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Research Article

A study of effect of *Nigella sativa* oil in paracetamol induced hepatotoxicity in albino rats

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ABSTRACT

Background: Acetaminophen (paracetamol) toxicity is a common cause of drug-induced hepatotoxicity in children and adults. Specific treatment of paracetamol induced hepatitis is available in the form of N-acetylcysteine only. *Nigella sativa* (NS) is used for the treatment of various ailments. Many studies have shown that NS plant has hepatoprotective potential. Hence, this study study was carried out to explore the prophylactic and therapeutic effect of NS oil against hepatotoxicity induced by paracetamol.
Methods: Hepatotoxicity was induced in rats by paracetamol and it was assessed using biochemical parameters such as serum (Sr.) alanine aminotransferase (ALT), Sr. aspartate aminotransferase (AST), Sr. bilurubin, Sr. alkaline phosphatase, and Sr. total protein. In addition, histopathological score was also assessed. The therapeutic and prophylactic effect of NS oil administration on paracetamol induced hepatotoxicity was investigated by using above mentioned biochemical and histopathological parameters.
Results: Paracetamol administration leads to rise in serum liver enzymes ad fall in Sr. total protein levels. NS oil has heptoprotective effect. NS oil significantly reversed changes in serum levels of AST, ALT, alkaline phophatase, bilurubin, and total protein produced by paracetamol. Furthermore, histopathological changes produced by paracetamol were reversed.
Conclusion: This study demonstrated that NS oil has hepatoprotective effect. NS oil administration can prevent or reverse the hepatotoxicity induced by paracetamol.

Keywords: Hepatotoxicity, *Nigella sativa*, Paracetamol

INTRODUCTION

Drugs are important and most common cause of hepatic injury.[1] This is not surprising, as the liver is predominant site of drug metabolism. Drug induced liver diseases is a major health problem in human beings. More than 900 compounds including chemicals, drugs, toxins and herbal medicines are involved in producing hepatotoxicity and these can produce the full spectrum of liver injuries.[2] Drug induced hepatotoxicity is one of the most common reasons for a drug to be withdrawn from the market. Several drugs were found to have hepatotoxic potential e.g. paracetamol, antitubercular drugs, antineoplastic agents, antiretroviral agents, antiepileptic drugs etc.[3]

Acetaminophen (also known as paracetamol, N-acetyl-p-aminophenol) is a popular antipyretic and analgesic found in many over-the-counter and prescription products, including various cough-and-cold remedies. It is remarkably safe in recommended doses, but because of its wide availability, deliberate or accidental overdoses are common. Paracetamol overdose may cause severe hepatotoxicity and sometimes even fatal liver failure and centrilobular hepatic necrosis in humans and experimental animals. Even therapeutic doses of paracetamol sometimes induce hepatic damage in the presence of risk factors such as chronic alcohol use, malnutrition, fasting and concomitant intake of hepatotoxic drugs. More recently concerns have been raised against toxicity of paracetamol

when used in fixed dose combinations. And dose of paracetamol is limited to 325 mg in fixed dose combinations with other analgesics.

A significant amount of evidence has pointed to the potential involvement of oxidative stress in acetaminophen toxicity.[4] Acetaminophen induced hepatotoxicity is caused by generation of reactive metabolite N-acetyl-p-benzoquinone imine (NAPBQI). It depletes glutathione and covalently binds to cellular proteins including a number of mitochondrial proteins and inhibition of mitochondrial respiration has been investigated as an important mechanism in acetaminophen toxicity.[5] When glutathione is depleted after large doses of acetaminophen or in malnourished people, the toxic metabolite accumulates, resulting in liver damage. N-acetylcysteine has been used for several decades and has proven to be the only antidote of choice in treating paracetamol-induced hepatotoxicity.

Nigella sativa (NS) (Family: Ranunculaceae), commonly known as black seed, black cumin or "Habbatul Barakah," is an erect herbaceous annual plant. The ripe seeds of NS are also known as Kalajira or Kalaonji. The seeds of NS have been used traditionally for centuries in the Middle East, Northern Africa and South Asia (including India) for the treatment of various diseases.[6,7]

Black seed is a complex substance of more than 100 compounds, some of which have not yet been identified or studied. Thymoquinone was identified as the main component (up to 50%) besides it contains *p*-cymene (40%), α-pinene (up to 15%), dithymoquinone and thymohydroquinone.[8] Furthermore, the essential oil contains significant (10%) amounts of fatty acid ethyl esters. On storage, thymoquinone yields dithymoquinonene and higher oligocondensation products (nigellone). Commercial nigella oil may also contain parts of the essential oil, mostly thymoquinone, by which it acquires an aromatic flavor.

NS extract and its active principle like thymoquinone have been shown to possess protective effect against hematological, hepatic and renal toxicities induced by anticancer drugs.[9] The mechanism of the hepatoprotective action of thymoquinone is not certain, but may be related to the preservation of intracellular glutathione, the depletion of which by oxidative stress is known to increase the susceptibility of cells to irreversible injury. It has been shown that pretreatment of rats with NS oil for 4 weeks was effective in protecting against carbon tetrachloride and D-galactosamine-induced hepatic damage.[10]

It is hypothesized that the beneficial effects of black seed and other herbs are most likely due to their protection against cellular damage caused by oxidative stress. The antioxidant properties of black seed oil are recently reviewed.[11] It has been shown that some of the compounds isolated from black seed have appreciable free radical scavenging properties.[6] This antioxidant property of black seed has also been reported by other investigators.[12-15]

NS oil has been shown to have hepatoprotective effect against carbon tetrachloride and D-galactosamine induced toxicity.[10] However in the best of our knowledge, there are no references regarding the effect of NS oil on paracetamol induced hepatotoxicity in rats. Furthermore, data is available on administration of NS extract by oral dose. However, very few studies provide information about intraperitoneal administration of NS oil. Hence, the work was planned to study the effect of NS oil on paracetamol-induced hepatotoxicity in rats.

METHODS

Animals

Male albino rats of either sex weighing 200-350 g were used for the experiment. Animals were kept on a balanced diet and water *ad libitum* in a well-ventilated animal unit. Permission for conduction of the study was taken from Institutional Animal Ethics Committee. The care and procedures adopted for the present investigation were in accordance with the approval of Institutional Animal Ethics Committee.

Study material

Hepatotoxic drug

Paracetamol was used to induce hepatotoxicity. It was obtained in tablet form from market. Paracetamol was purchased from the market with name pyremol of alembic limited of batch no. 5033510 dated October 2005 and expiry date September 2008. It was used in a dose of 33 mg/kg by the oral route.[16]

NS oil

NS oil was purchased from the market of Mohamodia products Karimnagar (Andhra Pradesh) of batch no. 006 dated 7-2003. It was used in the dose of 0.2 ml/kg i.p. daily.[17]

Study design

Study was conducted in two parts. After 10 days adaptation period, Rats were divided into groups. Each group contains six animals (n = 6). The groups were treated as follows:

Part A (Prophylactic effect)

In the first part of study, hepatoprotective effect of NS oil was studied by dividing rats into three groups. Each group contained 6 rats.

Group A-I - vehicle control: Group A-II - treated with paracetamol for 4 weeks: Group A-III - treated with paracetamol + NS oil for 4 weeks.

At the end of treatment, blood sample was collected by cardiac puncture for liver function tests. Liver of all rats was also removed for histopathological examination.

Part B (Therapeutic effect)

In the second part of study, therapeutic effect of NS oil was studied by dividing rats into five groups. Each group contained 6 rats.

Group B-I - Paracetamol treated group: Group B-II - Paracetamol for 30 days then no treatment for 15 days: Group B-III - Paracetamol for 30 days then NS oil for 15 days: Group B-IV - Paracetamol for 30 days then no treatment for 30 days. Group B-V - paracetamol for 30 days then NS oil for 30 days. Group A-II and B-I were the same group.

At the end of treatment, blood sample was collected by cardiac puncture for liver function tests. Liver of all rats was removed for histopathological examination.

Collection of blood and liver samples

At the end of the study period, after overnight fasting, blood was collected directly from the heart of rat anaesthetized with ether. Abdomen was opened by taking a midline incision. Diaphragm was cut with precaution and blood was collected slowly from left ventricle by 24 gauge needle. Blood was sent to biochemistry laboratory in plain bulb; plasma was separated by centrifugation. And biochemical tests were performed.

Livers were dissected from rat and kept in 10% formalin and sent to the pathology department for Histopathological report.

Assessment of liver damage

Assessment of liver damage was done by biochemical and histopathological investigations.

Biochemical investigations

The following biochemical parameters were used: Serum (Sr.) alanine aminotransferase (ALT) (serum glutamic-pyruvic transaminase [SGPT]), Sr. aspartate aminotransferase (serum glutamic-oxaloacetic transaminase [SGOT]), Sr. alkaline phosphatase, Sr. bilirubin, and total serum protein.

Histopathological examination of liver

Histopathological assessment of liver damage was done by using a method of scoring of structural changes as described by National Health Services Meryland, USA.[18]

Results were statistically analyzed by using student's unpaired t-test. $p < 0.05$ was taken as significant.

RESULTS

Part A

Effect of paracetamol (Group A-II)

After Paracetamol treatment for 30 days (Group A-II) following changes have been noted. Decrease in total protein level, rise in Sr. AST level, rise in Sr. ALT level, rise in Sr. alkaline phosphatase level, rise in Sr. bilirubin level. Histopathological changes such as degeneration, necrosis and fibrosis (Figures 2-6) were also noted. All of these alterations in the parameters were statistically significant as compared to control values (Tables 1 and 2).

Effect of simultaneous administration of paracetamol and NS oil (Group A-III)

Co-administration of NS oil with paracetamol significantly prevented the fall in total serum protein levels. The administration of paracetamol significantly elevated levels of Sr. AST, Sr. ALT, Sr. alkaline phosphatase and Sr. bilirubin. Co-administration of NS oil with paracetamol significantly prevented this rise. All of these alterations in the parameters were statistically significant as compared to Paracetamol treated group (Table 1).

Histopathology of the livers of rats that were fed with paracetamol exhibited classical changes of degeneration, necrosis and fibrosis. Co-administration of NS oil with paracetamol significantly reduced scores of degeneration (Figure 3), necrosis (Figure 6) and fibrosis (Figure 5). There was also evidence of regeneration ((Figure 8, Table 2).

Part B

Effect of withdrawal of paracetamol (Group B-II and Group B-IV)

After giving paracetamol for 30 days, paracetamol was withdrawn. Blood samples were taken after

15 days (Group B-II) and 30 days (Group B-IV) after withdrawal of paracetamol therapy.

The serum protein levels on 15th day and 30th day after withdrawal were increased as compared to the levels of paracetamol treated group. But the increase was not significant. Similarly the levels of Sr. bilirubin, Sr. AST, Sr. ALT and Sr. alkaline phosphatase on 15th day and 30th day after withdrawal were lower than the levels of paracetamol treated group but the results were not significant (Table 3).

Livers of all animals were removed on 30th day after withdrawal of paracetamol therapy and histopathological examination was done. After withdrawal of paracetamol, the score of degeneration, necrosis and fibrosis was reduced. However, the scores of necrosis and degeneration decreased significantly. While the change in scores of fibrosis and regeneration was not significant (Table 4).

Effect of administration of NS oil after withdrawal of paracetamol therapy (Group B-III and Group B-V, Table 3)

Paracetamol was withdrawn after 30 days of therapy and from 31st day onwards the rats were administered NS oil daily. Blood samples were taken and liver function tests were done on 45th day (B-III) and 60th day (B-V). Livers were removed on 60th day and histopathological examination was done.

Sr. AST and Sr. alkaline phosphatase on 15th day after withdrawal were significantly reduced compared to group for which NS oil was not administered. The serum protein levels on 15th day after withdrawal were increased as compared to group for which NS oil was not administered. But the increase was not significant. Similarly the levels of Sr. bilirubin and Sr. ALT on 15th day after withdrawal

Table 1: Effect of co-administration of NS oil on liver function tests in paracetamol treated rats.

Groups N=6	Sr. AST (Units/ml)	Sr. ALT (Units/ml)	Sr. AP (Units/ml)	Sr. bilirubin (Mg/dl)	Sr. total protein (g/dl)
Control (A-I)	37.54±0.80	34.0±1.89	12.67±0.65	0.87±0.10	7.68±0.32
Paracetamol (A-II)	84.72±5.96###	123.2±5.4###	24.84±0.87###	1.89±0.19###	6.42±0.40###
Paracetamol + NS oil (A-III)	58.68±2.23***	91.3±3.8***	16.54±0.79***	1.16±0.12***	7.46±0.46**

All values are mean ± SD, Data were analyzed by using students unpaired t-test, Sr. AST: Serum aspartate aminotransferase, Sr. ALT: Serum alanine aminotransferase, Sr. AP: Serum alkaline phosphatise, NS: *Nigella sativa*. #In comparison with control group, *In comparison with paracetamol treated group, #,*p < 0.05, ##,**p < 0.01, ###,***p < 0.001

Table 2: Effect of co-administration of NS oil on histopathology score in paracetamol treated rats.

Group	Degeneration	Necrosis	Fibrosis	Regeneration
Control (A-I)	0	0	0	0
Paracetamol (A-II)	2.82±0.52###	2.32±0.34###	1.83±0.27###	0
Paracetamol + NS oil (A-III)	1.76±0.39**	1.67±0.21**	1.18±0.26***	0.56±0.13***

All values are mean ± SD, Data were analyzed by using students unpaired t-test, #In comparison with control group, *In comparison with paracetamol treated group, #,*p < 0.05, ##,**p < 0.01, ###,***p < 0.001. NS: *Nigella sativa*

Table 3: Effect of administration of NS oil after withdrawal of paracetamol therapy on LFTs in rats (on 15th day and on 30th day after paracetamol withdrawl).

Groups N=6	Sr. AST (Units/ml)	Sr. ALT (Units/ml)	Sr. AP (Units/ml)	Sr. bilirubin (Mg/dl)	Sr. total protein (g/dl)
Paracetamol 30 days (B-I)	84.72±5.96	123.2±5.4	24.84±0.87	1.89±0.19	6.42±0.40
Paracetamol 30 day + no treatment for 15 days (B-II)	76.63±4.49	117.74±4.86	23.75±0.81	1.78±0.21	6.76±0.34
Paracetamol 30 days + NS oil for 15 days (B-III)	68.83±4.71*	96.17±4.32	22.08±0.76*	1.48±0.18	6.93±0.39
Paracetamol 30 day + no treatment for 30 days (B-IV)	70.76±3.77	110.46±3.4	23.26±0.89	1.68±0.16	6.83±0.39
Paracetamol 30 days + NS oil for 30 days (B-V)	52.47±2.84***	76.43±4.54***	16.49±0.74***	1.38±0.12***	7.45±0.48*

All values are mean ± SD, Data were analyzed by using student's unpaired t-test, Sr AST: Serum aspartate aminotransferase, Sr. ALT: Serum alanine aminotransferase, Sr. AP: Serum alkaline phosphatase, *In comparison with paracetamol treated rats for 30 days, #In comparison with paracetamol for 30 days + no treatment for 15 days, #,*p < 0.05, ##,**p < 0.01, ###,***p < 0.001. NS: *Nigella sativa*

were lower as compared to group for which NS oil was not administered but the result was not significant (Table 3).

The levels of Sr. bilirubin, Sr. AST, Sr. ALT and Sr. alkaline phosphatase on 30th day after withdrawal were significantly lower as compared to group for which NS oil was not administered. The levels of serum protein were significantly increased on 60th day. The scores of degeneration, necrosis and fibrosis on 60th day decreased significantly as compared to scores on 30th day (Table 4).

DISCUSSION

This study was conducted on albino rats to assess the hepatoprotective effect of NS oil. Liver damage was assessed by using various biochemical and histopathological parameters.

Liver damage leads to decrease in synthetic capability leading to fall in serum protein levels. SGOT, SGPT enzyme levels increases in hepatic damage due to leakage of these enzymes from damaged hepatocytes into vascular compartment. Rise in Sr. bilirubin and Sr. alkaline phosphatase is due to parenchymal damage and cholestasis.[19] Protection against liver damage is indicated by prevention of toxic changes in these parameters. Liver biopsy is the most reliable index of liver damage. The histopathological parameters used in the present study are degeneration, necrosis, fibrosis and regeneration. Liver damage is indicated by degeneration, necrosis or fibrosis,

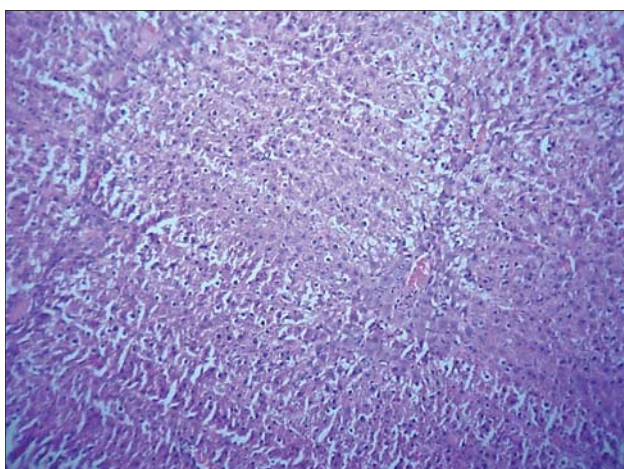

Figure 1: Normal histology of rat liver.

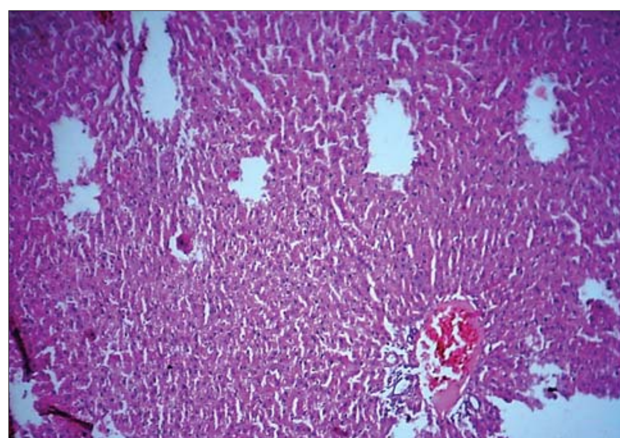

Figure 3: Degeneration.

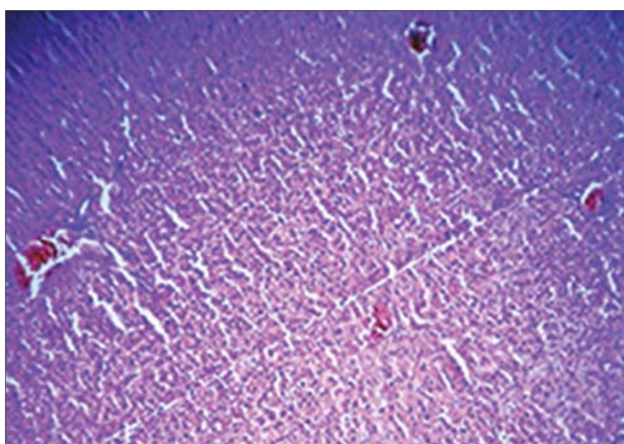

Figure 2: Congestion.

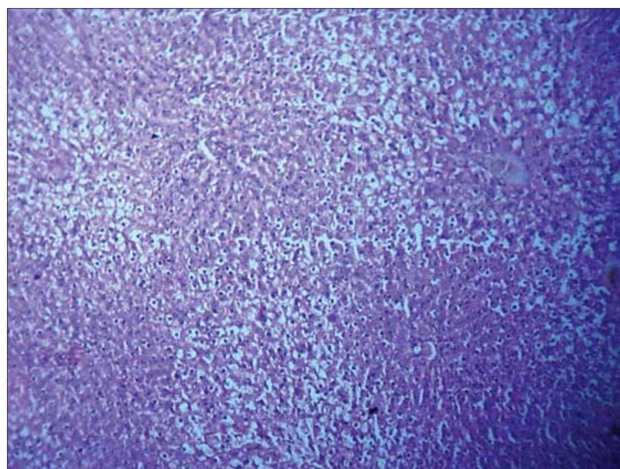

Figure 4: Fatty changes.

Table 4: Effect of administration of NS oil (for 4 weeks) after withdrawal of paracetamol therapy on histopathology score.

Group	Degeneration	Necrosis	Fibrosis	Regeneration
Paracetamol 30 days	2.82±0.52	2.32±0.34	1.83±0.27	0
Paracetamol + no treatment	2.18±0.36$^{\#}$	1.81±0.37$^{\#}$	1.44±0.26	0.65±0.11
Paracetamol + NS oil	1.23±0.41***	1.09±0.19**	1.03±0.14**	1.23±0.16***

All values are mean ± SD, Data were analyzed by using students unpaired t-test, $^{\#}$In comparison with paracetamol for 30 days, *In comparison with paracetamol for 30 days + no treatment for next 30 days, $^{\#}$*p < 0.05, $^{\#\#}$,**p < 0.01, $^{\#\#\#}$,***p < 0.001. NS: *Nigella sativa*

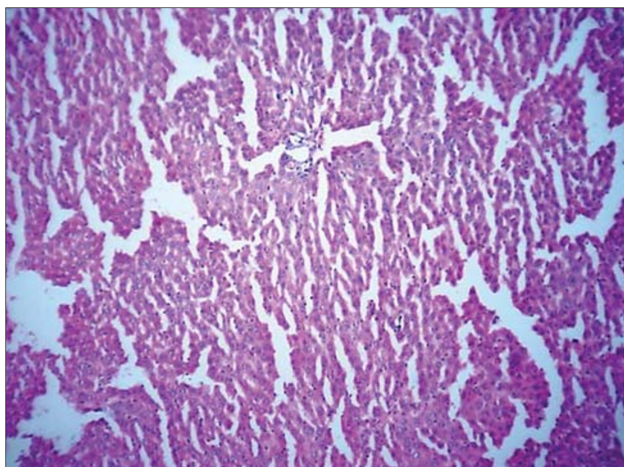

Figure 5: Fibrosis.

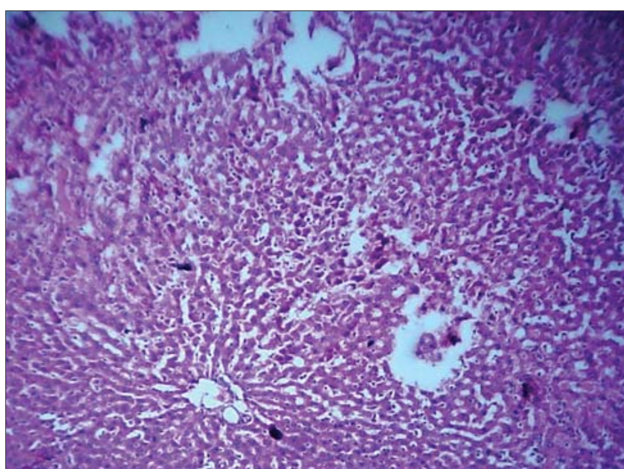

Figure 6: Focal necrosis with inflammatory cells.

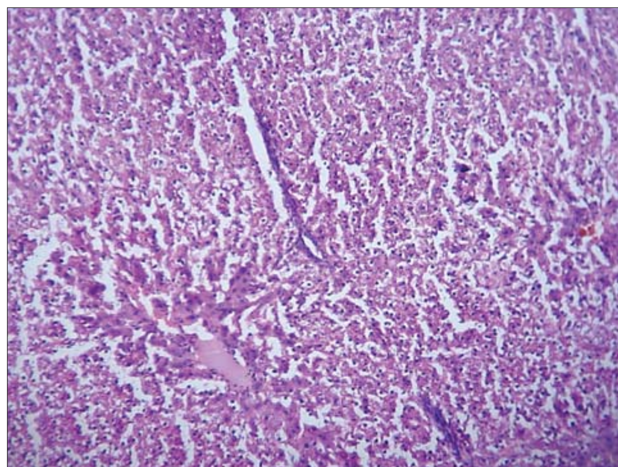

Figure 7: Necrosis.

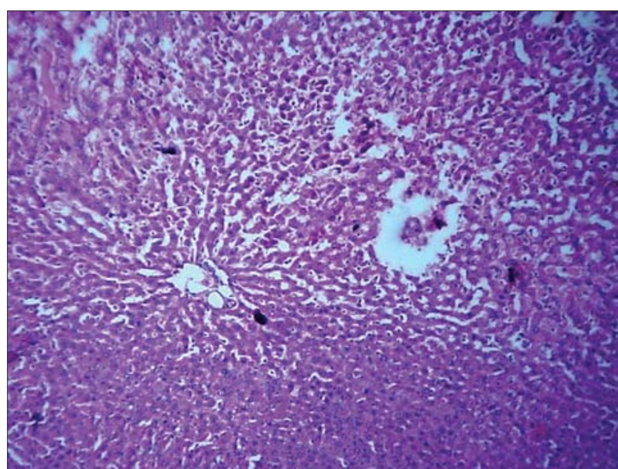

Figure 8: Regeneration.

while reduction in these parameters and evidence of regeneration is suggestive of hepatoprotection.

Hepatic injury was produced in albino rats by administration of Paracetamol in the present study. Hepatotoxicity was revealed by biochemical and histopathological findings. Paracetamol get activated by hepatic cytochrome P-450 to a highly reactive metabolite NAPBQI. NAPBQI is initially detoxified by conjugation with reduced glutathione to form mercapturic acid. However, when the rate of NAPBQI formation exceeds the rate of detoxification by Glutathione, it oxidizes tissue macromolecules such as lipid or SH group of protein resulting in cell necrosis and lipid peroxidation in the liver. This will result in hepatotoxicity.[31]

NS contain many active constituents that known to have marked antioxidant and reactive oxygen species scavenging potency.[21] Thymoquinone is the main constituent of the volatile oil obtained from NS seeds and has various pharmacological effects.[11] Machmudah et al. (2005) in their study found that antioxidant activity of NS is due to thymoquinone, which is an active principle of NS oil.[20] Thymoquinone is reported to possess strong antioxidant properties.[9] Oral administration of thymoquinone protected several organs against oxidative damage induced by free radical-generating agents including, doxorubicin-induced cardiotoxicity,[21] carbon tetrachloride evoked hepatotoxicity[12] and nephropathy produced by cisplatin.[22] Furthermore, Burits and Bucar found that NS essential oil and its four constituents (thymoquinone, carvacrol, t-anethol and 4-terpineol) had anti-oxidant effect in different chemical assays.[6]

Since oxidative stress plays an important role in paracetamol induced hepatotoxicity[5,23] and thymoquinone possess strong anti-oxidative properties, therefore, it is reasonable to hypothesize that the NS oil could protect against Paracetamol induced hepatotoxicity. Accordingly, this study was undertaken to investigate whether NS oil protects against Paracetamol induced hepatotoxicity. The biochemical and histological results proved that NS oil possess potential to protect the liver tissue against oxidative damages and could be used as protective drug against Paracetamol induced liver damages.

Previously performed clinical and experimental investigations have shown that NS has a protective effect against oxidative damage in isolated rat hepatocytes.[24] el-Dakhakhany et al.

have reported the protective effect of NS oil against CCl_4 and D-galactosamine induced hepatic toxicity in rats.[10] Mansour et al. also investigated the effect of NS oil by intraperitoneal[25] route on carbon tetrachloride-induced hepatotoxicity in mice. The results of the study indicated that Thymoquinone (12.5 mg/Kg, i.p.) may play an important role as antioxidant and may efficiently act as a protective agent against chemically-induced hepatic damage. These results are also similar to our findings.

Türkdoğan et al.[13] observed that NS has a significant hepatoprotective effect in CCl_4-administrated rabbits, and that hepatocellular degenerative and necrotic changes are slight without advanced fibrosis and cirrhotic process in NS treated group. The results of this study are consistent with our result, which shows that toxic histopathological changes can be prevented using NS oil. Nagi et al. found that thymoquinone has a promising prophylactic effect in a variety of conditions where cellular damage is a consequence of oxidative and/or nitrosative stress.[30] Al-Ghamdi[28] studied protective effect of NS seeds against carbon tetrachloride-induced liver damage. Animals treated with CCL_4 showed remarkable centrilobular fatty changes and this effect was significantly decreased in animals pretreated with NS. These histopathological changes were consistent with our findings.

Besides, hepatoprotective activity of NS in carbon tetrachloride treated rats has been studied and confirmed in various studies.[17,26-29]

Thus, all the references discussed as well present study indicates that NS oil has hepatoprotective action.

In the light of above references and present observations made in the study, it can be concluded that NS has a significant hepatoprotective action. It is probably by inhibiting lipid peroxidation and by increasing antioxidant defense mechanism.

However, more detailed experimental and clinical work on its various components will be required to suggest its use in human.

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Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Animal Ethics Committee

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