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The impact of Thymoquinone obtained from seeds of Nigella sativa, on hepatic and renal function

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A B S T R A C T

Introduction: Nigella sativa (habbat al-baraka) is commonly used in different countries for many diseases. It has been proved effective scientifically for the treatment of many ailments. The seeds of this plant have been utilized in various traditional medicine systems across the globe for centuries, treating a wide array of ailments ranging from digestive issues to respiratory conditions. The primary bioactive compound in Nigella sativa is thymoquinone (TQ), which is largely responsible for its medicinal properties. It plays a pivotal role in its therapeutic effects across a range of health issues, making it a subject of ongoing research and interest in the field of complementary medicine

Objectives: To evaluate the effects of thymoquinone on liver enzyme levels (e.g., Serum bilirubin, SGPT, alkaline phosphatase) and overall hepatic function in experimental models.

To investigate the influence of thymoquinone on kidney function markers, including serum creatinine and urea levels.

Methods: Thirty rabbits of local breed, weighing 1-1.5kg were used. Animals were divided into 3 groups 1, 2 & 3. Blood samples were taken from group 1 for liver & kidney function tests as control. Thymoquinone (TQ) 5 mg/kg & 10 mg/kg body weight were administered intraperitoneally for 45 days in groups 2 & 3 respectively. Blood samples were taken & tested for liver & kidney function by relevant kits. Results obtained were compared with control groups. P values were calculated

Results: The results showed that the P values for both low & high doses on liver & kidney function were non-significant after comparison with the control group showing that both the doses were safe on the above parameters.

Conclusions: The findings from this study indicate that both low and high doses of the tested substance (thymoquinone) demonstrate a non-significant impact on liver and kidney function when compared to the control group. Given that both dosages were well-tolerated and did not lead to significant alterations in liver and kidney function, it can be concluded that the substance is safe for use at the administered doses. Further studies may be warranted to explore long-term effects and potential benefits in different populations, but the current results provide a solid foundation for its continued investigation and application in clinical settings.

Keywords:*Thymoquinone; Liver & kidney function; Nigella sativa*

INTRODUCTION

Commonly used drugs have several side effects like osteoporosis, disturbance in small intestine flora, kidney stones, anaemia, and increased chance of occurrence of drug-induced diseases such as gastric cancer. Therefore, due to the side effects of conventional medicine, the use of natural products in the treatment of various diseases has been the center of attention in the last few decades. Ranunculalacae is the botanical family to which Nigella Sativa belongs. In the light of Hadeeth "Use this Black seed, it has a cure for every disease except death" (Sahih Bukhari), It commonly grows in different countries like Europe, Middle East, and Asia. In different countries it is called by different names, for example, Habbat Al-baraka, Al-habba Al-suda, Kali jeera. Nigella sativa (N. sativa) seeds are frequently used in Saudi Arabia, Middle East, and many other countries since ancient times as a natural remedy for many diseases. Nigella sativa seeds contain many active ingredients including thymoquinone (TQ) (Nigellone) [1]. Keeping in view, multiple uses of N. sativa, many investigators conducted various in vitro & in vivo studies on laboratory animals & human beings to know their pharmacological actions. Thymoquinone has been proved to have anti-inflammatory action [2]. Some researchers have proved its analgesic and anti-pyretic activity [3]. In multiple studies it has been proved to have antimicrobial activity [4,5,6,7].

In many researches the scientists have found strong antifungal activity [8,9,10]. According to a study, it has been proved scientifically that thymoquinone has hypoglycaemic effects and is good for treatment of diabetes mellitus [11]. According to another research, the antituberculosis activity has been documented [12].

TQ administration has proved to have hypotensive effect and is good for treatment of hypertension [13]. A study conducted by many authors proves that thymoquinone reduces gastric acidity & is most effective in the treatment of hyper gastric acidity condition like peptic ulcer or gastro- oesophageal reflux disease [14]. Neuroprotective activities of thymoquinone are well documented [15].

OBJECTIVES

To evaluate the effects of thymoquinone on liver enzyme levels (e.g., (Serum bilirubin, SGPT, alkaline phosphatase) and overall hepatic function in experimental models.

To investigate the influence of thymoquinone on kidney function markers, including serum creatinine and urea levels.

METHODS

Thirty rabbits of the local breed were selected for the present study. It was conducted in Department of Pharmacology, Saidu Medical College, Swat, KPK, Pakistan. Healthy animals of both sexes were used in the study. All the agents were injected intraperitoneally (I.P) on the bases of per Kg body weight. The animals were divided into 3 groups each containing 10 animals. Group 1 was considered as the control group. Blood samples were taken from this group. With the help of specific Kits kidney function tests (blood urea & serum creatinine) & liver function tests Serum bilirubin, SGPT, alkaline phosphatase) were estimated. and values recorded as control. Group 2 (Low dose group) was administered Thymoquinone 5 mg/kg body weight & group 3 (High dose group) with Thymoquinone 10 mg/kg body weight for 45 days twice daily. After 45 days, blood samples were taken from both groups 2 & 3. With the help of specific kits kidney function tests (blood urea & serum

creatinine) & liver function tests (Serum bilirubin, SGPT, alkaline phosphatase) were estimated. Values thus obtained were recorded in table 1 and 2.

Mean values and standard error of mean of group 1 & 2 were recorded in table1 & those of group 1 & group 3 were recorded in table 2.

The data thus obtained was subjected to statistical analysis by comparing the mean values of all the parameters with control for any significant difference. The data was entered into SPSS-IBM Version 19.

P value of <0.05 were considered to be statistically significant & more than 0.05 were non- significant.

RESULTS

LOW DOSE STUDIES: Effect of Thymoquinone on the kidney and liver function in low doses

The values for kidney function (serum creatinine, blood urea) and liver function (Serum bilirubin, S.G.P.T, alkaline Phosphatase) were found for the control group. Similar values for all the above parameters were obtained after 45 days of treatment with extract 5 mg/kg body weight. The mean values for serum creatinine before and after extract administration was 1.35 ± 0.024 and 1.35 ± 0.024 mg/dl, for blood urea it was 34.3± 0.87 and 36.7± 0.42 mg/dl, for serum billirubin it was 0.18± 0.03 mg/dl and 0.19 ± 0.02 mg/dl, for S.G.P.T it was 36.9± 0.90 I.U/L and 35.4 ± 0.54 I.U/L and for alkaline phosphatase it was 77.00 ± 0.63 I.U/L and 76.5± 0.45 I.U/L respectively. The changes in all these parameters were statistically non -significant (P>0.5). These changes are shown in Table 1.

Table 1: Effects of extract Thymoquinone on kidney function and liver function in rabbits after 45 days treatment by injecting the extract 5mg/kg twice daily as compared to control group.

	Values of Kidney function		**Values of liver function tests**		
Tests	Serum Creatinine (mg/dl)	Blood Urea (mg/dl)	Serum bilirubin (mg/dl)	S.G.P.T (I.U/L)	Alk. Phosphatase (I.U/L)
Control (before injecting the extract)	1.35± 0.024 (10)	34.3± 0.90 (10)	0.18± 0.03 (10)	36.9± 0.90 (10)	77.00± 0.63 (10)
Thymoquinone	1.35± 0.02 (10)	36.7± 0.42 (10)	0.19± 0.08 (10)	35.4± 0.541 (10)	76.5± 0.45 (10)

P. Values	>0.5	>0.5	>0.5	>0.5	>0.5

Each value represents the mean of the total observations.
Figures in parenthesis indicate the number of animals in each group.
± Indicates standard error of mean
P. Values between Control group and *Thymoquinone* treated group

	Kidney function tests		**Liver function tests**		
	S. Creatinine (mg/dl)	Blood Urea (mg/dl)	S. Bilirubin (mg/dl)	S.G.P.T (I, U/L)	Alk: phosphatase (I.U/L)
Control (before injecting the extract)	1.35± 0.024 (10)	34.3± 0.90 (10)	0.18± 0.03 (10)	36.9± 0.90 (10)	77.00± 0.63 (10)
Thymoquinone	1.24± 0.01 (10)	36.5± 0.64 (10)	0.19± 0.02 (10)	37.3± 0.65 (10)	76.8± 0.64
P Value	P>0.5	P>0.5	P>0.5	P>0.5	P>0.5

HIGH DOSE STUDIES

The mean values for kidney function (serum creatinine, blood urea) and liver function (Serum bilirubin, S.G.P.T, alkaline Phosphatase) were already found for the control group. Similar values for all the above parameters were obtained after 45 days treatment with Thymoquinone 10 mg /kg body weight. The mean value for serum creatinine before and after extract administration was 1.35 ±0.024 and 1.24 ± 0.010 mg/dl, for blood urea it was 34.3± 0.90 and 36.5 ± 0.64 mg/dl, for serum bilirubin it was 0.18± 0.03 mg/dl and 0.19 ± 0.02 mg/dl, for S.G.P.T it was 36. ± 0.90 I.U/L and 37.3 ± 0.65 I.U/L and for alkaline phosphatase it was 77.1 ± 0.63 I.U/L and 76.8 ± 0.64 I.U/L respectively. The changes in all these parameters were statistically non- significant (P>0.5). These changes are shown in Table 2.

Table 2: Effects of Thymoquinone on kidney function and liver functions in rabbits after the administration of 10 mg/kg body weight intraperitoneally twice daily for 45 days as compared to control.

Each value indicates mean of the total observations.
Figures in parenthesis indicate the number of animals in each group.
± Indicates standard error of mean.
P Value between the means of control group and after 45 days treatment with extract from *Thymoquinone*.

DISCUSSION

Herbal medicine has been traditionally used for the treatment of different ailments. *Nigella sativa* (*N. sativa*) is used as an important drug in traditional medicine like Unani and Ayurveda [16].

In a study the hepatoprotective effect of thymoquinone has been confirmed with the help of scientific research [17]. Our study is in complete agreement with the above study in which we have also proved that thymoquinone is safe for liver and kidney.

The protective effect of *N. sativa* (0.2 ml/kg, intraperitoneal (I.P) against hepatic ischemia/reperfusion injury was investigated in rats. Levels of serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), and lactate dehydrogenase (LDH) & total antioxidant capacity were measured. The results showed that *Sativa* has no adverse effect against hepatic ischemia/reperfusion injury and could act as a potent antioxidant agent [18]. Our study is in complete agreement with the above study in which we have also proved that thymoquinone is safe for liver by testing liver function. Besides our study also shows that thymoquinone, the main ingredient of Nigella sativa, is also safe for kidneys both in high & low doses.

In another study, the effects of *N. sativa* (0.2 mL/ kg, (I.P) on cholestatic liver injury were evaluated in rats. The authors found that *N. sativa* has a preventing effect on cholestatic liver injury in rats. The results also suggested that the reduction of neutrophil infiltration and oxidative stress in the liver was probably responsible for this protective effect [19].

In addition, the protective effect of *N. sativa* seeds (5% of the diet weight) against lead acetate-induced liver toxicity was documented in male rats. It improved biochemical and histopathological profiles and reduced damage areas [20].

The protective effects of *N. sativa* oil (0. 2 ml/kg, I.P) on carbon tetrachloride (CCl4)-induced liver toxicity were studied in rats. Findings showed that *N. sativa* enhanced antioxidant defense system activity in CCl4-treated rats [21].

The effect of TQ (10 mg/kg, orally) on hepato-renal dysfunction was evaluated in rats. According to this study, TQ has a protective action on renal ischemia/reperfusion-induced damage [22]. The protective effect of TQ against tert-butyl hydro peroxide toxicity was evaluated in isolated rat hepatocytes. The results showed that pre-treatment of hepatocytes with 1 mM TQ reduced the leakage of cytosolic enzymes, ALT and AST [23].

Oral administration of a single dose (100 mg/Kg) of TQ to male Swiss albino mice resulted in a protective effect against CCl4-induced hepatotoxicity which was probably due to the antioxidant property of TQ [24].

In another study, the protective effect of TQ (9 and 18 mg/kg, I.P) on Aflatoxin B1 -induced liver toxicity was evaluated in mice. Findings of this study showed protective effect. This effect may be mediated through increased resistance to oxidative stress [25].

TQ (10 mg/kg, oral) protective effect on sodium fluoride-induced hepatotoxicity improved the antioxidant status and reduced the alterations in biochemical parameters. This protective effect was perhaps due to the ability of TQ to antagonize increased lipid peroxidation (LPO) and in turn stabilizing the integrity of the cellular membranes and decreasing the leakage of liver enzymes [26].

TQ (0.5, 1 and 2mg/kg/day, oral) combated acetaminophen-induced hepatotoxicity and decreased acetaminophen-induced hepatotoxicity in a dose-dependent manner as evidenced by reduction in serum ALT activities. The hepatoprotective effect of TQ was probably mediated by increased resistance to oxidative stress [27].

In a clinical study, the effects of ethanolic extracts of *N. sativa* was evaluated in patients with hepatitis C virus (HCV) infection. HCV patients receiving a capsule containing 500 mg of *N. sativa* extract use twice daily. The results showed that extract had a significant effect in HCV patients as shown by a decrease in viral load and restoration of liver functions [28].

Long-term (6 months) administration of aspartame induced toxic effects on hepato-renal function and structure, whereas garlic, melatonin and thymoquinone resulted in hepato-renal ameliorative and protective effects [29].

Our study is in complete agreement with nearly all above studies regarding the hepato-renal protective effects of thymoquinone obtained from the seeds of Nigella Sativa.

CONCLUSION

Our study proves that the Thymoquinone (TQ) is safe for kidney and liver both in high and low doses. This finding is crucial as it supports the therapeutic potential of TQ without compromising organ health, thereby reinforcing its viability as a candidate for further clinical applications.

However, while these results are promising, they highlight the necessity for additional clinical investigations to thoroughly evaluate TQ's safety profile in human subjects. Such studies should aim to assess long-term effects, optimal dosing strategies, and any potential interactions with other medications or underlying health conditions.

In summary, thymoquinone presents a favorable safety profile that warrants further exploration in clinical settings, particularly given its wide array of pharmacological benefits. Continued research will be essential to establish comprehensive guidelines for its use in human health and disease management.

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