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Pharmaceutical Sciences **RESEARCH ARTICLE ……!!!**

RENOPROTECTIVE EFFECT OF RABEPRAZOLE IN STREPTOZOTOCIN-INDUCED DIABETIC NEPHROPATHY IN WISTAR RATS

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KEYWORDS:

Diabetic nephropathy, Rabeprazole, Glucose, Oxidativestress, proton pump inhibitor.

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ABSTRACT

Diabetic nephropathy is a leading cause of morbidity and mortility and its prevelence is continously increasing. The present study has been undertaken to investigate the renoprotective potential of rabeprazole in streptozotocin-induced diabetic nephropathy in wistar rats. Diabetic nephropathy was induced with a single injection of streptozotocin (STZ,45mg/kg,i.p.). Rabeprazole (20mg/kg; 40 mg/kg, p.o.; 4 weeks) was administered to diabetic rats after4weeksofSTZtreatment. Various biochemical test such as serum glucose, glycated hemoglobin, blood urea nitrogen(BUN), serum creatinine, albumin, and kidney weight/ body weight (%) ratio were performed to evaluate the renal functions. Administration of rabeprazole to diabetic rats significantly reduced serum glucose, glycated hemoglobin, BUN, creatinine, albumin levels, and oxidative stress. Serum lipids like TC and TG were decreased, and HDL was enhanced in rabeprazole treated STZ rats. The findings of our study indicate that renoprotective effects of rabeprazole may be attributed to its glucose-lowering, lipid-lowering, and antioxidative potential.

1. INTRODUCTION

Diabetes mellitus is a combination of heterogeneous disorders commonly presenting with episodes of hyperglycaemia and glucose intolerance, as a result of lack of insulin, defective insulin action, or both[1]. Diabetic nephropathy, also known as Kimmelstiel Wilson syndrome or nodular diabetic glomerulosclerosis or intercapillary glomerulonephritis, is a clinical syndrome characterized by albuminuria (>300 mg/day or >200 mcg/min) confirmed on at least two occasions 3-6 months apart, permanent and irreversible decrease in glomerular filtration rate (GFR) and arterial hypertension[2]. Diabetes nephropathy (DN) is a major microvascular complication of diabetes mellitus characterized by partial loss of kidney functions followed by nephrotic syndrome and glomerulosclerosis. DN is the leading cause of chronic kidney disease and end-stage renal disease (ESRD) that accounts for significantmorbidityandmortalityindiabeticpatients[3].Hyperglycemia, increased blood pressure levels, and genetic predisposition are the core risk factors for the advancement of DN (Freedman*et al.* 2007)[4].Studiesindicatethatelevatedserum lipids and smoking behavior also appear to play a key role as riskfactor[5]. Non-enzymatic glycosylation that produces advanced glycosylation end products (AGE) leads to the downstream activation of protein kinase C (PKC), polyol pathway, VEGF, with transforming growth factor-β1(TGF-β1), interleukins (IL-1, IL-6, and IL8), and tumor necrosis factor alpha[6]. Rabeprazole is mainly reduced via the no enzymatic pathway to rabeprazole ethicether. Therefore, the acid inhibitory effects of rabeprazole are less influenced by CYP2C19 genotype status[7].Rabeprazole is an inhibitor of the gastric proton pump. It causes dose-dependent inhibition of acid secretion and has a more rapid onset of action than omeprazole[8].Rabeprazole is a second-generation PPI that inactivates the gastric pump through covalent binding, causing a rapid and sustained inhibition of intracellular proton efflux, as well as raising the extracellular pH[9].Studies involving animals have demonstrated that PPIs also exhibit anti-oxidant effects in vivo. Rats subjected to restraint and cold stress develop gastric ulcers that are caused largely by the gastric mucosal production of hydroxyl radicals[10].

2. RESULT

Administration of single injection of streptozotocin (45 mg/kg, i.p.) produced hyperglycemia, and after 7 days of STZ administration, rats showing blood glucose level greater than 240 mg/dl were selected as diabetic rats. Rabeprazole low dose (20mg/kg/day) and high dose (40 mg/kg/day) was administered orally to diabetic rats after single injection of STZ administration, and their treatment was continued for 4 weeks. Drug per se (20 mg/kg/day, p.o.) did not produce any significant effect on various parameters of diabetic nephropathy in the present study. All the parameters were assessed at the end of 8thweek in normal and diabetic rats with or without drug treatment.

2.1 Effect of rabeprazole on serum glucose level

The marked increase in serum glucose level was noted in diabetic rats as compared to normal rats. However, there was a significant decline in serum glucose concentration of rats treated with rabeprazole at both the doses (20 and 40 mg/kg/day) when compared to the diabetic control rats (Fig. 1)

2.2 Effect of rabeprazole on glycated hemoglobin content

A significant accentuation was observed in the glycated hemoglobin content after the administration of STZ in comparison to the normal control group. However, there was a significant reduction in the glycated hemoglobin content of rats treated with rabeprazole (20 and 40 mg/kg/day, p.o. for 4 weeks) in comparison to the diabetic control rats (Fig. 2).

2.3 Effect of rabeprazole on serum albumin, creatinine levels, and BUN

Diabetic nephropathy is diagnosed by albuminuria (increase in the level of albumin in urine), accompanied by decrease in its level in serum. In our study, the diabetic rats showed significant decrease in the level of serum albumin when compared to normal control group. Treatment with rabeprazole (20 and 40 mg/kg/day, p.o. for 4 weeks) significantly elevated the serum albumin level of diabetic rats (Fig. 7). Diabetic rats showed a significant increase in the level of blood urea nitrogen (BUN) and serum creatinine content when compared to normal control group. Rabeprazole (20 mg/kg/day and 40 mg/kg/ day, p.o. for 4 weeks) showed a significant decrease in blood urea nitrogen and serum creatinine level as compared to STZ-treated diabetic animals (Figs. 8 and 9) showed a significant decrease in blood urea nitrogen and serum creatinine level as compared to STZ-treated diabetic animals (Figs. 3,4 and 5).

2.4 Effect of rabeprazole on lipid profile

A marked elevation was indicated in total cholesterol and triglycerides level in STZ-treated rats as compared to normal untreated group. However, a significant fall was observed in the serum cholesterol and triglycerides level of rats treated with rabeprazole (20 and 40mg/kg/day, p.o. for 4 weeks) in comparison to STZ-treated diabetic rats (Figs. 3 and 4). Furthermore, a significant decrease in HDL level was noted in diabetic rats treated with STZ (45 mg/kg, i.p.) as compared to normal control animals. Rabeprazole (20 and 40 mg/kg/ day, p.o. for 4 weeks) to diabetic group produced a marked increase in HDL level as compared to the diabetic group (Fig. 6,7and 8).

2.5 Effect of rabeprazole on kidney weight and body weight ratio

A significant increase in kidney weight/bodyweight ratio was noted in diabetic rats as compared to normal control. However, treatment with both low (20 mg/kg/day, p.o.) and high doses (40

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mg/kg/day, p.o.) of rabeprazole significantly decreased kidney weight/body weight ratio in STZ-treated diabetic rats (Fig. 9).

2.6 Effect of rabeprazole on oxidative stress parameters (TBARS, GSH, and total brain protein)

Diabetic rats after 7week (8 week of STZ administration showed markedly increase in renal TBARS as compared to normal rats. In addition, the renal concentration of GSH was noted to be decrease in diabetic rats as compared to normal rats. Treatment with rabeprazole (20mg/kg/day/p.o and 40 mg/kg/day/p.o) markedly attenuated diabetes – induced increase in renal TBARS and consequent decrease in renal GSH (Fig.10 and11,12).

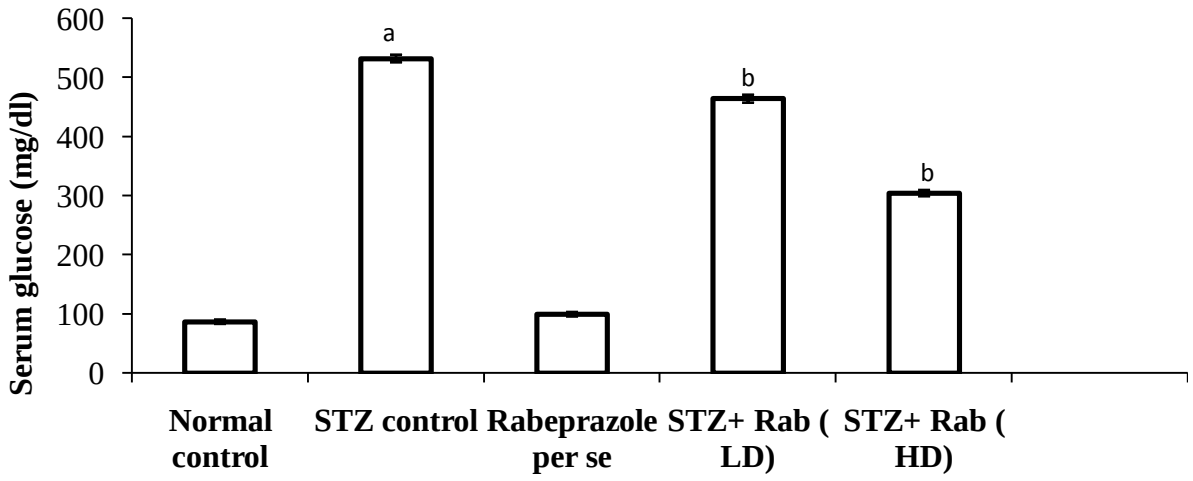

Fig.3 Effect of various pharmacological interventions on serum glucose level (mg/dl). STZ streptozotocin (45 mg/kg, i.p. Rabe, rabeprazole (40 mg/kg, p.o.), STZ + Rab(LD), streptozotocin (45 mg/kg, i.p.) + Rab low dose (20mg/kg, p.o.), STZ + Rab (HD) streptozotocin (45 mg/kg, i.p.) + Rab high dose (40 mg/kg, p.o.). Values are expressed as mean ± SEM, n = 6.

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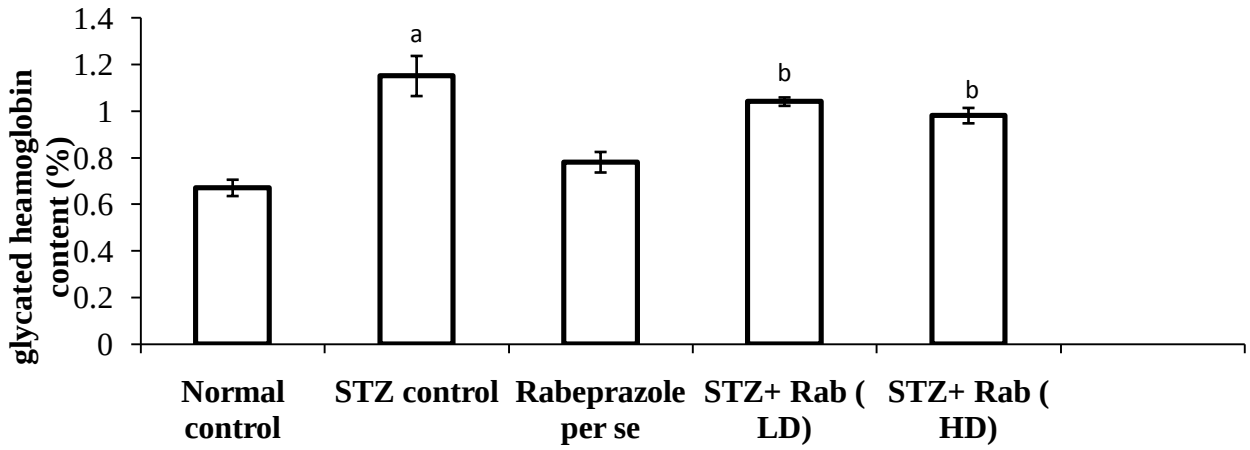

Fig. 2 Effect of various pharmacological interventions on serum glycated heamoglobin content (%). STZ streptozotocin (45 mg/kg, i.p. Rabe, rabeprazole (40 mg/kg, p.o.), STZ + Rab(LD) = streptozotocin (45 mg/kg, i.p.) + Rab low dose (20mg/kg, p.o.), STZ + Rab (HD) = streptozotocin (45 mg/kg, i.p.) + Rab high dose (40 mg/kg, p.o.).

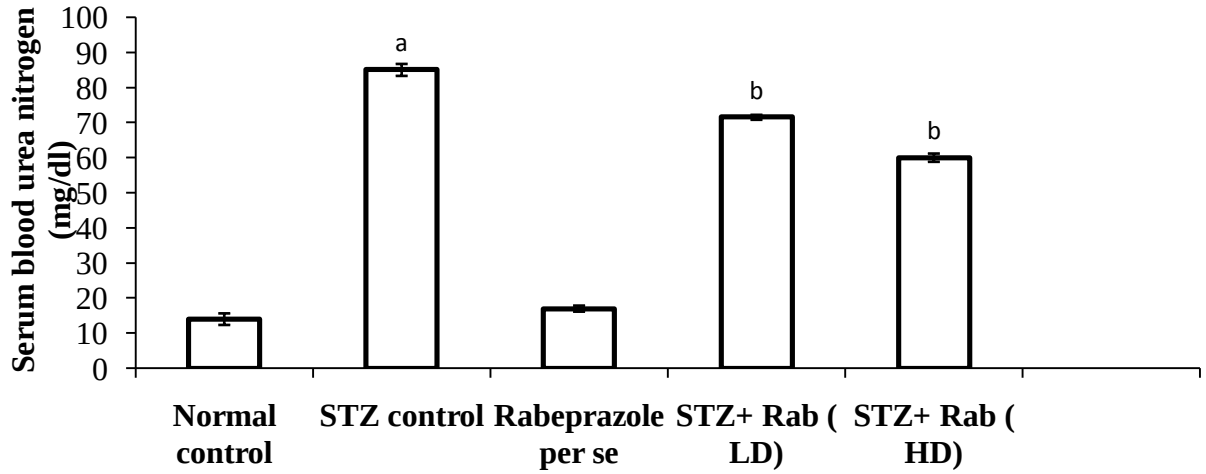

Fig.3 Effect of various pharmacological interventions on serum blood urea nitrogen level (mg/dl). STZ streptozotocin (45 mg/kg, i.p. Rabe, rabeprazole (40 mg/kg, p.o.), STZ + Rab(LD), streptozotocin (45 mg/kg, i.p.) + Rab low dose (20mg/kg, p.o.), STZ + Rab (HD) streptozotocin (45 mg/kg, i.p.) + Rab high dose (40 mg/kg, p.o.). Values are expressed as mean ± SEM, n = 6.

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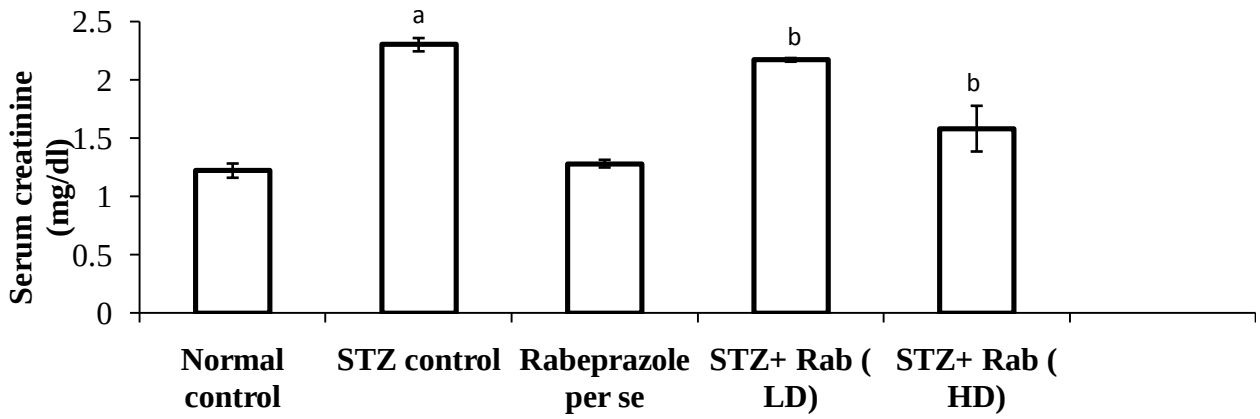

Fig. 4. Effect of various pharmacological interventions on serum creatinine level (mg/dl). STZ streptozotocin (45 mg/kg, i.p. Rabe, rabeprazole (40 mg/kg, p.o.), STZ + Rab(LD) streptozotocin (45 mg/kg, i.p.) + Rab low dose (20mg/kg, p.o.), STZ + Rab (HD) streptozotocin (45 mg/kg, i.p.) + Rab high dose (40 mg/kg, p.o.). Values are expressed as mean ±EM, n =6

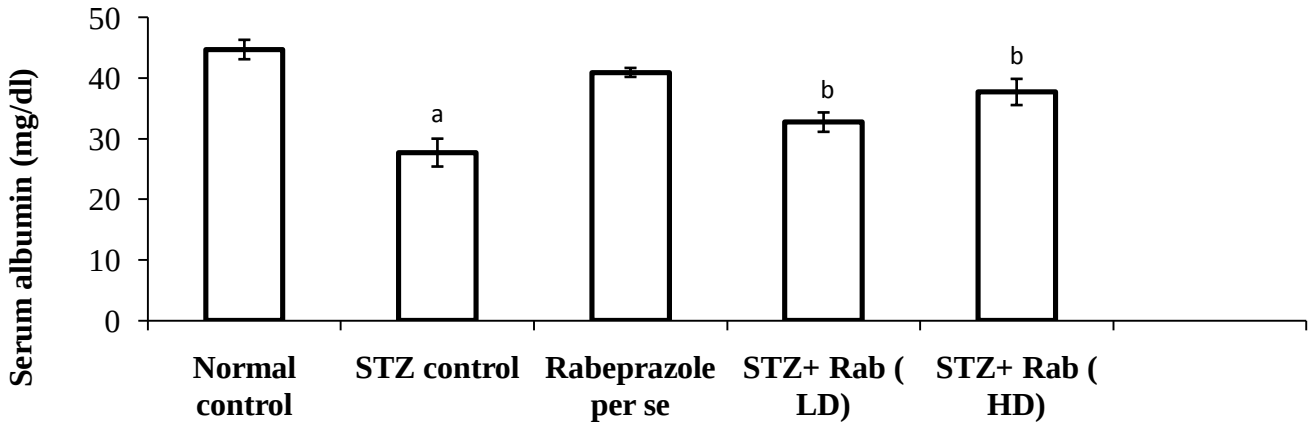

Fig. 5. Effect of various pharmacological interventions on serum albumin level (mg/dl). STZ streptozotocin (45 mg/kg, i.p. Rabe, rabeprazole (40 mg/kg, p.o.), STZ + Rab(LD) streptozotocin (45 mg/kg, i.p.) + Rab low dose (20mg/kg, p.o.), STZ + Rab (HD) ,streptozotocin (45 mg/kg, i.p.) + Rab high dose (40 mg/kg, p.o.). Values are expressed as mean ± SEM, n =6

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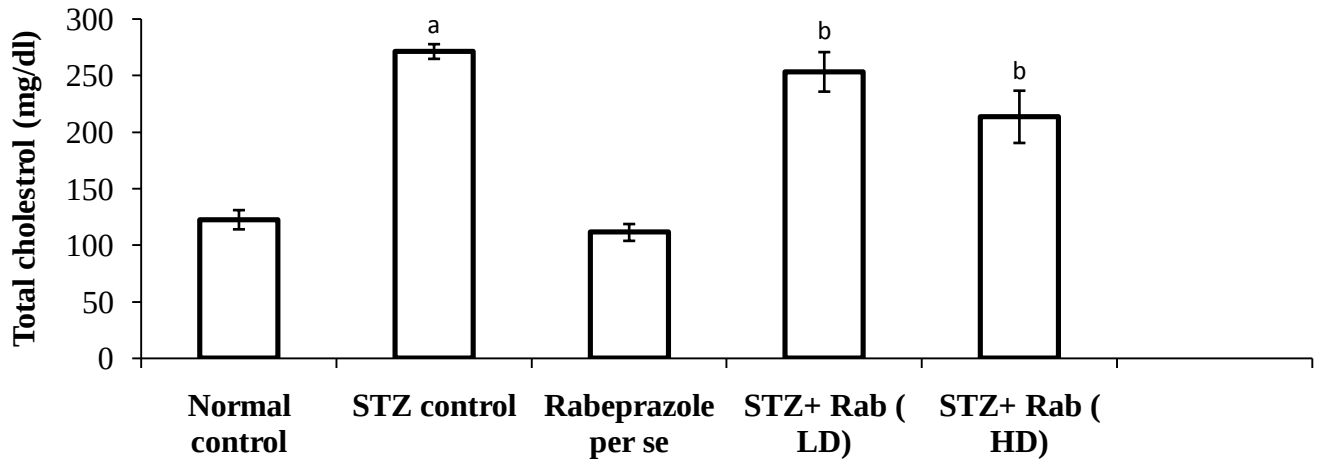

Fig. 6. Effect of various pharmacological interventions on serum total cholestrol level (mg/dl). STZ streptozotocin (45 mg/kg, i.p. Rabe, rabeprazole (40 mg/kg, p.o.), STZ + Rab(LD) streptozotocin (45 mg/kg, i.p.) + Rab low dose (20mg/kg, p.o.), STZ + Rab (HD) streptozotocin (45 mg/kg, i.p.) + Rab high dose (40 mg/kg, p.o.). Values are expressed as mean ± SEM, n =6

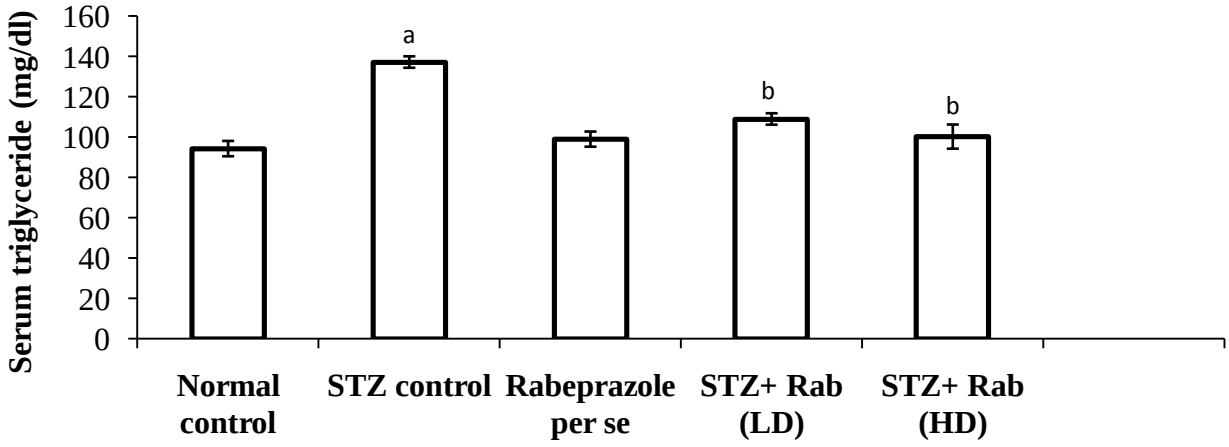

Fig. 7 Effect of various pharmacological interventions on serum triglyceride level (mg/dl).STZ streptozotocin (45 mg/kg, i.p. Rabe, rabeprazole (40 mg/kg, p.o.), STZ + Rab(LD) streptozotocin (45 mg/kg, i.p.) + Rab low dose (20mg/kg, p.o.), STZ +Rab (HD) streptozotocin (45 mg/kg, i.p.) + Rab high dose (40 mg/kg, p.o.). Values are expressed as mean ± SEM, n = 6

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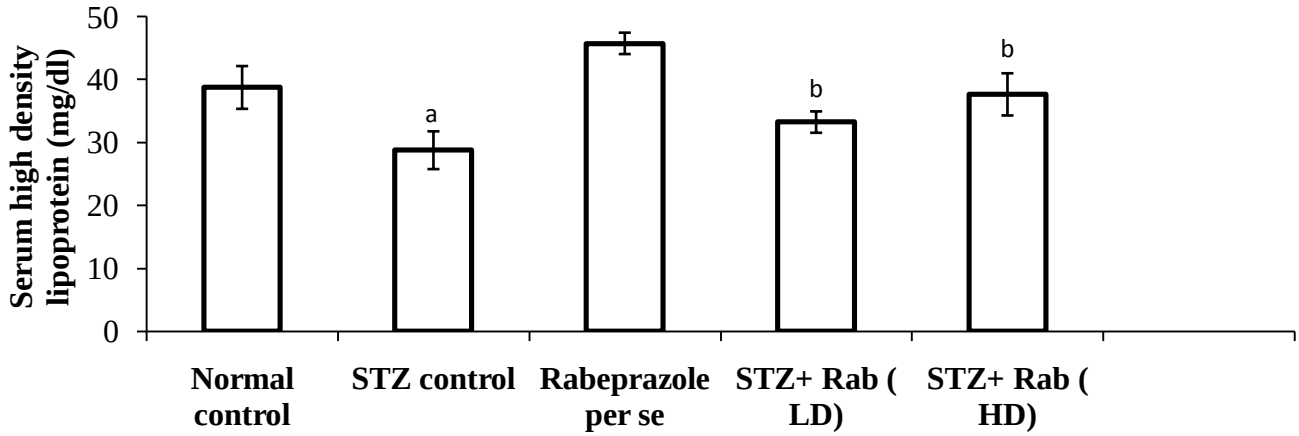

Fig.8. Effect of various pharmacological interventions on serum high density lipoprotein level (mg/dl). STZ streptozotocin (45 mg/kg, i.p. Rabe, rabeprazole (40 mg/kg, p.o.), STZ + Rab(LD); streptozotocin (45 mg/kg, i.p.) + Rab low dose (20mg/kg, p.o.), STZ + Rab (HD); streptozotocin (45 mg/kg, i.p.) + Rab high dose (40 mg/kg, p.o.). Values are expressed as mean ± SEM, n = 6

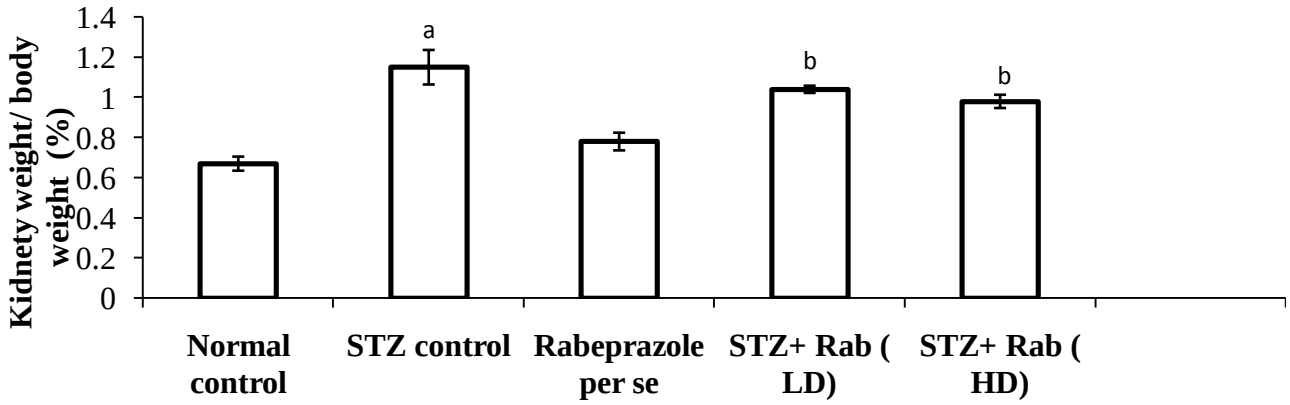

Fig. 9. Effect of various pharmacological interventions on kidney weight /body weight (%). STZ streptozotocin (40 mg/kg, i.p. Rabe, rabeprazole (40 mg/kg, p.o.), STZ + Rab(LD) streptozotocin (45 mg/kg, i.p.) + Rab low dose (20mg/kg, p.o.), STZ + Rab (HD) streptozotocin (45 mg/kg, i.p.) + Rab high dose (40 mg/kg, p.o.). Values are expressed as mean ± SEM, n = 6

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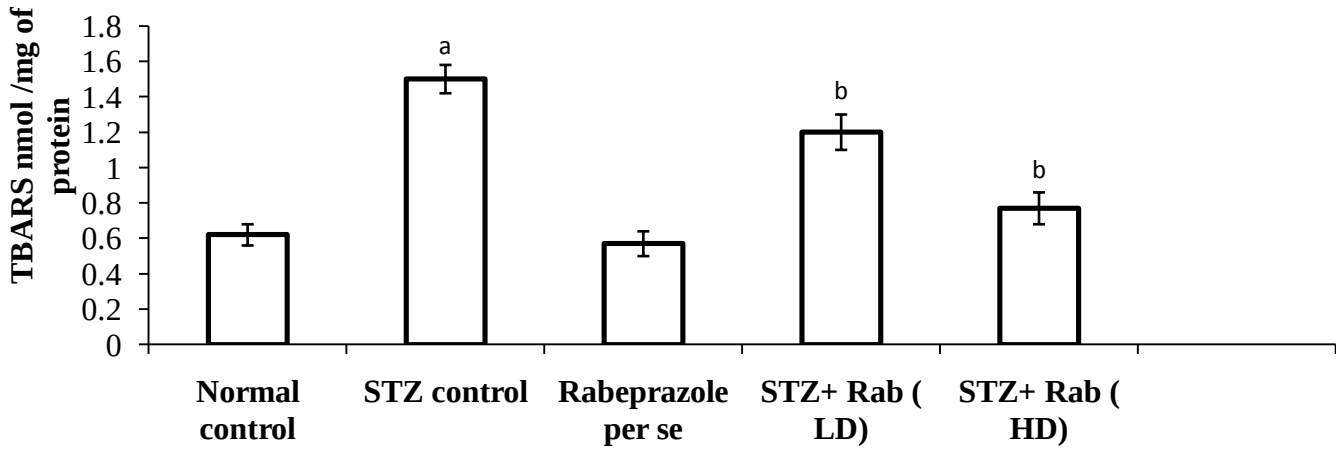

Fig. 10. Effect of various pharmacological interventions on reanal TBARS level (nmol/mg of proyein). STZ streptozotocin (40 mg/kg, i.p. Rabe, rabeprazole (40 mg/kg, p.o.), STZ + Rab(LD) ;streptozotocin (45 mg/kg, i.p.) + Rab low dose (20mg/kg, p.o.), STZ + Rab (HD) streptozotocin (45 mg/kg, i.p.) + Rab high dose (40 mg/kg, p.o.). Values are expressed as mean ± SEM, n =6

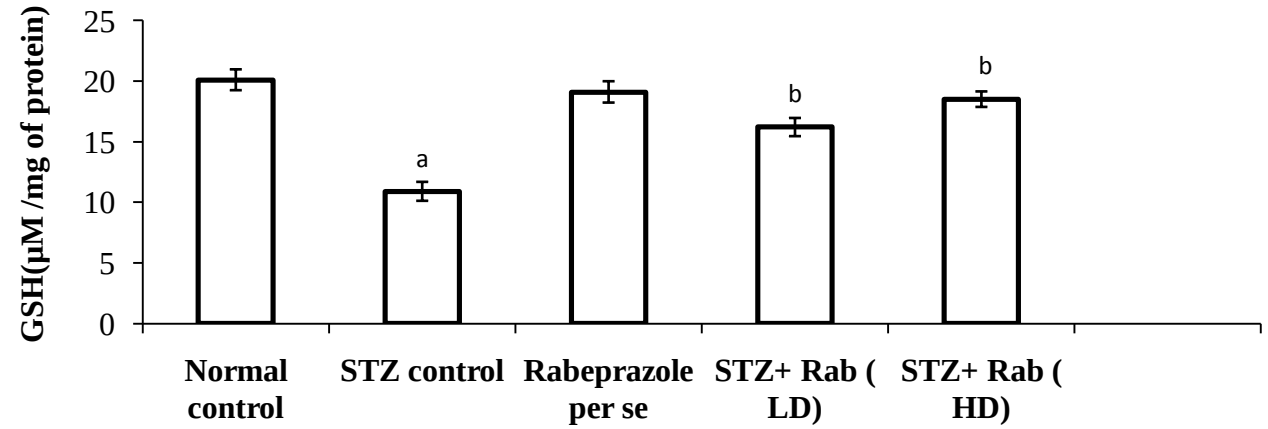

Fig. 11. Effect of various pharmacological interventions on renal glutathione level GSH µM/Mg of protein). STZ streptozotocin (45 mg/kg, i.p. Rabe, rabeprazole (40 mg/kg, p.o.), STZ + Rab(LD); streptozotocin (45 mg/kg, i.p.) + Rab low dose (20mg/kg, p.o.), STZ + Rab (HD); streptozotocin (45 mg/kg, i.p.) + Rab high dose (40 mg/kg, p.o.). Values are expressed as mean ± SEM, n = 6

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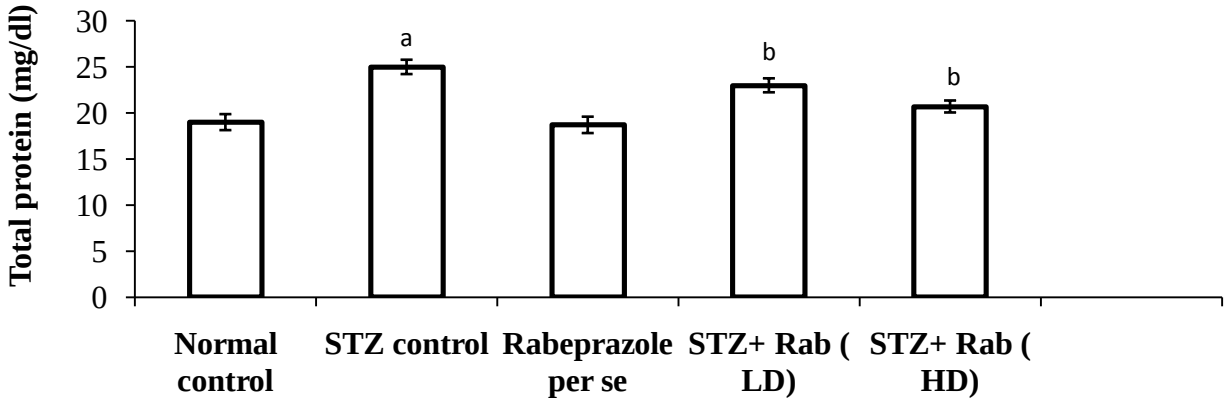

Fig. 12. Effect of various pharmacological interventions on total protein(mg/dl). STZ streptozotocin (45 mg/kg, i.p. Rabe, rabeprazole (40 mg/kg, p.o.), STZ + Rab(LD); streptozotocin (45 mg/kg, i.p.) + Rab low dose (20mg/kg, p.o.), STZ + Rab (HD); streptozotocin (45 mg/kg, i.p.) + Rab high dose (40 mg/kg, p.o.). Values are expressed as mean ± SEM, n =6

SUMMARY AND CONCLUSION

The kidneys are vital for removing toxic waste products from the body and for maintaining fluids, minerals, and electrolytes at physiological levels. Elevated blood glucose can damage the cells and micro. These effects are stable and long lasting. The extraction of one kidney can increase the burden on the contralateral kidney and accelerate the progression of the disease, accelerating the development of DN. Both decreases and gains in body weight were observed in conjunction with the progression of diabetes. Gastrin has been shown to increase proliferation of human and rodent duct-like pancreatic cells in culture, and administration of gastrin stimulates beta cell neogenesis and expansion of the BCM in rodents Rabeprazole and its primary thioether metabolite (secreted by gastric mucosal cells) have also been reported to show antimicrobial activity for *H. pylori* [11].Gastrin has been shown to increase proliferation of human and rodent duct-like pancreatic cells in culture, and administration of gastrin stimulates betacell neogenesis and expansion of the BCM in rodents.

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