

A Review on Nigella Sativa extract to enhance tissue and immune cells damage

محاضر مساعد / عبدالرؤوف عثمان يوسف¹
محاضر / على ارحومة الدويب²
عضو هيئة تدريس جامعة صبراته / كلية التمريض صرمان^{2,1}

ABSTRACT

Reactive oxygen species (ROS) and oxidative stress are known as the major causes of many diseases, tissue, immune cells damage, many substances and drugs can induce oxidative damage by generation of ROS in the body. This study aims to evidence the risks of damage in tissue, immune cells and to study the role of NS to inhibit inflammation, enhance Immunity and Immunomodulation. Nigella sativa is a widely used medicinal plant throughout the world. N. sativa is referred in the Middle East as a part of an overall holistic approach to health. Extensive studies on N. sativa have been carried out by various researchers and a wide spectrum of its Pharmacological properties of N. sativa including immune stimulant, hypotensive, antidiabetic, anticancer, immunomodulator, analgesic, antimicrobial, anti-inflammatory, hypoglycemic, spasmolytic, bronchodilator, hepato-protective, renal protective, gastro-protective, antioxidant properties, Thymoquinone protects tissue from injury via different mechanisms including inhibition of iron-dependent lipid peroxidation, elevation in total thiol content and glutathione level, radical scavenging, increasing the activity of quinone reductase, catalase, superoxide dismutase and glutathione transferase, inhibition of NF- κ B activity and inhibition of both cyclooxygenase and lipoxygenase. The previous studies indicate that Nigella sativa seeds exhibit immunostimulatory function through their antioxidant potential, induction of cytokine production, promotion of CD8 expression and reduction of tissue apoptosis. Due to its miraculous power of healing, N. sativa has got the place among the top ranked evidence based herbal medicines.

Keywords: Nigella sativa (NS), Reactive oxygen species (ROS), Immune cells damage, Inflammation, Tissue, IL-10, IFN- γ , WBC DC, NF- κ B, And Fibrosis/Cirrhosis.

Introduction

Oxidative stress is a distinctive and dangerous trait in a number of neurological disorders. The brain is the most susceptible to oxidation due to a high rate of metabolic activity of oxidative stress. As well as the antioxidants are the first line of defence the body against free radical damage and in general to maintain health.^{2,3,4,5,6,7} Inflammation is a response to tissue injury occurs knead by increasing blood flow and vascular Permeability with the accumulation of fluid and white blood cells in the inflamed area. Release of inflammatory mediators such as cytokines play role for



development of specific immune responses, humoral and cellular immunity in the area of injury.⁸ Cytokines has very important role on the interactions and communications between cells.⁹ Cytokines regulate the immune system, inflammation and hematopoiesis. IL-10 is an anti-inflammatory cytokine that was first called human cytokine synthesis inhibitory factor, IL-10 plays a role in inhibiting the synthesis of many cytokines involved in the inflammatory process.¹⁰ IFN γ was first named immune IFN, and then later type II. IFN γ as pro-inflammatory cytokines.¹¹ Cytokines also play role as the main key in the inflammatory.⁸ Also WBC count as one of the major components of inflammatory process.¹² inflammations is a physiological response of the organism to harmful physical, chemical, or biological stimuli. If the injurious agent is eliminated, resolution and tissue repair will follow .¹³

Thousands of years of traditional herbal medicine used by human, which is derived from natural plants for treatment of various diseases and to improve physical performance are known. In recent decades, an increase interest of researchers to understand the mechanism of action of plant extracts and their major components in the prevention and treatment of many diseases.

Nigella sativa is one of the most important herbal medicines in the world. *Nigella sativa* is used as the alternative treatments in spite of the trend towards synthetic medicine and the use of cutting-edge drugs. However, the traditional plants based on natural remedies still play an important role in the field of medicine in the world until now.^{14,15} *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,¹⁶ *Nigella sativa* is small herb and stylish,¹⁷ from 20 – 30 cm height, with a variable number of sepals and 5 - 10 petals that are about 2.5 cm wide small seeds usually from 1 - 5 mm long, black color with a rough surface is grooved, and an oily white inside it.¹⁶ *Nigella sativa* is an annual flowering plants with pale blue flowers, which belongs to the Ranunculaceae family. It is found in the wild in southern Europe, North Africa and Asia Minor.¹⁸ It is well known that *Nigella sativa* natural treatment for many diseases and as a flavoring agent in bread and some foods also used in most of the world as a spice.¹⁴ *Nigella Sativa* has aromatic scent and taste bitter.¹⁶ *Nigella sativa* has a strong anti-oxidant properties may protect the body organs from oxidative damage caused by a variety of agents to generate free radicals.¹⁹ *Nigella sativa* may suppress elevated levels of pro-inflammatory cytokines and pro-oxidant.²⁰ Experimentally, *Nigella sativa* has anti-inflammatory reaction against most inflammatory diseases, and significantly increase the level of anti-inflammatory cytokines in the body during inflammation,^{20,21,22,23}.

Interferon- γ (IFN- γ)

Interferon- γ (IFN- γ) was first named Immune IFN, then later Type II IFN. The major sources of IFN- γ are natural killer (NK) cells, T cells and NKT cells. Its receptor is expressed ubiquitously on almost all cell types. IFN- γ is an extraordinarily pleotropic



cytokine as pro-inflammatory cytokine. It can not only heighten both the innate and adaptive immune response against pathogens, but also has the ability to maintain immune homeostasis. IFN- γ can induce both pro- and anti-inflammatory responses, and its ability to induce these two responses is critical for a balanced immune response.²⁴

Interleukin-10 (IL-10)

IL-10 inhibits the synthesis of a number of cytokines involved in the inflammatory process including IL-2, IL-3, GM-CSF, TNF α and IFN γ . Based on its cytokine-suppressing profile, it also functions as an inhibitor of TH1 cells and by virtue of inhibiting macrophages. It functions as an inhibitor of antigen presentation. Interestingly, IL-10 can promote the activity of mast cells, B cells and certain T cells. First identified as an inhibitor of IFN γ synthesis in TH1 cells, IL-10 is an important immunoregulatory cytokine. It is an anti-inflammatory cytokine that was first called human cytokine synthesis inhibitory factor. IL-10 is secreted by macrophages, TH2 cells and mast cells. The major immunobiological effect of IL-10 is the regulation of the TH1/TH2 balance. IL-10 is a promoter of TH2 response by inhibiting IFN γ production from TH1 cells.¹⁰

Histology of kidney tissue

The Kidney is a paired organ located in the posterior abdominal wall, in which major functions include the removal of toxic metabolites and waste products from the blood and regulation of the amount of fluid and electrolytes balance in the body. The liver and kidney organs are mainly responsible for detoxification of foreign compounds in the body.²⁵

White blood cells differentiation count

White Blood Cells are mainly concerned with protecting the body against invasion by microorganisms. These cells are also called leukocytes which help the body fight infection. White Blood Cells are an important part of the body's defence system.²⁶ WBC count, as one of the major components of inflammatory process,¹² Elevated leukocyte count is a marker of inflammation,²⁷ also WBCs and neutrophil counts were significantly high in patients with inflamed disease.²⁸

Fibrosis/cirrhosis

Production of ROS and lipid peroxidation is associated with liver fibrosis and cirrhosis. This effect can lead to the death of hepatocytes and many researchers have shown that oxidative stress has a critical role in fibrosis and cirrhosis of liver. Free radicals initiate cell damage by binding to the membrane proteins. These effects are partially prevented by antioxidants.

Chemical pollutant-induced liver damage

Industrialization in today's world increases the environmental pollutant sources, such as mercury, carbon tetrachloride, arsenic, cadmium, thioacetamide etc. Mechanism of these chemicals is peroxidation of the hepatocyte lipids causing destruction of the cells and their intracellular organelles and covalent binding to the membrane proteins. Many researchers have shown that chemical pollutants increase oxidative stress and then the effects of this condition on the body organelles such as liver. Mechanisms mention above revealed that many liver damage causes are mediated by oxidative stress and production of ROS. Thus, the enhancement of antioxidant defence and increase of the glutathione resources in the body can attenuate oxidative damages to hepatocytes.⁴⁷

Nigella sativa

Herbal medicines which are derived from plants and plant extracts had been traditionally used for health improvement by human for thousands years to treat medical illness or to improve physical performance. Plants have been always a major source of nutrition and health care for both humans and animals, and scientists in recent decades are interested in understanding their mechanism of action and identifying their main constituents. Many studies have been done to show the beneficial therapeutic effects of herbal medicines. Despite the move toward synthetic medicine and use of sophisticated drugs, traditional plant-based remedies still play an important role in the world's medicine. Extremely, 80% of the world's population use plant-based remedies as their primary form of healthcare and the world market of herbal medicines based on traditional knowledge are estimated at USD 60 thousand million.¹⁵ Nigella sativa one of the most important Herbal medicines, 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,¹⁶ also has commonly known as upakunchika, ajaji, kalvanjika, kalika, kunchika, kalaunji, and black cumin, is a small elegant herb.¹⁷ Nigella sativa is an annual flowering plant with pale blue flowers that belongs to the Ranunculaceae family. It is found wild in southern Europe, northern Africa, and Asia Minor. It is a bushy, self-branching plant with white or pale to dark blue flowers. Nigella sativa reproduces with itself and forms a fruit capsule which consists of many white trigonal seeds. Once the fruit capsule has matured, it opens up and the seeds contained within are exposed to the air, becoming black in color.¹⁸ The plant has a fruit which contains angular black seeds, and the seeds are considered to be the most valuable part contributing beneficial health effects.²⁹ Nigella sativa (black cumene seeds) as herb of 20 - 30 cm height, with a variable number of sepals and 5 - 10 petals that are about 2.5 cm wide. Seeds are normally small (1 - 5 mm long), black or dark-grey with a rough grooved surface and an oily white interior, and odor slightly aromatic and taste bitter. Transverse section of seed shows

single layered epidermis consisting of elliptical, thick walled cells, covered externally by a papillose cuticle and filled with dark brown contents, parenchymatous cells and oil globules. Abu Huraira (Allah be pleased from him) narrated that Allah's Apostle Muhammad (peace be upon him) said use the black seed, which is a healing for all diseases except 'As-Sam' and As-Sam is Death.¹⁶ Black seed is also identified as the curative black cumin in the Holy Bible and is described as the Melanthion of Hippocrates and Discroides and as the Gith of Pliny. Historically, it has been recorded that *N. sativa* seeds were prescribed by ancient Egyptian and Greek. ¹⁸ *Nigella sativa* is well known as a natural remedy for many ailments and as a flavouring agent in bread and prickles. It is a common used in different parts of the world as a spice, food additive,¹⁴ especially in ingredient of Indian kitchen spices,³⁰ also use the capsules of seed powder, seed powder with tea; and its oil, cream, ointment and shampoo. Even in the veterinary medicine, besides the beneficial effects of *N. sativa* seed and its oil in many infectious diseases; there are reports that the addition of *N. sativa* seed cakes in the feed of buffalo and lambs improved their body weight and reproductivity; and the addition of *N. sativa* seed in the food of broiler chicks improved their immunity and feed conversion efficacy.³¹ Studies have revealed various therapeutic values of *Nigella sativa* such as Potent anti-inflammatory,^{32,20,33,21,34,35}, anti-oxidant potential,^{20,29,21,35,36} anti-microbial,^{35,2} anti-cancer,^{29,35} anti-bacterial, anti-fungal, anti-parasitic,²⁹ analgesic,³³ neurodegenerative diseases against, ²¹ proved hepato-protective, hepatotoxicity,¹⁵ anti-ulcerogenic,³⁷ anti-asthmatic,^{32,29} and anti-osteoporotic effects in diabetes.³⁸

Ingredients of *Nigella sativa* seeds

Nigella sativa contains 36 – 38 % fixed oils, proteins, alkaloids, saponin, and 0.4 – 2.5 % essential oil, High-performance liquid chromatography (HPLC) analysis of *Nigella sativa* essential oil revealed that the main active ingredients were thymoquinone (TQ), dithymoquinone (DTQ), which is believed to be nigellone, thymohydroquinone (THQ), and thymol (THY), are considered the main active ingredients. Among the compounds identified, thymoquinone (TQ) is the most abundant, which makes up 30 – 48 % of the total compounds. This quinone constituent is the most potent and pharmacologically active compound in *Nigella sativa*.^{29,18} *Nigella 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. Fractionation of whole *Nigella sativa* seeds using SDS – PAGE shows a number of protein bands ranging from 94 to 10 kDa molecular mass. Monosaccharides in the form of glucose, rhamnose, xylose, and arabinose, are also found. *Nigella 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. The major separate individual phospholipid classes is phosphatidylcholine, followed by phosphatidylethanolamine, phosphatidylserine, and phosphatidylinositol, respectively. The seeds contain carotene which is converted by the liver to vitamin A. The *Nigella sativa* seeds are also a source of calcium, iron, and potassium.¹⁸

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.¹⁶ The 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%),¹ cellulose (6.8–7.4%) and moisture (8.1–11.6%).⁷ 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.⁵⁴ Germination of seeds has been used for centuries to soften the kernel structure, to increase the nutritional value and to decrease the anti-nutritive compounds. During the recent years interest has arisen also in the secondary metabolites produced during germination which can have valuable health promoting properties and act as bioactive or functional compounds in foods. The seeds of *N. sativa* in different germination stages have revealed the presence of higher amount of alkaloids, tannins and flavonoids as compared to seed. So, successive germination phases for obtain on the higher anti-inflammatory and analgesic of *N. sativa* crude methanol extracts.³³

Traditional medicine, therapeutic and pharmacological uses of *Nigella sativa* Effect against inflammation

Nigella sativa may suppress the elevated levels of pro-inflammatory cytokines and pro-oxidants. anti-inflammatory and/or anti-oxidant interventions may provide a useful approach to attenuate disease progression.²⁰ It has been reported that inflammatory cytokines and mediators are key components in the inflammatory process. *Nigella sativa* seeds were used as anti-inflammatory agent. Several studies revealed that *Nigella sativa* seed oil contains potent, but non-toxic compounds that suppress excessive inflammatory molecules.²¹ *Nigella sativa* has been proved experimentally to be an anti-

inflammatory substance, It significantly reduced the levels of pro-inflammatory mediators {IL-1b, IL-6, TNF-a, IFN-c and PGE} and significantly increased anti-inflammatory cytokine such as (IL-10) in rats.^{20,21,22,23} Nigella sativa may likely interrupt these interactions via suppression of NF-κB and plays an important part in its anti-oxidant/anti-inflammatory activity, Nigella sativa could improve inflammation and reduce oxidative stress in patients with inflammatory disease.²⁰ Moreover, found that encephalomyelitis could be prevented and ameliorated by active compound of Nigella sativa TQ treatment. So Nigella sativa treated could be attributed to the suppression of inflammatory cells.²¹ Nigella sativa may have an anti-inflammatory role in allergic asthma in mice.³⁴ Nigella sativa could partly reduce the severity of chemotherapy induced oral mucositis and promote healing of the oral. Nigella sativa could protect the mucosa by increasing the bioavailability of anti inflammatory cytokines, resulting in biosynthesis of the cytoprotective prostaglandins. Nigella sativa may help to produce a marked inhibition on the release of leukotrienes, which cause mucosal tissue injury and hypoxemia. Therefore, it may alter the delicate balance between prostaglandins and leukotrienes in the oral mucosa favoring cytoprotection. ³⁷ the anti-inflammatory effect was demonstrated by its inhibitory effect on carrageenan induced paw edema. And analgesic effect by significant increase in hot plate reaction time in mice.¹⁶ N. sativa oil had a protective effect against the carbon tetrachloride-mediated suppression of hepatic cytochrome proteins CYPs expressions, and this protective effect was partly related to the reduction of nitric oxide via the down-regulation of inducible nitric oxide synthase.^{22,23}

Effect against oxidation

Nigella sativa inhibit non-enzymatic lipid per oxidation in liposome. Using thin-layer chromatography (TLC), it has also been shown that compounds isolated from Nigella sativa (including thymoquinone, carvacol, t-anethole and 4-terpinol) have appreciable free radical scavenging properties. Thymoquinone is reported to possess a strong antioxidant property. Thymoquinone protects organs against oxidative damage induced by a variety of free radical generating agents. ³⁶ the hepatoprotective effects of Nigella sativa were found via the antioxidant mechanism. Similarly, the protective effect of thymoquinone against doxorubicin induced nephrotoxicity and that against doxorubicin induced cardiotoxicity was also found to be due to its anti-oxidant activity.¹⁶ The anti-ulcerogenic effects of Nigella sativa can be attributed to the improvement of the antioxidant status of animals due to the presence of free radicals scavenging substances such as TQ which is the main active constituent of Nigella sativa.³⁷ Free radical-induced DNA damage has been shown to be increased in embryos from diabetic rats. Nigella sativa treatment was efficient in reducing blood glucose in diabetic rats. In Nigella sativa treated diabetic rats the blood glucose was significantly reduced. It may be because antioxidant property of Nigella sativa.³⁶

Oxidative stress and β -cell damage

The antioxidant status of a cell determines its susceptibility to oxidative damage, and is usually altered in response to oxidative stress. Accordingly, there has been increasing interest regarding the role and use of natural antioxidants as a means of preventing oxidative damage in diabetes due to high oxidative stress. The seed of *Nigella sativa* L. (NS), an annual Ranunculaceae herbaceous plant, Antioxidants (e.g., vitamins C and E, enzyme superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GSHPx)) have been shown to protect cells against lipid peroxidation, the initial step in many pathological processes. Reduced antioxidant levels as a result of increased free radical production to determine whether the pancreas is subjected to oxidative damage during diabetes, and to examine the accompanying changes in antioxidant status in order to elucidate its role in the pathogenesis of this disease. In addition, the researcher in this study explored whether NS treatment protects against pancreatic β -cell damage in STZ-induced diabetic rats. The experimental diabetes have been reported by many authors.⁴⁸

Effects on Diabetic condition

The hypoglycaemic effects of *Nigella sativa* was supposed to be mediated by extra pancreatic actions rather than by stimulated insulin release. 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.¹⁶ *Nigella sativa* may have improved the bone metabolism by improving the blood sugar levels. In certain parts of the world, *Nigella sativa* is frequently used as the traditional treatment of diabetes.^{32,29,30,36} Studies on streptozotocin-induced diabetic rats have shown that *Nigella sativa* may reduce hyperglycaemia, increase serum insulin concentrations, and promote partial regeneration or proliferation of pancreatic beta cells, causing an increase in insulin secretion. There is a possibility that *Nigella sativa* may have exerted its antiosteoporotic effects in diabetes by improving the blood sugar profile.³⁸

Effect against osteoporosis

Plenty of evidences had surfaced, linking inflammation to osteoporosis. This has led to the opinions that inflammation may contribute to osteoporosis. Inflammatory conditions such as ankylosing spondylitis, rheumatoid arthritis and systemic lupus erythematosus were associated with higher incidence of osteoporosis. The level of C-reactive protein, a marker of systemic inflammation was also found to be negatively associated with bone mineral density. The extend of osteoporosis is directly related to the degree of inflammation, whereby systemic inflammation resulted in general bone loss, while for local inflammation, bone loss is restricted to the site of inflammation. Elevations of proinflammatory cytokines with aging, gouty arthritis, rheumatoid arthritis and psoriatic

arthritis may also contribute to osteoporosis. so anti-inflammatory effects of *Nigella sativa* improving the osteoporosis.³⁸

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* Dahv2 infection. According to Hariharan et al.¹⁰ TQ has shown antimethicillin-resistant activity in *S. aureus*.⁵⁴

Nigella versus fungi

N. sativa acts against *Candida albicans* and *Madurella mycetomatis* and its isolated compound, TQ against *Aspergillus niger*, *Fusarium solani* and *Scopulariopsis brevicaulis*, where the activity was reported more effective than amphotericin-B and griseofulvin. The TQ also effective against *Trichophyton* spp., *Epidermophyton* spp., and *Microsporum* spp. In addition, TQ, thymohydroquinone and thymol are also demonstrated an antifungal effect against many clinical isolates, including dermatophytes, molds and yeasts.³ Black seed oil (10–200 µg/mL) is also evident to act against *Saccharomyces cerevisiae* and *C. utilis*.⁵⁴

Nigella as antiviral agent

N. sativa was shown to enhance helper-T-cell (T4) and suppressor-T-cell (T8) ratio and increased natural killer (NK) cell activity in human. Otherwise, it is proven as a good inhibitor to the human immunodeficiency virus (HIV) protease and murine cytomegalovirus. In the latter case, it was found to increase in number and function of M-phi and CD4+ve T cells with the production of interferon-gamma (INF-γ) was reported.⁵⁴

Nigella versus parasites

N. sativa was shown to have anti-leishmaniasis, anti-miracidia, anti-cercariae and anti-Schistosoma mansoni potentials. In the latter case the oil of the black seed showed strong activity as compared to a well-known anti-schistosomal and anthelmintic drug for domestic animals, praziquantel; where it produced a potentiating effect with co-

treatment.³ Simalango¹² suggested that ethanol extract of *N. sativa* (0.5–8%) produced significant anti-*Ascaris suum* activity.⁵⁴

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.⁵⁴

Effects on cardiovascular system

Nigella sativa exhibit a depressant action on the frog heart and a relaxant effect on isolated smooth muscles of rat. *Nigella sativa* was found to significantly lower serum cholesterol and blood pressure in spontaneously hypertension,^{32,29,14} cardio vascular system, hypercholesterolemia, hypo-lipidemic, anti-atherosclerosis, anti-arthritis,³⁰ astringent, bitter, stimulant, emmenagogue, anthelmintic, jaundice, dyspepsia, paralysis, piles, intermittent fever,^{17,16}

Effect on genito-urinary system

Nigella sativa were found to significantly reduce the cisplatin induced nephrotoxicity, blood urea nitrogen and serum creatinine levels as well as cisplatin-induced serum total lipids increases,¹⁶ *Nigella sativa* may also inhibit renal calculi and improve poultry quality.²⁹

Effect of Nigella sativa on cancer

Nigella sativa exhibit immunopotentiating, immunomodulatig and interferon-like activities. NS led immune system support.^{20,29,43} *Nigella sativa* extract was found to inhibit cancer cells and endothelial cells progression in vitro.¹⁶ *Nigella sativa* may change the set point of the immune system and stimulate both pro and anti-inflammatory cytokines.¹⁴ *Nigella sativa* has showed to induce apoptosis of human colon cancer cells and this might enhance progression of cell cycle which in turn enhances the healing process of mucosal lesions. ³⁷ *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. *Nigella sativa* extract was show an increase in macrophages and CD4+ T cell and decrease in both number and function of NK cells.¹⁶ some compound and oil from *Nigella sativa* showed beneficial immunomodulatory properties, augmenting the T cell-mediated immune responses. *Nigella sativa* extract has shown significant reduction in cell proliferation of tumor cells, DNA synthesis, mitotic percentage, toxicity of free radicals in animal tissues and prolongation of life span of the mice bearing the Ehrlich ascites tumor.³²



Effect of *Nigella sativa* on cell-mediated immune response and immunomodulation

The protective effect of *N. sativa* for T cell cytokines that a pivotal role in the promotion of immune responses against invading pathogens. There are two distinct cytokine producing T cell subtypes: CD4+ T helper and CD8+ T cytotoxic which T helpers have been appointed to type 1 and type 2 T lymphocytes based on their profile of cytokine production. Type 1 lymphocytes are essential for the cell-mediated immune and defense against intracellular pathogen by producing interferon γ (IFN γ), interleukin 2 (IL-2) and tumor necrosis factor- β cytokines. Whereas, type 2 lymphocytes produce cytokines including IL-4, IL-5, IL-6, IL-10, and IL-13 and are responsible for defense against extracellular pathogens by the development of humoral immunity. These two classes of cytokines have cross-regulatory signalling, for example IL-4 and IL-10 secretion causes the inhibition of Th1-type immune responses by down-regulating of macrophage-derived IL-12 production. But also, IFN γ changes the balance of Th1/Th2 by suppressing the Th2-type immune responses.⁵⁰ immunomodulatory and therapeutic properties of the *N. sativa* L. seed and emphasized the potent immunomodulatory effects of this plant. Our previous studies have also shown different pharmacological effects of *N. sativa* on guinea pig tracheal chains, including relaxant and functional antagonistic effects on muscarinic receptors, inhibitory effect on histamine (H1) receptors and calcium channels, opening effect on potassium channels, and stimulatory effect on β -adrenoceptors. The antitussive effect of this plant on the guinea pig has also been demonstrated.^{41,42} has also been demonstrated, and a possible prophylactic effect of this plant has been observed in asthmatic patients. In the present study, the protective effect of *N. sativa* on tracheal responsiveness and lung inflammation in sensitized guinea pigs was examined.⁴² Immunostimulants enhance the cell-mediated immune response by activating antigen-specific cytotoxic T lymphocytes and phagocytes and discharging several cytokines toward antigens to achieve a therapeutic response. Immunostimulants overwhelm the immunosuppressive effects of infectious agents and either induce stress on the interface and/or damage the function of immune cells. Diverse substances, including plants and animal derivatives, microbial products, hormones, synthetic chemicals and vitamins, exert immunostimulatory effects. Herbs, plant extracts and animal-originated products are widely used because they are not expensive, can be easily obtained and act against a wide-ranging spectrum of pathogens. The oral administration of plant or herbal extracts of NS as immunostimulants is considered the best method for immunostimulation. Herbal medicines extracted from plants or plant extracts have historically been used to enhance health, One of these herbal medicines is black seed, or *Nigella sativa* belonging to the family Ranunculaceae, which has a rich religious and historical background, Moreover, *Nigella sativa* activates bone marrow and immune cells and increases the production of interferon, which results in defending normal cells against cell death by virus killing, destroying tumor cells and increasing the amount of antibody-generating B cells.⁵¹

Effects on gastrointestinal system

Nigella sativa was exhibit anti ulcer activity by decreasing the volume of acid in gastric juice in acetyl salicylic acid treated rats. 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.¹⁶ Nigella sativa is also used hypercholesterolemia, gastrointestinal disorders, diarrhea, toothache,^{14,18} obesity, intestinal worms, increase milk production, as well as a diuretic to promote menstruation. ^{30,16}

Contraceptive and anti-fertility activity

Nigella sativa extract prevented pregnancy in rats and also showed possess significant anti-fertility activity in male rats.⁴⁰

Effect on CNS

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.¹⁶ and enhances neurodegenerative diseases like Parkinson and Alzheimer.²¹

Effects on respiratory system

Nigella sativa is widely used natural remedy for respiratory tightness, lung inflammation,³⁹ asthma,^{39,32} chest congestion, cough, bronchitis, fever, dizziness, influenza, oedema,³² general well-being,^{32,20} inflammation,^{32,29} colitis, peritonitis,^{32,20} respiratory system, bronchial asthma, nasal congestion, infections, nasal congestion, Nigella sativa, was found to inhibit effectively the histamine release from mast cells.¹⁶

Toxicity Effect of Nigella Sativa

Nigella sativa has no toxicity in the doses used. These results agree with previous data reporting that Nigella sativa has a wide margin of safety. Nigella sativa did not give any toxicity effect on liver to the parameters used, alanine aminotransferase (ALT) and aspartate aminotransferase (AST). The supplementations of Nigella sativa reduce the ALT level and AST level treated rats. The results of histopathologic examination of the liver showed no hepatic vacuolization, degeneration, inflammation and necrosis in liver tissues.¹⁵

Effect of Nigella sativa on NF-κB

Nigella sativa may likely interrupt these interactions via suppression of NF-κB and plays an important role in the antioxidant / anti-inflammatory activity, Nigella sativa



could reduce oxidative stress and inflammation, it improved in areas of inflammation in the body.²⁰ In inflammatory cells have found a decrease in the expression of inducible nitric oxide synthase after treated by *Nigella sativa*.^{34,22,23,55}

Effect of *Nigella sativa* and its bioactive compound on type 2 epithelial

A study on *Nigella sativa*'s chemical composition by supercritical carbon dioxide revealed few bioactive compounds; namely thymoquinone, dithymoquinone, and dihydrothymoquinone.⁴⁶ thymoquinone found as major component of the essential oil is the most bioactive compound and exhibits wide ranging therapeutic benefits.⁴⁴ Thymoquinone by itself exhibit strong anti-inflammatory, anti-bacterial, anti-diabetic] and anti-oxidant properties , Majority of the studies, reported better wound healing rate or significant prevention of tissue inflammation and organ fibrosis following *Nigella sativa* or thymoquinone treatments.⁴⁶ previous study shown also Epithelial to mesenchymal transition of type 2 is defined by the balance between wound healing and tissue fibrosis, which is dependent to the state of inflammation. This systematic review is conducted to provide an overview regarding the reported effect of *Nigella sativa* and its bioactive compound.⁵²

The Role of *Nigella sativa* and Its Active Constituents in Learning and Memory

NS has been reported to have many therapeutic properties such as immunopotential, bronchodilatation, and being antitumor, antihistaminic, antidiabetic, antihypertensive, anti-inflammatory, antimicrobial, hepatoprotective, and gastroprotective, which are attributed to its quinone constituents in the seeds. Identification of the therapeutic features of NS came from researches in various fields starting in the early 1970s. Nonetheless, there are comparatively only a few studies that scientifically support its positive role in treating central nervous system (CNS) related ailments. However, considering its significant antioxidant, anti-inflammatory, and immunomodulatory properties, consuming NS could be one of the promising health strategies to help prevent the oxidative damage to cells.⁴⁵

Effect of *Nigella sativa* on proliferation

In cultured animal cells, NS enhanced splenocyte proliferation, macrophage function, and natural killer cell anti-tumor activity in adose-responsive manner. Interestingly, NS aqueous extract favored thesecretion of Th2 cytokines (immunostimulant) versus Th1 cytokines (immune-suppressive) by splenocytes. The secretion of IL-6, TNF- α , and NO; key pro-inflammatory mediators, by primary macrophages wassignificantly suppressed by NS aqueous extract. In addition, NS exertedpotent anti-inflammatory effects in vitro whereby the aqueous extract of NS significantly enhanced the cytotoxic activity of natural killer cells against tumor cells.⁴⁹

***Nigella sativa* Preparations on Proinflammatory Mediators**

NS extracts and/or its active constituents (including TQ, nigellone, and alpha-hederin) showed anti-histaminic, anti-eosinophilic, anti-leukotrienes, anti-immunoglobulin and

reduced proinflammatory cytokines (interleukins-2, 4, 5, 6, 12, and 13) in in vitro/in vivo models, IL-2 may increase the production of IL-5 and attract eosinophils.⁵³

Effect of Nigella sativa on skin

Nigella sativa also uses in skin condition as eczema,^{18,17} and skin disorders,⁴³

Conclusion

In conclusion, this study revealed that Nigella sativa could enhance tissue and immune cells damage, inflammation and reduce oxidative stress, as well as increased anti-inflammatory cytokines as IL-10 and decreased pro-inflammatory cytokines as IFN- γ . Thus, this research suggested that Nigella sativa and its constitution have safety profile.

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