

Nigella sativa

Holy Herb of the Middle East

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Abstract

Nigella sativa (black seed or black cumin) originated from the Mediterranean region and has been used in cultures in that area since time immemorial. The well-named herb has jet-black seeds notable for their content of terpenoids, particularly thymoquinone, and fatty acids. Clinical trials have validated this herb's traditional use for treating atopic disorders. There is also clinical trial support, although preliminary, for the use of black seed in people withdrawing from, and trying to abstain from, opioids, and people who want to improve lipid profiles and/or decrease seizure frequency.

Other actions black seed shows are antidiabetic, antineoplastic, antimicrobial, inflammation-modulating, redox-modulating, immunomodulating, analgesic, hepatoprotective, nephroprotective, and gastroprotective effects. Animal studies suggest that this herb may be a useful adjunct to cancer chemotherapy and acetaminophen. Black seed is extremely safe if used in proper doses and is a widely utilized food item in the Middle East and India. Further research is needed but this resource should be more widely utilized in the West.

Introduction

Nigella sativa, known as black seed or black cumin in English and *habbat al-barakah* in Arabic (see Common Names for *Nigella sativa*), occupies an important place in the herbal materia medica in the Middle East, Eastern Africa, and Asia. Yet, the herb is much less well-known in Western Europe and the Americas.

Black seed is in the Ranunculaceae family. As the common name suggests, the tiny (2–4-mm long), black boat-shaped seeds are used in food and medicine. The beautiful white or blue flowers have finely divided sepals and leaves. This plant is widely cultivated and can be grown as an annual garden plant in many parts of the United States.

A flask dated back to ~1650 BC from a ruined temple of Hittite civilization in central Turkey has been shown to contain black seed.¹ It is not unequivocally known what the ancient Egyptian name of this herb is, so, whether it was

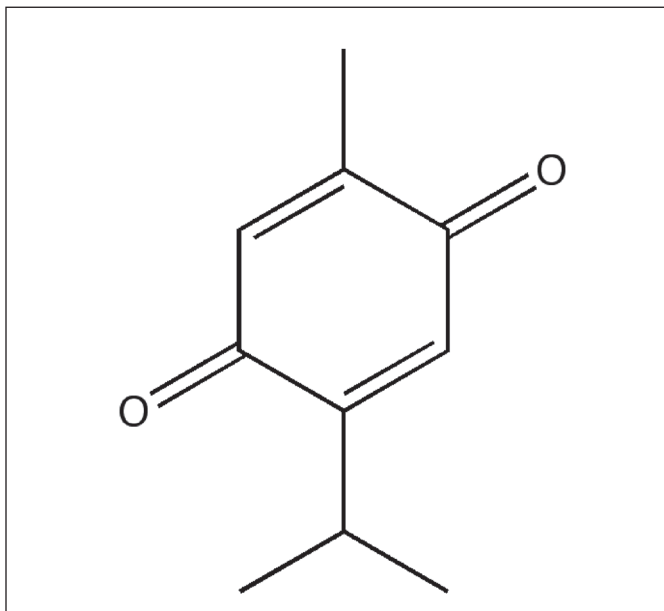
definitely used then is unclear but strongly suspected.² The seeds were reportedly found in the tomb of Pharaoh Tutankhamun.³ The Greek herbalist Dioscorides discussed what he called *melanthion* in section 79 of his third volume of his materia medica in the first century AD.⁴ His description of the plant unambiguously identifies it as *Nigella sativa*, including that it was used to make bread, which is still true in parts of the Middle East today. Dioscorides recommends black seed for headaches, swellings, warts, toothaches, colds, dyspnea, and spider bites among other things. It is reputedly the most-mentioned herb in the *Qur'an*. It is discussed as a remedy to improve bodily energy in Avicenna's (980–1037 CE) massive materia medica, *The Canon of Medicine (Qanun fi al-Tibb)*.⁵ The cultivation of black seed is discussed in the Bible in Isaiah 28:25–27.⁶

The chemistry, best-documented actions and uses, safety, and doses for black seed are discussed in depth below. See Table 1 for uses of black seed. The literature is so vast on this herb that it is simply not possible to discuss all its effects and aspects here.

Chemistry

Black seed contains a mixture of low-molecular-weight terpenoids. These can be isolated by steam distillation or supercritical carbon dioxide; the result is known as a volatile oil. Thymoquinone (see chemical structure) is the best characterized of these compounds and has been extensively researched. Typically, good-quality volatile oil contains 18%–24% thymoquinone.⁷ This substance also appears to dimerize to a substance known variously as nigellone or dithymoquinone in tiny amounts. Thymol and thymohydroquinone are also present in the oil.⁸

The seeds also contain a substantial quantity of fatty acids. When pressed out, a mixture of these is known as the fixed oil. The mixture is “fixed” because, unlike the small terpenoids in the volatile oil, these large molecules do not vaporize readily and thus are not odiferous. The omega-6 fatty acid, linoleic acid, makes up 50% of this oil; the omega-9 fatty acid, oleic



Chemical structure of thymoquinone.

acid, makes up 25%; and the saturated fat, palmitic acid, makes up 18% according to one analysis.⁹ The thymoquinone concentration in the fixed oil is 3.5–8.7 mg/g.¹⁰

Unfortunately, many research articles do not state clearly whether the researchers studied a volatile or fixed oil of black seed. Sometimes this becomes clear when the authors mention certain chemicals in the extract that are generally only found in one extract or the other. However, at times it is simply not clear. All studies of black seed should identify fully whatever extract is being used.

Asthma and Allergies

Many studies suggest that black seed can help people with asthma and allergies. Avicenna wrote in *The Canon of Medicine* that black seed might help people with dyspnea.⁵ In a preliminary double-blinded, randomized clinical trial, 29 Iranian adults with asthma were randomly given either black seed or placebo for 3 months.¹¹ The dose used was extremely unclear but was described as what appeared to be a steam-distilled volatile oil containing 100 mg of herb/100 mL of extract, and 15 mL/kg of body weight was given to the subjects per day. All patients took inhaled corticosteroids, and some patients took other oral antiasthma medications of various types. There was a significant reduction of all asthma symptoms assessed and improved scoring on pulmonary function tests (PFTs) in the black seed group, compared with the control group by the end of the trial. The authors did not mention the occurrence of any adverse effects.

In a double-blinded, crossover trial assessing the acute bronchodilating effects of a steam-distilled volatile oil of black seed, 15 adult Iranian patients with asthma volunteered.¹² All patients were regular users of inhaled corticosteroids. Although black seed significantly improved PFTs within 30 minutes of 50 mg/kg and 100 mg/kg doses of the

extract, lasting for about 150 minutes, the effect was significantly weaker than that of oral theophylline or inhaled salbutamol. The authors did not mention the occurrence of any adverse effects.

In another double-blinded trial, 40 male Iranian war veterans exposed to mustard gas with resulting respiratory problems were randomized to receive either 0.375 mL/kg body weight of a 50 mg/mL solution of black seed or placebo in a syrup base for 2 months.¹³ Respiratory symptoms and PFTs improved significantly in the black seed group, compared with the placebo group. Use of corticosteroids and β -agonists decreased in the black seed group but not in the placebo group. The authors did not mention the occurrence of any adverse effects.

Black seed appears to have serious potential to help patients avoid acute asthma attacks, as well as to reduce the severity of acute attacks if they occur. Further trials are warranted. A clarification of the product and dose used in the Iranian clinical trials is needed. For studies that have reported on the potential mechanisms of action of black seed in asthma, see Table 2. Pure thymoquinone may actually increase bronchoconstriction, an argument in favor of use of whole-plant extracts of black seed and not isolated constituents.¹⁴

In a double-blinded trial, 59 adult Iranians with allergic rhinitis were randomly assigned to take black seed oil or placebo for 30 days.¹⁵ Unfortunately, it was not stated if this was volatile oil or fixed oil, and no doses were stated, though each capsules was said to contain 0.5 mL of oil. Black seed oil significantly reduced symptoms, compared with placebo at the 15-day and 30-day marks, without any difference in nasal mucosal immunoglobulin (IgE) levels. No adverse effects were reported. The authors did not mention the occurrence of any adverse effects.

In a prior study involving many trials, a fixed oil of black seed was studied in an European population (adults and children).¹⁶ First, a group of 63 children with allergic rhinitis, atopic dermatitis, or asthma were randomly treated with black seed oil, 500 mg, three times per day, or placebo for 8 weeks. Symptoms were reduced more significantly in the black seed group than in the placebo group. The largest group had allergic rhinitis, and, thus, the results were most robust in this area, with 81% (25/31) of subjects who received black seed oil reporting reduced symptoms, compared with just 45% (9/20) in the placebo group reporting reduced symptoms. A second double-blinded trial in this study, in 20 subjects with allergic rhinitis, ages 15–65, with a crossover did not find a difference in symptom reduction between the black seed and placebo groups. Two other open trials were also conducted as part of this study and both showed that black seed oil was effective, although, these studies were much weaker methodologically.

Based on the studies discussed in this section, black seed appears to be a potentially helpful and safe treatment for people with atopic diseases, both for acute symptoms and to prevent them from occurring. A typical dose of fixed oil of black seed for preventing acute attacks is 500–1000 mg t.i.d. with food. A typical dose of volatile oil of black seed for acute symptoms is 3–5 drops every 15–30 minutes, repeated up to four times.



Nigella sativa (black seed). Drawing ©2011, by Eric Yarnell, ND.

Neurologic and Antiseizure Effects

Numerous experimental reports exist of the effects of black seed and thymoquinone on the nervous system. For example, thymoquinone, 5 mg/kg, by mouth, for 5 days, before inducing cerebral ischemia protected rats against hippocampal neurodegeneration.¹⁷ A defatted, methanol extract of black seed produced central nervous system (CNS)–depressant and analgesic activity in rats.¹⁸ Thymoquinone produced anticonvulsant activity in mice with seizures induced by pentylenetetrazole (PTZ) and maximal electroshock.¹⁹ Volatile oil of black seed had a similar benefit in mice with PTZ-induced seizures in another study.²⁰

A double-blinded clinical trial was therefore conducted in 22 Iranian children with any type of epilepsy not fully responding to pharmacologic treatment.²¹ They were randomly assigned to receive 0.5 mg/kg of thymoquinone or placebo twice per day in a syrup base for 4 weeks, followed by a 2-week washout period, then crossed over to the other treatment for 4 weeks. Subjects continued all antiseizure medications they were already taking throughout the trial. Seizure frequency was significantly reduced when the groups were taking thymoquinone, compared with placebo. Parental satisfaction with treatment for their children's epilepsy was significantly better during periods of use of thymoquinone, compared with placebo. Nausea, somnolence, and other adverse effects occurred with statistically similar frequency during the thymoquinone and placebo periods. Overall, this trial suggests that thymoquinone may have useful antiseizure activity and is no more dangerous than placebo when administered in an alcohol-containing syrup base.

Black seed has also been tested as a treatment for opioid addiction in an open trial in Pakistan.* Fifty male opioid

*Sangi S. Role of *Nigella sativa* in opioid dependence [masters thesis]. Karachi: University of Karachi, 2004.

Table 1. Major Uses for *Nigella sativa*

Indications	Clinical trials*
Asthma and allergies	Many
Cancer	None identified
Chemotherapy adjunct	None identified
Diabetes and metabolic syndrome	Preliminary
Emmenagogue; abortifacient (high-dose)	None identified
Hypertension	None identified
Liver protection	None identified
Opioid addiction	Preliminary
Rheumatoid arthritis	None identified
Seizure disorders	Preliminary

*Refers only to those published in English or indexed in PubMed.

abusers received placebo for 2 days after withdrawing from opioids, then half were given 250 mg of crude black seed powder and half 500 mg of the powder, three times per day, in capsules, for up to 12 weeks. All volunteers were hospitalized for the first 12 days and then released with ongoing treatment and weekly check-ins. Some patients took diazepam 5 mg at bedtime, as needed, to sleep. Both doses significantly reduced

Black seed should be investigated further as an aid to help people withdraw from, and stay away from, opioids.

acute withdrawal symptoms, compared with the placebo period. The higher dose was more effective than the lower dose. Cravings and relapses were reduced by both doses, compared with historical controls. Black seed should be investigated further as an aid to help people withdraw from, and stay away from, opioids.

Diabetes and Metabolic Syndrome

Black seed has a long history of use for diabetes and glucose-intolerance syndromes. Rodent studies have continually shown that black seed has antidiabetic effects, largely focused on improvement of hepatic glucose handling.^{22,23} However, black seed may also decrease glucose absorption and has been shown to be as effective as metformin for improving glucose tolerance in rats.²⁴

In a double-blinded clinical trial conducted in Pakistan, 73 adult men and women with dyslipidemia but not frank dia-

betes mellitus were randomized to receive 1 g of black seed powder or placebo twice daily for 6 weeks.²⁵ The change in total cholesterol level just missed statistical significance ($P = 0.06$), with the average being 188.95 in the black seed group and 199.64 in the placebo group at the end of the trial. All other measures including fasting blood glucose, low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol, triglycerides, waist circumference, and blood pressure (BP) were not significantly different, though the trend was in favor of black seed. It is likely that the sample size was insufficient to detect changes. The authors did not mention the occurrence of any adverse effects. Larger trials are warranted to determine whether black seed is helpful for patients with dyslipidemia, metabolic syndrome, or diabetes. The optimal dose form and dose also need to be assessed.

Cancer and Chemotherapy Adjunct

In vitro studies suggest that black seed and thymoquinone may have antineoplastic activity.²⁶ Thymoquinone was active against acute lymphoblastic leukemia cells in vitro, in part, through modification of epigenetic mechanisms that help cause and maintain cancer.²⁷ A saponin, hederin, was isolated in one study and found to be a significant contributor to anticancer activity.²⁸ An aqueous extract of black seed was active against hepatocellular carcinoma cells in vitro.²⁹ No human clinical trials have yet been published on black seed in patients with cancer.

In addition to producing apparent direct antineoplastic activity, black seed also influences the immune system in ways that may help fight cancer. In one study, black seed aqueous extract stimulated anticancer activity of natural killer (NK) cells among other beneficial immunologic effects in vitro.³⁰ Numerous other reports have been published on the complex effects of black seed and its constituents on immune function.³¹

Doxorubicin (Adriamycin) is a chemotherapy drug with well-established cardiotoxicity. In a study on rats, thymoqui-

none, 10 mg/kg p.o., for 5 days before a single injection of doxorubicin significantly reduced cardiac damage.³² This appeared to be at least partially as a result of scavenging of superoxide radicals generated by doxorubicin. Doxorubicin can also cause nephropathy and hyperlipidemia in rats. Pretreatment of rats with thymoquinone, 10 mg/kg p.o., daily for 5 days before doxorubicin administration greatly blunted these toxic effects, again as a result of the redox-modulating properties of the herb. Thymoquinone, 5 mg/kg p.o., for 5 days before ifosfamide administration greatly reduced the toxicity of this drug against the kidneys in rodents.³³

These protective effects might raise concerns that thymoquinone or black seed might interfere with the efficacy of chemotherapy drugs, although the literature is replete with evidence that redox modulators actually only enhance their effects while offsetting adverse effects in humans.³⁴

One in vitro study found that thymoquinone could increase sensitivity of pancreatic cancer cells to both gemcitabine and oxaliplatin, largely because of the ability of thymoquinone to downregulate NF κ B.³⁵ In the ifosfamide study mentioned above, total mortality in the rodents was reduced when they were given ifosfamide combined with thymoquinone, further indicating that black seed may potentiate the efficacy of chemotherapy while offsetting its toxicity. Human clinical trials are warranted.

Other Actions

Black seed has demonstrated many other actions in in vitro and animal studies that may be clinically relevant, though clinical trials or other clear proof of efficacy in humans is lacking. Black seed may protect a host of organs from damage, in part, because the plant is a redox and inflammation modulator. For a review of studies on the hepatoprotective effects of black seed and its constituents, see Table 3.

Black seed fixed oil protected rats against ethanol-induced gastric ulcers.³⁶ Mucin and glutathione levels increased under black seed oil treatment. In rats subjected to

Table 2. Potential Mechanisms of Action of *Nigella sativa* in Asthma

Mechanisms	Models	Extracts	References
Calcium-channel blocker	Guinea pig trachea	Crude extract	*
Anticholinergic	Guinea pigs trachea	Crude extract	†
Antihistamine	Guinea pig trachea	Crude extract; thymoquinone; thymohydroquinone; nigellone	‡,¶,§
β -2-agonist	Guinea pig trachea	Aqueous extract	

*Gilani AH, Aziz N, Khurram IM, et al. Bronchodilator, spasmolytic and calcium antagonist activities of *Nigella sativa* seeds (*Kalonji*): A traditional herbal product with multiple medicinal uses. *J Pak Med Assoc* 2001;51:115–120. †Boskabady MH, Shahabi M. Bronchodilatory and anticholinergic effects of *Nigella sativa* on isolated guinea-pig tracheal chains. *Iran J Med Sci* 1997;22:127–133. ‡Boskabady MH, Shiravi N. Inhibitory effect of *Nigella sativa* on histamine (H1) receptors of isolated guinea pig tracheal chains. *Eur Respir J* 2000;16(suppl31):461s. ¶Marozzi FJ, Kocalski AB, Malone MH. Studies on the antihistaminic effects of thymoquinone, thymohydroquinone and quercetin. *Drug Res* 1970;20:1574–1577. §Chakravarty N. Inhibition of histamine release from mast cells by nigellone. *Ann Allerg* 1993;70:237–242. ||Boskabady MH, Kiani S, Jandaghi P. Stimulatory effect of *Nigella sativa* on β 2-adrenergic receptors of guinea pig tracheal chains. *Med J IR Iran* 2004;18:153–158.

gastric ischemia and reperfusion, which also causes ulceration of the mucosa, black seed, fixed oil, and thymoquinone (5 or 20 mg/kg p.o.) was significantly protective against or reduced severity of such ulcers.³⁷ It should be noted that higher doses of thymoquinone (50 or 100 mg/kg p.o.) actually aggravated ulceration, at least in part by depletion of glutathione. A separate rat study has confirmed that thymoquinone, 20 mg/kg p.o., can be protective against ethanol-induced ulcers.³⁸

Thymoquinone and black seed volatile oil helped rats with acute respiratory distress syndrome and pulmonary aspiration.^{39,40} Thymoquinone inhibited NKκB in mast cells in vitro.⁴¹ This constituent protected rats against hyperhomocysteine-induced cardiovascular damage⁴² and protected mice against mortality caused by sepsis with *Escherichia coli*.⁴³ Black seed fixed oil and thymoquinone were analgesic in mice.⁴⁴ A range of antimicrobial actions have been reported for various black seed extracts.^{45,46} Many other actions could be listed but these mentioned here give a sense of the varied and intriguing potential of this herb.

Safety and Dosing

The use of black seed as food in many areas attests to its high degree of safety. Numerous preclinical studies have investigated black seed toxicology further and found the herb

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quite safe. In mice and rats, the LD₅₀ of fixed oil of black seed was very high at 29 mL/kg. Chronic intake of 2 mL/kg for 12 weeks was associated with no clear organ damage,

Common Names for *Nigella sativa*

Amharic—*tikur azmud*

Arabic—*kamun eswid* ("black cumin"), *habbat al-barakah* ("seed of blessing")

Assamese—*kaljeera*

Hindi—*kalonji, mangrail*

Hebrew—*ketzakh*

Malayalam—*karim jerrakam*

Persian—*siyah daneh*

Russian—*chernushka*

Tamil—*karum cheerakam*

Turkish—*çörek otu*

although leukocyte and platelet counts did fall but not to below normal limits.⁴⁷ Another chronic feeding test found that supplementing the diet of rats with 4% fixed oil or 0.3% volatile oil from black seed for 56 days had no harmful effects.⁴⁸ There was a minor weight loss in the fixed oil group. Feeding black seed fixed oil 0.8 mL daily to female rats through two pregnancies actually improved the health of their pups.⁴⁹

Most clinical trials as reported above have found minimal or no toxicity from crude black seed extracts. Isolated thymoquinone does appear to be able to be overdosed and should either be used in lower doses (maximum 0.5 mg/kg body weight per day, based on the one existing human study of this substance) or avoided until more human clinical trials are completed.

For most applications, 500–1000 mg of crude black seed powder, three times per day, is best. Fixed oil doses are similar. The dose of tincture would be 3–5 mL, three times per day, made with at least 60% ethanol.

Table 3. Hepatoprotective Effects of *Nigella sativa*

Extracts or compounds	Models	Hepatotoxins	References
Thymoquinone	Rat hepatocytes	Tert-butyl hydroperoxide	*
Thymoquinone	Mice	Carbon tetrachloride	†
Methanol extract of black seed	Rats	Carbon tetrachloride	‡
Black seed fixed oil	Rats	D-Galactosamine	¶
Black seed fixed oil	Mice	<i>Schistosoma mansoni</i>	§
Thymoquinone	Mice	Acetaminophen	

*Daba MH, Abdel-Rahman MS. Hepatoprotective activity of thymoquinone in isolated rat hepatocytes. *Toxicol Lett* 1998;95:23–29. †Mansour MA. Protective effects of thymoquinone and desferrioxamine against hepatotoxicity of carbon tetrachloride in mice. *Life Sci* 2000;66:2583–2591. ‡Abuelgasim AI, Omer EA, Elmahdi B. The effectiveness of *Nigella sativa* against liver damage in rats. *Res J Med Plant* 2008;2:43–47. ¶El-Dakhakny M, May NI, Halim MA. *Nigella sativa* L oil protects against induced hepatotoxicity and improves serum lipid profile in rats. *Arzneim Forsch* 2000;50:832–836. §Alhmod MR, El-Abhar HS, Saleh S. The effect of *Nigella sativa* oil against the liver damage induced by *Schistosoma mansoni* infection in mice. *J Ethnopharmacol* 2002;79:1–11. ||Nagi MN, Almakki HA, Sayed-Ahmed MM, Al-Bekairi AM. Thymoquinone supplementation reverses acetaminophen-induced oxidative stress, nitric oxide production and energy decline in mice liver. *Food Chem Toxicol* 2010;48:2361–2365.

Conclusion

Black seed is a well-researched herb with a strong historical basis for use. It is unfortunate that this sustainable, multifaceted herb is not more widely cultivated and used in the West. It is added to protocols for patients with allergies and asthma, but may also be effective in patients with seizure disorders, opioid addiction, dyslipidemia, and other conditions. More work is needed to determine ideal dose forms and doses, but enough has been done to allow clinicians to be comfortable with starting to include black seed in their protocols. ■

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