SUMMARY

Seeds of Nigella sativa (N. sativa) have been used for thousands of years as a spice and food preservative. The oil and seed constituents have shown potential medicinal properties in traditional medicine. This review lists and discusses different therapeutic trials of N. sativa seeds and its active ingredients in many diseases affecting body systems. It has anti-oxidant effects through enhancing the oxidant scavenger system that leads to antitoxic effects induced by several insults. Its anti-inflammatory effects through suppression of the inflammatory mediators prostaglandins and leukotriens. Its immunomodulatory properties proved by augmenting the T cell and natural killer cell-mediated immune responses. It expresses antimicrobial and anti-tumor properties toward different microbes and cancers. It decreases DNA damage and thereby prevents initiation of carcinogenesis in colonic tissue secondary to exposure to toxic agents. N. sativa is of immense therapeutic benefit in DM. It stimulates glucose-induced secretion of insulin besides having a negative impact on glucose absorption from the intestinal mucosa. N. sativa administration protects hepatic tissue from deleterious effects of toxic substances and attenuates hepatic lipid peroxidation. N. sativa provides a promising strategy that combines anti-inflammatory, antioxidants, and antineoplastics modes of action.

INTRODUCTION

Despite all the marvelous advancements in modern medicine, traditional herbal medicine has always been practiced [1]. Every culture and civilization, throughout history, has used a range of plant or plant derivatives for the prevention and treatment of diseases [2]. The rapid increase in consumption of herbal remedies worldwide has been stimulated by several factors, that all herbal products are safe and effective, fear or disrupt of physician, current interest of natural products, disappointment of prescribed drugs or traditional care, cultural influences and increase acceptance of alternative remedies [3].

Herbal medicine can be broadly classified into four basic systems: Traditional Chinese Herbalism, Ayurvedic Herbalism, Western Herbalism, which originally came from Greece and Rome to Europe and then spread to North and South America, and Arab traditional medicine, which forms the basis for alternative and herbal medicine in use today [3].
**Nigella sativa**

Among the promising medicinal plants, *N. sativa* is an amazing herb with a rich historical and cultural background. *N. sativa* is an annual herbaceous plant belongs to dicotyledon of the Ranunculaceae family. It has been employed for thousands of years as a spice and food preservative. It commonly grows in Europe, Middle East, and Western Asia. The seeds of *N. sativa* are the source of the active ingredients of this plant [4]. They are frequently used in folk medicine in the Middle East and some Asian countries for the promotion of good health, treatment of many ailments including fever, common cold, headache, asthma, rheumatic diseases, and various microbial infections, and to expel worms from the intestines. They also used for treatment of scorpion and spider stings and bites of snakes, as well as cat and dog. In addition, they are used as a flavoring food additive to bread and prickles [5].

**Synonyms:**

Coequal names of its seed in Arab countries are Al-Habbah Al-Sawda, Habbet El-Baraka, Kamoun Aswad, Schuniz and Khodria. In Pakistan, India and Sri Lanka it is called Kalvanji, Kalaunj, Azmut, Gurat, Aof and Aosetta. In English language it is known as Black Seed, Black Cumin, Black Caraway, Cinnamon flower, Nutmeg flower and Love-In-a-Mist [6].

**Historical background:**

*N. sativa* (Black Seed) was discovered in preserved seeds found with Tutankhamen’s tomb. It is known that Cleopatra had used it for its health and beauty giving qualities. Black seed is found in the book of Isaiah in the Old Testament 28: 25-27. Black seed is also identified as curative black cumin in the Holy Bible [7]. The Greek physician Dioscorides used Black Seed to treat headaches, nasal congestion, toothache and intestinal parasites. Hippocrates regarded *N. sativa* as a valuable remedy in hepatic and digestive disorders [8]. The Prophet Mohammed said “Hold on using the black seed, as it has a remedy for every illness except death” [4]. Ibn Sina [428 H], recommended it to stimulate the metabolism and to recover from dispiritedness and lethargy. The Arabian authors (Ibn-El-Bitar [646 H], Dawood El Antaki [1932]) claimed that the seeds are useful in expelling calculi, lactogouge, emmenagogue and diuretics [9].

**Chemistry:**

*N. sativa* oil has been shown to possess 67 constituents, many of which are capable of inducing beneficial pharmacological effects in humans [10]. By HPLC analysis of *N. sativa* oil, thymoquinone (TQ), dithymquinone (DTQ), thymohydroquinone, and thymol are considered the main active ingredients. *N. sativa* seeds contain other ingredients, including nutritional components such as carbohydrates, fats, vitamins, minerals and proteins, including eight of essential amino acids [11]. Fractionation of whole *N. sativa* seeds using SDS-
PAGE shows a number of protein bands ranging from 10 to 94 kDa molecular mass [12]. Monosaccharides in the form of glucose, rhamnose, xylose, and arabinose, are also found. *N. sativa* seeds are rich in the unsaturated and essential fatty acids. Chemical characteristics, as well as fatty acid profile of the total lipids, revealed that the major unsaturated fatty acid is linoleic acid, followed by oleic acid [11,13]. The major phospholipid is phosphatidylcholine, followed by phosphatidylethanolamine, phosphatidylserine, and phosphatidylinisitol, respectively. The seeds contain carotene which is converted by the liver to vitamin A [13]. The *N. sativa* seeds are also a source of calcium, iron, and potassium [14].

**Respiratory system:**

In Saudi Arabia and neighboring countries *N. sativa* seeds and oil are commonly used for the treatment of asthma. Nigellone (a carbonyl polymer of thymoquinone) proved to be an excellent prophylactic agent for both bronchial asthma and asthmatic bronchitis and was more effective in children than adults [15]. The curative and protective effects of *N. sativa* against asthma may be attributed to its anti-histaminic effect [16]. *N. sativa* volatile oil induced dose dependent increase in the respiratory rate and the intra-tracheal pressure, which were antagonized by mepyramine, atropine and reserpine but not by indomethacin, diethyl-carbamazine or hydrocortisone. A central mechanism was suggested for these effects [17]. In Kuwait the extract of *N. sativa* used with natural fat for epistaxis [18].

**Cardiovascular system:**

In Arabian folk medicine whole seeds of *N. sativa* alone or in combination with honey or garlic are promoted for the treatment of hypertension [19]. *N. sativa* extract lowered blood pressure in dog [20]. The volatile oil and thymoquinone produced a dose dependent decrease in the arterial blood pressure and the heart rate. Atropine, cyproheptadine, and hexamethonium significantly antagonized these effects. However reserpine only antagonized the effects of low doses of volatile oil but not of thymoquinone [21]. The antihypertensive effect may be due to diuretic action of *N. sativa* oil [22]. *N. sativa* seeds showed hypcholesterolemic as well as a reducing effect on triglycerides, HDL and LDL after 4 days of intraperitoneal thymoquinone treatment in albino rats [23].

**Genital system:**

In Omani medicine, *N. sativa* has been promoted for treatment of oligomenorrhoea, to induce menstruation and to treat infertility [24]. The ethanolic extract of *N. sativa* seeds showed antifertility effect in male rats that is probably due to its inherent estrogenic nature [25]. *N. sativa* crude oil induced uterine contractions both in vivo in pregnant rabbits and in vitro of non-pregnant rat uteri [26]. However, volatile oil of *N. sativa* inhibited spontaneous contractions of rat and guinea pig uterine smooth muscle and
those induced by oxytocin [27]. These differences may be due to the different doses, preparations and the animal species used. *N. sativa* oil could produce a spermicidal effect, if it was used locally intravaginally postcoitally in rats. So, *N. sativa* oil could be considered as a postcoital contraceptive [28].

**Urinary system:**

*N. sativa* aqueous extract showed a protective effect against gentamycin-induced nephrotoxicity in unilateral nephrectomized rats [29]. *N. sativa* extract improved phosphaturia, glucosuria, serum creatinine, urea, renal glutathione depletion and lipid peroxide accumulation in doxorubicin induced nephropathy [30].

**Gastrointestinal Tract:**

*N. sativa* used for stomachache, as a digestive, carminative, laxative and anti-jaundice [24]. The alcoholic extract of *N. sativa* had antiulcer activity in pyloric ligation and aspirin-induced gastric ulcer models [31]. The gastroprotective effect of *N. sativa* oil against gastric lesions may be related to the conservation of the gastric mucosal redox state [32]. *N. sativa* administration attenuated the ulcerative effects of ethanol on gastric mucosa by decreasing the glutathione-S transferase levels in gastric mucosa [33]. The anti-ulcer effect of *N. sativa* was possibly prostaglandin-mediated and/or through its antioxidant and anti-secretory activities [34].

The aqueous-methanolic extract of Nigella seeds showed spasmolytic effect mediated through calcium antagonist effect thus providing scientific basis for its traditional use in diarrhea [15]. Oral *N. sativa* powder was reported to relieve flatulence [19]. The smaller dose of thymoquinone (5 mg/Kg) produced partial protection; whereas, higher dose (10 mg /Kg) was found to give complete protection on acetic acid-induced colitis in rats. The possible mechanism of the protective effects might be partly due to an antioxidant action [35].

The hepatoprotective effect of Nigella oil was investigated in some models of liver toxicity. In *Schistosoma mansoni* infected mice, the oil succeeded partially to correct the previous changes in alanine aminotransferase (ALT), gamma glutamyl transpeptidase(GGT) and alkaline phosphatase (AP) activity as well as the albumin content in serum. Thus, *N. sativa* oil suggested to play a role against the alterations caused by *Schistosoma mansoni* infection, an effect which may be induced partly by improving the immunological host system and to some extent with its antioxidant effect [36]. In another study, thymol, one of the constituents of Nigella seeds, exerted hepatoprotective effect an rodents [37]. The protective effect of *N. sativa* oil against carbon tetrachloride and D-galactosamine induced hepatic toxicity in rats was measured as a significant decrease in serum activities of alkaline phosphatase, lactate dehydrogenase, malate dehydrogenase, aspartate aminotransferase, and alanine aminotransferase, and a significant increase in glutathione reductase
Similarly, *N. sativa* administration protected hepatic tissue from deleterious effects of toxic metals such as lead and attenuated hepatic lipid peroxidation following exposure to chemicals such as carbon tetrachloride [33;39]. *N. sativa* also relieved the deleterious effects of ischemia reperfusion injury in the liver [40].

**Central nervous system:**

The aqueous and methanol extracts of *N. sativa* seeds produced an alteration in the general behavior patterns, significant reduction of spontaneous motility, reduction in normal body temperature and significant analgesic action, suggesting CNS depressant action [41].

**Immune system:**

The administration of *N. sativa* one gram twice daily in human volunteers enhanced immune functions as manifested by 72% increase in T helper cell (T4) to T suppressor cell (T8) ratio and an improved natural killer cell activity. However, there was a decrease in the immune globulin (IgA, IgG and IgM) levels [11]. *N. sativa* enhanced the production of cytokines, interleukin-3 and tumor necrosis factor-alpha by human lymphocytes when cultured with pooled allogenic cells or without any added stimulator. They also observed an increase in interleukin-1 beta suggesting that *N. sativa* has an effect on macrophages as well [42]. On mixed lymphocyte culture, whole *N. sativa* seeds and its purified proteins demonstrated stimulatory as well as suppressive effects depending upon the donor and the concentration used [12]. The ethyl-acetate chromatographic of *N. sativa* ethanol extract stimulated cellular immune responses [43].

**Antioxidant:**

Thymoquinone and fixed oil of *N. sativa* were reported to inhibit non-enzymatic peroxidation in ox brain phospholipids liposome [44]. *N. sativa* extracts and thymoquinone, had protective effect against hematological, hepatic, renal and other toxicities induced by anti-cancer drugs and some toxins through their antioxidant action [30]. Thymol, thymoquinone and dithymoquinolone had free radical scavenging effects on the reactions generating reactive oxygen species such as superoxide anion radical, hydroxyl radical and singlet oxygen using the chemiluminescence’s and spectrophotometer methods [45]. *N. sativa* Oil prevented lipid peroxidation and increased the antioxidant defense system in diabetic rabbits [46].

Nigella grains produced about 80% protection against methylnitrosoourea-induced oxidative stress, inflammatory response and carcinogenesis in rats [47]. It decreased the lipid peroxidation, liver enzymes, and increased the antioxidant defense system activity in the carbon tetrachloride (CCl4) treated rats [48]. *N. sativa* attenuated the nephrotoxic side effects of cyclosporine due to its antioxidant properties [49].
Analgesics, anti-inflammatory, and anti-pyretic:

The analgesic effect of crude fixed oil of *N. sativa* and an active principle, thymoquinone, caused by inhibition of cyclooxygenase and 5-lipoxygenase pathways [43]. This effect was confirmed in experimental animal studies [50]. Another possibility for the analgesic action could be the activation of supraspinal mu (1)- and kappa-opioid receptors subtypes as elicited by the antagonistic effect of naloxone, naloxonazine and nor-binaltorphimine [51].

The anti-inflammatory, analgesic and antipyretic effects of the aqueous extract of *N. sativa* in animal models was investigated comparable to aspirin. The extract has anti-inflammatory effect demonstrated by its inhibitory effects on Carragenan induced paw edema. It also produced significant increase in the hot plate reaction time in mice indicating analgesic effect. However, *N. sativa* crude suspension had no effect on yeast induced pyrexia. This study supported its use in folk medicine both as analgesic and anti-inflammatory agents [52]. The aqueous extract of *N. sativa* inhibited the production of nitric oxide, thus its anti-inflammatory action might be mediated partly through this mechanism [53].

Anti-neoplastic:

The topical administration of *N. sativa* extract inhibited the two stages of initiation/promotion skin carcinogenesis. In mice, a dose of 100 mg/kg body weight of their extract delayed the onset of papilloma formation and reduced the mean number of induced papilloma per mouse [54]. Incubation of Nigella extract with cancer cells, the cells were found to be unable to produce fibroblast growth factor and the protein collagenase, which are necessary for blood vessel growth into the tumor, since without a blood supply, a tumor cannot grow [55]. The thymoquinone improved the anti-tumor activity in rats and mice most probably through its antioxidant action [56]. Thymoquinone inhibited tumor incidence and tumor burden significantly both, in-vivo and in-vitro in male Swiss albino rats on fibrosarcoma induced by 20-methylcholanthrene. The possible modes of action were including antioxidant activity and interference with DNA synthesis coupled with enhancement of detoxification processes [57]. The antitumor principle α-Hedrin (saponin) from the seeds of *N. sativa* was extracted and isolated. The extraction caused dose dependent inhibition of tumor induction and tumor growth when given before tumor implantation. The characteristic morphological changes of apoptosis had been observed with the extraction so, apoptosis could be an inducing major mechanism by which α-hedrin prevents tumor growth [43]. Also, α-hedrin had a stimulating effect on the release of nitric oxide by up regulation nitric oxide synthase gene expression in mouse macrophages. Thus explaining a mechanism responsible for its biological effects including its antitumor activities [58]. *N. sativa* alone or in combination with oxidative stress were
found to be effective in vitro in inactivating MCF-7 breast cancer cells, unveiling opportunities for promising results in the field of prevention and treatment of cancer [59]. Thymoquinone killed cancer cells by process that involved apoptosis and cell cycle arrest [60]. The volatile oil of *N. sativa* had the ability to inhibit colon carcinogenesis of rats in the post initiation stage. The inhibition associated, in part, with suppression of cell proliferation in the colonic mucosa [61]. *N. sativa* decreased DNA damage and thereby prevents initiation of carcinogenesis in colonic tissue secondary to exposure to toxic agents such as azoxymethane [62]. In fact, sustained delivery of thymoquinone (derived from *N. sativa*) is almost as effective in causing apoptosis of colon cancer cells as sustained delivery of 5-fluorouracil [63]. Similarly, hepatic metastasis from tumors such as mastocytomas is markedly decreased following administration of *N. sativa* [64]. *N. sativa*, when used in combination with *Hemidesmus indicus* and *Smilax glabra*, decrease hepatic carcinogenesis secondary to exposure to agents such as diethylnitrosamine [65]. These anti-carcinogenic effects are mediated in part by thymoquinone secondary to its inhibitory influence on the NF-kB activation pathway [66]. Thymoquinone induced apoptosis of human colon cancer cells via a p53-dependent mechanism [67]. Ethanolic extracts of *N. sativa* tested against N-methyl-N’-nitro-N-nitrosoguanidine (MNNG), a directly acting mutagen in pre-treatment, combined treatment and post-treatment modules proved an inhibitory effect of the extract on MNNG mutagenicity. A direct antimutagenic activity and an increased recovery at the chromosomal level was detected [68]. Thymoquinone, may be effective in treating hormone-sensitive and hormone-refractory prostate cancer. It inhibited DNA synthesis, proliferation, and viability of cancerous but not noncancerous prostate epithelial cell lines by selective effect on cancer cells, down-regulating androgen receptor [69].

**Anti-microbial, anti-fungal and anti-helminthic:**

The anti-bacterial effect of the phenol fraction of *N. sativa* oil was first reported by Topozada [70]. Thymohydroquinone had high activity against gram-positive microorganisms [71]. A concentration dependent inhibition of gram-positive bacteria (represented by Staphylococcus aureus) and gram-negative bacteria (represented by Pseudomonas aerogenosa and Escherichia coli) was reported. It also showed synergistic effect with streptomycin and gentamycin and additive effect with spectinomycin, erythromycin, tobramycin, doxycycline, chloramphenicol, nalidixic acid, ampicillin, lincomycin and co-trimoxazole [72]. In addition, the extract was found to have a concentration dependent inhibitory effect against pathogenic yeast, and Candida albicans. Crude extracts of *N. sativa* had a promising effect on multi-antibiotic resistant organisms including gram-positive and gram-negative bacteria [73]. The aqueous extract of the seeds possessed a potent in-vivo antifungal activity against candidiasis in mice [74].
N. sativa powder seeds were effective in treatment of cestodes in children [75]. N. sativa seed extract when given orally in a single dose of 40 mg/kg to Giardia lambia infected rats showed 80% cure rate while the same dose of metronidazole showed the same cure rate in another group of animals. They also tried to give the same previous dose of N. sativa seed extract before the animals’ exposure to Giardia lambia infection. The surprising result was 50% protection, i.e. 50% of the animals treated with N. sativa extract showed negative stool analysis for Giardia lambia in spite of exposure to infection. On the other hand, the same dose of metronidazole had only 10% protection [76].

N. sativa seed extract and its main constituent, thymoquinone had protective effects on mouse cells infected with schistosomiasis and against chromosomal aberrations induced as a result of schistosomiasis [77]. N. sativa had antiparasitic effects. Its administration decreased the number of eggs as well as worms in schistosomiasis, which affected hepatic and intestinal tissues [78].

**Hypoglycemic:**

The volatile oil of N. sativa produced a significant hypoglycemic effect on normal and alloxan-induced diabetic rabbits without changes in insulin levels [79]. A significant decrease in blood sugar of healthy human volunteers treated with 1 gram of N. sativa capsules twice daily was detected [80]. 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. The results showed that the hypoglycemic effect of N. sativa oil was, at least partly, because of a stimulatory effect on beta cell function with consequent increase in serum insulin level and possesses insulinotropic properties in type II like model [81]. Significant decrease in blood glucose level together with significant increase in serum insulin level were observed after treatment with N. sativa oil for 4 weeks. Big areas with positive immuno-reactivity for the presence of insulin were observed in the pancreases from N. sativa oil-treated group compared to non-treated one using anti-insulin monoclonal antibody immunohistochemical staining technique. N. sativa is of great therapeutic benefits in diabetic individuals and those with glucose intolerance, as it accentuated glucose-induced secretion of insulin, besides having a negative impact on glucose absorption from the intestinal mucosa [82]. In fact, N. sativa attenuated the damage to β-cells of the pancreas following exposure to toxic elements such as cadmium [83]. N. sativa treatment caused a decrease in the elevated serum glucose, an increase in the lowered serum insulin concentrations and partial regeneration/ proliferation of pancreatic beta-cells in streptozotocin -induced diabetic rats. The hypoglycaemic action of N. sativa could be partly due to
amelioration in the beta-cells of pancreatic islets causing an increase in insulin secretion [48]. Several studies showed that extracts from the seeds of *N. sativa* had antidiabetic effects. A plant mixture containing *N. sativa*, is used by diabetics in Kuwait [84].

**Anti-coagulant:**
A significant shortening of bleeding time in rats was observed after using *N. sativa* extract. 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 [18]. *N. sativa* also shortened the whole blood clotting time and plasma clot time of rabbits [19].

**Anti-histaminic:**
The antihistaminic effect was first investigated by El-Dakhakhany in 1982 [85]. Thymoquinone had protective action against histamine-induced bronchospasm in guinea pigs [85]. Furthermore, in an in vitro study, 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. These effects together with analgesic and anti-inflammatory actions recommended the use of *N. sativa* in folk medicine for treatment of eczema and asthma, as well as for scorpion and spider stings and bites of cat, dog and snake [16].

**Toxicity:**
The toxicity of the fixed oil of *N. sativa* seeds in mice and rats was investigated through the determination of LD50 values and examination of possible biochemical, hematological and histopathological changes. The low toxicity evidenced by high LD50 values, key hepatic enzyme stability and organ integrity suggested a wide margin of safety for therapeutic doses of fixed oil of the Nigella seeds [86].

The above examples clearly illustrate the massive clinical and therapeutic potentials of *N. sativa*. These promising results in prevention and treatment of many diseases deserve recommend use of *N. sativa* in combination of different medical treatments.
REFERENCES


