A REVIEW OF PLANT NIGELLA SATIVA: A BRIEF CONSIDERATION OF ITS PHARMACOGNOSTIC CHARACTERS, CHEMICAL CONSTITUENTS AND THERAPEUTIC BENEFITS

KS Sandhu¹*, AC Rana²

¹Department of Pharmacology, Punjab Technical University/Rayat Inst. of Pharmacy Railmajra, SBS Nagar, Punjab, India.
²Department of Pharmacology, Punjab Technical University/Rayat Inst. of Pharmacy Railmajra, SBS Nagar, Punjab, India.

ABSTRACT
Nigella sativa Lin. (family- Ranunculaceae) is a widely used medicinal plant throughout and popular in various Indigenous System of medicines. The seeds are used as astringent, bitter, stimulant, diuretics, emmenagogue and anthelmintic traditionally. They are also useful in jaundice, intermittent fever, dyspepsia, paralysis, piles and skin disease. The present review is therefore, an effort to give a detailed survey of the literature on Phytochemistry Pharmacognosy, and Pharmacological activities of the plant. The paper discusses all the chemical constituents including fixed oil, volatile oil and non oily components like minerals, saponins and alkaloids. The macroscopic, microscopic and physical constants of plant are discussed. Further, it also explores the medicinal potential and therapeutic values of some of the individual components present in the extracts of the seeds. All the potential researches on Nigella sativa on various disorders were concisely detailed. Thymoquinone, the most abundant constituent of black seed essential oil, has been shown to be the active principle responsible for many of the seed’s beneficial effects.

Keywords: Nigella sativa, Thymoquinone, Pharmacognosy, Pharmacology, CNS Disorders.

INTRODUCTION

Abu Huraira (Allah be pleased from him) narrated that Allah’s Apostle (peace be upon him) said “Use the black seed, which is a healing for all diseases except ‘As-Sam’ and As-Sam is Death [1].”

-Prophet Muhammad

Nigella sativa (N. sativa) seeds, called as ‘Black Seed’ in English language, ‘Al-Habba Al-Sauda’ or ‘Al- Habba Al-Barakah’ in Arabic and ‘Kalvanji’ in Urdu and some local languages in the Indian Subcontinent, is well known in the Middle East, Middle Asia and Far East as a natural remedy for many ailments and as a flavouring agent in bread and prickles¹. It belongs to family Ranunculaceae. The species is generally a short-lived
annual, herbaceous plant. The height of the plant is approximately 20-60 cm. It possesses grayish green linear leaves that are wispy and thread-like. The flowers are delicate, pale blue or white, with a variable number of sepals and 5-10 petals that are about 2.5 cm wide [2], [3], [4]. The flowers are distinguished by the occurrence of nectaries. The gynoecium consists of varied number of multi-ovulate carpels, which develop into follicles after pollination. The fruit is large and inflated, with 3-7 integrated follicles, each one with numerous seeds. Seeds are normally small (1-5 mm long), black or dark-grey with a rough grooved surface and an oily white interior [5], [6]. They are roughly triangular and possess a strongly pungent smell. They contain about 21% protein, 35% carbohydrates and 35-38% plant fats and oils. The seeds have an immense medicinal value and are known to have numerous medicinal properties, mainly in the Unani-Tibb/Greco-Arab and Ayurveda systems of medicine. Figure 1 shows the picture of Nigella sativa seeds.

PHARMACOGNOSTICAL STUDIES ON SEEDS

Macroscopical characteristics: They are small dicotyledonous, trigonus, angular, regulose-tubercular, 2-3.5 × 1-2 mm, black externally and white inside; odor slightly aromatic and taste bitter [7].

Microscopical and powder characteristics: Transverse section of seed shows single layered epidermis consisting of elliptical, thick walled cells, covered externally by a papilllose 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 seeds powder shows brownish black, parenchymatous cells and oil globules [8], [9].

Physical constant: Foreign matter-2% w/w; total ash-6% w/w; acid insoluble ash-0.2% w/w; alcohol soluble extractive-20% w/w; water soluble extractive-15% w/w; total fixed oil-25-32% w/w; volatile oil-0.42% w/w; organic matter-3.91% w/w; loss on drying-4% w/w [10].

TRADITIONAL USES
Nigella sativa is widely used natural remedy and the seeds are extensively used as spice, carminative, condiment and aromatic. Traditionally, they have been used as diuretic, diaphoretic, stomachic, liver tonic and digestive. As a confection with other ingredients, they are used in diarrhoea, indigestion, dyspepsia and sour belching; they also remove foul breath and watering from mouth. The seeds of Nigella sativa are given with buttermilk to cure obstinate hiccups and are also useful in loss of appetite, vomiting, and dropsy. In different combinations, the seeds of Nigella sativa have been used in obesity and dyspnoea. They have antibilious property and are administered internally in intermittent fevers [11]. The herb has been regarded as a valuable remedy in hepatic and digestive disorders. Constant inhalation of fried seeds relieves cold and catarrh. They have also been used in chronic headache and migraine [12]. The decoction of seeds with some sweet oil forms a useful application in skin diseases. They have been useful in mercury poisoning, sores and leprosy [13]. Brayed in water, its application removes swelling from hands and feet. Nigella sativa is also used externally in leucoderma, alopecia, eczema, freckles and pimples. The seeds of Nigella sativa have also been used as anthelmintic and antibacterial [14].

THE CHEMICAL COMPOSITION OF THE SEEDS

Historically, the chemical investigations on the Nigella sativa seeds started on the year 1880 by Greenish [15] published the first report concerning the presence of 37% oil and 4.1% ash (calcium salts) in the seeds. The general chemical composition of the seeds as we know it today is depicted in Table 1 [16], [17], [18].

Chemical Composition of Nigella sativa Oil: The chemical analysis of Nigella sativa total oil revealed the presence of both a fixed oil and a volatile oil. The major component was the fixed oil whereas the volatile oil ranged from 0.4-0.7% of the seeds’ weight [19]. The fixed oil chemical composition is outlined in Table 2 [20], [21].

Generally, there were no significant variations in the chemical composition of the fixed oils of seeds grown in Egypt, Sudan, Ethiopia, India, Turkey and Syria. However, Al-Jassir noted that the seeds grown in Qassim, Saudi Arabia, contained, in addition to the fatty acids depicted in Table 2, two more acids which were lignoceric acid about (1%) and myristoleic acid (0.18%) without the presence of eicosadienoic acid. Lignoceric acid is not found in many other edible vegetable oils.
Specific chemical analyses of the volatile oil started during the years 1960-1963 by Mahfouz and El-Dakhakhny [22] and Canonica et al. [23]. These studies were complemented by most recent ones which revealed various pharmacologically active constituents that included in Table 3. [24], [25], [26], [27], [28]:

**Non-Oily Components of the Seeds**

**Minerals**

Analysis of *Nigella sativa* seeds, ash revealed the presence of 0.5-1% calcium, 0.6% phosphorus, 0.6% potassium and 0.1% sodium of the total seeds weight.

**Saponins**

The major saponin in the defatted seeds of *Nigella sativa* is the glycoside alpha-hederin or Helixin or melanthin which on acid hydrolysis releases its sugar rhamnose/arabinose and gives the aglycone hederagenin (or melanthigenin) or caulosapogenin [29], [30], [31].

**Alkaloids**

Three types of alkaloids were isolated from the defatted seeds of *Nigella sativa*. These were identified as the indazole nigelicine [32], the isoquinoline nigellimine [33] and its N-oxide [34] and the indazole alkaloid nigellidine [35].

**THERAPEUTIC AND PHARMACOLOGICAL USES**

The popularity of the plant was highly enhanced by the ideological belief in the herb as a cure for multiple diseases. In fact, this plant has occupied special place for its wide range of medicinal value in Islamic civilizations. Due to the sayings of the HOLY prophet, Mohammed (peace be upon him) that the plant is full of medicinal value, it gained immense popularity. Consequently, Kalonji has been extensively studied particularly in Islamic world, which justifies its broad traditional therapeutic value.

**Effect on CNS:** Pharmacological studies have been conducted on the aqueous and methanol extracts of *Nigella sativa* L. seeds to evaluate their effects on the central nervous system.

Thymoquinone is major constituent of *Nigella sativa* seeds, a traditional medicine claimed to be useful in convulsions [36]. A study conducted for anticonvulsant effect of Thymoquinone using pentylenetetrazole and maximum electroshock induced seizures. The complete protective effect against mortality was reported in both the tests.
Nigella sativa oil was used to study its effect on anxiety [37] in rats. Open field and elevated plus maze models and brain 5-HT and 5-HIAA levels estimations were selected for the evaluation of anxiolytic effect of drug. Based on this study, it may be suggested that Nigella sativa oil is a useful choice for the treatment of anxiety.

Another study was to investigate the role of GABAergic and nitriergic modulation in the antianxiety [38] effect of thymoquinone, a major constituent of Nigella sativa, in mice under unstressed and stressed conditions using behavioral testing like elevated plus maze, the light/dark test and the social interaction test. The effects of the above-mentioned drugs on plasma nitrite, a stable metabolite of nitric oxide (NO) and brain GABA content were also studied. The present study suggests an involvement of NO-cGMP and GABAergic pathways in the anxiolytic-like activity of thymoquinone.

The protective effects of Nigella sativa oil (NSO), an antioxidant agent [39], against Propoxur-induced toxicity and oxidative stress in different brain regions of rats including cerebellum, cortex and hippocampus Lipid peroxidation (LPO), protein carbonyl content (PCC) and acetylcholine esterase activity (AChE) were determined. Enzymatic antioxidant activities [superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GSH-Px), glutathione-S-transferase (GST) and non-enzymatic antioxidants like reduced glutathione (GSH)] were determined. It was concluded that NSO significantly reduces Ppr induced toxicity and oxidative stress in rat brain regions via a free radicals scavenging mechanism. ROS are closely implicated in several diseases of nervous system including Parkinson’s disease, Schizophrenia and Alzheimer’s disease [40].

Oxidative stress is a characteristic feature in a number of neurodegenerative disorders [41]. The present study evaluates the antioxidant effect of Nigella sativa oil (NSO) in comparison to that of vitamin C in the cortex and hippocampus of rats pretreated with monosodium glutamate (MSG) as an animal model of oxidative stress using catalase, glutathione-S-transferase (GST), glutathione reduced (GSH) and malondialdehyde (MDA). In conclusion, although there are some antioxidant effects of NSO, the pro-oxidant effect of NSO cannot be ruled out in the present MSG model of oxidative stress. Oxidative stress is a characteristic feature in a number of neurodegenerative disorders such as stroke, Parkinson’s disease and Alzheimer’s disease.
Another antioxidant potential [42] reported that supercritical fluid extraction (SFE) could be used to obtain Nigella sativa extract rich in antioxidants. In the present study, Nigella sativa extracts prepared using the previously optimized SFE as well as the traditional Soxhlet extraction approaches were analyzed for various known antioxidants like reduced glutathione. The data indicates that the protective effects of Nigella sativa may not only be due to thymoquinone, but perhaps other antioxidants.

The fixed oil of black cumin seeds, Nigella sativa L. (NSO), has shown considerable antioxidant and anti-inflammatory activities [43]. Chronic cerebral hypoperfusion has been linked to neurodegenerative disorders including Alzheimer’s disease (AD) and its subsequent cognitive impairment in which oxidative stress and neuroinflammation are the principal culprits. Cerebrovascular hypoperfusion was experimentally achieved by bilateral common carotid arteries occlusion (2VO) in rats. Morris water maze (MWM) test was employed to assess the effects of NSO on spatial cognitive function before and after 2VO intervention. The fixed oil of Nigella sativa seeds has demonstrated noticeable spatial cognitive preservation in rats challenged with chronic cerebral hypoperfusion which indicates a promising prospective neuroprotective effect.

Effects on cardiovascular system: The essential oil from the seeds of Nigella sativa exhibit a depressant action on the frog heart and a relaxant effect on isolated smooth muscles of rat. The unsaponified matter of the fixed oil showed a marked depressant effect on heart and produced bradycardia, which is mainly mediated by indirect and direct mechanisms and involved both 5-hydroxytryptaminergic and muscarinic mechanisms [44]. In another study crude extract of Nigella sativa was found to significantly lower blood pressure in spontaneously hypertensive rats similar to that of nifidipine [45]. Recently, it was found that the active ingredient of Nigella sativa seeds, such as thymol [46] lower blood pressure through blockade of calcium channels. These studies showed that the plant contains multiple chemicals with antihypertensive effect acting at multiple sites.

Nigella sativa seed treatment was also found to lower the serum cholesterol [47]. The extract of Nigella sativa seeds was found to produce protection against cisplatin induced falls in haemoglobin levels and leukocytes [48].
Effects on respiratory system: Powdered seeds in suitable vehicles have been traditionally used to alleviate respiratory disorders; e.g. asthma, bronchospasm and chest congestion. Nigellone, an active ingredient of *Nigella sativa*, was shown to be an effective prophylactic agent in asthma and bronchitis with higher efficacy in children than in adults. Nigellone, an active ingredient of *Nigella sativa*, was found to inhibit effectively the histamine release from mast cells, thus showing basis for traditional use in asthma. It was also recently showed that the bronchodilatory effect of the crude extract of *Nigella sativa* seeds [49] was shown to mediate possibly through calcium channel blockade.

Effects on gastrointestinal system: The seeds of *Nigella sativa* have been traditionally used in a wide range of gastrointestional disorders. The aqueous extract of seeds was reported to exhibit anti ulcer activity by decreasing the volume of acid in gastric juice in acetyl salicylic acid treated rats [50]. In a study, the effect of alcoholic extract of *Nigella sativa* was investigated in rats to evaluate the antiulcer activity by using two models, i.e. pyloric ligation and aspirin-induced gastric ulcer. The volume of gastric acid secretions, free acidity, total acidity and ulcer index significantly reduced [51]. Administration of *Nigella sativa* oil in rats produced a significant increase in mucin content and glutathione level and a significant decrease in mucosal histamine content in the stomach, leading to significant protection against ethanol-induced ulcers in rats [52]. In a study, the aqueous seed extract of *Nigella sativa* caused mild to moderate dose dependent relaxation effects, increase the sensitivity of ileum to acetylcholine and interacted with serotonin in a dose-dependent manner [53].

Thymoquinone was found to be hepatoprotective against ter-butyl-hydroperoxide induced hepatotoxicity [54]. And protecting liver against carbon tetrachloride induced hepatic toxicity in mice via its antioxidant mechanism [55]. Another study showed the possible effects of thymoquinone on acetic acid-induced colitis in rats. The possible mechanism of the protective effects might be partly due to an antioxidant action [56].

Effect on genito-urinary system: The seeds of *Nigella sativa* were found to significantly reduce the cisplatin (a cytotoxic drug) induced nephrotoxicity, blood urea nitrogen (BUN) and serum creatinine levels as well as cisplatin-induced serum total lipids increases [57].
The ethanolic extract of *Nigella sativa* seeds shows antifertility effect in male rats that is probably due to its inherent estrogenic nature [58]. The volatile oil of *Nigella sativa* also inhibit the spontaneous movements of rat and guinea pig uterine smooth muscles and also the contractions induced by oxytocin, showing its antioxytocic potential [59]. Thymoquinone, the main constituent of volatile oil of Nigella sative seeds, was found to posses high antioxidant potential and was found to be applicable as a protective agent for doxorubicin-induced nephropathy, proteinuria, albuminuria and hyperlipidemia associated with nephrotic syndrome[60]. In a recent study, the protective effects of *Nigella sativa* oil on methotrexate induced toxicity were studied in albino rats [61].

Effect on immune system and cancer: *Nigella sativa* seeds and its oil have been traditionally used as tonic to promote health and prevent disease. They were reported to exhibit immunopotentiating, immunomodulating [62] and interferon-like activities. The ethanolic extract was found to inhibit cancer cells and endothelial cells progression in vitro [63], [64]. The protective effect of *Nigella sativa* grains as nutraceuticals was studied on the oxidative stress and carcinogenesis induced by methylnitrosourea in Sprague Dawley rats and it was found to produce about 80% protection against methylnitrosourea-induced oxidative stress, inflammatory response and carcinogenesis [65].

The alcoholic extracts also showed the cytotoxic activity and was found to cure oral cancers in in-vitro studies [66] In another study, thymoquinone inhibited the benzopyrene-induced forestomach carcinogenesis in mice. The possible modes of action were discussed to be through its antioxidant and anti-inflammatory activities coupled with enhancement of detoxification process [67].

In another study, the aqueous and alcoholic extracts of *Nigella sativa* alone or in combination with Hydrogen peroxide as an oxidative stressor, were found to be effective in-vitro in inactivating MCF-7 breast cancer cells [68].

In a study using murine Cytomegalovirus as a model, intraperitoneal administration of oil substantially decreased the viral load in liver and spleen. There was an increase in interferon-gamma, macrophages and CD4+ T cells and decrease in both number and function of NK cells. On day 10, the virus titer was undetectable in the spleen and liver of infected mice, while positive in control [69].
Effect against microbials: The plant extract and its constituents have been extensively studied for its their antimicrobial effect against a wide range of bacterial, fungal and parasitic organisms. Alcoholic extract of the seeds showed antibacterial activity against Micrococcus pyogenes [70], Shigella dysenteriae, S. boydii, S. Sonnei, Vibrio cholera and Escherichia coli [71]. The ether extract showed in vitro anti microbial activity against Gram positive bacteria; e.g. Staphylococcus aureus, Gram negative bacteria; e.g. Pseudomonas aeroginosa and Escherichia coli [72].

The essential oil the seeds of Nigella sativa in pure state and at varioua dilutions was screened in vitro against some microbes and helminths [73]. It show anhelmintic activity against hook worms and nodular worms [74]. The essential oil showed in vitro antifungal activity against Aspergillus species and Curvularia lunata as well as against pathogenic yeast Candida albicans [75]. In recent study, aqueous extract of the seeds posses potent in-vivo antifungal activity against Candidiasis in mice [76].

Effects on Diabetic condition: Various studies were carried out on plant mixture for its blood glucose lowering effects in rats and found effective. Further, it was showed that blood glucose lowering effect was due to the inhibition of hepatic gluconeogenesis and the plant extract mixture may prove to be useful therapeutic agent in the treatment of non-insulin dependent diabetes mellitus [77]. An aqueous decoction of a plant mixture containing Nigella sativa was found to lower the blood glucose level significantly after oral administration [78]. In a more recent study, the seed extract when given orally decreased the elevated glucose levels in alloxan–induced diabetic rabbits after two months of treatment [79].

In another study, the hypoglycaemic effets of Nigella sativa was supposed to be mediated by extra pancreatic actions rather than by stimulated insulin release [80]. A recent clinical study on human volunteer showed that 1 g of Nigella sativa seeds twice daily caused a decrease in blood glucose levels after 2 weeks of oral treatment [81].

Effect against inflammation: The aqueous extract was investigated for anti-inflammatory, analgesic and antipyretic activities in animal models. The anti inflammatory effect was demonstrated by its inhibitory effect on carrageenan induced-paw edema. And analgesic effect by significant increase in hot plate rection time in mice [82].
The essential oil of *Nigella sativa* seeds and its active principles thymoquinone, were found to possess dose-dependent anti inflammatory activities and inhibited edema and granuloma formation [83]. In a recent study, *Nigella sativa* oil, nigellone and derived thymoquinone were studied to evaluate their effect on the formation of 5-lipooxygenase (5-LO) products from polymorphonuclear leukocytes (PMNL). They were found to produce concentration dependent inhibition of 5-LO products and 5-HETE production, probably due to an antioxidant action, thus showing in part their role in ameliorating inflammatory disease. A recent study showed it inhibits nitric oxide production in macrophages on a study carried out on rats [84].

**Effect against oxidation:** The essential oil of *Nigella sativa* seeds was tested for a possible antioxidant activity. The free radical scavenging effects of thymol, thymoquinone and dithymoquinone were studied on the reactions generating reactive oxygen species such as superoxide anion radical (O2-) Hydroxyl radical and singlet oxygen using chemiluminescence and spectrophotometric methods [85].

The hepatoprotective effects of *Nigella sativa* [86] and thymoquinone [87] were found via the antioxidant mechanism. Similarly, the protective effect of thymoquinone against doxorubicin induced nephrotoxicity and that against doxorubicin induced cardiotoxicity [88] was also found to be due to its anti oxidant activity.

**Table 1.** General Chemical components of seeds.

<table>
<thead>
<tr>
<th>Constituents</th>
<th>% Range(w/w)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oil</td>
<td>31-35.5</td>
</tr>
<tr>
<td>Protein</td>
<td>16-19.9</td>
</tr>
<tr>
<td>Carbohydrates</td>
<td>33-34</td>
</tr>
<tr>
<td>Fibre</td>
<td>4.5-6.5</td>
</tr>
<tr>
<td>Ash</td>
<td>3.7-7</td>
</tr>
<tr>
<td>Saponins</td>
<td>0.013</td>
</tr>
<tr>
<td>Moisture</td>
<td>5.7</td>
</tr>
</tbody>
</table>
Table 2. Fixed oil components of seeds.

<table>
<thead>
<tr>
<th>Constituents</th>
<th>% Range (w/w)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Linoleic Acid</td>
<td>44.7-56</td>
</tr>
<tr>
<td>Oleic Acid</td>
<td>20.7-24.6</td>
</tr>
<tr>
<td>Linoleic Acid</td>
<td>0.6-1.8</td>
</tr>
<tr>
<td>Arachidic Acid</td>
<td>2-3</td>
</tr>
<tr>
<td>Palmitoleic Acid</td>
<td>3</td>
</tr>
<tr>
<td>Eicosadienoic Acid</td>
<td>2-2.5</td>
</tr>
<tr>
<td>Palmitic Acid</td>
<td>12-14.5</td>
</tr>
<tr>
<td>Stearic Acid</td>
<td>2.7-3</td>
</tr>
<tr>
<td>Myristic Acid</td>
<td>0.16</td>
</tr>
<tr>
<td>Sterols</td>
<td>0.5</td>
</tr>
</tbody>
</table>

Table 3. Volatile oil components of seeds

<table>
<thead>
<tr>
<th>Volatile Oils</th>
<th>% Range (w/w)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thymoquinone</td>
<td>27.8%</td>
</tr>
<tr>
<td>Carvacrol</td>
<td>5.8-11.6%</td>
</tr>
<tr>
<td>p-cymene</td>
<td>15.5-31.7%</td>
</tr>
<tr>
<td>alpha-pinene</td>
<td>9.3%</td>
</tr>
<tr>
<td>4-terpineol</td>
<td>2-6.6%</td>
</tr>
<tr>
<td>longifolene</td>
<td>1-8%</td>
</tr>
<tr>
<td>t-anethole benzene</td>
<td>0.25-2.3%</td>
</tr>
</tbody>
</table>

CONCLUSION

In recent years, ethanobotanical and traditional uses of natural compounds, especially of plant origin received much attention as they are well tested for their efficacy and generally believed to be safe for human use. They obviously deserve scrutiny on modern
scientific lines such as phytochemical investigation, biological evaluation on experimental animal models, toxicity studies and investigation of molecular mechanism of action of isolated phytoconstituents. *Nigella sativa* is reported to posses antitumor, antidiabetic, cardiovascular, pulmonary, gastroprotective, antifertility, diuretic, CNS depressant antispasmodic, anti-inflammatory, antimicrobial, antioxidant, anticonvulsant, antinociceptive, antiurithric, anxiolytic, nephroprotective, immunomodulatory and anthelmintic activities but number of other pharmacological activities are yet to be explored. In future studies, the isolated principles from seeds needs to be evaluated in scientific manner using specific experimental animal models and clinical trials are to be done to understand molecular mechanism of action, in search of lead molecule from natural resources.

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For Correspondence:
K S Sandhu
Email: pharmacology21@gmail.com