

Review

A review on therapeutic potential of *Nigella sativa* (kalonji) seeds

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***Nigella sativa* name as black seed or Kalonji seed belongs to family of ranunculaceae. It is widely grown in different part of world and is an annual herb cultivated in India and Pakistan, Phytochemically; it contains fixed oil, protein, alkaloids saponin and essential oil. *N. sativa* has been reported to possess potent antioxidant, hepatoprotective, antiparasitic, anticancer, antidiabetic, antimicrobial, antiparasitic, analgesic and anti-inflammatory, anti-nociceptive, anti-ulcer, anti-histaminic etc. The present article reviews on morphology, cultivation, chemical constituent and therapeutic potential as well as clinical aspect and toxicity of *N. sativa* seed.**

Key words: *Nigella sativa*, morphology, cultivation, chemical constituents, therapeutic potential, clinical aspects and toxicity.

INTRODUCTION

Amongst the promising medicinal plant, Kalonji (*Nigella sativa*) a dicotyledonous of ranunculaceae is an amazing herb with a rich historical and religious background. The seeds of *N. sativa* are the source of the active ingredient of this plant. The actual importance of *N. sativa* to the Muslims came from the holy saying of the Prophet Mohammed "Prayers and peace be upon him" in the black seed is the medicine for every disease except death (Ghaznavi, 1991). It is the same black seed referred by Prophet Mohammed as a panacea (universal healer), that is a remedy for all ailments but cannot prevent ageing or death (Ghaznavi, 1991). Historical use of black seeds has been mentioned in various religious and ethnic books. Black seeds are identified as the curative black cumin in the holy bible; it is also described as the melanthon of Hippocrates and Dioscorides. In the Greco Arab/ Unani-Tibb system of medicine which originate from Hippocrates, his contemporary Galen and Ibn-sina has regarded black seed as a valuable remedy

in hepatic and digestive disorder. The famous book of medicine by Ibn-sina "The cannon of medicine (980-1037) revealed historical importance of this Black seeds as the seeds "That stimulates the body's energy and help recovery from fatigue (Ghaznavi, 1991; Chevallier, 1996).

Through thousand of years, until the time being, millions of people in the mediterranean region and Far East countries use the oil of *N. sativa* seeds daily as a natural protective and curative remedy. Historically, it has been recorded that *N. sativa* seeds were prescribed by ancient Egyptian and Greek physicians to treat headache, nasal congestion, toothache and intestinal worm, as well as a diuretic to promote menstruation and milk production (Hajhashemi et al., 2004). In Ayurvedic system of medicine, the seeds are given with butter-milk to obstinate hiccups and are also used in loss of appetite, vomiting, drowsy. They are also used as emmenagogue and galactagogue and as an abortifacient in large doses.

In different combinations, the seeds of *N. sativa* have

been used in obesity and dyspnoea. They have antibilious property and are administered internally in intermittent fever. Constant inhalation of fried seeds releases cold and catarrh. The seeds have also been used in mercury poisoning, sores and leprosy (Ahmad et al., 2004).

Synonym of black seeds in various languages

English: Black cumins, Love-in-a-mist.
 Arabic: Habatut Barakah; Sonez ; Habatut – sauda; Kamune-asvad.
 Hindi: Kalonji.
 Sankrit: Krishana – Jiraka.
 Persian: Siyadanah (Ahmad et al., 2004; Chevallier, 1996).

MORPHOLOGY OF THE PLANT

N. sativa is a bushy, self branching plant of about 50 to 60 cm in height. Leaves are divided into linear segment 2 to 3 cm long; they are apposite in pairs on either side of the stem. Its lower leaves are small, and petiolate and upper leaves are long. The plant has finely divided foliage and pale bluish or white flowers. The flowers grow terminally on its branches. *N. sativa* reproduces with itself and forms a fruit capsule which consist of many white trigonal seeds, once the fruit capsule has matured, it opens up and the seeds contained within are exposed to the air becoming black in colour (black seeds), seeds are triangular in shape, black in colour and possess a severe pungent smell, contains considerable amount of oil (Chevallier, 1996).

SCIENTIFIC CLASSIFICATION OF THE PLANT

Kingdom: Plantae.
 Subkingdom: Tracheobionata that is, vascular plant.
 Supervision: Spermatophyte.
 Order: Ranunculales.
 Family: Ranunculaceae-Butter cup family.
 Genera: *Nigella*.
 Species: *sativa*.

CULTIVATION AND COLLECTION

The Plant is widely grown in different part of the world and is an annual herb cultivated in India and Pakistan. *N. sativa* is cultivated during winter season in much the same way as wheat. The areas where maize, green gram or black grams are grown can be used after harvesting these crops. Before sowing the seeds, 2 to 3 times ploughing is enough for good crops and weed control.

Heavy soils need more ploughing than light soils. The seeds are sown 30 cm apart. The seeds should not be sown deep because the germination is delayed. About 12 to 15 kg seeds per hectare are sown. Three to five irrigation are required that is, presowing, seeding stage, flowering stage, and fruit formation stage and seeds development stage. Crop matures during April and May. It should be harvested early in the morning. The crop is harvested when the fruit/capsule turn yellowish. The late harvesting may result in shattering the seeds. After harvesting and proper drying it can be threshed by trampling the crop with tractor or proper thresher. After threshing, the seeds should be properly stored in bags or containers (Ahmad et al., 2004).

Chemical constituents

In view of its wide range of medicinal uses, the plant has under gone extensive phytochemical studies. *N. sativa* seeds contain 36 to 28% fixed oil, proteins, alkaloid, saponin and 0.4 to 2.5% essential oil. The fixed oil is mainly composed of unsaturated fatty acid that includes arachidonic, eicosadienoic, linoleic and linolenic acid. The saturated fatty acid present in the oil are palmitic, stearic and myristic acid (Hajhashemi et al., 2004).

The essential oil present in the seeds was analyzed by gas chromatography-mass spectrometry (GC-MS). Many components were characterized but the pharmacologically active constituent of volatile oil are thymoquinone (Figure 1a), dithymoquinone, thymol (Figure 1b) and thymohydroquinone (Figure 1c). Dithymoquinone is the dimerised form of Thymoquinone (Ghosheh et al., 1999; Hajhashemi et al., 2004). The crystalline active principle, nigellone is the only constituent of the carbonyl fraction of the oil. The other constituents of the volatile oil of the seed are p-cymene carvacrol, t-anethole, 4-terpineol and longifoline. Four alkaloids have been reported as constituent of *N. Sativa* seeds. Nigellidine (Figure 1d) and nigellimine have an indazole nucleus whereas nigellimine (Figure 1e) and N-oxide of nigellimine are isoquinolines (Atta-ur-Rehman, 1985a, b, 1995). Recently, a triterpene saponin Alfa herein was isolated from the seeds of *N. sativa*. α -heredin (Figure 1f) is known to have antitumor activity (Kumara and Haut, 2001).

The ethanolic extract of the seeds was found to contain three flavonoids namely quercetin and kaempferol 3-glucosyl (1-2) galactosyl (1-2) glucoside and quercetin -3-(6-feruloyl glucosyl) (1-2) galactosyl (1-2) glucoside (Merfort et al., 1997). Other than those triglycoside quercetin 3-glucoside, kaempferol 3-glucoside and rutin were also isolated from the seeds of *N. sativa*.

N. sativa seeds contain other ingredient including nutritional components such as carbohydrates, fats vitamins mineral elements and proteins including eight or nine essential amino acid. Fractionation of whole *N. sativa* seeds using sodium dodecyl sulfate polyacrylamide gel

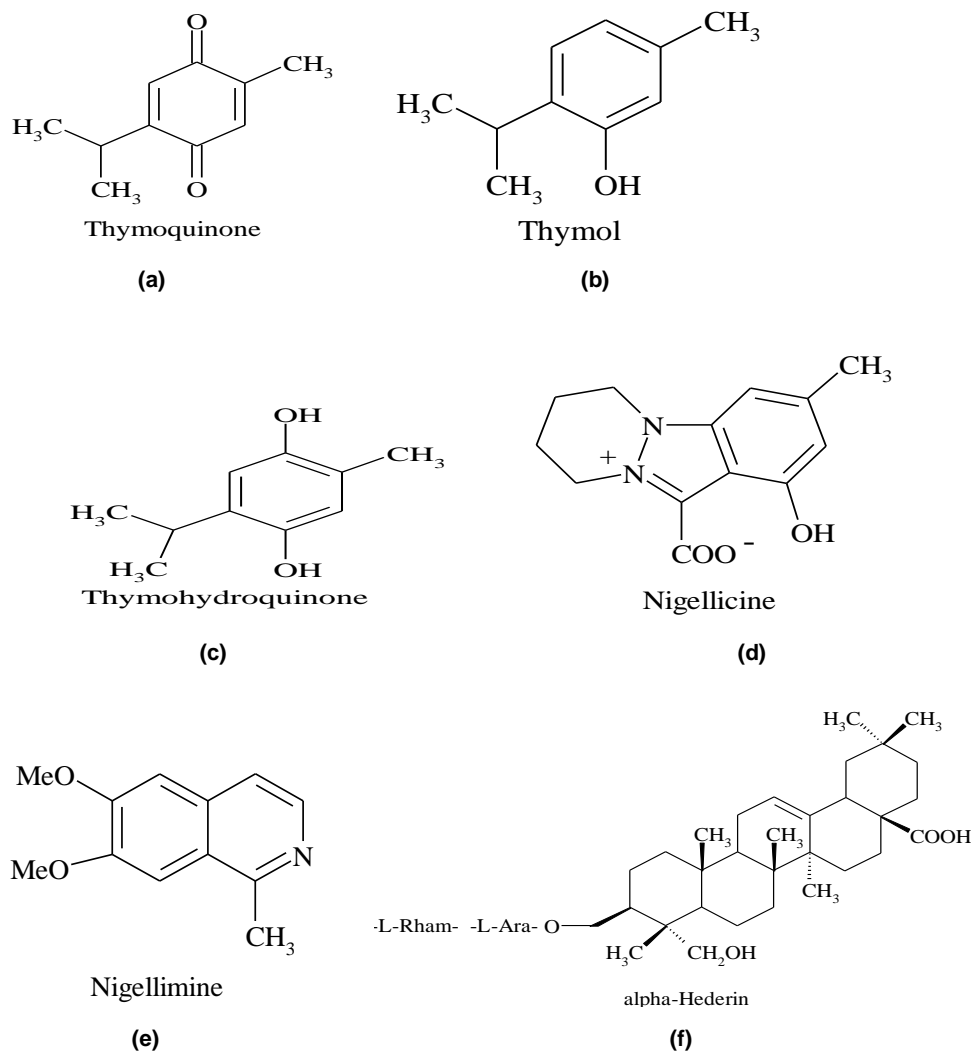


Figure 1. Chemical structure of active ingredient of *Nigella sativa* essential oil.

electrophoresis (SDS-PAGE) shows bands ranging from 94 to 100 KDa molecular mass (Haq et al., 1999). Monosaccharide in the form of glucose rhamnose, xylose and arabinose are also found. The seeds also contain carotene, which is converted by liver to vitamin A, the *N. sativa* seeds are also a source of calcium, irons and potassium (Salem et al., 2000). The summary of the all chemical composition and active principle in *N. sativa* are given in Table 1.

PHARMACOLOGICAL PROPERTIES OF *N. SATIVA* SEEDS

Many studies have been conducted particularly during the last two decades on the effect of *N. sativa* seeds extracts or its active compounds on the various body systems *in vivo* or *in vitro*. The following is the selection of some of these studies.

Antioxidant activity

Generation of free radicals may be at least partially the basis of many human diseases and conditions. Therefore the antioxidant action of *N. sativa* may explain its claimed usefulness in folk medicine. The essential oil of *N. sativa* was tested for a possible antioxidant activity. The essential oil, thymoquinone and other components like carvacrol, anethole and 4-terpineol demonstrated respectable radical scavenging property. The free radical scavenging effect of thymol, thymoquinone and dithymoquinone were studied on the reactions generating reactive oxygen species such as superoxide anion radical, hydroxyl radical and singlet oxygen using the chemiluminescence and spectrophotometer methods (Kruk et al., 2000). Thymoquinone and fixed oil of *N. sativa* were also reported to inhibit non-enzymatic peroxidation in ox brain phospholipid liposomes (Houghton et al., 1995). The antioxidant effect of thymoquinone (TQ)

Table 1. Chemical composition, including active principles, of *N. Sativa* seed.

Group	Sub-group	Components
Fixed oil (32-40 %) (Gad et al., 1963; Babayan et al., 1978; Salama 1973; Staphylakis and Gegiou 1986)	Unsaturated fatty acids	Arachidonic, eicosadienoic linoleic, linolenic, oleic and almitoleic acid. Palmitic, stearic and myristic acid. Beta-sitosterol, cycloeucaenol, cycloartenol, sterol esters and sterol glucosides
Volatile oil (0.4-0.45 %) (Enomoto et al., 2001; El-Dakhkhany 1963; Ghosheh et al., 1999)	Saturated fatty acids	Nigellone, thymoquinone, thymohydroquinone, dithymoquinone, thymol, carvacrol, α & β -pinene, d-limonene, d-citronellol, p-cymene and 2-(2-methoxypropyl)-5-methyl-1,4-benzenediol, 16-18
Proteins (Babayan et al., 1978) (16-19.9 %)*	Amino acids	Arginine, glutamic acid, leucine, lysine, methionine, tyrosine, proline and threonine, etc.13
Alkaloids (Atta-ur-Rehman et al., 1985; Atta-ur-Rehman et al., 1995)	-	Nigellicine, nigellidine, nigellimine-N-oxide
Coumarins (Atta-ur-Rehman et al., 1985; Atta-ur-Rehman et al., 1995; El-Zawahry, 1964; Drozed et al., 1973)	-	6-methoxy-coumarin, 7-hydroxy-coumarin, 7-oxy-coumarin
Saponins (Kumara and Haut 2001; Ansari et al., 1988)	Triterpenes, Steroidal	Alpha-Hedrin, Steryl-glucosides, acetyl-steryl-glucoside
Minerals (1.79-3.74 %) (El-Zawahry, 1997; Babayan et al., 1978)	-	Calcium, phosphorous, potassium, sodium and iron
Carbohydrates (33.9%) Fiber (5.5 %), Water (6 %) (Haq, et al., 1999; El-Zawahry, 1997)	-	-

and a synthetic structurally related ter-butyl thymoquinone (TBHQ) were examined *in vitro*. Interestingly, both TQ and TBHQ efficiently inhibited iron dependant microsomal lipid peroxidation in a concentration dependent manner (Badary et al., 2003).

Hepatoprotective activity

Hepatotoxicity is associated with alteration in the levels and activities of certain enzymes such as serum glutamic oxaloacetic transaminase (SGOT), serum glutamic-pyruvic transaminase (SGPT), oxidant scavenger enzymes system including glutathione (GSH), superoxide dismutase (SOD) and catalase (CAT).

The protective action of thymoquinone against the hepatotoxin: terbutyl hyderoperoxide has been demonstrated using isolated rat hepatocytes (Daba et al., 1998). In this study, the hepatoprotective activity of thymoquinone (TQ) was compared with that of silybin a known hepatoprotective agent. The mechanism of hepatoprotection of TQ is not certain but may be related to the preservation of intracellular gluathione (GSH), the depletion of which by oxidative stress is known to increase the susceptibility of cells to irreversible injury. It has also been shown that pretreatment of rats with *N. sativa* oil for 4 weeks was effective in protection against CCl_4 and D-galactosamine induced hepatic damage. No ill effects on liver function were observed when the oil was given orally at a

dose of 100 mg/kg/day for 4 weeks. In mice thymoquinone, 8 mg/kg/day for 5 days before and 1 day after CCl_4 treatment was found to protect against the biochemical and histological markers of liver damage (Nagi et al., 1991). Recently, it is also found to show protective effects against ischemia reperfusion injury on liver (Fahrettin et al., 2008).

Anti nephrotoxic activity

Administration of seed extract with cysteine, Vitamin E and *Crocus sativa* before administering the nephrotoxic drug cisplatin was effective in ameliorating the biochemical and physiological indices of nephrotoxicity (El-Dally et al., 1996).

This was also confirming with our previous results and reported results of Nephroprotective activity of *N. sativa* seed oil in nephrotoxicity induced by Cisplatin and Gentamycin (Tembhurne et al., 2008; Ali, 2004). The reason for the protective action is not certain but may be related to the antioxidant action of the drug and the fact that the nephrotoxic drug may induce its effects via generation of free radicals (El-Dally et al., 1996). Fanconi syndrome (FS) induced by ifosfamide is characterized by wasting off glucose, electrolyte and organic acids along with elevated serum creatinine and urea as well as decreased creatinine clearance rate. Administration of thymoquinone with the drinking water before and during ifosfamide treatment ameliorated the severity of ifosfamide induced renal damage and improved most of the alteration of biochemical parameters (Badary et al., 1996).

Anti cancer activity

Salomi et al. (1992) have shown that the crude methanolic extract of the seeds of this plant exhibited a strong cytotoxic action on Ehrlich ascites carcinoma, Dalton's ascites lymphoma and sarcoma 180 while exerting minimal cytotoxicity to the normal lymphocytes. In another study, the aqueous and alcoholic extract of *N. sativa* alone or in combination with H₂O₂ as an oxidative stressor were found to be effective in *in vitro* inactivating MCF-7 breast cancer cells (Farah and Begum, 2003). The antitumor effect of thymoquinone and β -elemene were investigated both *in vivo* and *in vitro* in male albino rats on fibrosarcoma induced by 20-methyl cholanthrene and it was found to inhibit tumor incidence and tumor burden significantly. The possible modes of action were discussed as its antioxidant activity and interference with DNA synthesis coupled with enhancement of detoxification process (Badary and Gamal-el-Din, 2001; Zhou et al., 2003; Gali-Muhtasib et al., 2006; Amr, 2009).

A fraction of the ethanolic extract of *N. sativa* seeds was studied in mice against intraperitoneally implanted murine P388 leukemia and subcutaneously implanted Lewis lung carcinoma cells. The life span of treated mice increased by 153% as compared to directly sulphoxide treated control mice. α -Hederin, a triterpene isolated from this fraction, produced significant tumor inhibition rates while the underline mechanism(s) of antitumor activity of hederin remained to be established. Topical application of *N. sativa* and *C. sativa* extracts inhibited two-stage skin carcinogenesis in mice induced by dimethylbenzanthracene and croton oil. The *in vivo* and *in vitro* inhibitory effect of thymoquinone against benzo (a) pyrene induced stomach carcinogenesis are also reported in mice (Salomi et al., 1991). Worthen et al. (1998) have tested *in vitro* a crude gum, a fixed oil and two purified components of the seeds thymoquinone (TQ) and dithymoquinone (DTM) for their cytotoxicity to several parental and multi-drug resistant tumor cell lines.

The gum and the oil were devoid of cytotoxicity while both TQ and DTM were cytotoxic to all of the cell lines. Both the parental cell lines and their corresponding MDR variant (that were resistant to several) standard antineoplastic drugs were equally sensitive to TQ and DTM. The study was also conducted on the structural activity relationship of 27 different analog of TQ. Among these compounds, TQ-2G, TQ-4A1 and TQ-5A1 were found to be more potent than TQ in terms of inhibition of cell growth, induction of apoptosis and modulation of transcription factor-NF- κ B. The novel analogs were also able to sensitize gemcitabine and oxaliplatin-induced apoptosis in MiaPaCa-2 (gemcitabine resistant) PC cells, which was associated with down-regulation of Bcl-2, Bcl-xL, survivin, XIAP, COX-2 and the associated Prostaglandin E₂ (Banerjee et al., 2010).

Antidiabetic activity

Al-Awadi and Gumma (1987) have reported the use of a plant mixture containing *N. sativa*, myrrh, gum, asafoetida and aloe by diabetics in Kuwait. They studied the effect of these drugs for their glucose lowering effect in rats and found it to be effective. Further studies on the plant mixture containing *N. sativa* revealed that the blood glucose lowering effect was due to the inhibition of hepatic gluconeogenesis and the plant extract mixture may prove to be useful therapeutic agent in the treatment of non-insulin dependent diabetes mellitus (Al-Awadi et al., 1991; Mohamed et al., 2009). The volatile oil of *N. sativa* alone also produced a significant hypoglycemic effect on normal and alloxan induced diabetic rabbits without changes in insulin levels (Al-Hader et al., 1993).

In a more recent study, the seed extract when given orally decreased the elevated glucose levels in alloxan induced diabetic rabbits after 2 months of treatment. Another study was designed to investigate the possible insulinotropic properties of *N. sativa* oil in streptozotocin plus nicotinamide induced diabetes mellitus in hamsters. After four weeks of treatment with *N. sativa* oil significant decrease in blood glucose level together with significant increase in serum albumin level were observed (Farah et al., 2002). The study was also confirmed for its protective effects in diabetes for crude extract and n-Hexane extract of *N. sativa* seed (Matira et al., 2008). The clinical study of *N. sativa* on 60 diabetic patients demonstrates significant improvement with reference to total cholesterol, low density lipoprotein cholesterol (LDL-C), and fasting blood glucose indicating effective as an add-on therapy in patients of insulin resistance syndrome (Najmi et al., 2008).

In another study, Nadia and Taha (2009) evaluated the effect of *N. sativa* seed oil and thymoquinone on oxidative stress and neuropathy in Streptozotocin induced diabetic rats. The results indicated to marked increase in norepinephrine and dopamine concentrations and a marked decrease in serotonin concentration compared to

the control group. These findings were partly reversed by oral administration of either NS oil or TQ.

Antimicrobial activity

The antibacterial effect of the phenolic fraction of *N. sativa* oil was first reported by Topozada et al. (1965). The extract and the oil have been reported to have a broad spectrum of activity against a number of microbes. *In vitro* antibacterial effects of the essential oil showed pronounced activity even in 1:1000 dilutions against several organisms that include *Staphylococcus albus*, *E. coli*, *Salmonella typhi*, *Vibrio cholera*. The oil was more effective against gram positive than gram negative organism. El-Kamali et al. (1998) using the plate diffusion method confirmed the report and showed that essential oil was effective against gram positive (*Bacillus subtilis* and *Staphylococcus aureus*) and gram negative bacteria (*E. coli* and *Pseudomonas aeruginosa*) the antibacterial effect was maximal when *Bacillus subtilis* was used. The oil was found to have excellent antifungal activity particularly against *Aspergillus* species. In a study using murine *cytomegalovirus* as a model intra-peritoneal administration of oil substantially decreased the viral load in liver and spleen (Salem et al., 2000).

Antiparasitic activity

N. sativa oil has been shown to possess anticestodal and antinematodal properties. In a recent study *N. sativa* oil was shown to be effective in reducing the number of *Schistosoma mansoni* worms in the liver and decreased the total number of ova deposited in both the liver and the intestine (Mahmoud et al., 2002; ElShenawy et al., 2008). *Nigella* has also recently been shown to be effective against other helminths such as *Hymenolepis nana* (Ayaz et al., 2007). It performs this function by augmenting host immunity. Similar protective effects were seen against other worms such as *Trichinella spiralis* and *Aspiculuris* (AbuEIEzz, 2005).

Antimalarial

Various extracts of *N. sativa* found to show antiplasmodial activity against both *in vivo* and *in vitro* plasmodia infections. It shows 100% inhibition of the parasite growth (*Plasmodium falciparum*) at concentration 50 ug/ml. *N. sativa* shows dose dependant activity against parasite (Abdulelah et al., 2007; El-Hadi et al., 2010).

Analgesic and Anti-inflammatory activity

Houghton et al. (1995) reported that crude fixed oil of *N. sativa* and an active principle thymoquinone (TQ) inhibits cyclooxygenase and 5-lipoxygenase pathway of arachi-

donate metabolism in rat peritoneal leukocytes. The effect was demonstrated via the dose dependant inhibition of the formation of thromboxane B₂ and leukotrienes B₄. This effect was later confirmed in experimental animal studies conducted using aqueous suspension of *N. sativa* crushed seed by Al-Ghamdi (2001). In this study, formation of edema in rat hind paw was inhibited and these effects were comparable with Aspirin used as a standard anti-inflammatory drug. Khanna et al. (1993) using three antinociceptive tests in rats and mice (hotplates test, tail pinched test, acetic acid induced writhing) conclude that the fixed oil of the seeds is endowed with strong antinociceptive actions and these actions were due to an opioid principle in the oil as they were antagonized by naloxone. Abdel Fattah et al. (2000) have used four different models of analgesia (hot plate test, tail pinched test, acetic acid induced writhing and formalin induced pain) for studying the analgesic activity of the drug. The mechanism of anti-inflammatory and analgesic effect seems to be related to the inhibition of eicosanoid synthesis as suggested by the study of Houghton et al. (1995).

Antinociceptive effects

Study showed that the oral administration of *N. sativa* oil extracted from Egyptian *N. sativa* seeds produces a suppressive effect on nociceptive responses caused by thermal, mechanical and chemical nociceptive stimuli in mice, and that the antinociceptive effect of *N. sativa* oil is partly attributable to its component, thymoquinone. It also revealed that at least the supraspinal opioid systems are involved in the antinociceptive effect of thymoquinone (Abdel Fattah et al., 2000; Al-Shebani and Al-Tahan, 2009).

Anti-ulcer activity

The aqueous extract of *N. sativa* seeds was effective in reducing the ulcer index induced by Aspirin by about 36% (Raj Kapoor et al., 1996). In other study oil of seed of *N. sativa* found to show protective effects on the formation of stress gastritis in hypothyroidal rats (Khaled et al., 2009). Recent clinical study is also supported with eradication of *Helicobacter pylori* in patient with non-ulcer dyspepsia (Salem et al., 2010).

Anti-histaminic action

The antihistaminic effect was first investigated by El-Dakhkhany et al. (1982) who reported the protective action of thymoquinone and carbonyl fraction of *N. sativa* against histamine-induced bronchospasm in guinea pigs. Furthermore, an *in vitro* study demonstrated that

nigellone, isolated from *N. sativa*, effectively inhibited the release of histamine from mast cells, possibly through decrease in intracellular calcium and inhibition of protein kinase C (Chakarvarti et al., 1993). These effects together with analgesic and anti-inflammatory actions, perhaps can be correlated with the use of *N. sativa* in eczema and asthma, for scorpion and spider stings and for the bites of cat, dog and snake, recommended in the folk medicine (Al-Jishi et al., 2003).

Effect on cardiovascular system

N. sativa alone or in combination with honey or garlic are promoted for the treatment of hypertension which drew the attention of El-Tahir et al. (1993) to investigate the action of the volatile oil of *N. sativa* and its active constituent thymoquinone on the arterial blood pressure and heart of anaesthetized rats. Both agents produce a dose dependent decrease in the arterial blood pressure and heart rates. These effects were significantly antagonized by atropine, cyproheptadiene and hexamethonium. This suggests that these effects were centrally antagonized mainly via the involvement of 5-hydroxy tryptaminergic and muscarinic mechanism. Oral dose of 0.6 ml/kg/day of *N. sativa* extract produced a significant hypotensive effect in spontaneously hypertensive rats. These findings were significantly comparable with the standard anti-hypertensive drug nifedipine (Zaoui et al., 2002). The effect of the drug was concluded to be partially due to its diuretic effect which was comparable to 0.5 mg/kg/day furosemide. In one of study, two-month dietary supplementation with *N. sativa* extract to normal rats has shown a homogenous cardiac hypertrophy and enhanced cardiac contractility at baseline conditions. The hearts of *Nigella*-treated rats developed a moderate but significant hypertrophy that was evident by an increase in the heart weight to body weight ratio. The observed *Nigella*-induced cardiac hypertrophy was associated with an increase in the baseline cardiac inotropic properties (Yar et al., 2008).

Antihyperlipedemic effects

Seeds of *N. sativa* were evaluated in several animals' models for lipid lowering activity in which orally administered extract of seed showed promising activity. It reduces the serum cholesterol and lipoprotein level significantly (Le et al., 2004; El Dakha Khani et al., 2000; Muhammad et al., 2007; Khadiga et al., 2009; Bahram et al., 2009; Ghanya et al., 2010). The study was also conducted on human being by administering the powder of seeds of *N. sativa* before breakfast for two months and was found to reduce the total cholesterol, triglycerides, LDL-cholesterol to a highly significant extent (Inayat et al., 2009; Datau et al., 2010).

Effect on gastro-intestinal tract

In Unani medicine *N. sativa* is used for stomachache and as a digestive, carminative, laxative and anti-jaundice (Chopra et al., 1956). Oral *N. sativa* powder was reported to relieve flatulence. While Nigellone, an active principle of *N. sativa* was found to antagonize histamine induced contractions of guinea pig intestine. In addition, to this a choleric effect of *N. sativa* oil and its active principles (thymoquinone, thymohydroquinone and dithymoquinone) reported, respectively (Mahfouz and El-Dakhakhany, 1960). El-Dakhakhani et al. (1965, 2000) investigated the effect of *N. sativa* oil on gastric secretion and ethanol-induced ulcer in rats. Reported to significant increase in mucin content, glutathione level as well as a significant decrease in mucosal histamine content and ulcer formation, with a protection ratio of 53.56%, was found in the *N. sativa* oil pretreated group. More recently, the crude extract of *N. sativa* was shown to cause a dose dependent (0.1 to 3.0 mg/ml) relaxation of spontaneous contractions of rabbit jejunum as well as inhibition of K⁺-induced contractions in a similar dose range, suggestive of calcium channel blockade (Gilani et al., 2001). Recently, Abdel-Sater (2009) investigated the protective effects of *N. sativa* on hypothyroidism induced development of acute cold restraint stress gastritis in rats.

Effect on respiratory system

El-Tahir et al. (1993) reported that volatile oil of *N. sativa* seeds produce dose dependent increases in the respiratory rate and intratracheal pressure of guinea pig. When the study was conducted only using thymoquinone, in the active principle of volatile, it was found that it only increased the intratracheal pressure without having a significant effect on the respiratory rate, thus the author suggest that volatile oil could be used as potential respiratory stimulant if thymoquinone is removed from the oil. Thus the oil then can be used in Asthma. Gilani et al. (2001) studied the effect of a crude extract of *N. sativa* seed on isolated rabbit jejunum and guinea pig tracheal preparation. The extract was found a dose dependant relaxation of spontaneous contraction in the rabbit jejunum and inhibition of KCl induced contractions. These actions were similar to those produced by verapamil, a Ca⁺⁺ - channel antagonist. The above pharmacological activities of the petroleum ether fraction of the extract were about 10 times higher than those of the crude extract. In an *in vitro* experiment carried out by Chakravarti et al. (1993) it is suggest that nigellone, a carbonyl polymer of thymoquinone isolated from seeds of *N. sativa* was found to inhibit effectively the histamine release from the mast cells thus showing the basis for its traditional use in Asthma. The results of clinical study of *N. sativa* conducted in children showed to manage the wheeze associated with lower respiratory tract illness

(Jameel et al., 2009). In another clinical study on forty (40) chemical war victims, Mohammad and Javed (2008) investigated the effect of *N. sativa* on respiratory symptoms. They were recorded symptoms score in three different visits and found significant improvement in all respiratory symptoms score and wheezing in second and third visits compared to first visits.

Effect on nervous system

N. sativa seeds revealed promising narcotic analgesic activity mediated possibly through opioid receptors (Khanna et al., 1993). The oil from the seeds exhibited central nervous system (CNS) depressant and potential analgesic effect. It was also found to potentiate pentobarbitone induced sleeping time. The study conducted on cultured cortical neurons and influence of neurotransmitters release showed to indicate increased secretion of neurotransmitters. It also modulates amino acid release in cultured neurons. There was increased in GABA activity while secretion of glutamate, aspartate and glycine was found to decrease. All the results represented the sedative and depressive effects of *N. sativa* seed extract (Tarek et al., 2010). Repeated administration of *N. sativa* was also found to decrease the turnover of 5HT and produces anxiolytics activity (Perveen et al., 2009). Thymoquinone is the major constituent of *N. sativa* seeds. In one of the study conducted in mice, thymoquinone reported to show the anticonvulsant activity (Hosseinzadeh et al., 2004; Hosseinzadeh et al., 2005).

Effect on immune system

As a natural remedy, people take *N. sativa* seeds or oil is a promoter of good health and for the prophylaxis of common cold and Asthama. In view of that, El-Kadi et al. (1986) investigated the effect of *N. sativa* on immune system and found that the drug has immuno potentiating properties in human T-cells *in vitro*. This was confirmed by Haq et al. (1995) who showed that *N. sativa* seeds activate T-lymphocyte to secrete the interleukin, IL-3 and IL-1B production. In further experiment, they purified the proteins in the whole *N. sativa* seeds and it should be noted that some proteins have suppressive and others have stimulatory properties in lymphocyte culture (Haq et al., 1999).

Effect on genitourinary system

The study showed that the volatile oil of *N. sativa* inhibited spontaneous contraction of rats guinea pig uterine smooth muscle induced by oxytocin (Aqel et al., 1996). It was also reported that *N. sativa* crude oil

induced uterine contractions both *in vivo* in pregnant rabbits and *in vitro* of non-pregnant rat uteri (El-Naggar and El-Deib, 1992). Similarly, it was found that the hexane extract of *N. sativa* exhibited mild uterotropic activity and prevented pregnancy in rats when given on day 1 to 10 post-coitum (Keshri et al., 1995).

Effect on reproductive system

Sixty days study of *N. sativa* seeds shows to increase in the weight of reproductive organs, sperm motility and count in cauda epididymides and testicular ducts. Spermatogenesis was found to increase at primary and secondary spermatocyte. While in fertility, there was increase in number of female pregnant rats (Mukhallad et al., 2009; Al-Sa'aidi et al., 2009).

Effect on blood

In view of that the petroleum ether extract of *N. sativa* was studied for its action on blood coagulation and was reported to shorten the whole blood clotting time, plasma clot time and kaolin-cephalin clotting time of male rabbits when compared to control. In addition, a significant shortening of bleeding time in rats was also observed. However, there were no significant effects on the thrombin time or prothrombin time but the partial thromboplastin time was shortened while euglobulin time was prolonged (Ghoneim et al., 1982).

TOXICOLOGICAL REPORT

The seed extract and its constituent appear to have a low level of toxicity. The toxicity of fixed oil (10 ml/kg for 12 weeks) of *N. sativa* seeds in mice and rats were investigated through the determination, of LD₅₀ values and examination of possible biochemical, hematological and histopathological changes. The low toxicity of *N. sativa* fixed oil was evidenced by high LD₅₀ values (11.915 ml/kg), key hepatic enzyme stability and organ integrity values. This suggests a wide margin of safety for therapeutic doses of fixed oil and *N. sativa* seeds. The LD₅₀ value of thymoquinone was found to be 2.4 g/kg. Inclusion of thymoquinone in the drinking water of mice at concentration of 0.03% for 90 days resulted in no signs of toxicity except for significant decrease in fasting plasma glucose concentration (Zaoui et al., 2002).

In a recent study of diazinon induced organ toxicity, with *N. sativa* seeds extract given orally for three and six weeks, the study observed attenuated extensive changes of hematological and biochemical parameters in diazinon-treated rats. Based upon these results, they suggested *N. sativa* seeds can be considered as a promising therapeutic agent against hematotoxicity, immunotoxicity,

hepatotoxicity, nephrotoxicity and cardiotoxicity induced by diazinon and may be against other chemical pollutants, environmental contaminants and pathogenic factors (Atef and Wafa, 2010). Some other studies also demonstrate that treatment with *N. sativa* resulted in significant decrease of haematological disorders induced by aflatoxin (Abdel-Wahhab and Aly, 2005) and cadmium (Demir et al., 2006). No remarkable pathological changes were recorded in bone marrow of animals treated with suspension of *N. sativa* in carbon tetrachloride induced bone marrow toxicity (Abou et al., 2007).

CONCLUSION

N. sativa seed and its components are frequently used as a natural remedy for many ailments. A lot of work has been done to evaluate the pharmacological basis of these uses. Most studies confirm its value in folk medicine as analgesic, anti-inflammatory, anti-oxidant, and anti-cancer, anti-microbial, anti-parasitic, antihypertensive and as an immune stimulant. However, controversial results have been reported for its effect on the respiratory system, blood coagulation and uterine motility. More work is needed to determine the pharmacokinetics, biochemical, pharmacodynamic and therapeutics of active components and their interactions with modern drugs and importance to human health with sufficient detail. The ethnobotanical approach, if combined with biochemical or physiological methods, would provide useful pharmacological leads.

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