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REVIEW ON PHARMACOLOGICAL INVESTIGATION OF NIGELLA SATIVA

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ABSTRACT

Nigella sativa (N. sativa) (Family Ranunculaceae) is a widely used medicinal plant throughout the world. It is very popular in various traditional systems of medicine like Unani and Tibb, Ayurveda and Siddha. Seeds and oil have a long history of folklore usage in various systems of medicines and food. The seeds of N. sativa have been widely used in the treatment of different diseases and ailments. In Islamic literature, it is considered as one of the greatest forms of healing medicine. It has been recommended for using on regular basis in Tibb-e-Nabwi (Prophetic Medicine). It has been widely used as antihypertensive, liver tonics, diuretics, digestive, anti-diarrheal, appetite stimulant, analgesics, anti-bacterial and in skin disorders. Extensive studies on N. sativa have been carried out by various researchers and a wide spectrum of its pharmacological actions have been explored which may include antidiabetic, anticancer, immunomodulator, analgesic, antimicrobial, anti-inflammatory, spasmolytic, bronchodilator, hepato-protective, renal protective, gastro-protective, antioxidant properties, etc. Due to its miraculous power of healing, N. sativa has got the place among the top ranked evidence based herbal medicines. This is also revealed that most of the therapeutic properties of this plant are due to the presence of thymoquinone which is major bioactive component of the essential oil. The present review is an effort to provide a detailed survey of the literature on scientific researches of pharmacognostical characteristics, chemical composition and pharmacological activities of the seeds of this plant.

KEYWORDS: *Nigella sativa*, Miracle herb, Ranunculaceae, Habat-ul-Sauda, Thymoquinone, Tibb-e-Nabwi, Black seeds, Anti-diabetic, Antioxidant.

INTRODUCTION

The plant *kalonji* or *Nigella Sativa* is an annual flowering plant, native to South West Asia and cultivated in countries like Middle Eastern Mediterranean region, South Europe, Syria, Turkey, Soudi Arabia, Pakistan, India. The above plant is small annual herb distributed all over India.[1,2] In the religion of Islam, the plant have been given a great importance because of its number of uses. As per the religion it is the one of the greatest healing plant. The Islamic Prophet Mohommad once stated that the black seed can heal every disease except death. Avicenna, most famous for his volues called the Cannon of Medicine, refers to *Nigella* as the seed that stimulates the body's energy and help recovery from fatigue and dispiritedness. It is also included in the list of natural drugs of 'Tibb-e-Nabawi', or "Medicine of the Prophet Mohommad", according to the tradition "hold on to the black seeds" for the healing all diseases. In the Unani Tibb system of medicine *N. Sativa* is regarded as a valuable remedy for the numbers of diseases. In the indian system of medicine, the seeds are used as astringent, anthelmintic, jaundice, intermittent fever, dyspepsia, paralysis, piles and skin diseases and many more.[3-5] The present article is an effort to present out the pharmacology, traditional uses and chemical constituents of the above plant.

Taxonomic Hierarchy of *N. Sativa*

Kingdom : Plantae

Division : Magnoliophyta

Class : Magnoliopsida

Order : Ranunculales

Family : Ranunculaceae

Genus : *Nigella*

Species : *N. sativa*

Morphology, Microscopy and Macriscopy of the plant

N. sativa is an annual flowering plant which grows to 20-90 cm tall, with finely divided leaves, the leaf segments narrowly linear to threadlike. The flowers are delicate, and usually colored white, yellow, pink, pale blue or pale purple, with 5-10 petals. The fruit is a large and inflated capsule composed of 3-7 united follicles, each containing numerous seeds.[5,7] Macroscopically, seeds are small dicotyledonous, trigonus, angular, regulose-tubercular, 2-3.5mm×1-2 mm, black externally and white inside, odor slightly aromatic and taste bitter. Microscopically, transverse section of seed shows single layered epidermis consisting of elliptical, thick walled cells, covered externally by a papillose cuticle and filled with dark brown contents. Epidermis is followed by 2-4 layers of thick walled tangentially elongated parenchymatous cells, followed by a reddish brown pigmented layer composed of thick walled, rectangular elongated cells. Inner to the pigment layer, is present a layer composed of thick walled rectangular elongated or nearly columnar, elongated cells. Endosperm consists of thin walled, rectangular or polygonal cells mostly filled with oil globules. The powder microscopy of seed powder shows brownish black, parencymatous cells and oil globules.[5,6]


CHEMICAL CONSTITUENTS

The chemical constituents reported in the above plant is been tabulated under.[8]

Fundamental Oil Composition(1.4%)	***Nigella Sativa***
Carvone	21.1%
Alfa-Pinene	7.4%
Sabinene	5.5.%
Beta-Pinene	7.7.%
P-cymene	46.8%
Fatty Acids	
Myristic Acid(C 14:0	0.5%
Palmitic acid(C16:0)	13.7%
Palmitoleic Acid(C16:1)	0.1%
Stearic Acid(C16:0)	2.6%
Oleic Acid(C18:1)	23.7%
Linoleic Acid(C18:2)(omega-6)	57.9%
Linolenic Acid(18:3n-3)(omega-3)	02.%
Arachidic acid(C20:0)	1.3%
Saturated and Unsaturated Fatty Acids	
Saturated Acid	18.1%
Monounsaturated Acids	23.8%
Polyunsaturated Acids	58.1%
Nutritional Value	
Protein	208ug/g
Thiamin	15ug/g
Riboflavin	1ug/g
Pyridoxine	5ug/g
Niacin	57ug/g
Folacin	610IU/g
Calcium	1.859mg/g
Iron	105ug/g
Copper	18ug/g
Zinc	60ug/g
Phosphourus	5.265mg/g

Nutritional Composition	
Protein	21%
Carbohydrates	35%
Fats	35-38%

Pharmacological Investigation

Antibacterial activity

The antibacterial effect of ground black seeds was studied in a modified paper disc diffusion method. A clear inhibition of the growth of Staphylococcus aureus was observed by concentration of 300 mg/mL with distilled water as control, this inhibition was confirmed by using the positive control Azithromycin. The inhibition obtained was higher with N. sativa ground seeds from Hadramout than with N. sativa ground seeds from Ethiopia. The positive inhibition may be attributed to the two important active ingredients of N. sativa, TQ and melanin.[9] Different crude extracts of N. sativa were tested for antimicrobial effectiveness against different bacterial isolates which comprised of 16 gram negative and 6 gram positive representatives. These isolates showed multiple resistances against antibiotics, specially the gram negative ones. Crude extracts of N. sativa showed a promising effect against some of the test organisms. The most effective extracts were the crude alkaloid and water extracts. Gram negative isolates were affected more than the gram positive ones.[10]

Antifungal activity

Methanolic extracts of N. sativa have the strongest antifungal effect followed by the chloroform extracts against different strains of Candida albicans. Aqueous extracts showed no antifungal activity. An intravenous inoculum of Candida albicans produced colonies of the organism in the liver, spleen and kidneys. Treatment of mice with the plant extract 24 h after the inoculation caused a considerable inhibitory effect on the growth of the organism in all organs studied. Khan et al. in 2003 reported that the aqueous extract of N. sativa seeds exhibits inhibitory effect against candidiasis in mice. A 5-fold decrease in Candida in kidneys, 8-fold in liver and 11-fold in spleen was observed in the groups of animals post-treated with the plant extract. These findings were also confirmed by Histopathological examination of the respective organs.[11]

Anti – schistosomiosis activity

The effect of NSO against the liver damage induced by Schistosoma mansoni (S. mansoni) infection in mice was studied by Mahmoud et al. When the NSO was given alone, it reduced the number of S. mansoni worms in the liver and decreased the total number of ova deposited

in both the liver and the intestine. When NSO was administered in combination with PZQ, the most prominent effect was a further lowering in the dead ova number over that produced by PZQ alone. Infection of mice with S. mansoni produced a pronounced elevation in the serum activity of ALT, GGT, with a slight increase in AP level, while reduce serum albumin level. Administration of NSO succeeded partially to correct the previous changes in ALT, GGT, AP activity, as well as the Alb content in serum. These results suggest that NSO may play a role against the alterations caused by S. mansoni infection.[12]

Antioxidant activity

It was also reported that oral feeding of the diet containing black seed powder at 10% level antagonized the oxidative stress effects induced by hepato-carcinogens like dibutylamine and Sodium Nitrate (NaNO3) in Swiss albino rats by normalizing GSH and NO levels.[13] Treating broiler chicks with black seed for 6 weeks prevented the liver from oxidative stress by increasing the activities of enzymes such as myeloperoxidase, glutathione-S-transferase, CAT, adenosine deaminase, myeloperoxidaseand bydecreasing hepatic lipid peroxidation.[14]

Antidiabetic activity

The protective effects of the volatile oil of N. sativa seeds on insulin immunoreactivity and ultrastructural changes of pancreatic β-cells in STZ-induced diabetic rats was reported by Kanter et al. 2009. STZ was injected intraperitoneally at a single dose of 50 mg/kg to induce diabetes. Increased intensity of staining for insulin, and preservation of β-cell numbers were apparent in the N. sativa-treated diabetic rats. The protective effect of N. sativa on STZ-diabetic rats was evident by a moderate increase in the lowered secretory vesicles with granules and also slight destruction with loss of cristae within the mitochondria of β-cell when compared to control rats. It is evident that N. sativa treatment exerts a therapeutic protective effect in diabetes by decreasing morphological changes and preserving pancreatic β-cell integrity.[15]

Anticancer activity

The anticancer effects of TQ on breast cancer cells, and its potential effect on the PPAR-γ activation pathway was investigated and it was found that TQ exerted strong anti-proliferative effect in breast cancer cells and when TQ combined with doxorubicin and 5-fluorouracil, cytotoxicity was found to be increased. TQ was found to increase sub-G1 accumulation and annexin-V positive staining, indicating apoptotic induction. In addition, TQ activated caspases 8, 9 and 7 in a dose-dependent manner. Migration and invasive properties

of MDA-MB-231 cells were also reduced in the presence of TQ. Interestingly, TQ was found to increase PPAR-γ activity and down-regulate the expression of the genes for Bcl-2, Bcl-xL and survivin in breast cancer cells. More importantly, the increase in PPAR-γ activity was prevented in the presence of PPAR-γ specific inhibitor and PPAR-γ dominant negative plasmid, suggesting that TQ may act as a ligand of PPAR-γ. It was observed by using molecular docking analysis that TQ indeed formed interactions with 7 polar residues and 6 non-polar residues within the ligand-binding pocket of PPAR-γ that are reported to be critical for its activity. Thus, it was concluded that TQ may have potential implication in breast cancer prevention and treatment and anti-tumor effect of TQ may also be mediated through modulation of the PPAR-γ activation pathway.[16]

Anti-inflamatory and Analgesic activity

The seeds hexane fraction of the methanol extract showed significant anti-inflammatory activity, inhibiting nitric oxide release with an IC50 value of 6.20 µg/mL in lipopolysaccharide-stimulated RAW 264.7 macrophages.[17]

Immunomodulatory activity

To determine the possible alleviating effect of N. sativa and TQ on food allergy, ovalbumin (OVA) -sensitized BALB/c-mice were pre-treated either with a hexanic N. sativa seed extract TQ and subsequently challenged intra-gastrically with OVA. All 4 treatments significantly decreased clinical scores of OVA-induced diarrhea. N. sativa seed extract, TQ decreased intestinal mast cell numbers and plasma mouse mast cell protease-1. It was demonstrated that N. sativa seed extract significantly improves symptoms and immune parameters in murine OVA-induced allergic diarrhea; this effect is at least partially mediated by TQ.[18]

Cardiovascular activity

The acute (at 4 and 18 h) effects of diesel exhaust particles (DEP) on cardiopulmonary parameters in mice and the protective effect of TQ were investigated. Mice were given, intratracheally, either saline (control) or DEP (30 µg per mouse). At 18 h (but not 4 h) after giving DEP, there was lung inflammation and loss of lung function. At both 4 and 18 h, DEP caused systemic inflammation characterized by leucocytosis, increased IL-6 concentrations and reduced systolic blood pressure. SOD activity was decreased only at 18 h. DEP reduced platelet numbers and aggravated in vivo thrombosis in pial arterioles. In vitro, addition of DEP (0.1-1 µg/mL) to untreated blood-induced platelet aggregation. Pretreatment of mice with TQ prevented DEP-induced decrease of systolic blood pressure and leucocytosis,

increased IL-6 concentration and decreased plasma SOD activity. TQ also prevented the decrease in platelet numbers and the prothrombotic events but not platelet aggregation in vitro.[19]

Gastro-protective activity

N. sativa prevents alcohol induced increase in lipid peroxidation (i.e. thiobarbituric acid reactive substances) and reduced gastric GSH content, enzyme activities of gastric SOD, GSH-S-Transferase.[20]

Hepato-protective activity

It is reported that N. sativa (0.2 mL/kg) intraperitoneally relieves the deleterious effects of ischemia reperfusion injury on liver. Biochemical parameters like the serum aspartate aminotransferase, alanine aminotransferase lactate dehydrogenase levels and total antioxidant capacity (TAC), CAT, total oxidative status (TOS), oxidative stress index (OSI) and MPO were determined in hepatic tissue in rats with hepatic ischemia. Results suggested that N. sativa treatment protects the rat liver against hepatic ischemia reperfusion injury.[21]

Nephroprotective activity

The nephro-protective effect of vitamin C and N. sativa oil was observed against gentamicin (GM) associated nephrotoxicity in rabbits. Serum creatinine, blood urea nitrogen, and antioxidant activity were measured as indicators of nephrotoxicity for all the groups of rabbits. It was revealed that vitamin C and N. sativa oil both had nephroprotective effect as they lowered the values of serum creatinine, blood urea nitrogen, and antioxidant activity as compared to GM control group values. When these two antioxidants were given as combination, they proved to have synergistic nephroprotective effect.[22]

Neuro-pharmacological activity

An anxiolytic drug acts by increasing the 5-HT and decreasing the 5-HIAA (hydroxyindole acetic acid) levels in brain. A long term administration of N. sativa increases 5-HT levels in brain and improves learning and memory in rats.[23]

Anticonvulsant activity

The antioxidant effects of curcumin, NSO and valproate on the levels of malondialdehyde, nitric oxide, reduced glutathione and the activities of CAT, Na+, K+-ATPase and acetylcholinesterase in the hippocampus of pilocarpine-induced animal model of epilepsy

was evaluated and left for 22 d to establish the chronic phase of epilepsy. The animals were then treated with curcumin, NSO or valproate for 21 d. Treatment with curcumin, NSO or valproate ameliorated most of the changes induced by pilocarpine and restored Na+, K+-ATPase activity in the hippocampus to control levels. Results indicated the anticonvulsant and potent antioxidant effects of curcumin and NSO in reducing oxidative stress, excitability and the induction of seizures in epileptic animals and improving some of the adverse effects of antiepileptic drugs.[24]

Antitoxytocic activity

The antioxytocic properties of N. sativa were reported in some preliminary studies. N. sativa seeds inhibit the uterine smooth muscle contraction induced by oxytocin stimulation.The volatile oil of N. sativa seeds inhibited the spontaneous movements of rat and guinea piguterine smooth muscle and also the contractions induced by oxytocin stimulation which suggest the anti-oxytocic potential of N. sativa seeds oil.[25]

CONCLUSION

The use of herbal drugs as complementary medicine is prevalent and gaining world wide popularity. Many drugs are derived directly from plants; while the others are chemically modified natural products. The original research articles published so far have confirmed the pharmacological potential of N. sativa seeds, its oil and extracts and some of its active principles, particularly TQ and alpha-hederin, possess remarkable in vitro and in vivo pharmacological activities against a large variety of diseases and found to be relatively safe.

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