups II-V compared with the colitis alone group (group I). The increase in blood sugar level was significant in groups II (Dia+Col) and V (Dia+Col+Silf) compared to group I (Col alone) 10 days after streptozotocin administration which corresponds to 7 days after colitis induction. However, both doses of MEMS (group 3-100mg/kg and group 4-200mg/kg) significantly decrease blood sugar level compared to groups II and V and showed no significant difference compared to group 1. At day 17 following streptozotocin administration corresponding to day 14 post colitis, blood sugar level had decreased compared to day 10. The MEMS groups (100 and 200 mg/kg) had returned blood sugar level to normal compared to group I. However, group II and V still showed significant increase compared to group I (Col alone) and group 3 (200mg/kg MEMS). The results are shown in figure 1.

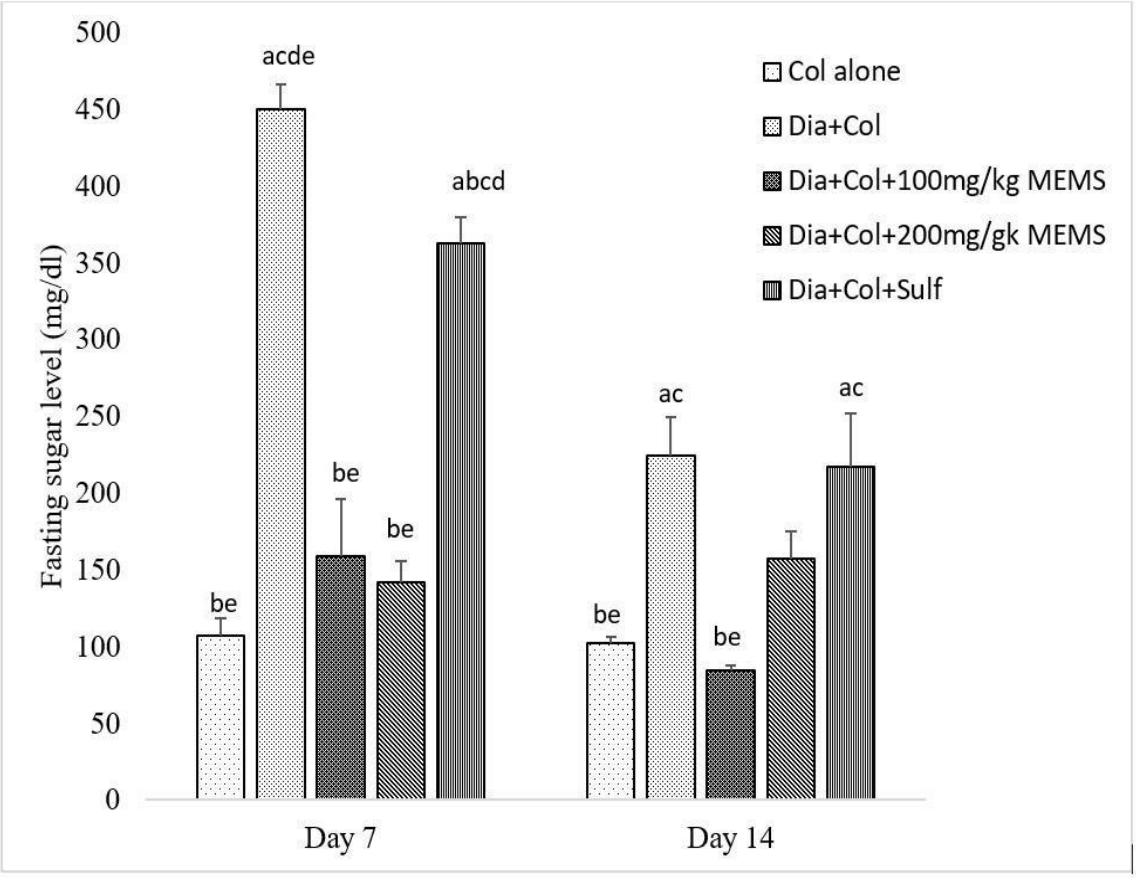

Figure 1: Effect of MEMS on fasting blood sugar level Values are expressed as Mean±SEM. n=5 per group.

[a] significant compared to Col alone (Colitis alone)

[b] significant compared to Dia+Col (Diabetes +Colitis)

[c] significant compared to Dia+Col+MEMS 100mg/kg (Diabetes+Colitis+ 100mg/kg Methanolic extract of *musa sapientum* peels)

[d] significant compared to Dia+Col+MEMS 200mg/kg (Diabetes+Colitis+ 200mg/kg Methanolic extract of *musa sapientum* peels)

[e] significant compared to Dia+Col+Sulf (Diabetes+Colitis+ Sulfasalazine)

Effect of MEMS on gross morphology and colitis sore in streptozotocin induced diabetic rat Figures 2 and 3 represents the effect of MEMS on colitis score in diabetic rats. At day 7 post colitis induction, the colitis score was significantly higher group 2 (Dia+Col group) compared to group 1 (Col alone). Groups 3 and 4 (100 and 200 mg/kg MEMS respectively) significantly decreased colitis score compared to both group 1 (colitis alone) and group 2 (Col+Dia). Sulfasalazine (group 5) significantly decrease colitis score compared to group 2 (Dia+Col) but not to group 1 (Col alone). At day 14 post colitis induction, Groups 3, 4 and 5 showed significantly reduced colitis score compared to group 2.

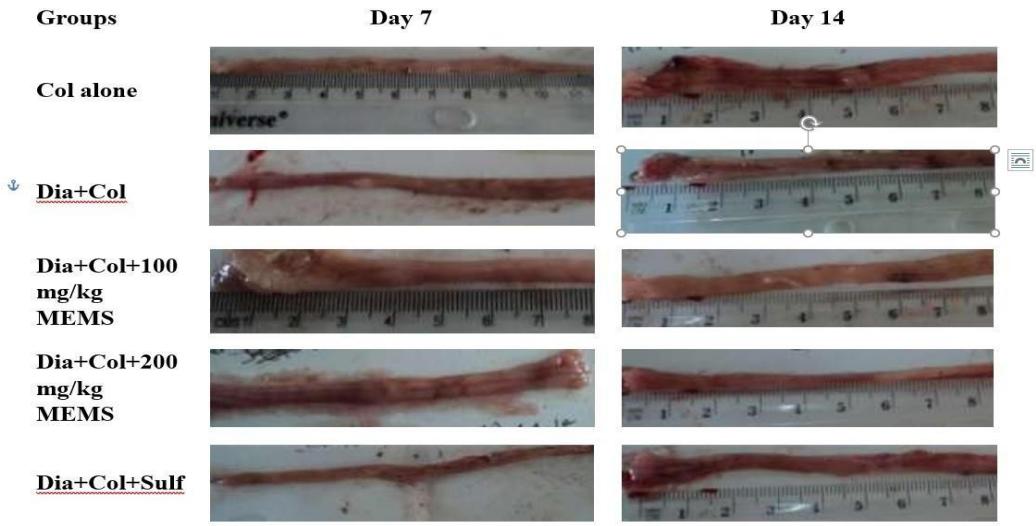

Figure 2: Gross morphology of colon at day 7 and 14 post colitis induction in both normal and diabetic rats.

Col alone (Colitis alone) Dia+Col (Diabetes +Colitis)

Dia+Col+MEMS 100mg/kg (Diabetes+Colitis+ 100mg/kg Methanolic extract of *musa sapientum* peels) Dia+Col+MEMS 200mg/kg (Diabetes+Colitis+ 200mg/kg Methanolic extract of *musa sapientum* peels) Dia+Col+Sulf (Diabetes+Colitis+ Sulfasalazine).

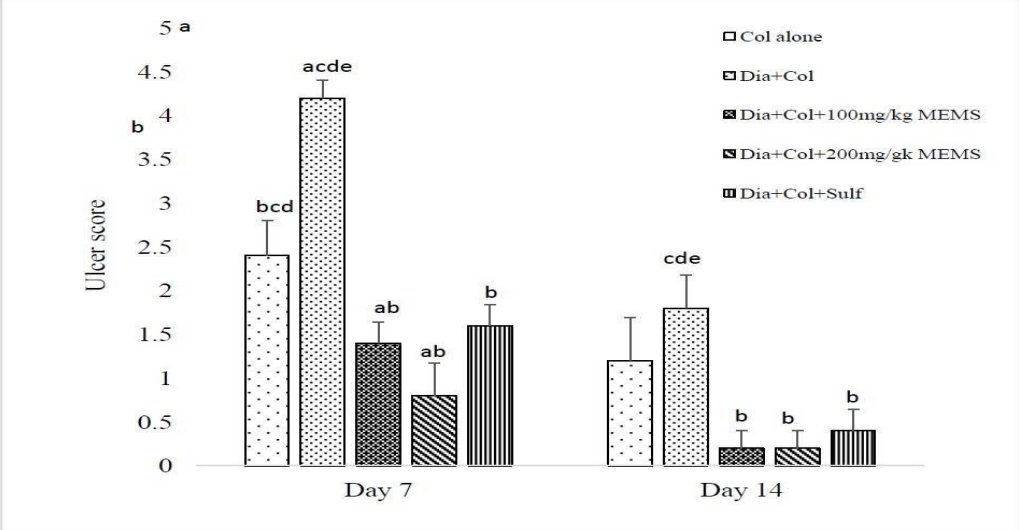

Figure 3: Effect of MEMS on colitis score.

[a] significant compared to Col alone (Colitis alone)

[b] significant compared to Dia+Col (Diabetes +Colitis)

[c] significant compared to Dia+Col+MEMS 100mg/kg (Diabetes+Colitis+ 100mg/kg Methanolic extract of *musa sapientum* peels)

[d] significant compared to Dia+Col+MEMS 200mg/kg (Diabetes+Colitis+ 200mg/kg Methanolic extract of *musa sapientum* peels)

[e] significant compared to Dia+Col+Sulf (Diabetes+Colitis+ Sulfasalazine)

Effect of MEMS on relative colon weight (rcw) in streptozotocin induced diabetic rat

The relative colon weight was significantly higher in group 2 (Dia+Col) compared to other groups at day 7 post colitis induction. There was no significant difference between MEMS groups compared to both group 1 (Col alone) and groups 5 (Dia+Col+Sulf). However, at day 14 post colitis, group 5 (Dia+Col+Sulf) had significantly higher relative colon weight compared to other groups. The result is represented in figure 4.

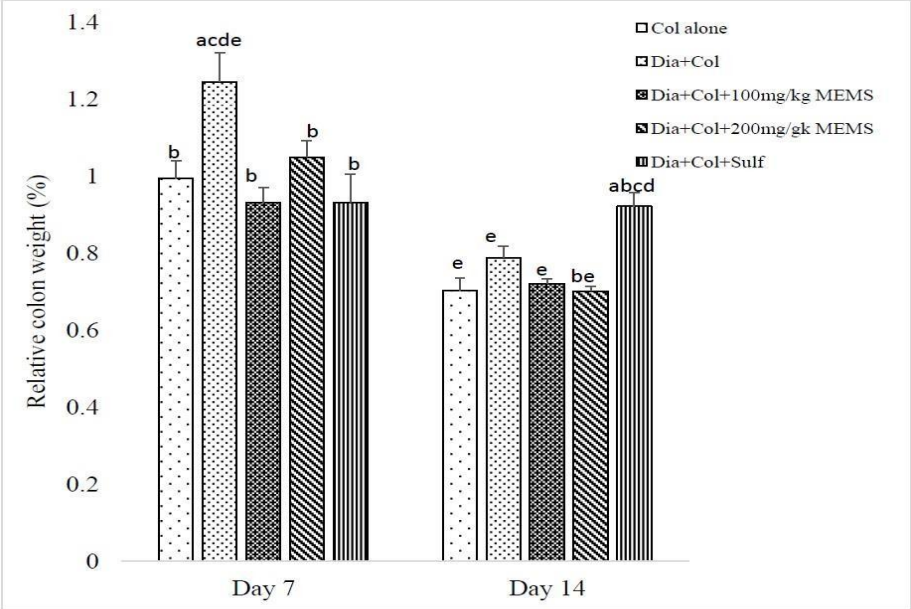

Figure 4: Effect of MEMS on relative colon weight.

[a] significant compared to Col alone (Colitis alone)

[b] significant compared to Dia+Col (Diabetes +Colitis)

[c] significant compared to Dia+Col+MEMS 100mg/kg (Diabetes+Colitis+ 100mg/kg Methanolic extract of *musa sapientum* peels)

[d] significant compared to Dia+Col+MEMS 200mg/kg (Diabetes+Colitis+ 200mg/kg Methanolic extract of *musa sapientum* peels)

[e] significant compared to Dia+Col+Sulf (Diabetes+Colitis+ Sulfasalazine)

Effect of MEMS on Histomorphometry and Histological scores in streptozotocin induced diabetic rat

Photomicrographs of colon section (Figures 5 and 6) post colitis revealed moderate erosion of surface epithelium and infiltration of inflammatory aggregates in group 1 (Col alone), however in group 2 (Dia+Col) the erosion was severe and infiltration of inflammatory aggregates was up to muscularis layer. Groups 3 (dia+Col+100 mg/kg MEMS), 4 (Dia+Col+200mg/kg MEMS) and 5 (Dia+Col+Sulf) significantly decrease the level of

erosion and infiltration of inflammatory aggregates to the level of submucosa layer only. Table 1 showed the scores for depth of necrosis, extent of necrosis, degree of inflammation, extent of inflammation and total histological score. Group 2 (Dia+Col) significantly aggravate these scores compared to group 1 (Col alone), however, both dosages of MEMS (100 and 200 mg/kg) as well as sulfasalazine significantly decrease these variables compared to group 2.

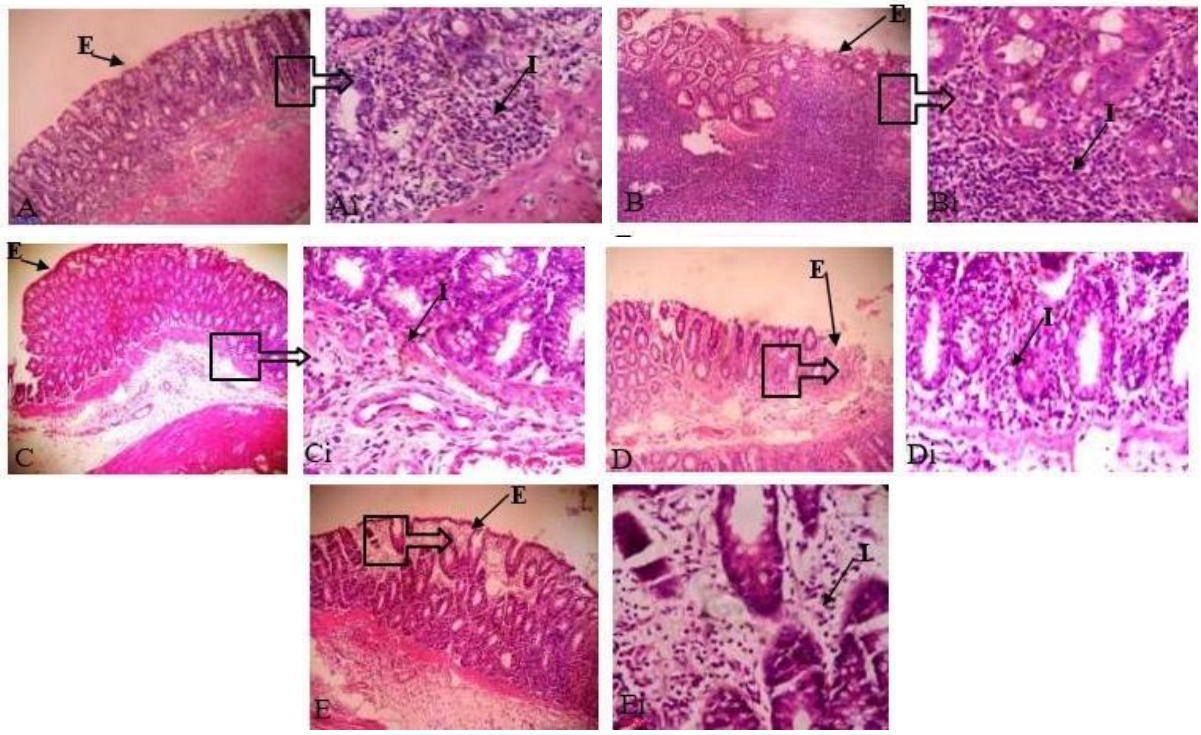

Figure 5: Photomicrograph of a colonic section Col alone (A and Ai X100 and X400 respectively) showing moderately preserved epithelial surface (E) of the colon mucosa and severe infiltration of the crypts and the propria up to submucosa (I). Dia+Col (B and Bi X100 and X400 respectively) surface epithelial of the colon mucosa is largely denuded (E) and severe infiltration that extends from B Bi muscularis the mucosa to mucosae (I). Dia+Col+100 mg/kg MEMS (C and Ci X100 and X400 respectively) showing normal epithelial surface of the colon mucosa (E) and very mild infiltration at the submucosa layer (I). Dia+Col+200 mg/kg MEMS (D and Di X100 and X400 respectively) showing mildly eroded epithelial surface of the colon mucosa (E), with moderate infiltration of the crypts and the propria and submucosa layer with infiltration of inflammatory cells (I). Dia+Col+Sulf (E and Ei X100 and X400 respectively) showing moderately preserved epithelial surface of the colon mucosa (E) with moderate infiltration of the crypts and the propria and submucosa layer with infiltration of inflammatory cells (I).

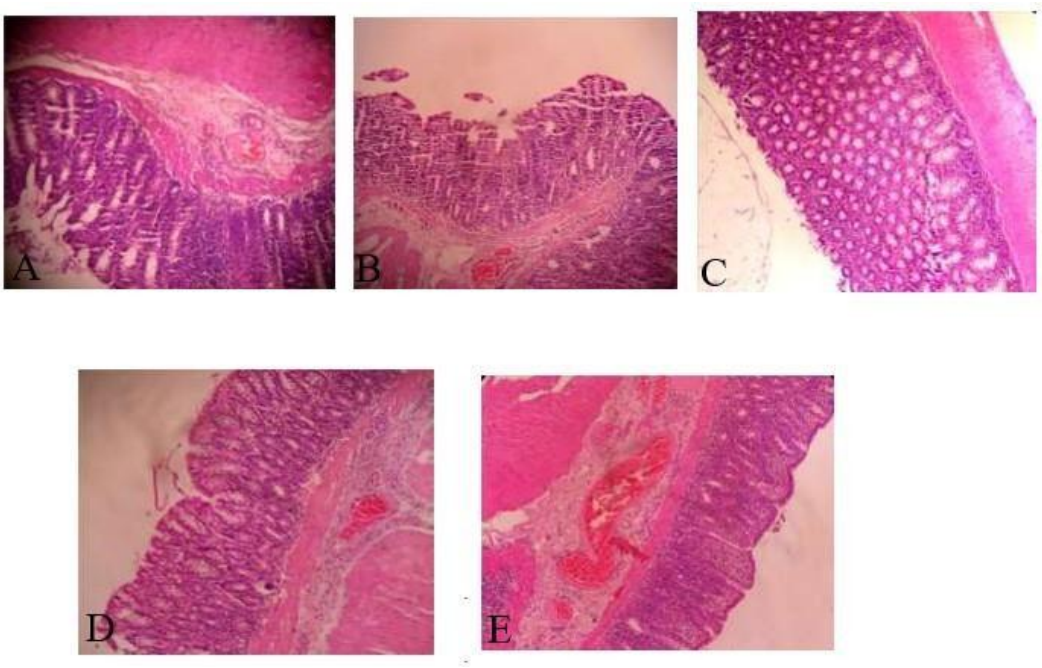

Figure 6: Photomicrograph collage (H&E staining X100) of rats 14 days post colitis induction: A (Col alone) showing mild erosion epithelial surface (E) and moderate infiltration of inflammatory aggregates in submucosa and muscularis (I). B (Dia+Col) showing moderate erosion epithelial surface (E) and large lymphoid aggregates infiltration in the submucosa and muscularis layer. C (Dia+Col+100mg/kg MEMS) showing mild erosion epithelial surface (E) and moderate infiltration of inflammatory aggregates only at the submucosa layer (I). D (Dia+Col+200mg/kg MEMS) showing mild erosion of epithelial surface (E) and mild infiltration of inflammatory aggregates only at the submucosa layer (I). E (Dia+Col+Sulf) showing mild erosion of epithelial surface (E) and mild infiltration of inflammatory aggregates at the submucosa.

Table 1: Effect of MEMSP on histological variables.

Variables	Groups / Days	Col alone	Dia +Col	Dia+Col+ 100mg/kg MEMS	Dia+Col+ 200mg/kg MEMS	Dia+Col+ Sulf
Depth of Necrosis	**Day 7**	1.40 ± 0.24[b]	3.00 ± 0.32acde	1.20 ± 0.20[b]	1.20 ± 0.37 *b*	0.80 ± 0.20 *b*
	Day 14	0.40 ± 0.24[b]	2.20 ± 0.20acde	0.80 ± 0.37[b]	0.80 ± 0.37 *b*	0.40 ± 0.24 *b*
Extent of Necrosis	**Day 7**	1.20 ± 0.20[b]	2.80 ± 0.37[ace]	1.00 ± 0.32[b]	1.60 ± 0.40	0.40 ± 0.24[b]
	Day 14	1.20 ± 0.58	2.20 ± 0.58[de]	1.20 ± 0.49	0.00 ± 0.00 *b*	0.40 ± 0.40 *b*
Degree of Inflammation	**Day 7**	2.60 ± 0.24	3.60 ± 0.24[cde]	2.00 ± 0.32[b]	2.20 ± 0.37[b]	1.60 ± 0.24[b]
	Day 14	1.40 ± 0.24[b]	2.60 ± 0.24[ace]	1.40 ± 0.24[b]	1.60 ± 0.40	1.20 ± 0.20[b]
Extent of Inflammation	**Day 7**	2.40 ± 0.24	3.00 ± 0.32[e]	2.00 ± 0.32	2.80 ± 0.37	1.20 ± 0.20[b]
	Day 14	0.80 ± 0.20[b]	2.00 ± 0.32[ae]	1.20 ± 0.20	1.00 ± 0.32	0.80 ± 0.20[b]
Total Histological score	**Day 7**	7.60 ± 0.68[b]	12.40 ± 0.75acde	6.20 ± 0.58[b]	7.80 ± 1.07[b]	4.00 ± 0.63abcd
	Day 14	3.80 ± 0.80 b	9.00 ± 1.00acde	4.60 ± 0.93[b]	3.40 ± 0.68[b]	2.80 ± 0.49[b]

Values are expressed as Mean±SEM. n=5 per group.

[a] significant compared to Col alone (Colitis alone)

[b] significant compared to Dia+Col (Diabetes +Colitis)

[c] significant compared to Dia+Col+MEMS 100mg/kg (Diabetes+Colitis+ 100mg/kg Methanolic extract of *musa sapientum* peels)

[d] significant compared to Dia+Col+MEMS 200mg/kg (Diabetes+Colitis+ 200mg/kg Methanolic extract of *musa sapientum* peels)

[e] significant compared to Dia+Col+Sulf (Diabetes+Colitis+ Sulfasalazine.

DISCUSSION

Comorbid conditions especially with inflammatory bowel disease cannot be overlooked as it significantly alters the management and prognosis of the disease condition.[26] Diabetes mellitus is a common disorder usually associated with ulcerative colitis. This study examined the effect of methanol extract of *Musa sapientum* (MEMS) peels on the healing of ulcerative colitis in diabetic rats. Following the administration of streptozotocin (STZ), fasting blood sugar level was significantly increased. The groups treated with MEMS peels had reduced fasting blood sugar level compared with the diabetic+ colitis rats. The concentration of blood sugar in rats treated with MEMS peels can be comparable with the colitis alone group that were not exposed to STZ. This is indicative of antidiabetic and glucose lowering properties of MEMS peels. However, sulfasalazine also slightly reduced fasting blood sugar level which also supports the reports of Haas *et al*.,[27] and Stamatiades *et al*.[28]

The macroscopic score revealed that diabetes mellitus aggravated the severity of ulcerative colitis and delay it healing as dia+col rats had significantly higher ulcer scores compared to colitis alone rats. This is in agreement with previous reports that diabetes mellitus has deleterious effect on the gastrointestinal tract and that it increases mucosa susceptibility to ulcerogenic stimuli.[6,29] Owu *et al*.,[30] had also reported that diabetic rats showed increased tendencies to gastric ulceration compared to control. However, MEMS peel groups had reduced ulcer score both at day 7 and 14 following colitis induction. This could be as a result of its dual action by being able to curb diabetes as well as ulcerative colitis therefore resulting in a faster healing compared to even colitis alone. A major feature of ulcerative colitis is infiltration of inflammatory aggregates (neutrophils and macrophages) and fluid accumulation (oedema) at the site of inflammation, thereby resulting in mucosa wall thickness.[31,32] As the wall of the mucosa thickens, the weight of the colon increases and similar effect was noticed in this study. The increased relative colon weight observed in dia+col rats compared to col alone was reversed by MEMS peel. Hence, a probable mechanism of action of MEMS peel is to decrease the infiltration of inflammatory aggregates, thereby preserving the colonic mucosa. Photomicrographs of the colon of both colitis alone rats and diabetic+colitic rats showed severe infiltration and necrosis in the later compared to the former. In addition, the epithelial surface of the colonic mucosa which was moderately eroded in the colitis alone group was largely denuded in diabetic+colitic rats. Treatment with MEMS peel however, reduced these changes and moderately preserved the epithelial surface of the colonic mucosa. These findings are similar to the reports of

Onasanwo *et al*.,[17] who found that MEMS peel possesses cytoprotective ability against ethanol induced gastric ulcer, and that of Adegoke *et al*.,[21] that demonstrated the ameliorative effect of *musa sapientum* peel extract in acetic acid induced colitis in rats. Methanolic extract of *musa sapientum* peels also decreased the degree of inflammation and depth of necrosis. This can be attributed to its anti-inflammatory and antioxidant properties which were reported by Phuaklee *et al*.,[18] In their reports, *Musa sapientum* peels exhibited DPPH (2,2-diphenyl-1-picrylhydrazyl) radical- scavenging properties and contains a high total phenol content which indicates that the plant material is a good source of antioxidant. Increased lipid peroxidation and decrease antioxidant defence have been implicated in the formation of diabetes[33] as well as ulcerative colitis[34], hence scavenging of free radicals and enhancing the antioxidant defence of the body is a probable mechanism of MEMS peel of which can be confirmed by further studies.

CONCLUSION

In conclusion, one of the most common and challenging problems in diabetic patients with ulcerative colitis is the medical treatment. The present study has demonstrated that the ulcerative colitis is aggravated in diabetic condition and MEMS peel offers protection to the colonic mucosa by probably due to its blood glucose lowering effect, anti-inflammatory and antioxidant properties. Thus, MEMS peel provided considerable hypoglycemic and anti-colitic effects in diabetic rats exposed to acetic acid-induced ulcerative colitis. This suggestion will however, require further studies to confirm the exact mechanism of action MEMS peel.

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