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Therapeutic Role of Prophetic Medicine *Habbat El Baraka (Nigella sativa* L.) - A Review

Mohammad Yaheya Mohammad Ismail

Dept. of Pharmacy, Higher College of Technology, P.O. Box 74 PC 133, Sultanate of Oman

Abstract: The seeds of *Nigella sativa* Linn. (Ranunculaceae), commonly known as black seed or black cumin, are used in herbal medicine all over the world for the treatment and prevention of a number of diseases. The seeds contain both fixed and essential oils, proteins, alkaloids and saponin. Much of the biological activity of the seeds has been shown to be due to thymoquinone, the major component of the essential oil which is also present in the fixed oil. The pharmacological actions of the crude extracts of the seeds (and some of its active constituents, e.g. volatile oil and thymoquinone) that have been reported include protection against nephrotoxicity and hepatotoxicity induced by either disease or chemicals. The seeds/oil has antiinflammatory, analgesic, antipyretic, antimicrobial, antidiabetic and antineoplastic activity. The oil decreases blood pressure and increases respiration. This article reviews the main reports of the pharmacological properties of *N. sativa* and its constituents.

Key words: *N. sativa* · Thymoquinone · Anticancer activity · Folk medicine

INTRODUCTION

The seed of *Nigella sativa* is known by many different names like black seeds or black cumin. In old Latin, it is called as 'Panacea' meaning 'cure all' while in Arabic it is termed as 'Habbah Sawda' or 'Habbat el Baraka' translated as 'seeds of blessing'. In China it is referred as Hak Jung Chou while in India it is called as Kalonji and in Persian, it is called as Shoneez. The plant belongs to the *Ranunculaceae* family of flowering plants and genus of about 14 species including *Nigella arvensis, Nigella ciliaris, Nigella damascene, Nigella hispanica, Nigella integrifolia, Nigella nigellastrum, Nigella orientalis and Nigella sativa, respectively*. Among these, *Nigella sativa* is the species most exhaustively investigated for therapeutic purposes although other species have also been implicated for therapeutic uses [1]. The historical references to these seeds are also found in some of the oldest religious and medical texts. For example, it is referred to as 'Melanthion' by Hippocrates and Dioscorides where as in Islamic culture *Nigella sativa* seeds are the common drug used in Tibbe-Nabvi (Prophet's Medicine) through out the world. Since, prophet Muhammad (PBUH) mentioned its therapeutic efficacy and potential of cure. It is stated in books of Seerat that Prophet Muhammad (PBUH), himself used to take these seeds with the syrup of honey for the therapeutic purpose. The Holy Prophet Muhammad (PBUH) said," The black seeds (*Nigellea sativa*) are the remedy for every disease except death." His one companion, Abu Hurairah (Radi Allaho Anho) narrates," I have heard from Prophet that there is cure for every disease in black seeds except death and black seeds are shooneez (Kalonji)" [2]. An attempt has been made in this review to cover the major therapeutic activities reported by the recent studies for *N. sativa* and its constituents.

Plant Description: It is a spice that grows in the mediterranean region and in western asian countries including India, Pakistan and Afghanistan.The species grow to 20-30 cm tall, with finely divided leaves wherein the leaf segments are narrowly linear to threadlike. The flowers are white, yellow, pink, pale blue or pale purple, with 5-10 petals. The fruit is a capsule composed of several united follicles, each containing numerous seeds while in some species (e.g. *Nigella damascena*), the capsule is large and inflated. The parts of the plant most commonly used for the therapeutic purposes in the "Alternative Medicinal" systems are the seeds which are contained in an inflated capsule formed from the united follicles containing considerable amount of oil having pungent and bitter taste. Commonly the seeds are used primarily as a spice and food preservative [1, 3].

Correspoding Author: Mohammad Yaheya Mohammad Ismail, Lecturer in Pharmacy, Dept. of Pharmacy, Higher College of Technology, P.O. Box 74 PC 133, Sultanate of Oman

Chemical Constituents: The chemical composition of the *Nigella sativa* seed contains amino acids, proteins, carbohydrates, fixed and volatile oils, alkaloids, saponins and many other compounds. Thin Layer Chromatography (TLC) screening of the oil samples showed the presence of four main components, viz. thymoquinone (TQ), carvacrol, tanethole and 4-terpineol [1, 3, 4].

Dosage and Administration: According to literature available the seeds are given in powder form in the dose of 0.5-1 gm alone or mixed with honey. Seeds are ground in vinegar to make a paste to be applied externally on vitiligo. Seeds are heated in vegetable oil (1:10) on slow fire to be used externally [1, 3].

Pharmacological Actions: The various pharmacological actions shown by the various studies by the extract of the black seed are as follows:

Anticancer Activity: N. sativa decreases DNA damage and thereby prevents initiation of carcinogenesis in colonic tissue secondary to exposure to toxic agents such as azoxymethane [5]. In fact, sustained delivery of TQ (derived from *N. sativa*) is almost as effective in causing apoptosis of colon cancer cells as sustained delivery of 5-fluorouracil [6]. Similarly, hepatic metastasis from tumors such as mastocytomas is markedly decreased following administration of *N. sativa* [7].

N. sativa, when used in combination with *Hemidesmus indicus* and *Smilax glabra*, also seems to decrease hepatic carcinogenesis secondary to exposure to agents such as diethylnitrosamine [8]. These anti-carcinogenic effects are mediated in part by TQ secondary to its inhibitory influence on the NF-κB activation pathway [9]. Shoieb and colleagues have investigated in 2003 the anti-proliferative effects of TQ in cancer and normal cell lines, viz. canine osteocarcinoma (COS31) and its cisplatin-resistant variant (COS31/rCDDP), human breast adenocarcinoma (MCF-7), Human ovarian adenocarcinoma (BG-1) and Mandin-Darby canine (MDCK) cells [10]. The compound was found to inhibit proliferation in a concentration-dependent manner as assessed by MTT assay. MDCK cells (normal kidney cells) were the most resistant cells to the inhibitory effects of TQ (IC_{50} = 101 μM). Ait and colleagues have evaluated in 2007 the anti-tumor properties of the black seed oil and its ethyl extract against P815 cell line and both were found to be cytotoxic. The extracts were also tested on a variety of cell lines such as ICO1, Vero cells and BSR cell line which showed that the extent of cytotoxicity depends upon the tumor cell type. In animal model employing DBA2/P815 (H2d) mouse model it was observed that the injection of the essential oil into the tumor site significantly inhibited solid tumor development as well as the incidence of liver metastasis, thus improving mouse survival. These results indicate that the anti-tumor activity or cell growth inhibition could in part be due to the effect of TQ on cell cycle.

Antidiabetic Activity: N. sativa is of great therapeutic benefit in diabetic individuals and those with glucose intolerance, as it accentuates glucose-induced secretion of insulin, besides having a negative impact on glucose absorption from the intestinal mucosa [10, 11]. In fact, *N. sativa* attenuates the damage to β-cells of the pancreas following exposure to toxic elements such as cadmium [12]. Similarly, *N. sativa* administration attenuates the ulcerative effects of ethanol on gastric mucosa by decreasing the glutathione-S transferase levels in gastric mucosa [13].

Antiparasitic Activity: N. sativa also demonstrates anti-parasitic effects. For instance, its administration decreases the number of eggs as well as worms in schistosomiasis, which tends to affect hepatic and intestinal tissues [14]. In addition, *N. sativa* attenuates the side effects associated with some common medications used by gastroenterologists. For instance, cyclosporine, used by gastroenterologists for disorders such as recalcitrant Crohn's disease, is often associated with nephrotoxic side effects, which can be limited by *N. sativa* due to its anti-oxidant properties [15].

Hepatoprotective Activity: N. sativa administration protects hepatic tissue from deleterious effects of toxic metals such as lead and attenuates hepatic lipid peroxidation following exposure to chemicals such as carbon tetrachloride [16, 17].

Antioxidant Activity: TQ has been shown to exhibit antioxidant property through different mechanisms in several recent reports. For example, it inhibits the production of 5-hydroxyeicosa-tetraenaoic as well as 5-lipoxygenase products [18], both of which are required for the viability of colon cancer cells. It was shown to work as a scavenger of various reactive oxygen species including superoxide radical anion and hydroxyl radicals [19-21]. Additionally, it was able to produce significant reductions in hepatic antioxidant enzymes such as

superoxide dismutase (SOD), catalase and glutathione peroxidase. It has been shown that TQ could inhibit iron-dependent microsomal lipid peroxidation efficiently in rats with doxorubicin-induced hyperlipidemic nephropathy [22]. The compound was observed to decrease cellular oxidative stress by inducing glutathione in experimental allergic encephalomyelitis in female Lewis rats [23].

Both *Nigella sativa* oil and TQ can partly protect gastric mucosa from acute alcohol-induced mucosal injury which is partly ascribed to their radical scavenging activity [24]. The state of hyperhomocysteinemia (HHcy) appears to be associated with higher risks of coronary, cerebral and peripheral vascular diseases as well as a number of other clinical conditions and is thought to be capable of inducing a pathogenic state of oxidative stress although its underlying molecular mechanisms are not fully elucidated. El-Saleh and co-workers [25] have shown that active antioxidant components of black seeds of *Nigella sativa* plants are capable of rendering protection against the development of methionine-induced HHcy and its associated state of oxidative stress. Pre-treatment of rats with an oral dose of 100 mg/kg of TQ for 30 min and for one week provided complete protection against induced HHcy after methionine load (100 mg/kg). Under the state of induced HHcy, there were significant increases in the plasma levels of triglycerides, lipid peroxidation and cholesterol as well as in the activities of glutathione peroxidase and SOD although catalase activity was not affected. The total antioxidant status was significantly depressed. All of these effects were almost totally blocked by the prior treatment with TQ.

Nephroprotective Activity: Sayed-Ahmed and co-worker [26] have investigated the possible protective effects of TQ against Gentamicin (GM)-induced nephrotoxicity. Supplementation with TQ resulted in significant decrease in reduced glutathione (GSH) and increased levels of glutathione peroxidase (GPx), catalase and ATP and a complete reversal of the GM-induced increase in blood urea nitrogen, creatinine, thiobarbituric acid-reactive substances (TBARS) and total nitrate/nitrite (NOx) and decrease in GSH, GPx, CAT and ATP to control values. Histopathological examination of kidney tissues confirmed the biochemical data wherein TQ supplementation prevents GM-induced degenerative changes in kidney tissues, suggesting that these effects, at least in part, may be related to the ability of TQ to modulate cellular oxidative stress.

Neuroprotective Activity: Al-Majed and co-workers [27] have evaluated the neuroprotective effect of TQ against transient forebrain ischemia-induced neuronal damage in the rat hippocampus. The pre-treatment of ischemic rats with the compound decreased the elevated levels of MDA and increased GSH, catalase and SOD activities to normal levels. TQ and its reduced product, THQ, inhibited the *in vitro* non-enzymatic lipid peroxidation in hippocampal homogenate induced by iron-ascorbate. The IC_{50} for TQ and THQ were found to be 12 and 3 μM respectively. This spectacular protection makes TQ a promising agent in pathologies implicating neurodegenaration such as cerebral ischemia.

Anti-inflammatory and Analgesic Activity: The compound is reported to be a potent inhibitor of leukotrienes formation in human blood cells. The inhibitory effect was found to be dose as well as time-dependent and the effect was exerted on both 5-lipooxgenase and Leucotiriene-C4-synthase (LT4synthase) activity [28]. In another study [29], the rats pre-treated with oral TQ doses showed complete protection against acetic acid-induced colitis compared to sulfasalazine (500 mg/kg) control group wherein TQ was found to suppress the production of NO by macrophages which is useful in ameliorating the inflammatory and autoimmune conditions [30]. The anti-inflammatory activity of Black cumin seed oil has also been evaluated using carrageenan-induced paw edema in rats and croton oil-induced ear edema in mice by Hajhashemi and colleagues in 2004. Although oral administration of the oil at doses of 100, 200 and 400 μl/kg did not exert a significant anti-inflammatory effect in the carrageenan test, the intraperitoneal injection of the same doses significantly inhibited carrageenan-induced paw edema [31].

The oil could also reduce croton oil-induced edema at smaller doses and was found to produce a significant analgesic effect in acetic acid-induced writhing, formalin and light tail flick tests. It seems that mechanism other than opioid receptors is involved in the analgesic effect of the oil since naloxone, an opioid antagonist, could not reverse this effect. Being one of the major components of the oil (13.5%), TQ obviously has an important role in these pharmacological effects. Experimental Allergic Encephalitis (EAE) is a T-cell mediated autoimmune disease, which resembles the human disease of Multiple Sclerosis (MS) in rodents. The infiltration of inflammatory cells and the induction of astrocyte proliferation correlate with the severity of the disease. Since oxidative stress has been postulated as the causative factor of initiation and

progression of MS, the amelioration of the inflammation by TQ showed potent effects, which were thought to occur via induction of glutathione [32].

Apoptosis Induction Activity: TQ has also been demonstrated to induce apoptosis of human colon cancer cells. It has been shown that TQ triggers apoptosis in HCT-116 cells in a dose and time-dependent manner, starting at a concentration of 100 μM after 12 h of incubation which is associated with a 2.5 to 4.5 fold increase in p53 and $p21^{WAF1}$ mRNA expression and a significant decrease in Bcl-2 protein levels [33]. Co-incubation with pifithrin, a p53 inhibitor, restored the Bcl-2, p53 and $p21^{WAF1}$ levels to the untreated control levels and absolved the effects of TQ.

These results suggest role of TQ in influencing cell cycle regulators involved in apoptosis as well as in down-regulating the anti-apoptotic proteins. This was supported by similar effects on primary mouse keratinocytes, papilloma (SP-1) and spindle carcinoma cells respectively. At longer incubation times (48 h) the compound induced apoptosis in both cell lines by increasing the ratio of Bax/Bcl-2 protein expression and down-regulating the Bcl-xL protein.

TQ has been shown to initiate apoptosis even via p53-independent pathways through activation of caspase-3, 8 and 9 in p53-null myeloblastic leukemia HL-60 cells [34]. It was observed that caspase-8 activity was highest after 1 h following the treatment of TQ, while caspase-3 activity was highest after 6 h respectively. These observations were explained on the basis of up-regulation of pro-apoptotic Bax protein along with down-regulation of anti-apoptotic Bcl-2 proteins resulting in enhance Bax/Bcl-2 ratio. It is thus apparent that TQ induces apoptosis through modulation of multiple targets and hence is a promising phytochemical that could be useful for the killing of many types of cancer cells. These results are also supported by reports in prostate and other cancer cells [1, 35, 36].

Immunomodulatory Activity: The immunomodulatory and immunotherapeutic potentials of black seed oil and its active ingredients have been investigated [37]. The oil and some of its active ingredients showed beneficial immunomodulatory properties, augmenting the T cell and natural killer cell-mediated immune responses.

Hypocholesterilemic Activity: According to the study done by Inayat *et al*, it was concluded that *N. sativa* produced antiatherogenic effect by decreasing low density lipoprotein cholesterol level significantly. It also increases high density lipoprotein cholesterol level [38].

Treating Skin Infections: There are reports that the oil from the seeds can be used to treat dermatitis topically [39].

Stimulation of Uterine Contractions: Seeds have shown to stimulate uterine contractions when used in large amounts, leading to abortion [40].

Antihypertensive and Diuretic Activity: Seeds have shown antihypertensive and diuretic activity when studied in rats [41].

Antimicrobial and Antifungal Activity: Seeds also possess considerable antimicrobial activity as reported by various studies. The antifungal activity was observed when the aqueous extract of the seeds was used in vivo studies [42, 43].

CONCLUSION

The pharmacological actions of the crude extracts of the seeds (and some of its active constituents, e.g. volatile oil and thymoquinone) that have been reported include protection against nephrotoxicity and hepatotoxicity induced by either disease or chemicals. The seeds/oil has antiinflammatory, analgesic, antipyretic, antimicrobial and antineoplastic activity. The oil decreases blood pressure and increases respiration. Treatment of rats with the seed extract for up to 12 weeks has been reported to induce changes in the haemogram that include an increase in both the packed cell volume (PCV) and haemoglobin (Hb) and a decrease in plasma concentrations of cholesterol, triglycerides and glucose. In folk medicinal practices they are ingested with food or mixed with honey and are primarily used as lactogogues, carminative and anthelmenthic agents. The seeds have also been used as diuretics, anti-hypertensive, muscle relaxants and as immunity enhancers in immune-compromised people. Importantly, the seeds have been reported to be safe when used orally in moderate amount in food They have been shown to stimulate uterine contractions when used in large amounts, leading to abortion There are reports that the oil from the seeds can be used to treat dermatitis topically. Several beneficial pharmacological effects have been attributed to various crude or purified components of these seeds including antihistaminic, antihypertensive, hypoglycemic antifungal, anti-inflammatory along with

significant anti-neoplastic activities. The seeds are characterized by a very low degree of toxicity. These studies collectively provide early indication that further development of agents derived from black cumin seeds could be useful in modern medicine.

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