The present study aimed to investigate the possible protective effects of trimetazidine, sildenafil and coenzyme Q10 against experimentally-induced nephrotoxicity by either ischemia/reperfusion (I/R) or tacrolimus.

To fulfill the aim of the present study, two different sets of experiments were used.

I. Ischemia/reperfusion-induced nephrotoxicity:

Bilateral renal ischemia was induced for 45 min followed by 24 h of reperfusion. Five groups of rats were used. Group I and II both administered 1% Tween 80 (p.o.) and served as sham-operated and I/R control groups, respectively. Group III, IV and V were orally administered trimetazidine (10 mg/kg), sildenafil (1 mg/kg) and coenzyme Q10 (10 mg/kg), respectively, as prophylactic treatment for two weeks. At the end of the treatment period, animals were subjected to I/R, then blood and kidney samples were collected.

The nephroprotective potentials of the test agents were evaluated based on:

1. Relative kidney weight.
2. Renal function tests: blood urea nitrogen (BUN) and serum creatinine levels.
3. Electrolyte levels: serum calcium (Ca^{2+}), sodium (Na^{+}), potassium (K^{+}) and chloride (Cl^{-}).
4. Adenosine triphosphate content in kidney tissues.
5. Inflammatory biomarkers: kidney tumor necrosis factor-alpha (TNF-α) content and myeloperoxidase (MPO) activity.
6. Oxidative stress biomarkers: kidney malondialdehyde (MDA), glutathione (GSH) and total nitrite/nitrate (NO_x) contents.

7. Histopathological examination of kidney sections.

II. Tacrolimus-induced nephrotoxicity:

Five groups of rats were used. Group I received 1% Tween 80 (p.o.) and served as normal control. Group II received tacrolimus (5 mg/kg, p.o.) for three weeks and served as tacrolimus control. Group III, IV and V received trimetazidine (10 mg/kg, p.o.), sildenafil (2 mg/kg, p.o.) and coenzyme Q10 (10 mg/kg, p.o.), respectively, for three weeks concomitantly with tacrolimus (5 mg/kg, p.o.). At the end of the treatment period, blood and kidney samples were collected.

The nephroprotective potentials of the test agents were evaluated based on:

1. Renal function tests: BUN and serum creatinine levels.
2. Oxidative stress biomarkers: kidney MDA, GSH and NO_x contents, as well as superoxide dismutase (SOD) activity.
3. Immunofluorescence analysis of inducible nitric oxide synthase (iNOS) and endothelial nitric oxide synthase (eNOS) protein expression on kidney tissue sections.
4. Histopathological examination of kidney sections.

Results of the present study can be summarized as follows:

I. Protective effects of trimetazidine, sildenafil and coenzyme Q10 on ischemia/reperfusion-induced nephrotoxicity:

1. I/R significantly caused nephrotoxicity as manifested by a significant increase in relative kidney weight, BUN, serum creatinine and Na^+ levels coupled with decrease in serum Ca^{2+}, K^+ and Cl^- levels.
2. There was a significant decrease in kidney ATP content after I/R.
3. I/R resulted in increased kidney TNF-α content and MPO activity.

4. There was a significant increase in kidney MDA and NO_x contents, while kidney GSH content was significantly reduced after I/R.
5. Histopathological examination of kidney sections from I/R control demonstrated the presence of severe hemorrhage, hematoma, vacuolar degeneration and coagulative necrosis in renal tubules.
6. Trimetazidine, sildenafil and coenzyme Q10 improved kidney function as evidenced by the reduction in BUN and serum creatinine levels. In addition, they ameliorated electrolyte disturbances associated with I/R injury.
7. All the test agents showed anti-ischemic activity as evidenced by restoration of kidney ATP content.
8. All the test agents showed anti-inflammatory activity as evidenced by reduced kidney TNF-α content and MPO activity.
9. All the test agents showed anti-oxidant activity as evidenced by reduced kidney MDA and restored GSH content. However, NO_x content was significantly elevated higher than that of I/R control.
10. There was apparent improvement in histopathological features of kidney sections from trimetazidine, sildenafil and coenzyme Q10 treated groups as demonstrated by the regenerative changes in renal tubular epithelial cells.

II. Protective effects of trimetazidine, sildenafil and coenzyme Q10 on tacrolimus-induced nephrotoxicity:

1. Tacrolimus administration for three successive weeks caused nephrotoxicity as manifested by increased BUN and serum creatinine levels.
2. Tacrolimus significantly increased kidney MDA and NO_x contents, while kidney GSH content and SOD activity were significantly reduced.

3. Immunofluorescence analysis of kidney sections from tacrolimus control rats showed marked expression of iNOS and very weak expression of eNOS.
4. Histopathological examination of kidney sections from tacrolimus control rats demonstrated the presence of interstitial nephritis, vacuolation and collapse in renal tubules, in addition to endothelial swelling, vacuolation and hyalinosis in renal arterioles.
5. Trimetazidine, sildenafil and coenzyme Q10 significantly improved kidney function as evidenced by reduced BUN and serum creatinine levels.
6. All the test agents showed anti-oxidant activity as evidenced by reduced kidney MDA and restored GSH content and SOD activity. However, NO_x content was significantly elevated higher than that of tacrolimus control in both trimetazidine and sildenafil treated rats.
7. Immunofluorescence analysis of kidney sections from trimetazidine, sildenafil and coenzyme Q10 treated rats showed weak expression of iNOS and marked expression of eNOS.
8. Histopathological examination of kidney sections from trimetazidine, sildenafil and coenzyme Q10 treated rats demonstrated absence of interstitial nephritis together with marked improvement in the structure of renal tubules and vasculature.

Depending on the present results it can be concluded that:

1. Trimetazidine, sildenafil and coenzyme Q10 ameliorated renal damage induced by I/R or tacrolimus.
2. The protective effects of these agents are attributed to their anti-ischemic, anti-inflammatory and anti-oxidant properties.

3. These results suggest the therapeutic potential of these drugs in kidney transplantation to avoid graft rejection due to I/R or immunosuppressive drugs. Further clinical trials are needed to prove this claim.