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MEDICINAL PROPERTIES OF *NIGELLA SATIVA* (KALONJI)

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ABSTRACT

Seeds of *Nigella sativa* (*N. sativa*) have been frequently used in folk medicine for several medicinal purposes including to treat cough, asthama, diarrhoea, fever, common cold, headache, rheumatic disease, stomach disorders, dyslipidaemia, infections and to expel worms from the intestine. It is also effective for scorpion and spider strings and bites of snake, cat and dog. Seeds of *N. sativa* have also hypoglycemic, antioxidant, antihistaminic and anti-inflammatory effects. Recently, antibacterial, antiviral, antifungal, antiparasitic, antiprotozoal, and anticancer properties of seeds of *N. sativa* have also been established. Nigellon, thymohydroquinone (THQ), thymoquinone and thymol (THY) are its active ingredients which are responsible for its therapeutic effects. *N. sativa* also contains carbohydrates, fats, vitamins, mineral elements, essential amino acids and proteins. The seeds of *N. sativa* can be poisonous to man in high doses.

Key words: *Nigella sativa*, thymohydroquinone (THQ), thymoquinone (TQ), thymol (THY), antibacterial, hypoglycemic.

INTRODUCTION

Nigella sativa L. is a dicotyledonous herb of family Ranunculaceae. Its seeds are commonly named as black seeds, black caraway, black cumin or black onion seeds in European countries. In Indo-Pak region it is commonly known as kalonji. Different forms of *N. sativa* (as a herb, seed oil and aqueous/alcohlic extracts) have been used for medicinal purposes to treat wide range of illnesses including cough, fever, common cold, bronchial asthma, respiratory oppression, flatulence, toothaches, headache, diarrhea, dyslipidemia, rheumatic and other allergic diseases and for menstrual irregularities (Ali and Blunden, 2003; Boskabady and Shahabi, 2004). Its medicinal significance is reviewed here in the light of recent studies conducted worldwide.

CHEMICAL COMPOSITION

Chemical composition of *N. sativa* seeds showed 32-40% fixed oils, 0.4-0.45% volatile oils, 16-19.9% proteins, 1.79-3.74% minerals (calcium, phosphorus, potassium, sodium and iron), 33.9% carbohydrates (glucose, rhamnose, xylose, and arabinose), 5.5% fiber and 6% water (Randhawa and Al Ghamdi, 2002). Nigellicine, nigellidine and nigellimine-N-oxide are important alkaloids of *N.sativa* (Randhawa and Al Ghamdi, 2002). Principle therapeutic ingredients of *N. sativa* oil obtained by HPLC were found to be thymoquinone, and dithymoquinone (Omar *et al*., 1999). Fixed oil of *N. sativa* as extracted with petroleum ether have 17% saturated and 82.5% unsaturated fats including 55.6% linoleic acid, 23.4% oleic acid and 12.5% palmitic acid (Nickavar *et al.*, 2003). *N. sativa* seeds are also the important source of some essential amino acids (methionine, tyrosine, leucine and lysine) (Chun *et al*., 2002) and phospholipids (phosphatidylcholine, phosphatidylethanolamine, phosphatidylserine, and phosphatitdylinositol) (El-Mahmoudy *et al*., 2002).

ANTIOXIDANT ACTIVITIES

Thymoquinone (TQ) which is a principle constituent of volatile *N. sativa* seed oil has potent superoxide anion scavanger activity. Badary *et al.* (2003) observed that TQ can inhibit iron dependent microsomal lipid peroxidation *in vitro*. In a study (El-Mahmoudy *et al*., 2002), TQ treatment to rat peritoneal macrophages showed dose dependent reduction in nitirte production and protein levels of inducible nitric oxide synthetase (iNOS) in macrophages and inhibition of increased expression of iNOS mRNA induced by lipopolysaccharides. In a study on CCl_4 treated rabbits, *N. sativa* oil treatement showed less parenchymal necrosis by improving cellular antioxidant status (Turkdogan *et al*., 2001). Oral consumption of *N. sativa* oil also prevents gentamicin-induced proximal tubular damage in rats and improves total antioxidant status (TAS) and glutathione (GSH) contents in kidney cortex (Ali, 2004). Yildiz *et al*. (2009) showed that intraperitoneal administration of *N. sativa* prevents ischemic reperfusion injury in rat liver. TQ showed hepatoprotective activity in isolated rat hepatocytes against tetrabutyl hydroperoxide toxicity by improving hepatic GSH contents and cell viability and by decreasing leakage of cytosolic enzymes (Daba and Abdel-Rahman, 1998). *N. sativa* oil administration in cyclosporin treated rats also showed protective effects on renal function and morphology (Uz *et al*., 2008). Ingestion of 10mg/Kg of body weight /day TQ in

drinking water significantly decreased serum levels of lactate dehydrogenase and creatine phosphokinase in doxorubicin treated rats and this cardioprotective effect of TQ may be because of its antioxidant property (Nagi and Mansour, 2000).

IMMUNOMODULATORY ACTIVITES

Immunomodulatory effects of *N. sativa* and some of its active constituents have been reported in many research studies. El-Kadi and Kandil (1986) suggested that regular consumption of *N. sativa* oil for four weeks in humans can improve immune responses with 30% increase in natural killer cells and 55% increase in CD4+ and CD8+ T cells ratio. The immunomodulatory effects of *N. sativa* were different for cellular and humoral immune responses. Islam *et al.* (2004) observed that consumption of *N. sativa* oil reduced antibody production in typhoid vaccinated rats as compared to control animals. In a recent study of Massadeh *et al*. (2007) this immunosuppressive effects of *N. sativa* were observed only at higher doses of 5-10 mg/ml in cadmium–lead mixture exposed mice. On the other hand studies involving T-cell mediated immune responses showed immunostimulatory effects of *N. sativa*. Abuharfeil *et al.* (2001) in his study showed that the number and cytotoxicity of splenic natural killer (NK) cells to YAC-1tumor targets increased with oral administration (1 week) of *N. sativa* seed extract in mice. In diabetic hamsters, Fararh *et al.* (2004) also reported similar effects of oral *N. sativa* oil administration on macrophage phagocytic activity and lymphocyte count. Based on these *in vitro* and *in vivo* studies it is now confirmed that *N. sativa* and its active constituents enhance cellular immunity but reduce humoral immune responses.

N. sativa also modulates cytokine production in both humans and animal models. In a study, Haq *et al*. (1995) demonstrated that production of IL-3 and IL-1 were increased by lymphocytes when they were incubated with or without allogenic cells but no effect was observed on the production of IL-2 and IL-4**.** However, it was found that fractionated *N. sativa* proteins were less effective in modulating the secretion of IL 8 as compared to whole *N. sativa* (Haq *et al*., 1999).

ANTIINFLAMMATORY EFFECTS

Antiinflammatory and antihistaminic property of *N. sativa* oil makes its use popular for the treatment of joint pain and stiffness. Al-Ghamdi (2001) observed anti-inflammatory and analgesic activity of aqueous extract of *N. sativa* with inhibitory effect on carrageenan induced paw edema in rats. In a study carried out by Hajhashemi *et al*. (2004), it was observed that only intraperitoneal administration of *N. sativa* seed essential oil inhibited carrageenan-induced paw edema and croton oil-induced ear edema. It was concluded that its essential oil has significant analgesic activity, as observed by acetic acid induced writhing and formalin and light tail flick tests and naloxone failure to antagonize this effect. Similar results were obtained by Ghannadi *et al*. (2005) with *N. sativa* polyphenols in mice and rats.

ANTIALLERGIC EFFECTS

In traditional medicine (Unani, Ayurvedic) *N. sativa* seed oil effectively been used for the treatment of different allergies. In a study by Kalus *et al*. (2003) on patients of allergic rhinitis, eczema and bronchial asthma, beneficial effects of *N. sativa* seed oil were observed on the severity of symptoms with decreased eosinophil count, Ig E and cortisol levels in plasma and urine. Antihistaminic effects of *N. sativa* extract on tracheal chains were also observed by Boskabady *et al*. (2004) in guinea pigs. In another study by El-Dakhakhny *et al.* (2000) decreased histamine content were observed in gastric ulcer rat models with *N. sativa* oil administration. El-Gazzar *et al*. (2006) showed that TQ supplementation in ovalbumin sensitized mice inhibited 5-lipoxygenase enzyme and in turn leukotriene biosynthesis was inhibited which is important for inflammatory phenomenon of allergic asthma.

EFFECTS ON THE RESPIRATORY SYSTEM

The studies of Badar-ud-Din (1960) and Mahfouz and El-Dakhakhany (1960) showed strong prophylactic activity of *N. sativa* against asthma and bronchitis in both children and adults due to an active constituent was found to be the nigellone. In urethane anesthetized guinea pigs intravenous administration of volatile oil of *N. sativa* produced dose dependent increase in intratracheal pressure and respiratory rate via direct activation of histaminergic pathways (El-Tahir *et al*., 1993). Later (Boskabady *et al*., 2008) it was noticed that aqueous extracts of *N. sativa* and its methanol and dichloromethane fractions has relaxant effect on methacholine precontracted guinea pig tracheal chains. Crude *N. sativa* seed extract also showed similar effects on guinea pig tracheal preparations and they were mediated by calcium channel blockade activity of the organic fractions of extracts (Gilani *et al*., 2001). In one of the human based study on chemical war victims, 0.375 ml/Kg administration of 50% aqueous decoction of *N. sativa* seeds showed improvement in respiratory symptoms, chest wheezing and pulmonary function test values after 2 months treatment (Boskabady and Farhadi, 2008). In a similar study on guinea pigs exposed to sulfur mustard gas *N.*

sativa administration showed protective effects on tracheal responsiveness to methacholine and lung inflammation (Hossein *et al*., 2008).

EFFECT ON REPRODUCTIVE SYSTEM

In folk medicie *N. sativa* has a long history of usage for many ailments of female reproductive system including dysmenorrhea, irregular menstrual cycle and insufficient lactation (Al-Jishi, 2000). In a study on dairy Ewes, Saleh (2005) showed that 5g /day administration of *N. sativa* seeds improved body condition and lactation during experimental period. *N. sativa* administration improves sperm motility and therefore is useful in treating male infertility. In an *in vitro* study carried out by Riad *et al*. (2006) addition of *N. sativa* extract to extended rabbit semen significantly improved in sperm motility and viability and reduced the percentage of acrosome damages and dead spermatozoa. Oral administration of 0.5 ml/day *N. sativa* oil in normal and hyperlipidemic male rats for 2 months showed significant increase in testosterone level, seminal vesicle weight and sperm count (Bashandy, 2007).

EFFECTS ON GASTROINTESTINAL TRACT

N. sativa seeds have long been used for the treatment of constipation, indigestion, stomachache and jaundice (El-Kadi and Kandil, 1986). El-Dakhakhany *et al*. (2000) observed protective effect of *N. sativa* oil consumption on ethanol induced ulcers in rats with significant increase of mucin and glutathione contents and with the decrease of mucosal histamine concentration. Antiulcer effect of both *N. sativa* oil and TQ was reported in male albino rats with alcohol induced gastric mucosal injury (Kanter *et al*., 2005). *N. sativa* oil ingestion also found to be hepatoprotective in *Schistosomiasis mansoni* infected mice with improvement in serum levels of alanine amino transferase, gamma glutamyl transferase and alkaline phosphatase. These effects were attributed to the antioxidant properties of *N. sativa* and its active constituents (Mahmoud *et al*., 2002).

EFFECTS ON CARDIOVASCULAR SYSTEM

Hypotensive and cardioprotective effects of *N. sativa* oil and its constituents have been confirmed through many animal based studies. In a study on urethane-anesthetized rats El-Tahir *et al*. (1993) reported that heart rate and arterial blood pressure were decreased by intravenous administration of volatile oil of *N. sativa*. In another study, similar hypotensive effects were observed with the oral ingestion of 0.6ml/Kg of body weight extract of *N. sativa* on spontaneously hypertensive rats (Zaoui *et al*., 2002). In addition with this hypotensive effect, *N. sativa* supplementation also modulates cardiac contractile properties. Al-Hariri *et al*. (2009) reported that the oral consumption of 800mg/Kg of body weight *N. sativa* in rats improved cardiac contractile activities without changing cardiac work load or energy consumption.

N. sativa consumption also modulates blood hemostatic functions. The whole blood and Kaolin-cephalin clotting time and bleeding time were reduced by petroleum ether extract of *N. sativa* but no significant change was observed in prothrombin time (Ghoneim *et al.*, 1982). In two other studies on normal and diabetic rats platelet aggregation was suppressed by *N. sativa* fixed oil ingestion (El-Tahir *et al.*, 1999; Enomoto *et al*., 2001). Hypolipidemic effects of *N. sativa* oil were reported by El-Dakhakhany (1965) in rats with 800 mg/Kg of body weight/day oral consumption for 4 weeks. Later these effects were confirmed in humans by Bamosa *et al*. (1997) with decreased levels of total cholesterol and triglyceride after 1gram ingestion of *N. sativa* capsules twice a day. Recently, Fatima *et al*. (2007) reported beneficial effects of *N. sativa* seed powder consumption on plasma lipid profile of the hyperlipidemic rabbits.

HYPOGLYCEMIC EFFECTS

Hypoglycemic effects of *N. sativa* are still controversial and conflicting. In 1985, Al Awadi *et al.* reported a significant decrease in blood glucose level in streptozotocin-induced diabetic rats with only one week administration of a hypoglycemic plant extract containing *N. sativa*. However, *N. sativa* alone did not show any significant effect on glucose tolerance in both normal and diabetic rats (Al-Awadi and Gumaa, 1987). Similarly, El-Naggar and El-Deib (1992) also reported that *N. sativa* seed powder administration in alloxan treated diabetic rats insignificantly reduced blood glucose levels. On contrary, Al-Hader *et al.* (1993) observed significant hypoglycemic effects of intraperitoneal *N. sativa* oil administration in normal and alloxon treated diabetic rabbits. This hypoglycemic effect was found to be due to inhibition of hepatic gluconeogenesis. In a study carried out by Fararh *et al.*, (2004), *N. sativa* oil administration (400 mg/Kg body weight) up to six weeks in streptozotocin-induced diabetic hamsters also significantly lowered blood glucose level. In another study, *N. sativa* whole seed extract enhanced the release of glucose-induced insulin from isolated pancreatic islets of rats (Rchid *et al*., 2004). Moreover, oral administration of *N. sativa* oil also improves glucose tolerance and insulin sensitivity in rats fed upon high fat diet and administered turpentine injection in dorsolumbar region (Alsaif, 2008).

ANTIBACTERIAL ACTIVITIES

Seeds of *N. sativa* were found to be effective against both Gram positive and Gram negative bacteria tested (Lai and Roy, 2004). Furthermore, oil of *N. sativa* has potent antibacterial activity against *Bacillus subtilis* ATCC6633 and *Escherichia coli* ATCC10536 (Minakshi *et al*., 1999). Tariq *et al*. (2005) studied the effect of *N. sativa* essential oil on sensitive and multi-drug resistant *Staphylococcus aureus*. The oil was found to be active against 50 strains out of 54. The study concluded that *N. sativa* oil is active against sensitive as well as multi-drug resistant strains of *S. aureus*. In a study different crude extracts of *N. sativa* were tested for antibacterial effectiveness against multi-drug resistant Gram positive and Gram negative bacteria. The most effective extracts were the crude alkaloid and aqueous extracts. It was found that Gram negative isolates were affected more than Gram positive ones (Morsi, 2000). Furthermore, crude seed extract of *N. sativa* was found to be active against *Bacillus subtilis, Klebsiella pneumoniae, Mycobacterium phlei* and methicillin sensitive and resistant *Staphylococcus aureus* (Mouhajir *et al*., 1999). In another study the aqueous extract of *N. sativa* did not show any effect but the methanol and chloroform extracts showed high inhibitory effects against the microorganisms tested (Mashhadian and Rakhshandeh, 2005).

The diethyl ether extract of *N. sativa* seeds were found to be effective against *S. aureus*, *P. aeruginosa* and *E. coli* (Hanafy and Hatem, 1991). In contrast, ethanolic extract of *N. sativa* was found ineffective against *E. coli* ATCC11230, *S. aureus* ATCC65380, *K. pneumoniae* UC57, *P. aerugiosa* ATCC27853, *P. vulgaris* ATCC8427, *B. cereus* ATCC7064, *Mycobacterium smegmatis* CCM2067, *Listeria monocytogenes* ATCC15313, and *Micrococcus luteus* CCM169 **(**Dulger and Gonuz, 2004). Similarly in another study carried out by Bonjar *et al.* (2004) methanol extract of *N. sativa* was found to be ineffective against *E. coli, P. aeruginosa, P. fluorescens, K. pneumoniae, Bordetella bronchiseptica, Serratia marcescens, S. aureus, S. epidermidis, M. luteus, B. cereus* and *B. pumilus.*

ANTIFUNGAL ACTIVITIES

N. sativa has also been reported to possess antifungal properties (Boyraz and Ozean, 2005). Its oil was found active against *Saccharomyces cerevisiae* ATCC9763 (Minakshi *et al*., 1999). In a study, essential oil of *N. sativa* seeds completely inhibited the growth of *Penicillium citrinum* (Singh *et al*., 2005). In a recent study, aqueous infusion, decoction and essential oil of *N. sativa* were investigated for their anticandidal activities against 4 different species of *Candida; C. albicans, C. tropicalis, C. parapsilosis*, and *C. krusei*. Only oil was found effective against all species while all isolates were found resistant to aqueous infusion and decoction (Saeed *et al*., 2006). In a study the effect of aqueous extract of seeds of *N. sativa* exhibited inhibitory effect against candidiasis *in vivo* (Khan *et al.*, 2003). In another study the aqueous, methanol and chloroform extracts of *N. sativa* seeds were evaluated for anticandidal activity against different strains of *C. albicans*. The methanol extract showed the stronger activity and the chloroform extract had a weaker activity while the aqueous extract did not show any anticandidal activity (Mashhadian and Rakhsandeh, 2005). In contrast, ethanolic extract of *N. sativa* seeds was not found to be effective against *C. albicans*, *Rhodotorula rubra* and *Klutveromyces fragilis* (Dulger and Gonuz, 2004). Similarly methanol extract of *N. sativa* seeds was also found to be ineffective against three yeast viz., *S. cerevisiae, C. albicans* and *C. utilis* (Bonjar *et al*., 2004).

The thymohydroquinones, a compound isolated from seeds of *N. sativa*, possesses antifungal activity (Mouhajir *et al*., 1999). The antifungal activity of ether extract of *N. sativa* seeds and its active priciple TQ were tested against eight species of dermatophytes viz., *Trichophyton rubrum* (4) and *T. intergitale* (1), *T. mentegrophyte* (1), *Epidermophyton floccosum* (1) and *Microsporum canis* (1). The minimum inhibitory concentrations (MICs) of the ether extract of *N. sativa* and thymoquinone were between 4 and 10 and 0.125 and 0.25 mg/ml, respectively. These results donate the potentiality of *N. sativa* as a source for antidermatophyte drug (Aljabre *et al.*, 2005).

ANTIVIRAL ACTIVITIES

Treatment with oil of *N. sativa* seeds exhibited a striking antiviral effect against cytomegalovirus (MCMV) infection which may be by increasing number and function of natural killer cells and interferon-gamma (INF-γ) production (Salem and Hossain, 2000). Extracts of seeds of *N. sativa* have pronounced activity against herpese simplex viruses (HSV I and II) but a slight antireteroviral activity against human immuno defficiency virus (HIV-I) (Sokmen, 2001).

ANTIPARASITIC ACTIVITIES

It has been reported that *N. sativa* oil possesses anticestode and antinematode actions *in vivo*. When the oil was given orally, it reduced the numberof *Schistosoma mansoni* worms in the liver and decreased the total number of ova depositied in both liver and intestine and also prevented liver damage induced by *S. mansoni* (Mahmoud *et al*., 2002). Similarly, Akhtar and Riffat (1991) also investigated the anticestodal effect of *N. sativa* seeds and its

ethanolic extract when given orally to infected children. Both were effective in reducing the percentage of faecal eggs per gram counts and the effect was compareable to niclosamide. More over, *N. sativa* menthol extract (1ml/Kg) and powder (200 mg/Kg) showed high efficacy, compareable to Hapadex (netobimin, 20mg/Kg), against rumin fluke in sheep (Korshom *et al*., 1998).

ANTICANCER ACTIVITIES

The anticancer activity of *N. sativa* was first revealed by El-Kadi and Kandil (1986) who observed enhancement of natural killer (NK) cell activity ranging from 200-300 % in advanced cancer patients receiving multimodality immunotherapy programme in which *N. sativa* was one of the components. Later on, the anti-cancer effect of *N. sativa* was investigated both *in vitro* using cancer cell lines and *in vivo* using animal models. Salomi *et al.* (1991) showed that topical application of *N. sativa* and *Crocus sativus* extracts inhibited two-stage initiation/promotion (dimethylbenz-a-anthracene/croton oil) of skin carcinogenesis in mice by delaying the onset of papilloma formation and reducing the number of papillomas per mouse. An active principle of *N. sativa* containing fatty acids show 50% cytotoxic activities *in vitro* against Ehrilch ascites carcinoma (EAC), Dalton's lymphoma ascites and sarcoma-180 cells and, *in vivo*, completely inhibited EAC tumor development in mice (Salomi *et al*., 1992). Worthen *et al*. (1998) investigated the anticancer effect of thymoquinone and dithymoquinone, active principles of *N. sativa* and confirmed that they had cytotoxic effect against parental and multi-drug resistant human tumour cell lines.

Oral administration of volatile oil of *N. sativa* has the ability to inhibit 1,2-dimethyl hydrazine induced aberrant crypt foci, putative preneoplastic lesions of colon cancer in rats in the postinitiation stage **(**Salim and Fukushima, 2003). Moreover, oral feeding with *N. sativa* extract suppressed hepatic tumor in rats induced by diethylnitrosamine or by partial hepatectomy **(**Iddamaldeniya *et al.,* 2003). Volatile oil of *N. sativa* seeds also expressed marked cytotoxic effects against a panel of human cancer cell lines (Islam *et al*., 2004). *N. Sativa* alone or in combination with oxidative stress also found to be effective *in vitro* in inactivating MCF-7 breast cancer cells (Swamy and Tan, 2000). These *in vitro* and *in vivo* studies indicate that both the oil and the active ingredients of *N. sativa* seeds possess anti-tumor effects.

CONTRAINDICATIONS

The seeds of *N. sativa* can be poisonous to humans in high doses (Tierra, 2006). Moreover, *N. sativa* has mild uterotropic effect and therefore not recommended during pregnancy (Saleh, 2005).

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