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Acute and chronic toxicity of *Nigella sativa* fixed oil

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Summary

We investigated the toxicity of the fixed oil of *Nigella sativa* L seeds in mice and rats through determination of LD_{50} values and examination of possible biochemical, hematological and histopathological changes. The acute toxicity of *Nigella sativa* fixed oil was investigated in mice. LD_{50} values, obtained by single doses, orally and intraperitoneally administered in mice, were 28.8 ml/kg body wt. p.o. [26.2–31.6] and 2.06 ml/kg body wt. i.p. [1.86–2.26], respectively. Chronic toxicity was studied in rats treated daily with an oral dose of 2 ml/kg body wt. for 12 weeks. Changes in key hepatic enzymes levels, including aspartate-aminotransferase, alanine-aminotranferase, and gamma-glutamyltransferase and histopathological modifications (heart, liver, kidneys and pancreas) were not observed in rats treated with *Nigella sativa* after 12 weeks of treatment. The serum cholesterol, triglyceride and glucose levels and the count of leukocytes and platelets decreased significantly, compared to control values, while hematocrit and hemoglobin levels increased significantly. A slowing of body weight gain was also observed in *Nigella sativa* treated rats, as compared to control animals. The low toxicity of *Nigella sativa* fixed oil, evidenced by high LD_{50} values, key hepatic enzyme stability and organ integrity, suggests a wide margin of safety for therapeutic doses of *Nigella sativa* fixed oil, but the changes in hemoglobin metabolism and the fall in leukocyte and platelet count must be taken into consideration.

Key words: *Nigella sativa*, fixed oil, toxicity, biochemical parameters, hematological parameters.

Introduction

Nigella sativa L. (ranunculaceae), known commonly as "black cumin", is a herbaceous plant that grows in Mediterranean countries and is also cultivated in northern Morocco. *Nigella sativa* seeds have been used traditionally in Middle Eastern folk medicine as a natural remedy for various diseases for over 2000 years (Phillips, 1992). Recently, many biological activities of *Nigella sativa* seeds have been reported, including: antibacterial (Ferdous et al. 1992), anti-tumor (Worthen et al. 1998), diuretic and hypotensive (Zaoui et al. 2000). *Nigella sativa* seeds decrease total serum lipids and body weight in *Psammomys obesus* sand rats (Labhal et al. 1997), decrease fasting plasma glucose in rabbits (Al-Hader et al. 1993), increase serum total protein (Al-Gaby, 1998), prevent dental plaques and caries (Namba et al. 1985). *Nigella sativa* can be used in the preservation of food and prevention of food poisoning, since bacterial species inhibited by *Nigella sativa* extract are known to be involved in food poisoning (Hanafy and Hatem, 1991). *Nigella sativa* seeds contain 0.4–0.45 w/w volatile oil, and more than 30% fixed oil (El-Alfy et al. 1975; Hashim and El-Kiey, 1962), with 85% total unsaturated fatty acids (Houghton et al. 1995), and some new flavonol triglycosides (Merfort et al. 1997). *Nigella sativa* seeds protect isolated hepatocytes against tert-butyl hydroperoxide (TBHP)-induced toxicity evidenced by decreased leakage of alanine aminotransferase (ALAT)

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and aspartate aminotransferase (ASAT) (Daba and Abdel-Rahman, 1998). *Nigella sativa* extract protects the liver and kidney from cisplatin-induced toxicity in rats by reducing key hepatic enzyme leakage, protects against cisplatin-induced falls in leukocyte counts, hemoglobin levels and mean osmotic fragility of erythrocytes, and prevents increase in hematocrit (El-Daly, 1998; Nair et al. 1991). The toxicity of *Nigella sativa* aqueous and alcoholic extracts has also been studied (Tenekoon et al. 1991; Mahfouz et al. 1965). *Nigella sativa* seeds contain sapon and various alkaloids (Atta-ur-Rahman et al. 1992; Atta-ur-Rahman et al. 1995). Serum gamma-glutamyl transferase (GGT) and ALAT concentrations were increased following administration of *Nigella sativa* aqueous extracts, without degenerative changes in hepatocytes (Tenekoon et al. 1991). While *Nigella sativa* fixed oil is used extensively in traditional medicine and gastronomy, to our knowledge, its toxicity has been not studied seriously. Therefore, the present study was designed to investigate the acute and chronic toxicity effects of fixed oil of *Nigella sativa* seeds, using mice and rats.

Experimental

Acquisition of plant material

The plant seeds were harvested (July) in northern Morocco. The plant was identified and authenticated by Prof. A. Ouyahya, a plant taxonomist. A voucher specimen has been deposited at the Scientific Institute of Rabat.

Extraction

The *Nigella sativa* seeds were powdered mechanically. The extract was obtained by cold shocking of powdered seeds in (3 × 1.5) liters of hexane thrice in 24 hours. The solvent was removed from the extract under reduced pressure.

Chemical characterization

Reversed-phase TLC (thin layer chromatography) was carried out following the method outlined in the British Pharmacopoeia for identification of fixed oil. 4 µl of a 0.5% w/v solution of the fixed oil in chloroform were applied to the TLC plate.

Experimental animals

• *Acute toxicity:* Acute toxicity studies were carried out in *Iops ofa* mice, 8–10 weeks old and weighing 20–22 g each, using a single dose, administered orally or intaperitoneally. Seventy mice, divided into 7 groups, were designed for study of acute toxicity via the oral route. Each group of 10 mice (5 males and 5 females) received, respectively, a single oral dose of 10, 15, 20, 25, 30, 40 or 50 ml/kg body weight of *Nigella sativa* fixed oil. Seventy other mice divided into 7 groups were used to study toxicity intraperitoneally. Each group received, respectively, a single dose of 0.25, 0.5, 1, 2, 3, 4 or 6 ml/kg body weight of *Nigella sativa* fixed oil, prepared in gum acacia (5%). The animals were observed for gross effects and mortality during the 15 days following the oil administration. Postmortem examinations were carried out on the dead animals.

• *Chronic toxicity:* 24 *Wistar kyoto* rats weighing 200 g each were selected for this study and divided into 2 groups of 12 rats each. The control group rats (C-rats) and *Nigella sativa*-treated rat group (Ns-rats) received, respectively, 2 ml/kg body weight of distilled water and *Nigella sativa* fixed oil via the oral route for 12 weeks.

Body weight was measured weekly and metabolic measurements were realized at J0 and 2, 4, 6, 8, 10 and 12 weeks following oil administration. The choice of doses used was based on LD_{50} values. Doses were elevated enough and caused no mortality during treatment.

All animals were kept on a 12-hour dark and light schedule and fed standard lab chow *ad libitum*.

Metabolic measurements

Animals were studied after a 15-hour overnight fast. Afterwards, blood was obtained from the retro-orbital sinus (2 ml). Key hepatic enzymes, cholesterol, glucose, and triglycerides were measured spectrophotometrically, according to standardized procedures, using automatic analyzer (TECHNICON RA-XT) and commercially available kits, purchased from BOEHRINGER Mannheim (Meylan, France). Hematological parameters were determined automatically using ABX COBAS LO.

Histopathology

After the 12-week treatment, the *Nigella sativa*-treated animals were sacrificed. The heart, liver, kidneys and pancreas were immediately removed, weighed, and introduced in Bouin liquid (commercial formol: 24%; permuted water: 71%; crystallizing acetic acid: 5%; picric acid: to saturation). After microscopic examination, fragments were removed from organs and included in paraffin. Several sections were realized and stained systematically. The stain techniques used were: heamatoxylin and eosin stain, collagen stain (Masson trichrom) and periodic acid-Schiff stain (PAS). These preparations were analyzed using a optical microscope and compared to control animal preparations.

Statistical analysis

All data are expressed as mean ± SD. Student's and Snedecor's tests were applied. Acute toxicity results were analyzed using the Micropharm Dose-Reponses program: MPD (Urien, 1995).

Results

TLC examination

The fixed oil obtained from *Nigella sativa* seeds (chestnut color, agreeable perfume, extraction yield: 26% w/w) was analyzed using thin layer chromatography (TLC). *Nigella sativa* extract was found to contain the following fatty acids: myristic, palmitic, stearic, oleic, linoleic, linolenic, and arachidic acids; triterpenes and saponosides.

Acute toxicity

The effects of oral and intraperitoneal single doses of *Nigella sativa* seed fixed oils on mortality and LD_{50} values in *Iops ofa* mice are summarized in Table 1. LD_{50} values were determined using the MPD program (Urien, 1995). All doses, orally and intraperitoneally administered, caused immediate agitation and behavioral perturbations with temporary writhing, followed by a quiet attitude period and sedation. Generally, diarrhea was observed and the animals died 12 hours after the administration of fixed oil. Autopsied dead animals showed congested lungs and hearts stopped in diastole. The surviving animals quickly recovered their normal activity and growth, after a period ranging from 4 to 8 days, depending on the dose and mode of administration.

Chronic toxicity

The effects of the chronic administration of *Nigella sativa* fixed oil (2 ml/kg body wt./day) on biochemical and hematological parameters, according to treatment time, are summarized in Table 2.

Biochemical parameters

After 12 weeks of treatment, key hepatic enzymes did not increase significantly as compared to control values, whereas serum cholesterol, triglycerides and glucose levels decreased significantly ($p < 0.05$).

Hematological parameters

After 12 weeks of treatment, the leukocyte and platelet counts decreased significantly as compared to control values ($p < 0.01$), whereas hematocrit and hemoglobin level (HGB) increased significantly ($p < 0.05$). Consequently, mean globular volume (MGV), mean corpuscular content of hemoglobin ($MCCH^1$), and mean corpuscular concentration of hemoglobin ($MCCH^2$) increased significantly ($p < 0.01$).

Effects on body weight and weight of organs

Figure 1 shows the evolution of the mean body weight in the *Nigella sativa*-treated and control rat groups.

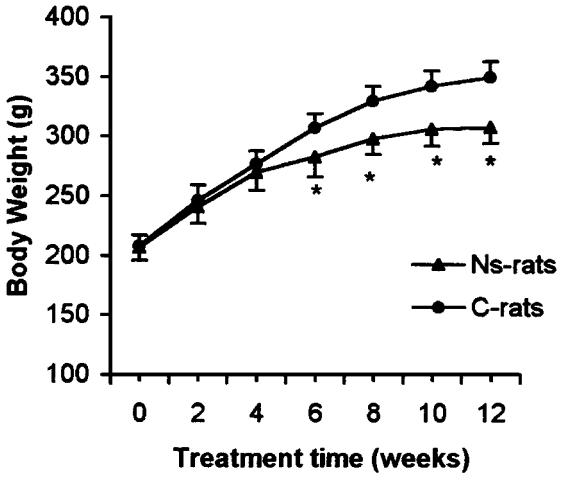

Figure 1. Effects of *Nigella sativa* fixed oil on rat body weight. C-rats – control-rats group (n = 12); Ns-rats – *Nigella sativa*-treated rats group (n = 12). Values are expressed as mean ± SD.
* significantly different from C-rats group as determined by student's test, $p < 0.01$.

Table 1. Mortality percentage and LD_{50} values in *Nigella sativa*-treated mice with oral or intraperineal single doses.

Oral administration	Dose (ml/kg body wt.)	5	10	20	25	30	40	50
	Mortality (%)	0	10	20	30	60	80	100
	LD_{50}: 28.8 ± 1; CI: [26.2–31.6] ml/kg body wt.							
Intraperitoneal administration	Dose (ml/kg body wt.)	0.25	1.0	1.5	2.0	3.0	4.0	
	Mortality (%)	0	10	20	50	90	100	
	LD_{50}: 2.06 ± 0,1; CI: [1.86–2.26] ml/kg body wt.							

LD_{50} – lethal dose 50; CI – confidence intervals; values are expressed as mean ± SD.
LD_{50} was determined using the MPD program (Urien 1995).

Table 2. Chronic effects of *Nigella sativa* fixed oil (2 ml/kg body wt./day) on biochemical and hematological parameters and organ weight.

		Ns-rats Treatment time		
Parameter (unit)	C-rats	4 weeks	8 weeks	12 weeks
ASAT (U/l)	128 ± 59	120 ± 40	156 ± 76	171 ± 72
ALAT (U/l)	47.5 ± 9.2	41.1 ± 12.1	38.4 ± 14.6	43.4 ± 15.7
T-bilirubin (mg/l)	1.34 ± 1.0	1.10 ± 0.94	1.50 ± 1.2	1.10 ± 0.7
ALP (U/l)	213.2 ± 68.4	187.8 ± 61.4	149.0 ± 57.4 *	139.4 ± 59.3 *
GGT (U/l)	4.40 ± 2.77	5.08 ± 2.15	3.85 ± 1.95	3.18 ± 1.83
Triglycerides (g/l)	0.68 ± 0.27	0.51 ± 0.21	0.55 ± 0.22	0.53 ± 0.12 *
Cholesterol (g/l)	0.71 ± 0.15	0.73 ± 0.10	0.59 ± 0.13 *	0.60 ± 0.09 *
HDL (g/l)	0.41 ± 0.1	0.71 ± 0.11 **	0.52 ± 0.11 *	0.58 ± 0.11 *
Uric acid (mg/l)	15.8 ± 5.8	15.5 ± 5.13	17.1 ± 7.3	14.2 ± 4.2
Creatinine (mg/l)	5.92 ± 1.32	6.36 ± 0.87	5.21 ± 0.85	6.76 ± 0.77
Glucose (g/l)	1.03 ± 0.20	0.89 ± 0.18	0.86 ± 0.2 *	0.89 ± 0.15 *
Erythrocytes (10^6/mm^3)	7.23 ± 1.03	7.05 ± 0.57	6.74 ± 0.44	6.91 ± 0.68
Leukocytes (10^3/mm^3)	7.25 ± 1.71	8.23 ± 1.6	7.6 ± 1.3	4.7 ± 1.5 **
Platelets (10^3/mm^3)	743 ± 121	680 ± 82	570 ± 109 **	504 ± 110 **
Haematocrit (%)	40.99 ± 4.32	39.26 ± 2.49	40.73 ± 3.15	43.60 ± 3.11 *
HGB (g/dl)	13.12 ± 1.45	13.53 ± 0.62	14.3 ± 0.94 *	15.4 ± 0.64 **
MGV (um3)	53.35 ± 0.14	52.75 ± 2.96	55.56 ± 2.01	56.3 ± 3.53 **
MCCH[1] (pg)	17.97 ± 0.95	18.77 ± 1.41	19.13 ± 1.48 *	19.26 ± 1.22 **
MCCH[2] (g/dl)	32.94 ± 1.81	34.82 ± 2.12	34.70 ± 1.84 *	34.80 ± 1.32 **
Organ weight (g)				
Heart	1.07 ± 0.10	–	–	1.03 ± 0.09
Liver	10.38 ± 1.19	–	–	9.73 ± 1.70
Pancreas	1.53 ± 0.23	–	–	1.57 ± 0.28
Kidneys	0.93 ± 0.23	–	–	1.11 ± 0.23

C-rats – control rats group; Ns-rats – *Nigella sativa*-treated rats group; ASAT – aspartate-aminotransferase; ALAT – alanine-aminotranferase; ALP – alkaline phosphatase; GGT – gamma-glutamyltransferase; HDL – high density lipoproteins; HGB – hemoglobin; MGV – mean globular volume; MCCH[1] – mean corpuscular content of hemoglobin; MCCH[2] – mean corpuscular concentration of hemoglobin. Values are expressed as mean ± SD (n = 12); * significantly different from C-group by student's test, $p < 0.05$; ** significantly different from C-group, $p < 0.01$

Changes in body weight were not similar for both groups. Indeed, the *Nigella sativa*-treated rats had significantly lower body weights than their control rat counterparts; this effect is statistically significant from the 6-week treatment point onward ($p < 0.01$). On the other hand, the weight of organs (heart, liver, kidneys and pancreas) was similar in both groups (Table 2).

No mortality or comportment abnormalities were noted during the treatment period. Values in control animals were sensibly similar at all time points and are grouped for the sake of simplicity.

Histopathology

No significant histopathological modifications were noted in any animal organs studied (heart, liver, kidneys and pancreas) in *Nigella sativa*-treated rats after 12 weeks of chronic treatment, as compared to control animals.

Discussion

The current study has shown a low toxicity of *Nigella sativa* fixed oil. The high values of oral and intraperitoneal lethal doses of *Nigella sativa* fixed oil (LD_{50} value = 28.8 ml/kg body wt., p.o. ; LD_{50} value = 2.06 ml/kg body wt., i.p.) show its low acute toxicity; and the key hepatic enzyme stability and organs integrity during and after 12 weeks of daily treatment show its low chronic toxicity. No evidence of *Nigella sativa* fixed oil toxicity was observed, however, when administered in different doses up to 10 ml/kg body wt., p.o. (Khanna et al. 1993). This suggests a low toxicity for *Nigella sativa* volatile oil, thymoquinone, alcoholic, and aqueous extracts, thymoquinone being the active principle (Houghton et al. 1995).

Nigella sativa fixed oil has been well-analyzed (Abdel-Aal and Attia, 1993; Aboul-Enein et al. 1995;

Houghton et al. 1995; Menounos et al. 1986). The TLC analysis of our fixed oil shows the same results as reported in literature. However, the chemical analyses of samples of *Nigella sativa* fixed oil from different countries have shown that the oils are very similar in composition, with 85% total unsaturated fatty acid (Houghton et al. 1995).

Key hepatic enzyme concentrations did not change significantly, while serum glucose, triglyceride and cholesterol levels decreased significantly and HDL concentration increased significantly, in *Nigella sativa*-treated rats. Sensibly different results have been obtained by use of *Nigella sativa* aqueous extract; serum ALAT and GGT increased, but serum ASAT and ALP level changes were not seen and histopathological modifications were not evident (Tenekoon et al. 1991). On the other hand, it has been shown that thymoquinone decreases-leakage of ALAT and ASAT in tert-butyl hydroperoxide-treated isolated rat hepatocytes (Daba and Abdel-Rahman, 1998). The decrease of serum ALP observed in *Nigella sativa* treated rats, has also been reported in rats treated with *Nigella sativa* together with vitamin E, *Crocus sativus* and cysteine (El-Daly, 1998).

Nigella sativa fixed oil, like the fibrates, decreases serum cholesterol and triglycerides, and ameliorates serum HDL. The fibrates act through PPARα (Peroxisome Proliferator-Activited Receptor α) activation (Martin et al. 2001; Torra et al. 2001). The same results have been obtained through use of troglitazone, a hypoglycemic agent that has been shown to ameliorate insulin resistance and hyperinsulinemia (Khoursheed et al. 1995).

Nigella sativa-treated rats had significantly lower body weights than the control rats. These effects may be related to the action of *Nigella sativa* on lipid metabolism. This effect was accompanied by concomitant alterations in plasma insulin levels, which might suggest a insulin-mediated mechanism of action (Labhal et al. 1997).

Nigella sativa fixed oil exhibits potent analgesic and sedative properties (Khanna et al. 1993), which may explain the quiet attitude and sedation following oil administration in mice and rats.

Hematological changes were observed in *Nigella sativa*-treated rats. The results shows a significant increase in hemoglobin concentration, associated to hematocrit, mean globular volume and mean corpuscular concentration of hemoglobin increases, and a significant fall in rat leukocyte and platelet count. Previous studies in mice and rats have shown that treatment with *Nigella sativa* extract significantly protects from cisplatin-induced falls in leukocyte count, hemoglobin level, mean osmotic fragility and hematocrit increase (El-Daly, 1998; Nair et al. 1991); influences leukocytes activities (Haq et al. 1995; Houghton et al. 1995) and causes the death of mice lymphocytes in vitro (Salomi et al. 1992). Further research is needed to elucidate the precise mechanisms of different actions of *Nigella sativa* fixed oil.

In conclusion, the low toxicity of *Nigella sativa* fixed oil, evidenced by high LD_{50} values, key hepatic enzyme stability, and organ integrity, suggests a wide margin of safety for therapeutic doses of *Nigella sativa* fixed oil, but the changes in hemoglobin metabolism and the fall in leukocyte and platelets count must be taken into consideration.

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