Original Article

Co-administration of Coenzyme Q10 and HMG-CoA Reductase Inhibitor Attenuates Oxidative Stress, TGF-β, TNF-α, Nitrite Content and MPO Levels against Experimentally-induced Diabetic Nephropathy in Rats

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ABSTRACT

Objectives: Diabetes is a major disease that causes a tremendous economic burden internationally. To tackle this horrible condition, good therapeutic intervention with nutraceutical is required. These include diabetic nephropathy, which ranges from chronic kidney disease to end-stage renal failure. Thus, this study used nutraceutical such coenzyme Q10 and HMG-CoA reductase inhibitor (rosuvastatin) to see how beneficial they are in treating diabetic nephropathy. **Materials and Methods:** The animal experiments were conducted to induce nephropathy by using streptozotocin-nicotinamide. Animals were divided into five groups such as control, diabetic control, coenzyme Q10, rosuvastatin and their combination. The renal function test was conducted by estimating uric acid, creatinine and urea. Antioxidant parameters were assessed by evaluating MDA, SOD, GSH and catalase activity in renal tissue. Levels of MPO, TGF-β, TNF-α and nitrite concentration were measured together with alterations in histopathology in the kidneys were observed in every treated animal. **Results:** Diabetic rats were studied for signs of nephropathy, and the results showed elevated levels of urea, creatinine, uric acid, MPO activity, TGF-β, TNF-α, nitrite and MDA as well as decreased levels of GSH, SOD and CAT activity. It was shown that when coenzyme Q10 and rosuvastatin were given combined, renal function tests improved far more quickly than when the two medications were given separately. **Conclusion:** This study found that combination therapy improved renal function and controlled free radical production, inflammatory mediators, and histological alterations that lead to kidney injury.

Keywords: Diabetic nephropathy, MPO activity, TNF-α, TGF-β, Coenzyme Q10.

INTRODUCTION

Most deaths and illnesses related to diabetes are caused by complications such as nephropathy and other cardiovascular diseases in those with type 2 diabetes.[1] In most of the cases, end-stage renal failure occurs due to diabetic nephropathy (DN).[2] As diabetic renal disease advances, proteinuria, a symptom of underlying DN, often develops swelling of the basement membrane and sclerosis of the mesangial cells in the kidneys are two of the most common symptoms of glomerular filtration rate decline. Increased levels of advanced glycation end products (AGEs), which lead to kidney damage in diabetics, have been linked to hyperglycemia.[3,4] It has been found that oxidative stress also play a key role in the development of DN.[5]

Presence of protein in urine and the development of chronic kidney disease (CKD) to end-stage renal disease (ESRD) can be slowed with angiotensin-converting

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enzyme inhibitors or angiotensin receptor antagonists. Many patients, on the other hand, fail to respond to these medications and develop ESRD at an early stage.[6] Dietary antioxidants may help delay or prevent diabetic complications, according to a prior study.[7,8]

Ubiquinone, another name for coenzyme Q10, is a vitamin-like molecule found in the phospholipid bi-layer of cell membranes, where it is lipid-soluble and hydrophobic. Different types of foods such as fish, red meat, nuts, and edible oils are rich with this nutrient.[9] Anti-inflammatory, antiulcer, antioxidant, and anti-diabetic effects of coenzyme Q10 have previously been demonstrated.[9-12] Additionally, 3-hydroxy-3-methylgluraryl-conzyme A (HMG-CoA) reductase inhibitors have numerous other favourable benefits, including the capacity to decrease cholesterol.[13]

Antioxidants like coenzyme Q10 and/or rosuvastatin were suggested to investigate their renoprotective effects in nephropathy. DN caused by STZ-nicotinamide was the focus of this study, which sought to see if coenzyme Q10 alone or in combination with rosuvastatin could provide protection.

MATERIALS AND METHODS

Drugs and Chemicals

Zydus Cadila, Ahmedabad, India, provided rosuvastatin and coenzyme Q10. Himedia (Mumbai, India) supplied the streptozotocin and nicotinamide. The study's kits were purchased from a standard company. Reagents and chemicals of analytical quality were utilized in the proposed work.

Experimental animals

This present research was permitted by IAEC which is official authority for the maintenance of experimental animals in all institutions. Wistar rats (200-250g) were housed in polypropylene cages and day night cycle of 12hr at 24°C with humidity of 35 to 60%. Water for drinking and diet for nutrition were provided.

Induction of diabetic nephropathy

The experimentally-initiated DN was conducted as per the earlier protocol.[14,15]

Experimental design

The experimental animals were divided into five groups which are as follows:

Experimental group 1 (a): Normal control group (distilled water10 ml/kg, p. o.)

Experimental group 2 (b): Diabetic control group

Experimental group 3(c): Coenzyme Q10 (10 mg/kg in 1% Tween 80 solution in water, p. o.)[16]

Experimental group 4 (d): Rosuvastatin (10 mg/kg, p. o)[17]

Experimental group 5 (e): Coenzyme Q10 + Rosuvastatin

DN was not carried out in experimental group 1 as it was in the other groups. The six-week treatment regimens for all of the aforementioned groups began on the seventh day following STZ-NA injection.

Glycated haemoglobin ($HbAC_1$) was calculated using whole blood. We used a standard diagnostic kit to assess the levels in the serum of uric acid, creatinine, and urea. For the purpose of collecting urine for testing, all animals were housed in metabolic cages for a period of 24 hr. In order to determine urinary micro protein levels, centrifugation of urine samples were carried out for five minutes at 1400 rpm and the supernatant was collected.

Renal indicators of oxidative stress include glutathione (GSH), catalase (CAT)/ superoxide dismutase (SOD) and malondialdehyde (MDA) were previously assessed by means of pre-existing methodologies.[18-21] The activity of MPO in renal tissue was assessed in accordance with the study's instructions.[22] The levels of TGF-β and TNF-α in kidney tissue homogenates were assessed making use of ELISA kits. Using the Griess reagent, we determined the quantity of nitrite in the protein-free supernatant of kidney homogenate.[23]

Histopathology

Kidney was extracted and kept in formalin (10 percent phosphate buffer), and processed for histological evaluation after the experimental animals from the aforementioned groups were sacrificed, as previously reported.[17]

Statistical analysis

For the assessment of degree of significance ($p < 0.05$) for all tests (one-way ANOVA), Bonferroni multiple comparison test was utilized. The data were displayed as Mean ± SEM.

RESULTS

Effect of Coenzyme Q10 and Rosuvastatin on Urinary Protein and Volume

In comparison with untreated control rats, diabetic untreated rats had higher urine volumes and urine proteins, as seen in Figures 1A-B, indicating kidney impairment. Neutraceutical or anti-hyperlipidemic treatment or their combination demonstrated a positive response in the reduction of urine volume and protein. However, coenzyme Q10 and rosuvastatin were administered together, urine protein levels were

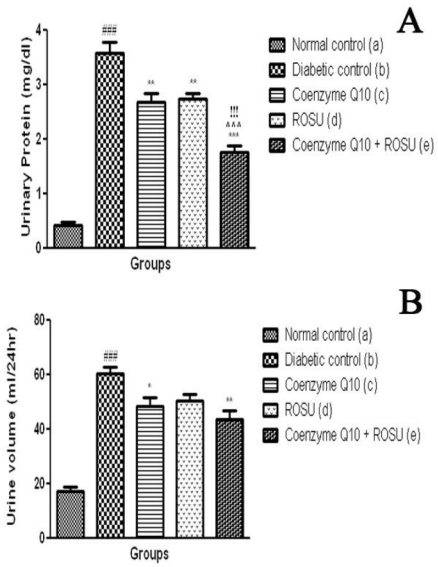

Figure 1: Effect of coenzyme Q10 and rosuvastatin on (A) urinary protein and (B) urine volume.

Values are expressed as mean ± SEM; n=6.
a vs. b, $^{###}p < 0.001$;
b vs. c, b vs. d and b vs. e, $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$;
c vs. e, $^{\wedge\wedge\wedge}p < 0.001$; d vs. e, $^{!!!}p < 0.001$

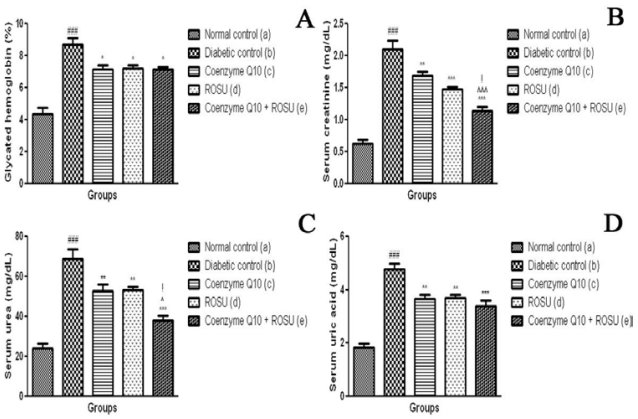

Figure 2: Effect of coenzyme Q10 and rosuvastatin on (A) glycated hemoglobin (B) serum creatinine (C) serum urea and (D) serum uric acid.

Values are expressed as mean ± SEM; n=6.
a vs. b, $^{###}p < 0.001$;
b vs. c, b vs. d and b vs. e, $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$;
c vs. e, $^{\wedge}p < 0.05$, $^{\wedge\wedge\wedge}p < 0.001$; d vs. e, $^{!}p < 0.05$.

significantly altered than monotherapy (coenzyme Q10 or rosuvastatin).

Effect of coenzyme Q10 and rosuvastatin on uric acid, urea, creatinine and HbA1c levels

Diabetic control rats had considerably greater levels of glycated haemoglobin compared to normal untreated animals. Rosuvastatin and/or coenzyme Q10 were found to lower glycated haemoglobin levels in diabetic animals than diabetic untreated rats. Glycated haemoglobin levels were not affected by coenzyme Q10 + rosuvastatin treatment in comparison with monotherapy.

Diabetic untreated rats had noticeable elevation in urea, uric acid, creatinine levels significantly as compared to those in normal untreated rats, indicating a serious decline in renal function. A single intraperitoneal injection of STZ-nicotinamide appears to impede kidney function, according to these data. Therapy with coenzyme Q10 and/or rosuvastatin resulted in considerable reductions in urea, uric acid, creatinine concentrations in diabetic rats. Coenzyme Q10 + rosuvastatin medication reduced serum creatinine and urea levels more than monotherapy did (Figure 2 A-D).

Effect of coenzyme Q10 and rosuvastatin on HDL-C, Triglyceride and Total cholesterol levels

The levels of total cholesterol, triglycerides, and HDL-C in diabetic rats were significantly different from those in non-diabetic rats. In comparison with diabetic untreated rats, administration of coenzyme Q10 and/or rosuvastatin lowered total cholesterol, triglycerides, and increased HDL-C level. Coenzyme Q10 in conjunction with rosuvastatin, on the other hand, had a greater impact on triglyceride and HDL-C levels than coenzyme Q10 alone (Figure 3 A-C).

Effect of coenzyme Q10 and rosuvastatin on TNF-α, myeloperoxidase activity, TGF-β and nitrite level

It was found that diabetic control rats had considerably greater renal levels of TNF-α, MPO activity, TGF-β, and nitrite content compared to study's normal animals. Aforementioned biomarkers were significantly reduced in renal tissue when treated with coenzyme Q10 and/or rosuvastatin than diabetic untreated animals. Coenzyme Q10 plus rosuvastatin reduced TNF-α and nitrite levels more than coenzyme Q10 or rosuvastatin alone in diabetic rats. Additionally, combination therapy was more effective than monotherapy of coenzyme Q10 at reducing MPO activity (Figure 4 A-D).

Effect of coenzyme Q10 and rosuvastatin on markers of oxidative stress in renal tissue

We discovered after six weeks that MDA, an oxidative stress marker, was higher in diabetes control rat's renal tissue than non-diabetic rats. Antioxidant like GSH, CAT and SOD were decreased in kidney tissue. Diabetic rats administered coenzyme Q10 and/or rosuvastatin had lower MDA and higher SOD, CAT, and GSH levels than diabetic control rats. MDA, SOD and GSH levels were considerably affected more when both used together than monotherapy of rosuvastatin (Figure 5 A-D).

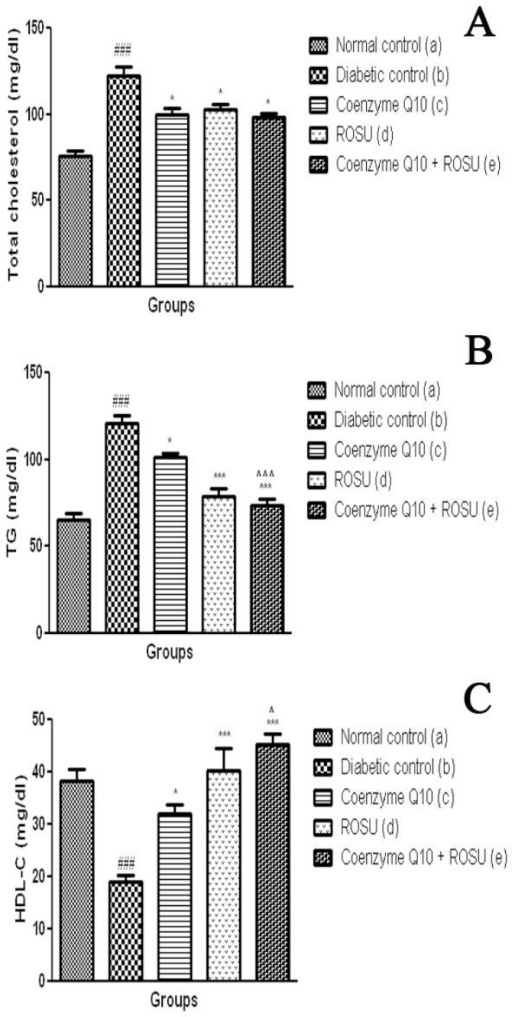

Figure 3: Effect of coenzyme Q10 and rosuvastatin on (A) Total Cholesterol (B) Triglyceride (C) HDL-C.

Values are expressed as mean ± SEM; n=6.
a vs. b, $^{###}p < 0.001$;
b vs. c, b vs. d and b vs. e, $^{*}p < 0.05$, $^{***}p < 0.001$;
c vs. e, $^{\wedge}p < 0.05$, $^{\wedge\wedge\wedge}p < 0.001$.

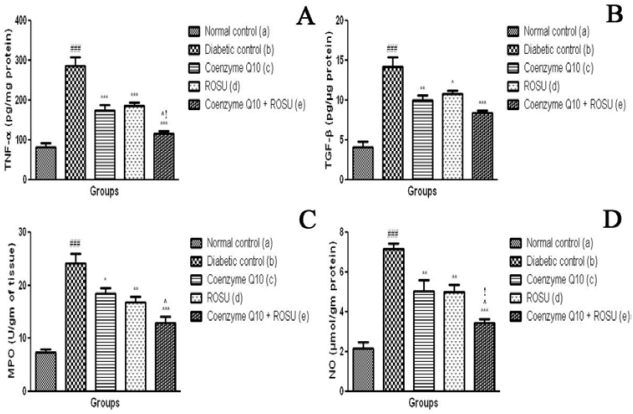

Figure 4: Effect of coenzyme Q10 and rosuvastatin on (A) TNF-α (B) TGF-β (C) MPO and (D) NO.

Values are expressed as mean ± SEM; n=6.
a vs. b, $^{###}p < 0.001$;
b vs. c, b vs. d and b vs. e, $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$;
c vs. e $^{\wedge}p < 0.05$; d vs. e, $^{!}p < 0.05$.

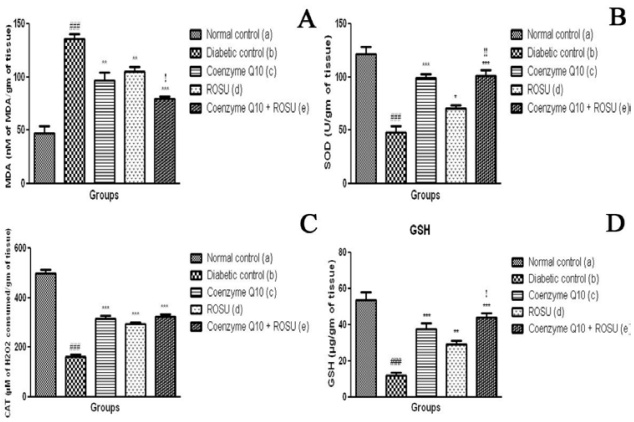

Figure 5: Effect of coenzyme Q10 and rosuvastatin on (A) MDA (B) SOD (C) CAT and (D) GSH.

Values are expressed as mean ± SEM; n=6.
a vs. b, $^{###}p < 0.001$;
b vs. c, b vs. d and b vs. e, $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$;
d vs. e, $^{!}p < 0.05$, $^{!!}p < 0.01$.

Histopathological Studies

Glomeruli and tubules in the normal control group were found to be normal in histological examination of kidney tissue. The thickening of the glomerular basement membrane (#), tubular vacuolization (*), interstitial fibrosis (+), and glomerulosclerosis ($) in diabetic rats were observed in the renal tissue sections. Moderate glomerular necrosis, interstitial fibrosis, tubular vacuolization, and glomerular basement membrane thickening were noted with coenzyme Q10 or rosuvastatin. No glomerulosclerosis was seen with coenzyme Q10 and rosuvastatin treatment, but mild tubular oedema, interstitial fibrosis, and thickening of the glomerular basement membrane (Figure 6).

DISCUSSION

It is among the main reasons of illness and death of mankind because of chronic renal disease.[24] In biomedical research, treating DN is a challenge. In our previous study, it was shown that experimentally induced DN characterised by elevated blood creatinine, BUN, uric acid, urine protein, TGF-β, TNF-α, MPO release and nitrite.[25,26] From the above study it was thought interesting to extend the our work by administering coenzyme Q10 and rosuvastatin in DN model. There is evidence that antioxidants like resveratrol and coenzyme Q10 can aid in the treatment of kidney disease, particularly in the case of DN.[27,28] Diabetic rats given coenzyme Q10 and rosuvastatin had considerably lower levels of elevated haemoglobin A1C, urea, creatinine, uric acid, and uninary protein than diabetic rats who were not given these treatment. These findings support the prior study that showed statins can help to prevent

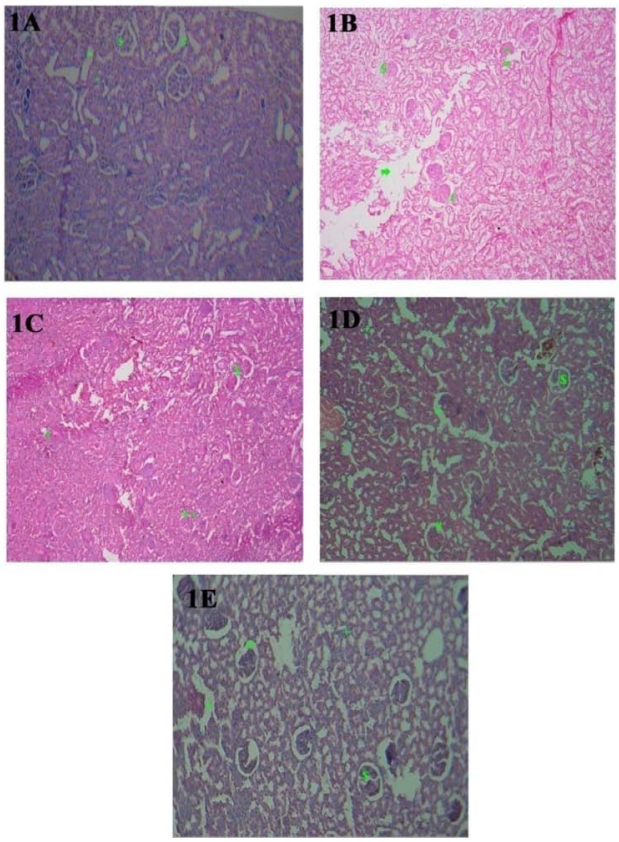

Figure 6: Light microscopy of kidney tissues from rats (HE stained kidney sections).

(A) Normal control group, (B) Diabetic control group, (C) Coenzyme Q10 (D) Rosuvastatin (E) Coenzyme Q10 + Rosuvastatin.

microalbuminuria and nephropathy.[29,30] Furthermore, in the study, the combination resulted in a significant alteration in lipid biomarkers. Despite being an anti-lipidemic medicine, rosuvastatin has been shown to prevent experimentally induced DN when given alone or in combination with an antioxidant such coenzyme Q10.

Reactive oxygen species (ROS) like hydroxyl radicals, superoxide anion, hydrogen peroxide, and lipid peroxidation products such as malondialdehyde have been associated to DN aetiology.[1,31,32] The current study found a rise in oxidative stress due to STZ-nicotinamide injection. GSH, CAT and SOD contents were considerably greater in rats with treatment of coenzyme Q10 and/or rosuvastatin. However, combined therapy had a stronger effect on oxidative stress indicators.

The progression of DN is mostly due to metabolic and hemodynamic variables. This effect is caused by TGF-β, TNF-α, and MPO release.[33,34] Diabetes rats treated with coenzyme Q10, rosuvastatin, or both had lower levels of kidney TGF-β, TNF-α and MPO than diabetes rats not treated. Concurrent dosing of coenzyme Q10 and rosuvastatin exhibited a greater renoprotective effect, reducing the above indicators. It has previously been shown that high nitrite levels are caused by peroxynitrite produced by NO interacting with superoxide radicals.[35] Our investigation found that coenzyme Q10 and rosuvastatin reduced kidney nitrite levels in diabetic rats.

CONCLUSION

These findings show that coenzyme Q10 or rosuvastatin have renoprotective effects against DN. The combination of coenzyme Q10 and rosuvastatin provided a greater renoprotective effect than monotherapy. This may be due to decreased lipid peroxidation, TGF-β, TNF-α, MPO, and nitrite levels in kidney tissue. Finally, combined therapy may help prevent DN.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

DN: Diabetic Nephropathy; **AGEs:** Advanced Glycation End Products; **CKD:** Chronic Kidney Disease; **ESRD:** End Stage Renal Disease; **ROS:** Reactive Oxygen Species; **STZ:** Streprozotocin; **NA:** Nicotinamide; **TGF-β:** Transforming Growth Factor - beta; **TNF-α:** Tumor Necrosis Factor - alpha; **MPO:** Myeloperoxidase; **BUN:** Blood Urea Nitrogen; **IAEC:** Institutional Animal Ethics Committee; **ELISA:** Enzyme Linked Immunosorbent Assay; **MDA:** Malondialdehyde; **SOD:** Superoxide Dismutase; **CAT:** Catalase; **GSH:** Glutathione; **SEM:** Standard Error of the Mean; **HMG-CoA:** 3-hydroxy-3- methylgluraryl-conzyme A.

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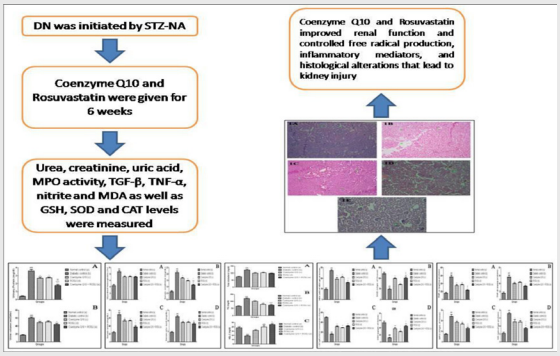
PICTORIAL ABSTRACT



SUMMARY

Diabetes is a global economic burden. Diabetes can cause chronic kidney disease and end-stage renal failure. Nutraceuticals are needed to treat this dreadful disease. The present study was employed to treat DN with coenzyme Q10 and rosuvastatin. Animals were given streptozotocin-nicotinamide to induce nephropathy. Five groups of animals: control, diabetes control, coenzyme Q10, rosuvastatin, and their combination. Serum Uric acid, creatinine, urea, MDA, SOD, GSH and catalase activities in renal tissue were evaluated. MPO activity, TGF-β, TNF-α, and nitrite levels, as well as kidney histology were assessed, in every treated animal. Diabetic rats revealed higher levels of urea, creatinine, uric acid, MPO activity, TGF-β, TNF-α, nitrite, and MDA and decreased GSH, SOD, and CAT activity. Coenzyme Q10 and rosuvastatin combination improved kidney function test by virtue of altering the abovementioned parameters.

About Authors

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