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Effect of *Nigella sativa* (Black Seed) on Subjective Feeling in Patients with Allergic Diseases

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***Nigella sativa* (black seed) is an important medicinal herb. In many Arabian, Asian and African countries, black seed oil is used as a natural remedy for a wide range of diseases, including various allergies. The plant's mechanism of action is still largely unknown. Due to the lack of study data on its efficacy in allergies, four studies on the clinical efficacy of *Nigella sativa* in allergic diseases are presented. In these studies, a total of 152 patients with allergic diseases (allergic rhinitis, bronchial asthma, atopic eczema) were treated with *Nigella sativa* oil, given in capsules at a dose of 40 to 80 mg/kg/day. The patients scored the subjective severity of target symptoms using a predefined scale. The following laboratory parameters were investigated: IgE, eosinophil count, endogenous cortisol in plasma and urine, ACTH, triglycerides, total cholesterol, LDL and HDL cholesterol and lymphocyte subpopulations.**

The score of subjective feeling decreased over the course of treatment with black seed oil in all four studies. A slight decrease in plasma triglycerides and a discrete increase in HDL cholesterol occurred while the lymphocyte subpopulations, endogenous cortisol levels and ACTH release remained unchanged. Black seed oil therefore proved to be an effective adjuvant for the treatment of allergic diseases. Copyright © 2003 John Wiley & Sons, Ltd.

Keywords: black seed; *Nigella sativa*; inhalation allergy; score of subjective feeling.

INTRODUCTION

Negative environmental factors cause an increase in allergic diseases. In Germany, one out of every three inhabitants suffers from typical allergy symptoms, the most prominent example of which is bronchial asthma. Childhood mortality due to bronchial asthma has even doubled during the past decade. In the USA, approximately 200 children die of asthma each year; over 150 000 are hospitalized because of asthma, and around 5 million have the disease (Landrigan, 1998). The incidence of asthma is on the rise, especially in urban areas, and the rising incidence rates are particularly prominent in American children of African and Latin descent. Asthma is the most common reason for hospitalization of children in New York, Chicago, Los Angeles, Atlanta and other metropolitan areas (CDC, 1996; Gottlieb *et al.*, 1995).

Bronchial asthma is a genetically based, multifactorial disease that is aggravated by a number of factors such as infections, allergen exposure, tobacco smoke and environmental pollutants. Inhalation allergies are regarded as an important risk factor for the development of bronchial asthma. Hay fever, a typical inhalation allergy, is generally triggered by wind-borne pollen and represents the acute form of seasonal allergic rhinitis. Pruritus and mucosal oedema are the chief complaints of hay fever sufferers. Next to inhalation allergies, food allergies are the second most common type of allergic disorders. The aetiopathology of most inflammatory bowel diseases, e.g. food allergies, is immunological. The lymphatic system of the intestines and bronchi is constantly confronted with numerous food and environmental antigens. In addition to its defensive function, the lymphatic system must ensure tolerance to its own intestinal flora and other substances. Stabilization of the arachidonic acid metabolism via modulation of prostaglandin and leukotriene production, and stabilization of interleukins and tumour necrosis factor (TNF) safeguards the body from allergic reactions. Foods or drugs that influence these messenger substances can be used to stabilize the immune system.

Allergic reactions can be prevented or reduced by total or partial avoidance of the causative allergens. Simple topical remedies such as mineral oil-based nasal

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ointments can help to reduce allergen exposure, e.g. in inhalation allergies (Bufe, 2000). Atopic allergic complaints can be alleviated by fatty oils that stabilize the immune system, e.g. the oils of evening primrose, borage and black seed (Handa and Kapoor 1988). Gas chromatography studies have shown that *Nigella sativa* oil contains pharmacologically active substances that modify leukotriene synthesis (Houghton *et al.*, 1995) and inhibit histamine release (Charakravary, 1993), e.g. thymoquinones, dithymoquinones, thymohydroquinones and thymol (Ghosheh *et al.*, 1999). These studies conducted to evaluate the antiallergic potency of black seed oil in animals demonstrated that even small concentrations of its active constituents effectively inhibited the release of histamine from mast cells (Charakravary, 1993). In modern medicine, inhalation allergy therapy is commonly based on the use of mast cell stabilizers such as cromoglycic acid. Since *Nigella sativa* oil works by the same mechanism, this makes it an especially attractive alternative drug for treatment of allergic/atopic diseases.

In naturopathic allergy treatment, black seed oil is used as a balanced diet. It is also reported to have other activities, such as providing protection against cytotoxic damage from chemotherapeutic drugs and oxidative stress (Badary *et al.*, 2000; Daba and Abdel-Rahman, 1998; El-Daly, 1998; Nagi *et al.*, 1999). Thymoquinones protect hepatocytes and the liver from exogenous toxins (Badary *et al.*, 2000; Daba and Abdel-Rahman, 1998); they also protect the liver from the toxic effects of cisplatin and carbon tetrachlorides (El-Daly, 1998; Nagi *et al.*, 1999). Thymoquinone enhances the antitumour effect of ifosfamide on induced ascites carcinomas (Badary, 1999). It also raises the resistance of mixed lymphocyte cultures to mitogens and exerts additional immunomodulatory effects by influencing the production of interleukin (IL) 1β, IL-8 and TNF-α (Haq *et al.*, 1995). Other investigators found that *N. sativa* provides increased resistance to mitogen-induced carcinogenesis (Salomi *et al.*, 1991; Worthen *et al.*, 1998). In order to assess the efficacy and possible mechanisms of action of black seed oil in adults and children with inhalation allergies, a total of four studies were conducted in patients with allergic diseases – two were placebo-controlled studies in 63 and 20 subjects, respectively, and two were open-label studies in 20 and 49 subjects, respectively.

MATERIALS AND METHODS

Patients and study design

Study I. The first study was a randomized, placebo-controlled, double-blinded trial that included a total of 63 patients (age 6–17 years) with allergic diseases (allergic rhinitis, atopic eczema, bronchial asthma) without a history of glucocorticoid treatment. Prick tests for inhalation allergens and blood tests (IgE, eosinophil count) were conducted in all test subjects. Forty-one patients were randomized to the *Nigella sativa* oil group, and 22 were randomized to the placebo group. All of the test subjects took either one black seed oil or one placebo oil capsule, three times daily (t.i.d.) for 8 weeks. Treatment was started at the first sign of allergy symptoms. The subjective severity of various clinical symptoms (hay fever, conjunctivitis, bronchial asthma, skin eczema, general condition) was assessed and IgE levels and eosinophil counts were determined before and after treatment.

Study II. This was an open-label study conducted in 49 patients (age 6–15 years) with atopic eczema (n = 6), bronchial asthma (n = 6) and/or seasonal allergic rhinitis (n = 45). A prick test for inhalation allergens was performed in all cases studied. All patients were treated with black seed oil capsules. Each patient took two capsules, three times daily, for 6–8 weeks. The subjective severity of various clinical parameters (hay fever, conjunctivitis, bronchial asthma, skin eczema, general condition) was assessed before and after treatment.

Study III. The third was a randomized, placebo-controlled, double-blinded study with a cross-over design. Twenty patients (12 women, 8 men; age 15–65 years) with allergic rhinitis that had not been treated with glucocorticoids were included in the study. The IgE levels of all patients were >100 KIU/L. The known allergens were grasses and cereal plants. Allergy symptoms affecting the eyes, nose, bronchi and skin were rated before and after treatment as 0 = not present, 1 = mild, or 2 = severe.

Study IV. The last was an open-label study in 20 adult subjects (5 men and 15 women), all of whom had inhalation allergies and were over 18 years of age. Apart from the history and physical examination, the following laboratory tests were performed in all patients (see Table 1): score of subjective feeling, cortisol in urine and plasma, ACTH, lymphocyte subpopulations, total cholesterol, triglycerides, LDL cholesterol, HDL cholesterol. All blood samples were drawn between 8:00 and 9:00 a.m. to take due account of potential circadian variations. Starting on day 0, each subject weighing ≤75 kg took three black seed oil capsules, twice daily (in the morning and at night), and subjects weighing >75 kg took three or four black seed oil capsules twice daily. Each patient was treated for a period of 28 days. The following clinical symptoms were rated as 0 = not present, 1 = mild, 2 = medium, 3 = severe, or 4 = unbearable at four sampling times during the treatment period: sneezing attacks, rhinorrhoea, itchy nose, nasal congestion, conjunctivitis and general condition.

Medications

The investigational product consisted of Egyptian black seed oil capsules (Immerfit®) manufactured by Phyt-Immun, 66424 Homburg/Saar, Germany. Each capsule contained 500 mg black seed oil (*Nigella sativa*) plus 6 mg vitamin E, 1.5 mg beta carotene, and 70 µg biotin for stabilization. The capsule shell was made of gelatin.

Sampling techniques

Blood sample collection. All blood samples were drawn from the non-occluded cubital vein with the patient sitting upright for standardization of the procedure.

Table 1. Study parameters and times of measurement (study IV)

Parameter	Time of measurement			
	Day –7	Day 0	Day 14	Day 28
History/physical examination	x	x		
Score of subjective feeling	x	x	x	x
ACTH	xx	xx	xx	xx
Cortisol in plasma	xx	xx	xx	xx
Cortisol in 24 h urine	x	x	x	x
Cholesterol	x	x	x	x
HDL	x	x	x	x
LDL	x	x	x	x
Triglycerides	x	x	x	x
Lymphocyte subpopulation	x			x

xx: before/after standard breakfast.

Table 2. Laboratory parameters and analytical techniques (study I–IV)

Parameter	Analytical technique	Test system
ACTH (pmol/L)	Immunoassays	Immulite Biermann
Cortisol in plasma/24 h urine (nmol/L)	Immunoassays	Immulite Biermann
Total cholesterol (mg/dL)	Immunoassays	Modular Analytics Roche
HDL cholesterol (mg/dL)	Immunoassays	Modular Analytics Roche
LDL cholesterol (mg/dL)	Immunoassays	Modular Analytics Roche
Triglycerides (mg/dL)	Immunoassays	Modular Analytics Roche
IgE (KIU/L)	Immunoassays	IMx Abbott
Eosinophil count (109/L)	Automated cell counter	Abbott CellDyn 3500
Lymphocyte subpopulations[a]	Flow cytometry	Becton Dickinson FACScan

[a] T-lymphocyte$_i$ CD3+; T-suppressor cell, CD3+/CD8+; T-helper cells, CD3+/CD4+; activated T-cell, CD3+/HLA-DR+; natural killer cells, CD3-/CD16/56.

Sterile, large-gauge disposable syringes were used. After collection, the blood samples were stored in closed polystyrene tubes until analysed in the laboratory.

Urine sample collection. Twenty-four hour urine samples were used.

Laboratory parameters and test methods

The laboratory parameters tested and the corresponding analytical techniques with the test systems used are listed in Table 2.

The lymphocyte subpopulations were analysed by flow cytometry. A standard flow cytometer (Becton Dickinson FACScan) was used. The leukocytes were analysed using fluorescein isothiocyanate (FITC) and phycoerythrin (PE) conjugated monoclonal antibodies (Becton Dickinson) against CD3 + CD4, CD3 + CD8, CD3 + CD 16/56 and CD3 + HLA-DR. The lymphocyte subpopulations were determined in T-lymphocyte (CD3+), T-suppressor cells (CD3+/CD8+), T-helper cells (CD3+/CD4+), activated T-cells (CD3+/HLA-DR+) and natural killer cells (CD3-/CD16/56+).

Statistical analysis

A statistical analysis of the data was performed using SPSS 10.0 software. The score of subjective feeling, the confirmatory variable, was analysed as a paired sample using Friedman's non-parametric two-way analysis of variance. The Wilcoxon test was used to analyse variables sampled at two different times. The null hypothesis H0 (uniform distribution at the sampling times) was rejected with a probability of error of ($p < 0.05$).

RESULTS

Score of subjective feeling

Study I. In the group treated with *Nigella sativa* (allergic rhinitis, atopic eczema, bronchial asthma), 25/41 patients (61%) had subjective improvement of clinical symptoms while 16/41 patients (39%) did not note any response to therapy; none of the patients' condition deteriorated. By comparison, only 9 of the 22 patients (40%) in the placebo group had subjective improvement, whereas 13/22 patients (60%) observed no response; one patient's condition deteriorated. The differences between the drug group and placebo group were significant ($p < 0.05$).

Regarding the patients with allergic rhinitis, 25/31 patients (81%) in the black seed oil group had subjective improvement of clinical symptoms and 6/31 (19%) did not observe any response to therapy, whereas 9/20 patients (45%) in the placebo group had subjective improvement and 11/20 patients (55%) did not observe any response. The differences between the drug and placebo groups were significant ($p < 0.05$). In patients with bronchial asthma, 2/3 patients on the drug had clinical improvement compared with 0/2 patients

Table 3. Score of subjective feeling of patients with allergic rhinitis (study III)

Symptom	Change in score of subjective feeling	
	N. sativa (mean)	Placebo (mean)
Eye complaints[a]	−1.23	−1.21
Nasal complaints[a]	−1.51	−1.53
Coughing/respiratory complaints[a]	−0.45	−0.43

[a] $p > 0.05$ (n.s.).

receiving the placebo. In atopic eczema, clinical improvement occurred in 2/6 patients on the drug compared with 1/3 patients in the placebo group.

Study II. In these 49 patients with allergic rhinitis, atopic eczema and/or bronchial asthma, subjective improvement of clinical symptoms occurred in 37/49 patients (76%) while 12/49 (24%) observed no response to therapy. In the subgroup with allergic rhinitis, 35/45 patients (78%) had subjective improvement of clinical symptoms while 10/45 (22%) remained unchanged. Worsening of symptoms was not observed in any of the patients. In the bronchial asthma subgroup, 4/6 patients (67%) had subjective improvement of clinical symptoms while 2/6 (33%) observed no therapeutic effect. These differences were significant ($p < 0.05$). In the subgroup with atopic eczema, 3/6 patients (50%) had subjective improvement of clinical symptoms, 2/6 (33%) remained unchanged and 1/6 (17%) had deterioration.

Study III. The analysis of the mean score of subjective feeling in these patients with allergic rhinitis showed that, over the course of treatment, the clinical symptoms of rhinitis and conjunctivitis decreased by an average of >1.2 points on the scale, and that the severity of coughing/respiratory symptoms decreased by an average of >0.4 points (Table 3). However, the differences between the drug and placebo groups were not statistically significant. The treatment period was too short.

Study IV. In allergic rhinitis, the mean score of subjective feeling for the target symptoms decreased continuously and significantly over the course of treatment (Friedman's test: $p = 0.017$), as is shown in Table 4 and in Fig. 1.

Laboratory variables

Study I. In the *Nigella sativa* group, the mean IgE level

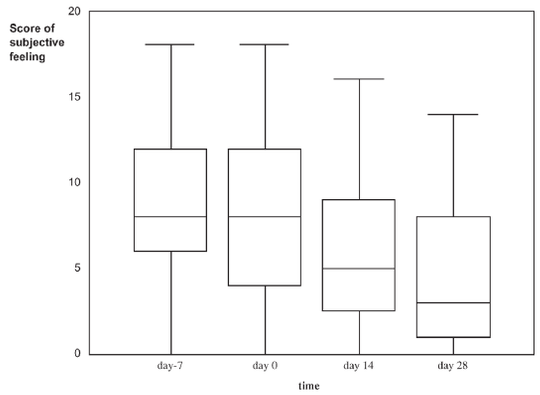

Figure 1. Box plot of scores of subjective feeling (study IV).

Table 4. Score of subjective feeling of patients with allergic rhinitis (study IV)

Time	Score of subjective feeling	
	Mean[a] ± SD	Median
Day −7	8.4 ± 4.9	8
Day 0	8.0 ± 5.1	8
Day 14	6.1 ± 4.5	5
Day 28	4.5 ± 4.5	3

[a] $p = 0.017$ (significant).

decreased insignificantly from 291.0 to 269.6 KIU/L ($p = 0.14$) and in the placebo group significantly from 387.6 to 337.9 KIU/L ($p = 0.02$). Statistically insignificant changes ($p = 0.07$) in the mean eosinophil count from 0.047×10^9/L to 0.044×10^9/L (*N. sativa*) and ($p = 0.87$) from 0.047×10^9/L to 0.047×10^9/L (placebo) were observed in both groups (Wilcoxon test of paired samples). The data for both variables are shown in Table 5.

Study IV. The measured values for ACTH before/after breakfast, cortisol before/after breakfast, cortisol in urine, total cholesterol and LDL cholesterol changed over the course of treatment (Friedman's test: $p = 0.13$). A slight insignificant increase in HDL cholesterol (Friedman's test: $p = 0.13$) and a significant change in triglyceride levels were observed (Friedman's test: $p = 0.02$). The mean triglyceride values rose from day −7 to day 0 and fell from day 0 to day 28 (Table 6). A 25% decrease occurred over the course of treatment.

The measured values for lymphocytes and lymphocyte subpopulations (T lymphocytes, activated T lymphocytes, T-helper cells, T-suppressor cells, B lymphocytes, natural killer cells) did not change significantly during

Table 5. IgE and eosinophils in the *N. sativa* and placebo group (study I)

Parameter	*N. sativa*		Placebo	
	Mean ± SD before treatment	Mean ± SD after treatment	Mean ± SD before treatment	Mean ± SD after treatment
IgE (KIU/L)	291.9 ± 650	269.6 ± 550[a]	387.6 ± 429	337.9 ± 374[c]
Eosinophil count ($\times 10^9$/L)	0.047 ± 0.03	0.044 ± 0.03[b]	0.047 ± 0.03	0.047 ± 0.03[d]

[a] $p = 0.14$ (n.s), [b] $p = 0.07$ (n.s), [c] $p = 0.02$ (significant), [d] $p = 0.87$ (n.s.).

Table 6. Changes in triglycerides (study IV)

Time	Mean[a] ± SD (mg/dL)	Median (mg/dL)
Day –7	100 ± 73	73
Day 0	127 ± 149	72
Day 14	116 ± 74	86
Day 28	95 ± 49	80

[a] $p = 0.02$.

the course of therapy (Wilcoxon test).

Adverse events

Study I. One child reported transient gastrointestinal problems.

Study II. Gastrointestinal complaints occurred in 9 of 49 children taking 3×2 capsules on an empty stomach. The dose of 80 mg/kg body weight was too high.

Study III/Study IV. No adverse events occurred in these studies.

DISCUSSION

The four studies presented above show that the oil of *Nigella sativa* (black seed) is indeed capable of relieving symptoms of allergic diseases (allergic rhinitis, atopic eczema, bronchial asthma). The effect of black seed oil on inhalation allergies, the most common type of allergic disease, was determined in two placebo-controlled studies (study I in children, study III in adults) and in two open-label studies (study II in children, study IV in adults). Depending on their body weight, the patients took three to seven 500 mg black seed oil capsules each day to achieve a dose of 40 mg/kg. The patients made subjective assessments of the severity of their clinical symptoms using the aforementioned scale. Improvement of allergy symptoms was observed in all four studies, i.e. the score of subjective feeling decreased over the course of treatment. The complaints of patients with allergic rhinitis decreased significantly. This was especially evident in studies I and II, where approximately 80% of the children had improvement of allergic rhinitis symptoms compared with only 45% and 22% of those who received the placebo in studies I and II, respectively. The children with bronchial asthma treated in study II also had relevant and significant improvement of clinical symptoms. In study IV, *Nigella sativa* oil proved to be very effective in adult subjects with allergic rhinitis but did not induce a significant response in those with bronchial asthma and atopic eczema. In study III, the drug did achieve some improvement of clinical symptoms, but this was not significantly different from that of the placebo.

A possible explanation for the positive clinical effects observed in our studies can be drawn from animal experiments. One study, for example, showed that *Nigella sativa* oil inhibiteds the cyclooxygenase and 5-lipoxygenase pathways of arachidonic acid metabolism (Houghton *et al.*, 1995), resulting in the decreased synthesis of thromboxane and leukotrienes. Leukotrienes, in particular, are causal factors for the development of bronchial asthma since they develop proinflammatory activity. Leukotriene receptor antagonists are therefore used for treatment of bronchial asthma (Jager and Kroegel, 1998). Investigators have not only found that this effect is induced by thymoquinone, but that other constituents of *Nigella sativa* oil can also modulate the magnitude of the effect (Charakravary, 1993). In an animal model, these investigators demonstrated that nigellone inhibits the release of histamine from sensitized mast cells after prior antigen exposure (Charakravary, 1993). The presumed mechanism of action is the reduction of intracellular calcium due to inhibition of intracellular Ca uptake because of the increased release and inhibition of protein kinase C. Significant target proteins that are modified by protein kinase C are involved in important physiological processes such as cell movement, secretion, membrane transport and regulation of the cell cycle. Mast cells are found in the connective tissues of the skin and organs and in the mucous membranes of the respiratory and gastrointestinal tracts, and are especially abundant near blood vessels. These cells contain large quantities of mediator substances. Once allergens bind to mast cell-bound IgE antibodies, the mediators are released together with intracellular calcium. The liberated mediators, especially histamine, play an important role in the development of immediate hypersensitivity type allergies (type 1). Histamine, for example, induces skin reddening by widening the blood vessels, induces itching by irritating sensitive nerve endings, and increases the permeability of the mucous membranes, resulting in increased fluid production and an increased tendency to oedema formation.

The antiinflammatory activity of black seed oil *in vivo* was confirmed in an animal model (Al-Ghamdi, 2001). After the investigators injected an inductor of inflammation, an oral dose of 500 mg/kg *Nigella sativa* oil was able to attenuate the resulting inflammatory response. This effect was comparable to that of a 100 mg/kg dose of acetylsalicylic acid (aspirin).

The quantitative analysis of lymphocyte subpopulations in our patients showed that the eosinophil count and cellular immune status remained unchanged or only exhibited a tendency to change under the influence of black seed oil. However, no evidence was found supporting the assumption that *Nigella sativa* oil increases the production of adrenocortical hormones in humans. The reason may be that, due to differences in causality/sensitivity, the animal values cannot be extended to humans or used to demonstrate the pharmacological effects of *Nigella sativa* oil when used at the recommended doses of approximately 40 mg/kg in humans. In most of the animal studies, the administered doses of black seed oil (usually >500 mg/kg body weight) were many times higher than those generally recommended for use in humans and used in the studies presented above. However, no evidence of hepatocellular damage was found in any of the studies despite the use of such high doses. The lack of hepatocellular toxicity of the drug was recently confirmed (Zaoui *et al.*, 2002). A rise in gamma-glutamyltransferase and alanine aminotransferase concentrations after administration of black seed oil was observed in only a single study (Tennekoon *et al.*, 1991).

In summary, we conclude that *Nigella sativa* oil significantly improved the clinical symptoms of allergic complaints in humans. Our findings in humans also indicate that the oil of *Nigella sativa* acts on the lipid metabolism, as was initially reported in animals and actually in humans too (El-Dakhakhny *et al*., 2000; Ibraheim *et al.*, 2001). *Nigella sativa* oil is presumed to modify the lipid profile by altering liver function, resulting in a change in lipid synthesis and lipid metabolism.

It may be possible to increase the clinical efficacy of *Nigella sativa* oil and to enhance its effect on the lipid metabolism by increasing the dose, but this may raise the risk of gastrointestinal side effects. The investigated *Nigella sativa* oil product, administered at doses of 40 mg/kg, was very well tolerated by adults and children. Adverse effects did not occur except in children receiving high doses of 80 mg/kg. We therefore recommend that, when *Nigella sativa* oil is used in children, it should be administered in weight-adapted doses given after meals. To better assess the pharmacological effects of *Nigella sativa* oil in humans, future studies should focus particularly on mast cell stabilization and the drug's ability to stabilize the immune system with its messenger substances. The future studies should also have longer observation periods to better assess the effects of the drug, especially its long-term effects.

REFERENCES

Al-Ghamdi M-S. 2001. The anti-inflammatory, analgesic and antipyretic activity of *Nigella sativa*. *J Ethnopharmacol* **76**: 45–48.

Badary OA. 1999. Thymoquinone attenuates ifosfamide-induced Fanconi syndrome in rats and enhances its antitumor activity in mice. *J Ethnopharmacol* **67**: 135–142.

Badary OA, Abdel-Naim AB, Abdel-Wahab MH, Hamada FM. 2000. The influence of thymoquinone on doxorubicin-induced hyperlipidemic nephropathy in rats. *Toxicology* **143**: 219–226.

Bufe A. 2000. A simple advice for the prevention of pollen-induced allergic rhinitis. *Int Arch Allergy Immunol* **121**: 85–86.

Centers for Disease Control and Prevention. 1996. Asthma mortality and hospitalization among children and young adults – United States 1980–1993. *MMWR* **45**: 350–353.

Charakravary N. 1993. Inhibition of histamine release from mast cells by nigellone. *Ann Allergy* **70**: 237–242.

Daba MH, Abdel-Rahman MS. 1998. Hepatoprotective activity of thymoquinone in isolated rat hepatocytes. *Toxicol Lett* **95**: 23–29.

El-Dakhakhny M, Naglaa I, Abdel Halim M, Abdel Halim MA. 2000. *Nigella sativa* L. oil protects against induced hepatotoxicity and improves serum lipid profile in rats. *Arzneimittelforschung* **50**: 832–836.

El-Daly ES. 1998. Protective effect of cysteine and vitamin E, *Crocus sativus* and *Nigella sativa* extracts on cisplatin-induced toxicity in rats. *J Pharm Belg* **53**: 87–93; discussion 93–95.

Ghosheh OA, Houdi AA, Crooks PA. 1999. High performance liquid chromatographic analysis of the pharmacologically active quinones and related compounds in the oil of the black seed (*Nigella sativa*). *J Pharm Biomed Anal* **19**: 757–762.

Gottlieb DJ, Beiser AS, O'Connor GT. 1995. Poverty, race, and medication use are correlates of asthma hospitalization rates: A small area analysis of Boston. *Chest* **108**: 28–35.

Handa SS, Kapoor VK. 1988. *Pharmacognosy*. Vallabh Prakashen: New Delhi.

Haq A, Abdullatif M, Lobo PI, Khabar KS, Sheth KV, al-Sedairy ST. 1995. *Nigella sativa*: Effects on human lymphocytes and polymorphonuclear leukocyte phagocytic activity. *Immunopharmacology* **30**: 147–155.

Houghton PJ, Zarka R, de las Heras B, Hoult JR. 1995. Fixed oil of *Nigella sativa* and derived thymoquinone inhibit eicosanoid generation in leukocytes and membrane lipid peroxidation. *Planta Med* **61**: 33–36.

Ibraheim ZZ, Aly AM, Naddaf AR. 2001. The effect of oral administration of *Nigella sativa* L. seeds and oil on some blood parameters. *Bull Pharm Sci* **24**: 29–39.

Jager L, Kroegel C. 1998. Leukotriene receptor antagonists and bronchial asthma. *Arzneimittelforschung* **48**: 205–211.

Landrigan PJ. 1998. Gesundheit von Kindern und Umwelt: Eine neue Agenda für Präventive Forschung. *Environ Health Perspects* **106**: 787–794.

Nagi MN, Alam K, Badary OA, al-Shabanah OA, al-Sawaf HA, al-Bekairi AM. 1999. Thymoquinone protects against carbon tetrachloride hepatotoxicity in mice via an antioxidant mechanism. *Biochem Mol Biol Int* **47**: 153–159.

Salomi NJ, Nair SC, Panikkar KR. 1991. Inhibitory effects of *Nigella sativa* and saffron (*Crocus sativus*) in chemical carcinogenesis in mice. *Nutr Cancer* **16**: 67–72.

Tennekoon KH, Jeevathayaparan S, Kurukulassooriya AP, Karunanayake EH. 1991. Possible hepatotoxicity of *Nigella sativa* seeds and *Dregea volubilis* leaves. *J Ethnopharmacol* **31**: 283–289.

Worthen DR, Ghosheh OA, Crooks PA. 1998. The anti-tumor activity of some crude and purified components of black-seed, *Nigella sativa* L. *Anticancer Res* **18**: 1527–1532.

Zaoui A, Cherrah Y, Mahassini N, Alaoui K, Amarouch H, Hassar M. 2002. Acute and chronic toxicity of *Nigella sativa* fixed oil. *Phytomedicine* **9**: 69–74.