

Role of *Nigella sativa* seeds in treatment and management of hypothyroidism - A review

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ABSTRACT

Nigella sativa is a small black seed that has been used for centuries in herbal medicine. The seed comes from a flowering plant (part of the Ranunculaceae family) native to Southwest Asia and the Mediterranean. The plant grows throughout India, the Middle East and Europe. The seeds contain fixed and essential oils, proteins, alkaloids and saponin. Much of the biological activity of the seeds has been shown to be due to thymoquinone, the major component of the essential oil, but which is also present in the fixed oil. Extensive studies on *N. sativa* have been carried out by various researchers and a wide spectrum of its pharmacological actions have been explored which may include antidiabetic, anticancer, antioxidant, immunomodulator, analgesic, antimicrobial, anti-inflammatory, spasmolytic, bronchodilator, hepatoprotective, renal protective, gastro-protective, antioxidant properties, pro thyroid etc. Due to its miraculous power of healing, *N. sativa* has got the place among the top ranked evidence based herbal medicines. In vitro, In vivo and clinical trials in humans revealed the prothyroid activity of *Nigella sativa* seeds. An updated comprehensive review on the prothyroid activity of *Nigella sativa* is required to appraise the current knowledge in particular field. The present review is an effort to provide a detailed survey of the literature on scientific researches of reported prothyroid activity of NS and its probable mechanism of action.

Key words: *Nigella sativa*, hypothyroidism, prothyroid, autoimmune disease.

I. INTRODUCTION

Hypothyroidism, also called underactive thyroid or low thyroid, is a disorder of the

endocrine system in which the thyroid gland does not produce enough thyroid hormone, which is readily diagnosed and managed but potentially fatal in severe cases if untreated. Clinical manifestations of hypothyroidism range from life threatening to no signs or symptoms. The most common symptoms in adults are fatigue, lethargy, cold intolerance, weight gain, constipation, change in voice and dry skin, but clinical presentation can differ with age and sex, among other factors[1]. Thyroid is a small gland with butterfly-shaped located in the front of neck. Thyroid hormones T3, T4, and calcitonin control how our body uses energy, so they affect nearly every organ in the body, including heart beats. Hence, with an insufficient amount of thyroid hormones, many of our body's functions are impaired and slowed down.

Primary hypothyroidism is caused by a problem with the thyroid gland itself. Secondary hypothyroidism occurs when another problem interferes with the thyroid's ability to produce hormones. For example, the pituitary gland or hypothalamuses produce hormones that trigger the release of thyroid hormone. A problem with one of these glands can make your thyroid underactive. Sometimes, an underactive thyroid that results from a problem with the hypothalamus is called tertiary hypothyroidism.

The prevalence of hypothyroidism, the most common type of thyroid dysfunction (2), in the developed world is 4-5% (3). Forty two million people in India suffer from thyroid diseases (4). An overall Indian prevalence ranging from 3.9-5.4%. Thyroid disorders are believed to be a common health issue in India, as it is worldwide.

Nigella sativa, a lovely plant native to the Middle East, is currently gaining increased attention throughout the world for its ability to decrease inflammation and improve patient outcomes for many chronic disease processes. There is data to indicate that it is similarly useful in the treatment of autoimmune thyroid disease, in particular Hashimoto's thyroiditis. Hypothyroidism and *Nigella sativa*, or black cumin seed extract, are highly related when considering the health-promoting effect of this medicinal plant in ameliorating the disease severity.

According to research, black cumin seed extract can be considered as a useful therapeutic approach in management of hypo thyroiditis. While research on *Nigella sativa*'s health effects is limited, findings from in vitro, animal and a small number of human studies show that it may offer prothyroid, immune-boosting and antioxidant benefits. It should be noted that black cumin seed oil does not contain the many side effects of Levothyroxine, a conventional medicine used for this disease. *Nigella sativa* can play an useful role in modifying the inflammatory process that can throw the thyroid out of balance. It decreases inflammation, helps to reduce TSH and anti-TPO antibodies, and raises T3. It also helps to reverse some of the weight gain associated with hypothyroidism. *Nigella* can be used as a powerful piece of a holistic approach to bringing the endocrine and immune systems back to a state of optimal health.

II. CHEMICAL COMPOSITION OF NIGELLA SATIVA

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%) [2], cellulose (6.8- 7.4%) and moisture (8.1-11.6%) [3]. The seeds are also rich in various vitamins (e.g. - A, B1, B2, B3 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 [2]. Some other fatty acids such as myristic acid, palmitoleic acid, linoleic acid, linolenic acid, arachidonic acid, cholesterol, campesterol, β -sitosterol, Δ 5-avenasterol, Δ 7-stigmasterol, and Δ 7-avenasterol are also reported by Gharby et al. [4] 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-methylbenzo1,4-quinone, 30-48%), thymohydroquinone, dithymoquinone, p-cymene (7-15%), carvacrol (6-12%), 4-terpineol (2-7%), t-anethol (1-4%), sesquiterpenelongifolene (1-8%), α -pinene and thymol etc. are the most important active components in *N. sativa*. The other chemical components are carvone, nigellicine [2], nigellone, citrotradienol, cycloecalenol, gramisterol, lophenol, ostusifoliol, stigmasterol, β -amyryn, butyrospermol, cycloartenol, 24-methylene-cycloartanol, taraxerol, tirucallol, 3-O- $[\beta$ -D-xylopyranosyl(1 \rightarrow 3)- α -L-arabino-pyranosyl]-28-O- $[\alpha$ -L-rhamnopyranosyl(1 \rightarrow 4)- β -D-glucopyranosyl(1 \rightarrow 6)- β -D-glucopyranosyl] hederagenin, esters of unsaturated fatty acids with \geq C15 terpenoids, esters of dehydrostearic and linoleic acid, aliphatic alcohol, β -unsaturated hydroxyl ketone, hederagenin glycoside, melanthin, melanthigenin, bitter principle, tannin, resin, reducing sugars, glycosidalsaponin, 3-O- $[\beta$ -D-xylopyranosyl(1 \rightarrow 2)- α -L-rhamnopyrasyl(1 \rightarrow 2)- β -D-glucopyranosyl]-11-methoxy-16, 23-dihydroxy-28-methylolean-12-enoate, stigma-5,22-dien-3- β -D-glucopyranoside, cycloart-23-methyl-7,20,22-triene-3 β ,25-diol, nigellidine-4-O-sulfite, N. mines A3, a4, A5, C, N. mines A1, a2, B1, and B2 [2]. Chemical structures of some important chemical moieties are shown in Figure 1.

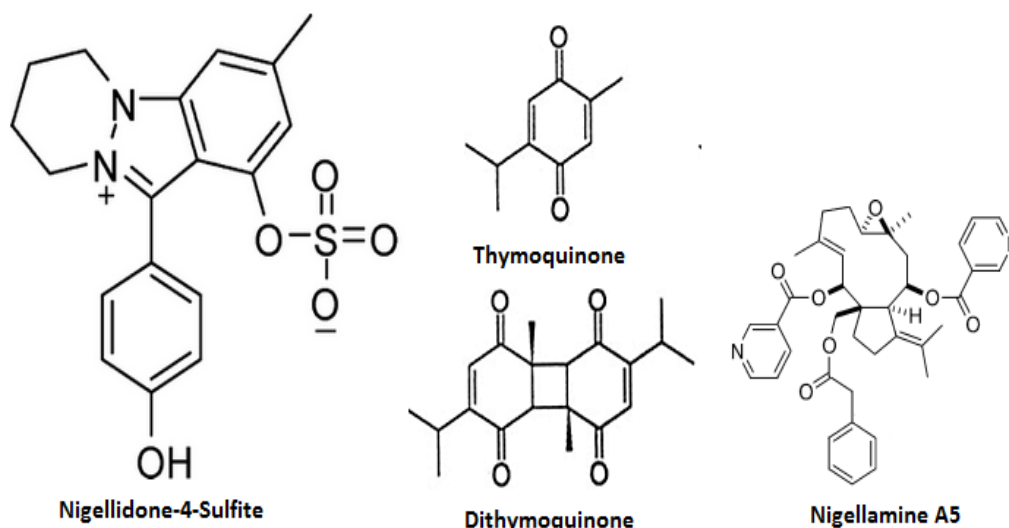


Figure 1. Chemical structures of some important chemical moieties in *Nigella sativa* seeds

III. SCIENTIFIC RESEARCHES ON THERAPEUTIC POTENTIAL OF NIGELLA SATIVA

Research finding showed that *Nigella sativa* can increase the triiodothyronine (T3) in blood serum by repairing the thyroid gland and also influence to increase the production of thyroid hormone. Researchers expect that this biological change occur after treating patients with *Nigella sativa* seeds due to its antioxidant property. However, *Nigella sativa* seed does not alter TSH level. Treating patients with higher dose of levothyroxine may increase TSH level, which increase the risk of thyroid tumor and miscarriage (in pregnant women), in addition to osteoporosis like adverse effects. [5,6,7]. Therefore, *Nigella sativa* seeds intervention can improve the underactive thyroid functioning without causing TSH level enhancement related risk. Daily oral administration of *Nigella sativa* L. ethanolic extract (1 g/kg Bwt.) for 14 days significantly increased the serum concentration of T4 in the normal Wistar albino rats. On the other hand the results revealed that treatment returned the serum concentration of T3 to the normal level [8]. N. Sative treatment for eight weeks significantly reduced serum IL-23 concentrations. Treatment with N. Sative also significantly reduced thyroid stimulating hormone (TSH) and anti-TPO antibodies in patients with Hashimoto's thyroiditis. Such changes were not observed in the placebo treated group. Serum T3 also increased significantly after treatment. There was a significant reduction in body weight after treatment with N. Sative [9]. NS oil treatment led to significant increase T3, T4 and TSH serum level

of control and treatment groups, The plasma concentration of T3 and T4 are significantly increased and TSH serum level significantly decreased in treatment groups compared with control groups [10] oral administration of NS not only increased serum T3 and decreased TSH but also has an anti-oxidant effect [11]. The oral administration with NS could raise T3 level without changing T4 and TSH serum concentration levels [12].

Hydro-alcoholic extract of *Nigella sativa* L. (NS) on performance of Forced Swimming Test also increased the blood concentration of T3 and T4, leading to the decrease of TSH serum level. Taken together, it is suggested that NS not only has anti-depressive effect and anti-fatigue like effects that might be useful in the development of physical strength, but also leads to hyperthyroidism in mice [13]. NS significantly increases the concentration of T3 and T4 and decreases the TSH in experimental groups compared to untreated mice. These results are in agreement with previous studies by Sharif et al. who indicated that treatment with oral administration of NS increased T4 levels in rabbits [14]. Auto-immune disease conditions like Hashimoto's thyroiditis is one of the cause of underactive thyroid gland and hypothyroidism condition. *Nigella sativa* has immuno-modulatory effects, as it can reduce auto-antibodies production, decreases innate and acquired immune cell markers and inhibits transforming growth factor (TGF)- β and interleukin (IL)-23 concentrations. Thus, the scope of developing Hashimoto's thyroiditis decrease with *Nigella sativa* seed treatment [15].

Goiter is one of the common inflammatory condition arises due to hypothyroidism. The anti-inflammatory effect of *Nigella sativa* able to inhibit the cyclooxygenase-2 concentration [15] and may be helpful to prevent goiter. Obesity and hypothyroidism are two associated co-morbidities. Hypothyroidism often leads to decreased rate carbohydrate and lipid metabolism, which increases the BMI without depending on physical activity [12]. Hypothyroidism related obesity can also be controlled by treating *Nigella sativa* seeds because of its anti-obesity effect [15]. As it is already mentioned hyperlipidemia is one of the primary complication associated with underactive thyroid, which also increase the risk of cardiac disorders which can be solved with *Nigella sativa* seeds due to its hypolipidemic effects [15]. Treatment with *Nigella sativa* significantly reduced body weight and body mass index (BMI). Serum concentrations of thyroid stimulating hormone (TSH) and anti-thyroid peroxidase (anti-TPO) antibodies decreased while serum T3 concentrations increased in *Nigella sativa*-treated group after 8 weeks. There was a significant reduction in serum VEGF concentrations in intervention group. None of these changes had been observed in placebo treated group. In stepwise multiple regression model, changes in waist to hip ratio (WHR) and thyroid hormones were significant predictors of changes in serum VEGF and Nesgfatin-1 values in *Nigella sativa* treated group [16]. Thymoquinone, the active ingredient of *Nigella sativa* improves the thyroid gland functioning and necessarily alter the thyroid hormone secretion [15]. The oil and seed constituents, in particular thymoquinone (TQ), have shown potential medicinal properties in traditional medicine. In view of the recent literature, this article lists and discusses different immunomodulatory and immunotherapeutic potentials for the crude oil of *N. sativa* seeds and its active ingredients. The published findings provide clear evidence that both the oil and its active ingredients, in particular TQ, possess reproducible anti-oxidant effects through enhancing the oxidant scavenger system, which as a consequence lead to antitoxic effects induced by several insults [17]. Obese subclinical hypothyroid women with Hashimoto's thyroiditis have a higher prevalence of metabolic syndrome when compared with subclinical hypothyroid women without thyroid autoimmunity. It is possible that in the crosstalking between subclinical hypothyroidism and metabolic syndrome, enhanced proinflammatory cytokine release in the course of immunological thyroiditis plays a role [18]. Several

studies have shown *Nigella*'s ability to improve glucose and lipid metabolism, including a positive impact on metabolic syndrome, insulin resistance, diabetes, and polycystic ovary syndrome (PCOS) [19-22]. *Nigella* also has been shown to assist with weight loss and to increase superoxide dismutase in obese women [23,24]. Considering the amount of research on this plant, there is a compelling theoretical reason to apply it for treatment and management hypothyroidism.

IV. CONCLUSION AND FUTURE PERSPECTIVES

The therapeutic effects of *Nigella sativa* against hypothyroidism is mostly attributed to its antioxidant effects which have been proved in numerous studies. It has also been suggested that *Nigella sativa* protects the hyperplasia changes of thyroid parenchyma in hypothyroid rats. It would appear that the beneficial effects of the use of the seeds and thymoquinone might be related to their cytoprotective and antioxidant actions, and to their effect on some mediators of inflammation. *Nigella sativa* could be a useful adjunct to holistic treatment of hypothyroidism. It decreases inflammation, helps bring down TSH and anti-TPO, and raises T3. It also helps to reverse some of the weight gain associated with hypothyroidism. It can be used as one powerful piece of a holistic approach to restoring the endocrine and immune systems to a state of optimal health.

The original research articles published so far have confirmed the pharmacological potential of *N. sativa* seeds, its oil and extracts and some of its active principles, particularly TQ and alpha-hederin, possess remarkable in vitro and in vivo pharmacological activities against a large variety of diseases and found to be relatively safe.

Further investigations are required to study the mechanism of actions of *N. sativa* seeds and its constituents by which they exert their therapeutic effects. Chemical modifications in the molecular structure of TQ and other constituents of *N. sativa* seeds could lead to more effective and safer drugs for the treatment and management of hypothyroidism in future.

This review article is dedicated to all those researchers who are interested in focusing their research on this miracle herb and hope, this review article would help them in investigating and conducting further preclinical and clinical studies on the use of *N. sativa* for the treatment of hypothyroid management.

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