

Nigella (*Nigella sativa* L.), a novel herb can cure many diseases: A review

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Abstract

Nigella (*Nigella sativa* L.) is an annual flowering plant belongs to the family *Ranunculaceae* and is an excellent phytomedicine widely used throughout the world. It is very popular in various traditional systems of medicine. The seeds of nigella and its oil were extensively used for centuries in the treatment of various ailments throughout the world. Now it is established that most of the potential and fruitful activities are innate in its volatile oil and protein components. Most of the therapeutic properties of this herb are due to the presence of thymoquinone and its isomers, which are the major active chemical component of the nigella essential oil. Since, it has very low level of toxicity its seeds are also used in food as flavouring agent, additive in the breads and pickles. Seeds and oil have a long history of folklore usage in various systems of medicines and food. The nigella seeds have been widely used in the treatment of different diseases and ailments. In Islamic literature, it is considered as one of the greatest forms of healing medicine. It has been recommended for using on regular basis in Tibb-e-Nabwi (Prophetic Medicine). It has been widely used as antihypertensive, liver tonics, diuretics, digestive, anti-diarrheal, appetite stimulant, analgesics, anti-bacterial and in skin disorders. Extensive studies on *Nigella* have been carried out by various researchers and a wide spectrum of its medicinal and pharmacological actions have been explored which may include antidiabetic, anticancer, immune modulator, analgesic, antimicrobial, anti-inflammatory, spasmolytic, bronchodilator, hepato-protective, renal protective, gastro-protective, antioxidant properties, etc. Due to its miraculous power of healing, nigella has got the place among the top ranked evidence based herbal medicines. The present review is an effort to compile detailed available information of the literature on scientific researches of pharmacognostical characteristics, chemical composition and pharmacological activities of the nigella seed and its oil. The review further highlighted the medicinal importance of *Nigella* seed to prevent and cure many common diseases (ailments) and looking to the current epidemic of viral disease (especially Corona virus) the latest information on *Nigella* shall be very useful to boost the immunity and enhance safety against viral and fungal disease in human beings.

Key words : Anti-diabetic, antioxidant, essential oil, miracle herb, nigellone, *Nigella sativa*, pharmacological profile, ranunculaceae, thymoquinone.

Nigella (*Nigella sativa* L.) is a very important seed spice crop. It is an annual and seasonal (winter) cross pollinated crop belonging to the family *Ranunculaceae*, commonly known as black cumin in English and Kalonji in Hindi. It is an elite, herbaceous plant, *Nigella* is native to Southern Europe, North Africa and Southwest Asia distributed widely in the Mediterranean countries, Southern Europe, North Africa, South and South West Asia. In India, nigella is cultivated in parts of Rajasthan, M.P., Punjab, Himachal Pradesh, Madhya Pradesh, Bihar and Bengal, Assam and Maharashtra states. As far as the research related to development of improved varieties, production and plant protection technologies and postharvest management is concerned, different research studies has been done on nigella crop (Meena *et al.*, 2012; Lal and Meena, 2018). Among various medicinal plants, *Nigella sativa* L. is

emerging as a miracle herb with a rich historical and religious background since many researches revealed its wide spectrum of pharmacological potential. *Nigella* is commonly known for its black color seed and in different pockets of India, people call it black cumin. The seeds of nigella and their oil have been extensively used for ancient times in the treatment of various ailments throughout the globe. It is an important drug in the Indian traditional system of medicine like Unani and Ayurveda (Nickavar *et al.*, 2003 and Bourgou *et al.*, 2008). In Islamic literature, it is considered as one of the greatest forms of healing medicine available and in one of the Prophetic hadith it was mentioned that black seed is the remedy for all diseases except death. It is also recommended for use on regular basis in Tibb-e-Nabwi (Prophetic Medicine) (Mehta *et al.*, 2009). *Nigella* has been extensively studied

for its biological activities and therapeutic potential and shown to possess various properties, as diuretic, antidiabetic, antihypertensive, anticancer and immunomodulatory, analgesic, antimicrobial, anthelmintics, analgesics, anti-inflammatory, spasmolytic, bronchodilator, gastroprotective, hepatoprotective, renal protective and antioxidant properties. The seeds of nigella are widely used in the treatment of various diseases like bronchitis, asthma, diarrhea, rheumatism and skin disorders. It is also used as liver tonic, digestive, anti-diarrheal, appetite stimulant, emmenagogue, to increase milk production in nursing mothers, to fight parasitic infections and to support immune system (Khare, 2004; Sharma *et al.*, 2005). Most of the therapeutic properties of this plant are due to the presence of thymoquinone which is a major active chemical component of the essential oil. Nigella seeds are also used in food like flavoring additive in the breads and pickles because it has very low level of toxicity (Goreja, 2003; Meena *et al.*; 2019).

General climate and soil conditions for nigella production

Nigella is a cool season crop and is cultivated in the northern plains during winter season. Fairly warm weather during sowing with a temperature of 20-27°C is desirable. Cold weather is congenial for the early growth period and crop requires warm sunny weather during seed formation and maturity. However, nigella can also be grown in other parts of the country having the above temperature range. Now a days it is becoming popular in Southern States of India where normally temperature does not go high especially in Andhra Pradesh, Karnataka and Maharashtra. Nigella can thrive on wide range of soils, which are rich in organic matter and free from water logging. However, loamy, medium to heavy soils with better fertility levels are most suitable. The land should get sufficient sunlight free from shade. The place should be airy with good provision of irrigation water. Soil pH range near to neutral reaction is better but can be grown well on soil pH 6 – 8. However, Loamy, medium to heavy soils with better fertility level are most favorable. Soil with high acidity, salinity and alkalinity are not suitable for germination, growth and development of this crop.

Promising nigella varieties for commercial production

Variety selection depends primarily on its adaptation to the soil and climate conditions and preferably on their having resistance/tolerance to pests and diseases. There are many varieties released for cultivation in different areas. The description of some of the important cultivated varieties is given as under:

Ajmer Nigella-1

It is developed by ICAR-National Research Centre on Seed Spices, Ajmer. It is suitable for cultivation in semi-arid region under irrigated conditions. The plants are 30-35 cm in height. This variety takes 135 days to reach seed maturity and has resistance to root rot. The ovary is pentamerous and each capsule contains 65 seeds. The seeds of this variety contains about 0.3 per cent of essential oil. The average seed yield of Ajmer Nigella-1 is 800kg ha⁻¹.

Ajmer Nigella-20

It is developed by ICAR-National Research Centre on Seed Spices, Ajmer through mass selection. This variety matures in 140-150 days. It is suitable for all parts of Rajasthan. Average yield of this variety is 10-12 q ha⁻¹. Suitable sowing time determined is 15-30 October. This variety contains ~28 per cent total oil and 0.3 per cent essential oil.

Azad Kolonji

This variety developed at Chandra Shekhar Azad University of Agriculture and Technology, Regional Research Station, Kalyanpur, Kanpur. It takes about 135-145 days to produce seed. Average seed yield of this variety is 900-1000 kg ha⁻¹.

Rajendra Shyama

It was released from Department of Horticulture, Tirhut College of Agriculture, RAU Dholi (Bihar). This variety is recommended for West Bengal and Bihar States. It takes above 140-150 days to produce seed. Average seed yield is 700-800 kg ha⁻¹.

Pant Krishna

This variety was developed by pure line selection from indigenous selection at Govind Ballabh Pant University of Agriculture Science and Technology, Pantnagar. Plants of this variety are medium, bold seed and suitable for cultivation in U.P. and Uttarakhand.

NS-44

This variety is developed by Jawaharlal Nehru Krishi Vishwa Vidyalaya, Jabalpur, Madhya Pradesh. It yields 4.5 to 6.5 qtl. ha⁻¹ and matures in 140 – 150 days.

NS-32

This is also cultivar produces 4.5 – 5.5 quintal/ha. seed and matures in 140 – 150 days. It was development by Jawaharlal Nehru Krishi Vishwa Vidyalaya, Jabalpur, Madhya Pradesh.

Kalajeera

Kalajeeraa variety of Nigella takes 135-145 days to produce seed. Average seed yield is 400– 500kg ha⁻¹.

Chemical composition of nigella seeds

Many active compounds have been isolated, identified and reported so far in different varieties of nigella. The

major active constituents are thymoquinone (30%-48%), thymohydroquinone, dithymoquinone, p-cymene (7%-15%), carvacrol (6%-12%), 4-terpineol (2%-7%), t-anethol (1%-4%), sesquiterpene longifolene (1%-8%), α -pinene and thymol *etc.* Seeds also contain two types of alkaloids; *i.e.* isoquinoline alkaloid *s.g.* nigellicimine and nigellicimine-N-oxide, and pyrazol alkaloids or indazole ring bearing alkaloids which include nigellidine and nigellicine. Nigella seeds also contain alpha-hederin, a water soluble pentacyclic triterpene and saponin, a potential anticancer agent (Padhye *et al.*, 2008; Hanafy and Hatem, 1991). Some other compounds namely carvone, limonene, citronellol were also found in traces. Most of the pharmacological properties of *Nigella sativa* are mainly attributed to quinine constituents, of which thymoquinone is the most abundant. On storage, thymoquinone yields dithymoquinone and higher oligocondensation products (Khan, 1999). The seed of nigella contains fat (28.5%), protein (26.7%), carbohydrates (24.9%), crude fibre (8.4%), total ash (4.8%) and fine amount of various vitamins and minerals like Cu, P, Zn and Fe *etc.* In addition to that it contains carotene precursor of vitamin 'A'. Its roots and shoots are reported to contain vanillic acid (Al-Ali *et al.*, 2008; Al-Jassir, 1992). The seeds reported to contain a fatty oil rich in unsaturated fatty acids, mainly linoleic acid (50-60%), oleic acid (20%), eicodadienoic acid (3%) and dihomolinoleic acid (10%). Saturated fatty acids (palmitic, stearic acid) amount to about 30% or less, α -sitosterol is a major sterol, which accounts for 44% and 54% of the total sterols in Tunisian and Iranian varieties of nigella seed oils respectively, followed by stigmaterol (6.57-20.92% of total sterols) (Atta-Ur-Rahman, 1995; Nickavar *et al.*, 2003). The other reported chemical components includes nigellone, avenasterol-5-ene, avenasterol-7-ene, campesterol, cholesterol, citrostadienol, cycloeucalenol, gramisterol, lophenol, obtusifoliol, stigmastanol, stigmaterol-7-ene, β -amyrin, butyro-spermol, cycloartenol, 24-methylene-cycloartanol, taraxerol, tirucallol, 3-O-[β -D-xylopyranosyl(1 \rightarrow 3)- α -L-rhamnopyranosyl(1 \rightarrow 2)- α -L-arabino-pyranosyl]-28-O-[α -L-rhamnopyranosyl(1 \rightarrow 4)- β -D-glucopyranosyl(1 \rightarrow 6)- β -D-glucopyranosyl] hederagenin, volatile oil (0.5-1.6%), fatty oil (35.6-41.6%), oleic acid, esters of unsaturated fatty acids with C15 and higher terpenoids, esters of dehydrostearic and linoleic acid, aliphatic alcohol, β -unsaturated hydroxy ketone, hederagenin glycoside, melanthin, melanthigenin, bitter principle, tannin, resin, protein, reducing sugar, glycosidal saponin, 3-O-[β -D-xylopyranosyl-(1 \rightarrow 2)- α -L-rhamno-pyranosyl-(1 \rightarrow 2)- β -D-

glucopyranosyl]-11-methoxy-16,23-dihydroxy-28-methyl-olean-12 enoate, stigma-5, 22-dien-3- β -D-glucopyranoside, cycloart-23-methyl-7, 20, 22-triene-3 β , 25-diol, nigellidine-4-O-sulfite, N. mines A3, A4, A5, C, N. mines A1, A2, B1, and B2 (Cheikh-Rouhou *et al.*, 2008; Bourgou *et al.*, 2008).

Traditional uses and folk remedies

Nigella has been traditionally known to treat a variety of disorders, diseases and conditions pertaining to respiratory system, digestive tract, kidney and liver function, cardio vascular system and immune system support as well as for general well-being (Sharma *et al.*, 2005; Goreja, 2003). Avicenna refers to black seeds in the "The Canon of Medicine", as seeds stimulate the body's energy and helps recovery from fatigue and dispiritedness. Nigella seeds and their oil have a long history of folklore usage in Indian and Arabian civilization as food and medicine (Atta-Ur-Rahman, 1995; Warriar *et al.*, 2004). Since long back nigella seeds have been traditionally used in Southeast Asian and the Middle East countries to cure several diseases and ailments including asthma, bronchitis, rheumatism and related inflammatory diseases. Because of its multiple uses nigella earned the Arabic approbation 'Habbatul barakah', meaning the seed of blessing. A tincture prepared from the seeds of Nigella is found useful in indigestion, loss of appetite, diarrhoea, dropsy, amenorrhoea and dysmenorrhoea and treatment of worms and skin eruptions. Externally the oil is used as an antiseptic and local anesthetic. Roasted nigella seeds are given internally to stop the vomiting (Sharma *et al.*, 2005; Warriar *et al.*, 2004; Yarnell and Abascal, 2011; Padhye *et al.*, 2008). The essential oil from Nigella seeds has also demand in the pharmaceutical and perfumery industry. The main alkaloids present in Nigella seeds are nigellmin, nigellidin, nigellicin and are known to possess anticarcinogenic properties. The seeds of Nigella are being used as spice from the ancient times in preparation of pickles, as one of the ingredient. Seeds are scattered as preservative between folders of linen or woolen to stop insect attack. The oil can be used as a stabilizing agent for edible fats. Indians, Middle Easterners, Turks and Egyptians commonly sprinkle whole Nigella seeds on breads to provide flavors and textures. In the Middle East Nigella is mixed to bread dough however in North Indian cooking, whole seeds are dry roasted or fried in oil to give a more intense aroma. They are used in curries, nans, dals, yogurts, vegetables and chutneys. In Iran, Nigella is used mostly to enhance vegetable dishes. Nigella is an essential ingredient in a spice mixture of Bengal, Bangladesh and Sikikim called panchphoron (five spice

blends). It is blended with cumin, mustard seed, ajowan and black pepper and is fried in mustard oil to flavor eggplant, cabbage, squash and meats.

Medicinal and Pharmacological Properties of Nigella

Antiviral activity

Seeds of Nigella have wide therapeutic effects on human and animal body and have been reported to have significant positive effects against many ailments such as gastrointestinal problems, anorexia, conjunctivitis, dyspepsia, rheumatism, diabetes, skin diseases, jaundice, hypertension, intrinsic hemorrhage, bronchitis, headache, fever, influenza, paralysis, amenorrhea, anorexia, asthma, cough, and eczema. Thymoquinone which is main active constituent of nigella oil and has variable beneficial health effects. In several studies it was found effective against murine cytomegalo virus infection, avian influenza (H9N2), Chistosoma Mansonii Infection, PPR virus, Broad bean mosaic virus, HIV virus, Hepatitis C Virus, Zucchini Yellow Mosaic Virus, and Papaya Ring Spot Virus (Molla *et al.*, 2019; Salem and Hossain, 2000). Various clinical and experimental studies have demonstrated many therapeutic effects of TQ including immunomodulatory, anti-inflammatory, anti-tumor, and antimicrobial (Umar *et al.*, 2016; Ahmad *et al.*, 2013; Azeem *et al.*, 2014; Al-Mufarrej, 2014). Due to an enormous number of biological targets and virtually no side effects, Nigella seeds have achieved the potential therapeutic interest to cure immunosuppressive viral diseases.

Antifungal activity

Nigella methanolic extracts of found strongest antifungal effect followed by the chloroform extracts against different strains of *Candida albicans*. An intravenous inoculum of *Candida albicans* produced colonies of the organism in the liver, spleen and kidneys. Treatment of mice with the plant extract 24 h after the inoculation caused a considerable inhibitory effect on the growth of the organism in all organs studied (Bhajji and Nitave, 2019). Khan *et al.*, (2005) reported that the aqueous extract of nigella seeds exhibits inhibitory effect against candidiasis in mice. These findings were also confirmed by Histopathological examination of the respective organs (Bita *et al.*, 2012). The anti-yeast activity of the black cumin seed quinines, dithymoquinone, thymohydroquinone, and Thymoquinone were evaluated and found that thymohydroquinone and TQ possessed significant anti-yeast activity (Halamova *et al.*, 2010). Two novel antifungal defensins named Ns-D1 and Ns-D2, were isolated from seeds of nigella and sequenced. The Ns-D1 and Ns-D2 defensins displayed

strong divergent antifungal activity towards a number of phytopathogenic fungi (Rogozhin *et al.*, 2011).

Antimicrobial activity

The essential oil of nigella shown to have activity against gram-positive and gram-negative bacteria. It exhibited strong antimicrobial activity against *Salmonella typhi*, *Pseudomonas aeruginosa* and others. Comparatively higher sensitivity against gram-positive bacteria *Staphylococcus aureus* and *Vibrio cholera* was found to be stronger than gram negative bacteria *Staphylococcus aureus*, *Staphylococcus pyogenes* and *Staphylococcus viridans* are more susceptible to *Nigella sativa* (Kahsai, 2002). The dried seeds of nigella exhibited bactericidal activity against *Pseudomonas aeruginosa* (Hanafy and Hatem, 1991; Kahsai, 2002). The activity of the volatile oil against drug-resistant strains of *Shigella spp.*, *Vibrio cholera* and *Escherichia coli* was found to have a synergistic action with streptomycin and gentamycin. A clear inhibition of the growth of *Staphylococcus aureus* was observed by concentration of 300 mg/ml. The positive inhibition may be attributed to the two important active ingredients of *Nigella sativa*, Thymoquinone and melanin. Thymoquinone exhibited a significant bactericidal activity against various human pathogenic bacteria especially gram positive cocci, *i.e.* *Staphylococcus aureus* and *Staphylococcus epidermidis* (Chaieb *et al.*, 2011; Morsi, 2000; Bakathir and Abbas, 2011; Salem *et al.*, 2010; Hannan *et al.*, 2008).

Anti-schistosomiasis activity

The study of effect of nigella seed oil against the liver damage induced by *Schistosoma mansoni* (*S. mansoni*) infection revealed reduction in the number of *S. mansoni* worms in the liver and decreased the total number of ova deposited in both the liver and the intestine. These results suggested that nigella seed oil may play a role against the alterations caused by *S. mansoni* infection (Mahmoud *et al.*, 2002). The *in vitro* testing of *N. sativa* seeds against *Schistosoma mansoni*, *miracidia*, *cercariae*, and adult worms also indicated its strong biocidal effects against all stages of the parasite and an inhibitory effect on egg-laying of adult female worms (Mahmoud *et al.*, 2002).

Antioxidant activity

Nigella seed prevented the liver from oxidative stress by increasing the activities of enzymes such as myeloperoxidase, glutathione-S-transferase, catalase, adenosine deaminase, myeloperoxidase and by decreasing hepatic lipid peroxidation in chicks. The crude methanolic extract of nigella seed cake was found to show significant antioxidant properties under *in vitro*

systems. The thymoquinone pre-treatment restored the increased level of malonyl di aldehyde and conjugated diene levels (Mariod *et al.*, 2009; Sogut *et al.*, 2008; Baldioli *et al.*, 1996; Burits and Bucar, 2000; Ramadan and Morsel, 2004; Turkdogan *et al.*, 2003).

Gastro-protective activity

The anti-ulcer effect of *Nigella sativa* is possibly prostaglandin-mediated and/or through its antioxidant and anti-secretory activities (Al Mofleh *et al.*, 2008). *Nigella* prevents alcohol induced lipid peroxidation (*i.e.* thiobarbituric acid reactive substances) and reduced gastric GSH content, enzyme activities of gastric SOD, GSH-S-Transferase (Khaled, 2009). The thymoquinone could be a potential therapeutic agent for the treatment of patients with inflammatory bowel disease (Lei *et al.*, 2012). Decoction of *nigella* with rock salt is given for relief in dyspepsia and stomachache (Katya *et al.*, 1999).

Hepato-protective and Nephro Protective activity

Studies revealed that *nigella* intraperitoneally relieves the deleterious effects of ischemia reperfusion injury on liver. *Nigella* treatment protected rat liver against hepatic ischemia reperfusion injury (Yildiz *et al.*, 2008). It was also administrated that it protects hepatic tissue from deleterious effects of toxic metals such as lead, and attenuates hepatic lipid peroxidation following exposure to chemicals such as carbon tetrachloride (Kapoor, 2009). The nephro protective effect of vitamin-C and *nigella* oil was observed against gentamicin (GM) associated nephrotoxicity it was also found that they lowered the values of serum creatinine, blood urea nitrogen and antioxidant activity as compared to gentamicin control group values. When these two antioxidants were given as combination, they proved to have synergistic nephro protective effect (Swamy and Huat, 2003; Al-Naggar *et al.*, 2003; Saleem *et al.*, 2012).

Antidiabetic and Anticancerous activity

Nigella seed extract possess hypoglycaemic activity and antihyperglycemic effects and it is also attributed to a combination of the therapeutically relevant insulinotropic and insulin-like properties (Benhaddou-Andaloussi *et al.*, 2008; Benhaddou-Andaloussi *et al.*, 2011; Salama, 2011). Polyherbal formulation of kalonji sugar powder has antidiabetic effect and water extract of this formulation is useful in maintaining healthy glucose levels and cholesterol levels (Alam *et al.*, 2013). It is also reported that combination of α -lipoic acid, L-carnitine and *nigella* may contribute significantly in improvement of the carbohydrate metabolism likewise the seed extract exerts an insulin-sensitizing action by enhancing ACC phosphorylation, a major component of the insulin-

independent AMPK signalling pathway and by enhancing muscle Glut4 content (Kapoor, 1999; Bamosa *et al.*, 2010; Rchid *et al.*, 2004; Najmi *et al.*, 2008).

Nigella volatile oil did not induce any dysplastic alterations or carcinomas (Salomi *et al.*, 1991). It was also found that *nigella* oil induced significant reductions in the colonic lesions via suppression of the cell proliferation in the colonic mucosa (Kumar and Huat, 2001). It was also not showed any harmful effects in the blood or urine parameters and no pathological changes in the various vital body organs. Furthermore, exposure of various human cancer cell lines to the volatile oil in concentrations of 120-380 $\mu\text{g/ml}$ induced significant death of the cells showing clear cytotoxic effect (Nazrul-Islam *et al.*, 2004; Rooney and Ryan, 2005; Harzallah *et al.*, 2012; Jeong, 1998; Salim *et al.*, 2003; El-obeid *et al.*, 2006; Worthen *et al.*, 1998).

Anti-inflammatory and analgesic activity

Nigella fixed oil and thymoquinone were found to inhibit membrane lipid peroxidation and eicosanoid generation in leucocytes similarly *nigellonein* low concentration is effective in inhibiting the histamine release from the mast cells (Mutabagani and El-Mahdy, 1997). Osteoporosis has been linked to oxidative stress and inflammation. The studies on the anti-osteoporotic effects of *nigella* and thymoquinone were carried out. It was revealed that *nigella* and thymoquinone were shown to inhibit inflammatory cytokines such as interleukin-1 and 6 and the transcription factor, nuclear factor κB . Both NS and TQ have shown potential as anti-osteoporotic agent (Shuid *et al.*, 2012). The anti-allergic effects of *nigella* seed components could be attributed to allergic rhinitis. Besides, *nigella* should be considered for treating allergic rhinitis when the effects of other anti-allergic drugs need to be avoided (Nikakhlagh *et al.*, 2011).

Immunomodulatory activity

The aqueous extract of *nigella* significantly enhanced NK cytotoxic activity against YAC-1 tumor cells and this documented anti-tumor effects of *N. sativa* may be, at least in part, attributed to its ability to serve as a stimulant of NK anti-tumor activity. It was anticipated that *N. Sativa* ingredients may be employed as effective therapeutic agents in the regulation of diverse immune reactions implicated in various conditions and diseases such as cancer (Majdalawieh *et al.*, 2010). The methanolic extract for *nigella* seed was found to enhance the total white blood cells count [up to 1.2×10^4 cells/ mm^3]. Bone marrow cellularity also increased significantly ($P < 0.01$) after the administration of the *nigella* seed extract. *Nigella sativa* seeds are found as a potential immunosuppressive

cytotoxic agent (Torres *et al.*, 2010). Nigella oil is a promising natural radio protective agent against immunosuppressive and oxidative effects of ionizing radiation (Assayed, 2010). Daily oral administration of *Nigella sativa* oil also helps in reduction of hemolysin antibodies titers (Boskabady *et al.*, 2011).

Pulmonary-protective activity and anti-asthmatic effects

Several studies showed that nigellone possesses an antispasmodic effect and an increase in mucociliary clearance and may be useful in treatment of different respiratory diseases (Wienkotter *et al.*, 2008; Dubey *et al.*, 2016). It showed relaxant effect of most fractions from Nigella on tracheal chains of guinea pigs which were more potent for methanol and dichloromethane fractions (Boskabady *et al.*, 2008). Results showed that *Nigella sativa* treatment inhibits the inflammatory pulmonary responses, reducing significantly peribronchial inflammatory cell infiltration, alveolar septal infiltration, alveolar edema, alveolar exudate, alveolar macrophages, interstitial fibrosis, granuloma and necrosis formation in different pulmonary aspiration models. Data also indicated a significant reduction in the activity of inducible nitric oxide synthase and a rise in surfactant protein D in lung tissue of different pulmonary aspiration models after *Nigella sativa* therapy which emphasized that nigella treatment might be beneficial in lung injury and have potential clinical use (Kanter, 2009). A study showed that nigella has a relatively potent antiasthmatic effect on asthmatic airways. However, the effects of boiled extract of this plant on most measured PFTs were less than those of theophylline at concentrations used (Boskabady *et al.*, 2010). It was also found thymoquinone may decrease the destructive effects of methotrexate on testicular tissue of patients using this agent (Gokce *et al.*, 2011).

Neuro pharmacological activities

The aqueous and methanol extracts of defatted nigella seeds were shown to possess a potent central nervous system and analgesic activities, especially depressant action in the case of the methanolic extract. The neuroprotective effects could be due to its antioxidant, free radical scavenging, and anti-inflammatory properties (Akhtar *et al.*, 2012; Aqel and Shaheen, 1996; El-Naggar *et al.*, 2010).

Contraceptive, Anti-fertility and Antioxytotic activity

Several research studies revealed that extract of Nigella seeds possess anti-fertility activity and that might be due to its inherent estrogenic activity (Keshri *et al.*, 1995; Agarwal *et al.*, 1990).

The antioxytotic properties of nigella seeds were reported in some preliminary studies. *N. sativa* seeds inhibit the uterine smooth muscle contraction induced by oxytocin stimulation. The volatile oil of nigella seeds inhibited the spontaneous movements of smooth muscle in rat and guinea pig uterine and also the contractions induced by oxytocin stimulation which suggest the anti-oxytotic potential of *Nigella sativa* seeds oil (Aqel and Shaheen, 1996).

Toxicological studies and Drugs-nigella interaction

Many toxicological studies have been carried out on *Nigella sativa* seeds. In a chronic toxicity study it was found that it changed in key hepatic enzyme levels particularly aspartate-aminotransferase, alanine-aminotranferase, and gammaglutamyl-transferase. Moreover, the histopathological results also showed to be normal for the tissues of heart, liver, kidneys and pancreas LD50 values of fixed oil of nigella obtained by single doses orally and intraperitoneally in mice. The low toxicity of *N. sativa* fixed oil, evidenced by high LD50 values, key hepatic enzyme stability and organ integrity, suggested a wide margin of safety for therapeutic doses of *Nigella sativa* fixed oil (Zaouiet *et al.*, 2002). In another trails it was postulated that thymoquinone is a relatively safe compound, particularly when given orally to experimental animals (Sharma *et al.*, 2005; Khader *et al.*, 2009). There is a possibility that nigella may interact with co-administered drugs and affect their intestinal availability and pharmacological effect. *In vitro* studies have shown that *N. sativa* extracts inhibit cDNA-expressed human cytochrome P-450 3A4, 2C9, 3A5 and 3A7-mediated metabolism of marker substrates therefore may affect and/or inhibit the metabolism of a wide range of drugs. Further, the *in vitro* studies both with methanol and hexane extracts of nigella increased the permeation of amoxicillin significantly and findings of trails suggest that it enhanced amoxicillin availability in both *in vivo* and *in vitro* studies (Ali *et al.*, 2012).

Conclusions

Nigella is an important herbaceous seed spice crop of India and Middle East. It has a spectrum of pharmacological and nutraceutical potentials. Its oil was widely used for centuries in the treatment of various ailments throughout the world. It is to be considered as an important drug in the Indian traditional medicine system and even in today's scenario. It is established that most of the potential and fruitful activities are inbuilt in its volatile oil and protein components. The presence of thymoquinone and its isomers which are the major active

chemical component of the essential oil is solely responsible for all the therapeutic properties of this herb. Nigella seeds are also used in food as flavouring, additive in the breads and pickles because it has very low level of toxicity. Mechanism of actions of Nigella seed extracts and its constituents by which they exert their therapeutic effects needs to be further investigated and tested. Chemical modifications in the molecular structure of Thymoquinone, a-Hederin and other constituents of nigella seeds could lead to prepare more effective and safer drugs for the treatment of wide variety of diseases in the future in suitable combinations. Moreover, further researches should focus and explore the specific cellular and molecular targets of various constituents of Nigella, particularly Thymoquinone. This review is dedicated to all those researchers and stakeholders who are interested in focusing their research and development activities on this miracle herb and hope, this review article would help them in investigating and conducting further preclinical and clinical studies on the use of seed spices for the treatment of variety of diseases and will also be useful for creating awareness among the population about the health benefits of Nigella and its curative action against many ailments especially viral disease.

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