

# Therapeutic Effect of *Nigella sativa* Oil in Hepatotoxicity Induced by Isoniazid in Rats

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## ABSTRACT

**Objectives:** Tuberculosis is one the most prevalent microbial diseases worldwide and hepatotoxicity is one of the major side effects of first line anti-tubercular drug, Isoniazid. The reported pharmacological activities of *Nigella sativa* oil include protection from liver damage caused by diseases, chemicals and chemotherapeutic agents. The aim of the present study was to evaluate therapeutic potential of *Nigella sativa* oil in hepatotoxicity induced by using Isoniazid. **Methods:** Isoniazid (50 mg/kg) was administered to all the animals for 28 days orally. Silymarin (50 mg/kg) was used as standard drug for this study. From 29<sup>th</sup> day onwards isoniazid was stopped and therapeutic agents - normal saline, silymarin, *Nigella sativa* oil 0.5 ml /kg and 1ml/kg were given orally for the next 15 days in different animal groups respectively. On 44<sup>th</sup> day rats were sacrificed, blood samples were collected for biochemical analysis and liver tissue was subjected to histopathological examination. **Results:** The rats treated with *N. sativa* oil showed significant reduction in the liver enzymes and total bilirubin levels when compared to negative control group. There was also significant improvement in the histopathological scores in *N. sativa* oil treated group when compared to the negative control group. **Conclusion:** This study demonstrates the effectiveness of *Nigella sativa* oil as a therapeutic agent in hepatotoxicity induced by isoniazid in a dose dependant manner.

**Key words:** *Nigella sativa*, Hepatoprotective, Isoniazid, Silymarin, Tuberculosis, Hepatotoxicity.

## INTRODUCTION

Tuberculosis is one the most prevalent microbial diseases worldwide. According to the WHO, India had the highest TB burden worldwide for the year 2014, with approximate 23% out of the global estimate of new incidences.<sup>1</sup> Hepatotoxicity is a well reported and documented adverse effect of the 1<sup>st</sup> line antitubercular drugs, which often leads to discontinuation of the drugs and relapse or failure of the therapy. The first line antitubercular drugs, which have the highest reported hepatotoxicity, are isoniazid and pyrazinamide and concomitant use of these drugs might lead to fulminant hepatitis with lethal consequences.<sup>2</sup> The drug isoniazid continues to be a leading cause of drug induced hepatic injury in the United States and its hepatotoxicity has often been

significantly under-reported.<sup>3</sup> Elevations in the levels of hepatic transaminases are often encountered with the use of the drug Isoniazid. Severe hepatic injury is seen in approximately 1% of the people taking isoniazid. Liver damage in isoniazid therapy is found out to be age dependent, as it rarely in individuals taking this drug below the age of 20, but the incidence of liver damage increases to 1.2% between the ages of 35 to 49 years and approximately 2.3% in the 50 and above age group.<sup>4</sup> The hepatotoxicity of isoniazid in most cases is dose related, however some instances can be ascribed to drug hypersensitivity. The hepatic damage caused by the drug isoniazid can be related to genetic polymorphism in acetylation of this drug whereas other risk factors include

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old age, malnutrition, alcoholism, HIV infection and Hepatitis B or C infection.<sup>5</sup>

Plant derivatives with purported hepatoprotective activity have been used in folk medicine and traditional systems of medicine around the world for centuries. *Nigella sativa* L. (Black cumin) is an herbaceous plant, which has used since time immemorial for treatment of various ailments in different systems of traditional medicine.<sup>6</sup> *Nigella sativa* seed possess various reported pharmacological properties like analgesic, anti-inflammatory, antipyretic, antineoplastic, antioxidant and others.<sup>7-9</sup> The hepatoprotective activity of *Nigella sativa* has also been explored.<sup>10,11</sup> But there are only few reports regarding the protective activity of *Nigella sativa* seeds against anti-tubercular drug induced hepatotoxicity. In view of the above, this study was planned to evaluate the therapeutic aspect of *Nigella sativa* oil in isoniazid induced hepatotoxicity in rats.

## MATERIALS AND METHODS

### Experimental Animals

Adult wistar albino rats of either sex (150-200g) were obtained from Central Animal House, Jawaharlal Nehru Medical College; Aligarh Muslim University, Aligarh, U.P. They were housed under standard conditions (temperature  $27 \pm 2^\circ\text{C}$ , Humidity 30-70% and 12 h light/dark cycles). They were fed with standard pellet diet and water *ad libitum*. The rats were acclimatized to the laboratory condition for 1 week prior to the experiments. The study protocol was approved by the Institutional Animal Ethics Committee (IAEC) on 20.12.2014. All the animal experiments were carried out as per the rules and regulations of IAEC and CPCSEA.

### Drugs and chemicals

- *Nigella sativa* oil (Kalonji oil) was obtained from (Mohammedia products, Aamirnagar, Shah Sahab Mohalla, Karimnagar – 505001, Telengana State., India).
- Isoniazid Dispersible Tablets (Macleod's Pharmaceuticals Ltd. Mumbai, Maharashtra India).
- Normal Saline (Swaroop Pharmaceuticals Pvt. Ltd. Aligarh).
- Silymarin suspension (Micro Labs Ltd. Bengaluru, Karnataka, India) was used as the standard drug for the purpose of this study.

Diagnostic kits used for the purpose of this study were Bilirubin kit (Accurex Biomedicals pvt. Ltd., Mumbai, India), Aspartate transaminase (AST), Alanine transaminase (ALT) kits - Span Diagnostics Ltd. (Surat, India.) and

Alkaline Phosphatase (ALP) kit – Beacon Diagnostics, Gujrat India.

### Induction of hepatotoxicity

Hepatotoxicity was induced in the animals by using isoniazid 50mg/kg orally for 28 days.<sup>12</sup>

### Experimental design

Thirty albino rats of either sex, weighing 100-200 g were divided into five groups of 6 animals each. All the drugs were administered orally.

Isoniazid dispersible tablets were dissolved in distilled water and administered to all the animals for 28 days orally. From 29<sup>th</sup> day onwards isoniazid was stopped and the therapeutic agent's normal saline, silymarin 50mg/kg<sup>13</sup> or *Nigella sativa* oil 0.5ml/kg and 1ml/kg were given orally for the next 15 days (Table 1).

The animals were sacrificed, blood samples were collected from the heart of animals using open approach on 44<sup>th</sup> day and were subjected to biochemical analysis (Serum Billirubin, AST, ALT and ALP), liver removed and physical parameters (weight of the liver per 100 gram of rat's weight and volume of the liver in ml per 100 gram of the rat's weight) were recorded. The liver tissues were then subjected to histo-pathological analysis.

### Biochemical analysis

The blood samples were collected by cardiac puncture (open approach) and centrifuged at 5000 rpm for 10 min, plasma was separated and subjected to biochemical analysis. Total bilirubin was estimated using the method described by Jendrassik L. *et al.* 1938<sup>14</sup> using reagent supplied by Accurex Biomedicals Pvt Ltd. India. AST and ALT levels were determined by the Reitman and Frankel<sup>15</sup> method using kits acquired from Span Diagnostics Ltd. (Surat, India). Serum ALP levels were estimated by King's method<sup>16</sup> using the ALP determination kit procured from Beacon Diagnostics, Gujrat India.

### Histological Examination

The liver samples were preserved in 10% formalin for 48 h, fixed in paraffin. The tissue samples were processed according to standard histological techniques

**Table1: Grouping of Animals.**

Groups	Day1-28	Day 29-43
Group I	Normal saline 1ml/kg.	Normal saline 1ml/kg.
Group II	Isoniazid 50mg/kg.	Normal saline 1ml/kg.
Group III	Isoniazid 50mg/kg.	Silymarin 50mg/kg.
Group IV	Isoniazid 50mg/kg.	<i>Nigella sativa</i> oil 0.5ml/kg.
Group V	Isoniazid 50mg/kg.	<i>Nigella sativa</i> oil 1ml/kg.

and stained with hematoxylin and eosin.<sup>17</sup> The assessment of damage of liver tissue was done by method described by Davidson C.S. 1979.<sup>18</sup> The various parameters used were degeneration, necrosis, fibrosis and regeneration.

The percent of hepatoprotection offered by the standard and test drug was calculated using the formula:

$$H = \left[ 1 - \left( \frac{T - V}{C - V} \right) \right] \times 100$$

Where H = Percentage of hepatoprotection, T = Mean value of group treated with test drugs, C = Mean value of group treated with Isoniazid, V = Mean value for normal control group animals.

### Statistical analysis

The data of study are expressed as Mean  $\pm$  Standard Error of Mean (SEM). The groups were compared by one way analysis of variance (ANOVA) followed by post hoc Tukey's test to analyze the statistical significance. P value of less than 0.05 was considered significant for this study.

## RESULTS

### Effects of *N. sativa* oil on the liver function parameters in isoniazid treated rats

The biochemical parameters studied were total bilirubin, AST (aspartate aminotransferase), ALT (alanine aminotransferase) and ALP (alkaline phosphatase). In the negative control (Group II) group the liver function parameters total bilirubin ( $p < 0.001$ ), AST ( $p < 0.001$ ) and ALT ( $p < 0.001$ ) showed significant rise and ALP level was also raised significantly ( $P < 0.01$ ) in comparison to the normal control group (Group I). All the liver function parameters except ALP in the animals of the positive control group (III) showed significant reduction, total bilirubin ( $p < 0.001$ ), AST ( $p < 0.001$ ) and ALT ( $p < 0.001$ ) in comparison to the negative control group (Group II). ALP values in the positive control group (Group III) also showed reduction but were not statistically significant when compared to the negative control

group (Group II). In the rats of the *N. sativa* oil low dose group (Group IV) bilirubin levels showed significant ( $p < 0.001$ ) reduction in comparison to the negative control group (Group II). Serum ALT levels also exhibited significant ( $p < 0.01$ ) reduction, serum AST and ALP levels were reduced but were not statistically significant in comparison to the negative control group (Group II). The animals treated with *N. sativa* oil high dose (Group V) exhibited significant reduction in the levels of total bilirubin ( $p < 0.001$ ), AST ( $p < 0.01$ ) and ALT ( $p < 0.001$ ) when compared to the negative control group (Group II), the ALP levels also showed reduction in comparison to the negative control group (Group II) but it was not statistically significant (Table 2).

All data are expressed as Mean  $\pm$  SE. Negative control (Group II) group was compared with Normal control group (Group I) and all other groups (Group III, IV and V) were compared with Negative control group (Group II), \*  $p < 0.05$ , \*\*  $p < 0.01$  and \*\*\*  $p < 0.001$  were considered significant.

### Percentage of Hepatoprotection offered by *N. sativa* oil low and high dose in isoniazid induced hepatotoxicity

The hepatoprotection offered by the test drugs was estimated by formula described in the section of material and methods. The percentage of hepatoprotection was determined as a function of AST, ALT, ALP and Total bilirubin in all test groups as shown in Table 3. Percentage of hepatoprotection was highest for the positive control group (Group III) i.e. 81%, 88%, 83% and 54 % for bilirubin AST, ALT and ALP respectively. Among the *N. sativa* oil test groups hepatoprotection for the low dose group (Group IV) was 65%, 29%, 58% and 29%

**Table 3: Percentage of Hepatoprotection offered by *N. sativa* in INH treated rats.**

S.N.	Groups n=6	Hepatoprotection (%)			
		T. Bilirubin	AST	ALT	ALP
1	Silymarin	81	88	83	54
2	<i>N. sativa</i> oil 0.5ml/kg	65	29	58	29
3	<i>N. sativa</i> oil 1ml/kg	72	66	72	36

**Table 2: Therapeutic effect of *N. sativa* oil on biochemical parameters in INH treated rats.**

Groups(n= 6)	T. Bilirubin (mg/dl)	S. AST (units/l)	S. ALT (units/l)	S.ALP (units/l)
Group I (N. saline 43 days)	0.29 $\pm$ 0.42	44.40 $\pm$ 5.01	20.64 $\pm$ 5.75	56.40 $\pm$ 4.82
Group II (INH for 28days + N. saline for 15 days)	1.86 $\pm$ 0.19***	115.40 $\pm$ 6.35***	116.76 $\pm$ 12.13***	118.36 $\pm$ 7.40**
Group III (INH for 28 days + Silymarin for 15 day)	0.59 $\pm$ 0.13***	52.64 $\pm$ 10.68***	36.60 $\pm$ 10.14***	85.18 $\pm$ 12.96
Group IV (INH for 28 days + <i>N. sativa</i> 0.5ml/kg for 15 days)	0.84 $\pm$ 0.05***	94.62 $\pm$ 4.26	61.30 $\pm$ 5.96**	100.88 $\pm$ 5.52
Group V (INH for 28days+ <i>N. sativa</i> 1ml/kg for 15 days)	0.73 $\pm$ 0.03***	68.38 $\pm$ 12.78**	47.11 $\pm$ 10.15***	94.20 $\pm$ 13.35

**Table 4: Therapeutic effect of *Nigella sativa* oil on histopathological scores in INH treated rats.**

Groups n= 6	Degeneration	Necrosis	Fibrosis	Regeneration
Group I N. saline for 43 days	0	0	0	0
Group II (INH for 28days+N. saline for 15 days)	2.75±0.25***	2.25±0.25***	3.00±0.40***	0
Group III (INHfor28 days+ Silymarin for 15 day)	0.50±0.29***	0.75±0.48*	1.25±0.47*	2.75±0.25***
Group IV (INHfor28 days+ <i>N. sativa</i> low dose for 15 days)	1.75±0.25	1.25±0.25	2.25±0.25	1.75±0.25**
Group V (INH for 28days+ <i>N. sativa</i> high dose for 15 days)	0.75±0.25**	1.00±0.40*	1.5±2.89*	2.50±0.28***

for bilirubin AST, ALT and ALP respectively and 72%, 66%, 72% and 36% for the high dose group (Group V).

#### Effects of *N. sativa* oil on the histopathological examination in isoniazid treated rats

The histopathological parameters studied were degeneration, necrosis, fibrosis and regeneration. The microscopic architecture of the liver appeared to be normal in the normal control group (Group I) with no degeneration, necrosis and fibrosis. In the negative control group (Group II) the liver histopathological score was grossly deranged with significant degeneration ( $p<0.001$ ), necrosis ( $p<0.001$ ) and fibrosis ( $p<0.001$ ) with no regeneration in comparison to normal control group (Group I). In the positive control group (Group III) the liver histopathological scores showed improvement. The degeneration ( $p<0.001$ ), necrosis ( $p<0.05$ ) and fibrosis ( $p<0.05$ ) scores exhibited significant reduction and also there was significant increase in regeneration ( $p<0.001$ ) in comparison to the negative control group (Group II). In *N. sativa* oil low dose group (Group IV), there was a decrease in the degeneration, necrosis and fibrosis scores but were not statistically significant and also there was significant regeneration ( $p<0.01$ ) in comparison to the negative control group (Group II). In *N. sativa* oil high dose group (Group V) the degeneration ( $p<0.01$ ), necrosis scores ( $p<0.05$ ) and fibrosis scores ( $p<0.05$ ) exhibited significant reduction and also there was significant regeneration ( $p<0.001$ ) in comparison to the negative control group (Group II) (Table 4).

All data are expressed as Mean± SE. Negative control (Group II) group was compared with Normal control group (Group I) and all other groups (Group III, IV and V) were compared with Negative control group (Group II), \*  $p<0.05$ , \*\* $p<0.01$  and \*\*\* $p<0.001$  were considered significant.

#### DISCUSSION

In day to day life, human body comes in contact with various toxins related to environment, indirectly. Ailments of liver are on the rise in the 21<sup>st</sup> century. The spectrum of liver disorders is vast and it ranges from hepatitis to cirrhosis of diverse etiologic origins such as viral diseases, autoimmune disorders; drug induced liver injury and different types of carcinomas. Despite advances in modern medicine there is no definitive cure for liver disorders. So, there is an emergent need to develop potent agents, which not only prevent hepatic damage but also be curative.

The drug isoniazid (INH) is one of the 1<sup>st</sup> line drugs used for prophylaxis as well as treatment of tuberculosis. INH is associated with significant hepatotoxicity. Hepatotoxicity in patients on INH treatment is encountered in approximately 2% cases, which if not recognized timely can have fatal outcome.<sup>19</sup> INH was found out to be the leading cause of drug induced liver injury in the United States and hepatotoxicity resulting from the use of INH treatment is significantly underreported.<sup>20</sup> The presumed mechanism of INH hepatotoxicity is that INH gets converted to acetylisoniazid by the enzyme NAT2 which then gets eliminated by the kidney; acetylisoniazid further gets transformed into acetylhydrazine and then to potential hepatotoxic metabolite acetyl diazine by the CYP enzymes which is toxic by itself as it gets converted to reactive acetyl onium ion, acetyl radical and ketene, which binds covalently to hepatic macromolecules causing irreversible damage to the hepatocytes.<sup>21</sup> In the present study INH was given to rats orally in a dose of 50mg/kg for 28 days to induce hepatotoxicity.

In India herbal therapy for liver ailments based on the traditional systems of medicine has been used for a long time. Despite the commercial popularity of several

herbal remedies for liver diseases in particular, they still remain unacceptable treatment modalities. In order to develop effective drugs for liver disease based on the knowledge of the traditional systems proper therapeutic evaluation of herbal products in animal models are imperative. It is of utmost importance to carefully combine the knowledge of the traditional systems of medicine with that of the modern concept of evidence-based medicinal evaluation, standardization and randomized placebo controlled clinical trials to support clinical efficacy of the new drug.<sup>22</sup> The seeds of *Nigella sativa* plant have a long history of being a diversely beneficial for numerous ailments. For thousands of years people all over the world have used the Black Seed to cure diseases and sustain health in general. Many studies have been conducted to demonstrate the hepatoprotective activity of *N. sativa* plant.<sup>23,24</sup> Also Trivedi et.al in 2013 demonstrated the hepatoprotective activity of thymoquinone, which is the active principle of *Nigella sativa* seed oil against the antitubercular drug induced hepatotoxicity in rats has been reported.<sup>25</sup>

In the present study we explored the hepatoprotective potential of the *N. sativa* oil in isoniazid (INH) induced hepatic damage in rats. The results of the biochemical parameters depicts that after 15 days of treatment with *N. sativa* oil 0.5ml/kg and 1ml/kg in INH induced hepatotoxicity there was reduction in the AST, ALT and bilirubin levels significantly in comparison to the negative control group. All the liver function parameters except ALP in the animals of the positive control group showed significant reduction, T. bilirubin ( $p < 0.001$ ), AST ( $p < 0.001$ ) and ALT ( $p < 0.001$ ) in comparison to the negative control group. ALP value in the positive control group also showed reduction but was not statistically significant when compared to the negative control group. In the rats of the *N. sativa* oil 0.5ml/kg group bilirubin level showed significant ( $p < 0.001$ ) reduction in comparison to the negative control group. Serum ALT level also exhibited significant ( $p < 0.01$ ) reduction, serum AST and ALP levels were reduced but were not statistically significant in comparison to the negative control group. The animals treated with *N. sativa* oil 1ml/kg exhibited significant reduction in the levels of total bilirubin ( $p < 0.001$ ), AST ( $p < 0.01$ ) and ALT ( $p < 0.001$ ) when compared to the negative control group, the ALP level also showed reduction in comparison to the negative control group but it was not statistically significant. The percentage of hepatoprotection offered by *N. sativa* oil 0.5ml/kg dose was 65%, 29%, 58% and 29% for bilirubin AST, ALT and ALP respectively. The percentage of hepatoprotection

in the 1ml/kg dose group was 72%, 66%, 72% and 36% for bilirubin AST, ALT and ALP respectively

The hepatoprotective activity of *N. sativa* oil shown in the biochemical parameters are supported by the findings of the histopathological examination in the therapeutic study. The histopathological parameters studied were degeneration, necrosis, fibrosis and regeneration. In *N. sativa* oil 0.5ml/kg dose group, there was a decrease in the degeneration, necrosis and fibrosis scores but were not statistically significant and also, there was significant regeneration ( $p < 0.01$ ) in comparison to the negative control group. In *N. sativa* oil 1ml/kg group the degeneration ( $p < 0.01$ ), necrosis scores ( $p < 0.05$ ) and fibrosis scores ( $p < 0.05$ ) exhibited significant reduction and also there was significant regeneration ( $p < 0.001$ ) in comparison to the negative control group. Both the doses of *N. sativa* oil showed therapeutic efficacy against INH induced liver injury by decreasing the elevation of AST, ALT, ALP and Total bilirubin. But the effect was more pronounced with *N. sativa* 1ml/kg dose. *N. sativa* oil 1ml/kg provided greater hepatoprotective effect. Comparative histopathological study of the liver from different groups of rats corroborated the hepatoprotective activity of *N. sativa* oil). Liver sections of the animals treated with *N. sativa* oil 0.5ml/kg and 1ml/kg dose exhibited significant liver protection against INH in this study, which is evident by the presence of regenerating and lesser degenerating hepatocytes, fibrotic bridges and necrotic foci in the prophylactic study. The protection offered by *N. sativa* oil 1ml/kg dose though somewhat lesser than the standard drug silymarin but was considerable when compared to the liver slices of the rats treated with isoniazid (INH) alone.

Oxidative stress has been postulated as one of the major mechanisms by which the antitubercular drugs, namely isoniazid (INH) and rifampicin cause damage to the hepatocytes. After combined treatment of INH and rifampicin the glutathione and related thiols, which serve the purpose of preventing tissue from oxidative damage, get reduced significantly in blood and liver tissue. The result of which is microvesicular deposition of fats in the hepatocytes and inflammation of the portal triad. Thus isoniazid's (INH) hepatotoxicity appears to be mediated by oxidative stress.<sup>26</sup> The hepatoprotective activity of the *N. sativa* oil can be ascribed to its well documented pharmacological properties like anti-inflammatory property which might be capable of preventing inflammatory damage to the liver tissue.<sup>27</sup> The probable mechanism by which *N. sativa* oil offers protection against antitubercular drug induced hepatotoxicity may be due to its immunomodulatory and antioxidant activity.<sup>28</sup>

Thymoquinone, active constituent of *N. sativa* oil has been reported to possess antioxidant and antiperoxidative effects.<sup>29</sup> This active principle of *N. sativa* has been reported to effectively improve plasma and liver antioxidant activity. It also enhanced the liver antioxidant genes.<sup>30</sup> The effectiveness of Thymoquinone, the active constituent of *N. sativa* in ameliorating the hepatotoxicity in rats induced by the antitubercular drugs used in combination has also been demonstrated.<sup>25</sup>

## CONCLUSION

The findings of our study demonstrate that *N. sativa* oil administration significantly improved the liver biochemical and histological parameters in a dose dependent fashion. The hepatoprotective action of *N. sativa* oil might be ascribed to the presence of antioxidant phytochemicals which might have countered the free radical damage to the hepatocytes caused by isoniazid (INH). These were the results of a preliminary study and further detailed investigations are required to pinpoint the mechanism of hepatoprotection offered by *N. sativa* oil.

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## CONFLICT OF INTEREST

The authors declare no conflict of interest.

## ABBREVIATIONS

**ad libitum:** At pleasure (as much as is wanted); **ALP:** Alkaline phosphatase; **ALT:** Alanine aminotransferase; **AST:** Aspartate aminotransferase; **°C:** Degree Centigrade; **CYP:** Cytochrome P<sub>450</sub>; **dL:** Deciliter; **et al.:** Et alia (and others); **INH:** Isoniazid (Iso-nicotinic Hydrazine); **IU/L:** International units per liter; **mg:** Milligram; **min:** Minute; **ml.:** Milliliter; **mm:** Millimeter; **No.:** Number; **N. sativa:** *Nigella sativa*; **N.S.:** Not significant; **p.o.:** Per oral; **SE:** Standard error; **SEM:** Standard error of mean; **Sec:** Second; **s.c.:** Subcutaneous; **T. bill:** Total bilirubin; **Via:** By way of; **viz.:** Videlicet (namely); **Vol.:** Volume; **v/v:** Volume by volume; **v/w:** Volume by weight; **wt.:** Weight; **%:** Percent; **&:** And; **α:** Alpha; **β:** Beta; **γ:** Gamma; **μg:** Microgram; **μl:** Microliter; **/:** Oblique; **<:** Less than; **>:** More than.

## REFERENCES

1. Global tuberculosis report [Internet]. World Health Organization. 2016. [cited 3 January 2016]. Available from: [http://www.who.int/tb/publications/global\\_report/en](http://www.who.int/tb/publications/global_report/en).

2. Durand F, Bernuau J, Pessayre D, Samuel D, Belaiche J, Degott C, et al. Deleterious influence of pyrazinamide on the outcome of patients with fulminant or subfulminant liver failure during antituberculous treatment including isoniazid. *Hepatology*. 1995;21(4):929-32.
3. Hayashi PH, Fontana RJ, Chalasani NP, Stolz AA, et al. Under-reporting and Poor Adherence to Monitoring Guidelines for Severe Cases of Isoniazid Hepatotoxicity. *Clinical Gastroenterology and Hepatology*. 2015;13(9):1676-82.
4. Gumbo T. Chemotherapy of Tuberculosis, Mycobacterium Avium Complex Disease and Leprosy. In: Brunton LL, Chabner BA, Knollmann BC. (eds.) Goodman and Gilman's. The Pharmacological Basis of Therapeutics. 12<sup>th</sup> ed. United States of America: The McGraw-Hill Companies Inc. 2011;1156-7.
5. Yew W, Leung C. Antituberculosis drugs and hepatotoxicity. *Respirology*. 2006;11(6):699-707.
6. Paarakh PM. *Nigella sativa* L. A comprehensive review. *Indian Journal of Natural Products and Resources*. 2010;1(4):409-29.
7. Rawoof KG, Suresh V, Dey T, Ata S, Singh JSD. Evaluation of antidiabetic, analgesic and antimicrobial activities of *Nigella sativa*. *Contemporary Investigations and Observations in Pharmacy*. 2013;2(1):13-6.
8. Hasan MN, Khan RA, Nasiruddin M, Khan AA. Protective effect of *Nigella sativa* against aspirin induced gastric damage in rats. *Int J Pharm Pharm Sci*. 2014;6(5):275-8.
9. Hadjzadeh MAR, Keshavarzi Z, Yazdi SAT, Shirazi MG, Rajaei Z, Rad AK. Effect of alcoholic extract of *Nigella sativa* on Cisplatin-induced toxicity in rats. *Iranian Journal of Kidney Diseases*. 2012;6(2):99-104.
10. Al-Suhaimi EA. Hepatoprotective and immunological functions of *Nigella sativa* seed oil against hypervitaminosis A in adult male rats. *International Journal for Vitamin and Nutritional Research*. 2012;82(4):288-97.
11. Hassan AS, Ahmed JH, Al-Haroon SS. A study of the effect of *Nigella sativa* (Black seeds) in isoniazid (INH)-induced hepatotoxicity in rabbits. *Indian Journal of Pharmacology*. 2012;44(6):678-82.
12. Attri S, Rana SV, Vaiphei K, Sodhi CP, Katyal R, Goel RC, et al. Isoniazid- and rifampicin-induced oxidative hepatic injury — protection by N-acetylcysteine. *Human and Experimental Toxicology*. 2000;19(9):517-22.
13. Singh G, Goyal R, Sharma P. Pharmacological potential of Silymarin in combination with Hepatoprotective plants against experimental Hepatotoxicity in rats. *Asian Journal of Pharmaceutical and Clinical Research*. 2012;5(s1):128-33.
14. Jendrassik L, Grof P. Method on photometric systems for *in vitro* determination of direct and total bilirubin. *Bioche Zeitschrift*. 1938;297:82-9.
15. Reitman S, Frankel S. A colorimetric method for the determination of serum glutamic oxalacetic and glutamic pyruvic transaminases. *American Journal of Clinical Pathology*. 1957;28(1):56-63.
16. King EJ, Kind PRM. *In-vitro* determination of serum alkaline phosphatase. *Journal of Clinical Pathology*. 1972;7:321-2.
17. Culling CFA, Alliston RT, Barr WT. *Cellular Pathology Technique* [Internet]. 4<sup>th</sup> ed. London: Butterworth and Co Ltd. 1985. [cited 29 May 2016]. Available from: [http://samples.sainsburysebooks.co.uk/9781483192192\\_sample\\_813090.pdf](http://samples.sainsburysebooks.co.uk/9781483192192_sample_813090.pdf).
18. Davidson CS. Guidelines for detection of hepatotoxicity due to drugs and chemical. USA. USA: NIH publication, U.S. Department of Health and Education and Welfare NIH. 1979.
19. Sarich T, Zhou T, Adams SP, Bain AI, Wall RA, Wright JM. A model of isoniazid-induced hepatotoxicity in rabbits. *Journal of Pharmacological and Toxicological Methods*. 1995;34(2):109-16.
20. Hayashi PH, Fontana RJ, Chalasani NP, Stolz AA, et al. Under-reporting and Poor Adherence to Monitoring Guidelines for Severe Cases of Isoniazid Hepatotoxicity. *Clinical Gastroenterology and Hepatology*. 2015;13(9):1676-82.
21. Ramappa V, Aithal GP. Hepatotoxicity Related to Anti-tuberculosis Drugs: Mechanisms and Management. *Journal of Clinical and Experimental Hepatology*. 2013;3(1):37-49.
22. Thyagarajan SP, Jayaram S, Gopalkrishnan V, Hari R, Jeyakumar P, Sripathi MS. Herbal medicines for liver diseases in India. *Journal of Gastroenterology Hepatology*. 2002;17(s3):S370-6.
23. Yesmin F, Rahman Z, Dewan JF, Helali AM, Rahman NIA, Ahmed AG, et al. Hepatoprotective role of aqueous and n-hexane extracts of *Nigella sativa* L. in experimental liver damage in rats. *Asian Journal of Pharmaceutical and Clinical Research*. 2013;6(3):205-9.
24. Essawy AE, Abdel-Moneim AM, Khayyat L, Elzergy AA. *Nigella sativa* seeds protect against hepatotoxicity and dyslipidemia induced by

- carbon tetrachloride in mice. Journal of Applied Pharmaceutical Science. 2012;2(10):21-5.
25. Trivedi M, Chansoria AK, Dixit AK. Protective effect of Thymoquinone against Antitubercular Drug Induced Hepatic Toxicity in Rats. International Journal of Universal Pharmacy and Bio Sciences. 2013;2(1):1-8.
  26. Sodhi CP, Rana SV, Mehta SK, Vaiphei K, et al. Study of oxidative stress in isoniazid-rifampicin induced hepatic injury in young rats. Drug and Chemical Toxicology. 1997;20(3):255-69.
  27. Houghton PJ, Zaraka R, Delas HB, Hoult JR. Fixed oil of *Nigella sativa* and derived thymoquinone inhibit eicosanoid generation in leucocytes and lipid peroxidation. Planta Medica. 1995;47(3):119-26.
  28. Mansour MA, Ginawi OT, EL-Hiday T, EL-Khatib AS, et al. Effects of volatile oil constituents of *Nigella sativa* on carbon tetrachloride induced hepatotoxicity in mice: evidence for antioxidant effects of thymoquinone. Research Communication in Molecular Pathology and Pharmacology. 2001;110(3-4): 239-51.
  29. Kanter M, Coskun O, Uysal H. The antioxidative and antihistaminic effect of *Nigella sativa* and its major constituent, Thymoquinone on ethanol-induced gastric mucosal damage. Archives of Toxicology. 2006;80(4):217-24.
  30. Ismail M, Al-Naqeeq G, Chan KW. *Nigella sativa* Thymoquinone-rich fraction greatly improves plasma antioxidant capacity and expression of antioxidant genes in hypercholesterolemic rats. Free Radical Biology and Medicine. 2010;48(5):664-72.

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## SUMMARY

- *N. sativa* oil has protective effect against Isoniazid induced Hepatotoxicity.



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