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The Various Effects of *Nigella Sativa* on Multiple Body Systems in Human and Animals

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Abstract-*Nigella sativa* (Black seeds) has been recognized as one of the most popular herbs in many parts of the world for centuries. It was used in the world as folk medicine to cure different kinds of diseases. This plant has been considered as one of the main sources of nutrition and healthcare for humans as well as animals. It has been perceived as Kalonji; it is a southwest Asian plant that flowers annually. The seeds and oil of this plant have been used in food; in addition, it has a long history in the making of medicines. In addition to its being a model plant for better realization of gene and chromosome relationship, the plant species is also significant cytogenetically. Plant based system has not been absorbed fully for human health care despite the remarkable advancements in the field of pharmacology. Cumin, as one of the medicinal plants gifted to humans by nature, has a number of potential uses. It has been proved to be a useful herbal medicines that can be used for human health and therefore has been extensively studied and investigated to further discover the advantages of this plant.

Keywords: Black seeds, Chemical constituent, Morphology, *Nigella sativa*, Thymoquinone

Introduction

Nigella sativa Linn is an annual herb that belongs to the family Ranunculaceae and is most extensively investigated for its therapeutic purposes (Figure 1) (Aggarwal *et al.*, 2008; Kamal *et al.*, 2010). It is a native plant from the Mediterranean area and it is also found growing in some other regions in the world such as in Saudi Arabia, Syria, Middle Eastern, North Africa and also has been widely cultivated throughout South Europe, Asia, Turkey, Pakistan, and India used for culinary and medical purposes by the Romans (Randhawa and Al-Ghamdi, 2002; Rifat-uz-Zaman and Khan, 2004; Kamal, Arif, & Ahmad, 2010; Rifqi, 2012; Gray, 2013).

Figure 1: Nigella sativa (Randhawa and Al-Ghamdi, 2002; Rifat-uz-Zaman and Khan, 2004; Aftab *et al.,* 2013).

There are several names attributed towards *Nigella sativa* in various countries of the world. In Arabic countries they are called as Al-habbah, Al-Sawda, Habbet el-Baraka and Kamounaswad. In Iran, it is known as Shonaiz, black cumin in America, Ajenue in Europe, Kalongi in India and Pakistan, and Schwarz kummel in Germany (Zahoor *et al*., 2004). In Islamic teaching, the plant is of great significance due to its wide range of uses particularly for healing purposes. Prophet Muhammad (PBUH) has mentioned *Nigella sativa* specifically that the black seeds of the plant which are able to heal all types of diseases except death (Ilaiyaraja and Khanum, 2010; Hajra, 2011). In the book "Cannon of Medicine", Avicenna has stated that *Nigella* assists recovery from fatigue and depression as well as stimulates energy in the body. It is also one of the natural medicines used by Prophet Muhammad, and is called Tibb-e-Nabavi. In the Ayurvedic medicine, the use of its seed was directed as stimulant, emmenagogue, diuretic, anthelmintic, intermittent fever, jaundice, dyspepsia, piles, skin diseases and many others. According to Unani Tibb medicine, *Nigella sativa* is observed as a medicine that could heal a number of diseases (Paarakh, 2010; Singh, 2011). The uses of herbal supplements have been increased greatly over the past three decades because this type of medicinal plants is locally available and cheap (Amin and Nagy, 2009). Nowadays use of medicinal herbs is the best solution to cure a disease as compared to other therapy and unhealthy products because of its natural properties, which are less toxic (Al-Attar and Wafa'a, 2010). Herbal medicines derived from plant extracts were also increasingly utilized to treat a wide variety of clinical diseases (Lee *et al.,* 2004).

Scientific Classification (Sharma, Ahirwar, Jhade, & Gupta, 2009).
Kingdom : Plantae
Division : Magnoliophyta
Order : Ranunculales
Family : Ranunculaceae
Genus : Nigella
Species : sativa

Morphology
Nigella sativa is a small herb with height around 45 cm; having slender leaves pinnatisect whose length 4cm cut into a linear segment. It is a herb with pale flowers, blue peduncles, and black trigonous seeds. It is characterized by the stiffness of its stem, which has greyish green leaves bearing

a terminal greyish blue flower that has toothed seed vessels with compressed three-cornered seeds. They have odour, which is similar to that of nutmegs and a taste that is spicy and pungent. Its flowers, with 5-10 petals, are blue in colour. Other morphological features of *Nigella sativa* are large and inflated capsule that is composed of 3-7 united follicles, the fruit which contains a large number of seeds and has bitter and pungent tastes and a smell that is as faint as that of strawberry (Varghese, 1996; Randhawa and Al-Ghamdi, 2002; Dwivedi, 2003; Rifat-uz-Zaman and Khan, 2004).

Types of *Nigella*

Nigella sativa Linn: is found in Iraq and especially cultivated in western area (Chakravarty, 1976).
Nigella arnvensis: distributed in Iraq particularly in the north of Iraq and this type is characterized by small seeds and leaves as compared with *N. sativa* Linn. (Chakravarty, 1976).

Nigella orientales: distributed in Syria and has pale greenish leaves and flowers are yellowish, reddish tinged (Sayed, 1980).

Nigella damascenna: distributed in Syria and it has large size and greenish color leaves (Ansari, Hassan, Kenne, & Wehler, 1988).
Nigella assyriaca Boiss, *Nigella oxypetala Boiss*, *Nigella deserti Boiss* (Zahoor, Ghafoor, & Aslam, 2004).

Comparative between types of *Nigella* spp.

Nigella sativa L., *Nigella damascene* L., and *Nigella arvensis* L. are examples of *Nigella* L (Ranunculaceae) which involve around 20 species which can be found in Mediterranean regions and West Asia (Gray, 2013). The consumption of *Nigella* species has been increasing noticeably for the past few years particularly in the Middle Eastern countries. It has been known to have a mutlti purpose properties with possible benefits (Riaz, Syed, & Chaudhary, 1996). *Nigella sativa* and *Nigella damascene* are considered to be a herbaceous plant which grows yearly. *Nigella* species are characterized by having nectariferous petals and androecium which has many stamens. Gynoecium has a number of multi-ovule carpals that could transform into a follicle after the process of pollination with single fruits capsule-like structure. *Nigella* seeds can be described as small with a rough surface and an oily white interior (Zohary, 1983). *Nigella* plants' reproductive system is characterized by its self-pollination and a limited extent of cross pollination (Ellmer, 2004).

Nutritive Composition of *Nigella sativa* Seeds

The seeds of *Nigella sativa* showed richness and diversity in its chemical composition. Carbohydrates, proteins, amino acids, volatile and fixed oils are contained in the seeds (Rajsekhar and Kuldeep, 2011). Thymoquinone proved to be the main active constituent of the volatile oil of the black seed (Gali-Muhtasib, El-Najjar, & Schneider-Stock, 2006). The carbonyl polymer of thymoquinone have medicinal properties that include anti-microbial, antitumor, anti-viral, anti-inflammatory, reduction in blood sugar, muscle relaxation and anti-oxidation (Janfaza and Janfaza, 2012). *Nigella sativa* is also a good source for high carbohydrates, fats and protein (Table 1).

Table 1: Chemical constituents of *Nigella sativa* seeds (Randhawa and Al-Ghamdi, 2002).

Group	Percentage (%)
Fixed oil	32- 40
Volatile oil	0.4- 0.45
Protein	16- 19.9
Minerals	1.79- 3.74
Carbohydrates	33.9
Fiber	5.5
Water	6

The constituents of *Nigella sativa* seeds are as follows:

Carbohydrates

Monosaccharides that are in the form of glucose, mannose, xylose, and arabinose are rich in *Nigella sativa*. It also has a non-starch polysaccharide component that is a valuable source of dietary fiber (Zahoor *et al*., 2004).

Lipids

Lipids of *Nigella sativa* include fixed oils and volatile oils. The fixed oils in *Nigella sativa* seeds are divided into triglycerides and sterols:

a. Triglycerides: They are further divided into:
   i. Saturated fatty acids that are composed of myristic acid, palmitic acid, and stearic acid (Nergiz and Otles, 1993).
   ii. Unsaturated fatty acids, which are essential in the diet of humans because they cannot be synthesized by the body (Al- Gaby, 1998; Murray *et al*., 2003).

b. Sterols

   Nigella sativa is rich in sitosterol that can inhibit the absorption of dietary cholesterol (Atta, 2003). It also contains small amounts of stigmasterol, campesterol, and lanosterol (Randhawa and Al-Ghamdi, 2002). In addition, thymoquinone, dithymoquinone, thymohydroquinones, Nigellone, and thymol have also been detected in *Nigella sativa* seeds (Ghosheh *et al*., 1999).

Vitamins

Chemical analysis of *Nigella sativa* seeds has revealed that it contains carotene (Nergiz and Otles, 1993). Carotene is converted into vitamin A by the liver (Murray, Granner, Mayes, & Rodwell,). In addition, *Nigella sativa* seeds contain many other vitamins as listed in Table 2.

Table 2: Important vitamins in *Nigella sativa* seeds (Zahoor *et al*., 2004).

Vitamin	Quantity
Thiamine	15µg/g
Riboflavin	1 µg/g
Pyridoxine	5 µg/g
Folic acid	610 I.U/g
Niacin	57 µg/g

Proteins

Nigella sativa contains 15 amino acids, which make up the component of its protein, including eight of the nine essential amino acids (Zahoor *et al*., 2004). Essential amino acids cannot be synthesized by the human body and thus, it is required from diet (Murray *et al*., 2003). The seeds also contain arginine (Zahoor *et al*., 2004) that is a semi-essential amino acid because it is synthesized at a rate that is inadequate to support the growth of children (Murray *et al*., 2003).The essential amino acids in *Nigella sativa* seeds are lysine, leucine, isoleucine, valine, threonine, methionine, phenylalanine, and tyrosine. They represent 32 - 42% of total amino acids (El- Faham, 1994).

Minerals

The mineral content of *Nigella sativa* seeds is listed in Table 3.

Table 3: Some mineral contents of *Nigella sativa seeds* (Zahoor *et al*., 2004).

Mineral	Quantity
Calcium	1.859 mg/g
Phosphorus	5.265 mg/g
Iron	105 µg/g
Copper	18 µg/g
Zinc	60 µg/g

Other Chemical Constituents

Two kinds of Coumarins are mentioned: scopolamine and umbelliferon, which act as anti-coagulant (Riaz *et al*., 1996) while Drozed, Komissarenko, & Litvinenko, (1970) pointed out that the presence of 7-oxy coumarone four alkaloids were identified as constituents of the seeds of *Nigella sativa* namely Nigellidine, nigellicine, Nigellamines, and Nigellamines-N-oxide. New types of Nigellamines are Nigellamines A3, A4, A5, and C, which were isolated from methanolic extracts of Egyptian *Nigella sativa* seeds and were found to lower the triglyceride levels in primary cultured mouse hepatocytes (Atta-Ur-Rahman, Malik, Hasan, Chudhary, & Clardy, 1995; Morikawa, Xu, Ninomiya, Matsuda, & Yoshikawa, 2004).

There are still many components that have not been identified yet and research is currently going on around the world in respect to this plant (Zahoor *et al*., 2004)**.** Al-Duri, (1998) has extracted and purified lectins in *Nigella sativa* seeds by using chromatography method on column of Sefadex. Lectins in *Nigella sativa* have been found to have a hypoglycemic and hypolipidemic activity in experimentally diabetic rabbits (Bailey and Day, 1989; Al-Asadi, 2000). *Nigella sativa* also contains the saponin called steryl-glucoside (Ansari *et al*., 1988). Moreover, it is reported that there is another kind of saponin found in *Nigella sativa* called alpha-hedrin (Kumara and Huat, 2001). Saponin may be responsible for different biological activities such as having an anti-inflammatory effect (Sagesaka *et al*., 1996), decreasing blood glucose and cholesterol levels (Potter, Topping, & Oakenfull, 1979), and anti-tumor effects (De-Tommasi *et al*., 2000).

Some Biological Activities of *Nigella Sativa*

Nigella sativa has been used in recent times as a curative substance for several diseases due to its medicinal and pharmacological benefits. In addition to that, cyclooxygenase enzyme is involved in reactive oxygen intermediate reduction (OH^-, O_2^- and H_2O_2), a major cellular membrane oxidizing agent (Halliwell and Gutteridge, 1984)**.** Pharmacological studies on *Nigella sativa* have found that it possessed an analgesic properties, stimulate bronchodilation, as well as having hypolipidemic, anti-

tumor, diuretic, immunomodulation, hypotensive, anti-diabetic, histamine release inhibitor and antioxidative effects. It also has a capability to protect the liver as well as having anti-helminthic, anti-fungal (Rogozhin *et al.*, 2011), anti-bacterial (Halamova *et al.*, 2010), anti-cancer, and anti-inflammatory activities (Ayed and Talal, 2011). Houghton, Zarka, De las Heras, & Hoult, (1995) discovered that thymoquinone inhibited non-enzymatic lipid peroxidation in brain phospholipids and suggested that it has a strong inhibition of eicosanoid generation namely leukotriene B_4 and thromboxane B_2 via inhibition of both lipoxygenase and cyclooxygenase enzymes, respectively. In addition, it can also cause delay or prevention of the onset of papilloma formation. It also increases the rate of growth, both acid and alkaline phosphatase and transaminase enzymes activities (Al-Gaby, 1998). However, the capability inhibition of lipid peroxidation *in vivo* was attributed to their constituent's thymoquinone, which inhibited 5-lipoxygenase and cyclooxygenase enzymes involved in prostaglandins release (Houghton *et al*., 1995).

Medical Studies about *Nigella sativa*

Antioxidant Activity

In aerobic organisms the oxygen metabolism has obvious beneficial effects, but adverse effects of oxygen also occur because of the generation of reactive oxygen species (ROS). Most macromolecules can undergo oxidative reactions that are mediated by ROS. The adverse effects of ROS on biological systems have become a major focus of current biomedical research (Uslu *et al.*, 2003). *Nigella sativa* extracts and many of its beneficial constituent, such as thymoquinone, were shown to have protective effect against toxicities caused by anti-cancer drugs as well as some other toxins. For instance, the extract of *Nigella sativa* prevents the decrease in both haemoglobin level and leukocyte count that were induced following cisplatin therapy in mice (Nair, Salomi, Panikkae, & Panikkar, 1991). Thymoquinone is shown to have protective effect against hepatotoxicity caused by ter-butyl-hydro-peroxide (Daba and Abdel- Rahman, 1998) as well as hepatoprotective effect against the toxicity caused by carbon tetra chloride in rats (El-Dakhakhny, Barakat, El-Halim, & Aly, 2000) and mice (Nagi *et al*., 1999). From the experimental and clinical studies performed on *Nigella sativa*, it seems that most of its pharmacological actions are due to its antioxidant activity, which is mainly due to its ability to scavenge free radicals and / or inhibit lipid peroxidation (Gupta, Mazumder, Kumar, Gomathi, & Kumar, 2004). The hepatoprotective effects of *Nigella sativa* (Mahmoud, El-Abhar, & Saleh, 2002) and thymoquinone (Nagi, Alam, & Badary, 1999; Mansour, 2000; Mansour, Nagi, El-Khatib, & Al-Bekairi, 2002) were found via the antioxidant mechanism. Furthermore, thymoquinone was found to exhibit renal protective effect in rats through its antioxidant action (Badary, 1999; Badary, AI-Shabanah, Nagi, AI-Rikabi, & Elmazar, 1999).

Anti-Microbial and Anti-Parasitic Action

Suresh Kumar, Negi, & Udaya Sankar, (2010) have done several investigations on *Nigella sativa* antibacterial properties. The preliminary studies on the influences of *in vitro* antimicrobial on different stages of germinating of *Nigella sativa* extracts have shown few basic results regarding its anti-microbial effect (Al-Khalafand Ramadan, 2013). Islam, Ahmad, & Salman, (2013) proved that comparing with seed extract; the methanol extracts of *Nigella sativa* has excellent restraining influence on Gram-negative and Gram-positive clinical bacterial strains during germination phases. It can present a maximum activity from 5^{th} day to 11^{th} day of germination the compounds of isolated saponin from *Nigella sativa* (seeds) produced significant effect of inhibition on the growth of some bacteria. They include: *Staphylococcus aureus*, *Bacillus subtilis*, *Salmonella typhi*, *Klebsiella pneumoniae*, *Proteus vulgaris* and *Pseudomonas aeruginosa* (Mohammed, 2009). *Nigella sativa* oil has been provened to have an active antibacterial properties in which it works effectively on wounds

infected by bacteria that was isolated. The oil from *Nigella sativa* extract has good inhibition effects on *S. aureus* and *Streptococcus spp*. (Khuder, 2012). The study also showed that thymoquinone and thymohydroquinones have antibacterial activity, which could be potentiated by antibiotics especially in case of *S. aureus* infection (Halawani, 2009). *Nigella sativa* extracts and its constituents were widely studied due to their antimicrobial influence on a broad range of parasitic organisms, bacterial, and fungal. However, *Nigella sativa* seeds have been shown to have antiparasitic action in which the schistosomicidal properties of *Nigella sativa* seeds against *Schistosoma mansoni* (*in vitro*), showed that *Nigella sativa* has a strong biocidal effect against all stages of the parasite and revealed an inhibitory effect on egg-laying of adult female worms (Gilani, Aziz, Khurram, Chaudhary, & Iqbal, 2004; Mohamed, Metwally, & Mahmoud, 2005). Methanol extract of *Nigella sativa* seeds exhibits anti-plaque action through effectively inhibiting *Streptococcus mutans* and, therefore, avoiding dental caries (Namba *et al.*, 1985). Analysis of the plant seeds by electron spin resonance (ESR), has revealed the presence of a high content of thymohydroquinones which showed activity against *Bacillus subtilis*, *Klebsiella pneumonia*, *Mycobacteriumphlei*, and methicillin sensitive and resistant *S. aureus*. In addition, the aqueous extract has shown to exhibit an inhibitory effect against candidiasis caused by *Candida albicans*. *Nigella sativa* also has a significant adjuvant effect on the response of *Brucella melitensis* vaccine in rats (Hailat *et al.*, 1998; Mouhajir, Pedersen, Rejdali, & Towers, 1999; Khan, Ashfaq, Zuberi, Mahmood, & Gilani, 2003). The alcoholic extract of *Nigella sativa* has suppressive effect on viability of *Ecchinococcus granulosus* protoscoleces from sheep origin *in vitro* and furthermore, the alcoholic extract was found to induce the same curative effect as metronidazole in the treatment of experimental giardiasis (Sawsan and Somia, 1992; Al- Roubaee, 2006).

Analgesic and Anti-Inflammatory Effects

Al-Ghamdi, (2001) has conducted a hot plate test on rats to determine the analgesic influence of aqueous suspension of crushed seeds of *Nigella sativa*, for the anti-inflammatory effects of *Nigella* seeds. A long list of studies has been conducted and concluded that most of the anti-inflammatory effects are derived from the thymoquinone, which can be found abundantly in the seeds of *Nigella sativa*. Nevertheless, *Nigella sativa* along with its derivative products were used as a treatment for liver diseases, rheumatism as well as relevant inflammatory disorders (Al-Khalaf and Ramadan, 2013). In acute respiratory distress syndrome or acute lung injury in rat models, thymoquinone (6 mg/kg, administered intraperitoneally) treatment has shown the ability to induce lung oxygenation recovery whereas its administration together with steroids (methylprednisolone 10 mg/kg plus thymoquinone 6 mg/kg, intraperitoneally) could protect the tissue of the lung from the risky influences of intratracheal instillation of human gastric juice (pH 1.2) (El Mezayen *et al*., 2006). The effects of thymoquinone as an anti-inflammatory substance were characterized by its capability in attenuating allergic airway inflammation via the inhibition of Th2 cytokines and eosinophil infiltration into the airways (Boskabady, Mohsenpoor, & Takaloo, 2010). The occurrence of attenuation of airway inflammation is inherent to the inhibition of COX-2 (cycloocygenase-2) prostaglandin D2 production and protein expression in an allergic airway inflammation in mouse model induced with ovalbumin (Boskabady *et al*., 2010).

Anti-Cancer Effect

Nigella sativa seed along with its oil, extracts and few of its active principles, basically thymoquinone and alpha-hederin, have considerable activities *in vivo* and *in vitro* that can work against various cancers. The therapeutic activities of *Nigella sativa*, namely antioxidant and anti-inflammatory can prevent and reduce the complications of neoplasms. Subjecting the molecular structure of thymoquinone and alpha-hederin to appropriate modifications may result in safer and more effective drugs for treating the neoplastic tumors. Furthermore, *Nigella sativa* seed; in addition, to its alpha-

hederin, thymoquinone, oil or their analogs can be utilized in appropriate combinations with already recognized agents like chemotherapeutic drugs (Randhawa and Alghamdi, 2011). The potential of *Nigella sativa* as an anti-cancer agent was first reported by (El-Kadi and Kandil, 1986). In addition, thymoquinone was found to decrease the nephrotoxicity induced by cisplatin in rodents and potentiates its anti-tumor activity (Badary *et al*., 1997). A combination of compounds comprised of *Hemidesmus indicus*, *Smilax glabra*, and *Nigella sativa* is used to treat cancer patients in Sri Lanka, and has the potential to protect the liver of rats against diethylnitrosamine-induced hepatocarcinogencity (Samantha, Nalinie, Ira, Neelakanthi, Mayuri, 2003).Thymoquinone, the main constituent of the volatile oil of *Nigella sativa* seed has the potential of being a potent chemotherapeutic agent against benzo (a) pyrene-induced stomach tumors in mice (Badary *et al.*, 1999).

Effects on Multiple Systems in the Body

Urogenital System

In Unani medicine, the black seed (*Nigella sativa*) is recommended for the oligomenorrhoea treatment, therapy for infertility and for inducing menstruation (Al-jishi, 2000). El-Naggar and El-Deib, (1992) stated that the black seed crude oil of *Nigella sativa* can induce uterine contractions both *in vitro* of uterus cells in non-pregnant rat and *in vivo* for pregnant rabbits. Likewise, Keshri, Singh, Lakshmi, V. and Kamboj, (1995) reported that when given on day 1 – 10 post-coital, the hexane extract of black seed of *Nigella sativa* prevents pregnancy in rats and showed mild uterotropic activity. On the other hand, Aqel and Shaheen, (1996) stated that the black seed of *Nigella sativa* volatile oil prevents spontaneous contraction of uterine smooth muscle of guinea pigs and rat and those induced by oxytocin. Also, the fixed oil of black seed from *Nigella sativa* has been used for the treatment of pregnant rats that have oxytocin-induced contraction stimulated for 2 weeks and also suppressed Prostaglandin E2 treated with diethylstilboestrol, hence suggesting the possible use of black seed of *Nigella sativa* oil in uterine disorders related to oxytocin and prostaglandin induced increased contractility e.g. some dysmenorrhea's, habitual abortions and premature deliveries (El-Tahir *et al.*, 1999). However, these variations might be because of the different in animal species, preparation and dosage used.

Gastro-Intestinal System

The desirable effects of *Nigella sativa* have been tested on digestive system (Mahmoud *et al.*, 2002; Abdel-Sater, 2009; Hassan, Mabrouk, Shehata, & Aboelhussein, 2012). In Unani medicine, the black seed of *Nigella sativa* is used for stomach ache besides its role of being carminative, anti-jaundice, digestive and laxative (El-Kadi and Kandil, 1986). El-Dakhakhny *et al.*, (2000) examined the influence of *Nigella sativa* oil on gastric secretion and ethanol-induced ulcer in rats. They reported that there was a significant increase in mucin content and significant decrease in mucosal histamine content together with the formation of ulcer, however, with a protection ratio of 53.56%, was found in the black seed (*Nigella sativa*) oil pre-treated group.

Respiratory System

Nigella sativa seeds and its oil are usually used in Saudi Arabia, as well as in neighbouring countries for the treatment of asthma (Randhawa and Al-Ghamdi, 2002). It has been found that Nigellone effectively inhibits the histamine, which is released from mast cells (Chakravarty, 1993). Nigellone, which is an active ingredient of *Nigella sativa*, is shown to be an effective prophylactic agent in asthma and bronchitis with a higher efficacy in children than in adults (Gilani *et al*., 2004). It has been

shown that the crude extract of *Nigella sativa* seeds has a bronchodilator effect, which was found to be mediated from calcium channel blockade (Gilani, Aziz, Khurram, Chaudhary & Iqbal, 2001).

Cardiovascular System

The desirable effects of *Nigella sativa* were studied extensively on cardiovascular system (Ali and Blunden, 2003; Najmi, Haque, Naseeruddin, & Khan, 2008; Qidwai, Hamza, Qureshi, & Gilani, 2009; Tasawar, Siraj, Ahmad, & Lashari, 2011). *Nigella sativa* seed treatment also has the potential to lower the levels of serum cholesterol (Hassanin and Hassan, 1996). Other studies revealed that, in spontaneously hypertensive rats, the blood pressure could be significantly decreased by crude extract of *Nigella sativa* treatment (Zaoui *et al*., 2002). In addition, the aqueous extracts from *Nigella sativa* caused a significant reduction in heart rate and contractility of isolated heart cells in guinea pigs (Boskabady *et al*., 2005). It has been reported that the extract of *Nigella sativa* seeds produce protection on cisplatin-induced decreased in leukocyte and haemoglobin (Nair *et al*., 1991).Thymoquinone also effectively lowered the levels of cholesterol in the blood, triglycerides, high-density lipoproteins (HDL), and low-density lipoproteins (LDL) in albino rats. Bamosa, Ali, & Al-Hawsawi, 2002, studied the thymoquinone influence on the blood levels of triglycerides, High-Density Lipoproteins (HDL), Low-Density Lipoproteins (LDL) and cholesterol in albino rats. The study came with the conclusion that thymoquinone has hypocholesterolaemia effects besides its potential in reducing the effect of triglycerides and LDL (Bamosa *et al.*, 2002).

Hepatobiliary System

Investigation on the role of *Nigella sativa* for preventing carbon tetrachloride (CCl4)-induced liver toxicity has been carried out. The results showed that *Nigella sativa* oil decreased the levels of the elevated serum of liver enzymes considerably and could improve the state of oxidative stress induced by CCl4 (Ahmed, 2010). Alcoholic extract of *Nigella sativa*, on the other hand, appears to have remarkable activity to ameliorate the oxidative stress and hepatotoxicity associated with naphthalene toxicity in rats. The change in some biological markers is related to liver disease (Hamad, 2012). In similar circumstances, an investigation on the protective role of vitamin E and flavonoids of *Nigella sativa* seed have shown that they are effective against hepatic dysfunction that is caused by sodium nitrate which is manifested by structural and functional changes (Al-Okaily, Mohammed, Al-Mzain, & Khudair, 2012). Another study has also proved that the black seed of *Nigella sativa* has a protective effect against aluminum chloride induced toxicity in rabbits (Mohammed, 2010).

Nervous System

The seeds of *Nigella sativa* showed encouraging narcotic analgesic activity mediated probably over opioid receptors (Khanna, Zaidi, & Dandiya, 1993). The seeds oil showed potential analgesic effects and depressant in central nervous system (CNS). The research on the effect of the release of neurotransmitters and cultured cortical neurons exhibited a raised neurotransmitters secretion. The seeds oil modulates amino acid release in cultured neurons. As there were reduced secretion of glycine, aspartate and glutamate, there was improvement in GABA activity. All results represent the depressive and sedative influences of seed extract *Nigella sativa* (El-Naggar, Gómez-Serranillos, Palomino, Arce, & Carretero, 2010). However, repeated administration of *Nigella sativa* was also discovered to give anxiolytic activity and reduces the 5-hydroxytryptamine turnover (Perveen, Haider, Kanwal, & Haleem, 2009). Thymoquinone is the main component of seeds of *Nigella sativa*. Thymoquinone, in a research on mice, showed an anticonvulsant activity (Hosseinzadeh, and Parvardeh, 2004; Hosseinzadeh, Parvardeh, Nassiri-Asl, & Mansouri, 2005).

Immune System

By using the volatile oil in the treatment of typhoid-antigen-challenged rat, it showed an immunosuppressant action as evidenced by the significant decreased in the antibody titre and the splenocytes and neutrophils count (El-Tahir and Bakeet, 2006). The desirable effects of *Nigella sativa* have been tested widely on immune systems (Al-Ghamdi, 2001; Al-Naggar, Gómez-Serranillos, Carretero, & Villar, 2003; Alsaif, 2008). *Nigella sativa*, oil or seeds, are taken by people as a remedy for the prophylaxis of cold and asthma. According to El-Kadi and Kandil (1986), *Nigella sativa* has positive effects on the immune system and it has immune potentiating characteristics *in vitro* in human T-cells. In a similar study, Haq *et al.* (1995) concluded that T-lymphocyte could be activated by the seeds of *Nigella sativa* by production of IL-3, IL-1B and interleukin. In additional experiment, it was noted that in the purification of the proteins of the whole seeds of *Nigella sativa*it has been provened that they have suppressive and other stimulatory properties in lymphocyte culture in some proteins (Haq *et al.*, 1999).

Hematopoietic System

Al-Awadi and Gumma, (1987) described the potential of a plant mixture, which contains black seed (*Nigella sativa*), myrrh, gum olibanum, aloe and gum asafoetida used for diabetic patients in Kuwait. The black seed (*Nigella sativa*) helps to reduce the impact of sugar in the blood, in a mixture with other herbs in rats. However, the mechanism of action of *Nigella sativa* in lowering blood glucose was due to the hepatic gluconeogenesis inhibition (Al-Awadi, Fatania, & Shamte, 1991). Likewise, the volatile substance of *Nigella sativa* black seed alone showed an important hypoglycemic influence on alloxan-induced diabetic as well as normal rabbits with no changes in the level of insulin (Al-Hader *et al.*, 1993). The hypoglycemic effect of black seed (*Nigella sativa*) combined with other herbs was also reported on alloxan-induced diabetic rats (El-Shabrawy and Nada, 1996).The effect of petroleum ether extract of black seed (*Nigella sativa*) on blood coagulation was investigated by Ghoneim, El-Gindy, El-Alami, Shoukry, & Yaseen,(1982) who concluded that *Nigella sativa* has the potential in shortening the blood clotting time. This study helped to detect the important bleeding time shortening in rats.

On the other hand, black seed (*Nigella sativa*) fixed oil suppressed the aggregation of adenosine diphosphate-induced platelet in both diabetic and normal rats (El-Tahir, Al-Tahir, & Ageel, 1999). Likewise, some researchers have recently observed that the menthol soluble component of the oil of black seed (*Nigella sativa*) including 4 benzene diol, 2-(2-methoxypropyl)-5-methyl-1, caracole and thymol and eight other related compounds strongly inhibits arachidonic acid resulted in platelet aggregation. The inhibitory effect of this platelet aggregation was stronger than that of aspirin (Sayed, 1980). Black seed (*Nigella sativa*) was found to have a potential in reducing the level of both glucose and cholesterol in blood (Bamosa, Ali, & Sowayan, 1997). The only study, which has been done on human, reported a significant decrease in glucose level in blood after 7 weeks of oral ingestion of black seed (*Nigella sativa*) powder at a dose of 2 g/day (Bamosa *et al.*, 1997). Also from the same study, the levels of triglycerides and cholesterol have been decreased (on day 7 and 14) in healthy human treated twice a day with 1 gm of black seed (*Nigella sativa*) capsules. This result was then established by El-Dakhakhny *et al.*, (2000) using black seed (*Nigella sativa*) oil (800 mg/kg orally for 4 weeks) in rats documented a noticeable low density lipoprotein and triglycerides levels, decrease in total cholesterol of serum and elevation of serum high density lipoprotein level**.** Moreover, black seed of *Nigella sativa* extract was reported to prevent decline in haemoglobin levels and leukocyte count in mice (Nair *et al.*, 1991). Furthermore Al-Awadi, Khattar, & Gumaa, (1985) reported a significant decrease in blood glucose produced by a plant mixture containing black seed (*Nigella sativa*) in normal and streptozotocin-induced diabetic rats. However, when black seed (*Nigella sativa*) was used

alone it produced no effect on the blood glucose level of both normal and diabetic rats (Al-Awadi and Gumaa, 1987). Also El-Nagger and El-Dieb, (1992) reported that oral administration of powdered black seed *Nigella sativa* for three weeks produced significant reduction in blood glucose in normal and alloxan-induced diabetic rats. A plant mixture containing black seed *Nigella sativa* administered once daily at dose of 0.5 – 1.5 ml/kg body weight for one month fed to normal and diabetic rats produced significant reduction in serum glucose level only in diabetic rats (El-Shabrawy and Nada, 1996). Results of a study conducted at Egypt to detect the influence of thymoquinone (active ingredient of *Nigella sativa* seeds) on doxorubicin-induced hyperlipidemic nephropathy in rats, showed that rats treated with thymoquinone (10 mg/kg/day) for five days significantly have lower serum urea, triglycerides and total cholesterol levels (Badary *et al.*, 2000). Recently, *Nigella sativa* black seed oil in rats was found to reduce the levels of glucose, serum cholesterol and triglycerides and also platelets and leukocytes counts by 22, 15.5,16.5, 35 and 32% respectively, whereas the levels of haemoglobin and haematocrit raised by 6.4 and 17.4% respectively (Zaoui *et al.*, 2002). However, when *Nigella sativa* black seed was given to normal rats, Al-Jishi, (2000) could not find any changes in blood cells.

Reproductive System

The administration of 1ml/kg/day of *Nigella sativa* oil caused an improvement in protein synthesis of hepatic enzymes and WBCs that led to a decrease in serum cholesterol concentration (Juma and Abdulrahman, 2011). In a study evaluating the probable effect of *N. sativa* L. seed extract on reproductive organs of male albino rats, it has been revealed that the thickness of the germinal layer of seminiferous tubules increased significantly, whereas the thickness of epithelial layer that lined the tubules also decreased significantly (Mohammad, Mohamad, & Dradka, 2009). Similar studies conducted on mice showed that there was a significant increase in the weight of seminal vesicle in mice administrated with 0.3 ml of crude oil of *Nigella sativa* in comparison to control group. In reproductive organs, it has been shown that there was a significant increase in the wall thickness of testicular seminiferous tubules in mice administrated with 0.3 ml of crude oil *N. sativa*, in contrast to control group (AL-Zuhairy, 2012).Significant increase in body weight gain, reproductive parameters (seminiferous tubules thickness and diameters, account of spermatogonia, primary and secondary spermatocytes, spermatids, free spermatozoa, account of Sertoli and Leydig cells, diameter of Leydig cells and the height of epithelial cells entirely covered epididymal caudal) and hormones (testosterone and follicle stimulating hormone) was caused by treatment of alcoholic extract of black seed (Al-Sa'aidi, Al-Khuzai, & Al-Zobaydi, 2009). *Nigella sativa* oil was characterized by its anti-oxidative actions to counteract the impairment that occur in the epididymal sperm characters caused by hydrogen peroxide (H2O2) treatment (Tawfeek, 2006).

Several studies were carried out to demonstrate the effect of certain plants and herbs extract on mammalian fertility; some of these studies attributed the improvement to follicle stimulating hormone and luteinizing hormone induction level (Shih, Chiang, & Wang 1990; Tisserand and Balacs, 1995). Research on *Nigella sativa* seeds extract refer to its role of inducting the expulsion of fetal membrane after parturition and stimulate return of uterus to normal condition, without any changes of progesterone hormone concentration during the first cycle in cows treated 100 mg/kg B.W. (El-Gaafarawy, Zaki, El-Sedfy, & El-Khenawy, 2003). Akhtar *et al*., (2003) demonstrated that diet of layer hens, which contain extract of *Nigella sativa* seeds lead to increase egg production and egg size**.** Furthermore, the oil extract of *Nigella sativa* seeds caused inhibition of uterus contraction resulting from oxytocin in rats (antioxytocin effects) (Aqel and Shaheen, 1996; AL-Asadi, 2000). El-Gaafarawy *et al*., (2003) pointed that Friesian cows treated with *Nigella sativa* seeds (100 mg/kg B.W.) have elevated levels of immunoglobulins (IgG, IgM and IgA) in milk at the first day of

parturition, as well as increase of this immunoglobulin in serum of the calves. On the other hand, some researchers have found that *Nigella sativa* seeds are used for improvement of infertility in male rat (Al-Jishi and Abuo Hozaifa, 2000; Al-Mayali, 2007). They have studied the effect of alcoholic extracts of *Nigella sativa* seeds and microbial phytase enzyme on fertility of male rat treated with cadmium chloride, and noted that *Nigella sativa* extract caused enhancement of testes histological function with decrease in the sperms abnormalities. Alcoholic extracts of *Nigella sativa* lead to activation of reproductive performance in male rats with decrease of sexual desire time and increase of concentration viability of sperms and decrease of sperm abnormalities (Al-Zubiady, 2007). Furthermore, the *Nigella sativa* seeds suspension caused significant increase in ejaculation volume, sperm activities and motility with enhancement of accessory glands secretion in rams (Al-Zamily, 2008).

Conclusions

Studies have proven that the seeds of *Nigella sativa* are reasonably safe for consumption and they have potential medicinal values. The mechanisms by which the seeds of *Nigella sativa* exert their therapeutic influences is an issue that requires more detailed research. With the increased understanding of the mechanism of its bioactivity, the incorporation of this medicinal herb as complementary medicine into mainstream medical science can be achieved in the future. The beneficial effects of *Nigella sativa* were not indicative on their method of preparation (i.e ether extraction, oil) and their mode of administration (oral) as it has a high safety and efficacy towards the host.

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