Review

Medicinal benefits of Nigella sativa in bronchial asthma: A literature review

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Article history:
Received 16 March 2017
Accepted 9 July 2017
Available online 11 July 2017

Keywords:
Nigella sativa
Black seed
Asthma
Traditional medicine
Clinical studies

Abstract

Nigella sativa L. (NS) seeds, known as black seed, is a spice and a traditional herbal medicine used in various diseases including bronchial asthma. This review aimed to assess the studies supporting the medicinal use of NS in asthma and to highlight future research priorities. Various medical databases were searched for the effects of NS and its active secondary metabolites in asthma inflammation and outcomes. There were fourteen preclinical studies describing multiple effects of NS in animal or cellular models of asthma including bronchodilation, anti-histaminic, anti-inflammatory, anti-leukotrienes and immunomodulatory effects. Furthermore, seven clinical studies showed improvements in different asthma outcomes including symptoms, pulmonary function and laboratory parameters. However, often these studies are small and used ill-defined preparations. In conclusion, NS could be therapeutically beneficial in alleviating airway inflammation and the control of asthma symptoms, but the evidence remains scanty and is often based on poorly characterised preparations. Accordingly, well-designed large clinical studies using chemically well characterised NS preparation are required.

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Contents

1. Introduction .............................................................. 1131
2. Methods ................................................................. 1131
3. Results. ........................................................................ 1131
3.1. Preclinical studies of Nigella sativa in cellular and animal models of asthma .............................................. 1131
3.2. Clinical studies of Nigella sativa in patients with asthma ........................................................................ 1133
4. Conclusion ............................................................... 1133
Funding. ........................................................................ 1135
References ..................................................................... 1135

Abbreviations: NS, Nigella sativa L.; GINA, Global Initiative for Asthma; IL, Interleukin; ACT, Asthma Control Test; FEV1, forced expiratory volume in one second; Th1, Type 1 T helper (Th1) cells; Th2, Type 2 T helper (Th2) cells; RDBPCT, Randomised Double-Blinded Placebo-Controlled Clinical Trial; RSBPCT, Randomised Single-Blinded Placebo-Controlled Clinical Trial; RDBCT, Randomised Double-Blinded Clinical Trial; FeNO, fractional exhaled nitric oxide; IgE, Immunoglobulin E.

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Peer review under responsibility of King Saud University.

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1. Introduction

The seeds of the medicinal plant *Nigella sativa* L. (NS) are commonly used as a spice known as black seed. It also has traditional medical applications and considered to be a characteristic traditional herbal medicine for diverse diseases in Unani, Arabic, Prophetic and Indian traditional medicines (Ahmad et al., 2013). Popular ancient physicians such as Hippocrates (460–370 BCE), Dioscorides (40–90 CE), Galen (130–210 CE), and Avicenna (980–1037 CE) reported various traditional therapeutic uses of NS (Botnick et al., 2012).

In the context of bronchial asthma and its symptoms, the Muslim scholar Imam Ibn Qayyim Al-Jawziyya (1292–1350 CE), author of the Prophetic Medicine, reported that NS aid in gasping and hard breathing (Abdullah, 2003). Avicenna has also reported its benefit for shortness of breath (مطاعم) (الاسم الفص) (Avicenna, 1593). Nowadays, NS is still a traditional remedy for many illnesses such as cough and asthma in Arabia (Leblang and Pepperdine, 2006).

The chemical composition of NS has been studied in considerable detail. Mainly, it contains fixed oil (24.76–40.35%), volatile oil (0.5–1.6%), alkaloids, saponins, and other compounds in trace amounts (Ahmad et al., 2013; Botnick et al., 2012; Liu et al., 2011). The activity of NS appeared to be mainly attributed to thymoquinone (Ahmad et al., 2013). Thymoquinone was first isolated from NS oil by El-Dakhakhny (1963).

The Global Initiative for Asthma defined asthma as “a heterogeneous disease, usually characterised by chronic airway inflammation. It is identified by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity, together with variable expiratory airflow limitation” (Global Initiative for Asthma, 2017). The Global Asthma Report 2014 considered asthma as an epidemic disease probably affecting about 334 million people worldwide and becoming a global health priority (Global Asthma Network, 2014). In Saudi Arabia (with a population of 28 million), the prevalence of asthma is increasing and affects more than 2 million Saudis (Al-Moamary, 2012).

Asthma is initiated by multiple interactions between inflammatory cells and mediators. After an exposure to a triggering factor, inflammatory mediators are released from mast, macrophages, T-cells and epithelial cells. This cause attraction of other inflammatory cells mainly eosinophil into the pulmonary tissues. These cause lung injury, mucus hypersecretion and smooth muscle hyperactivity. Furthermore, at least 27 cytokines and 18 chemokines play a role in asthma pathophysiology (Koda-Kimble, 2009). Th2 lymphocytes cytokines [interleukin IL-4, IL-5, and IL-13] and Th1 cytokine interferon-gamma are the main ones to provoke allergy and asthma (Ngoc et al., 2005).

Generally, the key goals for asthma management are to reach a good control of symptoms and minimize future risk of exacerbations, airflow limitation and treatment adverse events. Assessment of asthma control level can be done using several tools (Bateman et al., 2008). The Asthma Control Test (ACT) is a global validated numerical tool for the assessment of asthma control which is also commonly used by health care providers in Saudi Arabia (Al-Moamary, 2012). Future risk can be assessed by pulmonary function testing, particularly the forced expiratory volume in one second (FEV1) (Bateman et al., 2008).

From a global clinical perspective, achieving asthma control is considered to be suboptimal regardless of the availability of conventional treatments (Demoly et al., 2012; Price et al., 2014). Poor adherence to asthma medications is one of the factors leading to suboptimal asthma control (Haughney et al., 2008; Horne et al., 2007). Common medication-related reasons for non-adherence include difficulties with inhaler techniques, the complex course of therapy, adverse events, and cost of medications (Bateman et al., 2008; Dima et al., 2015). In Saudi Arabia, a survey of adult asthmatics found that asthma attacks were highly associated with patients on current asthma medications (Moradi-Lakeh et al., 2015). The Global Asthma Physician and Patient Survey reported that 76% of patients and 81% of physicians consider that new treatment options are required (GAPP, 2005). The introduction of novel treatment strategies (such as “add-on” treatments) is a key step for better asthma control (Lomnitzsch and Stoll, 2016).

Asthma patients tend to use herbal medicines as one of the common therapies of complementary and alternative medicine (Slader et al., 2006). However, these therapies often have insufficient evidence for their effectiveness in asthma. In Saudi Arabia, a questionnaire type study was done by Al Moamary (2008) in 200 asthmatic patients. He found that NS is one of the most commonly non-standard therapies used by 10% of the patients.

In this review, we aimed at exploring and assessing the relevant pre-clinical and clinical studies supporting the use of NS in patients with asthma, and evaluating the current evidence to highlight future research priorities.

2. Methods

A literature search for scientific studies published in electronic databases (PubMed, Science Direct, Scopus, and Google Scholar) was done using the terms *Nigella sativa*, Black seed, Thymoquinone and (their pharmacological effects) on asthma. Studies were searched for electronically between the years 1990 and 2017. Retrieved studies were assessed and the data was categorised into preclinical and clinical studies.

3. Results

At least nineteen preclinical studies and seven clinical studies reported the effects of NS in asthma. Details of the retrieved studies are summarised in the following.

3.1. Preclinical studies of *Nigella sativa* in cellular and animal models of asthma

NS and its active compounds thymoquinone, nigellone and α-hederin have been investigated in eighteen whole or cellular animal models and one human cellular model related to asthma. NS oil, thymoquinone or α-hederin showed anti-inflammatory and immunomodulatory effects in seven studies (Abbas et al., 2005; Balaha et al., 2012; El Gazzar et al., 2006; Mansour and Tornhamre, 2004; Saadat et al., 2015; Saleh et al., 2012; Shahzad et al., 2009). NS extracts, thymoquinone or α-hederin demonstrated a bronchodilatory or relaxant effect in six studies (Abd El Aziz et al., 2011; Al-Majed et al., 2001; Boskabady et al., 2008; Gilani et al., 2001; Keyhanmanesh et al., 2013; Saadat et al., 2015). The anti-histaminic effect was shown in four studies used NS oil/aqueous extract, nigellone or α-hederin (Abd El Aziz et al., 2011; Chakravarty, 1993; Saadat et al., 2015; Saleh et al., 2012). Pathological improvements were detected by thymoquinone or NS oil in five studies (Arabzadeh et al., 2016; Boskabady and Sheiravi, 2002; El Gazzar et al., 2006; Kalenci et al., 2013; Shahzad et al., 2009). The summary of findings of these studies are shown in Table 1.

Generally, these studies used animal models sensitisised with ovalbumin or isolated Guinea pig trachea. Some studies used cellular models such as human granulocytes or animal mast cells. However, these studies had limitations such as the variability of NS
Table 1
Effects of NS in pre-clinical studies of asthma.

<table>
<thead>
<tr>
<th>Studies</th>
<th>Study material</th>
<th>Minimal active dose</th>
<th>Model</th>
<th>Negative control</th>
<th>Positive control</th>
<th>Effects</th>
<th>Notes &amp; limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chakravarty et al. (1993)</td>
<td>Nigellone 11 µg/ml</td>
<td>Mixed peritoneal cells of egg albumin induced Wistar rats</td>
<td>N/A</td>
<td>N/A</td>
<td></td>
<td>↓</td>
<td>No control group without Thymoquinone</td>
</tr>
<tr>
<td>Giani et al. (2001)</td>
<td>NS (70% aqueous methanol extract) 0.1–3.0 mg/ml</td>
<td>Guinea pig trachea</td>
<td>N/A</td>
<td>N/A</td>
<td></td>
<td>+</td>
<td>No control group without Thymoquinone</td>
</tr>
<tr>
<td>Al-Majed et al. (2001)</td>
<td>Thymoquinone 50 µM</td>
<td>Guinea pig trachea</td>
<td>N/A</td>
<td>N/A</td>
<td></td>
<td>+</td>
<td>No control group without Thymoquinone</td>
</tr>
<tr>
<td>Bokabady and Shebani (2002)</td>
<td>Aqueous extracts of NS 0.3 ml</td>
<td>Guinea pig trachea</td>
<td>Saline</td>
<td>Chlorpheniramine</td>
<td></td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Mansour and Tomboulie (2004)</td>
<td>Thymoquinone 3 and 10 µM</td>
<td>Human granulocytes</td>
<td>Untreated</td>
<td>Human granulocytes</td>
<td></td>
<td>↓ leukotrienes</td>
<td>No positive control</td>
</tr>
<tr>
<td>Abba et al. (2005)</td>
<td>NS fixed oil 5 ml/kg/day injected (ip) for 17 days</td>
<td>Conalbumin sensitised (CD1) albaline mice</td>
<td>Dexamethasone</td>
<td>↓ IgG</td>
<td>↓ serum IL-2 &amp; IL-12</td>
<td>↓ blood eosinophil count</td>
<td></td>
</tr>
<tr>
<td>Boyko et al. (2005)</td>
<td>NS fixed oil 0.3 ml/day for 1 month</td>
<td>OVA sensitised BALB/c mouse</td>
<td>Saline</td>
<td></td>
<td></td>
<td></td>
<td>No positive control</td>
</tr>
<tr>
<td>El Gazzar et al. (2006)</td>
<td>Thymoquinone + 10% DMSO 3 mg/kg TQ in 10% DMSO injected (ip) for 5 days</td>
<td>OVA sensitised BALB/c mouse and lung cells</td>
<td>Saline + 10% DMSO</td>
<td>OVA IgE &amp; IgG1</td>
<td>↓ IL-4, IL-5, IL-13</td>
<td>eosinophils</td>
<td>↓ giladin cells hyperplasia</td>
</tr>
<tr>
<td>Bokabady et al. (2008)</td>
<td>Methanol and dichloromethane extracts of NS 0.8 g% of methanol extract-1.2 g% of dichloromethane extracts</td>
<td>Guinea pig trachea</td>
<td>Saline</td>
<td>Theophylline</td>
<td></td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Shafie et al. (2009)</td>
<td>NS fixed oil 4 ml/kg/day injected (ip) for 7 days</td>
<td>OVA sensitised E3 rats</td>
<td>Saline</td>
<td>↓ Total IgE</td>
<td>↓ OVA IgG</td>
<td>↓ mRNA expression of IL-4, IL-5, IL-6 and TGF-β1 from lung cells</td>
<td>↓ giladin cells hyperplasia</td>
</tr>
<tr>
<td>Abd El Aziz et al. (2011)</td>
<td>Thymoquinone 3 mg/kg injected (ip) for 5 days in guinea pig, 8 mg/kg injected (ip) for 21 days in rats</td>
<td>OVA sensitised guinea pig trachea mast cells of egg albumin sensitised rats</td>
<td>Saline</td>
<td></td>
<td>↓ OVA IgG1 &amp; IgE</td>
<td>↓ eosinophils, macrophages, lymphocytes</td>
<td>↓ giladin cells hyperplasia</td>
</tr>
<tr>
<td>Balba et al. (2012)</td>
<td>NS fixed oil Oral NS oil 4 ml/kg/day for 31 days</td>
<td>OVA sensitised BALB/c mouse</td>
<td>Saline</td>
<td>↓ Total IgE</td>
<td>↓ OVA IgG1 &amp; IgE</td>
<td>↓ BALF Th1 cytokines</td>
<td>↓ bronchial and alveolar epithelial hyperplasia</td>
</tr>
<tr>
<td>Saleh et al. (2012)</td>
<td>NS fixed oil Oral NS oil 2.5 ml/kg/day for 3 weeks</td>
<td>OVA sensitised guinea pig isolated rat peritoneal mast cells</td>
<td>Saline</td>
<td>↓ PGE2 in lung tissue</td>
<td>↓ leukotrienes</td>
<td>↓ Eosinophil</td>
<td></td>
</tr>
<tr>
<td>Keyhanmanesh et al. (2013)</td>
<td>Fractions of 20% methanolic extract of NS</td>
<td>(50, 100, 150, 200 mg/L)</td>
<td>Guinea pig trachea</td>
<td>Saline</td>
<td>Theophylline</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Kalemci et al. (2013)</td>
<td>Thymoquinone 3 mg/kg/day injected (ip) for 5 days</td>
<td>OVA sensitised BALB/c mouse</td>
<td>Saline</td>
<td>Dexamethasone</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Keyhanmanesh et al. (2014)</td>
<td>Thymoquinone 0.3 mg/kg i.p.</td>
<td>OVA-oosorised guinea pig</td>
<td>Saline</td>
<td>N/A</td>
<td>↓ Blood IPN-γ</td>
<td>↓ Eosinophil</td>
<td></td>
</tr>
<tr>
<td>Saadat et al. (2015)</td>
<td>α-helmins 0.1 mg/kg i.p.</td>
<td>OVA-oosorised guinea pig</td>
<td>Saline</td>
<td>Thymoquinone</td>
<td></td>
<td>↓ Total WBC, Eosinophils, Basophils</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>+</td>
<td>▼ Tracheal contractile response to histamine</td>
</tr>
</tbody>
</table>
3.2. Clinical studies of Nigella sativa in patients with asthma

Seven clinical studies showed a potential efficacy of NS on asthma outcomes and biomarkers. Three Randomised Double-Blinded Placebo-Controlled Clinical Trials (RDBPCT) and two Randomised Single-Blinded Placebo-Controlled Clinical Trials (RSBPCT) using NS crushed seeds powder or oil/aqueous extract, showed an improvement in clinical symptoms and pulmonary function test in adult asthmatics (Boskabady et al., 2007; Kalus et al., 2003; Kardani et al., 2013; Koshak et al., 2017; Salem et al., 2017). In addition, a reduction of blood eosinophilia was found in RDBPCT by Koshak et al. (2017). Also, a decrease in total serum IgE and FeNO, and an increase in serum INF-gamma cytokine were shown in the RSBPCT trial of Salem et al. (2017).

A Randomised Double-Blinded Clinical Trial (RDBCT) showed a short bronchodilatory effect in patients with asthma after administration of a single dose of NS (Boskabady et al., 2010). Two studies used NS in combination with other treatments showed an improvement in ACT and PFT scores (Al Ameen et al., 2011; Kardani et al., 2013) (Table 2).

However, these clinical trials appeared to have some important limitations (Table 2). In many of these studies, the standard of design was poor as three studies only were RDBPCT. The phytochemical characterisation of the investigational NS product was not shown in many studies. The sample size was comparatively small in most studies. The largest trial by Koshak et al. (2017) included 80 adult asthmatic patients. The measured outcomes were generally limited to symptoms or pulmonary function in several studies.

Therefore, there is a need for a longer, larger and high standard multicentre clinical trial (more than 80 asthmatic patients) with phytochemically well-characterised NS product. Also, to use validated asthma control measurement tools with consideration of additional asthma outcomes and biomarkers such as FeNO, Sputum eosinophils, total blood eosinophils, total serum IgE, allergen-specific IgE and urinary LTE4 (Szefler et al., 2012). Additionally, measuring serum inflammatory cytokines may be worth considering, since asthma is regulated by multiple inflammatory cytokines and some were associated with asthma control (Akiki et al., 2017).

4. Conclusion

This literature review showed that various preparations derived from Nigella sativa have a potential role for the clinical use in asthma. Preclinical studies of NS preparations showed bronchodilation, anti-histaminic, anti-inflammatory, anti-leukotrienes and immunomodulatory effects in animal or cellular models of asthma. Clinical studies of NS preparations showed an improvement of asthma symptoms control, lung function and asthma biomarkers. However, these studies have study design limitations and limited phytochemical characterisation of NS preparations used. Consequently, the current clinical evidence for the use of NS in patients with asthma is evolving in strength. In future, larger, longer, well-designed clinical trials including additional biomarkers and using phytochemically characterised NS preparations are required for assessing the clinical use of NS in asthma. Eventually, NS may offer a cost-effective and clinically proven effective add-on therapeutic option for asthmatics with fewer side, which may be used as integrative medicine within the Saudi healthcare system and beyond.
<table>
<thead>
<tr>
<th>Study reference</th>
<th>Study material</th>
<th>Study design</th>
<th>Control</th>
<th>NS dose</th>
<th>Duration</th>
<th>Sample</th>
<th>Effects</th>
<th>Pulmonary function</th>
<th>Blood</th>
<th>Other</th>
<th>Advantages (+) and limitations (−)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salem et al. (2017)</td>
<td>NS powder</td>
<td>RSBPCT</td>
<td>Placebo</td>
<td>1 and 2 g/day</td>
<td>3 months</td>
<td>76 adult asthmatics</td>
<td>↑ ACT</td>
<td>↑ FEV1 (% predicted)</td>
<td>↑ serum IgE</td>
<td>↑ FeNO</td>
<td>+ large sample size but still comparatively small&lt;br&gt;Longer duration&lt;br&gt;Single-Blinded&lt;br&gt;−NS was not chemically characterised&lt;br&gt;The largest study conducted but still a comparatively small&lt;br&gt;−NS chemically characterised&lt;br&gt;−High standard study design&lt;br&gt;−Short duration&lt;br&gt;−Small sample size&lt;br&gt;−NS not chemically characterised and was used in combination&lt;br&gt;−Single-blinded&lt;br&gt;−Outcomes limited to symptoms only</td>
</tr>
<tr>
<td>Koshak et al. (2017)</td>
<td>NS fixed oil</td>
<td>RDBPCT</td>
<td>Placebo</td>
<td>1 g/day</td>
<td>4 weeks</td>
<td>80 adult asthmatics</td>
<td>↑ ACT</td>
<td>Non-significant ↑ FEV1 (% predicted)</td>
<td>↑ eosinophils</td>
<td>No change in serum IgE</td>
<td>− Very small sample size&lt;br&gt;−NS was not chemically characterised and was used in combination&lt;br&gt;−Low standard study design&lt;br&gt;−Outcomes were very limited and compared between same group before and after treatment, and not between groups.&lt;br&gt;−No symptoms measurement&lt;br&gt;−NS was chemically characterised&lt;br&gt;−Very small sample size&lt;br&gt;−Not placebo controlled&lt;br&gt;−Outcomes was limited to symptoms</td>
</tr>
<tr>
<td>Kardani et al. (2013)</td>
<td>NS powder + IM (House dust mite)</td>
<td>RSBPCT</td>
<td>IM + placebo</td>
<td>15 mg/kg/day</td>
<td>14 weeks</td>
<td>31 Child asthmatics</td>
<td>↑ ACT</td>
<td>No change in number of Th17 cells</td>
<td></td>
<td></td>
<td>− Small sample size&lt;br&gt;−NS not chemically characterised and was used in combination&lt;br&gt;−Single-blinded&lt;br&gt;−Outcomes limited to symptoms</td>
</tr>
<tr>
<td>Al Ameen et al. (2011)</td>
<td>Whole NS seeds + bee honey</td>
<td>Non RCT</td>
<td>open-label</td>
<td>2 g of NS seeds + 1 tsp honey</td>
<td>3 months</td>
<td>5 adult asthmatics</td>
<td>↑ FVC in asthmatics</td>
<td>↑ PEF in non-asthmatics</td>
<td>No change in FEV1</td>
<td></td>
<td>− Small sample size&lt;br&gt;−NS not chemically characterised and was used in combination&lt;br&gt;−Limited outcomes to symptoms and pulmonary function&lt;br&gt;−Invalidated symptoms scoring system&lt;br&gt;−Sample of mixed allergic diseases with only 3 asthmatics&lt;br&gt;−No pulmonary function measurement&lt;br&gt;−Blood biomarkers were not compared between groups&lt;br&gt;−Limited NS characterisation&lt;br&gt;−Unclear and invalidated symptoms scoring system</td>
</tr>
<tr>
<td>Boskabady et al. (2010)</td>
<td>Aqueous extract of NS</td>
<td>RDBCT</td>
<td>Theophylline crossover</td>
<td>Single dose of 50 mg/kg</td>
<td>150 min</td>
<td>15 adult asthmatics</td>
<td>↑ FEV1</td>
<td>↑ MMEF</td>
<td>↑ PEF</td>
<td></td>
<td>− NS was chemically characterised&lt;br&gt;−Very small sample size&lt;br&gt;−Not placebo controlled&lt;br&gt;−Outcomes was limited to symptoms</td>
</tr>
<tr>
<td>Boskabady et al. (2007)</td>
<td>Aqueous extract of NS</td>
<td>RDBPCT</td>
<td>Placebo</td>
<td>15 mL/kg of 0.1 %</td>
<td>3 months</td>
<td>29 adult asthmatics</td>
<td>Improved asthma symptoms</td>
<td>↑ FVC</td>
<td>↑ FEV1</td>
<td>↑ PEF</td>
<td>↑ MMEF</td>
</tr>
</tbody>
</table>
| Kalus et al. (2003) | NS fixed oil | RDBPCT | Placebo | 40–80 mg/kg/day Times daily | 3 weeks | 63 adults: −31 allergic rhinitis, −3 bronchial asthma, −6 atopic eczema | Improved subjective severity of symptoms | | | | | − Eosinophils (not significant)<br>− Serum IgE (not significant)
Funding

This research is part of the PhD thesis of Mr. Abdulrahman Koshak funded by the Ministry of Education in Saudi Arabia. It did not receive any specific external grant from funding agencies in the public, commercial, or not-for-profit sectors.

References


