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Review

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

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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.

Contents

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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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 (انتصاب النفس) and for stopping phlegm (مقطع البلغم) (Avicenna, 1593). Nowadays, NS is still a traditional remedy for many illnesses such as cough and asthma in Arabia (Lebling 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 causes 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 (Lommatzsch 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; Kalemci 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 sensitised 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.

Studies	Study material	Minimal active dose	Model	Negative control	Positive control	Effects								Notes & limitations
						Serum immunoglobulins	Inflammatory mediators	Inflammatory cells, BALF	Inflammatory cells, lung	Histamine release	Block H1 receptors	Relaxation of SM	Other	
Chakravarty (1993)	Nigellone	11 μg/ml	Mixed peritoneal cells of egg albumin induced Wistar rats	N/A	N/A					↓				No control group (without Thymoquinone)
Gilani et al. (2001)	NS (70% aqueous-methanol extract)	0.1–3.0 mg/ml	Guinea pig trachea	N/A	N/A							+		No control group (without Thymoquinone)
Al-Majed et al. (2001)	Thymoquinone	50 μM	Guinea-pig trachea	N/A	N/A						+	+		No control group (without Thymoquinone)
Boskabady and Sheiravi (2002)	Aqueous extracts of NS	0.3 ml	Guinea pig trachea	Saline	Chlorpheniramine						+			
Mansour and Tornhamre (2004)	Thymoquinone	3 and 10 μM	Human granulocytes	Untreated human granulocytes	N/A		↓ leukotrienes							No positive control
Abbas et al. (2005)	NS fixed oil	5 ml/kg/day injected (ip) for 17 days	Conalbumin sensitised (CD1) albino mice	Untreated mice	Dexamethasone	↓ IgG	↓ serum IL-2 & IL-12		↓				↓ blood eosinophil count	
Büyüköztürk et al. (2005)	NS fixed oil	0.3 ml/day for 1 month	OVA sensitised BALB/c mice	Saline			No change in IL-4, IL-10 and IFN-γ in splenic mononuclear cells							No positive control
El Gazzar et al. (2006)	Thymoquinone + 10% DMSO	3 mg/kg TQ in 10% DMSO injected (ip) for 5 days	OVA sensitised BALB/c mice and lung cells	Saline + 10% DMSO	OVA + 10% DMSO	↓ OVA IgE & IgG1	↓ IL-4, IL-5, IL-13 ↑ IFN-γ in BALF	↓ eosinophils	↓ eosinophils				↓ goblet cells hyperplasia	
Boskabady et al. (2008)	Methanol and dichloromethane extracts of NS	-0.8 g% of methanol extract-1.2 g% of dichloromethane extracts	Guinea pig trachea	Saline	Theophylline							+		
Shahzad et al. (2009)	NS fixed oil	4 ml/kg/day injected (ip) for 7 days	OVA sensitised E3 rats	Saline	N/A	↓ Total IgE ↓ IgG1 ↓ OVA IgG1	↓ mRNA expression of IL-4, IL-5, IL-6 and TGF-β1 from lung cells ↓ nitric oxide in BALF	↓ eosinophils, macrophages & lymphocytes	↓ eosinophils, macrophages, lymphocytes				↓ bronchial and alveolar epithelial hyperplasia ↓goblet cells and collagen fibres	No positive control
Abd El Aziz et al. (2011)	Thymoquinone	3 mg/kg injected (ip) for 5 days in guinea pig-8 mg/kg injected (ip) for 21 days in rats	OVA sensitised guinea pig trachea Mast cells of egg-albumin sensitised rats	Saline	N/A					↓		+		No positive control
Balaha et al. (2012)	NS fixed oil	Oral NS oil 4 ml/kg/day for 31 days	OVA sensitised BALB/c mice	Saline	N/A	↓ Total IgE ↓ OVA IgE & IgG1	↑ BALF Th1 cytokines ↓ BALF Th2 cytokines	↓ leukocytes, macrophages & eosinophils					↓ Airway hyperresponsivness	No positive control
Saleh et al. (2012)	NS fixed oil	Oral NS oil 2.5 ml/kg/day for 3 weeks	OVA sensitised guinea pig Isolated rat peritoneal mast cells	Saline	N/A		↑ PGE2 in lung tissue ↓ leukotrienes			↓				No positive control
Keyhanmanesh et al. (2013)	Fractions of 20% methanolic extract of NS	(50, 100, 150, 200 mg/L)	Guinea pig trachea	Saline	Theophylline							+		
Kalemci et al. (2013)	Thymoquinone	3 mg/kg/day injected (ip) for 5 days	OVA sensitized BALB/c mice	Saline	Dexamethasone								↓ Subepithelial and epithelial hyperplasia ↓ Number of mast and goblet cells	
Keyhanmanesh et al. (2014)	Thymoquinone	0.3 mg/kg i.p.	OVA-sensitized guinea pig	Saline	N/A		↑ Blood IFN-γ	↓ Eosinophil ↓ Basophils					↓ Tracheal responsiveness ↓ Airway membrane hyperplasia ↓ Respiratory epithelial denudation ↓ Cellular infiltration ↓ Emphysema	No positive control
Saadat et al. (2015)	α-hederin	0.3 mg/kg i.p.	OVA-sensitized guinea pig	Saline	Thymoquinone			↓ Total WBC ↓ Eosinophils ↓ Basophils				+	↓ Tracheal contractile response to histamine	

Fallahi et al. (2016)	α-hederin	0.2 mg/kg i.p.	OVA-sensitized Wistar rats	Saline	Thymoquionone	↓ IL-13 mRNA ↓ miRNA-126	↓ Pneumocyte and fibroblastic hypertrophy and hyperplasia ↓ Hyperemia ↓ Haemorrhage ↓ Edematous and exudative changes	
Arabzadeh et al. (2016)	Ethanolic extract of NS	Oral 500 mg/kg/day for 3 weeks	Exercise-induced Wistar rats	Exercise-induced Wistar rats without NS	N/A		↓ thickness epithelial bronchi, tunica media (muscle) bronchi, and tunica adventitia bronchi ↓ number of goblet cells	No positive control

ip: intraperitoneal. OVA; ovalbumin. BALF; Bronchoalveolar lavage fluid. N/A; data not included in the original study.

preparations used between most them, and absence of control group in some studies (Table 1).

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 preparation 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 2
Effects of *Nigella sativa* on asthma in clinical studies.

Study reference	Study material	Study design	Control	NS dose	Duration	Sample	Effects				Advantages (+) and limitations (−)
							Symptoms	Pulmonary function	Blood	Other	
Salem et al. (2017)	NS powder	RSBPCT	Placebo	1 and 2 g/day	3 months	76 adult asthmatics −24 placebo −26 (1 g NS) −26 (2 g NS)	↑ ACT	↑ FEV1 (% predicted) ↑ FEF25-75% ↑ PEF	↓ serum IgE ↑ serum IFN-γ	↓ FeNO	+ Large sample size but still comparatively small +Longer duration −Single-Blinded −NS was not chemically characterised
Koshak et al. (2017)	NS fixed oil	RDBPCT	Placebo	1 g/day	4 weeks	80 adult asthmatics −40 active −40 placebo	↑ ACT	Non-significant ↑ FEV1 (% predicted)	↓ eosinophils No change in serum IgE		+The largest study conducted but still a comparatively small +NS chemically characterised −High standard study design −Short duration
Kardani et al. (2013)	NS powder + IM (House dust mite)	RSBPCT	IM + placebo	15 mg/kg/day	14 weeks	31 Child asthmatics −8 IM + placebo −8 IM + NS −8 IM + probiotic -7 IM + NS + probiotic	↑ ACT		No change in number of Th17 cells		−Small sample size +NS not chemically characterised and was used in combination −Single-blinded −Outcomes limited to symptoms only
Al Ameen et al. (2011)	Whole NS seeds + bee honey	Non RCT open-label	N/A	2 g of NS seeds + 1 tsp honey	3 months	5 adult asthmatics 22 non-asthmatics		↑ FVC in asthmatics ↑ PEF in non-asthmatics No change in FEV1			−Very small sample size −NS was not chemically characterised and was used in combination −Low standard study design −Outcomes were very limited and compared between same group before and after treatment, and not between groups. −No symptoms measurement
Boskabady et al. (2010)	Aqueous extract of NS	RDBCT crossover	Theophylline	Single dose of 50 mg/kg	150 min	15 adult asthmatics		↑ FEV1 ↑ MMEF ↑ PEF			+NS was chemically characterised −Very small sample size −Not placebo controlled +Outcomes was limited to pulmonary function
Boskabady et al. (2007)	Aqueous extract of NS	RDBPCT	Placebo	15 mL/kg of 0.1 g%	3 months	29 adult asthmatics 15 active 14 control	Improved asthma symptoms	↑ FVC ↑ FEV1 ↑ PEF ↑ MMEF		↓ asthma medication usage.	+NS was chemically characterised +High standard study design −Small sample size −Limited outcomes to symptoms and pulmonary function −Invalidated symptoms scoring system
Kalus et al. (2003)	NS fixed oil	RDBPCT	Placebo	40–80 mg/kg/day Three times daily	3 weeks	63 adults: −31 allergic rhinitis, −3 bronchial asthma, −6 atopic eczema	Improved subjective severity of symptoms		−↓ eosinophils (not significant) −↓ serum IgE (not significant)		−Sample of mixed allergic diseases with only 3 asthmatics −No pulmonary function measurement −Blood biomarkers were not compared between groups −limited NS characterisation −Unclear and invalidated symptoms scoring system

RDBPCT; Randomised Double-Blind Placebo-Controlled Trial. RSBPCT; Randomised Single-Blind Placebo-Controlled Trial. RDBCT: Randomised Double-Blind Controlled Trial. ACT; Asthma control test. FEV1; forced expiratory volume in 1 s. FVC; forced vital capacity. MMEF; maximal mid expiratory flow. PEF; peak expiratory flow. Tsp; tea spoonful. FeNO; fractional exhaled nitric oxide. FEF25-75%; mid expiratory flow. IM; Immunotherapy.

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