

## ORIGINAL ARTICLE

EFFECTS OF *NIGELLA SATIVA* ON VARIOUS PARAMETERS IN PATIENTS OF NON-ALCOHOLIC FATTY LIVER DISEASE

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**Background:** Non-alcoholic Fatty Liver disease (NAFLD) is the most common cause of progressive liver disorders worldwide. Drug options are limited with varying results. *Nigella sativa* in the form of herbal medicine could be another option because of its strong historical background. The objective of the study was to evaluate the effect *Nigella sativa* on various parameters in patients of NAFLD. **Methods:** A randomized controlled trial was conducted at outpatient clinic of medical unit-1 of Sheikh Zayed Medical College/Hospital, Rahim Yar Khan, in which seventy patients of NAFLD were divided in to interventional and non-interventional groups. The interventional group was given cap *Nigella sativa* 1g twice a day while non-interventional group was given cap placebo in a same way for three months. Body weight, BMI, liver enzymes and ultrasound finding of fatty liver were assayed before and after treatment.

**Results:** After 12 weeks treatment with *Nigella sativa* body weight decreased significantly from  $86\pm 13.8$  to  $76\pm 12.6$  kg vs placebo ( $p=0.041$ ). BMI also reduced significantly from  $29.06\pm 4.6$  to  $26.25\pm 6.2$  kg/m<sup>2</sup> vs placebo ( $p=0.012$ ). There is remarkable reduction in aminotransferases level after treatment with *Nigella sativa* vs placebo (ALT:  $78.05\pm 5.52$  to  $52.6\pm 5.65$  IU/L vs  $76.48\pm 4.95$ – $74.32\pm 5.58$  IU/L ( $p=0.036$ ). AST:  $65.54\pm 4.56$ – $44.56\pm 5.52$  IU/L vs  $63.25\pm 5.43$ – $59.43\pm 3.39$  IU/L ( $p=0.021$ ). There was overall 57.14 % patient had normal fatty liver grading on ultrasound after 12 weeks treatment with *Nigella sativa* as compared to placebo ( $p=0.002$ ).

**Conclusion:** *Nigella sativa* improves bio chemical and fatty liver changes in NAFLD patients. Its use in early stages of NAFLD is recommended in order to prevent its life-threatening complication.

**Keywords:** NAFLD; *Nigella sativa*; Body weight; ALT; AST; Fatty liver grading

J Ayub Med Coll Abbottabad 2017; 29(3):403–7

## INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is a burning health issue because of its increasing prevalence in developed 20–30% in contrast to developing countries 10–20%. In recent years the burden of NAFLD is on rise in Asian counties like Pakistan because of adaptation to Western diet, sedentary life style and urbanization pattern.<sup>1</sup> Moreover, in South Asian peoples there is an increase susceptibility of apolipoprotein C3 gene variants which is strongly associated with insulin resistance and NAFLD even in non-obese.<sup>2</sup> Therefore, a multidisciplinary and multifaceted approach is required to prevent and control major risk factors of NAFLD (obesity, metabolic syndrome, diabetes, hypertension and dyslipidaemia) in order to reduce this disease burden on health system.<sup>3</sup>

Majority of the patients of NAFLD are asymptomatic. Some have vague upper abdominal discomfort while others are diagnosed on routine medical check-up on the basis of asymptomatic elevation of liver enzymes and radiological finding of fatty liver.<sup>4</sup> There are three diagnostic criteria of NAFLD. Patients are non-alcoholic, having fatty liver on ultrasound or histology and absence of secondary causes of liver disease. The abdominal ultrasound is the

best tool to detect fatty liver because of its availability, cost effectiveness, screening on large population, non-invasiveness, easy handling and no special protocol required as compared to others test such as liver biopsy (gold standard), MRI, CT and Fibro scan.<sup>5</sup>

There is no licensed drug therapy for NAFLD up till now multiple drugs with varying results were used so far.<sup>6</sup> There is need to do a trial of herbal medicine on this disorder as use of herbal medicine already increases throughout the world because of belief that they are natural, cheap, easily available and free of side effect than conventional drugs in various diseases.<sup>7</sup> *Nigella sativa* a natural remedy for variety of medical ailment has been used from centuries due to its historical and religious background. Although it exists in several forms but according to our Prophet (PBUH) saying its seeds are the remedy for all the diseases except death. It is also called black seeds, black cumin, black caraway, fennel flower, nutmeg flower, kalonji and used from centuries as home remedies and culinary proposes in South Asia.<sup>8</sup> It is a miracle herb and has a potential for use in a variety of medical clinical condition such as diabetic mellitus, dyslipidemia, asthma, hypertension, diarrhoea, peptic ulcer, rheumatoid arthritis, osteoporosis. In addition, it has anti-inflammatory, anti-

oxidant, anti-fibrotic, anti-pyretic, analgesic, anti-bacterial, anti-fungal, anti-parasitic, anti-viral, anti-tumour and immunomodulatory properties.<sup>9</sup>

*Nigella sativa* has beneficial effects on all those risk factors which are associated with NAFLD in various clinical studies such as improvement in metabolic syndrome<sup>10</sup>, blood pressure<sup>11</sup>, and weight gain<sup>12</sup> and lipid profiles<sup>13</sup>. Moreover, it has also having anti-inflammatory and anti-oxidant properties<sup>14</sup> because inflammation and oxidative stress plays an important role in the progression as well as complication of NAFLD<sup>15</sup>. There is no study in humans so far to study the effect of *Nigella sativa* in patients of NAFLD. The present study was conducted to see effect of *Nigella sativa* on various parameters in NAFLD patients.

## MATERIAL AND METHODS

This randomized controlled trial was conducted by the cooperation of Pharmacology and Medicine Department, at outpatient clinic of medical unit-1 of Sheikh Zayed Medical College/Hospital, Rahim Yar Khan, for a period of three months (March to June 2016). An ethical committee approval and written informed consent from participants were obtained before enrolment. Initially one hundred patients were screened on the basis of presenting complaints such as vague abdominal discomfort, dyspepsia and generalized body weakness at the outdoor unit. Out of which seventy patients were enrolled in the study after fulfilling the inclusion and exclusion criteria. The inclusion criteria were patient aged 20–45, BMI  $\geq 25$ , presence of fatty liver grading 0–3 on abdominal ultrasound and mild to moderate elevation of aminotransferases level. All the test and ultrasound were performed at the same centre to avoid human errors. The exclusion criteria were positive test for HB<sub>s</sub> Ag, Anti HCV and HIV, hereditary defects of iron, copper and alpha-1 antitrypsin deficiency, any evidence of advanced liver disease in the form of very high level of aminotransferases and highly abnormal ultrasound. Secondary causes of NAFLD such as hypothyroidism, hypogonadism, short bowel syndrome, pancreato-duodenal resection and drugs which cause fatty liver such as corticosteroids, antiviral (nucleoside analogue), tetracycline, methotrexate, tamoxifen and amiodarone were also rule out. In addition, patients who were taking any drug for NAFLD were also excluded from the study.

*Nigella sativa* seeds purchased from local market of Rahim Yar Khan, Pakistan. Seeds were authenticated by department of botany Khawaja Farid Postgraduate College Rahim Yar Khan, Pakistan. Seeds were washed, dried and grinded to form fine powder by electric microniser. This powder was used to make 1 gram *Nigella sativa* capsule. Placebo

capsules were made in a similar way but it contained micro crystalline cellulose as an active ingredient.

Patients were randomly divided in two groups so that effect of *Nigella sativa* can be compared with placebo. A randomization was based upon the random number generated by computed software for each subject. First study group were given tab: *Nigella sativa* at a dose of 1 g twice a day for twelve weeks while second control group were given tab: placebo with same colour, size and appearance for similar periods but it contained micro crystalline cellulose as an active ingredient. Patients were advised to maintain their healthy life style as usual without any regular exercises and dietary modification which may affect our results. In addition, patients were advised not to take any medication for NAFLD. Body weight was measured by digital scale and standing height was measured by microtoise. Body mass index was calculated weight in kilogram divided by the square of the height in meters before and after the end of study. Fasting blood samples were drawn from the antecubital vein before and at the end of the study. The samples were used for analysing blood sugar, Lipid profile, AST and ALT. Blood sugar was measured by glucose oxidase peroxidase. Lipid profile and aminotransferases was done by semi-automated clinical chemistry analyser (Microlab 300) using spectrophotometry principal.

The high-resolution ultrasound machine (Toshiba Xario™ 200) was used to assess fatty liver grading by experienced radiologist who was unknown to clinical and laboratory data of the study subjects at baseline and after three months treatment with *Nigella sativa*. The classification of NAFLD was based upon the severity of fatty liver on ultrasound according to the given criteria.<sup>16</sup>

**Grade-0:** No fatty liver

**Grade-1 (Mild):** Mild diffuse increase in the echogenicity of liver parenchyma or increased hepatorenal contrast with normal diaphragm and intrahepatic vessel borders.

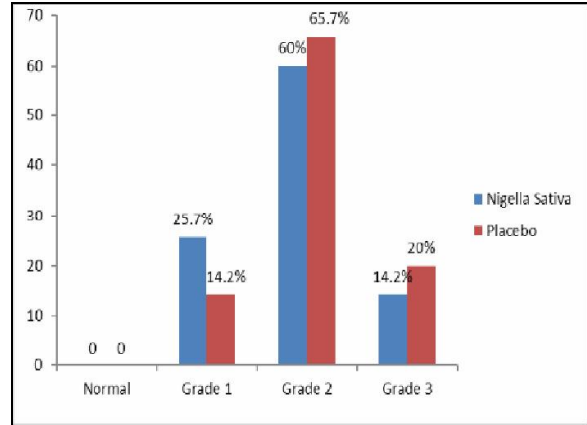
**Grade-2 (Moderate):** Moderate diffuse increase in the echogenicity of liver parenchyma and increased hepatorenal contrast with slight impairment of diaphragm and intrahepatic vessel borders

**Grade-3 (Severe):** In addition to moderate steatosis there was no visualization of posterior portion of the right lobe of liver, intrahepatic vessel borders and diaphragm. The SPSS-13 was used for the analysis of data. Values were presented as mean  $\pm$  standard deviation for quantitative variable and percentages for categorical variables. The two groups were compared by student's *t*-test for quantitative variable and chi-square for the categorical variables. Changes from baseline to 12 weeks were compared by paired *t*-test within each group. Wilcoxon test was used for rating variable comparison before and after treatment in each group. *p*-

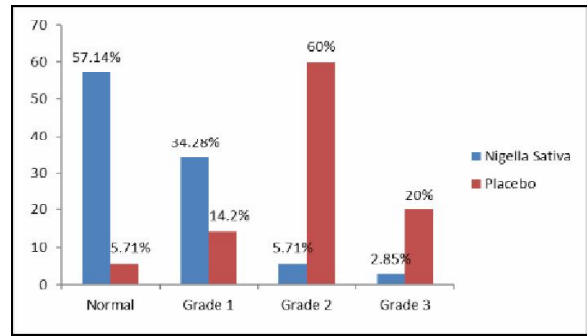
value of <0.05 were deemed to be statistically significant

**RESULTS**

The tolerability and safety profile of *Nigella sativa* and placebo was absolute. No major adverse effects were reported during the study period however four patients in *Nigella sativa* and two patients in placebo group had complaints of headache and abdominal distress during first week of therapy which were settle down itself without any intervention. There was no drop out from the study and all patients completed the study with nice cooperation. The baseline study parameters between two groups are shown in table-1. There was no significant difference between the two groups at baseline in terms of body weight, BMI, aminotransferases level and fatty liver grading on ultrasound. There was significant improvement in body weight after three months treatment with *Nigella sativa*. The body weight decreased significantly from 86±13.8 to 76±12.6 kg vs placebo 84.5±14.4 to 82.8±12.82 (p=0.041). There was notable reduction in BMI value from 29.06±4.6 to 26.25±6.2 kg/m<sup>2</sup> vs placebo 28.18±3.8 to 27.67±4.2 kg/m<sup>2</sup> (p=0.012). There is remarkable reduction in aminotransferases level after treatment with *Nigella sativa* vs placebo (ALT: 78.05±5.52 to 52.6±5.65 IU/L vs 76.48±4.95 to 74.32±5.58 IU/L (p=0.036). AST: 65.54±4.56 to 44.56±5.52 IU/L vs 63.25±5.43 to 59.43±3.39 IU/L (p=0.021). There was overall 57.14% patient had normal fatty liver grading on abdominal ultrasound after 12 weeks treatment with *Nigella sativa* as compared to placebo with (p=0.002). These results are shown in table-2 and figure-1, 2.



**Figure-1: Ultrasound of fatty liver grading before treatment. None of the patient had normal fatty liver grading on ultrasound at start of study**



**Figure-2: Ultrasound of fatty liver grading after treatment. Wilcoxon signed rank test showed significant decrease in fatty liver grading after treatment with *Nigella sativa* vs placebo with p<0.05 at end of study**

**Table-1: Baseline Characteristics of study groups**

Baseline Characteristics	<i>Nigella sativa</i> Group (n=35)	Placebo Group (n=35)	p-value
Age (years)	38±8.75	36±9.42	0.88
Male gender	23/35 (66%)	21/35 (60%)	0.73
Body weight(kg)	86±13.8	84 ±14.4	0.42
BMI (Body Mass index kg/m <sup>2</sup> )	29.06±4.6	28.18 ±3.8	0.62
Systolic Blood pressure (mm hg)	120±8.2	115±6.9	0.82
Diastolic Blood pressure (mm hg)	84±8.2	78±9.0	0.86
Blood sugar fasting(mg/dl)	86±18.4	83±16.5	0.03
Serum Total Cholesterol(mg/dl)	145±35.8	156±22.6	0.98
Serum Triglycerides(mg/dl)	95±35.2	110±45.5	0.04
Fatty liver grading (0/1/2/3)	35 (0/9/21/5)	35 (0/5/23/7)	0.72

Values are given±standard deviation

**Table-2: Results of *Nigella sativa* and Placebo group (pre and post treatment)**

Parameters	<i>Nigella sativa</i> Group (n= 35)		Placebo Group (n= 35)		p-value*
	Pre-treatment	Post treatment	Pre-treatment	Post treatment	
Body weight(kg)	86±13.8	76±12.6	84.5±14.4	82.8±12.82	0.041
BMI(kg/m <sup>2</sup> )	29.06±4.6	26.25±6.2	28.18 ±3.8	27.67±4.2	0.012
ALT(IU/L)	78.05±5.52	52.6±5.65	76.48±4.95	74.32±5.58	0.036
AST(IU/L)	65.54±4.56	44.56± 5.52	63.25±5.43	59.43±3.39	0.021
GGT (IU/L)	19.52±5.82	16.77±7.76	22.71±6.43	20.83±7.56	0.72
Fatty liver Grading (0/1/2/3)	35 (0/9/21/5)	35 (20/12/2/1)	35(0/5/23/7)	35 (2/5/21/7)	0.002

BMI: body mass index, ALT: alanine aminotransferases, AST: aspartate aminotransferases, GGT: gamma glutamyl Transpeptidase. Results are expressed as mean±standard deviation. p\* < 0.05

## DISCUSSION

In this placebo controlled trials we evaluated the effects of *Nigella sativa* on body weight, BMI, aminotransferases and various grading of fatty liver on abdominal ultrasound in patients of NAFLD. To our best knowledge this was the first clinical trial to determine the effect of *Nigella sativa* on various parameters in patients of NAFLD over a period of 12 weeks. In this study *Nigella sativa* causes a significant reduction in body weight after 12 weeks treatment. Most of the patients of NAFLD are obese so body weight reduction via life style modification is the initial step in the management of NAFLD and its effectiveness was proven in various studies<sup>17</sup>. The result of our study was close to Gomez *et al*<sup>18</sup> in which they concluded that 5–10 percent reduction in body weight improved NAFLD while more than 10 percent also improve histological features in patients of NASH.

Obesity has strong association with insulin resistance, oxidative stress and metabolic insults. *Nigella sativa* contains essential polyunsaturated fatty acid, fat soluble vitamins, essential amino acids and minerals which increases insulin sensitivity, reduces insulin resistance, reduce body weight, improve metabolic profile and reduce oxidative stress through its antioxidant mechanism.<sup>19</sup> In addition to dyslipidemic and insulin sensitizing activity *Nigella sativa* has also anorexic effect which also contributes to weight loss.<sup>20</sup>

In this study *Nigella sativa* causes a significant reduction in serum transaminases level. NAFLD is considered to be an inflammatory disease in which ongoing inflammation and oxidative stress causes the elevation of liver enzyme and the drugs such as vitamin E and Silymarin which are having anti-inflammatory and antioxidant properties are very beneficial in these patients.<sup>21</sup> In one study thymoquinone and p-cymene extract of *Nigella sativa* caused significant improvement in serum LFT'S through its antioxidant mechanism by decreasing the concentration of malondialdehyde (MDA) and tumour necrosis factor (TNF- $\alpha$ ) in fatty liver of rats.<sup>22</sup> In another study thymoquinone not only suppress oxidative stress but reduced inflammation, improved apoptotic and fibrosis status in experimental model of NAFLD.<sup>23</sup>

Although *Nigella sativa* has proven beneficial effects on all those risk factors that have strong association with NAFLD such as obesity, metabolic syndrome, dyslipidaemia, diabetes mellitus, and hypertension in various clinical studies<sup>10-13</sup> but clinical data about the effects of *Nigella sativa* on NAFLD is sparse and lacking. There are no clinical studies up till now on NAFLD patients while experimental studies showed the potential effects of *Nigella sativa* in disease induced model mostly. In these experimental studies *Nigella sativa* showed its hepatoprotective effect against

liver insult induced by various drugs and chemical like paracetamol, antiretroviral, carbon tetrachloride and ethanol. *Nigella sativa* showed improvement in biochemical and histopathological parameters through its various antioxidant and anti-inflammatory mechanisms in these experimental studies.<sup>24-27</sup> *Nigella sativa* also showed its hepatoprotective effect in experimental models of high fructose induced metabolic syndrome through peroxisome proliferate activated receptors PPAR- $\alpha$  and PPAR- $\gamma$  mechanism.<sup>28</sup> While in humans *Nigella sativa* showed hepatoprotective effect in patients of metabolic syndrome and diabetes mellitus because both are having strong association with NAFLD.<sup>29</sup> However so far no research had done in patients of NAFLD only one research was done in which *Nigella sativa* improved serum lipid profile in insulin resistant syndrome patients of NAFLD however it did not show that either there was improvement in serum aminotransferases and ultrasound grading of hepatic steatosis<sup>30</sup> but our studies showed that *Nigella sativa* not only reduce body weight and serum transaminases level but also showed more than 50% of regression of fatty liver on ultrasound in the form of decreased liver brightness and hepato-renal contrast after three months treatment. Although ultrasound is not a gold standard for NAFLD but its sensitivity is between 60-90% and it is comparable with MRI, CT-SCAN and liver biopsy.<sup>31</sup> There is a need for further clinical trials of long duration on *Nigella sativa* in patients of NAFLD. As herbal medicines are natural, cheap and less adverse effects as compared to conventional drug. Standardization protocol should be followed regarding its abstracts extraction, processing, storage and manufacturing.

## CONCLUSION

*Nigella sativa* improves bio chemical and fatty liver changes in NAFLD patients. Its use in early stages of NAFLD is recommended in order to prevent its life-threatening complication.

**Acknowledgement:** The authors are thankful to department of pathology & radiology Sheikh Zayed Medical College/hospital, Rahim Yar Khan for their cooperation regarding lipid profile, aminotransferases and ultrasound analysis.

**Conflict of interest:** There is no conflict of interest in this study

## AUTHORS' CONTRIBUTION

MH: Designed study, research concept and collect clinical data. AGT: Collected lab data and its analysis. LA did interpretation of all data and drafting the paper. KA did manuscript writing, review and final proof reading of manuscript.

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Received: 14 September, 2016

Revised: 23 March, 2017

Accepted: 25 March, 2017

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