Ocimum gratissimum impairs gut glucose absorption but enhances water absorption in Streptotozocin induced diabetic rats

Streptotozocin ile indüklenen diyabetik farelerde ocimum gratissimum bağırsak glukoz emilimini bozar ama su emilimini artırır

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Abstract
The handling of ingested glucose by the gut is important in the regulation of postprandial glucose concentrations and, hence glycaemic control and absorption of water is secondary to solute absorption. This study therefore assesses the effect of diabetes mellitus (DM) and treatment with *Ocimum gratissimum* (OG) on gut glucose and water absorption. Phytochemical analysis and LD_{50} of OG was conducted as preliminary studies. Diabetes was induced in group 2; diabetic untreated group (DM group) and 3; diabetic treated group (DMTgroup) with a single i.p dose of 65mg/kg of Streptotozocin (STZ), with the later treated with 1500mg/kg of OG. Tissue sections for histology were obtained by standard method and absorption of fluid and glucose conducted by the everted sac technique. The result showed that glucose uptake was significantly lower (P<0.05) in the DM and DMT groups compared to the control while the fluid uptake in the DMT group was significantly lower (P<0.05) than the DM group and lowest in the control group. OG treatment reduces glucose absorption but increases gut fluid intake. It is possible that the hypoglycemic effect of OG may be related to reduction in intestinal glucose absorption. This appears to be at the expense of the integrity of the intestinal epithelium.
Keywords: Diabetes mellitus, glucose absorption, ocimum gratissimum, water absorption

Özet
Bağırsak ile alınan glukozun kullanımı, postprandial glikoz konsantrasyonlarının regulasyonu için önemlidir, dolayısıyla glisemik kontrol ve suyun emilmesi çözünen madde absorbsiyonuna sekonderdir. Bu nedenle, bu çalışma diabetes mellitus (DM) ve Ocimum gratissimum (OG) ile tedavinin bağırsaktan glukoz ve su emilimi üzerinde etkisini değerlendirmektedir. Fitokimyasal analiz ve OG'un LD_{50}'si ön çalışmalar olarak yürütülmüştür. 65 mg/kg Streptotozocin'in tek bir IP dozu ile diyabet oluşturuldu ve tedavi edilmeyen grup 2 (DM grubu) ve daha sonra 1500mg/kg OG ile tedavi edilen grup 3 (DMT grubu) olarak belirlendi. Histoloji için doku kesitleri, standart metod ile elde edilmiş ve sıvı ve glikoz emilimi everted sac tekniği ile gerçekleştirilmiştir. Sonuçlar, kontrol grubu ile karşılaştırıldığında DM ve DMT gruplarının glukoz alımının anlamlı derecede düşük olduğunu (P <0.05), bununla birlikte DMT grubunda sıvı alımının DM grubuna göre (P <0.05) daha düşük olduğunu, kontrol grubunda ise en düşük olduğunu gösterdi. OG tedavisi glukoz emilimini azaltır, ancak bağırsaktan sıvı emilimini artırır. OG'un hipoglisemik etkisinin bağırsaktan glukoz emiliminin azalması ile ilişkili olması mümkündür. Bunu bağırsak epitel bütünlüğü üzerinden sağlamış olduğu görünmektedir.
Anahtar kelimeler: Diyabet, glikoz emilimi, ocimum gratissimum, su emilimi

Introduction

Transport of chyme through the intestine is closely linked to intraluminal digestion and absorption of nutrients. The efficacy of absorption of nutrients is therefore potentially affected by dysmotility of the small intestine observed in Diabetes Mellitus (DM) (1), and by alterations in the transport mechanisms facilitating nutrient uptake across the intestinal membrane (2).

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Carbohydrates must be digested to glucose, galactose, and fructose for absorption to proceed, as only monosaccharides are absorbed. Alpha (α) amylases (salivary and pancreatic) hydrolyse 1, 4-glycosidic bonds in starch, yielding maltose, maltotriose, and α-limit dextrins (3). Maltase, α-dextrins and sucrase in the intestinal brush border then hydrolyze the oligosaccharides to glucose (4). Lactose, trehalase, and sucrose degrade their respective disaccharides to monosaccharides (4). Glucose and galactose are transported from the intestinal lumen into the cells by Na^+ dependent co-

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transport (SGLTI) in the luminal membrane, this is facilitated diffusion. The sugar is transported 'uphill' and Na^+ is transported 'downhill' (5). The Na^+-K^+ pump in the basolateral membrane keeps the intracellular Na^+ concentration low, thus maintaining the Na^+ gradient across the luminal membrane. Poisoning the Na^+-K^+ pump inhibits Na^+ and glucose absorption by dissipating the Na^+ gradient (5). Fructose is transported exclusively by facilitated diffusion; therefore it cannot be absorbed against concentration gradient (6).

The handling of ingested glucose by the gut is important in the regulation of postprandial glucose concentrations and, hence glycaemic control**.** At the level of the liver, processing of glucose is influenced by the glucose gradient between portal venous and hepatic arterial blood (7); accordingly, high systemic blood glucose levels may favour a decreased availability of absorbed glucose to the systemic circulation. During hepatic glucose uptake, glycogenolysis and gluconeogenesis are concurrently suppressed; limiting the increase in systemic glucose (8, 9). Impairment of this suppression contributes to postprandial hyperglycemia in DM, especially in patients with Type II Diabetes Mellitus (T2DM).

The relative contribution of the stomach and small intestine to postprandial blood glucose concentrations, compared to the liver, is likely to vary over time after meal. Experimental diabetes in animals has been reported to enhance glucose absorption and increase glucose metabolism (10). The increase in glucose absorption in the enterocytes (11, 12) is accompanied by an increase in the expression of glucose transporters SGLTI and GLUT2 and their mRNAS in diabetic rats and humans (12, 13).

Diabetic animals exhibit increased capacity for glucose uptake from gut (14, 15), consistent with the observed changes in brush border enzyme expression. The observation that similar changes can be invoked by glucose administration for 4 hours or more (10) suggests that this is glucose driven.

Water and electrolytes may cross intestinal epithelial cells by either cellular or paracellular routes (16). Tight junctions attach the epithelial cells to one another at the luminal membrane (16). The permeability of the tight junctions varies with the type of epithelium. A 'tight' (impermeable) epithelium is the colon 'leak' permeable) epithelium are the small intestine and gallbladder (16).

Na^+ moves into the intestinal cells, across the luminal membrane, and down its electrochemical gradient by: passive diffusion(through Na^+ channels), Na^+-glucose or Na^+- amino acid co transport, Na^+ Cl^- co-transport and Na^+-H^+ exchange mechanisms (17). Na^+ is pumped out of the cell against its electrochemical gradient by the Na^+-K^+ pump in the basolateral membrane. Cl^- absorption accompanies Na^+ absorption throughout the GIT, by Na^+-Cl^- co-transport and Cl^--HCO_3^- exchange (17). Dietary K^+ is absorbed in the small intestine by passive diffusion via a paracellular route (17).

Absorption of water is secondary to solute absorption, and isosmotic in the small intestine and gallbladder. In the colon, water permeability is much lower than in the small intestine, and faces may by hypertonic (16).

Ocimum gratissimum (OG) – Lamiaceas commonly known as 'scent' leave, has been used naturally in the treatment of different diseases (18, 19). OG is believed to originate from central Africa and tropical Asia. It is also found in West Africa. In Nigeria it is found in the Savannah and Coastal areas. The wide usage of OG is as a result of its biological importance, ranging from traditional, nutritional and medicinal values. It is used as 'seasoning' leave due to its peculiar aroma and as vegetable.

OG is reputed for a number of therapeutic properties including hypoglycemic (21), antimutagenic activity, antibacterial activity, antihelminthic, antifungal, antidiarrhea (20) and anti-convulsant (21). Not much is known about the pathophysiology of DM in GI system. The mechanism by which OG exerts its previously reported hypoglycemic effect is not known. This study was therefore embarked upon with a view to assess the effect of DM and treatment with OG on gut glucose and water absorption.

Materials and Methods

2.1 Plant materials and Preparation of aqueous extract

The leaves of *Ocimum gratissimum* were obtained from the University of Calabar Botanical Garden and identified by the Chief Herbarium Officer of Botany Department of University of Calabar. The fresh leaves were rinsed with water to remove sand and debris and then allowed to drip off water. The leaves were then dried under shade for two days and then transferred into Astell Hearson Oven and dried at a temperature range of 40 – 45^{o}C.

The dried leaves were then ground in an electric blender into fine powder to give a gram weight of 527grams. This 527g weight was soaked in 2.65 liters of water (distilled water) and allowed over night for about 15 hours and stirred at interval. The mixture was filtered using a satin mesh material and the final filtrate was gotten by using Whatman's filter paper size 1. The final filtrate was dried in the Astell Hearson Oven at 45^{o}c to obtain a brown gummy paste. A mettler P163 electronic weighing balance was used to weigh the gummy paste before stock solution was prepared. The stock solution of the extract was prepared by dissolving 15gm of extract in 10ml of water to give a concentration of 1500mg/ml.The stock solution was labeled appropriately and refrigerated at 4^{o}C until required for use. The median lethal dose (LD_{50}) of the plant extract was determined by method of Lorke (23).

The phytoconstituents of the extracts was determined and were screened for the presence of carbohydrates, tannins, alkaloids, saponins, phenolics, anthraquinones and cardiac glycosides as described by Trease and Evans (24) and Sofowora (25).

2.2Animal Preparation, experimental groupings and treatment

Eighteen rats were used for the study, the animals were divided into three groups and were assigned randomly into each group which was made up of six rats each and housed in cages assigned to them.

The first group was made up of the control animals which were fed with normal rat chow (feed). The second group contained streptozotocin induced diabetic rat which were left untreated. The third group of animals contained the test group which were streptozotocin induced diabetic rats treated with aqueous leaf extract of *Ocimum gratissimum*. All experiments were examined and approved by the ethical committee of the University of Uyo on Animal Research and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. The ethical committee approval letter was dated 17th September, 2012.

2.2.1 Induction of diabetes mellitus

Diabetes mellitus was induced by a single injection of 65mg/kg streptozotocin. The injection was given intraperitoneally. The state of diabetes was observed after 48 hours by the symptoms of *polyuria* and glucosuria and this state was confirmed using uristic test strip (Bayer Health Care LLC, USA). Also, the blood glucose level was tested 1 week after induction using a Glucometer (ACCU-CHECK Advantage II, Roche Diagnostics (GmbH, Germany) and ACCU-CHECK Advantage II test strips.

2.2.2Extract administration and observation

One week after induction of diabetes, the extract was administered per oral to the Diabetes Mellitus Treated (DMT) group at a dose of 1500 mg/kg body weight daily for 28 days. Administration was facilitated by the use of a syringe and Orogastic tube.

All experiments were examined and approved by the appropriate ethics committee and were therefore performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

2.3 Histology of the Small gut

Tissue sections were obtained by standard method and treated with traditional haematoxilin and eosin stains. Other special stains used included silver, reticulum, trichrome and Periodic Acid Schiff (PAS). Permanent preparations using routine biopsy method (26) was employed.

2.4 Determination of fluid and glucose absorption by the small intestine

Absorption of fluid and glucose by the everted sac technique of Wilson and Wiseman (27) as modified by Adeniyi and Olowokoorun (28) was employed in this study. Four segments (I, II, III and IV) each 10cm long (2 from jejunum and 2 from ileum) were cut out in a manner shown below for sac making.

2.4.1 Fluid transfer

Each sac was made by tying the distal end of the segment with a dry thread having a standard. From the tied end a rod was placed to push the end inwards thereby averting the sac (mucosa end out, serosa in). The sac was then filled with 1ml Kreb's solution (serosa fluid) and the free end was tied afterwards with a similar thread. Forty millilitres (40ml) of the Kreb's bicarbonate solution was put in incubating flask labeled I, II, III and IV respectively and each flask was aerated using 95 per cent oxygen and 5 per cent carbondioxide gas mixture in a Gallen kamp shaker bath for 30 minutes. The sacs were immersed in the aerated fluid and aerated further for 2 minutes after which they were incubated for another 28 minutes.

2.4.2 Glucose transfer

The terms used for glucose transfer are mucosal glucose transfer (MGT), serosal glucose transfer (SGT) and gut glucose uptake (GGU). MGT is the amount of glucose that disappears from the mucosa fluid. SGT is the amount of glucose that entered the serosa fluid after incubation. The GGU indicates glucose metabolized and those found in the gut wall at the end of experiment.

A glucose kit (Ames blovel analyzer glucose kit UK) for blood and glucose was used. The concentrations of glucose in Kreb's bicarbonate solution and intestine segments before and after incubation as well as the concentration in the lumen of the sac after incubation were determined. The units for glucose transfer are same as for fluid transfer. The physiological solution was bubbled continuously with 95:5 per cent oxygen, carbondioxide mixture, the pH was between 7.35 and 7.40 and the temperature was maintained at 37°C.

2.5 Statistical analysis

All results are presented as mean + standard error of mean. Three sets of data were analyzed using one way ANOVA, followed by the least significant difference (LSD) procedure for significant F values, (P<0.05) was considered significant. Computer software SPSS by SPSS Incorporated, Chicago; was used for the analysis.

Results

Histology of the small intestine in the control, DM and DMT groups of rats

Normal small intestinal microscopic features were shown in the control group. Pathologic features seen in the DM group were minimal while that in the DMT group were severe and extensive, Figure 1, 2 and 3.

Gut glucose uptake in the control, DM and DMT experimental groups of rats

Mean values for control, DM and DMT are: 1.06 ± 0.1, 0.84 ± 0.05 and 0.74 ± 0.03mmol/L respectively glucose uptake was significantly lower ($p<0.05$) in the DM and DMT groups compared to the control, Figure 4.

3.3.Gut fliud uptake in the control, DM and DMT experimental groups of rats

The mean values were 0.16 ± 0.03, 0.52 ± 0.04 and 0.32 ± 0.02g/ml for control, DM and DMT groups respectively. The DMT group was significantly lower ($p<0.05$) than the DM group while fluid uptake was lowest in the control group as shown in Figure 5.

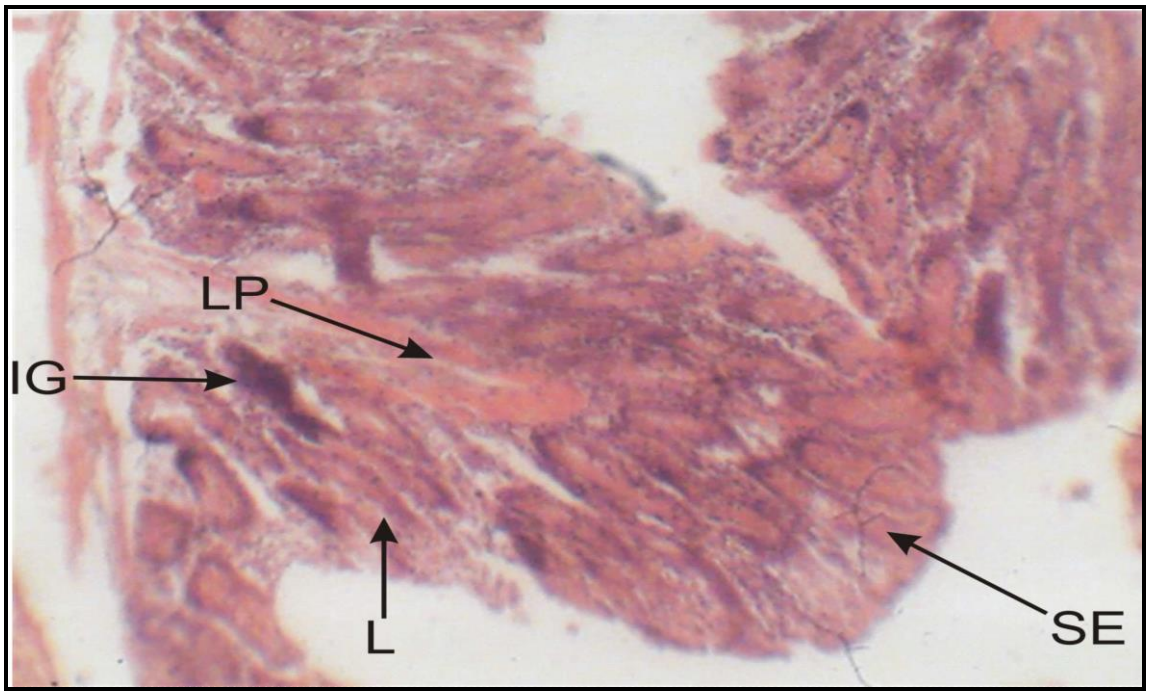

Figure 1. shows the photomicrograph of small intestine H&E ×100 (Control group)
Small intestine showing mucosa with normal surface. Epithelium (SE) with valvula corniventis each having a core of lamina (L), lamina propria (LP) containing blood vessels and glandular cells (IG) mucosa.

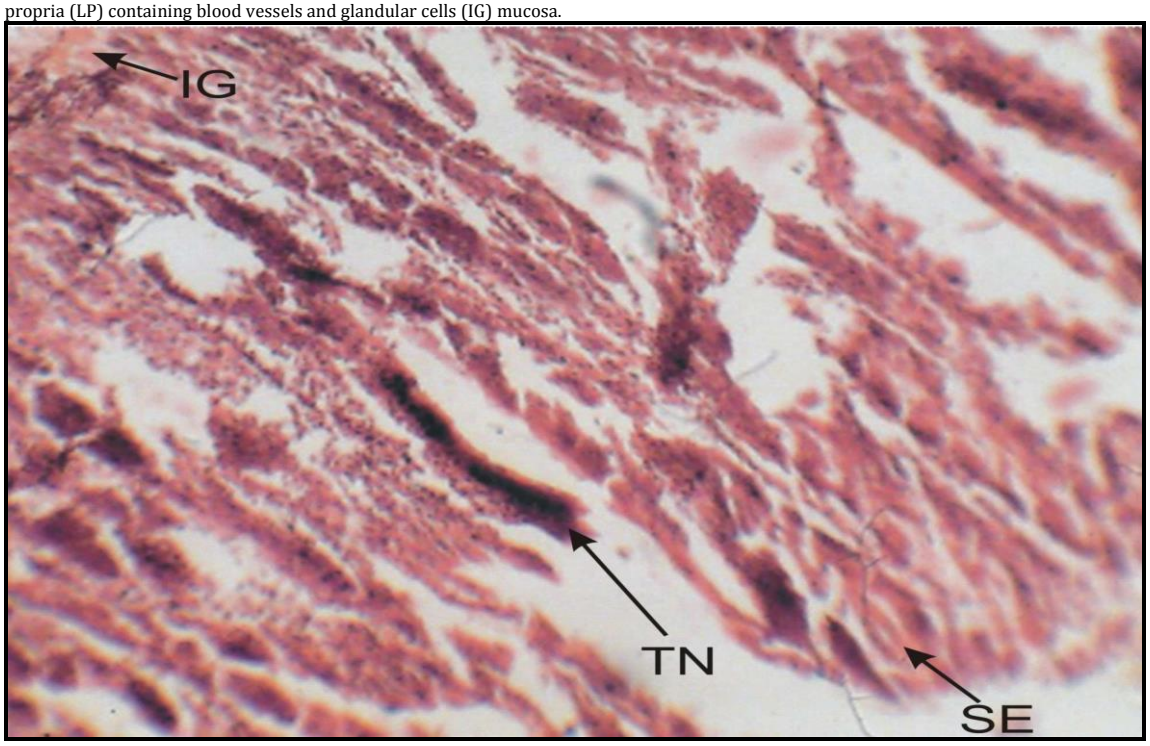

Figure 2. shows the photomicrograph of small intestine H&E × 100 (DM group).
Small intestine showing the mucosa with complete derangement of cellular architecture, the surface epithelium (SE) is distorted with areas of tissue necrosis (TN) and complete erosion of Lamina Propria (LP). Intestinal glands (IG) are distorted and atrophic.
Impression: Severe derangements of mucosal cellular architecture.

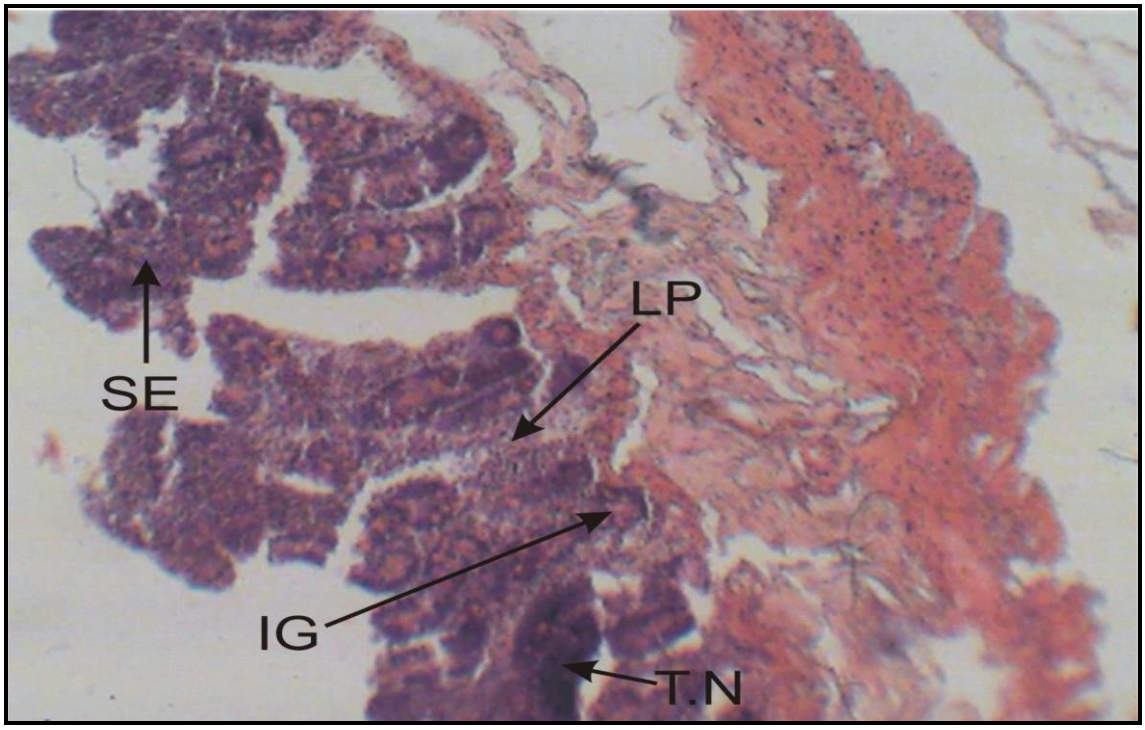

Figure 3. Shows the photomicrograph of small intestine H&E × 100 (DMT group).
Small intestine showing the mucosa, submucosa and muscularis externa infiltrated with inflammatory cells. There is distortion of the cytoarchitecture of the surface epithelium (SE), with areas of tissue necrosis (TN). The Lamina Propria (LP) and Lacteals (L) are smaller and distorted. The glandular cells (IG) are eroded and the mucosa tissue is grossly atrophic. The active tissue section appears edematous.
Impression: Derangements and distortion of the active architecture is suggestive of Pan Enteritis

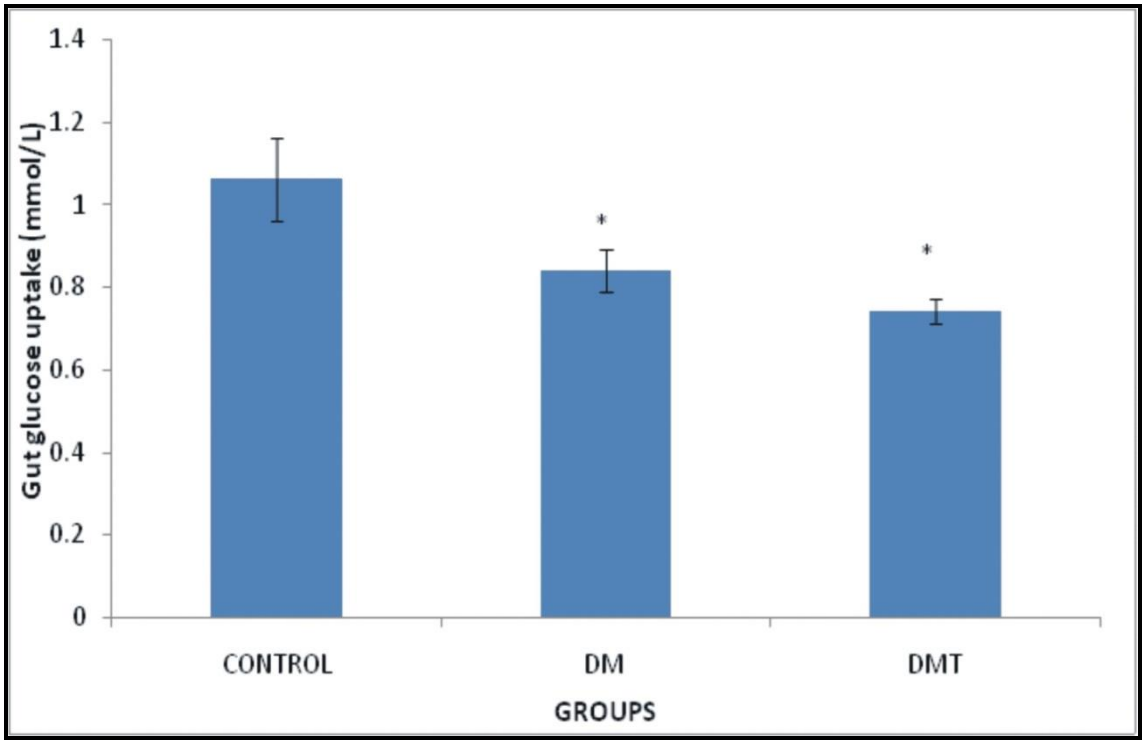

Figure 4. 4: Comparison of gut glucose uptake in the different experimental groups.
*=P<0.05 vs Control, n = 6

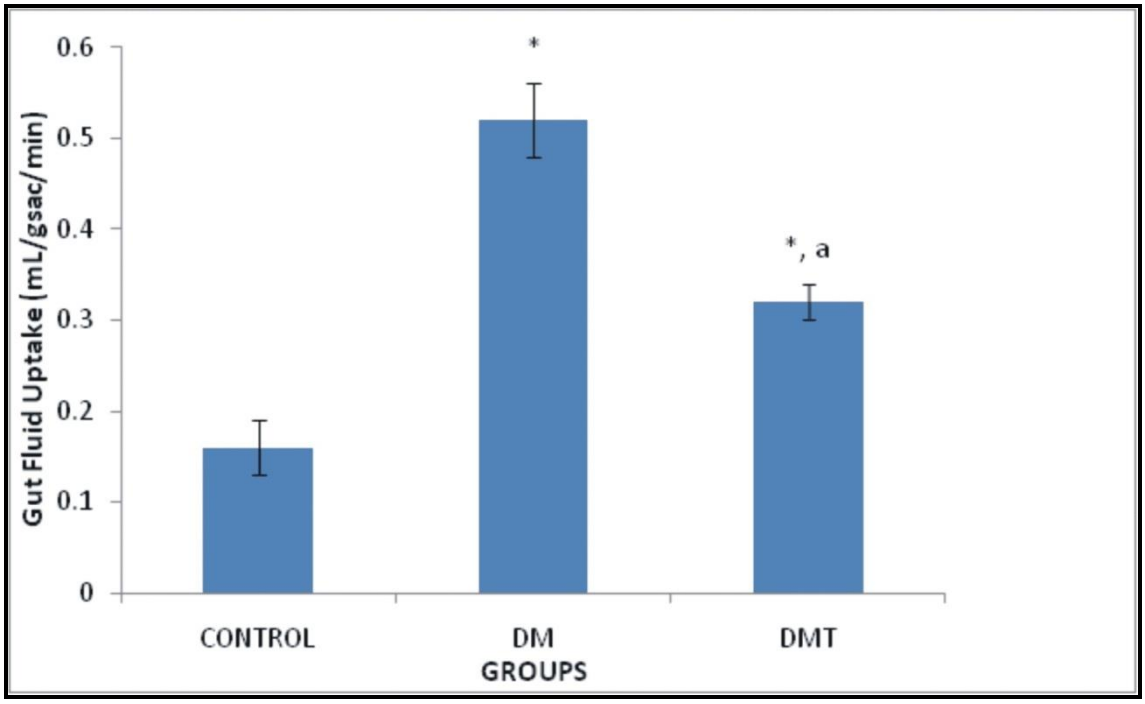

Figure 5. Comparison of gut fluid uptake in the different experimental groups
*=P<0.05 vs Control; a=DM vs DMT, n = 6

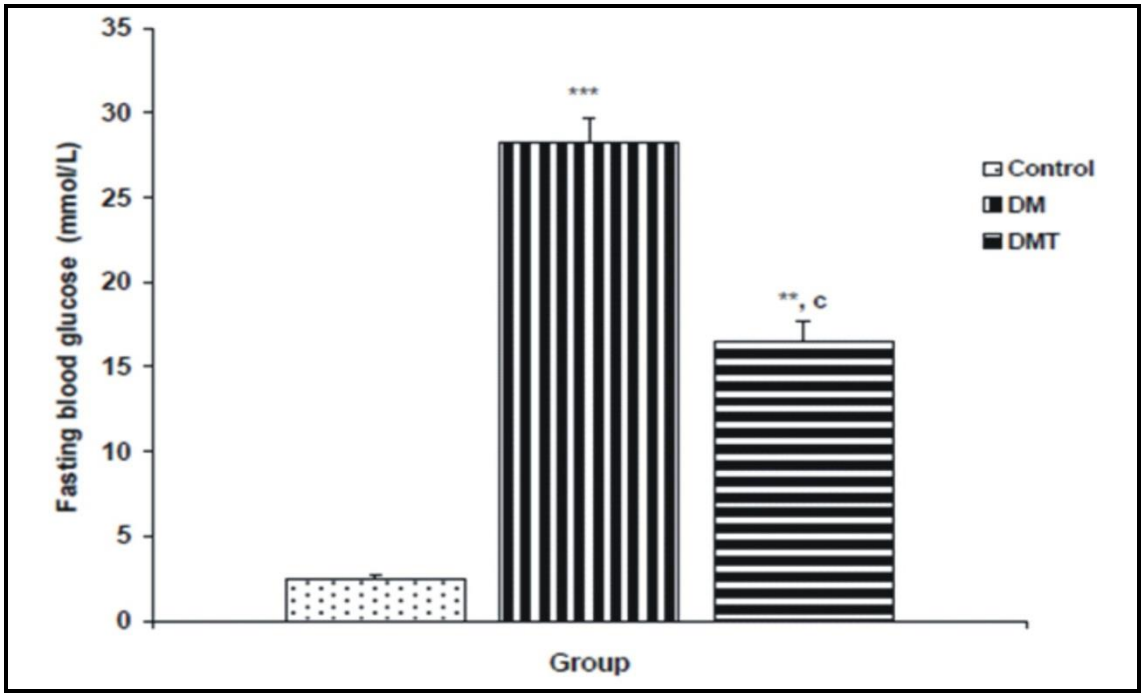

Figure 6. Comparison of Fasting Blood Glucose in the different experimental groups
***P<0.001, **P<0.01 vs control; c = P<0.001 vs DM, n = 6

3.4 Fasting blood glucose in control, DM and DMT experimental groups of rats

The mean values of fasting blood glucose in the control, DM and DMT experimental groups were 2.46 ± 0.192, 28.2 ± 1.52 and 16.5 ± 1.21mmol/l for control, DM and DMT groups respectively. All the groups were significantly different. The DM and DMT groups were significantly higher ($p < 0.001$) than the control. The DMT group was significantly lower ($p < 0.01$) than the DM group. (fig. 6)

Discussion

Estimation of the blood glucose levels for the control, diabetic (DM) and Diabetic treated (DMT) experimental groups confirmed hyperglycemia in the test groups (i.e. DM and DMT), thus suggesting that the insulin – producing pancreatic beta cells were destroyed by streptozotocin (STZ) administered for the induction of DM in these groups. Other studies had also reported the hypoglycaemic effect of OG. Aguiyi et al (21) reported the efficacy of OG in lowering the blood glucose level in STZ – induced diabetic animals (9, 17). Though treatment with the aqueous extract of OG did not return the blood glucose level to normal when compared to the control group, the level of reduction was significant when compared with the diabetic control group (29).

The histology of the small intestine revealed intact mucosal epithelium, glands and crypts of Lieberkhun with normal mucosal folds in the control group. The submucosa and muscular layers were also normal. These structures enhance the absorption of fluid and nutrients. A breach to this facility appears to compromise the absorption of glucose and water. Though mucosal tissue atrophy and epithelial erosion were noticed, the other features were largely normal in the DM group. In the DMT group, there was extensive distortion of most of the adaptive absorption mechanism structure. Both the epithelial cells and mucosal glands were markedly eroded. Distorted submucosa and muscularis externa with inflammatory cells invasion of all layers and edema were also noticed in the DMT group. The pan-enteritis poses a severe impediment to nutrient absorption in the DMT group. The OG constituent responsible for these pathologic changes is not yet known.

Glucose uptake was significantly lower in the DM and DMT groups compared to the control. These occurrences were consistent with histological findings of the small intestine. The intact absorptive surfaces and its absorption enhancing structures sustained high glucose absorption in the control group. On the other hand, the small intestine absorptive structures were damaged in the DM and more so in the DMT groups; this compromised the absorptive capacity of the small intestine in these groups, with the severity of the injury in the DMT group reflected in further reduction in glucose absorption.

Increased capacity for gut glucose uptake in diabetic animals, consistent with increase in brush border enzyme expression had been reported (15). In this study, there was severe epithelial and mucosal gland erosion in the DM and more so in the DMT groups. It is therefore, possible that the above brush border enzyme mechanisms for glucose uptake were interfered with. Damage to the mucosal and submucosal tissues may therefore account for the apparent reduction in glucose absorption in the DM and DMT groups. It is also possible that some active phytochemical constituents of OG could affect mitochondrial metabolism, leading to decreased availability of ATP, as glucose transport is an energy dependent process.

There is vidence that the passive component of sugar absorption is mediated by the glucose and hormone dependent regulation of GLUT-2 at the brush-border membrane (30). The release and action of hormonal substances from the gut mucosa, which regulate plasma glucose concentration has been widely reported as the incretin concept. Incretin hormones are gut factors, released in response to nutrient ingestion, that stimulate pancreatic β-cells, especially when plasma glucose is elevated. The secretion of gastric inhibitory polypeptide (GIP) from upper intestinal K-cells is closely associated with nutrient absorption; this is clearly the case for glucose since GIP release can be prevented by phlorizin (31). As seen in the histology, the extensive damage to the intestinal tissue in the DMT and to a lesser extent the DM groups may have compromised the incretin concept mechanism, leading to poor glucose absorption.

Fluid absorption is usually passive and follows solutes like sodium and glucose. However, a curious twist to this norm was observed in this study. Unlike glucose absorption, the gut fluid uptake appeared highest in the DM group followed by the DMT group. The DMT group was significantly lower than the DM group. Intestinal fluid uptake was lowest in the control group. This is a likely compensatory phenomenon to augment for the dehydration; secondary to osmotic dieresis, set up by the hyperglycemic state of DM. These findings further buttress the motion that the pathologic mechanism could be directly linked to the hyperglycemia of DM, as compared to the DM group. It is also possible that there was increased sodium absorption in the gut which attracted the fluid. This proposition is further strengthened by the fact that there was an exceptional increase in serum Na^+ concentration in this study (32). Increase fluid uptake usually alleviates hyperglycemia (33). This is clearly evident here and also buttresses the fact that the blood glucose level in the DMT group was closer to the control (normal) range due to the hypoglycemic action of OG. Reduction of hyperglycemic levels lessens the degree of osmotic diuresis with concomitant mitigation of the degree of polydypsia (34). This probably accounts for the reduction in gut fluid uptake in the DMT group. This is also in line with the findings in the water intake experiment, where the highest volume of water intake occurred in the DM group, followed by the DMT group, with the control group being the lowest (34).

5.Conclusion

STZ - induced T1DM was found to be associated with mucosal tissue atrophy and epithelial erosion. Treatment with OG appears to further aggravate the above findings, with features of panenteritis. OG treatment reduces glucose absorption but enhances

gut fluid intake. It is possible that the hypoglycemic property of OG, may be related to this reduction in intestinal glucose absorption. However, it should be noted that this appears to be at the expense of the integrity of the intestinal epithelium, same having been damaged by OG treatment. Therefore OG should be used with caution for whatever targeted therapeutic goal.

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