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Therapeutic Trials Of *Nigella Sativa*

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ABSTRACT

Nigella sativa (NS) (Ranunculaceae family) is generally utilized as a therapeutic plant all over the world. The seeds of the plant have a long history of use in different frameworks of medicines and food. N. sativa seed reveal a broad spectrum of pharmacological activities including immunopotentiation and antihistaminic, antiseptic, antiallergic, anti-hypertensive, anti-inflammatory, and antimicrobial activities. It is known as a source of thymoquinone, thymohydroquinone, dithymoquinone, p-cymene, carvacrol, 4-terpineol, t-anethol, sesquiterpene longifolene, nigellicimine and nigellicimine-N-oxide, α-pinene and thymol etc. Additionally, this is uncovered that the majority of therapeutic properties of this plant are due to the presence of thymoquinone (TQ) which is a major bioactive component of the essential oil. The incalculable medicinal properties and therapeutic uses of N. sativa prove its importance as a valuable medicinal plant. The aim of this review is to summarize some important pharmacological studies and phytochemical investigations on N. sativa and isolated principles which can be investigated further to get novel molecules in the search of novel herbal drugs.

Keywords

Nigella sativa, Medicinal plant, Phytoconstituent, Pharmacological activity.

Habitat

N. sativa is native to Southern Europe, North Africa and Southwest Asia and it is cultivated in many countries in the world like Middle Eastern Mediterranean region, South Europe, India, Pakistan, Syria, Turkey, Saudi Arabia.

Morphology of the plant

N. sativa is an annual flowering plant grows at 20-90 cm tall, with finely divided leaves; the flowers are white, yellow, pink, pale blue or pale purple color, with 5-10 petals.

Figure 1: Nigella. sativa flower.

Introduction

Medicinal plants have been utilized in the treatment of ailments for many years in different aboriginal medicine as well as folk medicine. Furthermore, therapeutic plants are additionally utilized as a part of the arrangement of home-grown pharmaceuticals as they are thought to be safe as to modern medical cares [1].

Among different therapeutic plants, *Nigella sativa* (NS), from Ranunculaceae family, normally develops in Eastern Europe, Middle East, and Western Asia. NS seed is known as "Al-Habba Al-Sauda" and Al-Habba Al-Barakah" in Arabic and black seed or dark cumin in English [2].

For many years, NS seeds have been reported to be utilized as a remedy for various ailments in the Middle East and some Asian nations [3].

Ingredients of *N. sativa* seeds

By HPLC analysis of *N. sativa* oil, thymoquinone (TQ), dithymquinone (DTQ), which is believed to be nigellone, thymohydroquinone (THQ), and thymol (THY), are considered the main active ingredients [4] (Figure 2). *N. sativa* seeds contain other ingredients, including nutritional components such as carbohydrates, fats, vitamins, mineral elements, and proteins, including eight of the nine essential amino acids [4-8]. Fractionation of whole *N. sativa* seeds using SDS–PAGE shows a number of protein bands ranging from 94 to 10 kDa molecular mass [9]. 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 [4,5,11-13]. The major separate individual phospholipid classes is phosphatidylcholine, followed by phosphatidyle thanolamine, phosphatidylserine, and phosphatitdylinisitol, respectively [4,5,14]. The seeds contain carotene which is converted by the liver to vitamin A [15]. The *N. sativa* seeds are also a source of calcium, iron, and potassium.

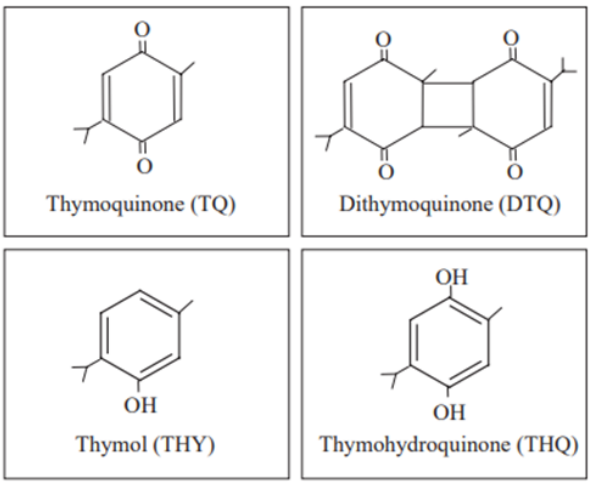

Figure 2: Chemical structure of the active ingredients: TQ, DTQ, THY, and THQ, in the oil of *N. Sativa* L. seed.

Anti-oxidant properties

Oxidant stress system and toxicity

Oxidative damage to biological structures has been implicated in the toxicity-induced pathophysiology of several diseases, in particular cardiovascular disease and cancer [16]. The cause of this oxidative damage has been reported to be due to the shift in the balance of the pro-oxidant (free radicals) and the anti-oxidant (scavenging) mediators, where pro-oxidant conditions dominate either due to the increased generation of the free radicals caused by excessive oxidative stress, or due to the poor scavenging capability in the body [17]. Free oxygen radicals, including O_2, OH, and NO (collectively known as oxidative stress), are electrically charged molecules that attack cells, tearing through cellular membranes to react and create havoc with the nucleic acids, proteins, and enzymes present in the body [18]. The attacks by ROS (Reactive Oxygene Species) cause damage to cell structure and function and can eventually destroy them. ROS are produced mainly by certain cells of immune system including macrophages (Mf) and neutrophils [19]. It has recently reported that suppression of immune cell function associated with chemotherapy [20], radiotherapy [21], infection [22,23] and in tumor-bearing hosts [24] is mediated by production of NO produced by immature myeloid cells that are massively generated under these conditions [25–26]. The central role of ROS in mediating the pathology in several diseases has stimulated interest in the possible role of natural anti-oxidant agents in preventing the development of these diseases. It has been reported that the health promotive, disease preventive and rejuvenation approach based on using medicinal plants in Ayurveda an ancient Indian systems, is due to the anti-oxidant effects of these plants [27-28]. One of the potential properties of *N. sativa* seeds is the ability of one or more of its constituents to reduce toxicity due to its anti-oxidant activities. Of the studies that have been performed to evaluate the different effects of *N. sativa*, majority (more than 35) of the studies have confined to address its antitoxic properties both in vitro and in vivo.

In vitro anti-oxidant activities

In vitro studies show that *N. sativa* seed extract induces inhibition of the hemolytic activities of snake and scorpion venoms [29], protects erythrocytes against lipid peroxidation, protein degradation, loss of deformability, and increased osmotic fragility caused by H_2O_2 [30]; and protects laryngeal carcinoma cells, from programmed cell death (apoptosis) induced by lipopolysaccharide (LPS) or cortisol [31]. These results indicate to the antitoxic effects of *N. sativa* seed components that could be attributed to its anti-oxidant properties. Several in vitro studies confirm this hypothesis. For instance, essential oil obtained from six different extracts of *N. sativa* seeds and from a commercial fixed oil showed antioxidant effects with almost identical qualitative effects. Differences, however, were mainly restricted to the quantitative composition [32]. The crude *N. sativa* oil and its fractions (neutral lipids, glycolipids, and phospholipids) showed potent in vitro radical scavenging activity that is correlated well with their total content of polyunsaturated fatty acids, unsaponifiables, and phospholipids, as well as the initial peroxide values of crude oils [33]. Moreover, preincubation of peritoneal Mf with aqueous extract or the boiled

fraction of the extract of *N. sativa* seeds caused a dose-dependent decrease in NO production when activated with LPS of E. coli [34]. Interestingly, TQ and a synthetic structurally-related tert-butylhydroquinone, also efficiently inhibited iron-dependent microsomal lipid peroxidation in vitro in a concentration-dependent manner [35]. TQ also induced significant protection of isolated hepatocytes against tertbutyl hydroperoxide induced toxicity evidenced by decreased leakage of ALT (aminotransferase) and AP (alkaline phosphatase) [36].

In addition, TQ in a dose- and time-dependently manner, reduced nitrite production, a parameter for NO synthesis, and decreased both gene expression and protein synthesis levels of iNOS in supernatants of LPS-stimulated Mf without affecting the cell viability [37]. Stimulation of polymorphonuclear leukocytes with TQ showed protective action against superoxide anion radical either generated photochemically, biochemically, or derived from calcium ionophore, indicating to its potent superoxide radical scavenger [38].

In vivo anti-oxidant activities

Both hepatoxicity and nephrotoxicity are associated with alteration in the levels and activities of certain mediators such as l-alanine ALT, alkaline phosphatase , lipid peroxide (LPD), and the oxidant scavenger enzyme system including, glutathione (GSH) and superoxide dismutase (SOD). The anti-oxidant effects of *N. sativa* have been examined using different hepatic and kidney toxicity in vivo murine models induced by tert-butyl hydroperoxide, carbon tetrachloride (CCl_4), doxorubcin (DOX), gentamicin, methionine, potassium bromate ($KBrO_3$), cisplatin, or Schistosoma manson infection.

N. SATIVA Effects on Immunity

Effects of *N. sativa* on cellular immunity

Aside from its established anti-inflammatory, antioxidant, and antitumor activities, research initiatives are growing extensively to assess the potential of *N. sativa* to modulate adaptive immunity. Haq and colleagues examined the effects of whole and soluble extracts of *N. sativa* seeds on human peripheral blood mononuclear cells (PBMC) response to different mitogens in vitro [39]. *N. sativa* extracts exhibited potent stimulatory effects on PBMC response to pooled allogeneic cells, but not to phytohemagglutinin (PHA) or concanavalin A (ConA), two T cell mitogens [39]. *N. sativa* extracts increased the secretion of IL-3 from PBMCs cultured in presence or absence of pooled allogeneic cells, but no effects on IL-2 secretion from mitogen-stimulated PBMCs were observed [39]. Later on, and using mixed lymphocyte cultures, the same group demonstrated that whole and purified protein extracts of *N. sativa* seeds exerted a stimulatory and suppressive roles on unstimulated lymphocytes and pokeweed mitogen (PWM)-activated lymphocytes, respectively [40]. *N. sativa* extracts had no effect on the secretion of IL-4 from lymphocytes, both in presence and absence of PWM [61]. IL-8 secretion was suppressed by *N. sativa* extracts when the lymphocytes were left un-stimulated, but it was enhanced in PWM activated lymphocytes [40]. These findings indicate that *N. sativa* exerts profound stimulatory effects on cellular immunity. In vivo, *N. sativa* oil has also been reported to stimulate CD^{4+} (helper) T lymphocytes in a murine cytomegalovirus (CMV) model using BALB/c mice [41]. Moreover, oral administration of *N. sativa* fixed oil (2 ml/kg) for a period of 12 weeks was demonstrated to cause a significant decrease in leukocyte and platelet counts in Wistar-Kyoto rats [42].

In another in vivo study, it was demonstrated that oral administration of *N. sativa* oil significantly improved lymphocyte count (i.e. lymphocyte proliferation) in the peripheral blood of streptozotocin (STZ)-induced diabetic hamsters [43]. The possible immunomodulatory effects of the volatile oil of *N. sativa* seeds were evaluated in Long–Evans rats that were challenged with a specific antigen (typhoid TH) [44]. Oral administration of *N. sativa* oil in antigen-challenged rats significantly decreased splenocyte and neutrophil counts while increasing peripheral lymphocyte and monocyte counts [44]. Ebaid and colleagues evaluated the immunomodulatory potential of *N. sativa* oil by assessing its ability to ameliorate the cellular immunological changes that accompany the treatment with chloramphenicol, an antibiotic [44]. Oral administration of chloramphenicol in albino rats led to a significant increase in total leukocyte count, a decrease in neutrophil and lymphocyte count, and a decrease in the values of both rosette and plaque forming cells [45]. Intriguingly, oral administration of *N. sativa* oil (90 mg/kg/day) for 30–60 days almost completely restored the indicated immunological parameters back to normal levels in a time-dependent manner [45], indicating that *N. sativa* oil can potentially enhance cellular immune responses in vivo. Onifade and colleagues presented a case study performed on a 46-year old human immunodeficiency virus (HIV)-infected man, who displayed complete recovery and sero-reversion of HIV infection after treatment with *N. sativa* concoction (60% *N. sativa* seeds and 40% honey) for a period of 6 months [46].

The study revealed that a daily consumption of 20 ml *N. sativa* concoction led to the disappearance of fever, diarrhea, and multiple pruritic lesions as early as day 5, day 7, and day 20 post administration of the *N. sativa* concoction [46]. CD^{4+} cell count significantly dropped from 250 cells/mm3 to 160 cells/mm^3 despite significant reduction in HIV viral load (~27, 000 copies/ml to ~ 1000 copies/ml) after 30 days of the *N. sativa* concoction regime [46]. By the end of the study (i.e. after 6 months), HIV screening was sero-negative and the CD^{4+} cell count significantly increased to 650 cells/mm^3 with undetectable viral (HIV-RNA) load, parameters that persisted at least 2 years after the completion of the *N. sativa* concoction therapy [46]. This case study uncovers the therapeutic efficacy of *N. sativa* against HIV infection. However, such studies must be performed using *N. sativa* seeds without any additives to conclusively confirm a therapeutic effect of *N. sativa* in the treatment of HIV infection.

Effects of TQ on cellular immunity

Despite the fact that numerous studies investigated the antiinflammatory, and antioxidant, and antitumor activities of TQ, relatively little research has been conducted to examine its role in modulating specific cellular and humoral responses. El

Gazzar investigated the possible modulatory effect of TQ on the production of Th2 cytokines, IL-5, IL-10 and IL-13, from LPS-activated RBL-2H3 cells, a rat mast cell line [47]. TQ (10 μM) significantly suppressed the expression of IL-5 and IL-13, but had no effect on IL-10 expression [48]. The expression of IL-5 and IL-13 is regulated by several transcription factors including globin transcription factor (GATA), activator protein 1 (AP-1), and nuclear factor of activated T cells (NF-AT). Further analysis revealed that TQ suppresses IL-5 and IL-13 expression by blocking GATA, but not AP-1 or NF-AT, promoter binding and transcriptional activity via inhibited expression of GATA-1 and GATA-2 [48]. A study by Xuan and colleagues investigated whether TQ has any effect on LPS-induced dendritic cell (DC) maturation, survival, and cytokine release using mouse bone marrow-derived DCs; chief regulators of innate and adaptive immune responses [49]. LPS is known to trigger DC maturation and cytokine production. It was demonstrated that LPS activated DCs expressed significantly higher levels of CD11c and major histocompatibility complex II (MHC-II) (surface markers), CD40 and CD86 (co-stimulatory molecules) and CD54 (adhesion molecule), factors that mediate DC-T cell clustering and antigen presentation [49].

Effects on humoral immunity

Effects of *N. sativa* on humoral immunity

In an in vitro study using splenic mixed lymphocyte cultures, an aqueous extract and an ethyl acetate column chromatographic fraction of *N. sativa* seeds significantly enhanced the proliferation of lymphocytes cultured in presence of ConA, but not LPS [50]. These findings indicate that *N. sativa* exerts profound suppressive effects on humoral immune responses. A study performed by Islam and colleagues investigated potential immunomodulatory effects of the volatile oil of *N. sativa* seeds in Long-Evans rats that were challenged with a specific antigen (typhoid TH) [51]. Results showed that oral administration of *N. sativa* oil in antigen-challenged rats significantly reduced serum antibody titer [51]. Recently, Ebaid and colleagues evaluated the immunomodulatory potential of *N. sativa* oil by assessing its ability to ameliorate humoral mediated immunological changes that accompany the treatment with chloramphenicol, an antibiotic [52]. Similarly, oral administration of chloramphenicol in albino rats led to a very low hemagglutination titer [52]. Oral administration of *N. sativa* oil (90 mg/kg/day) for 30-60 days almost completely restored the indicated immunological parameter back to normal levels in a time-dependent manner [52], indicating that *N. sativa* oil can potentially enhance humoral immune responses in vivo. Sapmaz and colleagues have recently reported that administration of *N. sativa* oil in rats led to a significant decrease in serum IgA, IgM and complement component 3 (C3) levels, which were induced by formaldehyde inhalation [53]. These findings suggest that *N. sativa* can significantly decrease acute antibody responses and C3 levels in formaldehyde-challenged rats, exerting an immunoregulatory role in humoral immunity.

Effects of TQ on humoral immunity

The only findings suggesting a possible immunomodulatory role of TQ in regulating humoral immune responses were reported by Mohany and colleagues who investigated TQ effects on pesticide induced immunotoxicity in male albino rats [54]. Among several biochemical and histopathological changes, imidacloprid (IC) Imidacloprid treatment caused a significant decline in total Ig levels (especially IgGs) and a significant inhibition of antibody hemagglutination [54]. Intraperitoneal injection of TQ (1 mg/kg, once every 7 days) reversed the IC-induced immunological effects, leading to significantly increased total Ig levels and antibody hemagglutination [54]. The findings of this study provided hints that TQ may potentially modulate the outcome of humoral immune responses.

Immunmodulatör activity

The oil and certain active ingredients showed beneficial immunomodulatory properties, augmenting the T cell and natural killer cell-mediated immune responses. Most importantly, both the oil and its active ingredients expressed antimicrobial and antitumor properties toward different microbes and cancers. Coupling these beneficial effects with its use in folk medicine, *N. sativa* seed is a promising source for active ingredients that would be with potential therapeutic modalities in different clinical settings. The efficacy of the active ingredients, however, should be measured by the nature of the disease. Given their potent immunomodulatory effects, further studies are urgently required to explore bystander effects of TQ on the professional antigen presenting cells, including macrophages and dendritic cells, as well as its modulatory effects upon Th1- and Th2-mediated inflammatory immune diseases. Ultimately, results emerging from such studies will substantially improve the immunotherapeutic application of TQ in clinical settings

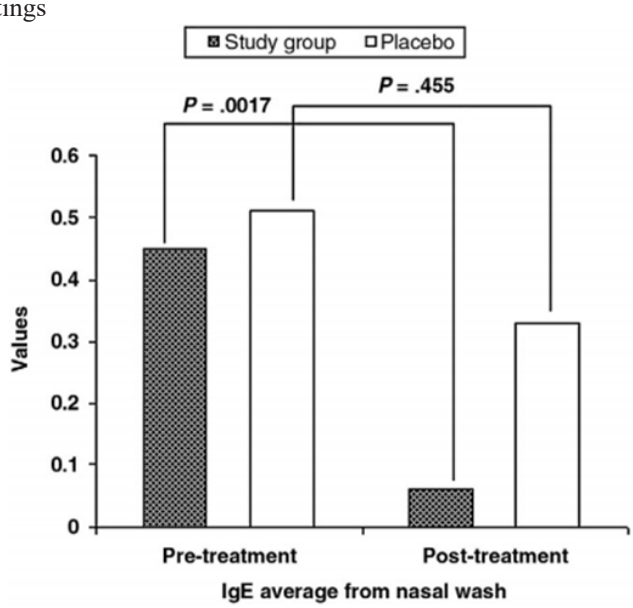

Figure 3: Comparing the mean IgE in nasal wash before and after the end of treatment with *N. sativa* between the study and placebo groups.

Effects on Th1/Th2 paradigm

Effects of *N. sativa* on Th1/Th2 paradigm once activated, CD^{4+} T helper cells further differentiate into Th1 or Th2 cells, which specialize in the secretion of Th1 cytokines (IL-2, IL-12, IFNγ,

and TNFα) and Th2 cytokines (IL-4, IL-5, IL-10, and IL-13) [55]. Ultimately, the decision to differentiate into Th1 or Th2 cells tips the balance either towards cellular or humoral immune response, and hence, agents that can influence the Th1/Th2 balance can potentially alter the outcome of the adaptive immune response in various diseases and medical conditions [55].

A crude extract of *N. sativa* seeds was shown to have no significant effects on IL-2 and IL-4 secretion from resting and activated human PBMCs [56]. *N. sativa* extracts had no effect on the secretion of IL-4 from lymphocytes, both in presence and absence of PWM [57]. However, whole and purified protein extracts of *N. sativa* seeds were shown to significantly enhance the production of TNFα from un-stimulated and PWM-activated lymphocytes [57]. In an attempt to explain the antiviral activity of *N. sativa* oil against CMV infection in BALB/c mice, Salem and Hossain demonstrated that intraperitoneal injection of *N. sativa* oil (100 µg/100 µl/mouse) elevated serum IFNγ levels in CMV-infected mice, but not in un-infected mice, 3 days post treatment [58]. Büyüköztürk and colleagues evaluated the effects of *N. sativa* oil on cytokine production of splenic mononuclear cells (MNCs) in ovalbumin-sensitized BALB/c mice [59]. It was demonstrated that oral administration of *N. sativa* oil (0.3 ml/mouse/day) for 1 month had no significant effects on the production of IL-4, IL-10, or IFNγ from splenic MNCs in ovalbumin-sensitized BALB/c mice, suggesting that *N. sativa* does not possess immunomodulatory properties with regard to Th1 and Th2 cell responsiveness to allergen stimulation [59]. Using an aqueous extract of *N. sativa*, we assessed the potential of the extract to modulate lymphocyte proliferation and alter Th1 and/or Th2 cytokine profile in vitro [60]. *N. sativa* aqueous extract (1–100 µg/ml) significantly enhanced the proliferation of BALB/c splenocytes in a time- and dose dependent manner [60].

Our study further revealed that the aqueous extract of *N. sativa* favored Th2 cytokine secretion and inhibited Th1 cytokine secretion in a dose-dependent manner [60]. The secretion of IL-4 and IL-10 was significantly enhanced when splenocytes were treated with the aqueous extract of *N. sativa* (50–100 µg/ml) in absence of ConA (concanavalin-A) The stimulatory effect of the aqueous extract of *N. sativa* on IL-4 and IL-10 secretion was potent enough to significantly enhance the secretion of IL-4 and IL-10 from splenocytes co-treated with ConA [60]. Conversely, IFNγ secretion from splenocytes was significantly inhibited by the aqueous extract of *N. sativa* even in the presence of ConA [60]. In a recent in vivo study, oral administration of an ethanolic extract of *N. sativa* (200 mg/kg/day) led to a significant increase in serum IL-10, but not IL-4 or IFNγ, levels in male Wistar rats after 24 h of treatment [61].

These findings indicate that *N. sativa* may play a critical role in modulating the balance of Th1/Th2 lymphocytes, leading to altered Th1/Th2 cytokine profiles. However, the reported effects of *N. sativa* on the Th1/Th2 paradigm are inconsistent, most likely due different experimental conditions including cell type, species, dose, mode of administration, and method of detection. Future studies are required to shed more light on the modulatory effects of *N. sativa* on Th1/Th2 cytokine balance using different in vitro and in vivo model systems. Such investigation is crucial given that altering the Th1/Th2 cytokine balance may lead to various medical conditions. For instance, Th2 cytokines produced by stimulated mast cells play a critical role in regulating allergic inflammatory responses and indeed, immunomodulation leading to enhanced Th1 response and suppressed Th2 response has been proposed as an immunotherapeutic approach to prevent and treat various allergic reactions [62].

Effects of TQ on Th1/Th2 paradigm

Noteworthy, while a number of studies have evaluated a possible role of *N. sativa* extracts in Th1/Th2 cell polarization [59], compelling experimental evidence suggesting that TQ may influence the Th1/Th2 balance is largely lacking. The only study that may suggest a role of TQ in regulating Th1/Th2 differentiation revealed that TQ (10 µM) can reduce the production of cytokines that induce Th2 differentiation (e.g. IL-5 and IL-13), but not IL-10, from LPS-activated RBL2H3 rat mast cells by down-regulating the transcriptional activity of GATA-1 and GATA-2, but not AP-1 or NF-AT [48]. Future in vitro and in vivo studies should examine the likely possibility that TQ may regulate Th1/Th2 differentiation.

Black Seed Oil in the Treatment of Allergic Rhinitis

Evaluation of Topical Black Seed Oil in the Treatment of Allergic Rhinitis

Allergic rhinitis (AR), is an inflammation of the nasal mucosal in response to natural allergen exposure and is a common health problem worldwide affecting 10-25% of the population [63]. Extensive research done recently has established this fact that there is a epidemiologic and therapeutic linkage present between AR and asthma [64]. This fact is further proven by number of epidemiologic studies done worldwide. In a review of five large studies which were performed on children and adults, [65] the prevalence of asthma ranged from 3.6% to 5% in subject without allergic rhinitis whereas those with history of asthma showed frequency of 10.8% to 32%. Similarly in a 23 year follow-up study conducted among university students, [66] asthma frequency was found to be 10.5% among those with AR, and 3.6% in those without AR. In addition, the reported lifetime prevalence of AR among adults with asthma demonstrated varied range from 50% to 100%, depending upon the type of study design used and geographical area where study was conducted [67].

Asthma and AR are both inflammatory diseases of the airways. Due to similarity in epidemiologic and pathophysiological features both allergic rhinitis and asthma are part of same syndrome, the chronic allergic respiratory syndrome [68]. A report of the American Academy of Allergy, asthma and ımmunology [69] estimated that up to 78% of patients with asthma have nasal symptoms and 38% of patients with AR have asthma. A large number of surveys have been conducted worldwide assessing the association between AR and asthma in different geographical areas, however none of them were large scale studies. A recent study in Iraq provided evidence that AR and asthma are strongly

associated with each other therefore treatment approach should consider the entire airway rather than only considering nasal passage [70]. The management of allergic rhinitis comprises of 3 major categories including environmental control measures and allergen avoidance, pharmacological management, and immunotherapy. Environmental control measures and allergen avoidance involves both the avoidance of known allergens and avoidance of nonspecific, or irritant, triggers. It is also advisable to consider environmental control measures, when practical, in all cases of allergic rhinitis [71].

However, global environmental control without identification of specific triggers is inappropriate. Although allergic rhinitis is not a life-threatening condition, various complications can occur and result in significant impairment in quality of life, [72,73] eventually leading to increase medical cost. Fifty-four randomized, placebocontrolled studies involving more than 14, 000 adults and 1, 580 children with AR met the criteria for review: 38 studies of seasonal allergic rhinitis (SAR; n = 11, 980 adults and 946 children) and 12 studies of perennial allergic rhinitis (PAR; n = 3, 800 adults and 366 children). The median percentage changes from baseline for total nasal symptom score for SAR were as follows: nasal antihistamines, -22.2%; oral antihistamines, -23.5%; intranasal steroids (INSs) -40.7%; and placebo -15.0%. For PAR, the changes were as follows: oral antihistamines -51.4%; INSs -37.3%; and placebo -24.8%. Data for mediator antagonists were limited [74]. The data, although limited, confirm that intranasal steroids (INSs) produce the greatest improvements in nasal symptoms in patients with seasonal AR (SAR). In addition, INSs were effective for perineal AR (PAR), but the data were of variable quality and oral antihistamines may be equally effective for some patients. The reporting of published data should be standardized to permit better comparisons in future studies. AR treatment should be based on the patient's age and severity of symptoms. Patients should be advised to avoid known allergens and be educated about their condition. Intranasal corticosteroids were the most effective treatment and should be first-line therapy for mild to moderate disease [75].

However, INSs were associated with some side effects such as mucus membrane atrophy and secondary bacterial infections. Moderate to severe disease unresponsive to intranasal corticosteroids needs to be treated with second-line therapies, including oral antihistamines, decongestants, cromolyn, leukotriene receptor antagonists and nonpharmacologic therapies such as nasal irrigation. With the exception of cetirizine, second-generation antihistamines were less likely to cause sedation and impair performance [76]. Immunotherapy another option of treatment is reserved for patients with a less than adequate response to usual treatments. More recent studies in children and adults show additional positive outcomes of specific immunotherapy (SIT) with decreased tendency for additional environmental sensitization [77] and decreased incidence of asthma in treated allergic rhinitis patients [78].

Although the effectiveness of SIT in the treatment of allergic rhinitis and allergic asthma has been proven, however its delayed time of action [79] and adverse local and systemic side effects have limited its use as a treatment modality by majority of the patients [79]. Although there is much and convincing evidence for SIT effectiveness and efficacy from reported international studies, however only single study had prospectively investigated the real-life efficacy in Iraqi patients showing that systemic use of black seed oil was effective treatment for AR [80].

Prevention therapy including house dust mite (HDM) immunotherapy for 3 years significantly reduced symptom and medication use in AR, asthma and patients with both conditions and prevents the subsequent development of asthma in patients with AR. This was associated with a greater subjective improvement in asthma control [81]. On the other literature does not support the use of mite-proof impermeable covers, air filtration systems, or delayed exposure to solid foods in infancy [76]. Anti allergic effects of *Nigella sativa* a herb in nature were reported [82]. It is assumed that thymoquinone with carbonyl polymer is an active ingredient of *N. sativa* is responsible for its antiallergic activity [82].

Recently reported study reported that the *N. sativa* usage can reduce the presence of the nasal mucosal congestion, nasal itching, runny nose, sneezing attacks, turbinate hypertrophy, and mucosal pallor during the first 2 weeks [83]. Furthermore, *N. sativa* supplementation during specific immunotherapy of AR may be considered as a potential adjuvant therapy [84] and was found to have equal therapeutic activity in relieving the symptoms of seasonal AR in comparison to cetirizine, without causing any adverse effects [85].

Similarly a recent study concluded that systemic use of *N. Sativa* extract is effective in mild and moderate allergic rhinitis symptoms reduction. Various factors may influence the response of systemic N.S treatment in allergic rhinitis and includes; multiple allergic diseases with high serum IgE level and atopic family diathesis, gender, perennial type and old age. Side effects of *N. sativa* extract use were trivial and easily controlled. *Nigella sativa* extract has proved to have a strong therapeutic effect in allergic rhinitis [85]. This prospective study of patients was performed to see efficacy of *Nigella sativa* oil topical application as a treatment remedy among patients presenting with allergic rhinitis in an outpatients setting.

Treatment of Allergic Rhinitis Result

Sixty eight patients were randomly selected from the previously treated patients after 2 weeks of withdrawal of systemic use of the herb oil. The recruited subjects were divided into 3 groups. (Mild, moderate and severe) and then subdivided into active and control groups (Table 1). The active group was consisted of 38 patients: of them 10 patients of mild active group, 16 patients of moderate active group and severe active group included 12 patients. While the control group consisted of 30 patients: of them, 9 patients were from mild control group, 12 patients from moderate control group and severe control group included 9 patients.

The most affected symptom by treatment was rhinorrhoea, followed by nasal itching, sneezing, nasal congestion and improvement of sleep. All these effects were better in topical NS oil treatment with the exception of conjunctivitis which was only affected by systemic treatment.

Variable	Percent Improvement Systemic Use	Percent Improvement Topical Use
Rhinorrhoea	80.4	100
Sneezing	79.4	89.7
Nasal itching	78.4	90.0
Nasal obstruction	50.9	73.5
Conjunctivitis	60.8	0
Sleep improvement	50.0	73.5
Smell sense improvement	21.5	39.7

Table 1: Effect of *N. sativa* oil treatment via both systemic and topical use on allergic rhinitis symptoms.

Evaluation of Topical Black Seed Oil in the Treatment of Allergic Rhinitis

Effect of *Nigella Sativa* oil on various clinical and biochemical parameters of metabolic syndrome

This study was conducted at a tertiary health care centre in North India. After final diagnosis and considering inclusion and exclusion criteria, sixty patients were enrolled in this study. Informed and written consent was taken from all the patients enrolled. Approval from institutional ethical committee was obtained. Patients were divided into two groups of thirty. In group I (standard group) patients were given tablet atorvastatin 10 mg once a day and tablet metformin 500 mg twice a day for a period of six weeks. In group II (*Nigella sativa*) group, patients were given tablet Atorvastatin 10 mg once a day, tablet metformin 500 mg twice a day and *Nigella sativa* oil 2.5 ml twice daily for a period of six weeks. Blood sugar, both fasting and postprandial, fasting lipid profile, body mass index, body weight and waist circumference were recorded before and after completion of therapy. Result: The above mentioned methodology was followed and it was found that the difference in percentage improvement in group II was significant with reference to total cholesterol, low density lipoprotein (LDL) and fasting blood glucose ($p<0.05$). *Nigella sativa* oil is effective as an add-on therapy in patients with metabolic syndrome. *Nigella sativa* oil has a significant therapeutic activity in diabetic and dyslipidemic patients.

Antihypertensive effect of *Nigella sativa* seed extract in patients with mild hypertension

Hypertension (HT) is a lifestyle-related disease and dietary modifications are effective for its management and prevention. We conducted a randomized, double-blind, placebo-controlled trial to evaluate the efficacy of treatment with an oral *Nigella sativa* (NS) seed extract supplement in patients with mild HT. Subjects were randomized into three groups: a placebo and two test groups that received 100 and 200 mg of NS extract twice a day. After 8 weeks, systolic blood pressure (SBP) values in both case groups were found to be significantly reduced when compared with the baseline values for each group. In addition, the decrease in SBP in the two case groups was statistically significant relative to the placebo group ($P < 0.05–0.01$). Meanwhile, diastolic blood pressure (DBP) values in the case groups were found to be significantly reduced from the baseline and a significant reduction was also observed in these groups ($P < 0.01$) when compared with the placebo group. In addition, extract administration reduced both SBP and DBP in a dose-dependent manner. Meanwhile, NS extract caused a significant decline in the level of total and LDL cholesterol relative to baseline data. No complications caused by NS were observed. The results suggest that the daily use of NS seed extract for 2 months may have a blood pressure-lowering effect in patients with mild HT.

Discussion & Conclusion

Nigella Sativa, a medicinal plant commonly used in a quite wide disease group, is one of the herbal plants with best known medicinal impact. *N. sativa* seed contains more than 100 compounds, some of which are not yet identified or studied. Its efficacy results from the combination of fatty acids. The immunomodulatory and immunotherapeutic potentials of particularly thymoquinone, one of the active ingredients of *N. sativa*, have been observed in the studies conducted. Different extracts of *N. sativa* and thymoquinone are potent therapeutic agents in the regulation of a wide range of stated immune reactions. In our country, studies on the use of black cumin and its oil in the treatment are almost negligible. In our article, the areas of usage of black cumin seed oil and especially the immune system, metabolic syndrome, allergic rhinitis, and antioxidant activity were examined.

In all of the specified indications, it was emphasized its reliability and that it can be used as a supplement for treatment. In the studies carried out, it has been indicated that black cumin seed oil is a highly effective biological agent in allergic rhinitis, both internally and topically. Besides, it has many regulatory functions on the immune system. In the studies, particularly the active ingredient of thymoquinone was isolated from the phenolic compounds found in black cumin seed oil and its efficacy in all these indications was compared with black cumin oil. The main objective here is to answer the question of whether these health benefits are caused by the effect of thymoquinone alone contained in black cumin oil or by the synergistic effect of all the components available in the oil.

Assessments support the strong therapeutic effects of the active ingredients of *Nigella sativa*. *N. sativa* and its components have been found to be effective in strengthening antioxidant, immunomodulatory, immune system, in regulating blood lipid levels, in relieving the symptoms of allergic rhinitis. In the study of diabetic and dyslipidemic patients, it has been shown to have significant therapeutic activity. In addition to studies conducted to evaluate the antitoxic properties of *N. sativa* both in vitro and in vivo, dose- and time-dependent larger studies were required. In clinical settings, there is a need for new studies on immunotherapeutic administration of TQ (inflammatory immune diseases). It has been shown that the incidence of asthma decreases in allergic rhinitis patients treated with *Nigella sativa* in allergic rhinitis. It has been shown to have a regulatory role in the immune

system. All effects of thymoquinone on the immune system have been mentioned.

In order to use black cumin seed and its active ingredients as a medication, the active compounds it contains must be determined and standardized, they must undergo further research stages, including clinical and toxicological studies, and should be assessed for quality, efficacy, and safety. More clinical studies are needed for mechanisms of action and unknown contraindications. We guess that future studies will prove the immunoregulatory functions of *N. sativa* and Thymoquinone and thus, confirm their possible therapeutic efficacy against various diseases and medical conditions.

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