BOLETIN LATINOAMERICANO Y DEL CARIBE DE PLANTAS MEDICINALES Y AROMÁTICAS
© / ISSN 0717 7917 / www.blacpma.ms-editions.cl

Revisión / Review

Evidence-based anti-viral and immunomodulatory potential of Black cumin (*Nigella sativa* L.) in COVID-19

[Potencial antivírico e inmunomodulador en COVID-19 del comino negro (*Nigella sativa* L.) basado en la evidencia]

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Section Review

Received: 7 May 2021
Accepted: 12 September 2021
Accepted corrected: 3 October 2021
Published: 30 March 2022

Citation:
Riaz M, Khan M, Ahmad R, AlLehaibi LH, Rahman N, Deqiang D. Evidence-based anti-viral and immunomodulatory potential of Black cumin (*Nigella sativa* L.) in COVID-19
Bol Latinoam Caribe Plant Med Aromat
21 (2): 176 - 206 (2022).
https://doi.org/10.37360/blacpma.22.21.2.11

Abstract: Currently, the whole world is facing a life-threatening novel coronavirus 2019 (COVID-19) pandemic. Natural products are well-known for their potential role against viral disease, and some anti-viral agents have been developed to combat these diseases. Herein, the authors investigated the possible effects of this Holy plant *Nigella sativa* L. (NS), against coronavirus, using evidence-based and mechanistic approaches to conclude the immune-boosting and alleviation of respiratory system effects of NS. The pharmacological studies established a prominent role in treating various respiratory, immune systems, cardiovascular, skin, and gastrointestinal disorders. Literature supported the significant anti-viral role and showed an inhibitory role for NS against MHV-A59 CoV (mouse-hepatitis virus–A59) infected Hela, i.e., HeLaCEACAM1a (HeLa-epithelial carcinoembryonic antigen-related cell adhesion molecule 1a) cell. NS is a safe herbal product or dietary supplement and could be an effective and affordable community adjuvant treatment for coronavirus in the current scenario.

Keywords: Anti-asthmatic; Anti-coronavirus herb; Black cumin; Immune-boosting; Covid-19; *Nigella sativa*

Resumen: Actualmente, el mundo entero se enfrenta a una pandemia del nuevo coronavirus 2019 (COVID-19) que amenaza la vida. Los productos naturales son bien conocidos por su papel potencial contra las enfermedades virales, y se han desarrollado algunos agentes antivirales para combatir estas enfermedades. En este documento, los autores investigaron los posibles efectos de esta planta sagrada *Nigella sativa* L. (NS), contra el coronavirus, utilizando enfoques mecanicistas y basados en la evidencia para concluir el refuerzo inmunológico y el alivio de los efectos del SN en el sistema respiratorio. Los estudios farmacológicos establecieron un papel destacado en el tratamiento de diversos trastornos respiratorios, del sistema inmunológico, cardiovasculares, cutáneos y gastrointestinales. La literatura apoyó el importante papel antivírico y mostró un papel inhibidor de NS contra células Hela infectadas con MHV-A59 CoV (virus de la hepatitis de ratón-A59), es decir, HeLaCEACAM1a (molécula de adhesión celular 1a relacionada con el antígeno carcinoembrionario epitelial de HeLa). NS es un producto a base de hierbas o un suplemento dietético seguro y podría ser un tratamiento adyuvante comunitario eficaz y asequible para el coronavirus en el escenario actual.

Palabras clave: Anti-asmático; Hierba anti-coronavirus; Comino negro; Estimulante inmunológico; Covid-19; *Nigella sativa*

ABBREVIATIONS

AUC: Area under the curve
CAT: Catalase
CLP: Cecal Ligation and Puncture
COPD: Chronic obstructive pulmonary disease
COX: Cyclooxygenase
CP: Cyclophosphamide
CYP3A: Cytochrome P450, family 3, subfamily A
DEP: diesel exhaust particles
DPPH: 2,2-diphenyl-1-picrylhydrazyl
FVC: Force Vital Capacity
IFN-g: Interferon gamma
IL: Interleukin
IP: Intraperitonially
IV: Intravenously
LDL: Low-density lipoproteins
LOOH: Lipid hydroperoxide
LOX: Lipoxygenases
LPS: Lipopolysaccharide
MCC: Mucociliary clearance
MDA: *malondialdehyde*
NF-kb: Necrosis factor kappa beta
NK: Natural killer
NS: *Nigella sativa*
OVA: Ovalbumin
PBUH: Peace Be Upon Him
PEFR: Peak expiratory flow rate
PFT: Pulmonary Function Test
PGE: Prostaglandin E
P-gp: *P-glycoprotein* 1
PGs: Prostaglandins
QOL: Quality of life
ROSs: Reactive oxygen species
SH: Sulfhydryl
SOD: Superoxide dismutase
TBA: Thiobarbituric acid
THQ: Thymoquinone
TNFα: Tumor necrosis factor alpha
TNFs: Tumor necrosis factors
TXA: Thromboxane

INTRODUCTION

Roman coriander or *Nigella sativa* L. (NS) (black seeds) is globally known as a spice and as a food item. Hazrat Abu Hurairah narrated from the Prophet (PBUH) that "Black caraway/ (الحبةالسوداء)/Kalonji has the cure for all diseases except death (Al-Masabih, undated). *Nigella sativa* Linn, derived from Latin "nigellus", means black. The NS plant finds common use, especially in Asian, the Middle East, and African communities. Where the common names are; Roman Coriander, Habbat-Al-Barakah means "seeds of blessings" (Arabic), Kalonji (Urdu), black seed or black cumin (English), Kalijeera (Bengali), Hak Jung Chou (China), black caraway seeds (USA), and Mangrail (Nepali/Hindi). In old Latin terminologies, the NS seeds are known as "Panacea," which stands for "cure-all." This plant is indigenous to Southern and Northern Africa, South Europe, India, Saudi Arabia, Turkey, Syria, Bangladesh, and Pakistan (Hussain & Hussain 2016; Dajani *et al.,* 2018).

N. sativa is a commonly used food spice, flavoring agent, cosmetics, and herbal supplement for a variety of minor elements. The dry-roasted NS seeds flavour curries, vegetables, and pulses. NS was traditionally used as a preservative in mummification in the ancient Egyptian civilization. NS has a long history of use as medicine in the traditional system of medicine like Unani and Ayurveda (Sharma *et al.,* 2005). It is classified as GRAS in the United States (FDA, 2019). The potential for NS use is evident from its 1.01% CAGR (compound annual growth rate) growth and a predicted estimated market value of 25M USD by the end of 2025. The food chemistry for NS reveals the presence of multi-diverse components such as alkaloids, amino acids, and fatty acids discussed in detail in forthcoming sections (Ahmad *et al.,* 2020). The NS seeds may be a useful dietary supplement or food preservative and improve human health and nutrition (Bourgou *et al.,* 2012a).

Coronavirus is a novel single-stranded RNA-enveloped virus with a spherical shape that bears club-shaped projections of glycoproteins. The novel virus has almost four serotypes like alpha, beta, gamma, and delta Coronavirus, with several further subtypes. The history of the infection dates back to the 1960s. Initially, it was considered a flu virus due to similarity in genetic makeup (RNA) till the outbreak reached in 2002-2003 in Guangdong province of China, where severe cases were found in Saudi Arabia in the year 2012. The recent epidemic started in Wuhan, China, in 2019, which was declared a pandemic in 2020 by the World Health Organization (Lau & Chan 2015; Al-Osail & Al-

Wazzah 2017; Li *et al.*, 2020). At present, the treatment of novel Coronavirus is the most significant challenge to world scientists. Only one drug remdesivir has been approved as an anti-SARS-CoV-2 treatment for severe or suspected COVID-19 cases (FDA, 2020). Natural products/foods are considered a suitable alternative in such conditions. The ease of accessibility, use, lower price, and safety concept makes them effectively applicable in such situations—another most important WHO also supports the search for a potential treatment for COVID-19.

NS may be the best alternate solution to boost immunity in these pandemic conditions if NS or its derived products have a rational approach. This review highlights the potential role of NS in alleviating the respiratory symptoms, cytokine storms and enhancing the immune system activity in COVID-19 patients with mechanistic and therapeutic approaches.

Phytochemistry and nutrients

This herb contains a variety of chemical constituents, as shown in Figure No. 1. and Table No. 1. The hot aqueous and ethanol extract of NS yields; alkaloids (nigellicimine, nigellimine), terpenes (thymoquinone, negellone) proteins, amino acids, carbohydrates (glucose, arabinose, rhamnose, xylose), volatile constituents (alpha-pinene, thymol, p-cymene, carvone, D-limonene) and fixed oils about 35%. The fixed oil yields high content (78%) of unsaturated fatty acids (arachidonic, eicosadienoic, oleic, linoleic, linolenic acid) and a lesser extent of saturated fatty acids. Minerals (calcium, potassium, iron, zinc, magnesium, selenium) and vitamins (vitamin- A, B, B_2, niacin, and C) are also present (Paarakh, 2010; Attia & Al-Harthi, 2015).

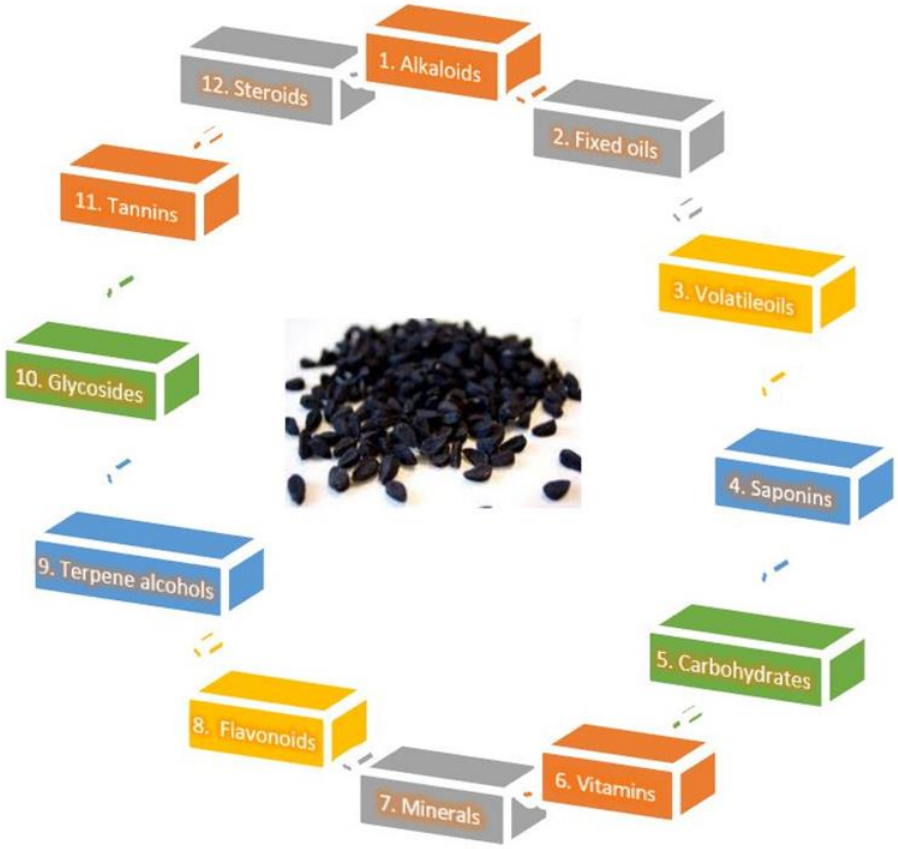


Figure No. 1
Chemical constituents of *Nigella sativa*

Pharmacological effects

Several studies support the use of black seeds in various disorders. The current review focuses on the research literature with relevancy in Corona disease and the treatment of its symptoms. The most common symptoms of COVID-19 are associated with inflammatory conditions characterized by fever, pain, and oxidative stress, which may be further complicated by fatigue, sore throat, and respiratory problems (WHO, 2020). In search of emergent solutions, the reported studies were critically analyzed in the context of COVID-19 symptoms.

Products	Organic black seeds (branded, 593406)	Amazing herbs, black cumin seed (branded, 468979)	Sweet sunnah, whole black seeds *Nigella sativa* (branded, 468991)	Organic black seeds ancient super seed *Nigella sativa* (branded, 593920)
Company	Sunfood LLC, US	AHN International Inc. US	Sweet Sunnah Black Seed Herbals, US	Sunfood LLC, US
Ingredients	certified organic Nigella sativa seeds	100% pure ground black cumin seed	pesticide and herbicide free select ground black seed	certified organic Nigella sativa seeds
Energy (kcal)	400	500	400	400
Protein (g)	0	20	16.67	0
Total lipid (g)	16.67	40	33.33	16.67
Carbohydrate (g)	50	40	50	50
Total dietary fiber (g)	33.3	20	0	33.3
Iron (mg)	16.67	7.2	12	16.67
Sodium (mg)	100	0	0	100
Cholesterol (mg)	0	0	0	0
Calcium (mg)	1000	Ng	0	1000
Magnesium (mg)	333	Ng*	Ng	333

Table No. 1
Nutrients values of *Nigella sativa* seeds (source Department of Agriculture USA, 2019), (Amount/per 100 g) *Ng= not given

The anti-inflammatory effect

The fixed oil of NS and isolated compound thymoquinone (THQ) (Figure No. 2), showed a dose-dependent anti-inflammatory activity against carrageenan-induced hind paw edema in rats (Pise & Padwal, 2017). In various tests in animal models, e.g., acetic acid-induced writhing, formalin, and tail-flick, the volatile oil of NS seed demonstrated a substantial pain-relieving effect (Hajhashemi *et al.,* 2004). The NS fatty oil as 500 mg capsule twice daily reduced the symptoms in forty female patients with rheumatoid arthritis (RA) compared to control (Gheita & Kenawy, 2012). NS fixed oil have been found to promote wound healing in rabbits (Elgohary *et al.*, 2018).

The water extract of NS produced anti-inflammatory effects in carrageenan-induced paw edema, but no antipyretic impact was shown in the yeast-induced pyrexia model (Al-Ghamdi, 2001). However, the analgesic effect was observed with the ingestion of alcoholic extract of NS in mice (Bashir & Qureshi, 2010). The ether extract of NS seed improved healing of the inflammatory condition produced topically onto mice skin *Staphylococcus* (Hanafi & Hatem, 1991). Similarly, a good wound healing effect was observed in a burn wound animal model by the topical application of NS (Abu-Al-Basal, 2011). The fatty oil of the NS has been reported for oral wound healing properties (Abu-Zinadah, 2009).

Inflammation is always associated with various disorders, trauma/injury, and infections (Fathy & Nikaido, 2018; Yimer *et al.,* 2019a). Therefore, the crucial anti-inflammatory role of NS preparations might be the possible sources for the development of an alternative to treat these wide-

ranging conditions as observed in COVID-19. As the hydroalcoholic extract of NS at the dose of 100, 200, 400 mg/kg via I.P. indicated a protective effect in LPS-induced lung injury (Mokhtari-Zaer *et al.*, 2020).

THQ and polyunsaturated fatty acids exert anti-inflammatory action due to the inhibition of the formation of the oxidative product of arachidonic acid, e.g., thromboxane-B_2 and leukotrienes (Houghton *et al.*, 1995; Mansour & Tornhamre, 2004; Khan *et al.*, 2016). The result is pain alleviation and decreased intensity of bronchospasm. Furthermore, the inhibition of LOX helps block; apoptosis, pro-inflammatory cytokines, and tumor necrosis factors (TNFα). Overall, the inhibition of COX and LOX pathways increases cellular immunity, WBCs production, gene expression for cytokines, stabilizing macrophages, and increases the production of lymphocytes in the body Figure No. 3. These pharmacological compensations suggest NS be an effective herb in subsiding the symptoms and management of COVID-19 (Khan *et al.*, 2016; Dajani *et al.*, 2018).

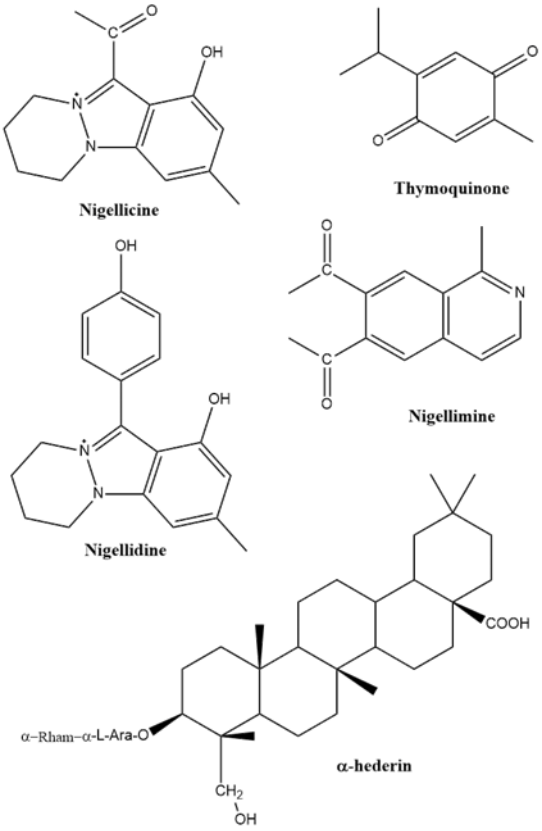


Figure No. 2
Some important isolated constituents of *Nigella sativa* L with anti-COVID-19 potentials

Antioxidant effect

CoVID-19 is associated with the overproduction of reactive oxygen species (ROS) and poor antioxidant management by the body (Delgado-Roche & Mesta, 2020). The over-productive ROSs during CoVID-19 infection includes H_2O_2 ($\bullet O_2^-$), ($\bullet$OH), etc. thus, a useful antioxidant may play a vital role in neutralizing the ROS generated during the cascading events of infection (Wang *et al.*, 2020). NS may be a promising and naturally proved antioxidant **(**Table No. 2**).** The antioxidant activity of NS seeds could be a useful compound for preventing and treating cerebral ischemic and neurodegenerative diseases due to their antioxidant property (Mahmoud *et al.*, 2002). Co-administration of NS fatty oil with cisplatin in male rats improves oxidative stress-induced in

testicles (Tayarani-Najaran *et al.*, 2009). The consumption of NS seeds at a dose of 3 g daily for two weeks has been reported in 64 healthy individuals to lower lipid peroxidation (Sharieatzadeh *et al.*, 2011).

The results indicate that different combinations of NS have synergistic effects. The combination of NS with iron prevents oxidation. In many diseases, such as cirrhosis or liver damage, NS anti-oxidant activity could eliminate free radicals (Houghton *et al.*, 1995; Nagi *et al.*, 1999). Flavonoids of NS have been reported for higher anti-oxidant effects and, consequently, more anti-radical effects (Comalada *et al.*, 2006).

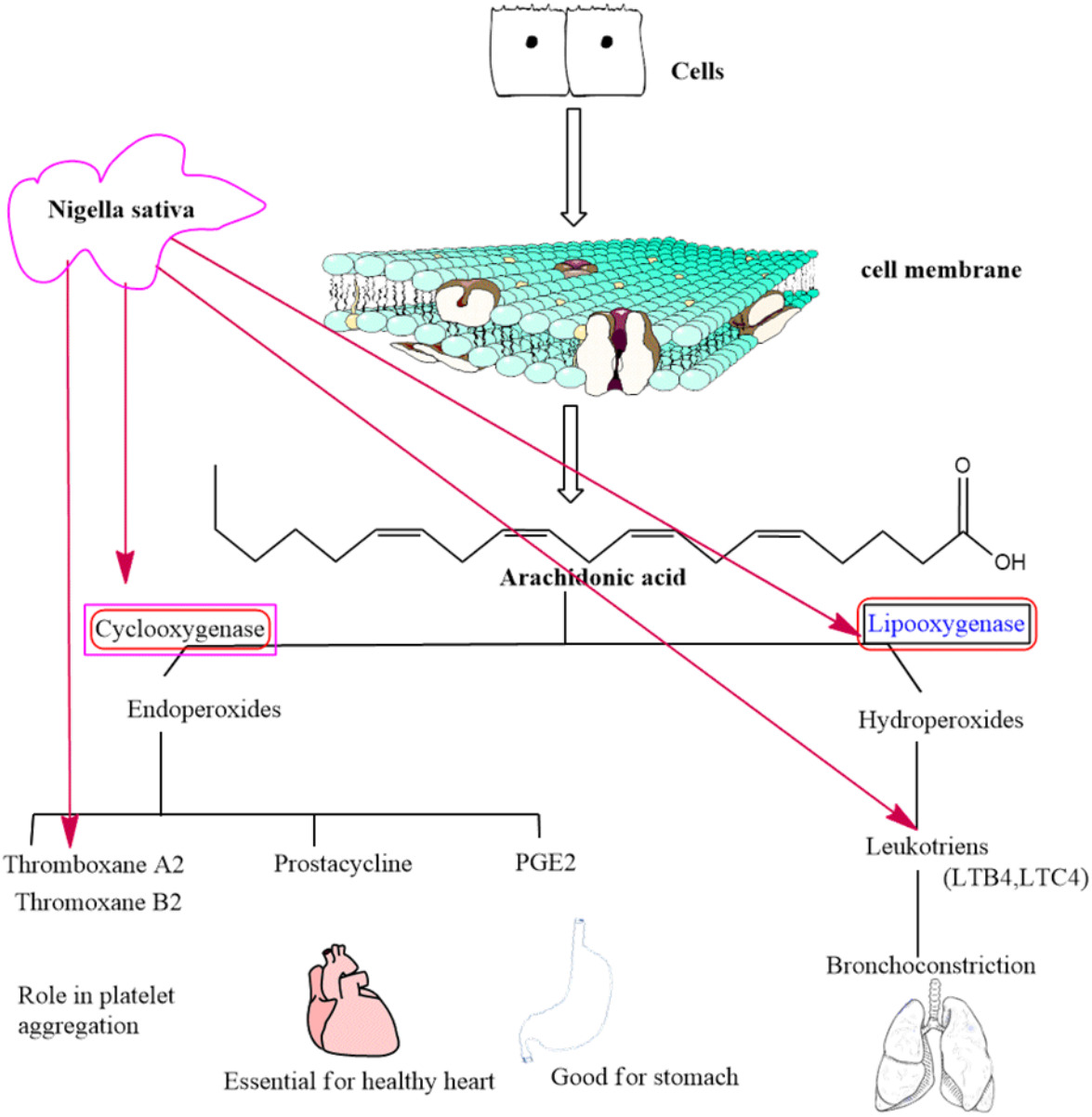


Figure No. 3
Blockade of inflammatory pathways

THQ suppressed mucosal production by goblet cell and reduced infiltration of eosinophils in the lung tissue and also decreased lung eosinophilia (El-Gazzar *et al.*, 2006). The pathological changes in lung tissues of animal asthma model was suppressed by THQ (Keyhanmanesh *et al.*, 2010a; Boskabady *et*

al., 2011a). Ammar *et al*. (2011), reported that pathological changes in bronchioles and bronchi was inhibited by THQ in mice asthmatic model (Ammar *et al*., 2011; Kalemci *et al*., 2013). THQ inhibited at (3 mg/kg, i.p.) inhibitory effects on histopathological changes in lung tissue of OVA-sensitized mice (Su *et al*., 2016). Similar inhibitory effects have been reported with administration of α-hederin (0.02 mg/kg, i.p.) in OVA-sensitized rats (Fallahi *et al*., 2016). THQ have also been recently reported for the protection against benzopyrene induced lung injury in rats (Al-Zohairy *et al*., 2021).

Table No. 2
Reported antioxidant studies of NS extract and isolated compounds

Type of component	Type of antioxidant assays	RESULTS	REFERENCES
Essential oil	DPPH, lipid peroxidation, deoxyribose,	THQ, carvacrol, t-anethole and 4-terpineol and oil possess antioxidant potentials	Burits & Bucar, 2000
Methanol extract and subfractions	DPPH, b-carotene lineolate bleaching, corn oil oxidation inhibition assay	The methanol extract and ethyl acetate fraction showed the highest antioxidant activity than other fractions	Mariod *et al.*, 2009
Fixed oil	*In vivo* (Rats)	Improve the level of glutathione peroxidase and superoxide dismutase	Bayrak *et al.*, 2008
THQ	Lipid peroxidation	Powerful anti-oxidant	Nagi & Mansour, 2000 Al-Majed *et al.*, 2006
THQ	In vivo (mice)	Reduces malondialdehyde in brain	Sheikh & Mohamadin, 2012
THQ	1,2-dimethylhydrazine-(DMH)-induced colon carcinogenesis rat model	Elevate erythrocyte lipid peroxidation and anti-oxidant status	Jrah Harzallah *et al.*, 2012
THQ	Pretreatment (rat)	Improve MDA and conjugated diene levels to normal, decrease CAT, glutathione peroxidase, and SOD	Jrah Harzallah *et al.*, 2012
THQ	Arthritis in rat (biochemical assays)	Significant changes in articular elastase and other enzymes	Umar *et al.*, 2012
n-hexane, petroleum ether, chloroform, methanol	Ferric thiocyanate, thiobarbituric acid (TBA) methods	Competitive to α-tocopherol showed strong antioxidant potentials	Al-Naqeeb *et al.*, 2009
Fixed oil extract using microwave assisted extraction	DPPH, ferric reducing antioxidant power assay	Stronger antioxidant	Abedi *et al.*, 2017
Essential oil and acetone extract	Peroxide, TBA, DPPH	Strong reducing power	Singh *et al.*, 2005
Essential oil terpenoids: *trans*- and, *cis*-sabinene hydrate methyl ether, 1,2-epoxy-menth-4-ene and 1,2-epoxy-menth-4(8)-ene	Oxygen radical scavenging assay, oxidative stress in WS-1 fibroblast, lipopolysaccharide-activated RAW 264.7 macrophages	Strong antioxidant effects (in vitro), inhibit oxidative stress in WS-1, inhibited nitric oxide release in RAW	Bourgou *et al.*, 2012a
Hexane fraction of seed	LPS Raw 264.7	Inhibit nitric oxide release	Bourgou *et al.*, 2012b

methanolic extract			
THQ	DPPH	Potent antioxidant comparative to other components in oil	Kazemi, 2014
THQ enriched fraction	Hydroxyl radical ($OH^{\cdot}$)-scavenging activity of plasma in rats	Decrease in plasma antioxidant capacity	Ismail *et al.*, 2010
Extract	DPPH	Antioxidant activity (IC_{50} = 12 256 mg/mL)	Mammad *et al.*, 2017
Methanolic extract	DPPH, β-carotene and linoleic acid system, reducing power assay	NS seed from Konya Turkey showed more antioxidant potentials	Şen *et al.*, 2010
20% ethanolic extract	DPPH	Antioxidant (IC_{50} = 1.26 ± 0.21 μg/mL)	Ahmed *et al.*, 2018

Role in respiratory disorders

The NS seeds have been reported in various traditions to use respiratory disorders (Duke 2002; Gilani *et al.*, 2004). The NS extracts, oil, and *α*-hederin showed an improvement of tracheal responsiveness and significant anti-inflammatory activity via decreasing the release of histamine and leukotrienes while increasing the release of PGE_2 from mast cells and perfused lungs in an animal model of allergic asthma (Boskabady *et al.*, 2011a; Keyhanmanesh *et al.*, 2013a; Saadat *et al.*, 2015; Ikhsan *et al*., 2018). Different clinical studies further substantiate this anti-asthmatic effect, and the majority of these studies reported an improvement of clinical symptoms and pulmonary function along with asthma biomarkers (Boskabady *et al.*, 2007; Boskabady & Farhadi, 2008; Boskabady *et al.*, 2010; Salem *et al.*, 2017; Koshak *et al.*, 2017a). These preclinical and clinical studies support the potential anti-asthmatic effects of NS given in Table No. 3. The limited clinical evidence, demands the further high-quality studies for a specific claim. As previous low-quality studies with broad claims are making the picture blurred.

Table No. 3
Preclinical and clinical studies using NS or its derivatives in respiratory disorders and allergic rhinitis

NS preparations	Study model	Dose	Effects	Ref.
Non-clinical studies				
Alcoholic extract	Pre-contracted tracheal chain of Guinea pig	0.8 to 2 g/100 mL	Relaxant effect	Boskabady *et al*., 2008
Ethanolic extract	CLP induced sepsis in rats	125, 250, 500 mg/kg	Reduce pro-inflammatory cytokines and oxidative stress	Bayir *et al*., 2012
Hydroethanolic extract	sulfur mustard (SM) exposed guinea pigs	0.08 g daily, orally	Preventive effect on tracheal response and lung inflammation	Boskabady *et al*., 2011a
Hydro-ethanolic extract	Bacterial Rhino-sinusitis in rabbits	50, 100, 200 mg/kg	Decrease NO level, Prevented histopathological changes	Yoruk *et al*., 2017
Hydro-ethanolic extract	guinea pigs exposed to cigarette smoke	0.125 mg/mL	Protective effect	Keyhanmanesh *et al*., 2014

Hydro-ethanolic extract	Ovalbumin sensitized guinea pigs	0.125 mg/mL	Preventive effect on tracheal response and inflammation	Boskabady *et al*., 2011b
Methanol fraction containing two flavonoids (20-20% and 21-20% fractions) and two polysaccharides (1-20% and 2-20% fractions)	contracted tracheal chains of guinea pigs	Dose for each (50, 100, 150 and 200 mg/L)	two flavonoids of 20%-methanolic fraction were the main constituent, showed relaxant effects	Keyhanmanesh *et al*., 2013a
Methanolic fractions (20%, 40%, 60%, 80%, and 100%)	tracheal chains of guinea pigs	Each 0.8, 1.2, 1.6, and 2.0 g%	potent relaxant effect of 20% methanolic fractions	Keyhanmanesh *et al*., 2013b
Nigellone	Ba^{2+}-, carbachol- and leukotriene-induced trachea contractions in C57BL/6 mice, rats, and guinea pigs	20 mg/kg for MCC and for relaxing effects 50 mg/mL	antispasmodic effect and an increase in MCC	Wienkötter *et al*., 2008
Fixed oil	Bleomycin induced pulmonary fibrosis in rat	1 mL/kg oral once daily	Controlled inflammatory index & fibrosis score	Abidi *et al*., 2017
Fixed oil	Hyperoxia induced lung injury in rats	4 ml per kg/day IP	Preventive effect on lung injury via reducing oxidative stress	Tayman *et al*., 2013
Volatile oil	urethane-anaesthetized guinea-pigs	4-32 mL/kg IV	Respiratory effects via direct histaminergic and indirect muscarinic cholinergic mechanism	El-Tahir *et al*., 1993
Volatile oil	Aspiration lung injury in rats	400 mg/kg/day by gavage for 7 days	Inhibited inflammation, fibrosis and edema	Kanter, 2009
Petroleum ether fraction	Isolated rabbit jejunum and guinea-pig tracheal preparations	0.1-0.3 mg/mL	Bronchodilator effect via calcium channel blocking	Gilani *et al*., 2001
THQ	Bleomycin induced pulmonary fibrosis in rats	5 mg/kg per day IP for 5 weeks	Inhibit NF-kb, antifibrotic effect	El-Khouly *et al*., 2012
THQ	CP induced pulmonary injury in rats	100 mg/kg/day orally for 14 days	Attenuated proinflammatory cytokines and TNF α	Suddek *et al*., 2013
THQ	diesel exhaust particles (DEP)	Pretreated 6 $g \cdot kg^{-1}$; IP	Protection against DEP pulmonary changes	Nemmar *et al*., 2011

	induced inflammation in mice lungs			
THQ	guinea pig model of asthma	3 mg/kg, IP	Asthma preventive effect	Keyhanmanesh *et al*., 2014
THQ	HBO2 induced lung injury in rats	50 mg/kg/day by gavage for five days	Prevent lung injury via reduction of LOOH and SH level	Gunes *et al*., 2017
THQ	Monocrotaline induced pulmonary artery hypertension	8, 12, 16 mg/kg per day for two weeks	inhibit pulmonary arterial remodeling	Zhu *et al*., 2016
THQ	OVA sensitized guinea pigs	20 µM (0.0033 g%) and 40 µM (0.0066 g%)	improved tracheal responsiveness, differential WBC count	Keyhanmanesh *et al*., 2010b
THQ	Paraquat induced pulmonary fibrosis in mice	20 and 40 mg/kg orally for 28 days	Inhibit oxidative stress, down regulate pro-fibrotic genes	Pourgholamhossein *et al*., 2016
THQ	Toluene exposed rat model	50 mg/kg/day for 12 weeks	Inhibited inflammation, fibrosis and edema	Kanter, 2011
α-hederin	OVA-sensitized guinea pigs	0.3 and 3 mg/kg IP	Decreased tracheal responsiveness & lung inflammation like THQ	Saadat *et al*., 2015
α-hederin	OVA-sensitized rats	0.02 mg/kg	Decrease IL-2 & IL-17 mRNA levels. alter miRNA-133a gene expression	Ebrahimi *et al*., 2016
Clinical studies				
Aqueous extract	Asthmatic patients (29)	15 mg/kg orally for three months daily	Improved asthmatic symptoms i.e., the prophylactic effect was observed	Boskabady *et al*., 2007
Aqueous extract (Boiled)	chronic asthmatic patients (54)	100 mg/kg by inhalation daily for 3 weeks	Improved overall clinical symptoms associated with asthma	Al-Jawad *et al*., 2012
Boiled aqueous extracts	Asthmatic patients (15)	50 and 100 mg/kg/day oral	significant increases in all measured pulmonary function tests	Boskabady *et al*., 2010
Fixed oil	Clinical study (152 patients)	40 to 80 mg/kg/day	Allergic rhinitis decrease in 80% of the cases	Kalus *et al*., 2003
Fixed oil	Asthmatic patients (80)	1000 mg/day orally for 4 weeks	Reduced eosinophil level, improved PFT	Koshak *et al*., 2017a
Fixed oil	Asthmatic patients (84)	0.09 mg/kg/day orally, 14 days	Pulmonary index decrease, PEFR improved	Ahmad *et al*., 2010
Cold pressed oil (1 spray contain 22.6 mg per 25 mL)	geriatric patients with nasal dryness	Three sprays per nostril three times daily for two weeks	Cure nasal dryness, Obstruction & crusting	Oysu *et al*., 2014
Fixed oil	Asthmatic Children	15-30	improves IFN-g/IL-4	Barlianto *et al*., 2017

	(14)	mg/kg/day for 8 weeks	balance and asthma control	
Seeds powder	asthmatic children	15 mg/kg/day for 14 weeks orally	Clinical symptoms improved	Susanti *et al*., 2013
Seeds powder	Asthmatic patients (5)	2 g/day, 26 mg/kg/day oral for 3 months	Increase FVC	Ameen *et al*., 2011
Seeds powder	Children with asthma (31)	15 mg/kg/day orally for 14 weeks	Clinical symptoms improved	Kardani *et al*., 2013
Seeds powder	Asthmatic patients (76)	1 and 2g/kg per day for three months	Along with inhaled maintenance therapy in asthma improve pulmonary function and inflammation	Salem *et al*., 2017
Seeds powder and *Phyllanthus niruri* extracts	Tonsillopharyngitis patients (200)	14.4 mg/kg/day for 7 days orally	Symptoms improved	Dirjomuljono *et al*., 2008
Seeds	Allergic rhinitis patients (20)	250 mg per day for 15 days	Symptoms reduced significantly	Ansari *et al*., 2006
Seeds	Allergic rhinitis patients (47)	250 mg per day for two weeks	Symptoms improved without causing side effects comparative to montelukast	Ansari *et al*., 2010
Fixed oil	Allergic rhinitis patients (66)	0.5 mL for 30 days	Symptoms improved, may be used as antiallergic if other medicines are avoided	Nikakhlagh *et al*., 2011
Fixed oil	Allergic rhinitis (68) patients	Nasal drops for six weeks	Allergic symptoms subsided	Alsamarai *et al*., 2014

Abbreviations: ACT; Asthma Control Test, CLP; Cecal Ligation and Puncture, CP; Cyclophosphamide, DEP; Diesel exhaust particles, FEF; Forced Expiratory Flow, FeNO; Fractional Exhaled Nitric Oxide, FEV; Forced Expiratory Volume, HBO2; Hyperbaric Oxygen, IP; Intraperitonially, IV; Intravenously, MCC; mucociliary clearance, NO; Nitric Oxide, OVA; ovalbumin, PEFR; Peak expiratory flow rate, PFT; Pulmonary Function Test, TR; Tracheal response, FVC; Force Vital Capacity

Anti-viral studies

A study of fixed NS oil, conducted in the murine model infected with cytomegalovirus, showed undetectable virus load both in the liver and spleen due to the increase in number and function of CD4+ T-cells and INF-α (Salem & Hossain, 2000). A clinical study conducted in hepatitis-C virus-infected patients, where 450 mg NS oil (capsule) were given after meal for three months, showed a significant decrease in viral load and other laboratory parameters (Barakat *et al.,* 2013). A clinical case was reported where NS oil (10 ml twice a day for six months) was administered to a 46-year-old HIV-positive patient. The study results showed complete seroversion and rescued (Onifade *et al*., 2013a). Another case reported a complete cure of a 27-year-old HIV-infected woman using NS and honey (10 mL) when used three times a day for one year (Onifade *et al.,* 2015). Sixty HCV patients were treated with ethanolic extract of NS and *Zingiber officinale* (1000 mg each daily and in combination for one month). The combined therapy was more potent via decreasing viral load and improving liver functions (Abdel-Moneim *et al.,* 2013). A pilot study conducted in 195 HCV patients treated with NS and chloroquine combined therapy resulted in negative

HCV-RNA (Sheir *et al.,* 2013).

Nowadays, COVID-19 is a serious global threat, and in this regard, NS may be a promising natural therapy to cure such infectious diseases via decreasing the viral load (Basurra *et al*., 2021).

Immuno-protective activity

Twenty-four allergic rhinitis patients were supplemented with NS (2 g/day daily) for one month; the results concluded the adjuvant role of NS as the effect was synergistic in immunotherapy (Işık *et al.,* 2010). The immunomodulatory role of NS oil (1 g in divided doses) was studied in forty-three female arthritis patients for 2 months. NS oil modulated T-lymphocytes revealing an application in rheumatoid arthritis (Kheirouri *et al.,* 2016).

In silico studies

The in silico study conducted so far has confirmed that several plant (NS) compounds have the potential to target the SARS-CoV-2 replication and host cell attachment. Isolated compound thymoquinone and thymohydroquinone have the potential to target main protease, heat shock protein A5, endoribonuclease, RNA-dependent RNA polymerase, and angiotensin-converting enzyme 2, of SARS-CoV-2 with moderate binding affinity (Barakat *et al.,* 2010; Onifade *et al*., 2013a; Onifade *et al*., 2013b; Mani *et al.,* 2020). Another study showed that nigellidine and α-hederin (Figure No. 2) had a significant binding affinity to the protease and peptidase of the virus comparative to the control (Ulasli *et al.,* 2014; Maiti *et al.,* 2020). Hederagenin has also been reported to have the highest binding affinity to main proteases, angiotensin-converting enzyme 2, and GRP78 (Oyero *et al.,* 2016; Barakat *et al.,* 2013). A compound nigellidine (Figure No. 2) in another in silico study showed high binding affinity to N-terminus-proteinase, nucleocapsid, and other molecular targets of SARS-CoV-2 (Barakat *et al.,* 2013). The silico studies have the disadvantage of inaccurate predictions due to molecule conformation, protein flexibility and promiscuity (Ekins *et al.,* 2007); thus, the anti-SARS-CoV-2 prediction of NS or derived compounds shall be considered with *in vivo* and *in vitro* studies.

Standardized NS product & dose selection

In this section, an attempt has been made to clarify some basic questions regarding the use of NS, i.e., what dose and dosage form should be used? And what is the therapeutic value/safety of the selected doses?

Herbs and herbal extracts/products may vary in the quality and quantity of the active constituents. This variation is due to various factors, including geographical origin, temperature, salinity, rainfall, altitudes, extraction solvents, techniques used, an analytical method developed, and storage of the final products. NS products are available in the form of whole seeds, powder, oil, etc. Generally, powder and fixed oil of the NS seeds are preferred due to more bioavailability and therapeutic potential. The quality of the product used is another challenge for consumers. In this regard, the world health organization (WHO) guidelines for quality variation and evaluation of herbal products may help evaluate the quality of a product. Several studies are available where the quality of herbal products is determined with the help of advanced hyphenated techniques of extraction and quantification. It is of utmost importance to select a product evaluated as per WHO guidelines or studies are available regarding quality standardization. Because the solvent compatibility, appropriate temperature, and time duration used during the extraction process may adversely affect the nature of active phytochemical responsible for the activity, a solvent with incompatible polarity, very high or very low temperature, and exposure of the herb/herbal sample to water or heat for a longer period during conventional extraction may decrease the potency of the final product. Green and advanced extraction techniques utilizing the lesser amount of solvent and least time of extraction with more extract yield are applied nowadays. The integrity of the final product remains intact, and the potency in terms of the active ingredient is less affected.

Another important challenge is the dose to be used during therapy. NS in low doses does not show any prominent adverse effects (Ahmad *et al.,* 2013). Literature shows the use of different treatments for NS. For instance, clinical studies used an oral dose of 500 mg NS powder in oil, water, or in the form of tea (Hussain & Hussain, 2016; Dajani *et al.,* 2018). Likewise, herbalists recommend two teaspoons/day of the NS seeds for an optimal therapeutic outcome.

NS has a wide-ranging therapeutic index with minimal or negligible adverse effects reported. The literature supports even the safety of its main phytochemical compound, i.e., THQ (Yimer *et al.,*

2019b). A study for NS in chickens at a dose of 5–20 g/kg orally in feed showed an improved antibody-mediated immunity (Islam *et al.,* 2017). A clinical study conducted for NS in diabetic patients showed better toleration up to a dose of 3 g/day (Bamosa, 2018).

Safety considerations and interactions

Safety and precautions of Nigella sativa

It has been mentioned earlier that NS is a relatively safe plant, and minimal adverse effects have been reported using optimal dose. However, high doses or concomitant administration with herbs and drugs possessing the same pharmacological action may result in untoward effects. The literature reports that THQ cause mild irritation, allergic and dermatitis when used in high doses (Kurihara *et al*., 2020). Likewise, nigellone has been alerted to be used in moderation (Kamil, 2013).

Interactions of Nigella sativa

NS shows interactions with various drugs and herbs. Some of the interactions are observed to be synergistic, while other inhibitory. Proper knowledge and care are important before use NS, along with any medications or herbs. A detailed account of NS drugs/herb interaction is provided in Table No. 4.

Toxicity studies

The NS seeds and their extracts appear to have a low level of toxicities. At a dose of 50 mg/kg daily for 5 days, the NS seed extract did not produce any toxicological symptoms in tested rats (El-Daly, 1998). A study conducted in Sprague Dawley rats at a dose of up to 1 g of dry powdered NS for 28 days daily showed no hepatotoxic effects (Dollah *et al.,* 2013). Daily administration of the NS aqueous extract to mice (5) at a dose of 6.4 g/kg for six weeks led to the death of one mouse after 2 weeks. However, few animals experienced death at the 3rd and 5th weeks while receiving 21 g/kg and 60 g/kg of the extract, respectively. Mice at a dose of 21 g/kg showed hepatotoxic effects while no such effects were observed at higher doses (Bensiameur-Touati *et al.,* 2017). Further in-depth studies are required to answer the questions raised during the research study of Bensiameur-Touati *et al*. (2017), a clinical study conducted on 27 humans consuming NS seeds at a dose of 2 g daily for three months showed no hepatic or renal toxicity (Ameen *et al.,* 2011).

Table No. 4
Drugs, herbs and food interactions known for NS

Interacting agent/class	Mechanism	Effect	References
	***NS vs.* drug interaction**		
Antibiotics	NS acts against Gram-positive (*Staphylococcus aureus*) and Gram-negative (*Pseudomonas aeruginosa* and *Escherichia coli*) species	Synergistic antibacterial activity	Aljabre *et al.*, 2015
Amoxicillin	Enhanced absorption due to long and medium chain fatty acids in NS	Enhanced amoxicillin bioavailability and effect	Ali *et al.,* 2012
Antifungal drugs	NS acts against *Candida albicans, Madurella mycetomatis, Fusarium solani, Scopulariopsis brevicaulis, Trichophyton* spp always without capital letters., *Epidermophyton spp.*, and *Microsporum spp*.	Synergistic antifungal activity	Nadaf *et al.,* 2015
Antiviral drugs	NS enhances helper-T-cell (T4) and suppressor-T-cell (T8) ratio and enhances natural killer (NK) cell activity in human	Synergistic antiviral activity	Aljabre *et al.*, 2015
Antiparasitic drugs	NS possesses anti-leishmanial, anti-miracidia, anti-cercariae activity	Synergistic activity	Simalango & Utami, 2014

Anti-inflammatory drugs	NS reduces NO production, interleukin-1 (IL-1), cyclooxygenase-1 (COX-1), cyclooxygenase-2 (COX-2), histone deacetylase (HDAC) and pro-inflammatory mediators (IL-1β, IL-6, TNF-α, IFN-γ, and PGE_2)	Synergistic anti-inflammatory activity	Ahmad *et al.*, 2013
Antitumor drugs	NS induces antioxidative-induced prooxidant effects and increases the ratio of apoptosis regulator (bcl-4)/cyclin-2 (bax/bcl-2) expression and decreasing cyclin-xl (bcl-xl) protein.	Synergistic antitumor activity	Aljabre *et al.*, 2015
Anti-asthmatic drugs	NS inhibits leukotriene-d4 (LT 4), reduces peribronchial inflammatory cell infiltration, alveolar septal infiltration, alveolar macrophages, necrosis formation, NOS and rises surfactant protein D in the pulmonary system	Synergistic anti-asthmatic activity	Ahmad *et al.*, 2013
Antioxidant drugs	NS traps free radicals and reduces lipid peroxidation inhibition	Synergistic antioxidant activity	Sharieatzadeh *et al.*, 2011
Antihypertensive (carvedilol)	Increased drug diffusion via stratum corneum due to linoleic acid	Enhanced effect of carvedilol	Harrison *et al.*, 1996
Antihypertensive (losartan)	Inhibits CYP3A activity	Decreased blood pressure	Ahad *et al.*, 2020
Antihyperlipidemic drugs	NS regulates cholesterol via HMG-CoA reductase, Apo-A1, Apo-B100 and LDL-receptor genes thus enhances liver cells efficiency to remove LDL	Synergistic antihyperlipidemic activity	Ibrahim *et al.*, 2014
Antidiabetic drugs	NS regulates liver enzymes activity associated with glucose metabolism, reduce gluconeogenesis and activates AMPK	Synergistic antidiabetic activity	Al-Hader *et al.*, 1993
Cardioprotective agents	NS decreases motor fuel (diesel particle)-induced systolic blood pressure, leukocytes, IL-6, plasma SOD activity, platelet counts and the prothrombin events rather than platelet aggregation	Synergistic cardiovascular protective activity	Ahmad *et al.*, 2013
Gastro protective agents	NS decreases gastric acid secretion, acid output (AO), pepsin, the mucosal content/activity of lipid peroxidase (LPO), proton (H+) pump, MPO and ulcer index (UI) and, increases content/activity of gastric mucin, GSH, total nitric oxide (TNO) and SOD	Synergistic gastro-protective activity	El-Abhar *et al.*, 2003

Antiepileptic (Pilocarpine)	Restoration of Na+, K+-ATPase activity in the hippocampus by NS	Antioxidant and antiepileptic effect	Haglund *et al.,* 1985
Immune protective agents	NS enhances NK cells and immune system via increase in macrophage and lymphocyte numbers	Synergistic Immune protective activity	Swamy & Tan, 2000
Immunosuppressant Cyclosporine	Decreased absorption via modulation of P-gp and CYP3A4 in intestine	Decreased cyclosporine activity	Al-Jenoobi *et al.,* 2013
	NS vs herb interactions		
Lepidium sativum	NS with *Lepidium* affects sildenafil absorption as indicated by the significant reduction in their $AUC_{0-\infty}$	Decreased sildenafil activity	Al-Mohizea *et al.,* 2015
Trigonella foenum-graecum	NS with *Trigonella* affects sildenafil absorption as indicated by the significant reduction in their $AUC_{0-\infty}$	Decreased sildenafil activity	Al-Mohizea *et al.,* 2015
	NS vs food interactions		
Natural contaminant microflora in complex food matrices (Milks)	NS inhibits *E. coli*, *coliforms* and *Staphylococcus*	Synergistic antibacterial activity	Georgescu *et al.,* 2018
Iron	NS increases liver storage of iron	An increased iron absorption	Jadayil *et al.,* 1999

NS seed oil at 10 mL/kg in rats and mice orally for two days did not produce toxic symptoms or mortality (Khanna *et al.,* 1993). In chronic toxicity testing for 12 weeks, NS oil at a dose of 2 mL/kg neither affected the major liver enzymes nor induced histopathological changes in vital organs (Zaoui *et al.,* 2002). The NS oil at 500 mg/kg/IP/day for 7 days in male BALB/c mice did not induce genotoxicity using the micronucleus test (Franco-Ramos *et al.,* 2020). In toxicity studies of the NS fixed oil in mice and rats, the LD_{50} values were 28.8 mL/kg (PO) and 2.06 mL/kg (IP).

The acute oral toxicity of THQ was determined in Swiss albino mice; the lethal dose 50 (LD_{50}) value was reported to be 2.4 g/kg. The hypo-activeness and difficulty in respiration was the sign and symptoms of toxicity that appears at higher doses. In sub-chronic toxicity study in mice for 90 days at dose 30 to 90 mg/kg/day of THQ caused no signs of toxicity or histopathological changes in vital organs. Still, decreased fasting plasma glucose, GSH content was observed (Badary *et al.,* 1998). This study confirmed the low order oral toxicity of THQ.

THQ is less toxic *in vivo* and *in vitro* at a dose of 20-500 mg/kg; however, it was found toxic in a dose of 500 mg/kg on the histopathological level in the form of oil in rats (Ermumcu & Şanlıer, 2017). *In vitro*, the toxicity of THQ was tested in rat hepatocyte cultures both for cyto and genotoxicity and found that THQ produces genotoxic and cytotoxic effects at concentrations ≥ 25 mM (Khader *et al.,* 2009). However, the *in vitro* studies could not be directly related to *in vivo*, as the average daily intake of THQ when consuming NS is 4,448.98 mg, this amount is very low compared to 100 mg/kg/day to achieve therapeutic benefits in animal studies, and the adverse effects could only be possible if the cellular concentration reaches to 25 mM or greater (Mansour *et al.,* 2002; Al-Saleh *et al.,* 2006; Khader *et al.,* 2009).

Bamosa (2018), reported the safety of the NS seeds to a dose of 3 g/day orally (Bamosa, 2018). The minor toxicological effects and wider therapeutic margin of NS and its active constituents, THQ, as evident by various scientific studies, support its safe use for long-term traditional food and medicinal purposes.

The NS is consumed as a spice, so it can be

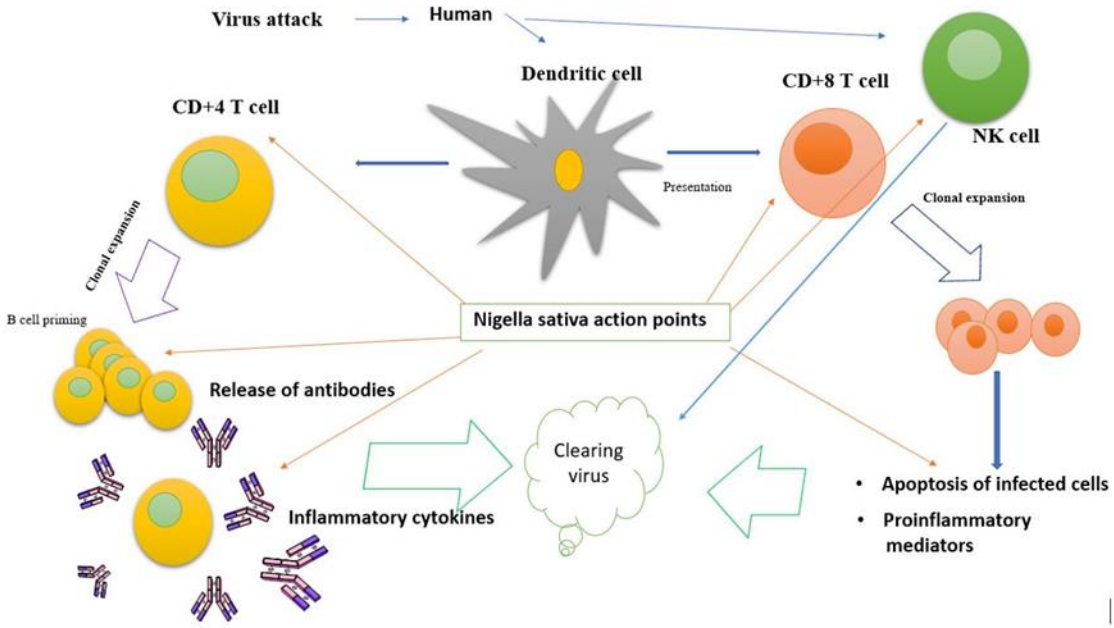
considered intrinsically safe. However, the safety profile needs to be evaluated for lipophilic extracts if recommended an adjuvant medication (Nguyen *et al.*, 2019). Overall, safety is high. But there is a lack of evidence for specific therapeutic benefits, and it is important to communicate this to potential users. There is insufficient evidence for use during pregnancy and while breastfeeding.

Registered patents associated with COVID-19 symptoms

Several products, formulations, and processes involving NS seeds or oil have been patented; the details of patents with some symptomatic relation with COVID-19 are listed below (Table No 5).

The oil of NS due to nigellone is used in the treatment of asthma, respiratory oppression, and cough (Mahfouz & El-Dakhakhny, 1960; Sayed, 1980). A chemically modified ethanolic extract of NS seed (20-40 g/day) increases immune function via CD19, HLA-DR, NKCD3-/CD56, CD38, and B-cells. It also stimulates bone marrow formation and protects against the cytopathic effects of the virus (Medenica Rajko, 2008). The ethanolic extract increases serum interferon level and provides stability to human amniotic "WISH" cells against vesicular stomatitis virus (20 to 40 g per day for an adult). At the same time, 30 g is an optimal dose in protecting against viral endemics (Medenica Rajko, 2008). The lipid fraction of the NS seeds has been recommended to treat respiratory disorders due to the production of PGE, mast cell stabilizing effects and inhibitory effects on the release of histamine and serotonin (Kandil, 2003b). Volatile oils of NS seeds at a dose of 4-32 µL/kg in guinea pigs exhibited an increase in respiratory rate and intratracheal pressure via direct histaminergic and indirect muscarinic cholinergic mechanisms (El-Tahir *et al.*, 1993).

Figure No. 4



***Nigella sativa* and its immune-modulatory role**

(Abuharfeil *et al.*, 2001; Fararh *et al.*, 2004; Nazrul Islam *et al.*, 2004; Majdalawieh *et al.*, 2010; Swamy & Tan, 2000; Salem & Hossain, 2000; Shabsoug *et al.*, 2008; Onifade *et al.*, 2013a; Onifade *et al.*, 2013b)

Table No. 5
List of patents (relevant to COVID-19 symptoms) registered till 2020; *not determined

Patent	Composition or strength	Purpose	Reference
Supercritical fluid extract of NS	1-40% THQ	As a dietary supplement to treat oxidative state, inflammation and thermogenesis	Babish *et al.*, 2013
Fixed? Oil of NS	2%W/W THQ	For inflammation	Albert *et al.*, 2019
NS extract	2.2% by weight of active substance	For cancer, prevention of side effects of cancer treatment and boosting immunity	Medenica Rajko, 1995 Medenica Rajko, 2008
Chemically modified Lipid fraction of NS seeds	contains, fatty acid fraction 97.2%, volatile oils 0.5%, and total sterols 2.3%	Respiratory disorders, CVS, wounds and infections	Kandil, 2005a Kandil, 2008
Sterol fraction of NS seeds	β-sitosterol, campesterol, β-amyrin, stigmasterol	Treat fungal and bacterial infections, vaginal diseases and inflammation	Kandil, 2002
NS seeds	1-50 wt % of the total weight or suspension (10 g/100 ml of distilled water)	Treat ischemia	Al Asoom, 2019
NS seed or extract	Pure seeds or extract (3.5 g fine powder/100 cc chloroform & 100 cc water)	Treatment and Prevention of asthma and allergy	Nasif Nedaa, 2006
A pharmaceutical composition contain NS or extract	2.2% w/w	To treat cancer and boost immunity	Medenica Rajko, 1996 Medenica Rajko, 1997
Polyunsaturated acid fraction of NS	octadecadienoic acid and/or octadecenoic acid	Treatment of bacterial, fungal infection, inflammatory conditions and allergy	Kandil, 2003a Kandil, 2005b Kandil, 2010
Composition contain NS fixed Oil	Olives, *Nigella* and Rosemary oils	Treatment of sinusitis	Çay, 2015
Aqueous NS extract	1 to 2 mg/kg IP	Antispasmodic, analgesic	Cherrah *et al.*, 2015
Nutraceutical composed of NS seeds	50 and 80 µg/ml of thymoquinone rich fraction or 0.5 and 3.5 g/kg NS seed powder	Cardioprotective effect	Ismail & Al-Naqeeb, 2011
Product contains NS extract	(1 to 2% DMSO)	Anticancer, anti-parasite, and antimicrobial effects	Duzgun, 2017
Ointment contains NS	olive oil; one-part *Hippophae rhamnoides* oil; one-part NS oil; odorants; and ointment base	For inflamed nasal mucosa	Rainer, 2003
Vaccine contain NS fixed oil as adjuvant	NS fixed oil	For Bursal disease virus	Madbouly, 2008

Clinical trials/human studies

Currently, seventeen clinical trials are registered for NS against various diseases, including diabetes, beta-thalassemia, hyperlipidemia, and hypertension. Regarding asthma inflammation, one study is registered for King Abdulaziz, University Hospital, Jeddah, Saudi Arabia. For clinical trials in CoV, two studies were found. One study is for the dietary supplement of NS in COVID-19 at King Abdulaziz, University Hospital, Jeddah, Saudi Arabia, and the other research is a collaborative research project for honey in combination with NS, among King Edward Medical University, Mayo Hospital Lahore, Federal Post-Graduate Medical Institute, Shaikh Zayed Hospital Lahore, and Services Institute of Medical Sciences, Services Hospital Lahore, Punjab, Pakistan (**www.clinicaltrials.gov**). A Multicenter, placebo-controlled, randomized clinical trial was conducted in 313 COVID-19 patients. Patients were given 80 mg/kg/body weight seed of NS with honey at a dose of 1 mg/kg body weight for 14 days along with standard medical care. The treatment significantly improved symptoms, viral clearance, and mortality in COVID-19 patients (Ashraf *et al.,* 2020). The weak points of the study were both natural products were not compositionally standardized and limited to a single dose. The patients were also receiving standard care, so the adjuvant role of honey and NS was the study's outcome but still needs to be elaborated on in large samples of different ethnicities. The additive effect and active compounds of both honey and NS may be pinpointed. A nutritional supplement TaibUVID (natural honey, NS, chamomile, costus, fennel, and/or senna) have been reported to enhanced immunity and rapid recovery of COVID-19; however, the product composition or chemical profile is not linked to the effects produced, and the sample size in the study is also small (El-Sayed *et al*., 2020a). The same rapid recovery for TaibUVID nutritional supplement has also been reported in 44-year-old physicians in Egypt (El Sayed *et al.,* 2020a). Another clinical trial was conducted using NS fixed oil as an adjuvant in 94 symptomatic COVID-19 patients (MARNYS® Cuminmar 500 mg twice daily for 10 days) with significant rapid recovery (Koshak *et al.,* 2020). The small sample size and unstandardized NS oil were the limitations of the trial.

DISCUSSION

Herein a phytochemical vs. pharmacological association is developed for the historical use of NS and its application in COVID-19 symptoms management. The evidence-based application of NS as an anti-viral, immunostimulant, and bronchodilator is stepwise discussed. The disease is extensively reported in the literature and well known with regards to symptoms and severity. For recall, COVID-19 has been investigated with a severe decrease in WBCs, lymphocytes, liver, and muscle enzymes whereas, myoglobin level, cytokines, leukotrienes, etc., are aggravated in the early phase (Shen *et al.,* 2020). Severe cellular body fluids (cytokine, leukotrienes, histamine storm) with weakened immunity are the hallmarks for COVID-19.

The history of the plant dates back to the Prophetic era (1400 years ago) to treat multiple ailments. The famous physician Avicenna (Ibne-Sina; 980-1037) mentioned in his well-known book “The Canon of Medicine” (Al-Qanoon fit-Tibb); “*Nigella sativa* stimulates the body’s energy and helps recovery from fatigue or dispiritedness.” Hippocrates (father of medicine) and Greek physicians used NS to treat nasal congestion, headache, and digestive disorders. Furthermore, Dioscorides declared and labeled “Melanthion, i.e., active chemical of NS” for its potential pharmacological properties (De Materia Medica, V-5) (Nadkarni, 1976; Tariq, 2008). Egyptian researchers “Mahfauz and Dakhakhny” isolated nigellone and essential oil from NS with an established potent bronchodilation effect (Mahfouz & El-Dakhakhny, 1960). THQ, another active phytochemical from NS were isolated and evaluated for its potent antioxidant, anti-inflammatory, and analgesic properties (Chehl *et al.,* 2009; Taka *et al.,* 2015; Amin & Hosseinzadeh, 2016). Studies show that the NS owes the immunostimulant properties due to THQ and nigellone (Hussain & Hussain, 2016; Islam *et al.,* 2017), so it may be used in various disorders like COVID-19. The mechanistic use of NS in COVID-19 symptoms is further explained by Figure No. 4 and Figure No. 5. COVID-19 patients present a cytokine storm where several cellular effects are produced. NS inhibits the majority of these cellular triggers (COX, LOX, leukotrienes, prostaglandins, thromboxanes, histamine) and enhances the production or release of important mediators (WBCs, RBCs, CD4 & CD8, cell-mediated

immunity, cytokines, antibodies, lymphocytes) to alleviate the severity of the disease.

The research regarding NS has proved an effective anti-viral role via different pathways. NS stimulates the immune cells and increases the production of interferon. It is a well-known anti-viral where it protects the body through increased production of natural killer cells (NK) and excessive activation of T-cells (Hussain & Hussain, 2016; Umar *et al.,* 2016). Umar *et al*. (2016), conducted a study against bird-influenza (H2N9) with a high success rate. The suggested mechanism was an increase in cytokines gene expression and enhanced immunomodulatory effect (antibody production), which reduced virus shedding, ultimately subsiding influenza symptoms. NS increases cellular and humoral immunity against infectious diseases (Umar *et al.,* 2016). Traditionally NS has been reported to treat several respiratory infections, including bronchitis and inflammatory disorders, where it relieves the symptoms through immune-boosting properties (Hussain & Hussain, 2016; Umar *et al.,* 2016). NS has been reported as an immune booster and effective anti-viral due to the increased production of lymphocytes (Omer *et al.,* 2014; Khan *et al.,* 2018). The significant bronchodilator, antitussive, and antiallergic effects of NS (due to antimuscarinic, histaminic, calcium channels blocking effects and stimulatory effects on potassium and beta-adrenergic effects) have been reported (Nasif Nedaa, 2006; Boskabady *et al.,* 2010).

A clinical study found NS as effective as theophylline for bronchodilation in asthmatic patients (Boskabady *et al*., 2010). Cough and bronchitis treatment in asthma have been reported for NS oil due to increased interferon-gamma production and T-cells. Immune-modulator, a bronchodilator, anti-inflammatory, and analgesic properties have been published for NS (Boskabady *et al*., 2007; Salem *et al*., 2017; Ikhsan *et al*., 2018). The Indian alternative system of treatments (Ayurveda and Siddha) effectively uses it for immune-boosting activity due to the presence of THQ and nigellone (Abdallah, 2017). The effectiveness in common cold is also reported (Ermumcu & Şanlıer, 2017). NS raises the level of CD8 cell and enhances the immunity in bronchial asthma and allergic rhinitis. The end effect is mediated through the stabilization of macrophages with the help of nigellone (Işık *et al*., 2010). It is well-known for its effective bronchodilator and immune booster properties in cough, bronchitis, and inflammations of lungs, fever, and allergy (El-Hack *et al*., 2016). The presence of nigellone, THQ, and numerous unsaturated fatty-acid-esters and terpene alcohols makes NS a potent immune system booster (Al-Osail & Al-Wazzah, 2017). Regarding resistant-boosting property, NS seeds significantly boost immune cell production, natural interferons, and related cell production in the bone marrow (Clark, 2014). Mechanistic approaches confirmed the improvement of immunity due to an increase in lymphocytes and natural killer cells (72% and 74%), respectively (Medenica Rajko, 1996; Al-Mufarrej, 2014). Concerning respiratory system activity, researchers elucidated the anti-histaminic activity for NS through protein-c kinase blockage in asthma (Boskabady *et al*., 2011b; Keyhanmanesh *et al*., 2013a; Saadat *et al*., 2015; Ikhsan *et al*., 2018). Nigellone inhibit effectively the histamine release from the mast cells, thus showing the basis for its traditional use in asthma (Chakarvarti, 1993). THQ is considered superior to fluticasone in asthmatic patients (Dajani *et al*., 2018). Several studies using NS in asthma showed potential therapeutic benefits (Koshak *et al*., 2017b). Recent studies showed anti-viral potential for NS against the hepatitis-C virus (Oyero *et al*., 2016). Ulasli *et al*. (2014), reported a viral inhibitory activity for NS against MHV-A59 CoV (mouse hepatitis virus), tested in HeLa-epithelial carcino-embryonic antigen-related cell adhesion molecule-1a (HeLaCEACAM1a) (Ulasli *et al*., 2014). The aforementioned literature is an unequivocal evidence to propose the use of NS in COVID-19, where the significant challenges faced are related to immunity and respiratory systems.

Herbs/herbal extracts are mixtures of phytochemicals, and at times, it is challenging to explore the appropriate mechanism in pharmacological studies. However, NS has been studied extensively in the form of the herb, herbal extract, and individual phytochemical constituents i.e., THQ, nigellone, and essential oil. Likewise, herbs and herbal extracts do vary concerning the quality and quantity of active phytochemicals. These studies may help sort out the product with high purity, potency and quality. Most of the herbs are difficult to estimate for an optimal dose and may produce toxicity when administered in high doses. This necessitates formal studies to select/declare an effective and safe dose. For NS, the plant is relatively

safe even at high doses up to 3 g/day, as studied in diabetes patients. Besides, the authors have collected all the available relevant literature and calculated an average dose for adults in this review. Furthermore, many clinical trials and patents are available for NS in diseases rather than Covid-19; however, the phytochemical, pharmacological, and clinical data available for the plant in respiratory disease and immune-boosting properties predicts NS to be an effective plant to alleviate the symptoms and improve the quality of life (QOL) for Covid-19 patients.

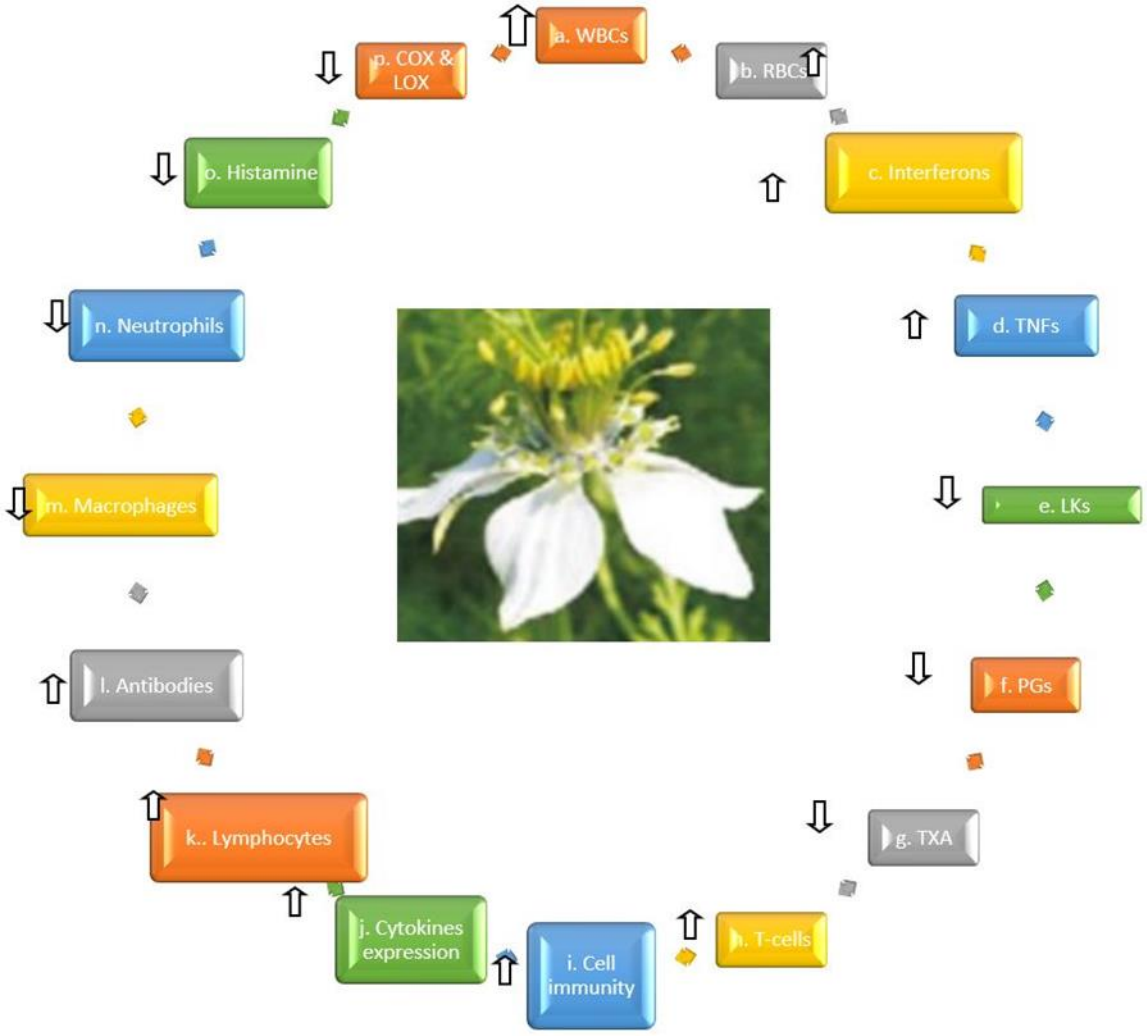


Figure No. 5
Effects of *Nigella sativa* at Cellular level
(a. (Kamil, 2013), b. (Khan *et al*., 2018), c. (Işık *et al*., 2010; Ahmad *et al*., 2013; Forouzanfar *et al*., 2014; Umar *et al*., 2016), d. f, and g (Işık *et al*., 2010), e. (Işık *et al*., 2010; Ahmad *et al*., 2013), h. (Ahmad *et al*., 2013; Forouzanfar *et al*., 2014; Abd El-Hack *et al*., 2016; Umar *et al*., 2016), i. (Abd El-Hack *et al*., 2016; Hussain & Hussain, 2016), j. (Işık *et al*., 2010; Umar *et al*., 2016), k. (Işık *et al*., 2010; Ahmad *et al*., 2013; Umar *et al*., 2016; Khan *et al*., 2018). L. (Umar *et al*., 2016), m. (Ahmad *et al*., 2013; Forouzanfar *et al*., 2014; Khan *et al*., 2018), n. (Kamil, 2013), o. (Işık *et al*., 2010; Abd El-Hack *et al*., 2016; Abdallah, 2017; Dajani *et al*., 2018), p. (Işık *et al*., 2010; Abd El-Hack *et al*., 2016)

CONCLUSION

NS may be a useful tool that can immune the host against Covid-19 and also has the potential to combat its symptoms. Although black seed may be useful in the symptomatic relief of respiratory symptoms, especially associated with the severe asthmatic cough, the clinical evidence is very limited yet. A particular concern, in this case, is the many well-intended but very low-quality studies and the broad range of claims they try to support, making any assessment problematic. In conclusive remarks, it is confirmed that most NS products claim to 'cure' the Covid-19? with little or no evidence or just claim for 'immune-boosting or 'virus-clearing' properties. Most of the products are not chemically characterized and have no detailed and valid description of their composition. These products have not been assessed for a medical claim by a recognized regulatory authority.

The studies conducted on NS during COVID-19 were merely assessing their adjuvant role. Studies on NS standalone products are required. Sufficient preclinical and clinical evidence is mandatory to recommend NS or derived products in the management of Covid-19. In the current scenario, where there is a lack of appropriate treatment with a high mortality rate for Covid-19, NS may be a natural alternative to manage symptoms of Covid-19 patients and improve QOL.

REFERENCES

El-Hack MEA, Alagawany M, Farag MR, Tiwari R, Karthik K, Dhama K. 2016. Nutritional, healthical and therapeutic efficacy of black cumin (*Nigella sativa*) in animals, poultry and humans. **Int J Pharmacol** 12: 232 - 248. **https://doi.org/10.3923/ijp.2016.232.248**

Abdallah EM. 2017. Black Seed (*Nigella sativa*) as antimicrobial drug: a mini-review. **Novel Approches in Drug Designing and Develop** 3: 1 - 5.

Abdel-Moneim A, Morsy BM, Mahmoud AM, Abo-Seif MA, Zanaty MI. 2013. Beneficial therapeutic effects of *Nigella sativa* and/or *Zingiber officinale* in HCV patients in Egypt. **Excli J** 12: 943 - 955.

Abedi AS, Rismanchi M, Shahdoostkhany M, Mohammadi A, Mortazavian AM. 2017. Microwave-assisted extraction of *Nigella sativa* L. essential oil and evaluation of its antioxidant activity. **J Food Sci Technol** 54: 3779 - 3790.

Abidi A, Robbe A, Kourda N, Khamsa SB, Legrand A. 2017. *Nigella sativa*, a traditional Tunisian herbal medicine, attenuates bleomycin-induced pulmonary fibrosis in a rat model. **Biomed Pharmacother** 90: 626 - 637.

Abu-Al-Basal MA. 2011. Influence of *Nigella sativa* fixed oil on some blood parameters and histopathology of skin in staphylococcal-infected BALB/c mice. **Pak J Biol Sci** 14: 1038 - 1046.

Abuharfeil NM, Salim M, von Kleist S. 2001. Augmentation of natural killer cell activity *in vivo* against tumour cells by some wild plants from Jordan. **Phytother Res** 15: 109 - 113.

Abu-Zinadah OA. 2009. Using *Nigella sativa* oil to treat and heal chemical induced wound of rabbit skin. **J King Abdulaziz Univ** 21: 335 - 346.

Ahad A, Raish M, Jardan YAB, Alam MA, Al-Mohizea AM, Al-Jenoobi FI. 2020. Potential pharmacodynamic and pharmacokinetic interactions of *Nigella Sativa* and *Trigonella Foenum-graecum* with losartan in L-NAME induced hypertensive rats. **Saudi J Biol Sci** 27: 2544 - 2550. **https://doi.org/10.1016/j.sjbs.2020.05.009**

Ahmad A, Husain A, Mujeeb M, Khan SA, Najmi AK, Siddique NA, Damanhouri ZA, Anwar F. 2013. A review on therapeutic potential of *Nigella sativa*: A miracle herb. **Asian Pacific J Tropical Biomed** 3: 337 - 352. **https://doi.org/10.1016/s2221-1691(13)60075-1**

Ahmad J, Khan RA, Malik MA. 2010. A study of *Nigella sativa* oil in the management of wheeze associated lower respiratory tract illness in children. **Afr J Pharm Pharmacol** 4: 436 - 439.

Ahmad R, Ahmad N, Shehzad A. 2020. Solvent and temperature effects of accelerated solvent extraction (ASE) coupled with ultra-high pressure liquid chromatography (UHPLC-DAD) technique for determination of thymoquinone in commercial food samples of black seeds (*Nigella sativa*). **Food Chem** 309: 125740. **https://doi.org/10.1016/j.foodchem.2019.125740**

Ahmed AF, He N, Xia ZY, Kang WY. 2018. Total phenolic and flavonoid content and antioxidant properties of *Nigella sativa* L. Seeds. **Curr Top Nutraceutical Res** 16.

Al Asoom LIA. 2019. Method for effecting angiogenesis by administering *Nigella sativa*. **US** 2019/0030110 A1.

Albert R, Albert G, Rapaport D, Zeilkha MOR. 2019. *Nigella sativa* oil composition. **WO** 2019/180719 A1.

Al-Ghamdi MS. 2001. The anti-inflammatory, analgesic and antipyretic activity of *Nigella sativa*. **J Ethnopharmacol** 76: 45 - 48. **https://doi.org/10.1016/s0378-8741(01)00216-1**

Al-Hader A, Aqel M, Hasan Z. 1993. Hypoglycemic effects of the volatile oil of *Nigella sativa* seeds. **Int J Pharmacogn** 31: 96 - 100. **https://doi.org/10.3109/13880209309082925**

Ali B, Amin S, Ahmad J, Ali A, Ali M, Mir SR. 2012. Bioavailability enhancement studies of amoxicillin with Nigella. **Indian J Med Res** 135: 555.

Aljabre SHM, Alakloby OM, Randhawa MA. 2015. Dermatological effects of *Nigella sativa*. **J Dermatol Dermatol Surg** 19: 92 - 98. **https://doi.org/10.1016/j.jdds.2015.04.002**

Al-Jawad FH, Al-Razzuqi RAM, Hashim HM, Ismael AH. 2012. Broncho-relaxant activity of *Nigella sativa* versus anthemisnobilis in chronic bronchial asthma; a comparative study of efficacy. **IOSR J Pharmac** 2: 81 - 83. **https://doi.org/10.9790/3013-24208183**

Al-Jenoobi FI, Al-Suwayeh SA, Muzaffar I, Alam MA, Al-Kharfy KM, Korashy HM, Al-Mohizea AM, Ahad A, Raish M. 2013. Effects of *Nigella sativa* and *Lepidium sativum* on cyclosporine pharmacokinetics. **BioMed Res Int** 2013: Article ID 953520 **https://doi.org/10.1155/2013/953520**

Al-Majed AA, Al-Omar FA, Nagi MN. 2006. Neuroprotective effects of thymoquinone against transient forebrain ischemia in the rat hippocampus. **Eur J Pharmacol** 543: 40 - 47. **https://doi.org/10.1016/j.ejphar.2006.05.046**

Al-Mohizea AM, Ahad A, El-Maghraby GM, Al-Jenoobi FI, AlKharfy KM, Al-Suwayeh SA. 2015. Effects of *Nigella sativa*, *Lepidium sativum* and *Trigonella foenum-graecum* on sildenafil disposition in beagle dogs. **Eur J Drug Metab Pharmacokin** 40: 219 - 224. **https://doi.org/10.1007/s13318-014-0199-4**

Al-Mufarrej SI. 2014. Immune-responsiveness and performance of broiler chickens fed black cumin (*Nigella sativa* L.) powder. **J Saudi Soc Agric Sci** 13: 75 - 80. **https://doi.org/10.1016/j.jssas.2013.01.006**

Al-Naqeeb G, Maznah I, Al-Zubairi AS. 2009. Activity of oil extracted from *Nigella sativa* seeds. **Int J Pharmacol** 5: 244 - 250.

Al-Osail AM, Al-Wazzah MJ. 2017. The history and epidemiology of Middle East respiratory syndrome corona virus. **Multidiscip Respir Med** 12: 20. **https://doi.org/10.1186/s40248-017-0101-8**

Al-Saleh IA, Billedo G, El-Doush II. 2006. Levels of selenium, dl-α-tocopherol, dl-γ-tocopherol, all-trans-retinol, thymoquinone and thymol in different brands of *Nigella sativa* seeds. **J Food Compos Anal** 19: 167 - 175. **https://doi.org/10.1016/j.jfca.2005.04.011**

Al-Zohairy MA, Khan AA, Alsahli MA, Almatroodi SA, Rahmani AH. 2021. Protective effects of thymoquinone, an active compound of *Nigella sativa*, on rats with *Benzo(a)pyrene*-induced lung injury through regulation of oxidative stress and inflammation. **Molecules** 26: 3218. **https://doi.org/10.3390/molecules26113218**

Alsamarai AM, Abdulsatar M, Alobaidi AHA. 2014. Evaluation of topical black seed oil in the treatment of allergic rhinitis. **Anti-Inflamm Anti-Allerg Agents Med Chem** 13: 75 - 82. **https://doi.org/10.2174/18715230113129990014**

Ameen NMAL, Altubaigy F, Jahangir T, Mahday IA, Mohammed EA, Musa OAA. 2011. Effect of *Nigella sativa* and bee honey on pulmonary, hepatic and renal function in Sudanese in Khartoum state. **J Med Plant Res** 5: 6857 - 6863. **https://doi.org/10.5897/jmpr11.1357**

Amin B, Hosseinzadeh H. 2016. Black cumin (*Nigella sativa*) and its active constituent, thymoquinone: an overview on the analgesic and anti-inflammatory effects. **Planta Medica** 82: 8 - 16. **https://doi.org/10.1055/s-0035-1557838**

Ammar ESM, Gameil NM, Shawky NM, Nader MA. 2011. Comparative evaluation of anti-inflammatory properties of thymoquinone and curcumin using an asthmatic murine model. **Int Immunopharmacol** 11: 2232 - 2236. **https://doi.org/10.1016/j.intimp.2011.10.013**

Ansari MA, Ahmed SP, Haider S, Ansari NL. 2006. *Nigella sativa*: A non-conventional herbal option for the management of seasonal allergic rhinitis. **Pak J Pharmacol** 23: 31 - 35.

Ansari MA, Ansari NA, Junejo SA. 2010. Montelukast versus *Nigella sativa* for management of seasonal allergic rhinitis: A single blind comparative clinical trial. **Pak J Med Sci** 26.

Ashraf S, Ashraf S, Ashraf M, Imran MA, Kalsoom L, Siddiqui UN, Farooq I, Habib Z, Ashraf S, Ghufran M,

Akram MK, Majeed N, Abdin Z, Akmal R, Rafique S, Nawaz K, Yousaf MIK, Ahmad S, Shahab MS, Nadeem MF, Azam M, Zheng H, Malik A, Ayyaz M, Mahmud T, Saboor QA, Ahmad A, Ashraf M, Izhar M, Zayed S, Hilal A, Muhammad A, Shaukat Z, Khaqan A, Hayat K, Arshad S, Hassan M, Awais A, Ahmad A, Mughal T, Virk AR, Umer M, Suhail M, Zulfiqar S, Sarfraz S, Anwar MI, Humayun A, Khokhar RA, Siddique S. 2020. Honey and *Nigella sativa* against Covid-19 in Pakistan (HNS-Covid-PK): A multi-center placebo-controlled randomized clinical trial. **medRxiv** **https://doi.org/10.1101/2020.10.30.20217364**

Attia YA, Al-Harthi MA. 2015. Nigella seed oil as an alternative to antibiotic growth promoters for broiler chickens. **Eur Poult Sci** 79: 10.1399. **https://doi.org/10.1399/eps.2015.80**

Babish JG, Linda MP, Debenedetto JAN. 2013. Compositions from *Nigella sativa*. **US** 8535740 B2.

Badary OA, Al-Shabanah OA, Nagi MN, Al-Bekairi AM, Elmazar M. 1998. Acute and subchronic toxicity of thymoquinone in mice. **Drug Develop Res** 44: 56 - 61. **https://doi.org/10.1002/(sici)1098-2299(199806/07)44:2/3<56::aid-ddr2>3.0.co;2-9**

Bamosa A. 2018. *Nigella sativa* is a safe herbal product. **J Integrat Med** 12: 66 - 66.

Barakat AB, Shoman SA, Dina N, Alfarouk OR. 2010. Antiviral activity and mode of action of *Dianthus caryophyllus* L. and *Lupinus termes* L. seed extracts against *in vitro* herpes simplex and hepatitis A viruses infection. **J Microbiol Antimicrob** 2: 23 - 29.

Barakat EMF, El-Wakeel LM, Hagag RS. 2013. Effects of *Nigella sativa* on outcome of hepatitis C in Egypt. **World J Gastroenterol** 19: 2529.

Barlianto W, Rachmawati M, Irawan M, Wulandari D. 2017. Effects of *Nigella sativa* oil on Th1/Th2, cytokine balance, and improvement of asthma control in children. **Paediatrica Indonesiana** 57: 223 - 228. **https://doi.org/10.14238/pi57.5.2017.1399**

Bashir MU, Qureshi HJ. 2010. Analgesic effect of *Nigella sativa* seeds extract on experimentally induced pain in albino mice. **J Col Physicians Surgeons - Pak** 20: 464 - 467.

Basurra RS, Wang SM, Alhoot MA. 2021. *Nigella safiva* (black seed) as a natural remedy against viruses. **J Pure Appl Microbiol** 15: 29 - 41. **https://doi.org/10.22207/jpam.15.1.26**

Bayir Y, Albayrak A, Can I, Karagoz Y, Cakir A, Suleyman H, Uyanik H, Yayla N, Polat B, Karakus E. 2012. *Nigella sativa* as a potential therapy for the treatment of lung injury caused by cecal ligation and puncture-induced sepsis model in rats. **Cell Mol Bio** 58.

Bayrak O, Bavbek N, Karatas OF, Bayrak R, Catal F, Cimentepe E, Akbas A, Yildirim E, Unal D, Akcay A. 2008. *Nigella sativa* protects against ischaemia/reperfusion injury in rat kidneys. **Nephrology Dialysis Transplantation** 23: 2206 - 2212. **https://doi.org/10.1093/ndt/gfm953**

Bensiameur-Touati K, Kacimi G, Haffaf EM, Berdja S, Aouichat-Bouguerra S. 2017. *In vivo* subacute toxicity and antidiabetic effect of aqueous extract of *Nigella sativa*. **Evid-Based Complement Alt Med** 2017: Article ID 8427034. **https://doi.org/10.1155/2017/8427034**

Boskabady MH, Javan H, Sajady M, Rakhshandeh H. 2007. The possible prophylactic effect of *Nigella sativa* seed extract in asthmatic patients. **Fundamental Clin Pharmacol** 21: 559 - 566. **https://doi.org/10.1111/j.1472-8206.2007.00509.x**

Boskabady MH, Keyhanmanesh R, Saadatloo MAE. 2008. Relaxant effects of different fractions from *Nigella sativa* L. on guinea pig tracheal chains and its possible mechanism (s). **Indian J Exp Biol** 46: 805 - 810.

Boskabady MH, Farhadi J. 2008. 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 Alt Complement Med** 14: 1137 - 1144. **https://doi.org/10.1089/acm.2008.0049**

Boskabady MH, Mohsenpoor N, Takaloo L. 2010. Antiasthmatic effect of *Nigella sativa* in airways of asthmatic patients. **Phytomedicine** 17: 707 - 713. **https://doi.org/10.1016/j.phymed.2010.01.002**

Boskabady MH, Keyhanmanesh R, Khameneh S, Doostdar Y, Khakzad MR. 2011c. Potential immunomodulation effect of the extract of *Nigella sativa* on ovalbumin sensitized guinea pigs. **J Zhejiang Univ Sci B** 12: 201 - 209. **https://doi.org/10.1631/jzus.b1000163**

Boskabady MH, Vahedi N, Amery S, Khakzad MR. 2011b. The effect of *Nigella sativa* alone, and in combination with dexamethasone, on tracheal muscle responsiveness and lung inflammation in sulfur mustard exposed

guinea pigs. **J Ethnopharmacol** 137: 1028 - 1034. **https://doi.org/10.1016/j.jep.2011.07.030**

Boskabady MH, Keyhanmanesh R, Khamneh S, Ebrahimi MA. 2011a. The effect of *Nigella sativa* extract on tracheal responsiveness and lung inflammation in ovalbumin-sensitized guinea pigs. **Clinics** 66: 879 - 887. **https://doi.org/10.1590/s1807-59322011000500027**

Bourgou S, Pichette A, Lavoie S, Marzouk B, Legault J. 2012a. Terpenoids isolated from Tunisian *Nigella sativa* L. essential oil with antioxidant activity and the ability to inhibit nitric oxide production. **Flav Fragrance J** 27: 69 - 74. **https://doi.org/10.1002/ffj.2085**

Bourgou S, Pichette A, Marzouk B, Legault J. 2012b. Antioxidant, anti-inflammatory, anticancer and antibacterial activities of extracts from *Nigella sativa* (black cumin) plant parts. **J Food Biochem** 36: 539 - 546. **https://doi.org/10.1111/j.1745-4514.2011.00567.x**

Burits M, Bucar F. 2000. Antioxidant activity of *Nigella sativa* essential oil. **Phytother Res** 14: 323 - 328. **https://doi.org/10.1002/1099-1573(200008)14:5<323::aid-ptr621>3.0.co;2-q**

Çay S. 2015. Combination of olive oil, *Nigella sativa* seed oil and rosemary oil. **WO** 2015/060794 A1.

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

Chehl N, Chipitsyna G, Gong Q, Yeo CJ, Arafat HA. 2009. Anti-inflammatory effects of the *Nigella sativa* seed extract, thymoquinone, in pancreatic cancer cells. **HPB** 11: 373 - 381. **https://doi.org/10.1111/j.1477-2574.2009.00059.x**

Cherrah Y, Abbes FM, Meddah B, Doudach L. 2015. Composition of the aqueous extract of *Nigella sativa* having antispasmodic and analgesic activity. **WO** 2015/170948 A1.

Clark I. 2014. Black cumin seed oil: Your ultimate life elixir. **Founder of Activation Products on January** 9.

Comalada M, Ballester I, Bailon E, Sierra S, Xaus J, Gálvez J, Sánchez de Medina F, Zarzuelo A. 2006. Inhibition of pro-inflammatory markers in primary bone marrow-derived mouse macrophages by naturally occurring flavonoids: analysis of the structure–activity relationship. **Biochem Pharmacol** 72: 1010 - 1021. **https://doi.org/10.1016/j.bcp.2006.07.016**

Dajani EZ, Shahwan TG, Dajani NE. 2018. Overview of the human investigations of *Nigella sativa* (Black Seeds): A complementary drug with historical and clinical significance. **Gen Internal Med Clin Innov** 4: 1 - 16. **https://doi.org/10.15761/gimci.1000171**

Delgado-Roche L, Mesta F. 2020. Oxidative stress as key player in severe acute respiratory syndrome coronavirus (SARS-CoV) infection. **Arch Med Res** 51: 384 - 387. **https://doi.org/10.1016/j.arcmed.2020.04.019**

Department of Agriculture USA. 2019. Food data central, food search *Nigella Sativa* **https://fdc.nal.usda.gov/fdc-app.html#/?query=nigella%20sativa**

Dirjomuljono M, Kristyono I, Tjandrawinata RR, Nofiarny D. 2008. Symptomatic treatment of acute tonsillo-pharyngitis patients with a combination of *Nigella sativa* and *Phyllanthus niruri* extract. **Int J Clin Pharmacol Ther** 46: 295 - 306. **https://doi.org/10.5414/cpp46295**

Dollah MA, Parhizkar S, Latiff LA, Hassan MHB. 2013. Toxicity effect of *Nigella sativa* on the liver function of rats. **Adv Pharmaceut Bull** 3: 97.

Duke JA. 2002. **Handbook of medicinal herbs**, CRC Press, Boca Raton, USA.

Duzgun B. 2017. The anti cancerous, antiparasite (toxoplasma Gondii (protozoon) and antimicrobial effect and dosage of Nigella (*Nigella sativa*) extract. **US** 2017/0348371 A1.

Ebrahimi H, Fallahi M, Khamaneh AM, Saadatlou MAE, Saadat S, Keyhanmanesh R. 2016. Effect of α-Hederin on IL-2 and IL-17 mRNA and miRNA-133a levels in lungs of ovalbumin-sensitized male rats. **Drug Develop Res** 77: 87 - 93. **https://doi.org/10.1002/ddr.21292**

Ekins S, Mestres J, Testa B. 2007. *In silico* pharmacology for drug discovery: applications to targets and beyond. **Br J Pharmacol** 152: 21 - 37. **https://doi.org/10.1038/sj.bjp.0707306**

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

El-Gazzar M, El-Mezayen R, Nicolls MR, Marecki JC, Dreskin SC. 2006. Downregulation of leukotriene biosynthesis by thymoquinone attenuates airway inflammation in a mouse model of allergic asthma. **Biochim Biophys Acta** 1760: 1088 - 1095. **https://doi.org/10.1016/j.bbagen.2006.03.006**

El-Sayed SM, Bahashwan SA, Aboonq MS, Baghdadi H, Elshazley M, Okashah AM, El Rashedy AG, El-Magd

RMA, Aljehani YT, El-Tahlawi R, Nabo MMH, Hamouda O, El-Murr AR, Soliman TM, Mahmoud HS, Abu-Elnaga M, Hassan MM. 2020a. Adjuvant TaibUVID nutritional supplements proved promising for novel safe Covid-19 public prophylaxis and treatment: enhancing immunity and decreasing morbidity period for better outcomes (A retrospective study). **Int J Med Develop Countries** 4: 1375 - 1389. **https://doi.org/10.24911/ijmdc.51-1594011487**

El-Sayed SM, Aboonq MS, Aljehani YT, Hassan MA, El-Magd RMA, Abdelrahman AI, El-Tahlawi R, Nabo MMH, Yousef RS, Mahmoud AA. 2020b. TaibUVID nutritional supplements help rapid cure of Covid-19 infection and rapid reversion to negative nasopharyngeal swab PCR: for better public prophylaxis and treatment of Covid-19 pandemic. **Am J Blood Res** 10: 397.

El-Tahir KEH, Ashour MMS, Al-Harbi MM. 1993. The respiratory effects of the volatile oil of the black seed (*Nigella sativa*) in guinea-pigs: elucidation of the mechanism (s) of action. **Gen Pharmacol** 24: 1115 - 1122. **https://doi.org/10.1016/0306-3623(93)90358-5**

El-Abhar HS, Abdallah DM, Saleh S. 2003. Gastroprotective activity of *Nigella sativa* oil and its constituent, thymoquinone, against gastric mucosal injury induced by ischaemia/reperfusion in rats. **J Ethnopharmacol** 84: 251 - 258. **https://doi.org/10.1016/s0378-8741(02)00324-0**

Elgohary HM, Al-Jaouni SKH, Selim SA. 2018. Effect of ultrasound-enhanced *Nigella sativa* seeds oil on wound healing: An animal model. **J Taibah Univ Med Sci** 13: 438 - 443. **https://doi.org/10.1016/j.jtumed.2018.02.008**

El-Khouly D, El-Bakly WM, Awad AS, El-Mesallamy HO, El-Demerdash E. 2012. Thymoquinone blocks lung injury and fibrosis by attenuating bleomycin-induced oxidative stress and activation of nuclear factor Kappa-B in rats. **Toxicology** 302: 106 - 113. **https://doi.org/10.1016/j.tox.2012.09.001**

Ermumcu MŞK, Şanlıer N. 2017. Black cumin (*Nigella sativa*) and its active component of thymoquinone: effects on health. **J Food Health Sci** 3: 170 - 183. **https://doi.org/10.3153/jfhs17020**

Fallahi M, Keyhanmanesh R, Khamaneh AM, Saadatlou MAE, Saadat S, Ebrahimi H. 2016. Effect of alpha-Hederin, the active constituent of *Nigella sativa*, on miRNA-126, IL-13 mRNA levels and inflammation of lungs in ovalbumin-sensitized male rats. **Avicenna J Phytomed** 6: 77 - 85.

Fararh KM, Atoji Y, Shimizu Y, Shiina T, Nikami H, Takewaki T. 2004. Mechanisms of the hypoglycaemic and immunopotentiating effects of *Nigella sativa* L. oil in streptozotocin-induced diabetic hamsters. **Res Vet Sci** 77: 123 - 129. **https://doi.org/10.1016/j.rvsc.2004.03.002**

Fathy M, Nikaido T. 2018. *In vivo* attenuation of angiogenesis in hepatocellular carcinoma by *Nigella sativa*, **Turk J Med Sci** 48: 178 - 186.

FDA. 2019. **Spices and other natural seasonings and flavorings**. In 21CFR182.10, edited by US Department of Health and Human Services. US: US Food and Drug Administration, Code of Federal Regulations, USA. .

FDA. 2020. FDA approves first treatment for Covid-19. **https://www.fda.gov/news-events/press-announcements/fda-approves-first-treatment-covid-19**

Forouzanfar F, Bazzaz BSF, Hosseinzadeh H. 2014. Black cumin (*Nigella sativa*) and its constituent (thymoquinone): a review on antimicrobial effects. **Iran J Basic Med Sci** 17: 929.

Franco-Ramos RS, López-Romero CA, Torres-Ortega H, Oseguera-Herrera D, Lamoreaux-Aguayo JP, Molina-Noyola D, Juárez-Vázquez CI, Torres-Bugarín O. 2020. Evaluation of anti-cytotoxic and anti-genotoxic effects of *Nigella sativa* through a micronucleus test in BALB/c mice. **Nutrients** 12: 1317. **https://doi.org/10.3390/nu12051317**

Georgescu M, Tăpăloagă PR, Tăpăloagă D, Furnaris F, Ginghină O, Negrei C, Giuglea C, Bălălău C, Ștefănescu E, Popescu IA. 2018. Evaluation of antimicrobial potential of *Nigella sativa* oil in a model food matrix. **Farmacia** 66: 1028 - 1036. **https://doi.org/10.31925/farmacia.2018.6.16**

Gheita TA, Kenawy SA. 2012. Effectiveness of *Nigella sativa* oil in the management of rheumatoid arthritis patients: a placebo controlled study. **Phytother Res** 26: 1246 - 1248. **https://doi.org/10.1002/ptr.3679**

Gilani AH, Aziz N, Khurram IM, Chaudhary KS, Iqbal A. 2001. Bronchodilator, spasmolytic and calcium antagonist activities of *Nigella sativa* seeds (Kalonji): a traditional herbal product with multiple medicinal uses. **J Pak Med Assoc** 51: 115.

Gilani AH, Jabeen Q, Khan MAU. 2004. A review of medicinal uses and pharmacological activities of *Nigella*

sativa. **Pak J Biol Sci** 7: 441 - 451.
Gunes AE, Gozeneli O, Akal AA, Guldur ME, Savik E. 2017. Reduction of side effects of hyperbaric oxygen therapy with thymoquinone treatment in rats. **Undersea Hyperbaric Med** 44: 337 - 343. **https://doi.org/10.22462/7.8.2017.6**
Haglund MM, Stahl WL, Kunkel DD, Schwartzkroin PA. 1985. Developmental and regional differences in the localization of Na, K-ATPase activity in the rabbit hippocampus. **Brain Res** 343: 198 - 203. **https://doi.org/10.1016/0006-8993(85)91180-1**
Hajhashemi V, Ghannadi A, Jafarabadi H. 2004. Black cumin seed essential oil, as a potent analgesic and antiinflammatory drug. **Phytother Res** 18: 195 - 199. **https://doi.org/10.1002/ptr.1390**
Hanafi MS, Hatem ME. 1991. Studies on the anti-microbial activity of the *Nigella sativa* seed (Black Cumin). **J Ethnopharmacol** 34: 275 - 278. **https://doi.org/10.1016/0378-8741(91)90047-h**
Harrison JE, Watkinson AC, Green DM, Hadgraft J, Brain K. 1996. The relative effect of Azone® and Transcutol® on permeant diffusivity and solubility in human stratum corneum. **Pharmaceut Res** 13: 542 - 546.
Houghton PJ, Zarka R, de las Heras B, Hoult JRS. 1995. Fixed oil of *Nigella sativa* and derived thymoquinone inhibit eicosanoid generation in leukocytes and membrane lipid peroxidation. **Planta Medica** 61: 33 - 36. **https://doi.org/10.1055/s-2006-957994**
Hussain DA, Hussain MM. 2016. *Nigella sativa* (black seed) is an effective herbal remedy for every disease except death-a prophetic statement which modern scientists confirm unanimously: a review. **Adv Med Plant Res** 4: 27 - 57.
Ibrahim RM, Hamdan NS, Mahmud R, Imam MU, Saini SM, Rashid SNA, Ghafar SAA, Latiff LA, Ismail M. 2014. A randomised controlled trial on hypolipidemic effects of *Nigella sativa* seeds powder in menopausal women. **J Translational Med** 12: 82. **https://doi.org/10.1186/1479-5876-12-82**
Ikhsan M, Hiedayati N, Maeyama K, Nurwidya F. 2018. *Nigella sativa* as an anti-inflammatory agent in asthma. **BMC Res Notes** 11: 1 - 5. **https://doi.org/10.1186/s13104-018-3858-8**
Işık H, Çevikbaş A, Gürer US, Kıran B, Üresin Y, Rayaman P, Rayaman E, Gürbüz B, Büyüköztürk S. 2010. Potential adjuvant effects of *Nigella sativa* seeds to improve specific immunotherapy in allergic rhinitis patients. **Med Principles Practice** 19: 206 - 211. **https://doi.org/10.1159/000285289**
Islam MT, Guha B, Hosen S, Riaz TA, Shahadat S, Sousa LR, Santos JVO, Silva Júnior JJ, de Lima RTM, Braga AL. 2017. Nigellalogy: a review on *Nigella sativa*. **MOJ Bioequival Bioavail** 3: 00056.
Ismail M, Al-Naqeeb G. 2011. Cardioprotective effects of nutraceuticals isolated from *Nigella sativa* seeds. **EP** 2349302 A1.
Ismail M, Al-Naqeep G, Chan KW. 2010. *Nigella sativa* thymoquinone-rich fraction greatly improves plasma antioxidant capacity and expression of antioxidant genes in hypercholesterolemic rats. **Free Rad Biol Med** 48: 664 - 672. **https://doi.org/10.1016/j.freeradbiomed.2009.12.002**
Jadayil SA, Tukan SK, Takruri HR. 1999. Bioavailability of iron from four different local food plants in Jordan. **Plant Foods Human Nut** 54: 285 - 294. **https://doi.org/10.1023/a:1008195019618**
Jrah Harzallah H, Grayaa R, Kharoubi W, Maaloul A, Hammami M, Mahjoub T. 2012. Thymoquinone, the *Nigella sativa* bioactive compound, prevents circulatory oxidative stress caused by 1, 2-dimethylhydrazine in erythrocyte during colon postinitiation carcinogenesis. **Oxid Med Cell Long** 2012: Article ID 854065. **https://doi.org/10.1155/2012/854065**
Kalemci S, Micili SC, Acar T, Senol T, Dirican N, Omeroglu G, Ilmaz O. 2013. Effectiveness of thymoquinone in the treatment of experimental asthma. **Clin Therapeut** 164: 155 - 158.
Kalus U, Pruss A, Bystron J, Jurecka M, Smekalova A, Lichius JJ, Kiesewetter H. 2003. Effect of *Nigella sativa* (black seed) on subjective feeling in patients with allergic diseases. **Phytother Res** 17: 1209 - 1214. **https://doi.org/10.1002/ptr.1356**
Kamil ZH. 2013. Spectacular black seeds (*Nigella sativa*): Medical importance review. **Med J Babylon** 10: 1 - 10.
Kandil O. 2002. Sterol fractions of *Nigella sativa* L. seeds. **US** 2002/0132019 A1.
Kandil O. 2003a. Polyunsaturated fatty acid fractions of *Nigella sativa* L. seeds. **US** 2003/0060508 A1.
Kandil O. 2003b. Total lipid fraction of *Nigella sativa* L. seeds. **US** 2003/0060454 A1.
Kandil O. 2005a. Lipid fraction of *Nigella sativa* L. seeds. **US** 2005/0214393 A1.

Kandil O. 2005b. Polyunsaturated fatty acid fractions of *Nigella sativa* L. seeds. **US** 2005/0214241 A1.
Kandil O. 2008. Lipid fraction of *Nigella sativa* L. seeds. **US** 2008/0152736 A1.
Kandil O. 2010. Polyunsaturated fatty acid fractions of *Nigella sativa* L. seeds. **US** 7722906 B2.
Kanter M. 2009. Effects of *Nigella sativa* seed extract on ameliorating lung tissue damage in rats after experimental pulmonary aspirations. **Acta Histochem** 111: 393 - 403. **https://doi.org/10.1016/j.acthis.2008.10.008**
Kanter M. 2011. Thymoquinone attenuates lung injury induced by chronic toluene exposure in rats. **Toxicol Ind Health** 27: 387 - 395. **https://doi.org/10.1177/0748233710387630**
Kardani AK, Fitri LE, Barlianto W, Olivianto E, Kusuma C. 2013. The effect of house dust mite immunotherapy, probiotic and *Nigella sativa* in the number of Th17 cell and asthma control test score. **IOSR J Dent Med Sci** 6: 37 - 47. **https://doi.org/10.9790/0853-0643747**
Kazemi M. 2014. Phytochemical composition, antioxidant, anti-inflammatory and antimicrobial activity of *Nigella sativa* L. essential oil. **J Essent Oil Bearing Plant** 17: 1002 - 1011. **https://doi.org/10.1080/0972060x.2014.914857**
Keyhanmanesh R, Boskabady MH, Khamneh S, Doostar Y. 2010a. Effect of thymoquinone on the lung pathology and cytokine levels of ovalbumin-sensitized guinea pigs. **Pharmacol Rep** 62: 910 - 916. **https://doi.org/10.1016/s1734-1140(10)70351-0**
Keyhanmanesh R, Boskabady MH, Eslamizadeh MJ, Khamneh S, Ebrahimi MA. 2010b. The effect of thymoquinone, the main constituent of *Nigella sativa* on tracheal responsiveness and white blood cell count in lung lavage of sensitized guinea pigs. **Planta Medica** 76: 218 - 222. **https://doi.org/10.1055/s-0029-1186054**
Keyhanmanesh R, Bagban H, Nazemieh H, Bavil FM, Alipour MR. 2013a. The main relaxant constituents of *Nigella sativa* methanolic fraction on guinea pig tracheal chains. **Iran J Allergy Asthma Immunol** 12: 136 - 143.
Keyhanmanesh R, Bagban H, Nazemiyeh H, Bavil FM, Alipour MR, Ahmady M. 2013b. The relaxant effects of different methanolic fractions of *Nigella sativa* on guinea pig tracheal chains. **Iran J Basic Med Sci** 16: 123.
Keyhanmanesh R, Nazemiyeh H, Mazouchian H, Asl MMB, Shoar MK, Alipour MR, Boskabady MH. 2014. *Nigella sativa* pretreatment in guinea pigs exposed to cigarette smoke modulates *in vitro* tracheal responsiveness. **Iran Red Crescent Med J** 16.
Khader M, Bresgen N, Eckl PM. 2009. *In vitro* toxicological properties of thymoquinone. **Food Chem Toxicol** 47: 129 - 133. **https://doi.org/10.1016/j.fct.2008.10.019**
Khan AU, Tipu MY, Shafee M, Khan NU, Tariq MM, Kiani MR, Shah SIA. 2018. *In-ovo* antiviral effect of *Nigella sativa* extract against Newcastle disease virus in experimentally infected chicken embryonated eggs. **Pak Vet J** 38: 434 - 437. **https://doi.org/10.29261/pakvetj/2018.075**
Khan SA, Khan AM, Karim S, Kamal MA, Damanhouri GA, Mirza Z. 2016. Panacea seed "Nigella": A review focusing on regenerative effects for gastric ailments. **Saudi J Biol Sci** 23: 542 - 553. **https://doi.org/10.1016/j.sjbs.2014.10.001**
Khanna T, Zaidi FA, Dandiya PC. 1993. CNS and analgesic studies on *Nigella sativa*. **Fitoterapia** 5: 407 - 410.
Kheirouri S, Hadi V, Alizadeh M. 2016. Immunomodulatory effect of *Nigella sativa* oil on T lymphocytes in patients with rheumatoid arthritis. **Immunol Invest** 45: 271 - 283. **https://doi.org/10.3109/08820139.2016.1153649**
Koshak AE, Koshak EA, Mobeireek AF, Badawi MA, Wali SO, Malibary HM, Atwah AF, Alhamdan MM, Almalki RA, Madani TA. 2020. *Nigella sativa* supplementation accelerates recovery from mild Covid-19: first randomized controlled clinical trial. **Trials** 21: 703. **https://doi.org/10.1186/s13063-020-04647-x**
Koshak A, Wei L, Koshak E, Wali S, Alamoudi O, Demerdash A, Qutub M, Pushparaj PN, Heinrich M. 2017a. *Nigella sativa* supplementation improves asthma control and biomarkers: A randomized, double-blind, placebo-controlled trial. **Phytother Res** 31: 403 - 409. **https://doi.org/10.1002/ptr.5761**
Koshak A, Koshak E, Heinrich M. 2017b. Medicinal benefits of *Nigella sativa* in bronchial asthma: A literature review. **Saudi Pharmaceut J** 25: 1130 - 1136. **https://doi.org/10.1016/j.jsps.2017.07.002**
Kurihara F, Soria A, Lepoittevin JP, Chasset F, Barbaud A, Pecquet C. 2020. Thymoquinone as a causative allergen

in *Nigella sativa* oil contact dermatitis with cross-reactivity to tert-butylhydroquinone. **Contact Dermatitis** 83: 132 - 134. **https://doi.org/10.1111/cod.13542**

Lau SKP, Chan JFW. 2015. Coronaviruses: emerging and re-emerging pathogens in humans and animals. **Virol J** 12: 209. **https://doi.org/10.1186/s12985-015-0432-z**

Li Q, Guan X, Wu P, Wang X, Zhou L, Tong Y, Ren R, Leung KSM, Lau EHY, Wong JY. 2020. Early transmission dynamics in Wuhan, China, of novel coronavirus - infected pneumonia. **New England J Med** 382: 1199 - 1207. **https://doi.org/10.1056/NEJMoa2001316**

Madbouly HM. 2008. Preparation of inactivated vaccines against infectious bursal disease virus from Egyptian strain isolated from El-fayoum Governorate 1997 and supplemented with *Nigella sativa* oil as adjuvant. **EG** 24131 A.

Mahfouz M, El-Dakhakhny M. 1960. Chemical and pharmacological properties of the new anti-asthmatic drug, nigellone. **Egypt Pharm Bull** 42: l - 424.

Mahmoud MR, El-Abhar HS, Saleh S. 2002. The effect of *Nigella sativa* oil against the liver damage induced by *Schistosoma mansoni* infection in mice. **J Ethnopharmacol** 79: 1 - 11. **https://doi.org/10.1016/s0378-8741(01)00310-5**

Maiti S, Banerjee A, Nazmeen A, Kanwar M, Das S. 2020. Active-site molecular docking of Nigellidine with nucleocapsid-NSP2-MPro of COVID-19 and to human IL1R-IL6R and strong antioxidant role of *Nigella sativa* in experimental rats. **J Drug Targeting** 1 - 23. **https://doi.org/10.1080/1061186x.2020.1817040**

Majdalawieh AF, Hmaidan R, Carr RI. 2010. *Nigella sativa* modulates splenocyte proliferation, Th1/Th2 cytokine profile, macrophage function and NK anti-tumor activity. **J Ethnopharmacol** 131: 268 - 275. **https://doi.org/10.1016/j.jep.2010.06.030**

Mammad Z, Mammad K, Aqeil T, Kribii A, Ounine K. 2017. Antibacterial and Antioxidant activity of *Nigella sativa*. **Int J Innovation Scient Res** 31: 167 - 172.

Mani RJ, Sehgal N, Dogra N, Saxena S, Katare DP. 2020. Deciphering underlying mechanism of Sars-CoV-2 infection in humans and revealing the therapeutic potential of bioactive constituents from *Nigella sativa* to combat COVID19: in-silico study. **J Biomol Struct Dynam** 1 - 13. **https://doi.org/10.1080/07391102.2020.1839560**

Mansour MA, Nagi MN, El-Khatib AS, Al-Bekairi AM. 2002. Effects of thymoquinone on antioxidant enzyme activities, lipid peroxidation and DT-diaphorase in different tissues of mice: a possible mechanism of action. **Cell Biochem Funct** 20: 143 - 151. **https://doi.org/10.1002/cbf.968**

Mansour M, Tornhamre S. 2004. Inhibition of 5-lipoxygenase and leukotriene C4 synthase in human blood cells by thymoquinone. **J Enzyme Inhib Med Chem** 19: 431 - 436. **https://doi.org/10.1080/14756360400002072**

Mariod AA, Ibrahim RM, Ismail M, Ismail N. 2009. Antioxidant activity and phenolic content of phenolic rich fractions obtained from black cumin (*Nigella sativa*) seedcake. **Food Chem** 116: 306 - 312. **https://doi.org/10.1016/j.foodchem.2009.02.051**

Medenica Rajko D. 1995. *Nigella sativa* as a medicinal treatment. **WO** 1995/005839 A1.

Medenica Rajko D. 1996. Use of *Nigella sativa* to increase immune function. **US** 5482711 A.

Medenica Rajko D. 1997. Use of *Nigella sativa* to increase immune function. **US** 5653981 A.

Medenica Rajko D. 2008. *Nigella sativa* as a medicinal treatment. **EP** 0804212 B1.

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

Nadaf NH, Gawade SS, Muniv AS, Waghmare SR, Jadhav DV, Sonawane KD. 2015. Exploring anti-yeast activity of *Nigella sativa* seed extracts. **Ind Crops Prod** 77: 624 - 630. **https://doi.org/10.1016/j.indcrop.2015.09.038**

Nadkarni K. 1976. *Crocus sativus*, *Nigella sativa*. **Indian Materia Medica** 386 - 411.

Nagi MN, Alam K, Badary OA, Al-Shabanah OA, Al-Sawaf HA, Al-Bekairi AM. 1999. Thymoquinone protects against carbon tetrachloride hetatotoxicity in mice via an antioxidant mechanism. **Int Union Biochem Mol Biol Life** 47: 153 - 159. **https://doi.org/10.1080/15216549900201153**

Nagi MN, Mansour MA. 2000. Protective effect of thymoquinone against doxorubicin–induced cardiotoxicity in

rats: A possible mechanism of protection. **Pharmacol Res** 41: 283 - 289. **https://doi.org/10.1006/phrs.1999.0585**

Nasif Nedaa AG. 2006. Asthma/allergy therapy using *Nigella sativa*. **EP** 1709995 A1.

Nazrul Islam SK, Begum P, Ahsan T, Huque S, Ahsan M. 2004. Immunosuppressive and cytotoxic properties of *Nigella sativa*. **Phytother Res** 18: 395 - 398. **https://doi.org/10.1002/ptr.1449**

Nemmar A, Al-Salam S, Zia S, Marzouqi F, Al-Dhaheri A, Subramaniyan D, Dhanasekaran S, Yasin J, Ali BA, Kazzam EE. 2011. Contrasting actions of diesel exhaust particles on the pulmonary and cardiovascular systems and the effects of thymoquinone. **Br J Pharmacol** 164: 1871 - 1882. **https://doi.org/10.1111/j.1476-5381.2011.01442.x**

Nguyen T, Talbi H, Hilali A, Anthonissen R, Maes A, Verschaeve L. 2019. *In vitro* toxicity, genotoxicity and antigenotoxicity of *Nigella sativa* extracts from different geographic locations. **South Afr J Bot** 126: 132 - 141. **https://doi.org/10.1016/j.sajb.2019.02.015**

Nikakhlagh S, Rahim F, Aryani FHN, Syahpoush A, Brougerdnya MG, Saki N. 2011. Herbal treatment of allergic rhinitis: the use of *Nigella sativa*. **Am J Otolaryngol** 32: 402 - 407. **https://doi.org/10.1016/j.amjoto.2010.07.019**

Omer MO, AlMalki WH, Shahid I, Khuram S, Altaf I, Imran S. 2014. Comparative study to evaluate the anti-viral efficacy of *Glycyrrhiza glabra* extract and ribavirin against the Newcastle disease virus. **Pharmacognosy Res** 6: 6.

Onifade AA, Jewell AP, Adedeji WA. 2013a. *Nigella sativa* concoction induced sustained seroreversion in HIV patient. **Afr J Tradit Complement Alt Med** 10: 332 - 335. **https://doi.org/10.4314/ajtcam.v10i5.18**

Onifade AA, Jewell AP, Ajadi TA, Rahamon SK, Ogunrin OO. 2013b. Effectiveness of a herbal remedy in six HIV patients in *Nigeria*. **J Herb Med** 3: 99 - 103. **https://doi.org/10.1016/j.hermed.2013.04.006**

Onifade AA, Jewell AP, Okesina AB. 2015. Seronegative conversion of an HIV positive subject treated with *Nigella sativa* and honey. **Afric J Infectious Dis** 9: 47 - 50. **https://doi.org/10.4314/ajid.v9i2.6**

Oyero OG, Toyama M, Mitsuhiro N, Onifade AA, Hidaka A, Okamoto M, Baba M. 2016. Selective inhibition of hepatitis c virus replication by Alpha-zam, a *Nigella sativa* seed formulation. **Afr J Tradit Complement Alt Med** 13: 144 - 148. **https://doi.org/10.21010/ajtcam.v13i6.20**

Oysu C, Tosun A, Yilmaz HB, Sahin-Yilmaz A, Korkmaz D, Karaaslan A. 2014. Topical *Nigella sativa* for nasal symptoms in elderly. **Auris Nasus Larynx** 41: 269 - 272. **https://doi.org/10.1016/j.anl.2013.12.002**

Paarakh PM. 2010. *Nigella sativa* Linn.–A comprehensive review. **Nat Prod Res** 1: 409 - 429

Pise HN, Padwal SL. 2017. Evaluation of anti-inflammatory activity of *Nigella sativa*: An experimental study. **Nat J Physiol Pharm Pharmacol** 7: 707 - 711. **https://doi.org/10.5455/njppp.2017.7.0204705032017**

Pourgholamhossein F, Sharififar F, Rasooli R, Pourgholi L, Nakhaeipour F, Samareh-Fekri H, Iranpour M, Mandegary A. 2016. Thymoquinone effectively alleviates lung fibrosis induced by paraquat herbicide through down-regulation of pro-fibrotic genes and inhibition of oxidative stress. **Environm Toxicol Pharmacol** 45: 340 - 345. **https://doi.org/10.1016/j.etap.2016.06.019**

Rainer E. 2003. New ointment for treating dry and/or inflamed nasal mucosa, comprises synergistic combination of olive, *Hippophae rhamnoides* and *Nigella sativae* oils, odorants and ointment base. **DE** 20211988 U1.

Rana Keyhanmanesh LP, Omrani H, Mirzamohammadi Z, Shahbazfar AA. 2014. The effect of single dose of thymoquinone, the main constituents of *Nigella sativa*, in guinea pig model of asthma. **BioImpacts** 4: 75.

Saadat S, Mohammadi M, Fallahi M, Aslani MR. 2015. The protective effect of α-hederin, the active constituent of *Nigella sativa*, on tracheal responsiveness and lung inflammation in ovalbumin-sensitized guinea pigs. **J Physiol Sci** 65: 285 - 292. **https://doi.org/10.1007/s12576-015-0367-6**

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

Salem ML, Hossain MS. 2000. Protective effect of black seed oil from *Nigella sativa* against murine cytomegalovirus infection. **Int J Immunopharmacol** 22: 729 - 740. **https://doi.org/10.1016/s0192-0561(00)00036-9**

Sayed MD. 1980. Traditional medicine in health care. **J Ethnopharmacol** 2: 19-22.

Şen N, Kar Y, Tekeli Y. 2010. Antioxidant activities of black cumin (*Nigella sativa* L.) seeds cultivating in different regions of Turkey. **J Food Biochem** 34: 105 - 119. **https://doi.org/10.1111/j.1745-4514.2009.00309.x**

Shabsoug B, Khalil R, Abuharfeil N. 2008. Enhancement of natural killer cell activity *in vitro* against human tumor cells by some plants from Jordan. **J Immunotoxicol** 5: 279 - 285. **https://doi.org/10.1080/15376510802312027**

Sharieatzadeh SM, MalkyRad AA, Hovaida R, Rahzani K, AghaJohary M, Fazli D. 2011. The effect of *Nigella sativa* on oxidative stress. **J Shahrekord Univ Med Sci** 12: 21 - 26.

Sharma PC, Yelne MB, Dennis TJ. 2005. **Database on medicinal plants used in Ayurveda** (CCRAS New Delhi). **https://agris.fao.org/agris-search/search.do?recordID=US201300132829**

Sheikh BY, Mohamadin AM. 2012. Thymoquinone a potential therapy for cerebral oxidative stress. **Asian J Nat Appl Sci** 1: 76 - 92.

Sheir Z, Badra G, Salama O, Gomaa AI, Saber W. 2013. Effect of combination of some natural products and chloroquine on HCV infection in Egyptian patients: Pilot study. **J Liver** 2: 116. **https://doi.org/10.4172/2167-0889.1000116**

Shen K, Yang Y, Wang T, Zhao D, Jiang Y, Jin R, Zheng Y, Xu B, Xie Z, Lin L. 2020. Diagnosis, treatment, and prevention of 2019 novel coronavirus infection in children: experts' consensus statement. **World J Pediatrics** 1 - 9.

Simalango DM, Utami NV. 2014. *In-vitro* antihelminthic effect of ethanol extract of black seeds (*Nigella sativa*) against Ascaris suum. **Proc Chem** 13: 181 - 185. **https://doi.org/10.1016/j.proche.2014.12.024**

Singh G, Marimuthu P, Heluani CS, Catalan C. 2005. Chemical constituents and antimicrobial and antioxidant potentials of essential oil and acetone extract of *Nigella sativa* seeds. **J Sci Food Agric** 85: 2297 - 2306. **https://doi.org/10.1002/jsfa.2255**

Su X, Ren Y, Yu N, Kong L, Kang J. 2016. Thymoquinone inhibits inflammation, neoangiogenesis and vascular remodeling in asthma mice. **Int Immunopharmacol** 38: 70 - 80. **https://doi.org/10.1016/j.intimp.2016.05.018**

Suddek GM, Ashry NA, Gameil NM. 2013. Thymoquinone attenuates cyclophosphamide-induced pulmonary injury in rats. **Inflammopharmacology** 21: 427 - 435. **https://doi.org/10.1007/s10787-012-0160-6**

Susanti N, Barlianto W, Kalim H, Kusuma HC. 2013. Asthma clinical improvement and reduction in the number of CD4 CD25 foxp3 Treg and CD4 IL-10 cells after administration of immunotherapy house dust mite and adjuvant probiotics and/or *Nigella Sativa* powder in mild asthmatic children. **IOSR J Dent Med Sci** 7: 50 - 59.

Swamy SMK, Tan BKH. 2000. Cytotoxic and immunopotentiating effects of ethanolic extract of *Nigella sativa* L. seeds. **J Ethnopharmacol** 70: 1 - 7. **https://doi.org/10.1016/s0378-8741(98)00241-4**

Taka E, Mazzio EA, Goodman CB, Redmon N, Flores-Rozas H, Reams R, Darling-Reed S, Soliman KFA. 2015. Anti-inflammatory effects of thymoquinone in activated BV-2 microglial cells. **J Neuroimmunol** 286: 5 - 12. **https://doi.org/10.1016/j.jneuroim.2015.06.011**

Tariq M. 2008. *Nigella sativa* seeds: folklore treatment in modern day medicine. **Saudi J Gastroenterol** 14: 105 - 106. **https://doi.org/10.4103/1319-3767.41725**

Tayarani-Najaran Z, Sadeghnia HR, Asghari M, Mousavi SH. 2009. Neuroprotective effect of *Nigella sativa* hydro alcoholic extract on serum/glucose deprivation induced PC12 cells death. **Physiol Pharmacol** 13: 263 - 270.

Tayman C, Cekmez F, Kafa IM, Canpolat FE, Cetinkaya M, Tonbul A, Uysal S, Tunc T, Sarici SU. 2013. Protective effects of *Nigella sativa* oil in hyperoxia-induced lung injury. **Arch Bronconeumol** 49: 15 - 21. **https://doi.org/10.1016/j.arbr.2012.11.003**

Ulasli M, Gurses SA, Bayraktar R, Yumrutas O, Oztuzcu S, Igci M, Igci YZ, Cakmak EA, Arslan A. 2014. The effects of *Nigella sativa* (Ns), *Anthemis hyalina* (Ah) and *Citrus sinensis* (Cs) extracts on the replication of coronavirus and the expression of TRP genes family. **Mol Biol Rep** 41: 1703 - 1711. **https://doi.org/10.1007/s11033-014-3019-7**

Umar S, Zargan J, Umar K, Ahmad S, Katiyar CK, Khan HA. 2012. Modulation of the oxidative stress and

inflammatory cytokine response by thymoquinone in the collagen induced arthritis in Wistar rats. **Chem Biol Interact** 197: 40 - 46. **https://doi.org/10.1016/j.cbi.2012.03.003**

Umar S, Munir MT, Subhan S, Azam T, Nisa Q, Khan MI, Umar W, Rehman Z, Saqib AS, Shah MA. 2016. Protective and antiviral activities of *Nigella sativa* against avian influenza (H9N2) in turkeys. **J Saudi Soc Agric Sci https://doi.org/10.1016/j.jssas.2016.09.004**

Wang JZ, Zhang RY, Bai J. 2020. An anti-oxidative therapy for ameliorating cardiac injuries of critically ill COVID-19-infected patients. **Int J Cardiol** 312: 137 - 138. **https://doi.org/10.1016/j.ijcard.2020.04.009**

WHO. 2020. Q & A on coronaviruses (COVID-19), World Health Organization. **https://www.who.int/emergencies/diseases/novel-coronavirus-2019/question-and-answers-hub/q-a-detail/q-a-coronaviruses#:~:text=symptoms**

Wienkötter N, Höpner D, Schütte U, Bauer K, Begrow F, El-Dakhakhny M, Verspohl EJ. 2008. The effect of nigellone and thymoquinone on inhibiting trachea contraction and mucociliary clearance. **Planta Med** 74: 105 - 108. **https://doi.org/10.1055/s-2008-1034280**

Yimer EM, Surur A, Wondafrash DZ, Gebre AK. 2019a. The effect of metformin in experimentally induced animal models of epileptic seizure. **Behav Neurol** 2019: Article ID 6234758. **https://doi.org/10.1155/2019/6234758**

Yimer EM, Tuem KB, Karim A, Ur-Rehman N, Anwar F. 2019b. *Nigella sativa* L.(black cumin): a promising natural remedy for wide range of illnesses. **Evid-Based Compl Alt Med** 2019: 1528635. **https://doi.org/10.1155/2019/1528635**

Yoruk O, Tatar A, Keles ON, Cakir A. 2017. The value of *Nigella sativa* in the treatment of experimentally induced rhinosinusitis. **Acta Otorhinolaryngol Ital** 37: 32 - 37. **https://doi.org/10.14639/0392-100X-1143**

Zaoui A, Cherrah Y, Mahassini N, Alaoui K, Amarouch H, Hassar M. 2002. Acute and chronic toxicity of *Nigella sativa* fixed oil. **Phytomedicine** 9: 69 - 74. **https://doi.org/10.1078/0944-7113-00084**

Zhu N, Zhao X, Xiang Y, Ye S, Huang J, Hu W, Lv L, Zeng C. 2016. Thymoquinone attenuates monocrotaline-induced pulmonary artery hypertension via inhibiting pulmonary arterial remodeling in rats. **Int J Cardiol** 221: 587 - 596. **https://doi.org/10.1016/j.ijcard.2016.06.192**