Nigellology: A Review on *Nigella Sativa*

**Abstract**

*Nigella sativa* and its constitutions including some isolated compounds are the potential remedies of varieties of ailments such as antioxidant, anti-inflammatory, antibacterial, antifungal, antiparasitic and antiprotozoal, antiviral, cytotoxic, anticancer, neuro-, gastro-, cardio-, hepato- and nephroprotective activities. In addition, the *N. sativa* implies beneficiary effects on reproductive, pulmonary and immune systems along with diabetes mellitus (DM), fertility, breast cancer; dermatological complications, dehydration, dyspepsia, osmotic balance and so on. Among the other isolated chemical moieties, thymoquinone (TQ) is a good target for its potential antimicrobial, antifungal, anti-inflammatory, chemopreventive, antitumoral and other activities. The *N. sativa* is evident to promote health in some non-clinical and clinical studies. Otherwise, TQ in a number of animal test systems is evident to produce no negative alterations of the body biomarkers in contrary it improved health quality. This paper depicts a more mechanistic revision on *N. sativa* and its constitutions. In conclusion, findings on *Nigella* may be featured as a health jackpot.

**Keywords:** *Nigella sativa* L.; *Nigella*-constituents; Shrub

**Abbreviations:** 5-HIAA: Hydroxyindole Acetic Acid; 5-HT: Serotonin; ACC: Acetyl Coa Carboxylase; AChE: Acetylcholineesterase; ADA: Adenosine Deaminase; Akt: Protein Kinase B; ALT: Alanine Aminotransferase; AOG: Acid Output; APAP: Acetylcholinesterase; ADA: Adenosine Deaminase; AKT: AkT; ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; bax/bcl-2: Apoptosis Regulator; bcl-1: Cyclin b1; bcl-2: Cyclin b2; bcl-xl: Cyclin b XL, BUN: Blood Urea Nitrogen; CAT: Catalase; CDK-p: Cyclin-Dependent Kinase p; CDK-p: Conjugated Diene; c-JUNK: c-Jun-N-Terminal Kinase; CK: Creatinine; COX-2: Cyclooxygenase-2; CP: Cisplatin; CVS: Cardiovascular System; DM: Diabetes Mellitus; FABPs: Fatty Acid Binding Proteins; FAS: Fatty Acid Synthase; GPx: Glutathione Peroxidase; GSH: Reduced Glutathione; GSH-ST: Glutathione-S-Transferase; HbA-c: Glycosylated Haemoglobin; HDAC: Histone Deacetylase; HDL-C: High-Density Lipoprotein-C; HIV: Human Immunodeficiency Virus; i.: Intra gastric; i.p.: Intrapertitoneal; INF-γ: Interferon-Gamma; IL-1: Interleukin-1; IL-10: Interleukin-10; IL-1β: Interleukin-1 beta; IL-6: Interleukin-6; LDH: Lactate Dehydrogenase; LDL-C: Low-Density Lipoprotein-C; LPO: Lipid Peroxidase; MDA: Malonaldehyde; MPO: Myeloperoxidase; MFI: Mean Fluorescent Intensity; NF-kB: Nuclear Factor-Kappa-B; NK: Natural Killer; NLRP3: Nucleotide-Binding Oligomerization Domain Receptor 3; NO: Nitric Oxide; OSI: Oxidative Stress Index; OXT: Oxytocin; p.o.: Per Oral; PET: Pulmonary Function Test; PGD: Prostaglandin; PGF: Prostaglandin E2; ROS: Reactive Oxygen Species; SCC: Squamous Cell Carcinoma; SOD: Superoxide Dismutase; SP-1: Protein Expression In Papiloma; TAC: Total Antioxidant Capacity; TBA: Thiobarbituric Acid Substances; TC: Cholesterol; TG: Triglycerides; TOS: Total Oxidative Status; TQ: Thymoquinone; TSH: Thyroid Stimulating Hormone; UI: Ulcer Index

**Introduction**

This revision is stimulated by the talks of the noble man, the last Prophet of the religion Islam, Hazrat Mohammad (Sm); who told that the black seed (Scientific name: *Nigella sativa*; Urdu: Kalonji; Arabic: Habba-tu sawda; Habba Al-Barakah; English: Black cumin/ Black seed; Persian: Shonaiz; Bengali: Kalajira; Hindi/Nepali: Mangrai) [1] contains all kinds of remedies except death. When we started, we found large amount of evidence (No. 1290) on this miraculous medicinal plant, belonging to its parts extracts (with aqueous/organic/aqueous-organic solvents), seed oil, essential oil, fatty acids, conjugations, and isolated compounds. A few of them covered co-treatments with other agents including biochemicals. We found a major revision on this plant done by Ahmad et al. [2] along with a dermatological revision of Aljabre et al. [3], an immunomodulatory and anti-inflammatory revision of Amin et al. [4], an anti-inflammatory, antioxidant, an immunomodulatory revision of Gholamnezhad et al. [5], male fertility revision of Mahdavi et al. [6], and metabolic parameters in diabetes mellitus revision of Heshmati & Namazi [7]. These six articles inspired me to take them as a guide for previous evidences on *N. sativa*. Finally, we selected the potential publications on this plant from 2014 to March 15, 2016 and from the accumulated data we present here an activity-wise revision of this plant with an emphasized on mechanism of action way.

*Nigella sativa* L. (*N. sativa*) is a small shrub (20-90 cm in tall) under the botanical family, Ranunculaceae. It is native to...
Southern Europe, North Africa and Southeast Asia; cultivated in many countries in the world like Middle Eastern, Mediterranean region, South Europe, India, Pakistan, Syria, Turkey, Saudi Arabia [1]. *N. sativa* has tapering green leaves and rosaceous white, yeallow, pink, pale blue or purplish flowers with 5-10 petals. The ripe fruit (capsule: 3-7 united follicles) contains numerous tiny seeds, dark black in color. The seed and oil of *N. sativa* was frequently used in ancient remedies (Unani, Ayurveda, Chinese and Arabic) in Asian countries and in the Middle-East. The use of *N. sativa* seeds had been mentioned by Ibne-Sina (980–1037) in his famous book Al-Qanoon fitt-Tibb [2]. Traditionally *N. sativa* is used as a medicament of a variety of disorders in the respiratory system, digestive tract, cardiovascular system (CVS), kidney, liver, and immune system. Its uses in fatigue and dispiritedness are antique. The most common traditional uses belong to the ailments, including asthma, bronchitis, rheumatism and related inflammatory diseases, indigestion, loss of appetite, diarrhea, dropsy, amenorrhea, dysmenorrhea, worms and skin eruptions. It is also used as antiseptic and local anesthetic [1].

**Chemical Composition**

The black seeds contain protein (26.7%), fat (28.5%), carbohydrates (24.9%), crude fiber (8.4%), total ash (4.8%), volatile oil (0.5-1.6%), fatty oil (35.6-41.5%) [1], cellulose (6.8-7.4%) and moisture (8.1-11.6%) [7]. The seeds are also rich in various vitamins (e.g. - A, B₃, B₄, B₅ and C) and minerals (e.g. - Ca, K, Se, Cu, P, Zn, Fe). Carotene and vanillic acid are also found existing in seeds and roots, and shoots. As fatty components, linolic acid (50-60%), oleic acid (20%), dihomolinoleic acid (10%) and eicodadienoic acid (3%) are the main unsaturated fatty acids. The palmitic acid and stearic acid belong to two main saturated fatty acids, in which α-sitosterol (44-54%) and stigmasterol (6.57-20.92%) are the pioneers [1]. Some other fatty acids such as myristic acid, palmitoleic acid, linoleic acid, arachidonic acid, cholesterol, campesterol, Δ5-avenasterol, Δ7-stigmasterol, and Δ7-avenasterol are also reported by Gharby et al. [8] in *N. sativa*.

The seed contains alkaloids that isoquinoline alkaloids (e.g. - nigellicimine, nigellicimine N-oxide), pyrazole alkaloids or imidazole ring bearing alkaloids (e.g. - nigellidine, nigellicine). It also contains terpenes (e.g. - α-hederin) and saponins. Evidences tell that thymoquinone (2-isopropyl-5-methylbenzo-1,4-quinone, 30-48%), thymohydroquinone, dithymoquinone, p-cymene (7-15%), carvacrol (6-12%), 4-terpineol (2-7%), t-anethol (1-4%), sesquiterpene longifolene (1-8%), α-pinene and thymol etc. are the most important active components in *N. sativa*. The other chemical components are carvone, nigellicine [1], nigellone, citrostradienol, cycloecualenol, gramisterol, lophenol, ostusfoliol, stigmastanol, β-amin, butyrospermol, cycloartenol, 24-methylene-cycloartanol, taraxerol, tirucallol, 3-O-[β-D-xylopyranosyl(1→3)-α-L-arabinopyranosyl]-28-O-[α-L-rhamnopranosyl(1→4)-β-D-glucopyranosyl(1→6)-β-D-glucopyranosyl] hederagenin, esters of unsaturated fatty acids with ≥ C₁₅ terpenoids, esters of dehydrostearic and linoleic acid, aliphatic alcohol, β-unsaturated hydroxyl ketone, hederagenin glycoside, melanthin, melanthigenin, bitter principle, tannin, resin, reducing sugars, glycosidal saponin, 3-O-[β-D-xylopyranosyl(1→2)-α-L-rhamnopraosyl(1→2)-β-D-glucopyranosyl]-11-methoxy-16, 23-dihydroxy-28-methylen-12-enoate, stigma-5,22-dien-3-β-D-glucopyranoside, cycloart-23-methyl-7,20,22-triene-3β,25-diol, nigellicine-4-O-sulite, N. mines A₃, a₂, B₂, N. mines A₁, a₂, B₁, and B₂ [2]. Chemical structures of some important chemical moieties are shown in Figure 1.
Potential Activities

**Nigella versus bacteria**

*N. sativa* is reported to have strong antibacterial activity against gram positive (*Staphylococcus aureus*) and gram negative (*Pseudomonas aeruginosa & Escherichia coli*) species. It shows synergistic effects with streptomycin and gentamycin, while additive with spectinomycin, erythromycin, tobramycin, doxycycline, chloramphenicol, nalidixic acid, ampicillin, lincomycin and co-trimoxazole and similar to topical mupirocin. It can fight against resistant microorganisms, including against many multi-drug-resistant gram positive and gram negative bacteria [3]. According to Manju et al. [9] the EO from *Nigella* is able to protect Artemia spp. from *Vibrio parahaemolyticus*. Dahv [10] suggested that ethanol extract of *N. sativa* (0.5-8%) produced significant anti-Ascaris suum activity.

**Nigella in wound infection**

The wound healing capacity of *N. sativa* was evaluated in farm animals, mice and human gingival fibroblast. The accumulation result were indicated that there was a reduction in absolute differential WBC counts, local infection and inflammation, bacterial expansion and tissue impairment, and free radical production. An elevation of basic fibroblast growth factor and transforming growth factor beta were also reported [3].

**Antioxidant capacity of Nigella**

A number of *in vitro* and *in vivo* antioxidant studies have been conducted with *N. sativa* extracts, seed oil and TQ. The finding is suggesting having potential radical scavenging and inhibitory effects of oxidative stress. TQ effectively changed the parameters including adenosine deaminase (ADA), catalase (CAT), myeloperoxidase (MPO), lipid peroxidase (LPO), reduced glutathione (GSH), glutathione-S-transferase (GST), glutathione peroxidase (GPx), superoxide dismutase (SOD) and nitric oxide (NO). It also reduced the malonilealdehyde (MDA), conjugated diene (CGD) levels and pro-inflammatory mediators interleukin-1beta (IL-1β), interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), interferon-gamma (IFN-γ), and prostaglandin (PGE2) rather than interleukin-10 (IL-10) [1,4]. Figure 2 tells the basic antioxidant pathways of *Nigella* and its constitution.

**Nigella in inflammation**

Findings from different animal models suggest that *N. sativa* extracts, seed oil and TQ have anti-inflammatory potentials. This activity belongs to the reduction of NO production, interleukin-1 (IL-1), cyclooxygenase-1 (COX-1), cyclooxygenase-2 (COX-2), histone deacetylase (HDAC) along with other pro-inflammatory mediators such as - IL-1β, IL-6, TNF-α, IFN-γ, and PGE$_2$ [2].
application of TQ induced the expression of hemeoxygenase-1, NAD(P)H-quinoneoxidoreductase-1, GSH-ST and glutamate cysteine ligase in mice; while the seed oil inhibited COXs, 5-LPO in the pathways of arachidonate metabolism in rats [3]. TQ was also shown to diminish nuclear translocation and the DNA binding of nuclear factor-kappa-B (NF-κB), c-Jun-N-terminal kinase (c-JUNK) and p38 mitogen-activated protein kinase (MAPK-p38). A decrease in expression of NLRP3 (NACHT, LRR, and pyrin domain-containing protein 3) in B16F10 mouse resulted in inactivation of caspase-1 followed by the inhibition of IL-1β and IL-18. In addition, the inhibitory effect of TQ to NF-κB and reactive oxygen species (ROS) resulted in the partial inactivation of NLRP3 inflammasome [3-5]. Figure 3 tells the basic anti-inflammatory activity pathways of Nigella and its constitution.

**Figure 2:** Anti-oxidative action pathways of Nigella and its recipe.

**Figure 3:** Anti-inflammatory capacity pathways of Nigella and its recipe.

### Nigella in cancer

The black seed oil is an enhancer of the NK cells, which is a potential applicability in immune therapy. However, the components in oil may induce antioxidative-induced prooxidant effects thus the carcinogenetic effect. In addition, TQ tested in a number cancer cells derived from mice, suggesting its ability to arrest G0/G1 phases of cell-cycle, which correlated with sharp increases in the expression of the cyclin-dependent kinase p16 (CDK-p16) and a decrease in cyclin-d1 (dcl-1) protein expression in papiloma (SP-1) cell line and G/M arrest associated with an increase in the expression of the tumor suppressor protein p53 with a decreased level of cyclin-b1 (bcl-1) protein. The chemopreventive potential of TQ may be due to its ability to increase the ratio of apoptosis regulator (bcl-4)/cyclin-2 (bax/bcl-2) expression and decreasing cyclin-xl (bcl-xl) protein. The antitumor activity of TQ was also reported in squamous cell carcinoma (SCC-VII), B16 and murine tumor models of fibrosarcoma and SCC. TQ showed potent anticancer activity in A549 and Hep-2 cells via apoptosis by increasing the sub-G0 population, live/dead cytotoxicity, chromatin condensation, DNA laddering and TDT-positive cells. Along with an increase in bax/bcl-2 ratio activation of cell proliferation of caspases and cleavage of poly ADP ribose polymerase were observed [3]. A research done by Khalife et al. [13] suggesting that TQ induced apoptosis through p53-independent pathway with an expression of p21 and arrested cell-cycle S phase in human colon cancer cells. TQ is also anticancer agent to a number of cell lines including MCF-7/Tpox breast carcinoma cells and is a significant down-regulator of NF-κB and MMP-9 in Panc-1 cells and bcl-2 in gastric cancer cells, while up-regulator of caspase-3 and caspase-9 in the latter one. A number of derivatives of TQ namely 6-menthoxybutyryl, 6-hencosahexanyl conjugate, 4-acylhydrazones and 6-alkyl derivatives are also evident to produce anticancer activity in cancer cell lines [1]. Recent evidence suggests that the nanoemulsion of Nigella oil at a dose of 20-80µL/mL caused cell membrane blebbing, cytoplasmic vacuolation, marginalization of chromatin, and fragmentation of the nucleus in MCF-7 cells [14]. A recent evidence suggests that topical use of black seed oil (600mg) reduced cyclic mastalgia in woman (n=52) and the activity is significantly comparable to the painkiller, diclofenac [15]. A basic Nigella-anticancer potential has been sketched in Figure 4.

### Nigella in diabetes

*N. sativa* was found playing an important role in the reduction of blood glucose level with an augmenting insulin level and C-peptide in rats. TQ reduces the tissue MDA levels, DNA damage, mitochondrial vacuolization and fragmentation, and preserves pancreatic β-cell integrity via antioxidant capacity. In a study TQ is evident to increase the levels of insulin, Hb with a significant
Possible anti-diabetic action pathways of \(N.\ sativa\) and retinopathy. Figure 5 tells the possible anti-diabetic action pathways of \(N.\ sativa\) and its derivatives.

\(N.\ sativa\) on immune system

Along with NK antitumor activity, \(N.\ sativa\) is a demodulator of secretion of a number of pro-inflammatory mediators with up-modulation of secretion of Th\(_1\) versus Th\(_\gamma\) cytokines in splenocytes. The black seed extract also evident to restore the resistance against granulocyte-dependent \(C.\ albicans\). A study performed by the oil suggests decreasing antibody production in typhoid vaccination, which may be due to its immunosuppressive cytotoxic effect. It is also evident to correct the imbalance situation caused by oxytetracycline (OXT) in leukocyte, lymphocyte counts, heterophil: lymphocyte ratio, lysosomal enzyme activity and reticuloendothelial system function. However, it produced immunoprotective effect when chronic administration of antibiotic occurred in pigeons. The black seed oil also acted as a radioprotective agent against immunosuppressive and oxidative effects of ionizing radiation. In addition, an increased level of IFN-\(\gamma\) with a significant decreased in pathological changes of the guinea pigs’ lung was reported by \(N.\ sativa\) oil treatment. It is also effective in allergic diarrhea [2,4,5]. A recent evidence suggests that seed oil is protective against \(\gamma\)-radiation-induced damage in jejunal mucosa [19]. \(N.\ sativa\) EO at a dose range of 5-20\(\gamma\)/kg (oral feed) in chickens improved FCR and plasma lipid profile [19]. In addition, \(N.\ sativa\) oil reduced thyroid stimulating hormone (TSH) and anti-thyroid peroxidase antibodies in patients with Hashimoto’s thyroiditis [21].

Methanolic extract of \(N.\ sativa\) is a potent analgesic and antidepressant. In addition, an anxiolytic activity via increasing serotonin (5-HT) and decreasing hydroxyindole acetic acid (5-HIAA) levels were noticed in rat brain. An increased 5-HT secretion along with improving learning and memory capacity were detected in rats. As it caused an augment in tryptophan levels, it may be helpful in anxiety treatment. Otherwise, TQ produced GABA-mediated anxiolytic-like effect in mice with a decline of NO and MDA production [2]. The possible neuroprotective activity may be due to its antioxidant, free radical scavenging and anti-inflammatory capacities. Along with these phenomena anti-acetylcholinesterase (anti-AChE) suggests \(N.\ sativa\) and TQ having anticonvulsant activity. There is a suggestion for GABAAergic anticonvulsant effect of TQ [2], \(N.\ sativa\) EO at 1\(\gamma\)/kg/day and TQ 30\(\gamma\)/kg/day (i.p.) in Wistar albino rats produced anti-nitrosative effects after a 10 days treatment [22]. \(N.\ sativa\) EO is also evident to prevent cerebral edema in the hippocampus.
tissue of the rat brain [23]. Fahmy et al. [24] suggested that oil at a dose of 2.8g/kg when treated orally (p.o.) in autoimmune encephalomyelitis rats for 4 weeks reduced oxidative stress parameters in the cortex and hippocampus as well as enhanced remyelination in the hippocampus. Otherwise, oil at a dose of 4mL/kg/day (p.o.) in tramadol treated male albino rats protected the cortical neurons and myelinated axons [25]. Nigella EO at 500mg in adolescent human males (n=48) stabilized mood, decrease anxiety and modulate cognition for a 4 weeks treatment [26]. A possible neuroprotectivity and activity on NS is shown in Figure 6.

**Nigella on gastrointestinal tract (GIT) system**

TQ is gastroprotective as it decreases gastric acid secretion, acid output (AO), pepsin, the mucosal content/activity of lipid peroxidase (LPO), proton (H+) pump, MPO and ulcer index (UI) while an increased in the content/activity of gastric mucin, GSH, total nitric oxide (TNO) and SOD. Decreased ulcer severity in rats was guessed via prostaglandin (PGD)-mediated and/or through antioxidant and antisecretion pathways. A decreased LPO and lactate dehydrogenase (LDH), MPO, MDA and increased GSH, SOD, GPx, GSH-ST without altering of gastric CAT was also reported in rats. TQ was found significant effects in diarrhea, colitis, inflammatory bowel diseases, anti-Helicobacter pylori and body weight loss [1]. Possible GIT protective pathways of *Nigella* and its constitution are shown in Figure 7.

**Nigella on cardiovascular system (CVS)**

TQ is evident to decrease motor fuel (diesel particle)-induced systolic blood pressure, leukocytes, IL-6 and plasma SOD activity. It is also prevented to decrease platelet counts and the prothrombin events rather than platelet aggregation [2]. The black seed oil reduced the total cholesterol (TC), low-density lipoprotein-C (LDL-C), and thyroglobulin (TG) with an increased high-density lipoprotein-C (HDL-C) level [27].

**Nigella in hepatic system**

*N. sativa* effect on alanine aminotransferase (ALT), aspartate aminotransferase (AST), LDH, total antioxidant capacity (TAC), CAT, MPO, total oxidative status (TOS) and oxidative stress index (OSI) tells that it has hepatoprotective activity. In addition GSH, TQ increased protein carbonyl content, thus the attenuation of protein oxidation and upgrading of the depleted antioxidant cellular fraction [2]. *N. sativa* oil at a dose of 25-100μg/mL protected hepatocytes from N-acetyl-p-aminophenol (APAP)-induced hepatotoxicity and metabolic disturbances in TIB-73 cells of mice [28]. A similar activity was also observed by Hamza & Salem Al-Harb [29] with aqueous extract of *N. sativa*, where the activity was thought to be linked with improving antioxidant potential and suppressing both lipid peroxidation and ROS generation [28]. The black seed oil at a dose of 2mg/kg (p.o.) with cisplatin (CP)-treated rats are also evident for its hepatoprotective activity via improving energy metabolism and strengthening antioxidant defence pathways [30].

**Nigella in urinary system**

*N. sativa* along with ascorbic acid (Vitamin C) produced a nephroprotective effect by lowering serum creatinine (CK), blood urea nitrogen (BUN) and antioxidant activity in rabbits. Otherwise, TQ showed an effect on renal expression of organic ion transporters and multidrug resistance-associated proteins in rats. An increased protein levels of the efflux transporters MRP2 and MRP4 and decreased expression of OAT1, OAT3, OCT1 and OCT2 was observed in rats. Along with decreasing tubular necrosis score, *N. sativa* is a good reducer of CK, urea, MDA, NO, ROS, OSI and TOS levels and augmenter of TAC, SOD, GPx in kidney tissue and blood. TQ is evident to have a complete reversal of the gentamicin (GM)-induced alteration of serum CK, BUN, thiobarbituric acid
substances (TBARS), total nitrite/nitrate content, GSH, GPx, CAT and ATP values in rats [2]. The black seed ethanol extract at 250-100mg/kg (p.o.) in female Wistar Albino rats showed a significant nephroprotective activity on paracetamol-induced nephrotoxicity [31]. Otherwise, Cd-induced nephroprotectivity is also evident in rats by Erboga et al. [32].

**Nigella on pulmonary system**

Both nigellone and TQ are evident to inhibit leukotriene-d₄ (LT₄) in the trachea, where the activity of the first one was concluded via mucociliary clearance. *N. sativa* reduced a significant peribronchial inflammatory cell infiltration, alveolar septal infiltration, alveolar edema, alveolar exudates, alveolar macrophages, intestinal fibrosis, granuloma, necrosis formation, NOS and a rise in surfactant protein D in the pulmonary system. *N. sativa* is also evident to have beneficial effects against lung injury and hypoxia-induced lung damage. Moreover, *N. sativa* puffs are proven to relieve asthma symptoms, frequency of asthma symptoms/weakness, chest wheezing and pulmonary function test (PFT) values with a bronchodilatory effect [2].

**Nigella on reproductive system**

TQ decreased TAC and MPO levels in C₅7BL/6 male mice. In addition, TQ alerted the events produced by methotrexate such as intestinal space dilatation, edema, disruption in the somniferous epithelium and reduced diameter of the seminiferous tubules. Infertile men (n=34) when treated with 2.5mL black seed oil for 2 months improved abnormal semen quality without producing any adverse effect was observed [33]. According to Mahdavi et al. [6] the black seed oil is a good candidate for treating male infertility. Hexane and methanol extracts of *N. sativa* produced significant anti-fertility in Sprague-Dawley male and female rats, respectively. Otherwise, *N. sativa* inhibited uterine smooth muscle contraction in rats and guinea pigs [2,6]. TQ when treated with olive oil caused reduction of polycystic overy in rats via NF-κB signaling pathway [34].

**Nigella in dyspepsia**

Patients (n=70) with functional dyspepsia when treated with *Nigella* oil of 5mL (p.o.) for 8 weeks, a significant lowering of dyspepsia was observed [35].

**Nigella in osmotic balance**

The geriatric patients (n=42) when treated with black seed oil (22.6µg/25µL) for 2 weeks, it was concluded that it should be an alternative therapy of the isotonic sodium chloride (0.9% NaCl) solution [36].

| Form/Chemicals          | Dose/R.O./Test Systems                | Activity                                                                 | References                              |
|-------------------------|--------------------------------------|--------------------------------------------------------------------------|-----------------------------------------|
| Essential Oil           | 5-50g/L for antioxidant assay, 0.2-2.0µg/mL for antimicrobial | Produced antioxidant activity and protected the *Artemia spp.* after experimental infection of Vibrio parahaemolyticus Dahv-2. | Manj et al. [41]                        |
| Oil                     | p.o. Administration in 22-50 yrs old patients | Reduced thyroid stimulating hormone (TSH) and anti-TPO antibodies in patients with Hashimoto’s thyroiditis. | Tajmiri et al. [21]                     |
| Essential Oil Nanoemulsion (20-50nm diameter) | 20-80µL/mL in MCF-7 cells | Produced cell membrane blebbing, cytoplasmic vacuolation, marginalization of chromatin, and fragmentation of the nucleus. | Periasamy et al. [14]                   |
| Oil                     | -                                   | Reduced total cholesterol, LDL-C, and TG levels and increased HDL-C.     | Sahebkar et al. [27]                    |
| Oil                     | 400mg/kg (l.g.) in Wistar albino rats | Lower malondialdehyde (MDA) levels, raised reduced glutathione peroxidase (GSH-Px) and superoxide dismutase (SOD) activity in intestinal tissues samples. | Orhon et al. [42]                      |
| Oil                     | 25-100µg/mL in TIB-73 cells in mice  | Protective effects against N-acetyl-p-aminophenol (APAP)-induced hepatotoxicity and metabolic disturbances by improving antioxidant activities and suppressing both lipid peroxidation and ROS generation. | Adam et al. [28]                       |
| Oil                     | -                                   | Antioxidant and antimicrobial activities.                                | Ramadan [43]                            |
| Phenolic-Protein Complexes | 100µL in in vitro test.             | Antioxidant and ACE inhibitory properties.                              | Alu’datt et al. [44]                    |
| n-Hexane and Ethanol Fractions | 50-2000µg/mL in ACHN (human renal adenocarcinoma) and GP-293 (normal renal epithelial) cell lines | Cytotoxic activity.                                                      | Shahraki et al. [45]                    |
| Oil                     | 2mg/kg (p.o.) in cisplatin (CP) treated rats | Induced hepatoprotective by improving energy metabolism and strengthening antioxidant defense mechanism. | Farooqui et al. [30]                   |
| Compound                  | Effect                                                                 | Study Reference |
|--------------------------|------------------------------------------------------------------------|-----------------|
| Gold Coated Nanoparticles| Inhibited A<sub>50</sub> lung cancer cells and S. aureus.              | Manju et al. [41]|
| TQ                       | Remedy for polycystic ovary via NF-κB signaling pathway.               | Arif et al. [34]|
| TQ                       | Strongly inhibited fMLF-induced superoxide production and granules exocytosis in neutrophils. | Boudiaf et al. [46]|
| Seeds Ethanol Extract    | Significant nephroprotective activity on paracetamol-induced nephrotoxicity. | Canayakin et al. [31]|
| TQ                       | Significant nephroprotective potential against Cd-induced toxicity.    | Erboga et al. [32]|
| TQ                       | Antimethicillin-resistant activity.                                    | Hariharan et al. [10]|
| TQ                       | Induced apoptosis through p53-independent pathway with an expression of p21 and arrested cell-cycle S phase. | Khalife et al. [13]|
| Oil                      | Clinical effectiveness comparable to topical diclofenac in the treatment of cyclic mastalgia. | Huseini et al. [15]|
| Oil                      | Oral health and hygiene.                                              | Al-Attass et al. [37]|
| Oil                      | Ameliorated the toxic changes caused by formaldehyde on corneas.       | Salem et al. [47]|
| Oil                      | Decreased levels of MDA, NO, TNF-α, IL-1, increased activities of SOD, GPx, CAT with reduction of motor neuron apoptosis. | Gökce et al. [48]|
| TQ                       | Protective action associated with normalization of chronic accumulation of malonyl CoA, and elevation of acetyl CoA carboxylase (ACC), fatty acid synthase (FAS) and fatty acid binding proteins (FABPs) following chronic glucose overload. Thus the modulated β-cell redox circuitry and enhancing sensitivity of β-cell metabolic pathways to glucose and glucose-stimulated insulin secretion (GSIS) under both normal conditions and hyperglycemia. | Gray et al. [18]|
| EO                       | Antioxidant and anti-yeast activities.                                 | Nadaf et al. [11]|
| Oil                      | Protected the cortical neurons and myelinated axons.                  | Omar [25]|
| Methanol Extract         | Antioxidative and hypolipidemic effects.                               | Ahmad & BEG [49]|
| Ethanol Extract          | Increased cytokines balance in Th<sub>1</sub>/Th<sub>2</sub>            | Gholamnezhad et al. [50]|
| Oil                      | Modulated systemic inflammatory biomarkers.                            | Mahdavi et al. [51]|
| Oil                      | Lowered dyspepsia                                                     | Mohtashami et al. [35]|

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| Component | Method of Administration | Dosage | Effects |
|-----------|--------------------------|--------|---------|
| EO and TQ | 1g/kg (i.g.)/day and TQ 30 mg/kg/day (i.p.) in Wistar albino rats for 10 days | Produced anti-nitrosative effects. | Ahlati et al. [22] |
| EO | 1-5mg/kg (i.p.) in Wistar rats | Prevented cerebral edema in the hippocampus tissue of the brain. | Hobbenaghi et al. [23] |
| EO | 5-20g/kg (oral feed) in chickens for 6 weeks | Improved FCR of boilers and improved plasma lipid profile and antibody-mediated immunity. | Ghasemi et al. [20] |
| Methanol Extract | 200mg/kg (p.o.) in male albino Wistar rats for 2 months | Anti-inflammatory activity by down-regulation of the expression of ASC protein of NLRP3 inflammasome in pancreas to minimize the activation of caspase-1. | Suguna et al. [58] |
| EO | 500mg in adolescent human males (n=48) for 4 weeks | Stabilized mood, decrease anxiety and modulate cognition. | Sayeed et al. [26] |
| Ethanol Extract | 0.5-8% in Ascaris suum | Anti-helminthic effect. | Simalango & Utami [12] |
| Aqueous extract | 0.25g/kg in mice for 30 days | Powerful reducing capacity of APAP-induced hepatotoxicity and antioxidant activity. | Hamza & Salem Al-Harbi [29] |
| Oil | 3g/day (one three times a day) in T2DM patients (n=72) | Improved glycemic status and lipid profile. | Heshmati et al. [17] |
| Oil | 100-400mg/kg (i.p.) in rats | Prevented hippocampal neural damage which is accompanied with improving effects on memory. | Seghatoleslam et al. [53] |
| Hydro-Alcoholic Extract | 100-400mg/kg (p.o.) in rats for 8 weeks | Decreased MDA concentration, improved learning and memory capacity through antioxidative ways. | Beheshti et al. [54] |
| Methanol Extract | 0.1mg/disc in Trichophyton mentagrophytes, Microsporum canis and Microsporum gypseum | Antifungal activity. | Mahmoudvand et al. [55] |
| Oil | 1mg/kg in tramadol-induced male albino rats for 30 days | Hepato- and nephroprotective effects. | Elkhateeb et al. [56] |
| Oil | 2.8g/kg (p.o.) in autoimmune encephalomyelitis rats for 4 weeks | Reduced oxidative stress parameters in the cortex and hippocampus as well as enhanced remyelination in the hippocampus. | Fahmy et al. [24] |
| Lipid (4%) and Volatile (5%) Fractions | In streptozotocin induced diabetes mellitus Sprague Dawley rats for 56 days | Reduced toxicological and adverse consequences of diabetes mellitus. | Sultan et al. [16] |
| Oil | 2.5 and 5.0mL/kg (p.o.) in rats for 3 weeks | Increased plasma transaminase activities, hepatic triglyceride, malondialdehyde (MDA) levels and decreased hepatic glutathione (GSH) levels | Develi et al. [57] |
| Oil | 2.5mL in infertile men (n=34) for 2 months | Improved abnormal semen quality without producing any adverse effect. | Kolahdooz et al. [33] |
| Oil | 22.6µg/25µL in geriatric patients (n=42) for 2 weeks | Can be used as an alternative to the isotonic sodium chloride solution. | Oysu et al. [36] |
| EO and TQ | EO 1g/kg (i.g.) and TQ 30 mg/kg/day (i.p.) in Wistar albino rats for 10 days | Produced anti-nitrosative effects. | Ahlati et al. [22] |
| EO | 1-5mg/kg (i.p.) in Wistar rats | Prevented cerebral edema in the hippocampus tissue of the brain. | Hobbenaghi et al. [23] |
| EO | 5-20g/kg (oral feed) in chickens for 6 weeks | Improved FCR of boilers and improved plasma lipid profile and antibody-mediated immunity. | Ghasemi et al. [20] |
| Methanol Extract | 200mg/kg (p.o.) in male albino Wistar rats for 2 months | Anti-inflammatory activity by down-regulation of the expression of ASC protein of NLRP3 inflammasome in pancreas to minimize the activation of caspase-1. | Suguna et al. [58] |
| EO | 500mg in adolescent human males (n=48) for 4 weeks | Stabilized mood, decrease anxiety and modulate cognition. | Sayeed et al. [26] |
| Ethanol Extract | 0.5-8% in Ascaris suum | Anti-helminthic effect. | Simalango & Utami [12] |
**Topical Applications**

TQ-induced skin darkening via cholinergic mechanisms of muscarinic receptor in the melanin dispersion is evident, whereas, *N. sativa* oil for decreasing vitiligo area scoring index without seeing adverse effects. However, TQ and nigellone inhibited histamine release, protected histamine-induced bronchospasm in guinea pigs, decreased lung ensphilia, elevated Th$_2$ cytokines and raised Ig$_e$ and IgG$_1$ antibodies in mice. Otherwise, *N. sativa* is a good recommendation in hand eczema. Linoleic acid from this plant is known for its percutaneous adsorption enhancing capability of drugs, while the oil emulsion for reducing skin irritation and improving moisturizing and epidermal barrier function. It has also anti-aging, mitigating, and protective potentials [3]. There is evidence on oral health and hygiene of black seed oil and TQ [37].

**Nigella lethal dose (LD)**

In mice, the dose causing death of fifty percent experimental animals (LD$_{50}$) values of fixed oil of black seed was reported to be 26.2-31.6mg/kg and 1.86-2.26mg/kg with single oral (p.o.) and intraperitoneal (i.p.) doses, respectively. In another study, calculated LD$_{50}$ for TQ was 89.7-119.7mg/kg and 647.1-1094.8mg/kg after i.p. and p.o. administrations, respectively. In rat it was found to be 45.6-69.4mg/kg and 469.8-1118.8mg/kg after i.p. and p.o. administration, respectively. Data, suggesting TQ is more tolerated than the extract from *N. sativa* [2].

**Drug interactions**

Table 2 tells that *N. sativa* has a good number of beneficial drug/chemical/biochemical interactions.

| Drug/Chemical/Biochemical (Induced Activity) | Nigella Recipe | Observations     |
|---------------------------------------------|----------------|-----------------|
| Ampicillin                                  | //             | //              |
| Amoxicillin                                 | Methanol and Hexane Extract | Increased Availability |
| Antibiotics                                 | *Nigella*      | Decreased Resistance |
| Antiasthmatic Drugs                         | //             | Like/Synergistic |
| Ascorbic Acid (Vitamin C)                   | TQ             | //              |
| Ba/Carbachol/Leukotriene                    | TQ             | //              |
| Cadmium/Gd$_{12}$                           | //             | //              |
| Chloramphenicol                             | //             | //              |
| Cisplatin                                   | TQ             | Antagonistic    |
| Collagen                                    | TQ             | Antagonistic    |
| Co-Trimoxazole                              | //             | //              |
| Curcumin/Valproate Ameliorate               | //             | Agonistic       |
| Cyclosporine A                              | Seed Oil       | //              |
| 1,2-Dimethylhydrazine                       | Methanol Extract/TQ | //              |
| Diesel Exhaust Particle                     | //             | //              |
| Doxycycline                                 | //             | //              |
| Doxorubicin                                 | Seed Extract/TQ | Synergistic     |
| Ethynlestradiol                             | Seed Oil       | Like/Synergistic |
| Ethanol/NaOH/NaCl/Indomethacin              | //             | Antagonistic    |
| Erythromycin                                | //             | //              |
| Fe-NTA                                      | //             | //              |
| 5-Fluourouracil                             | TQ             | //              |
| Formaldehyde                                | //             | //              |
| Garlic Extract                              | //             | //              |
| Gentamycin                                  | *Nigella* Oil  | Synergistic     |
| Ionizing Radiations                         | *Nigella* Extract/TQ | //              |
| L-carnitine/α-Lipoic Acid | Nigella | Synergistic |
|--------------------------|--------|------------|
| Lincomycin               | //     | //         |
| L-N(G)-Nitroarginine Methyl Ester/ N-Acetylcysteine | Seed Oil | // |
| Methicillin              | //     | Antagonistic |
| Methotrexate             | //     | //         |
| Methylene Blue/Diazepam  | //     | //         |
| Mupirocin                | //     | //         |
| NaNO$_3$                 | Seed Powder | // |
| Nalidixic Acid           | //     | //         |
| Nicotinamide             | //     | //         |
| NO Precursor/L-Arginine  | //     | Antagonistic |
| Olive Oil                | //     | //         |
| Omeprazole               | TQ     | Agonistic |
| OVA-Antigen              | TQ     | Antagonistic |
| Oxytocin                 | //     | Antagonistic |
| Oxytetracycline          | //     | //         |
| Paracetamol              | TQ     | Antagonistic |
| Parath-Hormone           | Nigella | Synergistic |
| p-Cymene/α-Piene         | TQ     | //         |
| Pilocarpine              | //     | //         |
| Prazequental             | //     | Synergistic |
| Spectinomycin            | //     | Additive |
| Streptomycin             | //     | //         |
| Streptozotocin           | TQ     | Antagonistic |
| Tobramycin               | //     | //         |
| Topotecan                | //     | Additive |
| Typhoid Vaccine          | Seed Extract | Antagonistic |

**Conclusion**

Drugs from the shrubs are one of the potential plant derived sources. Interestingly, now a day herbal medicaments are in a great attention to the consumers world-wide. Otherwise, traditional medicines are still occupying a remedy-kingdom in particular areas. A potential and diverse activity of a scrupulous source is the stimulation to the drug researchers. *N. sativa*, in the previous literatures showing the shot, particularly TQ and its derivatives, nigellone, α-hederin and linoleic acid produced remarkable pharmacological activities. In addition, few clinical uses of human, suggesting that *N. sativa* and its constitution have safety profile.

**Featuring**

At low levels and temporary spikes of ROS are beneficial for health [38] rather than high production and chronic effects as they cause induction of pro-inflammatory cytokines, chemokines and pro-inflammatory transcription factors (NF-κB) [39] as well as induction of cell death by damaging macromolecules such as lipids, DNA, RNA, and other proteins. In extrinsic pathway, excessive ROS are generated by Fas ligand which in association with death domain and caspase 8 cause apoptosis [39]. Otherwise, in the caspase cascade pathway (intrinsic) ROS facilitate to release cytochrome C by activating bcl-2 and bcl-xl and bcl-2-associated X protein as well as bcl-2 homologous antagonist/killer [40]. ROS implicates a variety of detrimental responses including CVS diseases (e.g. stroke and heart attack), hearing impairment via cochlear damage, decline memory capability (degenerative diseases, e.g. AD), ischaemic injury, and so on. Unlike apoptosis and necrosis, autophagy cell death occurs by self-digest of the damaging portion to take an attempt to minimize the damage and can no longer survive. However, it is possible to make available ROS to the other normal cells by this process as cellular

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programming is enough for a programmed cell death. Radiations form radiotherapy induces ROS-mediated cell death and mitotic failure [39]. However, an ideal ROS neutralizer (antioxidant/ cytoprotective agent) is not enough in the cancer therapy, even if it has antioxidant-mediated prooxidant capacity, as it may act like dual nature of ROS! Therefore, cell targeting, self-redox balancing; genotoxic, but non-mutagenic, exact concentrations of ROS at the targeted site along with action period are the major concerns in the chemo-/radio-therapeutic cancer treatments.

In the above discussion, TQ, the well-known *Nigella* derived quinone and other *N. sativa* constitutions are evident to have target for a range of cellular proteins in their activity pathways. Having strong antioxidant capacity through antiradical including ROS, direct reduction of oxidizable substrates and induction of cellular antioxidant molecules, they may be good sources as cytoprotectives agents, especially, the TQ, although the whose mutagenic effect is yet to be found out. The carcinogenic and immunosuppressive cytotoxic effects of *N. sativa* oil can be overcome by co-treatment with antibiotics or radiotherapy. Being a spacious habitual world-wide and having a good number already isolated chemical moieties of *N. sativa* is a weapon to the drug scientists. A number research has been done on this plant and its isolated compounds, especially on TQ and its derivatives and nigellone telling that chemical modification may bring a fruitful outcome to the drug library. In addition, some clinical uses suggest that *N. sativa* is safe and health promoter, especially observed in anti-fertility test. Although, the exact mechanism of action of the investigated pharmacological potentials yet to be found out, but the toxicological and its interaction profiles suggesting beneficial rather than detrimental effects. Generally, substances having antioxidant, antimicrobial cytotoxic other than genotoxic and mutagenic potentials are good for healthy consumption. TQ falls in this category, although the genotoxic and mutagenic potentials are still to be investigated. Finally, for its wide variety of activities, *Nigella* may be called the ‘marvelous shrub’.

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