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Review Article
Nutritional, Healthical and Therapeutic Efficacy of Black Cumin (*Nigella sativa*) in Animals, Poultry and Humans

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Abstract

In the present era of emerging antibiotic/drug resistance against pathogenic organisms and food safety concerns of their toxic residues as well as slow process of discovering newer antibiotics, there is a dire need for using natural and effective alternatives. In this regard, herbal and aromatic plants and/or their extracts are gaining attention of worldwide researchers. Studies on *Nigella sativa* (black cumin) seeds show promising results that it could provide a suitable alternative to antibiotics as growth promoter and safeguard various health issues of animals and humans. The seeds of black cumin with thymoquinone as its main active constituent are mainly used for medicinal purposes and could be used as food spice and nutritional supplements. These have beneficial antinociceptive, antimicrobial, growth enhancing, antiparasitic, immunomoulatory, hepatoprotective, analgesic, anti-inflammatory, antioxidative and bronchodilating effects. Blood pressure regulating as well as bile flow stimulating effects have also been observed. Black cumin seeds have been used widely against several diseases, disorders and ailments of humans and animals including bronchial asthma, cough, bronchitis, lung inflammation, microbial infections, fever, dysentery, gastrointestinal problems, gastric ulcers, hypertension, neurodegenerative diseases, epilepsy, alzheimer disease, headache, diabetes, allergy, obesity, back pain, skin diseases, eczema, jaundice, anorexia, conjunctivitis, dyspepsia, rheumatism, diabetes, intrinsic hemorrhages, amenorrhea and immune disorders, which altogether indicate their potent therapeutic values and biomedicinal perspectives. The aim of this study is to provide comprehensive and recent information about the nutritional, healthical, pharmaceutical, therapeutic and biomedical applications and prospects of *Nigella sativa* seeds in feeding humans, animals and poultry.

Key words: *Nigella sativa*, black cumin, seeds, health, production, poultry, animal, human

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Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Antibiotics and several feed additives have been used in the livestock and poultry industry in a large scale for a long time (Dhama *et al*., 2014; El-Hack *et al*., 2016; Alagawany *et al*., 2015a). Nowadays, many people have been cautious about possible antibiotic residues and disease resistance in use of antibiotics in the animal and poultry industry besides in medical science (Jang *et al*., 2007; Kocyigit *et al*., 2009; Tiwari and Dhama, 2014). As a result of the ban of using antibiotics as feed additives, using alternative feed additives has accelerated and led to more investigations in animal production (Dhama *et al*., 2014). These additives could be medicinal/herbal and aromatic plants and/or extracts from these plants. Several herbs and plants were used for this purpose like *Azadirachta indica*, *Withania somnifera*, *Zingiber officinale*, *Allium sativum*, *Rosmarinus officinalis*, *Thymus vulgaris*, *Yucca schidigera* and others (Abd El-Hack *et al*. 2015; Alagawany and Abd El-Hack, 2015; Alagawany *et al*., 2015b). Also, one of these alternatives is *Nigella sativa* seed/oil (Sener *et al*., 1985). *Nigella sativa* seed is small in size, a dicotyledon and has one of many slang names of the herb *Nigella-sativa* which attributes to the botanical family of Ranunculacease. Other colloquial names for *Nigella sativa* involve: Black cumin, kalonji, black caraway, iranian black cumin, habbatulbarakah, seed of blessing (Habatul-barakah in Arabic countries), Al Habbah Al Sawda, qazheshuniz and probably some else (Akhtar and Riffat, 1991; Tembhurne *et al*., 2014). The black seed is a herb, which had been used as a natural medication for lot of diseases for over 2000 years. Black seed have an important position in the prophetic medicine of the Prophet Mohammad (PBUH) and Abu Hurayrah (RA) narrated that the Prophet (PBUH) said "Use black seed regularly, because it is a cure for every disease, except death (Al-Bukhari, 1976; Rahmani and Aly, 2015). Black seed is described as the curative black cumin in the Holy Bible and is explained as Melanthion by Hippocrates and Dioscorides and as Gith by Pliny (Worthen *et al*., 1998). The origin of black seed is Eastern Europe, South Europe, East Mediterranean, Southern Mediterranean basin, Western Asia and Asia minor. In the Middle East, North Africa, far East Iran, Pakistan and in the Indian subcontinent the seed dry powder or extract of *Nigella sativa* Linn., have been used widely as traditional medicine by Ayurvedic, Unani and herbal medicine practitioners to prop up menstruation, as diuretics and to increase the milk yield (Hosseinzadeh *et al*., 2013; Gharby *et al*., 2015).

Black cumin seeds were used widely against variety of health disorders including bronchial asthma, allergy, lung inflammation, respiratory distress, dysentery, dyslipidaemia, microbial infections, headache, obesity, back pain, hypertension, immune disorders, neurological disorders, skin ailments and gastrointestinal problems (Riaz *et al*., 1996; Schleicher and Saleh, 2000; Ali and Blunden, 2003; El Gazzar *et al*., 2006; Ahmad *et al*., 2013; Gokce *et al*., 2016). Furthermore, in the black seed oil, the content of polyunsaturated fatty acids represents double than the normal mono-unsaturated fatty acids, which helps in reducing the total cholesterol content. This plant is grown particularly in Burdur, Afyon, Karaman, Isparta and Konya localities in Turkey (Baytop, 1994, 1999; Baydar, 2009). *Nigella sativa* seed contains 210 g kg^{-1} protein, 350-380 g kg^{-1} oil and 350 g kg^{-1} carbohydrate. The weight of 1000 seeds is about 2-3 g. The seed efficiency varies between 75-150 kg day^{-1} depending on soil, climate and cultivation conditions (Baydar, 2009). The seeds of black cumin are mainly used for medicinal purposes and could be used as food spice, condiment and nutritional supplements as well due to their bitter peppery taste and characteristic aroma (Kar, 2008). The oil obtained from cumin seeds is enriched with nutritive values but still market share in economic contribution is less significant due to certain spirituous reasons of its mention in sacred texts and describing its presence in Tutankhamen tomb (Padhye *et al*., 2008; Gharby *et al*., 2015).

Recently, animal studies have shown that the extracts of the *Nigella sativa* seed have significant therapeutic effects against variety of ailments such as headache, fever, cough, bronchitis, asthma, skin diseases, eczema, warts, jaundice, liver damage, anorexia, gastrointestinal problems, conjunctivitis, dyspepsia, rheumatism, diabetes, hypertension and intrinsic hemorrhage, amenorrhea, dysmenorrhea, scorpion poisoning and snake bite (Tasar *et al*., 2012; Najmi *et al*., 2013; Forouzanfar *et al*., 2014; Kolahdooz *et al*., 2014; Sobhi *et al*., 2016). They have beneficial antitussive, antinociceptive effects, antiosteoporotic property, hypotensive, antibacterial effect, antifungal, anticestodal, hepatoprotective effect, potent analgesic, anti asthmatic effect, anti-inflammatory, antioxidant, spasmolytic, lactagogue, vermifuge, galactagogue, diaphoretic, antineoplastic, antihistaminic, bronchodilating effect, carminative, a blood pressure regulating effect as well as a bile flow stimulating effect (El-Zawahry, 1964; Akhtar and Riffat, 1991; Abdel-Fattah *et al*., 2000; Ali and Blunden, 2003; Hajhashemi *et al*., 2004; Kanter *et al*., 2005; Halawani, 2009; Boskabady *et al*., 2010; Tembhurne *et al*., 2014). The aim of this study is to provide comprehensive and recent information about the nutritional and pharmaceutical benefits of *Nigella sativa* seeds in feeding human, animal and poultry as well.

Fig. 1: *Nigella sativa* plant and seeds

MORPHOLOGY OF *NIGELLA SATIVA* AND CHEMICAL COMPOSITION

Figure 1 shows black cumin is a small annual herb about 45 cm high 2-3 slender leaves pinnatisect, 2-4 cm long cut into linear segment, segments are oblong. The flowers pale, blue on solitary long peduncles, seeds trigonous and black in color. The black cumin plant has a rather stiff, erect, branching stem, bears deeply-cut greyish-green leaves and terminal grayish blue flowers, followed by odd, toothed seed vessels, filled with small somewhat compressed seeds, usually three-cornered, with two sides flat and one convex, black or brown externally white and oleaginous, strong agreeable aromatic odour, like that of nutmegs and a spicy, pungent taste.

The flowers of *Nigella sativa* are delicate and usually colored pale blue and white, with 5-10 petals. The fruit is a large and inflated capsule composed of 3-7 united follicles, each containing large number of seeds. It has a pungent bitter taste and a faint smell of strawberries (Varghese, 1996; Dwivedi, 2003; Venkatachallam *et al*., 2010).

The pharmacognosy and pharmacology of *Nigella sativa* elaborates all active principles and many functional components of this magical black cumin (Rajsekhar and Kuldeep, 2011). Studies elaborates plentiful beneficial pharmacological effects of their active principles in different almost all parts of the body (Ustun *et al*., 1990; Agbaria *et al*., 2015). As reported by Sharma *et al.* (2009) seeds contain many esters of structurally unusual unsaturated fatty acids with terpene alcohols (7%) furthermore, traces of alkaloids are found which belong to two different types: Isochinoline alkaloids are represented by nigellimin and nigellimin-N-oxide and pyrazol alkaloids include nigellidin, alphahederin and nigellicin (Khan, 1999). The seeds hold fixed and essential oils, sterols, flavonoid triglycerides, fatty acids, proteins, alkaloids, tocopherol and saponin (Salama, 1973; Menounos *et al*., 1986; Abd El-Aal and Attia, 1993a, b; Merfort *et al*., 1997; Ali and Blunden, 2003; Bourgou *et al*., 2010; Matthaus and Ozcan, 2011). In the essential oil (avr. 0.5%, max. 1.5%), thymoquinone was identified as the main component (up to 50%) besides p-cymene (40%), pinene (up to 15%), dithymoquinone, thymol and thymohydroquinone (Ustun *et al*., 1990; Lutterodt *et al*., 2010). Other terpene derivatives were found only in trace amounts: Carvacrol, limonene, carvone, 4-terpineol and citronellol. Moreover, the essential oil contains significant (10%) amounts of fatty acid ethyl esters. On storage, thymoquinone yields dithymoquinonene and higher oligocondensation products. The seeds also contain a fatty oil rich in unsaturated fatty acids, mainly linoleic acid (50-60%), oleic acid (20%), eicodadienoic acid (3%) and dihomolinoleic acid (10%). The saturated fatty acids (palmitic, stearic acid) amount to about 30% or less. Also contain parts of the essential oil, mostly thymoquinone, by which it acquires an aromatic flavour. By using steam-distillation the seeds give a yellowish brown volatile oil with an unpleasant odor. This oil contains carvone, d-limonene and a carbonyl compound nigellone. Thymoquinone is fat soluble, that's why as compared to aquous extract or dry powder form seed oil exhibited more therapeutic potential (Ahmad *et al*., 2013). However, studies reported that seed oil composition varies with the geographical regions, where the plant is cultivated (D'Antuono *et al*., 2002; Cheikh-Rouhou *et al*., 2007; Matthaus and Ozcan, 2011).

Nigella sativa has high-quality nutritive values as evident from the studies performed to know about nutrients, protein content and evaluation of protein quality by measuring Protein Efficiency Ratio (PER), calculating Net Dietary Protein Energy percent (NDPE%) after Net Protein Utilization (NPU) experiments. Obtained results showed good concentration of protein, crude protein, fat, crude extract, nitrogen free extract, vitamins, variety of minerals and moisture content on the basis of dry matter analysis (Zeitoun and Neff, 1995; Ali and Blunden, 2003).

Based upon dry matter content analysis approximately crude protein content equals to 216 g kg^{-1}, nitrogen-free extract 249 g kg^{-1}, fat 406 g kg^{-1}, crude fibre 84 g kg^{-1}, iron 105 mg kg^{-1}, copper 18 mg kg^{-1}, zinc 60 mg kg^{-1}, phosphorus 527 mg kg^{-1}, calcium 1860 mg kg^{-1}, thiamin 15.4 mg kg^{-1}, niacin 57 mg kg^{-1}, pyridoxine 5.0 mg kg^{-1} and folic acid 160 μg kg^{-1} were reported and documented in the study (Ali and Blunden, 2003; Sultan *et al*., 2009).

Beneficial effects of *Nigella sativa*: Many beneficial healthical activities and mechanisms of action could be obtained by using *Nigella sativa* (Table 1). The seeds/oil has various health benefits as it lessen blood pressure, raise respiration and modify the haemogram by increasing the Packed Cell

Table 1: Beneficial healthical activities and mechanisms of action of *Nigella sativa*

Activities	Mechanisms of actions	References
Antioxidant impact	*Nigella sativa* decrease the production of hydroxyl (OH), hydrogen peroxide (H_2O_2) and superoxide (O_2) radicals. Experiments showed depressed MDA and raised GSH levels	Badary *et al.* (2003), Ilhan *et al.* (2005), Machmudah *et al.* (2005), Mohamed *et al.* (2005), Guler *et al.* (2007), Yildiz *et al.* (2008), Mariod *et al.* (2009), Awad *et al.* (2011), Zafeer *et al.* (2012), Al-Okbi *et al.* (2013) and Mollazadeh and Hosseinzadeh (2014)
Antibacterial impact	The volatile oil which exists in *N. sativa* has a comparable activity not only to ampicillin, but also to drug-resistant strains and has activity against many Gram-positive and Gram-negative bacteria	Arici *et al.* (2005), Halawani (2009), Abdel Azeiz *et al.* (2013), Forouzanfar *et al.* (2014) and El-Hack and Alagawany (2015)
Antiviral impact	Black cumin improves the function of T cells and boosts the cell mediated immunity	El-Kadi and Kandil (1986), Salem and Hossain (2000), Barakat *et al.* (2013) and Onifade *et al.* (2013).
Antifungal impact	*Nigella sativa* could inhibit a wide range of fungal species such as *Candida albicans*, *Aspergillus niger*, *Scopulariopsis brevicaulis* and *Fusarium solani*	Al Jabre *et al.* (2003), Aljabre *et al.* (2005), Rogozhin *et al.* (2011), Bita *et al.* (2012), Harzallah *et al.* (2012) and Ahmad *et al.* (2013)
Antiparasitic impact	*Nigella sativa* has anti-coccidial, antimalarial and antiparasitic properties against different stages of life of parasite	Aboul-Ela (2002), Mahmoud *et al.* (2002), Baghdadi and Al-Mathal (2011) and Okeola *et al.* (2011)
Immunomodulatory impact	*Nigella sativa* inhibits many inflammatory mediators,	Haq *et al.* (1999), Salem (2005), Al-Saleh *et al.* (2006),
Anticancerous impact	*Nigella sativa* could inhibit tumor growth through reducing cell count and inhibiting tumor development	Iddamaldeniya *et al.* (2003), Musa *et al.* (2004), Mbarek *et al.* (2007), Al-Mofleh *et al.* (2008) and Alenzi *et al.* (2010)
Antiepileptic impact	The use of *N. sativa* extract showed a positive results in epilepsy patients	Akhondian *et al.* (2007) and Biswas and Guha (2007) and Noor *et al.* (2012)
Anti-neurodegenerative impact	The phenolic compounds are equipped with neuroprotective capabilities to play important part in treating different diseases and disorders of nervous system	Kanter (2008a, b, 2011), Khazdair (2015) and Gokce *et al.* (2016)
Anti-alzheimer impact	Based on the antioxidant activity of *N. sativa,* it could fight alzheimer disease	Selkoe (2001), Al-Majed *et al.* (2006) and Alhebshi *et al.* (2013)

Volume (PCV) and haemoglobin (Hb) and by reducing the plasma concentrations of cholesterol, triglycerides and glucose. The valuable effects of black cumin seeds and thymoquinone are attributed to their antioxidant, cytoprotective effects and their impact on inflammatory mediators (Ali and Blunden, 2003). They exert beneficial pharma-therapeutic effects in cases of integumentary disorders, cardiovascular, endocrine, respiratory disorders and many other systemic ailments involving other parts of body (Randhawa and Al-Ghamdi, 2002; El-Tahir and Bakheet, 2007; Gharby *et al.*, 2015).

PHARMATHERAPEUTIC ACTIVITIES

Antioxidant effects and anti-inflammatory activities: Findings of different studies have reported that the whole herbal plants, cold pressed or essential oil, extracts and their active molecules, especially, thymoquinone, possess antioxidants and anti-inflammatory impacts, supporting the common folk perception of black cumin as antioxidant and anti-inflammatory factors (Amin and Hosseinzadeh, 2016). *Nigella sativa* was documented to act as excellent superoxide anion scavenger as confirmed by workers (Badary *et al.*, 2003; Machmudah *et al.*, 2005; Ersahin *et al.*, 2011; Leong *et al.*, 2013). Oral intake of thymoquinone have protective effects against various conditions of liver disorder as of fatty liver, fibrosis/cirrhosis, liver injury due to ischemia, alcoholic liver disease, paracetamol induced or chemical as cadmium induced liver damage, viral hepatitis, even cases of hepatocellular carcinoma and renal damage occurring due to oxidative stress (Yildiz *et al.*, 2008; Zafeer *et al.*, 2012; Al-Okbi *et al.*, 2013). Diverse mechanisms imparting antioxidant benefits are by inhibiting iron-dependent lipid peroxidation, reducing expression of spermidine/spermine N-1-acetyl-transferase (SSAT) mRNA, decreasing CYP3A1 mRNA expression, elevating the total thiol concentration and function of quinone reductase and glutathione transferase, scavenging free radicals, increasing the activity of catalase (CAT), superoxide dismutase, lessening NF-κB activity and causing inhibition of cyclooxygenase and lipoxygenase (Mohamed *et al.*, 2005; Awad *et al.*, 2011; Mollazadeh and Hosseinzadeh, 2014).

Atta and Imaizumi (1998) reported that the addition of *Nigella sativa* ethanolic extracts to the corn oil prevented triglycerides from the oxidative damage. The antioxidant activity of *Nigella sativa* attributed to the inhibition of thromboxane B_2, leukotriene B_4 and eicosanoid generation because of inhibition of 5-lipooxigenase and cyclooxigenase. Ilhan *et al.* (2005) performed an experiment, where *Nigella sativa* oil was given to pentylenetatrazol induced seizure kindled mice and observed the antioxidant activity by capturing free radicals. These impacts of *Nigella sativa* seeds could be due to the active components such as carvacrol, thymoquinone, 4-terepinol and anethole

(Guler *et al*., 2007; Toma *et al*., 2015). Mariod *et al*. (2009) demonstrated that chicken diet supplemented with 0.5 and 1% *Nigella sativa* seeds caused insignificantly depression in concentration of erythrocyte MDA, lipid peroxidases, meanwhile glutathione (GSH) concentration increased comparing with the control group. The latter authors concluded that *Nigella sativa* inhibits free radical production and regulates glutathione which prevent oxidative stress. It has been established that black seeds may decrease the production of hydroxyl (OH), hydrogen peroxide (H_2O_2) and superoxide (O_2) radicals which are produced by aerobic respiration (Burits and Bucar, 2000; Tuluce *et al*., 2009). In addition, Ilhan *et al*. (2005) reported that *Nigella sativa* oil remarkably raised the GSH levels and depressed the MDA level in rats. The thymoquinone present in volatile oil of black cumin had protective effect on acute gastric damage in the rats (Arslan *et al*., 2005).

Nigella sativa seed extracts showed a protective impact on oxidative stress by STZ (60 mg kg^{-1}) induced diabetic rats and on pancreatic beta cells of streptozotocin induced diabetic rats (Abdelmeguid *et al*., 2010). Using *Nigella sativa* extract at level of 200 mg kg^{-1} diet increased the thiol content of hippocampus as compared to untreated diabetic treatment group. The content of malondialdehyde (MDA) in hippocampus significantly declined in *Nigella sativa* extracts (200 and 400 mg kg^{-1}) treated rats as compared to the untreated diabetic rats, whilst the dose of 200 mg kg^{-1} was more effective to minimize oxidative stress in hippocampus of rats as explained by Abbasnezhad *et al.* (2015). Hosseinzadeh *et al.* (2007) study pretreatment with *Nigella sativa* extract (0.048, 0.192 and 0.384 mg kg^{-1}) injected intraperitoneally immediately after administration and reperfusion was continued every 24-72 h after induction of ischemia caused a significant decrease in the level of MDA as compared to ischemic group. When thymoquinone, the major constituent of *Nigella sativa* seeds were administered intracerebro-ventricular it suppresses epileptic seizures in rats due to anticonvulsant effects of thymoquinone (Hosseinzadeh and Parvardeh, 2004; Hosseinzadeh *et al*., 2005). Beheshti *et al.* (2014) and Vafaee *et al.* (2015) investigated the therapeutic influences of *Nigella sativa* hydroalcoholic extract in PTZ-induced repeated seizures on brain tissues oxidative damage. Researchers observed that the treatment with *Nigella sativa* extract at levels of 200 and 400 mg kg^{-1} diet depressed the MDA concentration in hippocampus tissues, while total thiol concentration in hippocampus in *Nigella sativa* extract (400 mg kg^{-1}) treated category was improved comparing with the PTZ group. Thymoquinone improves the enzymatic activity in the peripheral leukocytes of diabetic rats concerning to energy metabolism (Fararh *et al*., 2010).

Antimicrobial activity: Using herbal plants and their extracts as well as phytochemicals isolated from these plants have antimicrobial activities against several species of harmful bacteria can be of great significance in therapeutic treatments (Nascimento *et al*., 2000). The seeds of *N. sativa* were reported to exhibit antibacterial effect against many species of bacteria such as Gram-positive and Gram-negative bacteria (Kumar and Berwal, 1998). Regarding the bioactive components, thymoquinone (TQ) present in different extracts of *N. sativa* has a broad antimicrobial including antibacterial, antifungal, antiviral and antiparasitic spectrum against many Gram-positive, Gram-negative bacteria, viruses, fungi, *Candidia* spp., parasites including schistosoma and cestodes (Halawani, 2009; Abdel Azeiz *et al*., 2013; Forouzanfar *et al*., 2014; Ratz-Lyko *et al*., 2014). The use of *Nigella sativa* showed a strong antimicrobial activity against *Pseudomonas aeruginosa*, *Salmonella typhi* and other bacteria as well. Several investigations using the essential oil of *Nigella sativa* have been reported to have activity against Gram-negative and Gram-positive bacteria both (Haron *et al*., 2014; Forouzanfar *et al*., 2014; Abd El-Hack *et al*., 2015). Moreover, the sensitivity against Gram-positive bacteria like bacterial agents involved in of mastitis, *Staphylococcus aureus* and *L. monocytogenes* were observed to be stronger (Monika *et al*., 2013). Some kinds of bacteria like *S. viridans*, *Staphylococcus aureus* and *S. pyogenes* are reported to be more susceptible to *Nigella sativa* (El-Kamali *et al*., 1998). In an *in-vitro* study, Ferdous *et al.* (1992) suggested that volatile oil have a comparable activity not only to ampicillin, but also to drug-resistant strains of *Escherichia coli*, *Shigella* spp., *Protius Vulgaris*, *K. pneumoniae* and *Vibrio cholerae*, besides a synergistic action with gentamycin and streptomycin (Toppozada *et al*., 1965; Arici *et al*., 2005). Another study showed that when children naturally infected with the cestode worms were treated with oral administration of *Nigella sativa* seeds (kalonji), percentage reductions in the faecal Eggs Per Gram (EPG) counts was observed, indicating anticestodal efficacy of *Nigella sativa* seeds (Akhtar and Riffat, 1991; Forouzanfar *et al*., 2014). Furthermore, the growth rate of *Salmonella typhimurium* (0.084%), *Bacillus cereus* (1.72%), *Staphylococcus aureus* (1.88%) and *Pseudomonas aeruginosa* (1.88%) were inhibited by the minimum inhibitory value of ethanol extract, essential oil, ethyl acetate extract and methanol extract of *N. sativa*, respectively (Yasni *et al*., 2009).

A study by Alam *et al.* (2010) showed that ethanol extract of *N. sativa* was as reported to be very effective against *B. subtilis* and *S. aureus*. The complete inhibition of growth rate of *E. coli* required high concentration from *N. sativa* extract. These results suggest that black cumin seeds may have potential antibacterial activity against multiple antibiotic resistant bacteria. Ishtiaq *et al.* (2013) carried out an experiment to study the *in vitro* antibacterial effect of black cumin extracts against seven human pathogenic bacteria including Gram-negative bacteria (*Escherichia coli* IARS3, *Acinetobacter junii* IARS2, *Serratia marcescens* IARS6, *Enterobacter cloacae* IARS7 and *Proteus mirabilis* IARS5) and Gram-positive bacteria (*Staphylococuss aureus* IARS4 and *Enterococcus faecalis* IARS1). They found that the bioactive molecules from this plant or extracts, which can act as strong inhibitor of growth against wide range of infectious disease caused by harmful and pathogenic bacteria.

Antiviral effects: In the absence of any viral infection also intake of black cumin improve the function of NK cell along with augmenting the ratio of helper T cell to suppressor T cell (T4/T8), hence boosts the cell mediated immunity (El-Kadi and Kandil, 1986; Abdel-Shafi, 2013). Enriched with antiviral potential black seed oil from *Nigella sativa* showed protective effect against murine Cytomegalovirus infection in infected mice when administered intraperitoneally for a period of 10 days. Treated mice showed increased level and action of INF-gamma and CD4 T lymphocytes as compared to control group of mice (Saxena and Vyas, 1986; Salem and Hossain, 2000). Barakat *et al.* (2013) study revealed that patients infected with Hepatitis C Virus (HCV) who were not eligible for IFN/ribavirin therapy when treated with *N. sativa* administration, herbal therapy decreased viral load, improved oxidative stress, clinical condition and glycemic control in diabetic patients. Adult HIV patient with history of chronic fever, diarrhoea, weight loss and multiple papular pruritic lesions persisted for 3 months when treated with Nigella concoction for the period of six months they showed complete recovery, sero-reversion to sero-negative state, aviraemia and normal CD4 count. This study concluded the presence of active therapeutic principle in the *Nigella sativa* which hamper the activity of HIV protease enzyme in the patient (Ma *et al.*, 1994; Onifade *et al.*, 2013).

Antifungal effects: Active principles of *N. sativa* especially thymoquinone ((TQ), thymol (THY) and thymohydroquinone (THQ) have demonstrated their antifungal potential against various fungal species viz., *Candida albicans*, *Aspergillus niger*, *Scopulariopsis brevicaulis*, *Fusarium solani*, clinically pathogenic fungus *Madurella mycetomatis* and important members of dermatophyte group as *Trichophyton rubrum*, *Trichophyton interdigitale*, *Trichophyton mentagrophytes*, *Epidermophyton floccosum* and *Microsporum canis* (Harzallah *et al.*, 2012). Study conducted over animals experimentally infected with *Candida albicans* showed that when diethyl-ether extract of *N. sativa* was used, extract slowed down the progression of infection by reducing the growth of fungi in affected organs (Bita *et al.*, 2012; Ahmad *et al.*, 2013). Another study performed to compare the antifungal potential of thymoquinone with amphotericin-B, griseofulvin and clotrimazole against *Aspergillus niger*, *Fusarium solani* and *Scopulariopsis brevicaulis* also suggested that though clotrimazole was efficient but as compared to amphotericin-B and griseofulvin, thymoquinone was more effective even when used in less doses (Al Jabre *et al.*, 2003; Aljabre *et al.*, 2005).

Similarly, thymoquinone, thymohydroquinone and thymol present in the ether extract of *N. sativa* proved their antifungal efficacy by regressing the growth of *Madurella mycetomatis*, causative agent of fungal tumor known as mycetoma and other molds and yeasts also (Rogozhin *et al.*, 2011; Sunita and Meenakshi, 2013). Antifungal effect of thymoquinone and ether extract was evident against different genera of Trichophyton, Epidermophyton and Microsporum under *in vitro* condition when isolated Dermatophytes from skin infection of sheep were inhibited under laboratory conditions. Though studies demonstrated that MIC of ether extract of *N. sativa* is comparatively more than thymoquinone alone, signifying the strong potential of thymoquinone (Aljabre *et al.*, 2005).

Antiparasitic effects: *Nigella sativa* seeds and oil both possess anti-coccidial, antimalarial and antiparasitic properties against different stages of life of parasite as evident from the literature (Baghdadi and Al-Mathal, 2011; Okeola *et al.*, 2011). Antimalarial property of black cumin seed extract is seen in mice infected with *Plasmodium yeolii nigeriensis* (Okeola *et al.*, 2011). In a study performed over mice infected with *Schistosoma mansoni* antiparasitic efficacy of *N. sativa* oil was compared with the drug praziquantel. Study concluded that oil contained antischistosomal activity hence combined treatment with herbal oil and drug had better results. Antischistosomal prospects of *N. sativa* seeds are documented as it has reduced the number and frequency of egg laying besides killing various life stages as miracidia, cercariae and even adult worms of *S. mansoni*. In mouse infected with *Schistosoma mansoni* cytogenetic studies through karyotyping have also been done after the TQ therapy (Aboul-Ela, 2002; Mahmoud *et al.*, 2002).

Immunomodulatory effects: Many studies reported that black cumin has an excellent potential as alternative to vaccines and antibiotics in improving poultry immunity and reducing mortality due to immunomodulatory and therapeutic properties (Haq *et al*., 1999; Salem, 2005; Janfaza and Janfaza, 2012; Majdalawieh and Fayyad 2015). *Nigella sativa* inhibits many inflammatory mediators as prostaglandins and leukotriens, amends splenocyte proliferation, Th1/Th2 cytokine profile, macrophage function and NK anti-tumor activity (Mutabagani and El-Mehdy, 1997; Mbarek *et al*., 2007; Majdalawieh *et al*., 2010; Gholamnezhada *et al*., 2015). Akhtar *et al*. (2003) stated that mortality was depressed from 16.67-4.17% by the addition of 1.5% black cumin to layer diet. Mansour *et al*. (2002) found that viability rate of broilers fed diet containing 1% powdered *Nigella sativa* seeds were increased by 50% compared to the control group. Also, Al Jabre *et al.* (2003) demonstrated that volatile oils derived from *Nigella sativa* have 67 constituents capable to induce pharmacological and beneficial impacts against bacteria such as Staphylococcus and *E. coli*. The active components of black seeds are acting as antioxidant, antibacterial, anti-proliferative and anti-inflammatory which induce positive influences on the immunity and organs involved (Arslan *et al*., 2005; Al-Saleh *et al*., 2006; Ravindran *et al*., 2010).

The studies of Toghyani *et al.* (2010) revealed that the antibody titer against Infectious Bursal Disease (IBD) and Newcastle Disease (ND) significantly increased by substituting grounded *Nigella sativa* seed for bacitracin methylene disalicylate in broiler diets. This improvement in IBD and ND titer belonged to *Nigella sativa* oil constituents such as carvacrol, thymol, thymoquinone, nigellimine and nigellicine (Al-Beitawi *et al*., 2009; Alagawany *et al*., 2015c). Toghyani *et al*. (2010) also found an increase in the lymphoid organ weight when broilers fed diet supplemented with 0.2 and 0.4% black seeds. On the other hand, the supplementation of *Nigella sativa* seeds had no significant effect on antibody titers against ND and influenza virus at 18 and 28 days of age as well as albumin to globulin and heterophil to lymphocyte ratios.

Anticancerous effects: Several investigations were performed using laboratory animals to study the anticancerous impacts of *Nigella sativa*. Anticancerous activity has also been reported due to the bioactive compounds in black cumin. Since, El-Kadi and Kandil (1986) observed an improved activity of Natural Killer (NK) cells up to 200-300% in patients suffering from advanced cancer and receiving a multi-modality immunotherapy in which black seeds were a part of remedy. Salomi *et al.* (1991) postulated that *Nigella sativa* seed extract inhibited dimethylbenz[α]anthracene/croton oil induced skin carcinogenesis in mice, reduced the number of papillomas per mouse and delayed the onset of papilloma formation. Moreover, Iddamaldeniya *et al.* (2003) indicated that *Nigella sativa* inhibits the growth of two leukemic cell lines and five solid tumor cell lines. Musa *et al.* (2004) explained that ethanol extracts derived from *Nigella sativa* could inhibit ehrilich ascites tumor growth through reducing cell count besides inhibiting tumor development. The various extracts of black cumin seeds produce different levels of cytotoxic impacts on different cell lines, for instance, essential oil produced the most cytotoxic impacts versus the P815 cell line when comparing with butanolic and ethanol acetate extracts (Randhawa and Alghamdi, 2011). Where ethyl acetate extracts exhibited, more cytotoxicity against the BSR line of cells. Moreover, Mbarek *et al.* (2007) found that the treatment of the essential oil into the tumor site improved the mouse livability and prevented the incidence of liver metastasis. Through p53-dependent pathway thymoquinone causes the death and destruction of cancerous cells by apoptotic mechanisms in cases of human colorectal cancer (Gali-Muhtasib *et al*., 2004; Woo *et al*., 2012). Studies showed that NS aqueous suspension of black seeds *Nigella sativa* containing fixed oil and volatile oil exert antiulcer potential in treating gastric ulcers in Wistar albino rats (El-Dakhakhny *et al*., 2000; Al-Mofleh *et al*., 2008). In a study performed over male albino rats outcome of study suggested the protective beneficial role of *Nigella sativa* seed, oil and thymoquinone against toxicity induced by the anticancer drug cyclophosphamide and recommend the clinical use of *N. sativa* as supportive anticancer therapy to reduce the side effects of long term chemotherapy (Alenzi *et al*., 2010). *Nigella sativa* seed play an important role as anticancer agent associated with high level of thymoquinone oil, as well as inhibits the NF-κB signaling pathway (Agbaria *et al*., 2015).

Antiepileptic effects: Noor *et al.* (2012) investigated the effect of *Nigella sativa* extract on alterations of amino acid neurotransmitters (epilepsy) induced by pilocarpine (380 mg kg^{-1}, i.p.) in hippocampus. Authors found a decrease in glycine and taurine, while, aspartate, glycine, GABA, glutamate and taurine levels increased significantly in the cortex after injection of pilocarpine. In another study, Biswas and Guha (2007) examined the impacts of the aqueous seed extract of *Nigella sativa* on pentylenetetrazole

(PTZ, 40 mg kg^{-1} b.wt.) induced seizure on rats model. Results revealed that *Nigella sativa* extract depressed locomotor activity, impaired motor coordination and increased sleeping time. Also, the resistance to convulsion in the pretreated animals with *Nigella sativa* extract was better than the control animals. Danger score depressed, while duration of onset of seizure increased in groups treated with *Nigella sativa*. Moreover, *Nigella sativa* inhibited prolongation of seizure latency and picrotoxin (a GABAA antagonist) as well. Akhondian *et al.* (2007) performed a clinical trial to study the effects of *Nigella sativa* extract at level of 40 mg kg^{-1} in reducing the frequency of seizures epilepsy in 13 years old children. All the patients (20 children) received the extract (40 mg kg^{-1}) or placebo three times per day for a period extended for 4 weeks. The mean frequency of seizures were significantly declined during the treatment as a result of using *Nigella sativa* extract.

Antineurodegenerative effects: The impacts of *Nigella sativa* on induced neuronal injury by chronic toluene exposure in the frontal cortex and brain stem in rats were evaluated in rats by Kanter (2008a, b, 2011). Chronic toluene exposure for 12 weeks resulted in severe degenerative changes involving: Shrunk cytoplasm, swelled mitochondria, the cisternae of endoplasmic reticulum were dilated and nuclear membrane broke down in neurons of the frontal cortex and brain stem. In the *Nigella sativa* treated group, after chronic toluene exposure did not exhibit any pathological changes in the nerve cells. Different phenolic bioactive compounds mainly thymoquinone equipped with neuroprotective capabilities plays important part in treating different diseases and disorders of nervous system including cases of induced neurotoxicity alzheimer disease and epilepsy etc (Khazdair, 2015; Gokce *et al*., 2016).

Antialzheimer effects: Alzheimer Disease (AD) is a well-known disease. It is a neurodegenerative disorder. As described by Selkoe (2001), alzheimer disease is characterized by an accumulation of cortical senile plaques which pathologically formed by aggregation of the 4.2-kD amyloid beta peptide (Ab), in the central nervous system, besides a progressive brain atrophy. Alhebshi *et al.* (2013) studied the impacts of *Nigella sativa* against different concentrations of ab1-42 induced cell death in cultured hippocampal neurons (*in vitro*). Results indicated that ab-induced raised cell death with dose dependent manner in the hippocampal cell culture. The exposure to various concentrations of *Nigella sativa* (0.1, 1, 10 and 100 nm) in hippocampal cells did not exert a significant effect on the rate of survival of hippocampal neurons. While, continuous use of *Nigella sativa* with ab1-42 caused a significant improvement in cell survival. *Nigella sativa* inhibited the reactive oxygen species and potential depolarization in mitochondrial membrane.

In a similar study, Al-Majed *et al.* (2006) evaluated the influence of *Nigella sativa* (5 mg kg^{-1} day^{-1}, p.o.) on transient forebrain ischemia induced neuronal damage in the rat hippocampus. The ischemia induced oxidative injury in rats demonstrated by remarkable elevation in MDA and significant depression in catalase and superoxide dismutase (SOD) activities and glutathione (GSH) contents in the hippocampal tissue comparing to the control group. The number of hippocampal cells death was significantly decreased by pretreatment of 24% *Nigella sativa* compared to 77% in ischemia group. The pretreatment with *Nigella sativa* was not only enhanced SOD, GSH and catalase activities, but also decreased the elevated MDA levels and inhibited lipid peroxidation induced by iron-ascorbate in hippocampal homogenate. Memory was improved with *Nigella sativa* oil (1 mL kg^{-1}, p.o.) administration, this effect may be returned to antioxidant and anti-inflammatory activities of *Nigella sativa* (El-Marasy *et al*., 2012). Supplementation of *Nigella sativa* extract to animal diets through neonatal and juvenile growth has positive impacts on learning and memory, this positive impacts might be attributed to the antioxidant activities (Beheshti *et al*., 2015).

APPLICATIONS OF *NIGELLA SATIVA* IN ANIMALS

Study was performed to evaluate the protective effects of *Nigella sativa* oil against oxytetracycline induced hepato-renal toxicity in forty white New Zealand male rabbits. Result conferred the preventive role of *N. sativa* oil upon oral administration. Owing to antioxidant defense mechanism by scavenging the free radical to impart hepatoprotective effect herbal oil minimized the damage in liver and kidney tissue (Abdel-Daim and Ghazy, 2015). In an experiment thymoquinone (TQ) was administered in adult Wistar albino male rats via intra-peritoneal route to assess the cardioprotective effect of thymoquinone against myocardial Ischemia/Reperfusion (I/R) injury and ischemia and reperfusion induced ventricular arrhythmias in anaesthetized rats. Results showed reduction in the size of infarct, frequency of myocardial ischemia/reperfusion and lowers the reperfusion-induced arrhythmias after treatment with TQ (Gonca and Kurt, 2015). Another study conducted to judge the antihistaminic effects of single dose of thymoquinone against lung inflammation and asthma in guinea pig model of asthma. Thirty guinea pigs were used and prophylactic effect of single

dose of thymoquinone was evident in form of reduced lung inflammation and diminished pathological changes (Keyhanmanesh *et al*., 2010). Literature revealed the protective effect of thymoquinone and α-Hederin, both the active principles of *Nigella sativa* in 48 male adult guinea pigs experimentally sensitized with ovalbumin by reducing the inflammation in lung and by altering the levels of IL-4, IFN-γ and IL-17 cytokines (Keyhanmanesh *et al*., 2015). Another study revealed that intra-peritoneal administration of crude aqueous extract of *Nigella sativa* in albino rats demonstrated the diuretic activity by increasing the volume and electrolyte composition of urine at the dose rate of 50 mg kg^{-1} without any acute toxicity even at higher dosage upto 5000 mg kg^{-1} (Zaoui *et al*., 2000; Asif *et al*., 2015). In an experiment to see the bone healing potential of *N. sativa* in rats results suggested that fracture healing of a traumatized bone is promoted with continuous intake of thymoquinone with a persistent level in the body (Kirui *et al*., 2004; Shuid *et al*., 2012). In Sprague-dawley rats hexane extract of *N. sativa* has shown anti-fertility potentials when given orally even after the 1-10 days of coitus, hence, disclosed contraceptive property also though in the rats and need more research and validation (Ahmad *et al*., 2013).

Several investigations confirmed the ability of black cumin and its extracts to improve feed efficiency when supplemented to poultry rations (Halle *et al*., 1999; Soliman *et al*., 1999; Al-Homidan *et al*., 2002; Abd El-Hack *et al*., 2015). On the other hand, Guler *et al*. (2006) found no significant changes in broiler feed intake by consuming feed containing antibiotics and black cumin. In this context, Durrani *et al*. (2007) observed that broiler diets with 4% grounded *Nigella sativa* resulted in less feed consumption but better feed efficiency comparing with the control diet. Similarly, feed consumption still unaltered by supplementing diet with 1, 2 and 3 mL kg^{-1} *Nigella sativa* oil (Bolukbasi *et al*., 2009) in 27 weeks of age laying hens and 1, 2 and 3% black cumin seeds (Aydin *et al*., 2008).

El-Ghamry *et al*. (2002) and Hassan *et al*. (2004) claimed an increased body weight by adding grounded *Nigella sativa* seeds to broiler diet. Many researches such as Guler *et al*. (2006), Durrani *et al*. (2007) and Al-Beitawi and El-Ghousein (2008) reported improved average daily weight gain and better Feed Conversion Ratio (FCR) in broilers by feeding of 1% *Nigella sativa* seed incorporated in the diet. Feed conversion ratio was better by using level of 1.5% black cumin seeds (Abu-Dieyeh and Abu-Darwish, 2008), 4 g kg^{-1} black seeds (Toghyani *et al*., 2010) and 1.5% powdered *Nigella sativa* in 4 weeks old broilers (Abu-Dieyeh and Abu-Darwish, 2008; Hermes *et al*., 2009). The beneficial impacts of *Nigella sativa* on poultry performance could be due to the pharmacologically active substances present in the seeds and high nutritive value as well. Black cumin seeds contain mixture of essential fatty acids, especially linoleic, linolenic and oleic acids that cannot be synthesized in the body. Takruri and Dameh (1998) theorized that there are fifteen amino acids represent the proteins of *Nigella sativa* out of which eight are essential. A stimulating effect of black seed on digestive system were reported by Jamroz and Kamel (2002), this effect resulting in better absorption and consequently better performance. Because the addition of *Nigella sativa* in feed increases the flow rate of bile, this effect results in increased emulsification which activates the pancreatic lipases and then help in fat digestion and absorption of fat-soluble vitamins. Furthermore, thymoquinone and black seeds oil have a hepatoprotective activity (Mahmoud *et al*., 2002; Mansour *et al*., 2002), as a result, these seeds have been traditionally used of gastrointestinal disorders (El-Abhar *et al*., 2003). Gilani *et al*. (2004) suggested that the improved performance of poultry could be due to the antimicrobial activity of the active components of black seeds. This activity of *Nigella sativa* could inhibit *Shigella sonnei*, *Bacillus suptilus*, *Staphylococcus lutea, Shigella dysenteriae*, *Vibrio cholera, Escherichia coli* (Ferdous *et al*., 1992), *Shigella flexneri* (Chowdhury *et al*., 1998), *Bacillus pumilus*, (El-Kamali *et al*., 1998), *Pseudomonas aeruginosa* and *Staphylococcus aureus* (Sokmen *et al*., 1999). The antifungal activity against pathogenic yeast *Candida albicans* (Hanafy and Hatem, 1991) and anthelmintic activity of black cumin was observed by researchers (Agarwal *et al*., 1979).

Therapeutic applications in humans: The therapeutic effects of *N. sativa* were seen in patients infected with Hepatitis-C (HCV) Virus. Reduction in viral count and recovery from malformed functions of liver due to viral induced fibrosis and cirrhosis were resulted after treatment with *N. sativa* (Abdel-Moneim *et al*., 2013). Similarly oral administration of *N. sativa* oil prevented the hepatotoxicity and damage to the liver of young kids occurring due to lymphoblastic leukemic malignancy and long term antiviral treatment with methotrexate drug (Hagag *et al*., 2013). Significant anti-asthmatic effect of the boiled extract of *Nigella sativa* seed in asthmatic patients is documented depicting the potent bronchodilatory effect of extract in terms of pulmonary function tests when compared with salbutamol and theophylline. Extract caused increased value of all pulmonary function tests performed such as Peak Expiratory Flow (PEF), Maximal Mid Expiratory Flow (MMEF), Maximal Expiratory Flow (MEF) and Forced Expiratory Volume in one second

(FEV (1) in the patients under study. Results suggested that oral administration of the plant seed extract is beneficial in the asthmatic patients in dose dependant manner (Boskabady *et al*., 2007, 2011).

CONCLUSION

This study summarized variety of studies in order to find out the beneficial effects of *Nigella sativa* and its constituents on different healthical and nutritional aspects. Based on the present study, it is concluded that *Nigella sativa* seeds and its extracts have important activities such as antioxidant, antifungal, antibacterial, immunomodulatory, hepatoprotective, analgesic and anti-inflammatory. It could fight several diseases such as cancer, epilepsy and alzheimer. Furthermore, the addition of *Nigella sativa* seeds or extracts to poultry or animal diets could improve feed efficiency and general productive or growth performance. The beneficial impacts of *N. sativa* in enhancing animal productivity and growth performances could be due to the pharmacologically active substances present in the seeds, high nutritive value, increasing feed efficiency and feed conversion ratio and may partially or fully replace antibiotics especial in poultry diets. Exploring the multiple health benefits and therapeutic potential of *N. sativa* to its full capacity could provide valuable nutraceuticals and pharmaceutical products to boost growth and counter various diseases and disorders of animals and humans.

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