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Therapeutic use of *Nigella sativa*: A review

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Abstract

Nigella sativa also called prophetic medicine. Prophet Muhammad (Peace Be Upon on Him) recommended and used it to maintain health. Although the seeds of cumin (*Cuminum cyminum* L.) are widely used as a spice for their distinctive aroma, they are also commonly used in traditional medicine to treat a variety of diseases. The literature presents ample evidence for the biomedical activities of cumin, which have generally been ascribed to its bioactive constituents such as terpenes, phenols, and flavonoids. Those health effects of cumin seeds that are experimentally validated are discussed in this review. Numerous pre-clinical and clinical trials have investigated its efficacy using the seed oil, essential oil, and its main constituent thymoquinone (TQ). These investigations support its use either independently or as an adjunct along with conventional drugs in respiratory problems, allergic rhinitis, dyspepsia, metabolic syndrome, diabetes mellitus, inflammatory diseases, and different types of human cancer. Multiple studies made in the last decades validate its health beneficial effects particularly in diabetes, dyslipidemia, hypertension, respiratory disorders, inflammatory diseases, and cancer. *Nigella sativa* seeds also possess immune stimulatory, gastroprotective, hepatoprotective, nephroprotective, and neuroprotective activities. TQ is the most abundant constituent of volatile oil of *N. sativa* seeds, and most of the medicinal properties of *N. sativa* are attributed mainly to TQ. All the available evidence suggests that TQ should be developed as a novel drug in clinical trials.

Keywords: medicine, traditional, thymoquinone, diabetes, evidence

1. Introduction

Nigella sativa 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) [47]. 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) [47]. 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 melanthion of Hippocrates. 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) [87, 21]. 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) [50].

2. Synonym of black seeds in various languages

English: Black cumins, Love-in-a-mist.

Arabic: Habatut Barakah; Sonez ; Habatut – sauda; Kamune-asvad.

Hindi: Kalonji.

Sanskrit: Krishana – Jiraka.

Persian: Siyadanah (Ahmad *et al.*, 2004; Chevallier, 1996) [5, 21].

3. Morphology of the plant

N. sativa is a braky, 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) [21].

4. Scientific classification of the plant

Kingdom: Plantae.

Subkingdom: Tracheobionata that is, vascular plant.

Supervision: Spermatophyte.

Order: Ranunculaceae.

Family: Ranunculaceae-Butter cup family.

Genera: *Nigella*.

Species: *sativa*

5. Chemical constituents

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) [50]. 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. Dithymoquinone is the dimerised form of Thymoquinone (Ghosheh *et al.*, 1999; Hajhashemi *et al.*, 2004) [48, 50]. 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 and nigellidine have an indazole nucleus whereas nigellimine and N-oxide of nigellimine are isoquinolines (Atta-ur-Rehman, 1985a, b, 1995) [14, 15]. Recently, a triterpene saponin Alfa herein was isolated from the seeds of *N. sativa*. α -heredin is known to have antitumor activity (Kumara and Haut, 2001) [64, 65].

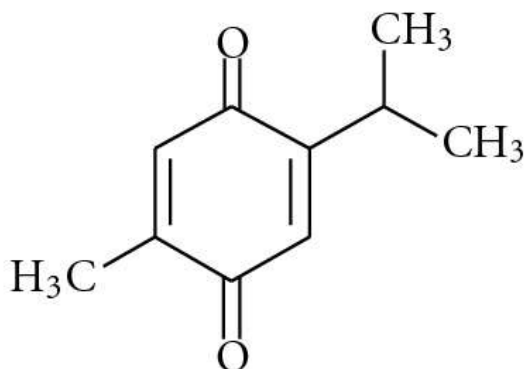


Fig 1a: (Thymoquinone)

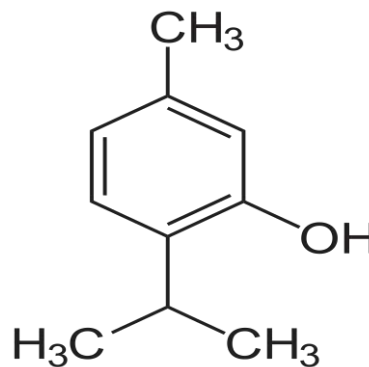


Fig 1b: (Thymol)

6. Pharmacological activity

There are 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.

6.1. Antioxidant activity

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) [63]. Thymoquinone and fixed oil of *N. sativa* were also reported to inhibit non-enzymatic peroxidation in ox brain phospholipid liposomes (Houghton *et al.*, 1995) [55]. The antioxidant effect of thymoquinone (TQ) 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) [18, 19].

6.2. Hepatoprotective activity

The protective action of thymoquinone against the hepatotoxin: terbutyl hyderoperoxide has been demonstrated using isolated rat hepatocytes (Daba *et al.*, 1998) [23]. 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.

6.3. Anti-nephrotoxic activity

Administration of seed extract with cysteine, Vitamin E and *Crocus sativa* before administrating the nephrotoxic drug cisplatin was effective in ameliorating the biochemical and physiological indices of nephrotoxicity (El-Dally *et al.*, 1996) [31]. 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) [84, 10]. 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) [31]. 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) [18, 19].

6.4. Antidiabetic activity

Al-Awadi and Gumma (1987) [7] have reported the use of a plant mixture containing *N. sativa*, myrrh, gum, asafetida 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) [6].

6.5. Antimicrobial activity

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) [34] 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 intraperitoneal administration of oil substantially decreased the viral load in liver and spleen (Salem *et al.*, 2000) [79].

6.6. 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 (El-Hadi *et al.*, 2010) [32].

6.7. Analgesic and Anti-inflammatory activity

Houghton *et al.* (1995) [55] reported that crude fixed oil of *N. sativa* and an active principle thymoquinone (TQ) inhibits cyclooxygenase and 5-lipoxygenase pathway of arachidonate 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) [8]. 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 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. In a study 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) [55].

6.8. 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.

6.9. Anti-ulcer activity

The aqueous extract of *N. sativa* seeds was effective in reducing the ulcer index induced by Aspirin by about 36% (Rajkapoor *et al.*, 1996) [77]. 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) [60]. Recent clinical study is also supported with eradication of *Helicobacter pylori* in patient with non-ulcer dyspepsia (Salem *et al.*, 2010) [79].

6.10. Anti-histaminic action

The antihistaminic effect was first investigated by ElDakhkhany *et al.* (1982) [32] 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) [20]. 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) [11].

6.11. 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) [37, 38] 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) [88, 89]. 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) [87].

6.12. 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) [22]. 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 ElDakhkhany, 1960) [67]. El-Dakhkhani *et al.* (1965, 2000) [27, 28] 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) [49]. Recently, Abdel-Sater (2009) [1] investigated the protective effects of *N. sativa* on hypothyroidism induced development of acute cold restraint stress gastritis in rats.

6.13. 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) [33] 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) [51] 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) [52, 53].

6.14. 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) [72, 12].

6.15. 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) [88, 89]. 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 diazinontreated 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) [13]. Some other studies also demonstrate that treatment with *N. sativa* resulted in significant decrease of haematological disorders induced by aflatoxin and cadmium (Demir *et al.*, 2006) [25]. 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) [3].

7. Conclusion

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.

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