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Evaluation of Protective Effect of Thymoquinone against Anti-tubercular Drug Induced Nephrotoxicity in Rats

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ABSTRACT

Present study was done to see the protective effect of thymoquinone against antitubercular drugs induced nephrotoxicity in rats. Thymoquinone significantly reduced serum urea, serum creatinine and K+ levels in ATT induced renal toxicity. No effect was seen in serum serum Na^+ level. Higher dose was found to reduce serum urea to greater extent than 5 mg TQ dose. The nephroprotective effect of thymoquinone was found to be significant. Hence the present study throws light on usefulness of TQ in protection against ATT induced renal injury. This might prove useful for combating the serious renal adverse effects of ATT regimen without eliminating the use of standard first line drugs.

KEYWORDS

Nephrotoxicity, Anti-tubercular drugs, Thymoquinone.

INTRODUCTION

Tuberculosis (TB) is a major global health threat as per the World Health Organization (WHO). It is the leading cause of death by a single treatable infectious disease; killing approximately 5,000 people per day throughout the world. In order to kill the persistent or slow growing strains of Mtb, the continuation phase of the treatment is essential.TB can be treated effectively by using the first line drugs which are Isoniazid (INH), Rifampin (RIF), Pyrazinamide (PZA) and Ethambutol (ETH).[1]

Among the adverse effects of Anti-Tubercular Therapy (ATT) Rifampcin causes hemoglobingnuria, hematuria, renal insufficiency and sometimes acute renal failure. Sterptomycin(S) caused toxicity results from accumulation and retention of aminoglycoside in the proximal tubular cells.

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The world health organization (WHO) estimates that 80% of the populations in some Asian and African countries are mostly dependent to traditional medicine for their health cares (Traditinal medicine Fact Sheet WHO 2008). In other words, about 4 billion people in the world rely on plants as source of drugs. Among the promising medicinal plants, *Nigella sativa*, also known as Black seeds and Black cumin, has been called the "Blessed Seed" for its miraculous curing ability. These studies found Black Seed to have analgesic, antilipemic, post coital contraceptive, diuretic and antihypertensive, bronchodilator and calcium antagonist, histamine release inhibitor, hepatoprotective, antihelminthic, antifungal, antimicrobial (against a wide range of organisms), and anticancer activities.[2] Thymoquinone is the active principle of *Nigella sativa* has been used for medicinal purpose for more than two thousand years. It has been demonstrated that the *Nigella sativa* and its chemical components produce a variety of pharmacological actions such as anti-inflammatory, anticancer and antioxidant

properties and many of these effects are due to TQ. Thymoquinone is the active principle of *Nigella sativa* has been used for medicinal purpose for more than two thousand years. Hepatoprotective role of *Nigella sativa* has been well documented. Nephroprotective property has also been demonstrated.[3] Since oxidative stress plays an important role in drug induced renohepatotoxicity, it was hypothesized that active constituent of *Nigella sativa,* Thymoquinone (TQ) could protect ethambutol and streptomycin induced nephrotoxicity. To investigate this hypothesis, this study was undertaken to investigate whether treatment of TQ ameliorates ATT induced nephrotoxicity. The aim of the study was to study the effect of Thymoquinone on ATT induced altered renal function. The objectives of the study were to study the effect of Thymoquinone on ATT induced altered renal function test parameter, to study the effect of Thymoquinone on ATT induced changes in renal histopathology.

MATERIAL AND METHODS

Thymoquinone, ethambutol(E), streptomycin(S), were procured from Sigma Aldrich company USA. The animals were male Wistar rats (weighing 180-250gm). Rats were obtained from CDRI, (The Central Drug Research Institute) Lucknow. They were housed in polycarbonate cages with a 12 day –night cycle, temperature of 22º-C ±2 º-C and humidity of 45%-64%.The animals were fed with a standard pellet diet (Hindustan Lever Ltd, Mumbai, India) and water ad libitum. Animals were divided in following groups containing 8 rats each.

Group1: Normal Control: Animal received distilled water orally for 28 days.

Group 2: Renototoxicity was produced using Ethambutol & Streptomycin in a dose of 200,150 mg/kg respectively for 28 days.

Group: 2a Received Thymoquinone extract in dose of 5mg/kg/day with Ethambutol & Streptomycin in a dose of 200 & 150mg/kg respectively for 28 days. Streptomycin was given i.m. whereas other drugs were administered orally.

Group: 2b Received thymoquinone extract in dose of 10mg/kg/day with Ethambutol & Streptomycin in a dose of 200 & 150mg/kg respectively for 28 days. Streptomycin was given i.m. whereas other drugs were administered orally.

At the end of day 28 blood of 2 ml was collected by cardiac puncture. The blood was allowed to clot and centrifuged at 350 rpm for 10min. The serum was separated and used for assay of study parameters. After blood collection rats were sacrificied for collection of renal tissue for the histopathological examination.

Results were tabulated and subjected to descriptive analysis using ANOVA .Statistical analysis was done using SPSS 16.0 software (p value <0.05 was considered as significant). The power of study was taken as 80%.

OBSERVATIONS

Serum Urea

Observations made are tabulated in Table No.1. TQ significantly decreased serum urea level. 10mg TQ reduced serum urea level to significantly (p=0.012) greater extent than 5mg TQ. TQ significantly decreased serum urea level. 10mg TQ reduced serum urea level to greater extent than 5mg TQ.

Serum Creatinine

Observations made are tabulated in Table No. 1. TQ significantly decreased serum creatinine level. Reduction in serum creatinine level by 10mg TQ dose was similer to that by 5mg TQ dose.

a-P<.05 as compared to control, b-P<.05 as compared to group.1, c-P<.05 as compared to group.4,d-P<.05 as compared to group.2, e-P<.05 as compared togroup.5.

Administration of HRZES for consecutively 28 days caused significant Atrophy of glomeruli, interstitial degeneration and inflammation of tubule. Treatment group of *Thymoquinone* (10

mg/kg) showed normal renal architecture. Treatment group *Thymoquinone* of 5 mg/kg showed near normal architecture of kidney with persisting mild chronic inflammation. No significant histopathological changes were seen in groups receiving HRZ. The histopathlogical change are depicted in figure 1,2,3,4.

Table 1 : Renal Function Test

Group	**Serum Urea (mg/dl) (mean ±SD)**	**Serum Creatinine (mg/dl) (mean±SD)**	**Serum Na^+ (m.mol/l) (mean± SD)**	**Serum K^+ (m.mol /l) (mean ±SD)**
Ethambutol And Streptomycin	101.13 ±7.35 a,b,c	2.10±0.22 a,b,c	125.62 ±4.30	5.91± 0.30 a
ES + 5TQ	72.25± 7.16 a,c	1.65±0.15 a,c	131.±1.67	5.25± 0.14 a,c
ES + 10TQ	51.88± 4.01 a,c,e	1.45±0.09 a,c	133.38 ±1.50	5.08± 0.06 a,c
Control	29.50± 2.97	0.96±0.17	138.13 ±2.29	3.95± 0.22

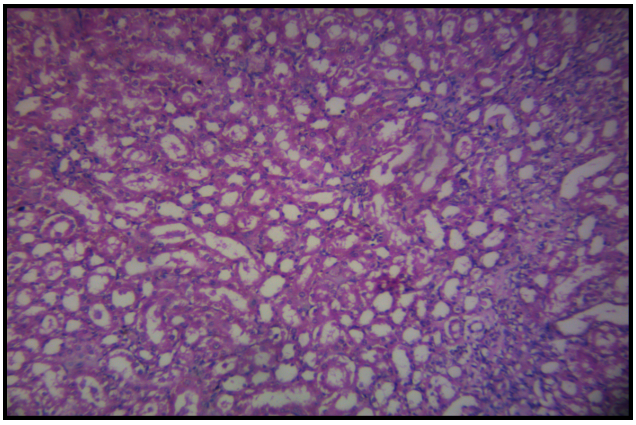

Figure 1: HRZES 5mg TQ group (H & E 40x)

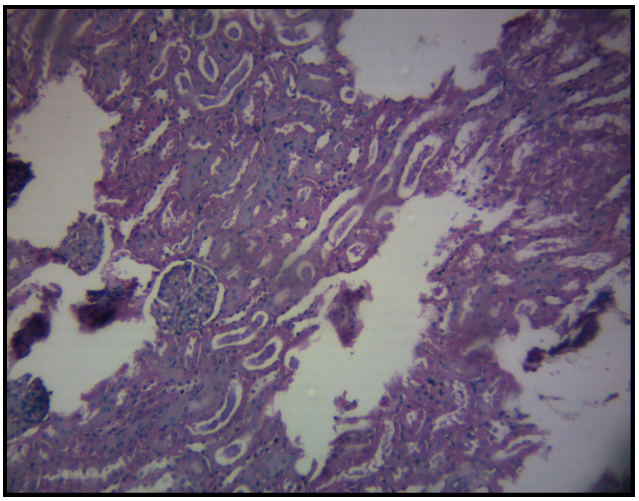

Figure 2: HRZES group (H & E 40x)

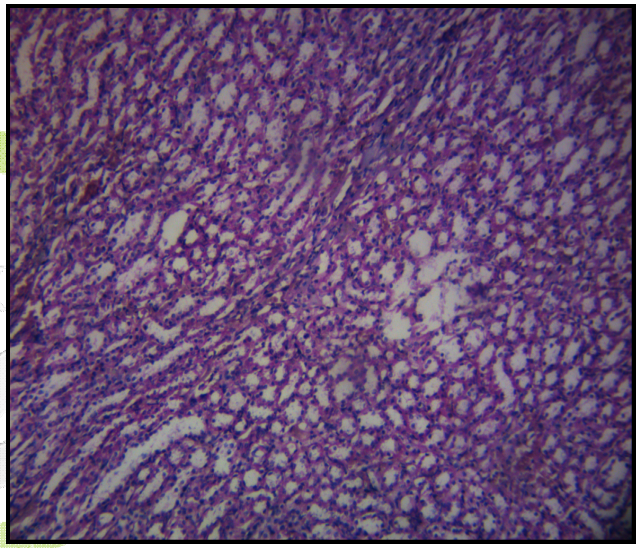

Figure 3: HRZES 10mg TQ group (H & E 40x)

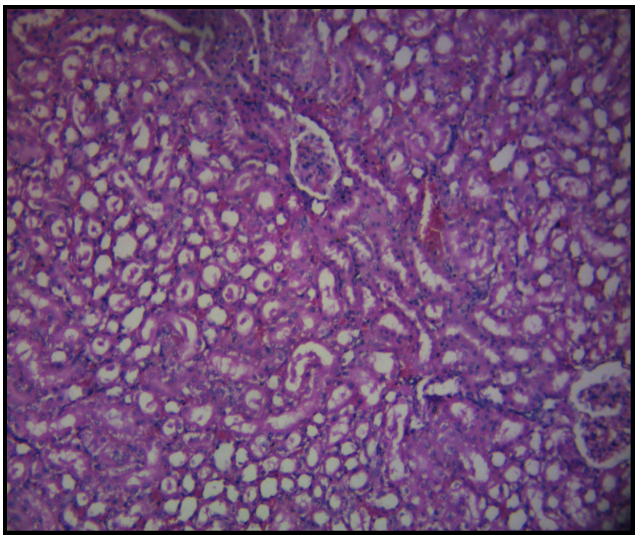

Figure 4: Control group (H & E 40x)

DISCUSSION

Thymoquinone has also been documented to protect renal tissue by significantly reducing the side effect of nephrotoxicity associated with various medications[4]. In one study TQ synergizes with its nephroprotective effect against cisplastin induced acute kidney injury in rats Oxidative stress has been implicated as a potential responsible mechanism in the pathogenesis of vancomycin (VCM)-induced renal toxicity[5]. TQ produces a protective mechanism against VCM-induced nephrotoxicity and suggest a role of oxidative stress in pathogenesis.

In present study HRZES combination was observed to produce higher toxicity than HRZ combination. TQ significantly reduced serum urea, serum creatinine in ATT induced renal toxicity. 10 mg TQ dose was found to reduce serum urea to greater extent than 5 mg TQ dose. Reduction in serum creatinine 10 mg TQ dose was similar to that by 5 mg TQ dose when toxicity was induced by HRZES. Hence the nephroprotective effect of thymoquinone was found to be similar to that observed in above studies

In present study TQ has been observed to effectively control serum level of Urea, Creatinine .According to the previous studies, it might be due to the role of TQ as antioxidant and due to the preservation of intracellular glutathione or may be related to inhibition of thromboxane B2 production.[6]

Hence the present study throws light on usefulness of TQ in protection against ATT induced renal injury. Further studies need to be conducted to determine the full impact of TQ on kidney against ATT induced damage. This might prove useful for combating the serious renal adverse effects of ATT regimen without eliminating the use of standard first line drugs.

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