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Evaluation of Insulinotropic Effect of *Garcinia cambogia* in Streptozotocin Induced Diabetic Rats

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ABSTRACT
The present study aimed to determine the effect of an aqueous extract of Garcinia cambogia (AQGC) on the insulinotropic effect in streptozotocin-induced diabetic rats. The AQGC (200 and 400 mg/kg body weight) was administered orally once a day for 28 days in STZ-induced diabetic rats. A significant increase in blood glucose and glycosylated hemoglobin (HbA1c) with decreased serum insulin and total protein levels was observed in diabetic rats. Treatment with AQGC reduced the elevated levels of blood glucose, HbA1c, and significant increase insulin and total protein levels in diabetic rats. Significant decrease in malondialdehyde with an increase in the levels of superoxide dismutase, catalase, and glutathione peroxidase in the pancreas and liver homogenates of diabetic rats, the levels were normalized with AQGC treatment. Pancreatic insulin and intestinal proglucagon expression levels were decreased in diabetic rats. In AQGC-treated diabetic rats, the pancreatic insulin and intestinal proglucagon levels were elevated to normal levels. This indicates AQGC has protective effects on insulin and proglucagon, which is further responsible for elevated levels of GLP- 1 activity. It concludes that AQGC has significant antioxidant, antihyperglycemic activity, and protective activity on GLP-1. This may be due to hydroxy citric acid in Garcinia cambogia.
Keywords: *Diabetes; Garcinia cambogia, Proglucagon, Insulin.*

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INTRODUCTION

Incretins, hormones produced by the gastrointestinal tract in response to nutrient entry, stimulate insulin secretion (MacDonald et al., 2002). Incretins were first defined in the 1930s but little work was done in the period between 1930 and 1960 because incretins were not believed to be present or have significant physiologic effects. Since the insulinotropic actions of incretins were confirmed in the 1960s, the progressive development of knowledge about their secretion and actions has now led to incretin-based therapies for type 2 diabetes. There are many incretin hormones, but the 2 major incretin hormones belong to the glucagon peptide superfamily. They are Gastric inhibitory peptides also known as GIP and GLP-1. GLP-1 may also mediate its effects on glucose-induced stimulation of insulin biosynthesis and secretion, inhibition of glucagon secretion, β-cell proliferation, and survival (Deacon, 2005). Further important effects of GLP-1 include inhibition of gastrointestinal secretion and motility and food intake (Naslund et al., 1999). However, the half-life of GLP-1 is very short (1-2 min) due to the cleavage and inactivation of these proteins by dipeptidyl peptidase IV (DPP IV). Hence, the use of DPP-IV inhibitors increases the GLP-1 time of action (Stephan et al., 2011).

It is estimated that more than 50% of postprandial insulin secretion is triggered by intestinal peptide hormones. In presence of elevated blood glucose, glucagons like peptide 1 (GLP-1) stimulate the release of insulin by interacting with specific receptors on pancreatic beta cells. In addition to potentiating glucose-induced insulin secretion, GLP-1 stimulates proinsulin gene expression and proinsulin biosynthesis (Drucker DJ, 1987). By stimulating insulin release and increasing insulin-dependent glucose disposal, GLP-1 enhances glucose tolerance (D Alessio DA, 1994). The potential action of this hormone on carbohydrate metabolism makes it potentially applicable in the treatment of non-insulin-dependent diabetes mellitus.

There are several GLP-1 Analogues available in the market such as Exenatide Liraglutide. But the long-term use of these drugs produces several side effects such as pancreatitis, renal failure, thyroid tumors, and GI disturbances such as nausea, and diarrhea (Vishal Gupta, 2013). Now a day, the potential use of herbal drugs was found to be more beneficial than the use of allopathic medications because of their fewer side effects.

Garcinia cambogia, earlier phytochemical reports on the plant led to the isolation of various organic acids, benzophenones, and xanthones as major constituents and numerous scientific studies have indicated biological activity such as anti-obesity, hypolipidaemic and anticancer activity amongst numerous others (Badoni Semwal R., 2015). Hence the present work was undertaken to study the effect of *Garcinia cambogia* on antioxidant and anti-hyperglycemic activity in streptozotocin-induced diabetes in rats.

MATERIAL AND METHODS

Plant extract:

Aqueous fruit extract of *Garcinia cambogia* was obtained from Laila Impex, Vijayawada.

Chemicals and drugs:

TRIzol reagent was purchased from GeNei, Bangalore, India. Taq DNA polymerase was acquired from Invitrogen (Carlsbad, CA, USA). Sitagliptin was purchased from Himedia Chemicals (Hyderabad). All other chemicals and reagents used were of analytical grade.

Acute toxicity studies:

Healthy adult albino mice of either sex, starved overnight were divided into five groups (n=6). They were orally fed with the *AQGC* extract in increasing dose levels of 100, 500, 1000, 1500, and 2000 mg/kg b.wt (Patel et al., 2008). The animals were observed continuously for 72 h for any signs of behavioral, neurological, and autonomic profile, toxicity, and mortality.

Animals:

Adult albino Wistar rats (180 ± 10 g), and Swiss albino mice (18-20 g bw) were obtained from Mahaveer Enterprises, Hyderabad, India. They were kept under a temperature of (23± 2) ºC, a humidity of 50 %, and 12 h: 12 h of light and dark cycles, respectively. They were fed with a Commercial pellet diet (Rayon s Biotechnology Pvt Ltd, India) and water was provided *ad libitum*. The prior approval for conducting the experiments in rats was obtained from our Institutional Animal Ethics Committee and our lab is approved by CPCSEA, Government of India (Regd. No. 516/01/A/ CPCSEA).

Experimental design:

Rats were acclimatized to the environment for 15 days before the experiment; animals were divided into five groups. Each group contains 6 rats. Fasted animals were deprived of food for at least 16 hr but were allowed free access to water. Fasting blood was collected for blood glucose estimation before starting the treatment on the first day. The first group was used as a control and received H_2O as a vehicle. The second group received a single dose of STZ (60 mg/kg b.wt) dissolved in citrate buffer and was divided into four subgroups after establishing diabetes for 1 week. The first subgroup was kept as a diabetic control while the second, third, and fourth subgroups received orally 1.0 ml of sitagliptin (5mg/kg), *AQGC* (200 mg/ kg), and *AQGC* (400 mg /kg) respectively by gastric intubation daily for 28 days. Blood was collected from the retro-orbital plexus. All five groups were sacrificed on the 28th day in fasting condition by cervical dislocation and then blood was collected for various biochemical estimations.

Biochemical Estimation:

At the end of 28 days the serum blood glucose levels, HbA1C, and insulin levels were estimated. The pancreas was isolated and cut into small pieces, placed in chilled 0.25 M sucrose solution, and blotted on a filter paper. The tissues were then homogenized in 10 % chilled Tris hydrochloride buffer (10 mM, pH 7.4) by tissue Homogenizer (Remi Motors, Mumbai, India) and centrifuged at 12000rpm for 15 min at 0ºC using a cooling centrifuge (R-247, Refrigerated Centrifuge, Mumbai, India) Lipid peroxidation (LPx) was estimated in terms of malondialdehyde (MDA) content and determined by using the thiobarbituric acid (TBA) by the method of Hiroshi et al. 1979. The activity was expressed as µmol of malondialdehyde formed/g wet weight of tissue. Superoxide dismutase (SOD) was assayed for its ability to inhibit the autooxidation of epinephrine in an alkaline medium (Misra and Fridovich, 1972). The SOD activity levels were expressed in units per mg of protein per min. Catalase was assayed by the method of Maehly and Chance (1954) by determining the decrease in the concentration of hydrogen peroxide (H_2O_2). The activity of the enzyme was expressed in µmol of hydrogen peroxide (H2O2) metabolized/mg protein/min. Glutathione peroxidase (GPx) was assayed by the method of Rotruck et al., 1973. The activity was expressed as µmol of GSH consumed/mg protein/min. The protein concentration was determined by using bovine serum albumin as the standard (Lowry et al., 1951).

Total RNA extraction and reverse transcription and polymerase chain reaction:
Total RNA was isolated from the intestinal samples using TRIzol reagent (GeNei, Bangalore, India) according to manufactures instructions. The quality of RNA was confirmed by formaldehyde gel in comparison with 28S and 18S RNA. The RNA concentration was measured at 260 nm using a UV spectrophotometer (UV-1800 UV-Vis Spectrophotometer, Japan). The RNA pellet was dissolved in diethylpyrocarbonate (DPEC) -treated water. cDNA was synthesized using 9µL of total RNA and reverse transcriptase (Invitrogen, Carlsbad, CA, USA).
Polymerase chain reaction (PCR) was performed on a Thermal Cycler PCR Machine (Model No. LT-240)using Taq DNA polymerase with the following thermal cycle profiling: initial denaturation at 95°c for 5 min followed by 30 cycles (Denaturation at 95°c for 5 min, annealing at 60°c for 30 Sec, renaturation at 72°c for 30 Sec, and extension at 72°c for 10 min).
The following primer sets were used to amplify proglucagon and insulin gene expression. All the primers were ordered from GeNei, Bangalore, India.
Proglucagon:
Forward: PLG-F_R: GTAATGCTGGTACAAGGCAG
Reverse: PLG-R_R: TTGATGAAGTCTCTGGTGGCA
Insulin:
Forward: INSULIN-F_384: CCCTAAGTGACCAGCTACA
Reverse: INSULIN-R_384: TTGCAGTAGTTCTCCAGTTG

RESULTS
Effect of *AQGC* on blood glucose levels, body weight, and food intake:
STZ-induced diabetic rats showed a significant increase in blood glucose levels when compared with controls (fig 1). Whereas *AQGC* and sitagliptin-treated diabetic rats showed decreased blood glucose levels significantly ($p<0.05$). In diabetic rats body weight increased and food intake decreased when compared to normal rats, whereas in *AQGC*-treated diabetic rats, the body weight increased and food intake decreased when compared to diabetic rats.

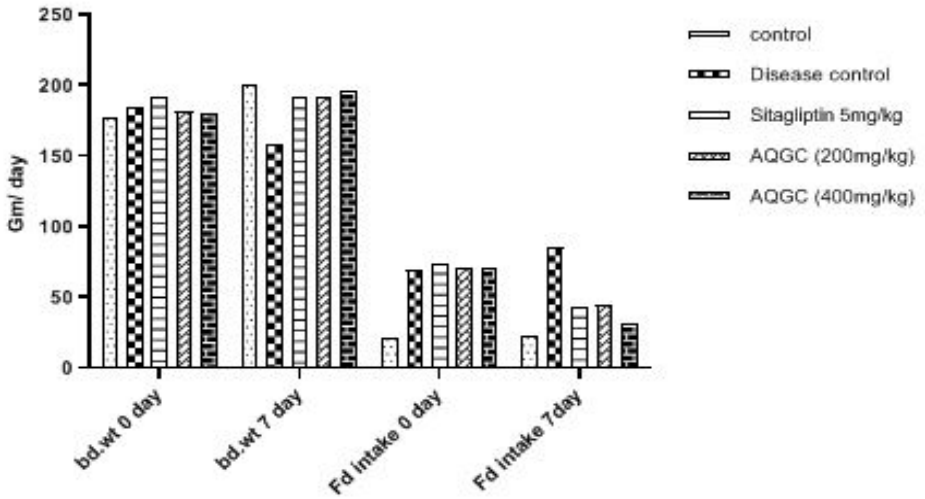

Figure 1: Effect of AQGC on body weight and food intake on STZ induced diabetic rats.

Effect of *AQGC* on blood glucose, HbA1c, and insulin:
STZ-induced diabetic rats showed a significant increase in blood glucose and HbA1c levels when compared with controls (Tab 1). Whereas *AQGC* and sitagliptin treated diabetic rats blood glucose and HbA1c levels were significantly ($p<0.05$) decreased. In diabetic rats, insulin levels were significantly ($p<0.05$) decreased when compared to normal rats, whereas, in *AQGC*-treated diabetic rats, the insulin levels were significantly ($p<0.05$) increased when compared to diabetic rats.

Table 1: Effect of AQGC of blood glucose, %HbA1c and insulin levels in STZ induced diabetic rats.

Groups	Blood Glucose (mg/dL)	%HbA1c	Insulin(uIU/ml)
Normal	88.05±1.8*	2.89±0.10*	4.86±0.22*
Diabetic control	366.2±6.5	10.12±0.33	3.29±0.89
Sitagliptin (5mg/kg)	95.1±3.5*	3.55±0.23*	4.65±0.45*
AQGC(200mg/kg)	102.4±2.8*	5.31±0.11*	4.54±0.76*
AQGC(400mg/kg)	93.23±5.7*	3.77±0.18*	4.88±0.77*

P>0.05* significance followed by two way ANOVA followed by Bonferroni s post test when compared with toxicant group.

Effect of *AQGC* on protein, MDA, and antioxidant enzyme levels in the pancreas and liver:

The MDA contents were significantly ($p<0.05$) increased in both the pancreas and liver of diabetic rats when compared to that of normal control rats (tab 2). However, *AQGC* and Sitagliptin-treated diabetic rats showed a significant ($p<0.05$) decline in MDA contents when compared to diabetic rats. The antioxidant enzymes like SOD and catalase levels were significantly ($p<0.05$) decreased in both pancreas and intestine of diabetic rats. Furthermore, *AQGC* extract and Sitagliptin treatment increase the levels of SOD, and CAT when compared to diabetic rats (tab 2).

Table 2: Effect of AQGC on SOD, catalase and MDA levels in STZ induced diabetic rats.

Groups	**MDA levels (nmoles of MDA/mg of protein)**		**SOD (U/min/mg of protein)**		**Catalase (n moles of H_2O_2/ min/mg of protein)**	
	Liver	Pancreas	Liver	Pancreas	Liver	Pancreas
Normal	1.07±0.03*	3.83±0.05*	3.76±0.10**	1.40±0.15**	1.48±0.08*	1.13±0.13*
Diabetic control	14.3±0.35	13.32±0.43	0.74±0.04	0.47±0.03	0.48±0.02	0.52±0.05
Sitagliptin (5mg/kg)	4.0±0.16*	3.250±0.13*	4.06±0.12**	3.41±0.19**	1.03±0.05*	0.55±0.05*
AQGC (200mg/kg)	6.0±0.1*	5.44±0.18*	2.30±0.14**	2.46±0.17**	0.71±0.02*	0.57±0.02*
AQGC (400mg/kg)	3.5±0.2*	2.50±0.18**	3.63±0.20**	4.00±0.09**	1.18±0.13*	1.05±0.04*

*p value <0.05, **p value <0.01, when compared to diabetic control followed by Dunnett s multiple comparison test, ns-non-significant.

Effect of *AQGC* on intestinal proglucagon and pancreatic insulin gene expression levels:

STZ-induced diabetic rats significantly ($p<0.05$) decreased intestinal proglucagon gene expression levels as compared to control rats. Whereas, in *AQGC* and sitagliptin-treated diabetic rats, proglucagon gene expression levels were significantly increased (fig 2) when compared with diabetic rats. The pancreatic insulin gene expression levels were significantly ($p< 0.05$) decreased in diabetic rats when compared to control rats. However, in *AQGC* and sitagliptin-treated diabetic rats insulin gene expression levels were significantly ($p< 0.05$) increased when compared with diabetic rats (fig 3).

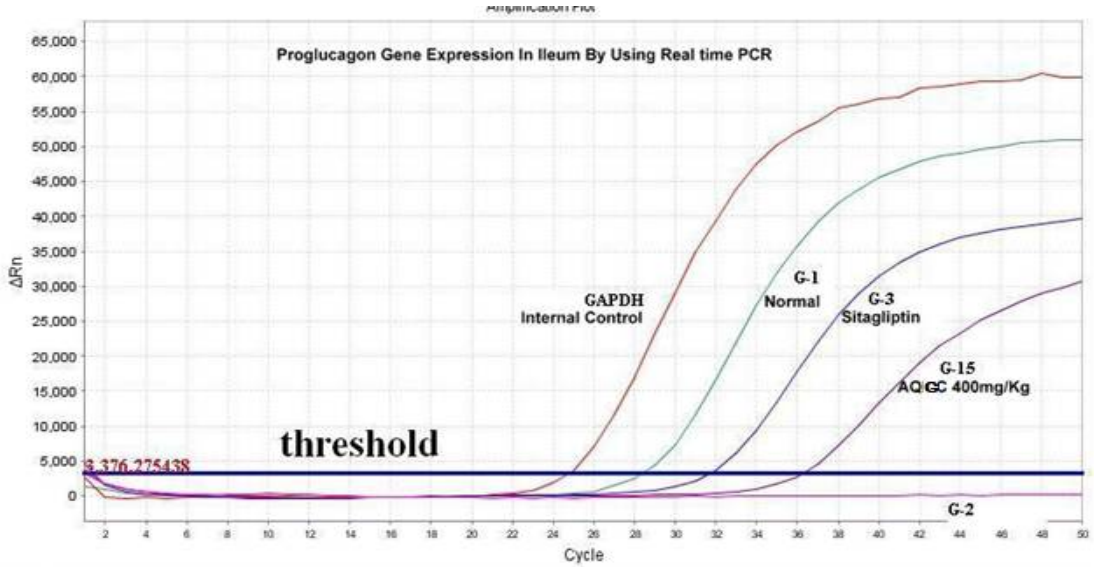

Figure 2: Effect of AQGC on proglucagon expression levels STZ induced diabetic rats during 28 day study period.

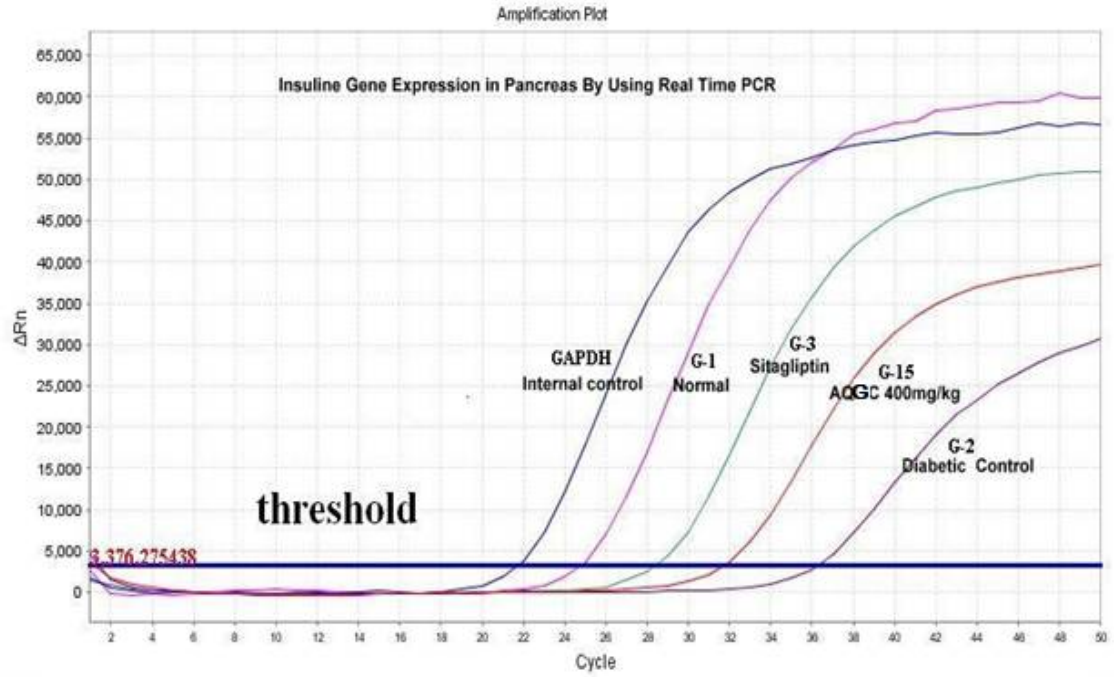

Figure 3: Effect of AQGC on insulin gene expression levels STZ induced diabetic rats during 28 day study period.

Effect of *AQGC* on Histopathology:

Figure 4: The control pancreas indicated that light microscopic examination of the pancreatic sections of the control group of animals revealed that the pancreas is composed of exocrine tissue where pyramidal shape acini are closely packed and endocrine tissue which is the islet of Langerhans. The acini are separated by septa made of connective tissue (collagen fiber). The islets are composed of granular cytoplasm with dark alpha (α) cell nucleus and light beta (β) cell nucleus. In the Diabetic group, pancreatic section irregular outlining and deformed islets with vacuolated cytoplasm due to necrosis in the center were observed. The number of islets and beta cells also decreased. Some areas with dense collagen fiber induced pressure atrophy of the surrounding cells which lead to the flattened epithelium of acinar cells. The pancreatic section of the diabetic group treated with gliclazide showed a regular outline of islets of Langerhans with regenerated beta cells and granular cytoplasm. Closely packed Acini were observed. The collagen fiber is sparse around the blood vessel, dilated duct, and acini. Whereas diabetic animals treated with AQGC (400mg/kg) shows the recovery of islets outline to a regular shape, collagen fiber was less around the blood vessel and acini were closely packed.

Figure 5: Light microscopic examination of the Ileal sections of the control group of animals revealed that the ileum is composed of different layers *Viz.*, Outermost peritoneum, serosa, muscularis, submucosa, and innermost mucosa. The mucosal layer is thrown into many circular folds called villi. Each villus is composed of more mature columnar epithelial cells called enterocytes with columnar basal nuclei and occasional goblet cells. The tips of the villi are intact. In the Diabetic group ileum section reveals degeneration and separation of the epithelium from the core of villi with rounded nuclei. More number of goblet cells is noticed. The tip of the villi is damaged and the microvilli are almost detached from the epithelium. Vacuolated regions as a result of damaged epithelial cells are noticed. In Ileal section of the diabetic group treated with gliclazide showed intact microvilli and epithelium with less number of goblet cells. The cryptal space is also wide. The diabetic rats treated with the AQGC (400mg/kg) treatment showed completely regenerated epithelial cells with columnar nuclei. Less number of goblet cells and intact microvilli are noticed.

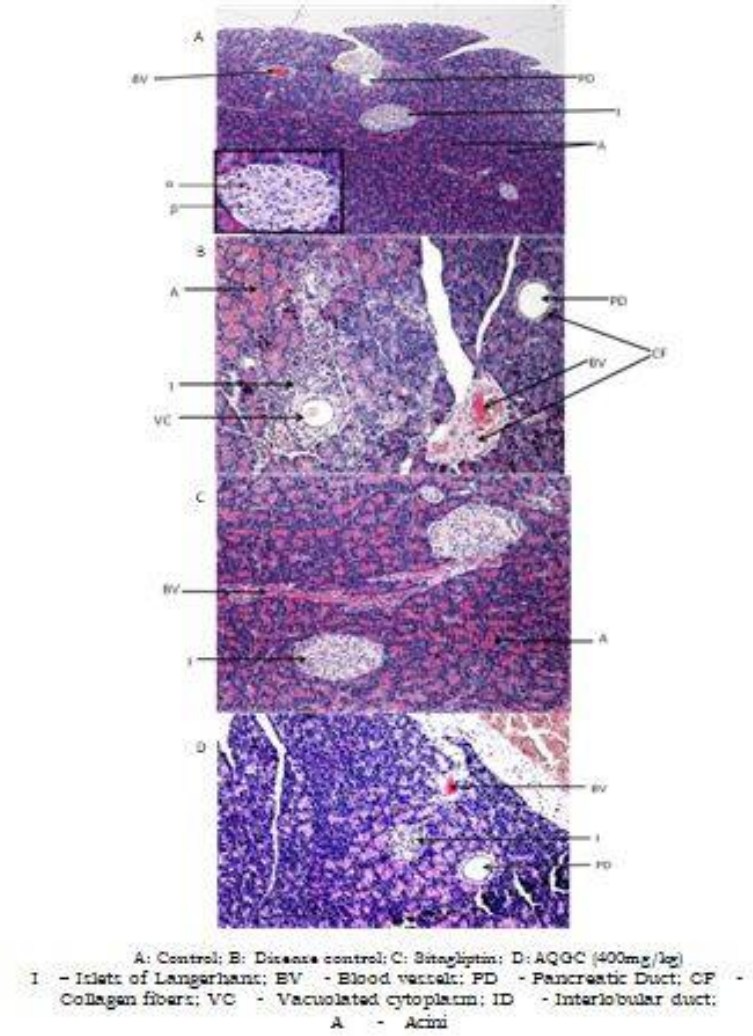

Figure 4 : Effect of AQGC on histopathology of pancreas in STZ induced diabetic rats during 28 day study period.

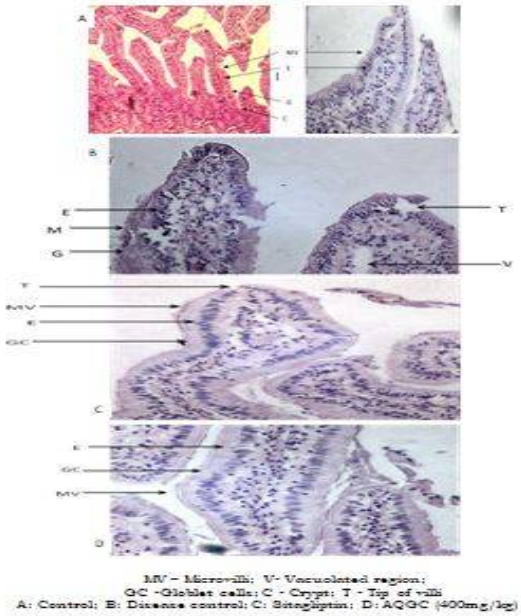

Figure 5: Effect of AQGC on histopathology of ileum in STZ induced diabetic rats during 28 day study period.

DISCUSSION

Diabetes mellitus is associated with the increased formation of free radicals and decreased antioxidant potential. An imbalance of oxidant/antioxidant defense systems results in an alteration in the antioxidant enzyme activity [13]. Hyperglycemia causes the generation of reactive oxygen species which in turn causes lipid peroxidation. *AQGC* extract possesses significant antioxidant activity in various *in vitro* models, it may be due to *AQGC* extract contains compounds that are electron donors, which can react with free radicals to convert them to more stable products and terminate radical chain reaction [2].

Diabetic rats exhibited increased food and water intake and decreased body weight than control rats. These effects were attributed to polyphagia accompanied by weight loss due to the excessive breakdown of tissue protein [21]. Studies suggest that a deficiency of hormones, particularly insulin, and leptin, causes hyperphagia in streptozotocin (STZ) diabetic rats by altering the balance of hypothalamic neuropeptides [9, 20]. Irrespective of food intake, the dynamics of amino nitrogen conversion are changed in a way that favors protein catabolism of diabetic animals causing weight loss [2].

Glycosylated hemoglobin was an indicator of irreversible condensation of glucose with the N terminal residue of the β-chain of hemoglobin (O'Hea et al., 2009). In our study, the diabetic rats had higher levels of glycosylated hemoglobin, the significant decrease in glycosylated hemoglobin was observed in diabetic rats after treatment with *AQGC* extract indicating that the overall blood glucose levels were controlled which might be due to an improvement in insulin secretion.

In the present study in STZ-induced diabetic rats, MDA content was increased. Treatment with *AQGC* extract for 28 days significantly reduced the pancreatic MDA content indicating a protective role of extract, this may be attributed to the presence of phytochemicals such as alkaloids, glycosides, and steroids. This is further supported by *AQGC* extract-treated diabetic rats showed a significant abrogates MDA level, suggesting that *AQGC* extract might have antioxidant principles to produce a response [4]. The SOD plays a pivotal role in oxygen defense metabolism by reducing superoxide to hydrogen peroxide [5]. The decrease in SOD activity in diabetic rats could result from the inactivation of H_2O_2 or from glycosylation of the enzyme which has been reported to occur in diabetes [18]. The enzymes CAT and GPx are involved in the elimination of H_2O_2. The CAT activity decreased due to inactivation by superoxide radicals and glycation of the enzyme by the treatment with *AQGC* extract. Also, CAT is involved in the detoxification of high H_2O_2 concentrations [4]. *AQGC* extract treated diabetic rats' pancreatic antioxidant enzymes were significantly increased which could be attributable to strong antioxidative properties [1].

Proglucagon is cleaved to glucagon by prohormone convertase 2 (PC2) in pancreatic α-cells but is cleaved to glucagon-like peptide-1 (GLP-1) by PC1 in intestinal L-cells. This study aimed to identify mechanisms that switch the processing of proglucagon to generate GLP-1 in the pancreas; given that GLP-1 can increase insulin secretion and β-cell mass [22]. Post-translational processing of proglucagon in enteroendocrine L cells leads to the liberation of glicentin, oxyntomodulin, two intervening peptides (IP-1 and IP-2), and two GLPs (GLP-1 and GLP-2) [23]. As mentioned above during STZ induced diabetes, results in the enhanced generation of pancreatic GLP-1. The present study resulted in increased proglucagon and insulin expression in STZ-induced diabetic rats might be due to incretin mimetic activity.

CONCLUSION

The antioxidant and antihyperglycemic and insulin tropic action via Glucose-dependent insulinotropic peptide stimulate the release of insulin from the beta cells in the pancreas to maintain low blood sugar levels after eating might be due to the presence of active phytochemical hydroxyl citric acid a principal active constituent of *Garcinia cambogia.*

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