Physiology and Pharmacology 26 (2022) 119-126
Review Article

Therapeutic effects of *Nigella sativa* on asthma: a systematic review of clinical trial

Mohammad Reza Khazdair*, Alireza Amirabadizadeh

Cardiovascular Diseases Research Center, Birjand University of Medical Sciences, Birjand, Iran.

ABSTRACT

Introduction: *Nigella sativa (N. sativa)* in the family of Ranunculaceae, has been traditionally used as food additive and spice. *N. sativa* showed protective effects on respiratory system including trachea responsiveness and lung inflammation in various animals' models studies. The possible therapeutic effects of *N. sativa* on asthma were investigated in this systematic review study..

Methods: The published studies were searched in the different databases including; PubMed, Web of Science (ISI), Scopus and Cochrane, until September 2020, by: (asthma) AND ("*Nigella sativa*") OR ("*Nigella sativa* oil") OR (Black seed). All unrelated articles such as duplicates, animal and review studies as well as clinical studies without control group were excluded from obtained studied. Then 9 articles were considered for further evaluation.

Results: After analyzing 9 articles including 434 participants, these following results were achieved: *N. sativa* improved the asthma control test and pulmonary function tests values, while reduced respiratory symptoms including, cough and wheeze. Furthermore, *N. sativa*, reduced eosinophils count and serum levels of pro-inflammatory mediators such as interleukin-4 and immunoglobulin E, while increased production of anti-inflammatory mediator such as interferon-γ in the serum.

Conclusion: The results of this systematic review article revealed that supplementation of *N. sativa* might be effective in the control or treatment of asthma.

Keywords:
Nigella sativa
Asthma
Airway inflammation
Pulmonary function test
Respiratory symptoms

Introduction

Asthma is an inflammatory disease which is characterized by eosinophilic inflammation, hyper-responsiveness and inflammation in the airway as well as hyper-secretion of mucus (Bousquet et al., 2000). This disorder is triggered by interaction between high levels of immunoglobulin E (IgE) and production of inflammatory mediators including interleukin (IL)-4, IL-5 and IL-13 by T-helper 2 (Th2) cells (Alavinezhad et al., 2018). Also, asthma is two module diseases including airway inflammation and smooth muscle dysfunction (Janssen and Killian, 2006). Inflammation was enhanced by responses of the epithelium, fibroblasts cells and smooth muscle through the production of mediators and proteases. Increase airway responsiveness is the main characteristic of asthma, which leads to the lung inflammation (Cohn

* Corresponding author: Mohammad Reza Khazdair, khazdairMR@Bums.ac.ir; M.khazdair@yahoo.com
Received 20 December 2022; Revised from 10 April 2021; Accepted 17 April 2021

Citation: Khazdair MR, Alireza Amirabadizadeh A. Therapeutic effects of Nigella sativa on asthma: a systematic review of clinical trial. Physiology and Pharmacology 2022; 26: 119-126. http://dx.doi.org/10.52547/phypha.26.2.2

et al., 2004). The control of symptoms and decline of airflow limitation and risk of exacerbations are the main goals for asthma management (Bateman et al., 2008).

The asthma control test (ACT) is the global validated tool for the assessment of asthma (Al-Moamary et al., 2012). The future risk of asthma was assessed by pulmonary function testing (PFT), especially the forced expiratory volume in first second (FEV1) (Bateman et al., 2008). Corticosteroids are capable to inhibit eosinophil function or infiltration and genes expression of inflammatory cytokines, enzymes and receptors and bronchodilator drugs are anticipated for the treatment of asthma (Barnes, 2006; Mortazavi Moghaddam et al., 2020). The combination therapy of corticosteroids (fluticasone propionate) and β-agonists significantly improved lung function and symptoms compared to the single therapy. In addition, combination therapy reduced tracheal hyper-responsiveness and lung inflammation in sensitized animals model of asthma (Gholamnezhad et al., 2014; Khazdair et al., 2013). The uses of medicinal plants as one of the common therapies of complementary medicine have been increased in asthmatic patients (Slader et al., 2006). However, there is insufficient evidence for the effectiveness of herbal medicine in asthma.

Herbs have long been used traditionally for the treatment of various inflammatory disorders such as asthma. The medicinal plant with anti-inflammatory, immuno-modulatory, antihistaminic and smooth-muscle relaxants effects were used for asthma (Greenberger, 2003; Khazdair et al., 2019b). Therapeutic effects of medicinal plants such as *Nigella sativa (N. sativa)* for chronic cough had been reported (Mortazavi Moghaddam et al., 2020).

N. sativa belongs to the Ranunculaceae family, which grows widely in the Mediterranean region, the middle east, southern Europe and north Africa (Tembhurne et al., 2014). *N. sativa* traditionally used for the treatment of infertility, fever, cough, bronchitis, dysmenorrhea, obesity, diabetes and diarrhea (Durmuskahya and Ozturk, 2013; Nasir et al., 2014). The main active component of *N. sativa* is thymoquinone, which has anti-inflammatory properties due to suppression of prostaglandins and leukotrienes (Hajhashemi et al., 2004). *N. Sativa* also has several pharmacological effects including anti-inflammatory (Chehl et al., 2009), antioxidant (Bordoni et al., 2019; Mohebbatia et al., 2017a), antimicrobial (Emeka et al., 2015), neuroprotective (Khazdair et al., 2019a; Mohebbatia et al., 2017b) and *renoprotective (Mohebbati et al., 2017) effects. The protective effects of N. Sativa* and thymoquinone on the central nervous system including anti-epileptic, anti-Alzheimer's and anti-Parkinson's effects due to their antioxidant properties were also reported (Khazdair, 2015). Therefore, we aimed to review the potential effects of *N. Sativa* on different clinical and biochemical parameters in asthmatic patients.

Materials and methods

We searched for the published articles in the databases such as PubMed, Web of Science (ISI), Scopus and Cochrane, in the English language until September 2020. ITLE-ABS-KEY ("asthma") AND TITLE-ABS-KEY ("*Nigella sativa*") OR TITLE-ABS-KEY ("*Nigella sativa* oil") OR TITLE-ABS-KEY (Black seed)) in the Scopus: 97; (("Asthma"[MeSH Terms] [Title/Abstract]) AND (((("*Nigella sativa*"[MeSH Terms] OR nigella [Title/Abstract]) OR oil [Title/Abstract]) OR "*Nigella sativa* oil"[Title/Abstract]) in PubMed: 324; "Asthma" in Title Abstract Keyword AND "*Nigella sativa*" OR "*Nigella sativa* oil" OR "Nigella" OR "Black seed" in Title Abstract Keyword, in Cochran: 23; TS= (Asthma) AND TS= ("*Nigella sativa*" OR "*Nigella sativa* oil" OR Black seed) in ISI=87.

Search strategy

All clinical studies that investigated the effect of *N. sativa* seeds, oil and extracts on asthma were included in the study. Review articles, animal studies, clinical studies about the effect of *N. sativa* seeds, oil and extracts on asthma patients without control group, and/or effect of *N. sativa* seeds, oil and extracts in combination therapy on asthma were excluded from the study.

Study selection

Initially, 531 articles were extracted. All unrelated studies including duplicates, animal and review studies as well as clinical studies without control group were removed, and 9 articles were considered for further evaluation after reviewing titles and abstracts of the extracted articles (Figure 1).

Results

Demographic and characteristics of the included nine randomized controlled trials where showed in Table 1.

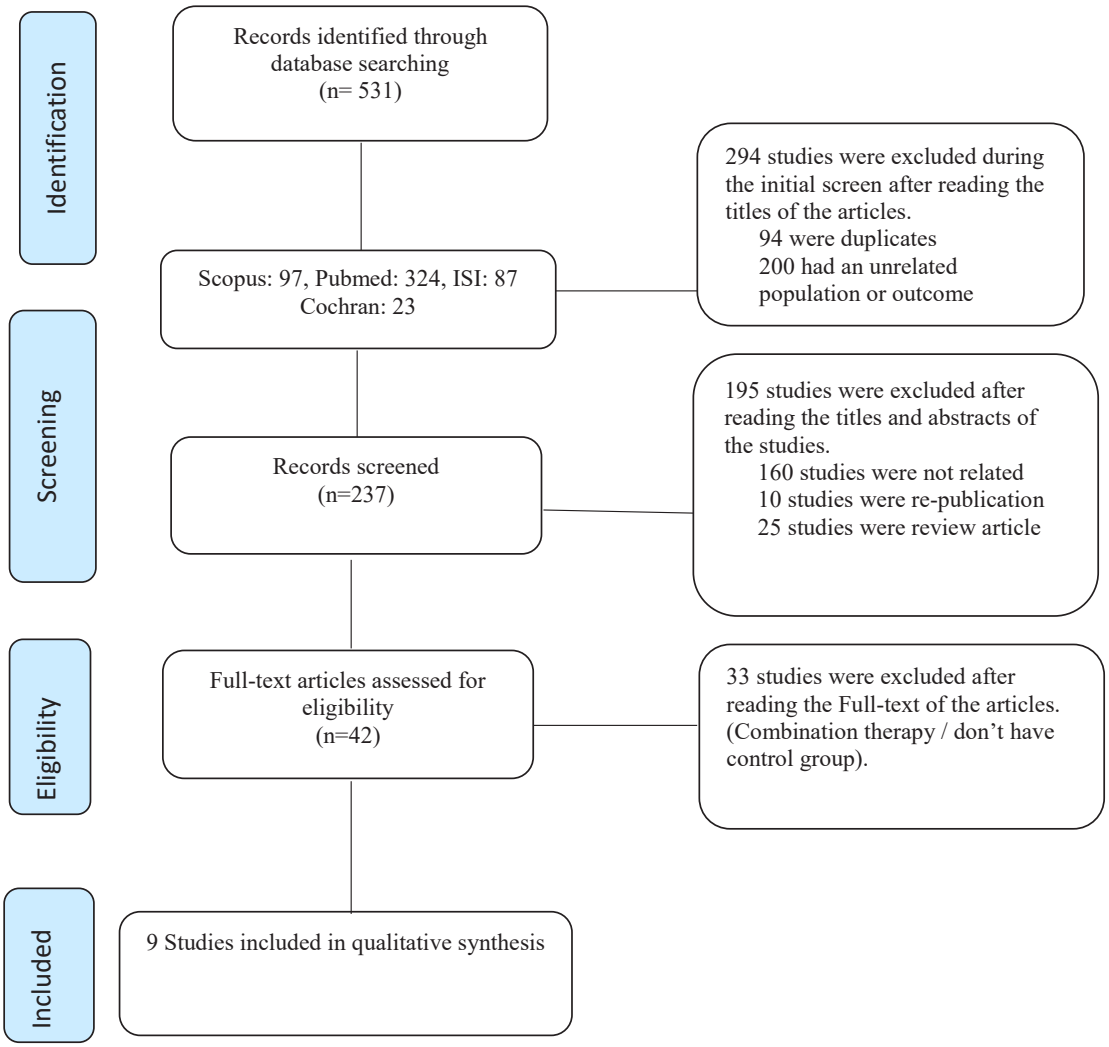

FIGURE 1. Flowchart of the literature search and strategy for the selection of relevant studies.

The total sample size of patients is 434 in the studies that were published between 2007 and 2017. The duration of *N. sativa* administration ranges from 1 day to 12 weeks. All inclusion studies were clinical trials on different aged asthmatic patients included 3 studies on children (Ahmad et al., 2010; Barlianto et al., 2017; Düzelme, 2018) and 6 studies on adult subjects including, asthma (Al-Jawad et al., 2012; Boskabady et al., 2010; Boskabady et al., 2007; Koshak et al., 2017; Salem et al., 2017) and 1 study on sulfur mustard exposure induced asthma (Boskabady and Farhadi, 2008).

With regard to the form of supplement, 3 studies (Boskabady et al., 2010; Boskabady and Farhadi, 2008; Boskabady et al., 2007) have used boiled extract of *N. sativa*, 2 studies (Ahmad et al., 2010; Koshak et al., 2017) used oil from the plant seed, 1 article (Salem et al., 2017) used from seed powder of *N. sativa* and in 2 others studies (Barlianto et al., 2017; Barlianto et al., 2018) soft gel capsule of *N. sativa* oil was provided for subjects.

Effects of N. sativa on clinical and biochemical parameters

Effects on the ACT

The influence of *N. sativa* in improving of ACT score reported in 3 trials (Barlianto et al., 2018; Koshak et al., 2017; Salem et al., 2017), treatment of asthmatic children and adults with capsules of whole ground *N. sativa* seeds or soft gel oil significantly improved ACT score compared to the baseline or standard treatment group.

Effects on the PFTs

The effects of *N. sativa* for improving of PFTs values was reported in 3 trials (Boskabady et al., 2010;

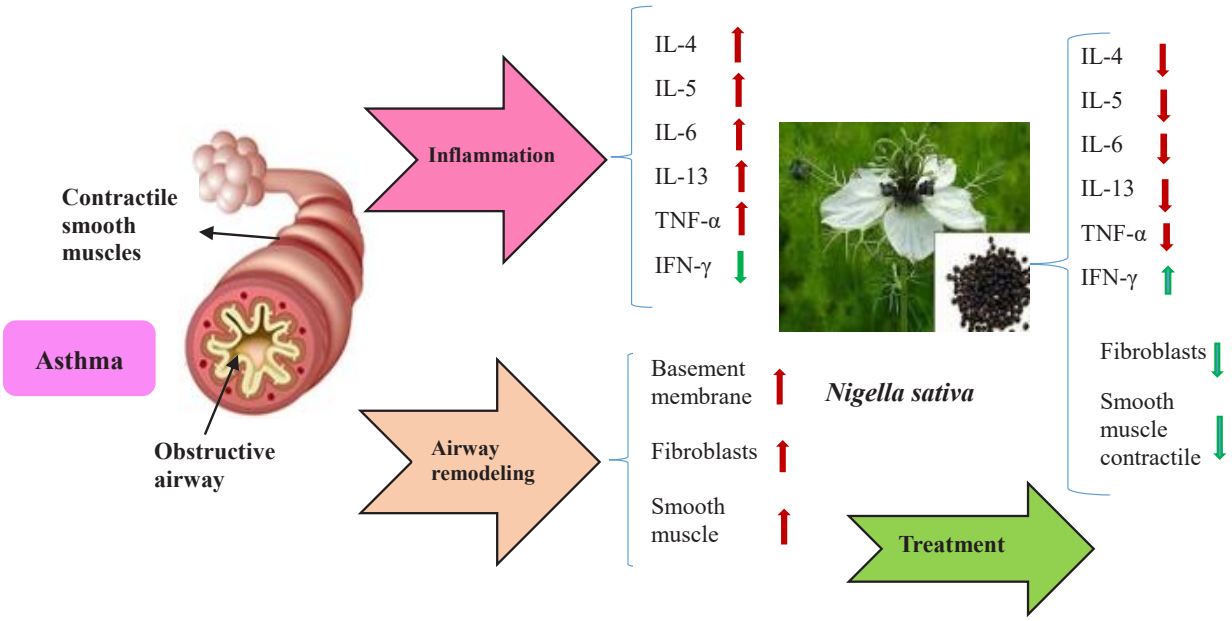

FIGURE 2. Therapeutic effects of Nigella sativa on asthma.

Boskabady and Farhadi, 2008; Boskabady et al., 2007), that significant increased all measured PFT. Treatment of adult asthmatic and sulfur mustard exposed patients with boiled extract of *N. sativa* significantly improved PFT values at the middle as well as at the end of study compared to the baseline. Furthermore, improved all respiratory symptoms at the end of study were compared to the control group. In one study treatment of adult asthmatic patients with *N. sativa* significantly elevated the values of FEV1% and forced volume capacity (Al-Jawad et al., 2012). In the other study *N. sativa* significantly increased the percent predicted of $FEF_{25-75\%}$, FEV1 and peak expiratory flow after 6 and 12 weeks of treatment compared with the control group (Salem et al., 2017).

Effect of N. sativa on the inflammatory and anti-inflammatory mediators

Treatment of asthmatic patients with capsules of whole ground *N. sativa* seeds (1 and 2 g/day) remarkably reduced fractional exhaled nitric oxide (FeNO) and serum IgE compared to the baseline after 12 weeks of treatment. Both doses of *N. sativa* remarkably increased production of interferon (INF)-γ in the serum after 12-week treatment compared to the baseline (Salem et al., 2017). *N. sativa* oil (15-30 mg/kg) as soft gel capsules in asthmatic children (aged 6-15) remarkably increased serum level of IFN-γ, while reduced the level of IL-4 compared to the control group (Barlianto et al., 2017). In a similar study, the oils of *N. sativa* in asthmatic children remarkably decreased Th17, but increased regulatory T cells (Treg). Additionally, Th17/ Treg ratio was lower in the *N. sativa* treatment group compared to the standard treatment group (Barlianto et al., 2018). Therapeutic effects of *N. sativa* on asthma were summarized in Table 1 and Figure 2.

Discussion

The results of five included studies indicated that *N. sativa* improved PFT values. Several studies have also been documented that *N. sativa* is useful for control of bronchial asthma and showed the positive effects on asthma such as PFT, inflammatory mediators, IgE and FeNO (Al Ameen et al., 2011; Mahmood et al., 2003; Shahzad et al., 2009). These effects may be due to relaxant effects of this plant on smooth muscle of tracheal chains.

Moreover, the relaxant and bronchodilatory effects of *N. sativa* on smooth muscle of tracheal chains *in vitro* were reported (Boskabady et al., 2004). The exhibits spasmolytic and bronchodilator activities of *N. sativa* crude extract through calcium channel blocking was also reported (Gilani et al., 2001). The results of a study showed that *N. sativa* has a favorable effect on lung function tests in asthmatic patients (Al Ameen et al., 2011). The ACT score includes items on shortness of

TABLE 1: Demographic characteristics of the included studies

Author/Year	Country	Mean age (years)	Gender	Sample size	Duration	Intervention	Randomization	Dosage of *N. sativa*	Results
(Boskabady et al., 2007)	Iran	48.2±11.9 35.8±12.7	Male and female	14 15	12 weeks	Boiled extract of *N. sativa*	Double Blind, randomized-Controlled Trial	0.375 ml/kg of 50 g%	Improved chest wheezing, and pulmonary function tests (PFTs) values at the middle and at the end of study compared to the baseline. Additionally, all respiratory symptoms were significantly improved compared to the control group at the end of trial.
(Boskabady et al., 2008)	Iran	Unknown	Male	40	8 weeks	Boiled extract of *N. sativa*	Double Blind, randomized-Controlled Trial	0.375 ml/kg of 50 g%	The respiratory symptoms such as, wheeze in the chest, and PFT values were remarkably improved in 1 and 2 months of treatment compared to the baseline. Two months after treatment, all PFT values and respiratory symptoms were significantly improved compared to the control group at the end of trial.
(Boskabady et al., 2010)	Iran	42.80±11.4	Male and female	15	30-180 min	Boiled extract of *N. sativa*	Cross-Over Clinical Trials	50 and 100 mg/kg	All measured PFT values significantly increased in the most time intervals compared to baseline. The onset of brochodilatory effect of extract was similar to that of theophylline.
(Ahmad et al., 2010)	India	5 to 7	Male and female	43 41	2 weeks	Essential oil of *N. sativa*	Double Blind, randomized - Controlled Trial	0.1 ml/kg	The pulmonary index (PI) was reduced significantly in treated group compared to control group in all days of treatment. In addition, PI significantly reduced in the inter-group comparison on 3rd, 7th, 10th and 14th day in treated group compared to control group. Peak expiratory flow rate (PEFR) significantly improved in all days of treatment compared to control group.
(Al-Jawad et al., 2012)	Iraq	38.16 ± 1.9	Male and female	54	3 weeks	Boiled and used by inhalation for 5-10 minutes	Randomized, open, and comparative clinical study	100 mg/kg	Significant elevated the values of forced expiratory volume in 1 second (FEV1%) and forced volume capacity (FVC).
(Salem et al., 2017)	Eastern Saudi Arabia	39.2±13.6 37.5±12.7 37.1±11.2	Male and female	26 26 24	3 months	Capsules of whole ground seeds	Single-blind, placebo-controlled, randomized study	1 and 2 g/day	FEF25-75% and FEV1% predicted was increased significantly after 6 and 12 weeks of treatment. PEF significantly improved at 6 and 12 weeks as compared with the controls. FeNO and serum IgE decreased significantly after 12 weeks in the treatment group vs baseline. *N. sativa* significantly increased the serum level of IFN-γ at 12 weeks vs baseline and significantly improved the ACT score at 6 and 12 weeks vs baseline.
(Koshak et al., 2017)	Saudi Arabia	39±13 42±15	Male and female	40 40	4 weeks	*N. sativa* oil capsule	Double Blind, Placebo-Controlled Trial	100 mg/kg	*N. sativa* significantly improved the mean ACT score and also significantly reduced blood eosinophils. The oil of *N. sativa* also improved FEV1 %.
(Barlianto et al., 2017)	Indonesia	8.79 ±2.9 8.71±3.7	Male and female	14 14	8 weeks	Soft gel capsules of *N. sativa* oil	Single blind, controlled trial	500 mg	*N. sativa* oil treatment significantly elevated IFN-γ and reduced IL-4 compared to control treatment group.
(Barlianto et al., 2018)	Indonesia	4–14	Male and female	28	8 weeks	Soft gel capsules of *N. sativa* oil	Single blind, controlled trial	15-30 mg/kg	Treatment with *N. sativa* oil remarkably reduced Th17, and increased Treg percentages. Also, Th17/Treg ratio was lower in treatment group compared to the standard treatment group. ACT was improved significantly in *N. sativa* oil compared to the standard treatment group.

breath, night time waking and rating of asthma control. The ACT score was used for evaluation of the degree of asthma control (Koolen et al., 2011). Supplement therapy with *N. sativa* can substantially improve ACT scores and PFT values including forced volume capacity and FEV1 in asthmatic patients (Al-Jawad et al., 2012). Moreover, supplementation of *N. sativa* was improved expiratory flow during the mid-part of vital capacity (FEF25-75%) (Salem et al., 2017), which indicated the beneficial effects of *N. sativa* for the function of the small airways. These effects may be due to antioxidant and anti-inflammatory properties of *N. sativa.*

The changes in the balance of pro-inflammatory and anti-inflammatory cytokines in chronic inflammatory process are associated with pathogenesis of bronchial asthma. IL-4 as an inflammatory mediator and IFN-γ as anti-inflammatory mediators produced by Th2 and Th1 cells, respectively, have a contribution in bronchial asthma (Packard and Khan 2003). One study revealed that *N. sativa* elevated IFN-γ and reduced IL-4 (Barlianto et al., 2017). The aqueous extract of *N. sativa* (1-100 µg/ml) stimulated secretion of Th2, versus Th1 cytokines by splenocytes. Moreover, this extract significantly suppressed secretion of IL-6, TNFα and NO as key pro-inflammatory mediators (Majdalawieh et al., 2010). Oral administration of *N. sativa* oil (1.82 ml/kg) showed anti-inflammatory, anti-nociceptive and anti-arthritic effects on complete Freund's adjuvant induced arthritis in a rat model study (Nasuti et al., 2019).

Intraperitoneal administration of *N. sativa* extract (100-400 mg/kg) reduced oxidative stress markers and inflammatory mediators such as TGF-β1, IFN-γ, PGE2, IL-4 levels in the broncho-alveolar fluid and serum of LPS-induced rat (Mokhtari-Zaer et al., 2020). The results of the above studies indicated that *N. sativa* exerts potent anti-inflammatory effects. In addition, supplementation of *N. sativa* oil remarkably reduced Th17, but enhanced Treg percentages in asthmatic children (Barlianto et al., 2018). Treatment patients with *N. sativa* oil (750 mg/kg) significantly reduced production of prostaglandin E_2 compared to the placebo treated group (750mg soybean oil) (Wu et al., 1999). *N. sativa* oil capsules (40-80 mg/kg/day) treatment in patients with allergic rhinitis and asthma remarkably reduced the levels of IgE, eosinophil count and endogenous cortisol in plasma and urine compared to their pre-treatment values (Kalus et al., 2003). The results of the included clinical studies as well as experimental animal models of different respiratory diseases, indicated that *N. sativa* showed the preventive effects on asthma by mechanisms such as antioxidant, immuno-modulatory and anti-inflammatory effects. The broncho-dilatory and preventive effects of the plant on asthma were also shown in the clinical studies.

Conclusion

N. sativa supplement improved the respiratory symptoms, PFT values and asthma control test. The plant also enhanced the anti-inflammatory cytokines as well as declined pro-inflammatory cytokines in asthmatic patients. Eventually, *N. sativa* supplement may offer a cost-effective and clinically proven effective therapeutic option for asthmatics with fewer side effects.

Conflict of interest

There is no conflict of interest or disclosure.

Acknowledgment

We thanks from research council of Birjand University of Medical Sciences.

References

Ahmad J, Khan RA, Malik MA. A study of Nigella sativa oil in the management of wheeze associated lower respiratory tract illness in children. Afr J Pharm Pharmacol 2010; 4: 436-9.

Al-Jawad FH, Al-Razzuqi RA, Hashim HM, Ismael AH. Broncho-relaxant activity of Nigella sativa versus anthemisnobilis in chronic bronchial asthma; a comparative study of efficacy. IOSR J Pharmac 2012; 2: 81-3. https://doi.org/10.9790/3013-24208183

Al-Moamary MS, Alhaider SA, Al-Hajjaj MS, Al-Ghobain MO, Idrees MM, Zeitouni MO, et al. The Saudi initiative for asthma-2012 update: guidelines for the diagnosis and management of asthma in adults and children. Ann Thorac Med 2012; 7: 175. https://doi.org/10.4103/1817-1737.102166

Al Ameen N, Altubaigy F, Jahangir T, Mahday IA, Mohammed EA, Musa O. Effect of Nigella sativa and bee honey on pulmonary, hepatic and renal function in Sudanese in Khartoum state. J Med Plant Res 2011; 5: 6857-63. https://doi.org/10.5897/JMPR11.1357

Alavinezhad A, Khazdair MR, Boskabady MH. Possible therapeutic effect of carvacrol on asthmatic patients: A random-

ized, double blind, placebo-controlled, Phase II clinical trial. Phytother Res 2018; 32: 151-9. https://doi.org/10.1002/ptr.5967

Barlianto W, Rachmawati M, Irawan M, Wulandari D. Effects of Nigella sativa oil on Th1/Th2, cytokine balance, and improvement of asthma control in children. Paediatr Indones 2017; 57: 223-8. https://doi.org/10.14238/pi57.5.2017.223-8

Barlianto W, Wulandari D, Chusniyah M, Chandra Kusuma HMS, Prawiro SR. Improvement of th17/treg balance and asthma control test score by nigella sativa supplementation in asthmatic children: a new approach to managing asthma. Turk J Immunol 2018; 6: 1-7. https://doi.org/10.25002/tji.2018.686

Barnes PJ. Drugs for asthma. Br J Pharmaco 2006; 147: S297-S303. https://doi.org/10.1038/sj.bjp.0706437

Bateman E, Hurd S, Barnes P, Bousquet J, Drazen J, FitzGerald M, et al. Global strategy for asthma management and prevention: GINA executive summary. Eur Respir J 2008; 31: 143-78. https://doi.org/10.1183/09031936.00138707

Bordoni L, Fedeli D, Nasuti C, Maggi F, Papa F, Wabitsch M, et al. Antioxidant and anti-inflammatory properties of Nigella sativa oil in human pre-adipocytes. Antioxidants 2019; 8: 51. https://doi.org/10.3390/antiox8020051

Boskabady M, Kiani S, Jandaghi P. Stimulatory effect of Nigella sativa on β2-adrenoceptors of guinea pig tracheal chains. Med j Islam Repub Iran 2004; 18: 153-158.

Boskabady M, Mohsenpoor N, Takaloo L. Antiasthmatic effect of Nigella sativa in airways of asthmatic patients. Phytomedicine 2010; 17: 707-13. https://doi.org/10.1016/j.phymed.2010.01.002

Boskabady MH, Farhadi J. The possible prophylactic effect of Nigella sativa seed aqueous extract on respiratory symptoms and pulmonary function tests on chemical war victims: a randomized, double-blind, placebo-controlled trial. J Altern Complement Med 2008; 14: 1137-44. https://doi.org/10.1089/acm.2008.0049

Boskabady MH, Javan H, Sajady M, Rakhshandeh H. The possible prophylactic effect of Nigella sativa seed extract in asthmatic patients. Fundam Clin Pharmacol 2007; 21: 559-66. https://doi.org/10.1111/j.1472-8206.2007.00509.x

Bousquet J, Jeffery PK, Busse WW, Johnson M, Vignola AM. Asthma: from bronchoconstriction to airways inflammation and remodeling. Am J Respir Crit Care Med 2000; 161: 1720-45. https://doi.org/10.1164/ajrccm.161.5.9903102

Chehl N, Chipitsyna G, Gong Q, Yeo CJ, Arafat HA. Anti-inflammatory effects of the Nigella sativa seed extract, thymoquinone, in pancreatic cancer cells. HPB 2009; 11: 373-81. https://doi.org/10.1111/j.1477-2574.2009.00059.x

Cohn L, Elias JA, Chupp GL. Asthma: mechanisms of disease persistence and progression. Annu Rev Immunol 2004; 22: 789-815. https://doi.org/10.1146/annurev.immunol.22.012703.104716

Durmuskahya C, Ozturk M. Ethnobotanical survey of medicinal plants used for the treatment of diabetes in Manisa, Turkey. Sains Malaysiana 2013; 42: 1431-8.

Düzelme D. Improvement of Th17/Treg balance and Asthma Control Test score by Nigella sativa supplementation in asthmatic children: a new approach to managing asthma. Turk J Immunol 2018; 6: 1-7. https://doi.org/10.25002/tji.2018.686

Emeka LB, Emeka PM, Khan TM. Antimicrobial activity of Nigella sativa L. seed oil against multi-drug resistant Staphylococcus aureus isolated from diabetic wounds. Pak J Pharm Sci 2015; 28: 1985-90.

Gholamnezhad Z, Boskabady MH, Khazdair MR, Hosseini M, Abbasnejad M. Effect of fluticasone and salmeterol on tracheal responsiveness to ovalbumin and lung inflammation, administrated during and after sensitization. Sci World J 2014; 2014. https://doi.org/10.1155/2014/865292

Gilani A, Aziz N, Khurram I, Chaudhary K, Iqbal A. 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.

Greenberger P A. Therapy in the management of the rhinitis/asthma complex. Allergy Asthma Proc 2003; 24: 403-7.

Hajhashemi V, Ghannadi A, Jafarabadi H. Black cumin seed essential oil, as a potent analgesic and antiinflammatory drug. Phytother Res 2004; 18: 195-9. https://doi.org/10.1002/ptr.1390

Janssen L J, Killian K. Airway smooth muscle as a target of asthma therapy: history and new directions. Respir Res 2006; 7: 123. https://doi.org/10.1186/1465-9921-7-123

Kalus U, Pruss A, Bystron J, Jurecka M, Smekalova A, Lichius JJ, et al. Effect of Nigella sativa (black seed) on subjective feeling in patients with allergic diseases. Phytother Res 2003; 17: 1209-14. https://doi.org/10.1002/ptr.1356

Khazdair MR, Boskabady M, Tabatabaee A, Hosseini M, Abbasnejad M. Effect of inhaled fluticasone and salmeterol on tracheal responsiveness and lung inflammation: influence of administration time and allergen-free period. Indian J Med Res 2013; 67: 78. https://doi.org/10.4103/0019-

5359.121121

Khazdair MR. The protective effects of Nigella sativa and its constituents on induced neurotoxicity. J Toxicol 2015; 2015. https://doi.org/10.1155/2015/841823

Khazdair MR, Anaeigoudari A, Hashemzehi M, Mohebbati R. Neuroprotective potency of some spice herbs, a literature review. J Tradit Complement Med 2019a; 9: 98-105. https://doi.org/10.1016/j.jtcme.2018.01.002

Khazdair MR, Anaeigoudari A, Kianmehr M. Anti-asthmatic effects of Portulaca Oleracea and its constituents, a review. J Pharmacopunct 2019b; 22: 122.

Koolen B, Pijnenburg M, Brackel H, Landstra A, Van den Berg N, Merkus P, et al. Comparing global initiative for asthma (GINA) criteria with the childhood asthma control test (C-ACT) and asthma control test (ACT). Eur Respir J 2011; 38: 561-6. https://doi.org/10.1183/09031936.00173710

Koshak A, Wei L, Koshak E, Wali S, Alamoudi O, Demerdash A, et al. Nigella sativa supplementation improves asthma control and biomarkers: a randomized, double-blind, placebo-controlled trial. Phytother Res 2017; 31: 403-409. https://doi.org/10.1002/ptr.5761

Mahmood MS, Gilani A, Khwaja A, Rashid A, Ashfaq M. The in vitro effect of aqueous extract of Nigella sativa seeds on nitric oxide production. Phytother Res 2003; 17: 921-4. https://doi.org/10.1002/ptr.1251

Majdalawieh A F, Hmaidan R, Carr R I. Nigella sativa modulates splenocyte proliferation, Th1/Th2 cytokine profile, macrophage function and NK anti-tumor activity. J Ethnopharmacol 2010; 131: 268-75. https://doi.org/10.1016/j.jep.2010.06.030

Mohebbati R, Shafei MN, Beheshti F, Soukhtanloo M, Roshan NM, Anaeigoudari A, et al. Mixed hydroalcoholic extracts of Nigella sativa and Curcuma longa improves adriamycin-induced renal injury in rat. Saudi J Kidney Dis Transpl 2017; 28: 1270. https://doi.org/10.4103/1319-2442.220880

Mohebbatia R, Khazdair MR, Karimia S, Abbasnezhadd A. Hepatoprotective effects of combination hydroalcoholic extracts of Nigella sativa and Curcuma Longa on adriamycin-induced oxidative stress in rat. J Rep Pharm Sci 2017a; 6: 93-102.

Mohebbati R, Khazdair MR, Hedayati M. Neuroprotective Effects of medicinal plants and their constituents on different induced neurotoxicity methods: a review. J Rep Pharm Sci 2017b; 6: 34-50.

Mokhtari-Zaer A, Norouzi F, Askari VR, Khazdair MR, Roshan NM, Boskabady M, et al. The protective effect of Nigella sativa extract on lung inflammation and oxidative stress induced by lipopolysaccharide in rats. J Ethnopharmacol 2020; 253: 112653. https://doi.org/10.1016/j.jep.2020.112653

Mortazavi Moghaddam SG, Kianmehr M, Khazdair MR. The possible therapeutic effects of some medicinal plants for chronic cough in children. Evid Based Complement Alternat Med 2020; 2020. https://doi.org/10.1155/2020/2149328

Nasir A, Siddiqui M, Mohsin M. Therapeutic uses of Shoneez (Nigella sativa Linn.) mentioned in unani system of medicine-A Review. Int J Pharm Phytopharmaco Res 2014; 4: 47-9.

Nasuti C, Fedeli D, Bordoni L, Piangerelli M, Servili M, Selvaggini R, et al. Anti-Inflammatory, anti-arthritic and anti-nociceptive activities of Nigella sativa oil in a rat model of arthritis. Antioxidants 2019; 8: 342. https://doi.org/10.3390/antiox8090342

Packard K A, Khan MM. Effects of histamine on Th1/Th2 cytokine balance. Int Immunopharmacol 2003; 3: 909-20. https://doi.org/10.1016/S1567-5769(02)00235-7

Salem AM, Bamosa AO, Qutub HO, Gupta RK, Badar A, Elnour A, et al. Effect of Nigella sativa supplementation on lung function and inflammatory mediators in partly controlled asthma: a randomized controlled trial. Ann Saudi Med 2017; 37: 64-71. https://doi.org/10.5144/0256-4947.2017.64

Shahzad M, Yang X, Asim MR, Sun Q, Han Y, Zhang F, et al. Black seed oil ameliorates allergic airway inflammation by inhibiting T-cell proliferation in rats. Pulm Pharmacol Ther 2009; 22: 37-43. https://doi.org/10.1016/j.pupt.2008.11.006

Slader C A, Reddel HK, Jenkins CR, Armour CL, Bosnic-Anticevich SZ. Complementary and alternative medicine use in asthma: who is using what? Respirology 2006; 11: 373-87. https://doi.org/10.1111/j.1440-1843.2006.00861.x

Tembhurne S, Feroz S, More B, Sakarkar D. A review on therapeutic potential of Nigella sativa (kalonji) seeds. J Med Plant Res 2014; 8: 167-77. https://doi.org/10.5897/JMPR10.737

Wu D, Meydani M, Leka LS, Nightingale Z, Handelman GJ, Blumberg JB, et al. Effect of dietary supplementation with black currant seed oil on the immune response of healthy elderly subjects. The Am J Clin Nutr 1999; 70: 536-43. https://doi.org/10.1093/ajcn/70.4.536