



Black Seed (*Nigella sativa*): A Favourable Alternative Therapy for Inflammatory and Immune System Disorders

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Abstract

In the recent years, various food additives, medicinal plants, and their bioactive components have been utilized in anti-inflammatory and immunomodulatory therapy. *Nigella sativa* is a key dietary supplement and food additive which has a strong traditional background. It is also one of the most broadly studied seeds in the global pharmaceutical and nutraceutical sector. *N. sativa* seeds are potential sources of natural metabolite such as phenolic compounds and alkaloids. The anti-inflammatory and immunomodulatory abilities of these seeds, most peculiarly with reference to some inflammatory and immune mediators, are reviewed. *N. sativa* and its bioactive compounds modulate inflammatory and immunomodulatory mediators including tumor necrosis factor-alpha (TNF- α), interferon gamma (IFN- γ), nuclear factor kappa B (NF- κ B) cyclooxygenase (COX), lipoxygenase (LOX), transforming growth factor beta (TGF- β), interleukins, and immunoglobulin levels. This paper comprehensively describes the biomarkers and signaling pathways underlying the anti-inflammatory and immunomodulatory potential of *N. sativa*. This review also explains the scientific basis and the pharmacological properties of core bioactive ingredients of *N. sativa* responsible for these biological activities which indicates that their bioactive components could be possibly regarded as favorable therapy for disorders linked to inflammation and immune-dysregulation.

Keywords *N. sativa* · Cytokines · Phenolics · Alkaloid · Anti-inflammation · Immunomodulation

Abbreviations

<i>N. sativa</i>	<i>Nigella sativa</i>	DNA	Deoxyribonucleic Acid
TNF- α	Tumor necrosis factor	Ig	Immunoglobulin
IL-6	Interleukin 6	IRAK	Interleukin-1 receptor-associated kinase 1
LOX	Lipoxygenase	MUC5	Mucin 5
LDL	Low-density lipoprotein	TGF- β	Transforming growth factor β (TGF- β)
BALF	Bronchoalveolar lavage fluid	ALI	Acute lung injury
SOD	Superoxide dismutase	TBK	TANK-binding kinase
GPx	Glutathione peroxidase	AP 1	Activator protein 1
OH	Hydroxyl radical	STAT	Signal transducer and activator of transcription
TBARS	Thiobarbituric acid reactive substance	TQ	Thymoquinine
ROS	Reactive oxygen species	COX	Cyclooxygenase
MCP	Monocyte chemoattractant protein	PGE2	Prostaglandin
		INOs	Inducible nitric oxide synthase
		NF- κ B	Nuclear factor kappa B
		CAT	Catalase
		NO	Nitric oxide
		MDA	Malondialdehyde
		RBCs	Red blood cells
		PDA	Pancreatic ductal adenocarcinoma
		CD	Clusters of differentiation
		LPS	Lipopolysaccharide
		Th cells	T helper cells
		OVA	Ovalbumin

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CRP	C-reactive protein
HIF-1 α	Hypoxia-inducible factor 1-alpha
JAK	Janus kinase
IFN- γ	Interferon gamma
GM-CSF	Granulocyte macrophage-colony-stimulating factor

Introduction

Pragmatically, all through the continents, several plants and their derived substances are used in the treatment and prevention of varieties of pathologies. The proof of the favorable curative and medicinal effect is observed in their incessant utility. The advancement of recent chemistry authenticated the isolation of chemicals from plant and plant seeds that have inevitably been an alternative and indispensable ample source for new drugs. Approximately ten percent (10%) of drugs are derivatives of natural plant materials endorsed by U.S. Food and Drug Administration (FDA) (Patridge et al., 2016). *Nigella sativa* (*N. sativa*) is a chief therapeutic herb widely cultivated in Mediterranean, Middle East, South Asia, Europe, and North Africa (Khare et al., 2004; Hussain and Hussain, 2016; Hossain et al., 2021). *N. sativa* is a flowering plant classified scientifically as the Ranunculaceae-butter cup family whose common names are black seed or black cumin (Fig. 1). Others names include devil in a bush, love in a mist, fennel flower, etc. It is about twenty-to-fifty centimeters (20–50 cm) tall. It is identified as white petals and pale blue with its fruits consisting of several stark black seeds and it grows annually (Eid et al., 2017). *N. sativa* has been widely utilized as essential pharmaceutical and nutraceuticals agents as well as traditional remedy for many ailments (Periasamy et al., 2016). *N. sativa* also functions as food additives in diets, such as pickles, salads, bread, pastries, sauces, smoothies, oatmeal, and youghurt. It is also utilized as spices, food preservatives, and flavoring agents (Bashir et al., 2021) and abundant in bioactive phytochemicals. *N. sativa* utility can be traced to 1300 BC, and was unveiled in Egyptian pharaoh's tomb known as Tutankhamun (Ali et al., 2003). An authentic saying from Prophet Mohammed revealed that black seed, indisputably,



Fig. 1 Schematic diagram showing Black Seed (*Nigella sativa*)

can be used to cure all diseases except “*As Sam*” (death) (Al-Bukhari et al., 1976; Hadith Al-Bukhari 7:591). The treasured “Canon of Medicine” encyclopedia by Avicenna, designed *N. sativa* study as a core curriculum for medical scholars. In Northern Africa, it is used as a natural remedy for treating several inflammatory disorders, allergies, and infections (Hussain and Hussain, 2016). The diverse utility of *N. sativa* in folklore motivated various researchers to distinguish its bioactive constituents. Acute and chronic toxicity studies on laboratory animals have reported that *N. sativa*, its oil and thymoquinone, the most widely studied active principle, are quite safe, particularly when given orally (Badary et al., 1998; Mansour et al., 2001; Al-Ali et al., 2008). Dollar et al. reported that the *N. sativa* (0.1 and 1 g/kg/day) supplementation administered to male Sprague Dawley rats for a period of 28 days revealed no changes in hepatic enzyme levels (serum alanine aminotransferase (ALT) and aspartate-aminotransferase (AST)) and did not exert any toxic effect on the liver function (Dollah et al., 2013). The low acute toxicity of *Nigella sativa* fixed oil in mice, indicated by high values of oral and intraperitoneal lethal dose (LD50=28.8 ml/kg body wt., p.o.; LD50 value=2.06 ml/kg body weight., i.p) values, principal hepatic enzyme stability and organ integrity, demonstrates a broad margin of safety for therapeutic doses of *N. sativa* oil. Additionally, chronic toxicity test experimented on rats treated daily with an oral dose of 2 ml/kg body weight for a period of 12 weeks showed no alteration in the hepatic enzyme levels [gamma-glutamyltransferase, alanine-aminotranferase (ALT), and aspartate-aminotransferase (AST)] as well as histopathological modifications in rats treated with *N. sativa* oil (Zaoui et al., 2002). A particular study also revealed that TQ at a dose level (30, 60, or 90 mg/kg/day.) administered for 90 days in drinking water demonstrated absence of mortality and showed no signs of toxicity in mice. Intriguingly, histological analysis also revealed no tissue damage. The plasma levels of total protein, urea, creatinine and triglycerides, and enzyme activities of ALT, lactate dehydrogenase (LDH), and creatine phosphokinase (CPK) were not altered (Badary et al., 1998) (Fig. 2).

Inflammation is a physiological response of the biological system to injury and can evolve from a physiological state to a pathological state. It is indicated by immune and non-immune cell activation which preserves the host from parasites, bacteria, and viruses (Kumari and Kumar, 2022). It can be grouped into two; acute and chronic inflammation. The normal process of inflammation occurs in three phases which includes: (1) vascular inflammatory response, which is concerned with healing of acute injury enhancing tissue recovery, elevated blood flow, as well as the transportation and mobilization of cells to the affected local area; (2) new collagen formation with the collagen fibers arranged in disorganized state in the form of scar with

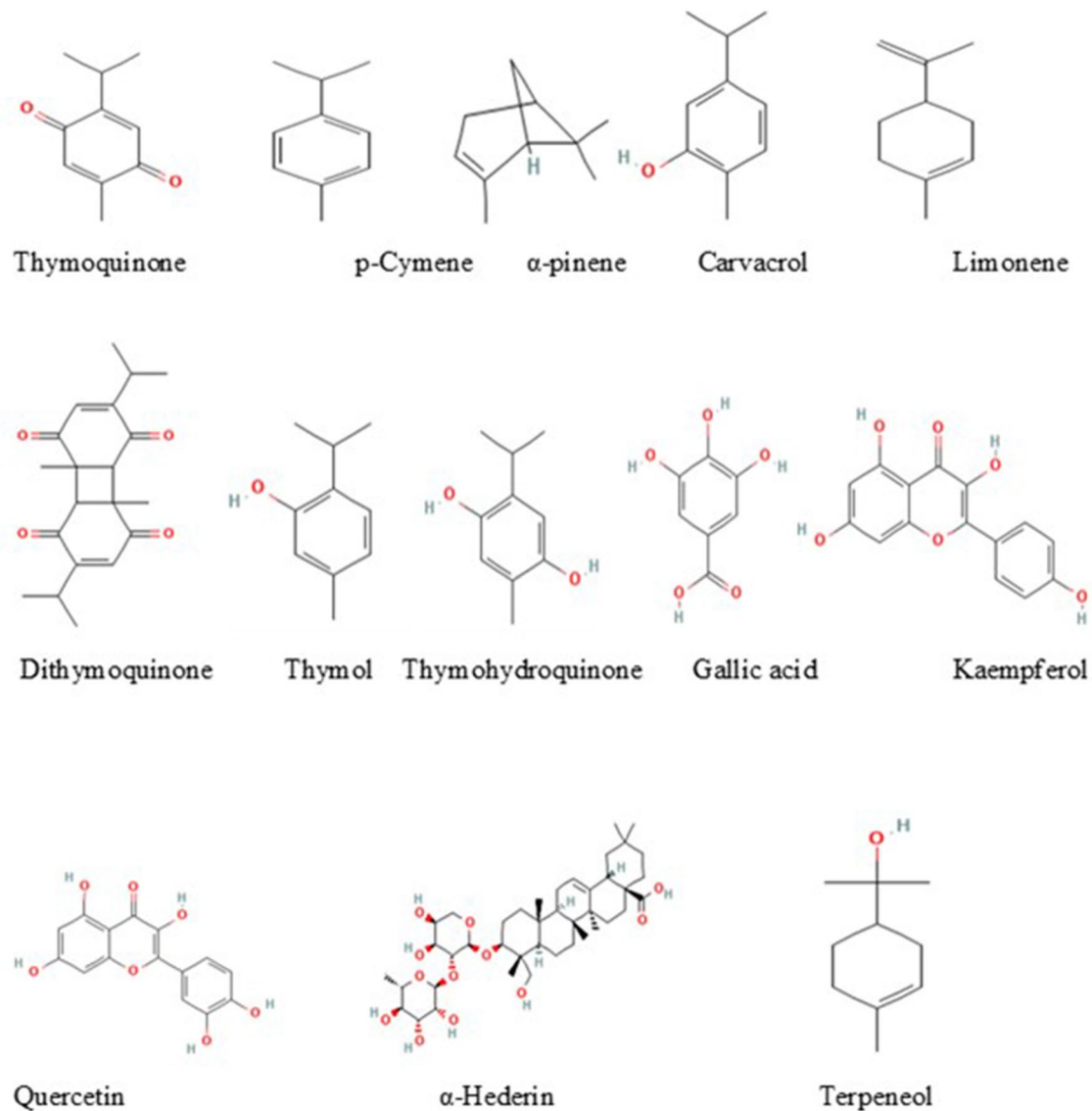


Fig. 2 Some bioactive constituents of Black Seed (*N. sativa*) (Khan, 1999; NCBI, 2022)

frail fiber linkage; (3) tissue remodeling and maturation, a healing process characterized by reduced collagen production but increased arrangement of collagen fibers coupled with strong fiber bond. This enhances cellular organization with regulated inflammatory response (Hench, 2005; Kotas and Medzhitov, 2015). In acute inflammation, it involves early response and the healing process commences when the body sends inflammatory cells to the site of the injury, but in chronic inflammation, the body continues to send inflammatory cells in an unregulated manner. Nevertheless, unregulated acute inflammation can lead to chronic, resulting in diverse inflammatory disorders. Immune disorder is a dysregulation of the immune system and it occurs from an abnormally low or over activity of immune response in the biological tissue or system. Chronic inflammatory and

immune diseases, including diabetes mellitus, cancer, cardiac disorders, chronic respiratory diseases, arthritis, stroke, chronic kidney diseases, liver diseases, etc., are the most notable cause of mortality in the world and more than 50% of deaths have been attributed to it (Feigin and GBD., 2017; Furman et al., 2019; Pahwa et al., 2021). Oxidative stress occurs when reactive oxygen species overwhelms or overshadows the antioxidant defense system in the biological system. Oxidative stress elevates the various inflammatory genes expression and upregulates the inflammatory mediators' cascade, such as the prooxidant molecules, neutrophils, lytic enzymes, cytokines, chemokines, and nitric oxide (Gholamnezhad et al., 2016). The excessive production of these mediators as well as both reactive nitrogen and oxygen species contributes to the pathogenesis of inflammatory and

immune disorder (Abel-Salam, 2012; Shuid et al., 2012). Special interest has grown toward the immune modulatory abilities of *N. sativa*. Some detailed studies have explored the antioxidant, anti-inflammatory, and immunomodulatory abilities of this dynamic seed (Salem, 2005; Majdalawieh and Fayyad, 2015; Islam et al., 2021). However, some scientific findings have unraveled the signaling system inherent in the immunomodulatory and anti-inflammatory abilities of *N. sativa* (Kulyar, et al., 2021; Mahmoud et al., 2021; Montazeri et al., 2021). This review explicitly describes the pharmacological, anti-inflammatory, and immune-modulating potential of *N. sativa* and its constituents in folklore (Fig. 1).

Traditional uses of *Nigella sativa*

Nigella sativa (*N. sativa*) has been cultivated for thousands of years for the therapy of various infectious and non-infectious diseases. *N. sativa* is a principal traditional medicinal herb extensively cultivated in Mediterranean, Middle East, South Asia, Europe, and North Africa (Khare et al., 2004; Hussain et al., 2021). *N. sativa* is used as a flavoring agent in several pastries and beverages, and has been placed among the highly ranked and effective seeds. In the traditional system of medicine, it represents a promising natural remedy extensively recommended for ailments, including nasal congestion, headache, migraine, dizziness, dysentery, fever, cough, bronchitis, asthma, dysmenorrheal, obesity, rheumatoid arthritis, hypertension, and gastrointestinal problems. *N. sativa* has been applied topically on abscesses, nasal and diabetic ulcers, eczema, and swollen joints. The mixture of *N. sativa* oil with beeswax can serve as a therapy for skin infection, burns and wrinkles (Gilani et al., 2004; Hossain et al., 2021). *N. sativa* has also been utilized as a liver tonic, emmenagogue, diuretic, and diaphoretic. It can be prepared synergistically with other ingredients, including honey, milk, and syrup to treat nausea, prolonged hiccups, diarrhea, edema, high blood cholesterol, dyspepsia, dyspnea puerperal disease, and bad breath. The powdered pods are inhaled to reinstate sense of smell (El-Dakhkhny et al., 2002; Gilani et al., 2004; Botnick et al., 2012). Intriguingly, modern medicine has progressively shown interest in folk medicine, utilizing medicinal plants in the prevention and treatment of various diseases. To date, numerous bioactive compounds present in *N. sativa* have been isolated, identified, and described (Toma et al., 2015; Topcagic et al., 2017). The health-promoting properties of *N. sativa* could be attributed to their various bioactive constituents present in them including thymoquinone, phenolics, and alkaloids (El Mezayen et al., 2006; Kalantar et al., 2018; Dabeek et al., 2019; Anand et al., 2016).

Some active ingredients of *Nigella sativa* seeds and their biological activities

Nigella sativa (*N. sativa*) has been recognized as a medicinal remedy for over four millennia in many parts of the continents. The therapeutic and the antioxidant abilities of *N. sativa* have been ascribed to the bioactive phytochemicals present in them. In modern era, the seeds of *N. sativa* have been exposed to a broad variety of phytochemical investigation. Several studies have revealed the presence of diverse active phytochemical constituents present in the seeds of *N. sativa*. Thymoquinone (TQ) represents a major and abundant bioactive phytochemical in the essential oil of *N. sativa* (Kannan, 2022). TQ effectively modulates anti-inflammatory and immunomodulatory signaling pathways. The treatment with TQ via oral administration brought about a significant suppression in various pro-inflammatory mediators including tumor necrosis factor (TNF- α), Interleukin (6 and 1 β), interferon gamma as well as prostaglandin E2 in rat model (Umar et al., 2012; Chen et al., 2018). More so, a study carried out by Ammar et al. demonstrated that TQ down-regulated inducible nitric oxide synthase (NOS) messenger RNA's expression inhibiting inflammatory pathways linked with asthma (Ammar et al., 2011). Another study revealed that TQ suppressed type 2 T helper cytokines. Nemmar and colleagues observed reduction in exaggerated white blood cell count and interleukin 6 levels in the plasma of diesel exhaust particle induced lung inflammation in mice treated with TQ via intraperitoneal injection (Nemmar et al., 2011). The anti-inflammatory ability of TQ in adjuvant induced-arthritis has been revealed to be caused by the suppression of TNF- α and IL-1 β (Tekeoglu et al., 2007; Vaillancourt et al., 2011). In addition, TQ expends its effectiveness through COX modulation. Cyclooxygenase (COX) is excessively expressed during inflammation and regulated by cytokines. Chen and his team members revealed that the treatment with thymoquinone blocked the expression of PGE2, lowered COX-2 protein expression levels, and enhanced activated peroxisome proliferator-activated receptor γ expression in rats induced with spinal cord injury (Chen et al 2018). Also, this is consistent with a previous study which revealed that TQ remarkably decreased the expression of COX-2 and the recurring synthesis of prostaglandins in mice model of allergic airway inflammation (El Mezayen et al., 2006).

Carvacrol, a phenolic monoterpene found in *N. sativa* possesses inhibitory potential on neutrophil elastase which could be a therapy for anti-inflammatory disease such as emphysema, arthritis, and cardiac disease (Kacem and Meraihi 2006). Quercetin has been recorded over time as an effective bioactive ingredient of *N. sativa* that have a potent anti-inflammatory ability. Weng et al. reported that the oral administration of quercetin capsule ameliorated nickel patch induced dermatitis as well as ultraviolet B-induced

skin erythema in patients (Weng et al., 2012). A study by Pfeuffer et al. demonstrated that quercetin suppressed markers of inflammation including TNF- α and IL-8 in patients diagnosed with sarcoidosis (Pfeuffer et al., 2013). Quercetin possesses cytoprotective, mast cell stabilizing, as well as immunosuppressive ability on the accessory (dendritic) cells (Huang et al., 2010). It also prevents disorders such as cardiovascular disease, osteoporosis, and cancer of the lungs (Mirsafaei et al., 2020; Derakhshanian et al., 2013; Zhao and Zhang, 2015). A particular finding demonstrated that quercetin prevents lipopolysaccharide-induced TNF- α generation in macrophages and lipopolysaccharide-induced interleukin 8 generation in A549 lung epithelial cells of tumor model (Gerates et al., 2007). However, in neuroglia, quercetin was reported to suppress lipopolysaccharide-induced mRNA TNF- α levels and IL-1 α . This activity of quercetin brought about a notable apoptotic cell death in the neurons triggered by microglial (the innate immune cells of the central nervous system) activation (Bureau et al., 2008). Quercetin prevents COX and LOX through the blockage of phosphatidylinositol-3-kinase tyrosine phosphorylation and Toll-like receptor production that suppresses downstream signaling in RAW 264.7 cells (Endale et al., 2013; Lhadiee et al. 2010). Interestingly, quercetin revealed protective ability against hydrogen peroxide-induced inflammation in the cells of human umbilical vein endothelium. This protective ability was mediated through the suppression of adhesion molecule 1 of vascular cells and the expression of cluster of differentiation 80 (Dabeek et al., 2019; Anand et al., 2016). Kaempferol, a type of antioxidant polyphenol, was reported to prevent the oxidative damage of cells and the pathogenesis of atherosclerosis by suppressing platelet formation in the blood and low-density lipoprotein oxidation. The phenolic compound, kaempferol, also prevented atherosclerosis by blocking the oxidation of low-density lipoprotein (LDL) and development of platelet in the blood (Dabeek et al., 2019; Anand et al., 2016). The mice administered with α -terpineol was reported to inhibit the expressions of some pro-inflammatory cytokines such as COX-2, iNOS, IL1 β , and TNF- α in peritoneal macrophages and NF- κ B transcription factor activation (Kalantar et al., 2018). The α -terpineol was also observed to suppress myeloperoxidase activities in vaginal tissues of mice (Kacem, 2011). Histopathological findings revealed that *p*-cymene significantly suppressed lipopolysaccharide (LPS)-induced neutrophils in the tissue of the lung when compared to the control group. The study also demonstrated that *p*-cymene had a preventive effect against LPS-induced acute lung injury-induced mice (Jayakumar et al., 2020). Jayakumar et al. revealed that oral administration with the *p*-cymene notably ameliorated inflammatory cells in the bronchoalveolar lavage fluid (BALF), enhanced superoxide dismutase (SOD) activity, and lowered the lungs'

NF- κ B protein and myeloperoxidase levels (Jayakumar et al., 2020).

Nigellone, also known as dithymoquinone, is a dimerized structure of TQ. Nigellone, a crystalline bioactive compound, is the only constituent of the carbonyl fraction of the *N. sativa* oil. Nigellone is involved in histamine secretion causing relief in inflammatory conditions such as asthma (Wienkotter et al., 2008; Islam et al., 2017). The relaxation effect of black seed during inhalation in asthmatic patient could also be attributed to its bioactive component "nigellone" that prevents histamine release from mast cells (Chakravarty, 1993). Interestingly, phytonutrients studies have revealed that *N. sativa* are categorized according to their dual groups of alkaloid skeletons which include; isoquinoline alkaloids (nigellalicyclamine-N-oxide, nigellalicyclamine) and pyrazole or indazole alkaloids (nigellalicyclamine, nigellidine) (Fig. 3) (Akram Khan and Afzal, 2016; Ahmadi et al., 2016) as well as the Dolabellane-type diterpene alkaloids: nigellamines A1 (1), nigellamines A2 (2), nigellamines B1 (3), nigellamines B2(4) (Ambati et al., 2021; Hossain et al., 2021) promotes lipid metabolizing ability, thus modulating inflammatory pathways. *N. sativa* functions as a panacea showing a broadly diversified therapeutic properties which also have been ascribed to the chemistry of their alkaloid composition, although several studies have focused on the pharmacologic benefits of the phenolic constituents of *N. sativa* seed (Fig. 3).

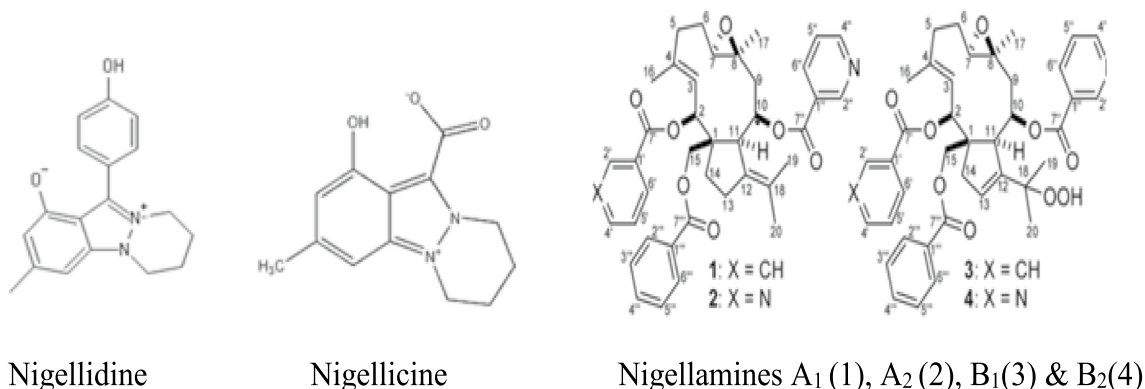
Therapeutic and pharmacological values of black seed (*N. sativa*)

Several researchers have been investigated on the ability of *N. sativa* seed and its active constituents in the biological system (both in vitro and in vivo). The therapeutic and medicinal abilities of *N. sativa* seeds have been experimentally validated in pre-clinical and clinical trials (Table 1). Numerous findings have established the therapeutic and pharmacological abilities of these seeds as analgesic, immunomodulatory, anti-inflammatory, antioxidant, antipyretic, anticancer, antimicrobial, antiparasitic, antiviral, cardioprotective, and immune modulatory (Aikemu et al., 2013; Ahmad et al. 2013; Feng et al., 2020; Koç et al., 2019; Randhawa et al., 2011; Ugur et al., 2016; Yimer et al., 2019; Umar et al., 2016) in folk medicine.

Antioxidant activity of black seed (*N. sativa*)

The anti-inflammatory and immunomodulatory properties of *N. sativa* have been well documented and have been reported to be hinged on the wheels of its antioxidant potentials. Some research studies have suggested the implication of reactive free radicals in immunomodulatory and anti-inflammatory functions (Islam et al., 2021).

Pyrazole or Indazole Alkaloids



Isoquinoline Alkaloids

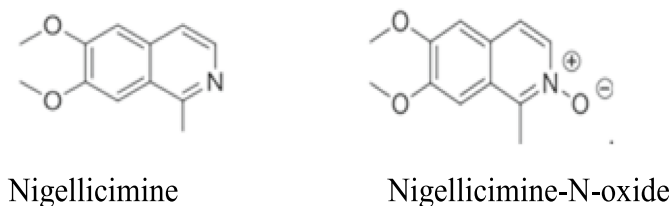


Fig. 3 Alkaloids present in Black Seed (*N. sativa*) (Akram Khan & Afzal, 2016)

Oxidation reaction in foods is brought about by reactive oxygen species; reactive oxygen species (ROS) alter the functionalities of macromolecules like DNA, carbohydrates, proteins, and lipids (Yousefi et al., 2021). Oxidative stress, one of the key factors linked to inflammation and immune system dysfunction, results in the excessive production of reactive oxygen species when compared to the antioxidant defense system such as superoxide dismutase (SOD), glutathione peroxidase (GPx), glutathione-s-transferase (GST), and catalase (CAT). Antioxidants prevent and protect cellular systems from the destructive activity of reactive oxygen and nitrogen species. Antioxidants play the role of scavenging ROS. It can be produced by the cells either endogenously or through diet. *N. sativa* extract comprises various phenolics compounds responsible for its antioxidant property including carvacrol, gallic acid, kaempferol, etc. (Feng et al., 2020). Additionally, TQ and black seed-supplemented diets enhance enzymatic (SOD, CAT, GPX, and GST) and non-enzymatic activities (GSH and ascorbic acid) of antioxidants. *N. sativa* treatment caused a notable elevation in glutathione levels in the red blood cells (RBCs) and possesses a potent

defensive ability against reactive oxygen and nitrogen species (ROS and RNS), along with inhibiting the mononuclear cells infiltration in the central nervous system (CNS) (Majdalawieh and Fayyad, 2015). *N. sativa* suppresses the reactive nitrogen species, hydrogen peroxide (H₂O₂), and hydroxyl (OH), superoxide (O₂) radical's generation (Gius and Spitz., 2006). The ROS synthesized in the joints has been implicated in arthritis as a result of the degradation of matrix constituents by biological oxidants via the latent collagenases activation (Luchian et al., 2022). Malondialdehyde (MDA) and thiobarbituric acid reactive substance (TBARS) are biological markers of lipid peroxidation. The oxidation of polyunsaturated fatty acids occurs via an array of chain reaction causing membrane destruction. *N. sativa* with potent antioxidant activities decreased the generation of ROS, thus, inhibiting lipid peroxidation (Burits et al., 2000; Al-Majed et al., 2006). *N. sativa* also lowered malondialdehyde (MDA) level in mice brain, liver, spleen, and blood plasma (Ardiana et al., 2020; Perera et al. 2021; Majdalawieh and Fayyad, 2015) (Table, 2, 3).

Table 1 Therapeutic properties of black seed (*N. sativa*) and its bio-active constituents

Therapeutic effects	References
Anti-inflammatory	Montazeri et al., (2021)
Immunomodulatory	Aikemu et al., (2013)
Antioxidant	Feng et al., (2020)
Bronchodilator	Boskabady et al., (2010)
Anticonvulsant	Jaykare et al., (2013)
Hepatoprotective	Mushtaq et al., (2021)
Antidiabetic	Al Wafai, (2013)
Neuroprotective	Asiaei et al., (2017)
Anticancer	Randhawa et al., (2011)
Gastroprotective	Shahid et al., 2018
Antimicrobial	Ugur et al., 2016
Nephroprotective	Ikram et al., (2021)
Antiparasitic	Yimer et al., (2019)
Cardioprotective	Hadi et al., (2021)
Antiviral	Umar et al., (2016)
Analgesic	Al-Ghamdi, (2001)
Antihistaminic	Koç et al., (2019)
Spasmolytic	Mukhtar et al. (2019)
Antidiarrheal	Islam et al., (2017)
Detoxification	Ates et al., (2021)
Antimalarial	Okelola et al., (2011)
Diuretic	Vaz et al., (2018)
Antipyretic	Koç et al., (2019)
Anti-ulcer	Bruce et al., (2021)

Effect of black seed (*N. sativa*) on anti-inflammation

The recent proof of anti-inflammatory ability of *N. sativa* is favorable. Diverse research studies have established the anti-inflammatory abilities of black seed in the biological system. The predominant inflammatory mediators (cytokines, prooxidants, lytic enzymes, nitric oxide, and eicosanoids including prostaglandins and leukotrienes) are often produced by neutrophils, lymphocytes, macrophages, as well as impaired tissue itself (Majdalawieh and Fayyad, 2015; Mahboubi et al., 2018). Excessive generation of pro-inflammatory cytokines, ROS, eosinophils, and neutrophils have been implicated in the pathophysiology of inflammation (Byun et al., 2021). *N. sativa* and its active phytochemical, TQ have been reported to significantly decrease the synthesis of inflammatory cytokines including tumor necrosis factor-alpha (TNF- α), nuclear factor kappa B (NF- κ B), lipoxigenase, cyclooxygenase-2, monocyte chemoattractant protein (MCP-1), C-reactive protein (CRP), and interleukin (IL-1 β) in pancreatic ductal adenocarcinoma (PDA) cell in animal model (Sallehuddin et al., 2020; Mahmoud and Abdelrazek, 2019; Chehl et al., 2009; Al-Ghamdi 2001). The abilities of *N. sativa* oil and some of its active components have been

recorded in various models of inflammation (including peritonitis, encephalomyelitis colitis, edema, and arthritis) to cause suppression of inflammatory mediators (Sallehuddin et al., 2020). Some studies revealed the inhibitory activity of *N. sativa* on protein synthesis and mRNA expression on IL-4, IL-5, and TNF- α , and also stimulated IFN- γ production (El Gazzar et al., 2006; Aslam et al., 2018). The Plasmodium parasite and ruptured erythrocytes activates inflammatory response in the host. Ojueromi et al reported that the dietary supplementation of *N. sativa* seed at percentage inclusion of 5% and 10% significantly suppressed TNF- α , IL-6 levels and increased IL-10 levels in Plasmodium berghei -infected mice (Ojueromi et al., 2022)

Intriguingly, the treatment of Algas-induced paw edema, with *N. sativa* oil (400 mg/kg), brought about a notable reduction in the pro-inflammatory cytokines including interleukins, and TNF- α in paw serum and pus of rats (Attia et al., 2016). However, topical medication with balm stick containing *N. sativa* oil (10%) in wistar rats with paw edema decreased inflammatory response with a significant edema inhibition (between 60 and 64%), decreased white blood cell count (approximately 44% lower than control), and TNF- α (55% lower than control) at the inflammatory site (Dwita et al., 2019). An in vivo finding done by Houghton et al. revealed that the administration of *N. sativa* fixed oil to rats brought about a significant inhibition in 5-LOX and COX of arachidonate metabolic pathway in the peritoneal leukocytes due to the suppression of leukotriene B4 (LTB4) and thromboxane B2 (TXB2) metabolites (Houghton et al. 1995; Salem, 2005). Most studies revealed that *N. sativa* seed and its biological constituents inhibit various inflammatory mediators and hence may be advantageous in mitigating autoimmune and inflammatory conditions. The seeds of *N. sativa* are efficient for treating patients with chronic anti-inflammatory disease (Eid et al., 2017; Koshak et al., 2018). Thymoquinone derived from *N. sativa* seeds can decrease oxidative stress and regulate the pro- and anti-inflammatory cytokines balance (Elsherbiny et al., 2017). The seeds were also observed to cause an elevation in the ratio of helper to suppressor T cells and to augment natural killer cell activity in human (Majdalawieh and Fayyad, 2015). A recent research study revealed the suppression of tumor necrosis factor-alpha (TNF- α) levels in septic peritonitis of murine model by thymoquinone (Theofanidou et al., 2021) and the distinctive immune modulatory ability of *N. sativa*. The capacity of TQ to regulate chemokines synthesis and boost immunity could be the major factor for its protective property in the liver against schistosomiasis (Mahmoud et al., 2021; Mushtaq, et al., 2021). Thriving evidence also showed that elevated NO levels have been implicated in the pathogenesis of inflammation and arthritis. Nitric oxide (NO) is a signaling molecule that performs a crucial function in the pathogenesis of inflammation. It plays a regulatory role in

Table 2 Anti-inflammatory ability of *N. sativa*

Experimental model	Treatment	Anti-inflammatory effect	References
Pancreatic ductal adenocarcinoma (PDA) cell in animal model	<i>N. sativa</i> seed and TQ	Suppressed tumor necrosis factor-alpha, alpha (TNF- α), nuclear factor kappa B (NF- κ B), lipoxxygenase, cyclooxygenase-2, interleukin-1 β	Sallehuddin et al., (2020) Mahmoud and Abdelrazek, (2019) Chehl et al., (2009) Al-Ghamdi, (2001)
Algas-induced paw edema in rat model	<i>N. sativa</i> oil	Suppressed interleukins and TNF- α in the serum and pus Decreased inflammatory response Decreased white blood cell count	Attia et al., (2016) Dwita et al., (2019)
Clinical trial	<i>N. sativa</i> seed	Elevated ratio of helper to suppressor T cells Augmented natural killer cell activity	Majdalawieh and Fayyad, (2015)
<i>Plasmodium berghei</i> -infected mice	<i>N. sativa</i> seed	Suppressed TNF- α and IL-6 levels Elevated IL-10 level	Ojueromi et al. (2022)
Murine acute peritonitis model	TQ	Suppressed TNF- α	Theofanidou et al., (2021)
LPS-induced peritoneal macrophages in murine model; Murine macrophages; RAW264.7 cells	<i>N. sativa</i> seed	Reduced NO, IL-6 and TNF α levels	Bahrami et al., 2021 Hadi et al., 2015 Majdalawieh and Fayyad (2015)
Peritoneal macrophages in wistar rat model	TQ	Lowered iNOS	El-Mahmoudy et al., (2002)
Streptozotocin (STZ)-induced diabetic rats	<i>N. sativa</i> seed and TQ	Prevented cyclooxygenase (COX-2) expression in pancreatic tissue	Al Wafai et al., (2013)
Bare mouse skin	<i>N. sativa</i> seed	Suppressed NF- κ B and COX-2 expression	Kundu et al., (2013)
Arthritis patients	<i>N. sativa</i> oil	Elevated IL-10 Reduced TNF α Attenuated inflammatory response	Majdalawieh et al., (2010)

several inflammatory conditions. Conversely, NO is regarded as a pro-inflammatory mediator that incites inflammation and tissue damage as a result of excessive production in aberrant condition. Elevated serum NO levels and synovial fluid have been recorded in rheumatoid arthritis and osteoarthritis patients (Fonseca et al., 2019). However, reducing NO through inducible nitric oxide synthase (iNOS) inhibition decreased aggravated inflammatory response (Mahboubi et al., 2018). Bahrami and colleagues showed that *N. sativa* remarkably inhibited NO level in peritoneal macrophages and RAW264.7 cells (Bahrami et al., 2021). More so, treatment with *N. sativa* caused a significant reduction in NO, IL-6, and TNF α levels of lipopolysaccharide (LPS)- and IFN γ -induced peritoneal macrophages in dose-dependent manner in vitro (Hadi et al., 2015). These studies are in concordance with a finding which showed that *N. sativa* demonstrated inhibitory ability on NO level in murine macrophages Majdalawieh and Fayyad, 2015). Also, the findings done by El-Mahmoudy et al. revealed that TQ decrease the NO level of lipopolysaccharide-activated macrophages as well as preserving the cell's viability (El-Mahmoudy et al., 2002). The levels of protein and mRNA of inducible nitric oxide

synthase (iNOS) in peritoneal macrophages of the rats were also lowered by TQ.

Lipoxygenase (LOX) and cyclooxygenase (COX) are core lipid mediators of inflammatory pathways. They are essential enzymes that catalyze the conversion of arachidonic acid to eicosanoids. *N. sativa* also lowered the lipoxygenase and cyclooxygenase activity of the arachidonate metabolic pathway, which have been involved in the generation of various inflammatory biomarkers (Montazeri et al., 2021). Furthermore, Al Wafai et al. assessed the synergistic ability of *N. sativa* and TQ supplementation in streptozotocin (STZ)-induced diabetic rats and it was observed to prevent COX-2 expression in pancreatic tissue (Al Wafai et al., 2013). Another study also reported the anti-oxidative and anti-inflammatory efficacy of *N. sativa* via the suppression of NF- κ B and COX-2 expression as well as the preservation and up-regulation of protein expression of the cells of the bare mouse skin (Kundu et al., 2013). Some plausible anti-inflammatory mechanisms of *N. sativa* could be linked to the suppression of TNF- α -linked stimulation of NF- κ B via lowering the ability of the NF- κ B kinase (IKK) inhibitor, and also decreasing the transfer of NF- κ B (transcription factor

Table 3 Immunomodulatory ability of *N. sativa*

Experimental	Treatment	Immunomodulatory effect	References
STZ-induced diabetic rats	<i>N. sativa</i> oil	Reduced immunological markers Pan B-lymphocytes (CD19) Pan innate cells (CD 1 1b) Pan B-lymphocytes (CD 90)	Hmza et al., (2013)
Dexamethasone immunosuppressed rabbit	<i>N. sativa</i> seed	Elevated immunoglobulin (IgG); Enhanced cellular immunity; Enhanced lymphocytes; Suppressed neutrophil levels; Increased phagocytic activity; Stimulated immune cells; Elevated aggregation and degranulation of leukocytes inflammatory foci.	Al-Saadi et al., (2012) Klymenko and Kozyrieva (2002) Jeklova et al., (2008)
Cisplatin-induced mice model	<i>N. sativa</i> seed	Enhanced leukocytes hemoglobin and T-lymphocytes production.	Paarakh, (2010)
Cisplatin-induced mice model	<i>N. sativa</i> seed	Increased CD8 plus suppressor to cytotoxic T cells; Increased CD4 plus helper T cells; Increased CD3 plus T cells; Elevated total leukocytes' count.	Mills and Bones, (2010)
<i>Plasmodium berghei</i> -infected mice	<i>N. sativa</i> seed	Elevated IgG and IgM levels	Ojueromi et al. (2022)
Allergic rhinitis patients	<i>N. sativa</i> oil	Enhanced polymorphonuclear leukocytes functions (PMNs) and clusters of differentiation 8 (CD8) counts.	Alsamarai et al., (2009)
Lipopolysaccharide- induced lung damage in rats	<i>N. sativa</i> seed	Reduced total leukocytes, neutrophils, monocytes, eosinophils, basophils count; Increased lymphocytes' count.	Mokhtari-Zaer et al., (2020)
Murine macrophage J774A.1 cell line	<i>N. sativa</i> seed	Enhanced proliferation rate of macrophages	Sheik et al., (2017)
Patients with allergic disease (allergic rhinitis, bronchial asthma, atopic eczema)	<i>N. sativa</i> oil	Suppressed immunoglobulin levels (IgE), eosinophil count and endogenous cortisol in the urine and blood plasma.	Kalus et al., (2003)
Ovalbumin- induced asthmatic mice	Thymoquinone	Reduced T helper type 2 cytokines; Suppressed eosinophilia and goblet cells hyperplasia	El Mezayen et al., (2002)

provoking inflammation) from the cytosol to the nucleus (Woo et al., 2012). This is in agreement with a study which revealed that TQ blocked TNF- α -induced nuclear factor kappa B initiation via the inhibition of I Kappa B Kinase (IKK) activity causing reduced phosphorylation and the breakdown IKB alpha inhibitor (Sethi et al., 2008). However, these molecular occurrences could significantly reduce the pro-inflammatory mediators like TNF- α , matrix metalloproteinases (MMPs), IL-1 β , COX-2, and PGE2 expression (Majdalawieh & Fayyad, 2015). Interleukins (IL-6 and IL-18) have been reported to trigger some inflammatory disorder such as atherosclerosis (Coveney et al., 2021). One of the major anti-inflammatory cytokines observed in atherosclerosis and rheumatoid arthritis is Interleukin-10 (IL-10) synthesis. The IL-10 was shown to prevent age-connected elevation in oxidative stress and IL-6 levels (Girard et al., 2016). The oral administration of encapsulated *N. sativa* oil (1 g/patient/day) for 2 months caused a notable elevation in IL-10 level but significantly

reduced TNF α levels in the serum, showing that *N. sativa* could attenuate the inflammatory responses in rheumatoid arthritis patients (Majdalawieh et al., 2010). Much emphasis has been laid on the inflammatory mechanism of *N. sativa* compared to its anti-inflammatory mechanism. Both inflammatory and anti-inflammatory role possess similar mechanism of action. Persistent inflammatory response can lead to chronic inflammation which can damage the biological tissue and cause the failure of the target organ.

Effect of black seed (*N. sativa*) on immunomodulation

Nigella sativa performs a pertinent role in the immune-boosting ability and treatment of disorders such as rheumatoid arthritis, Hashimoto's thyroiditis, eczema, allergic asthma, etc. Drug resistance and residual of immunomodulatory drugs like thalidomide, lenalidomide, pomalidomide, and antibiotics are common upon administration against

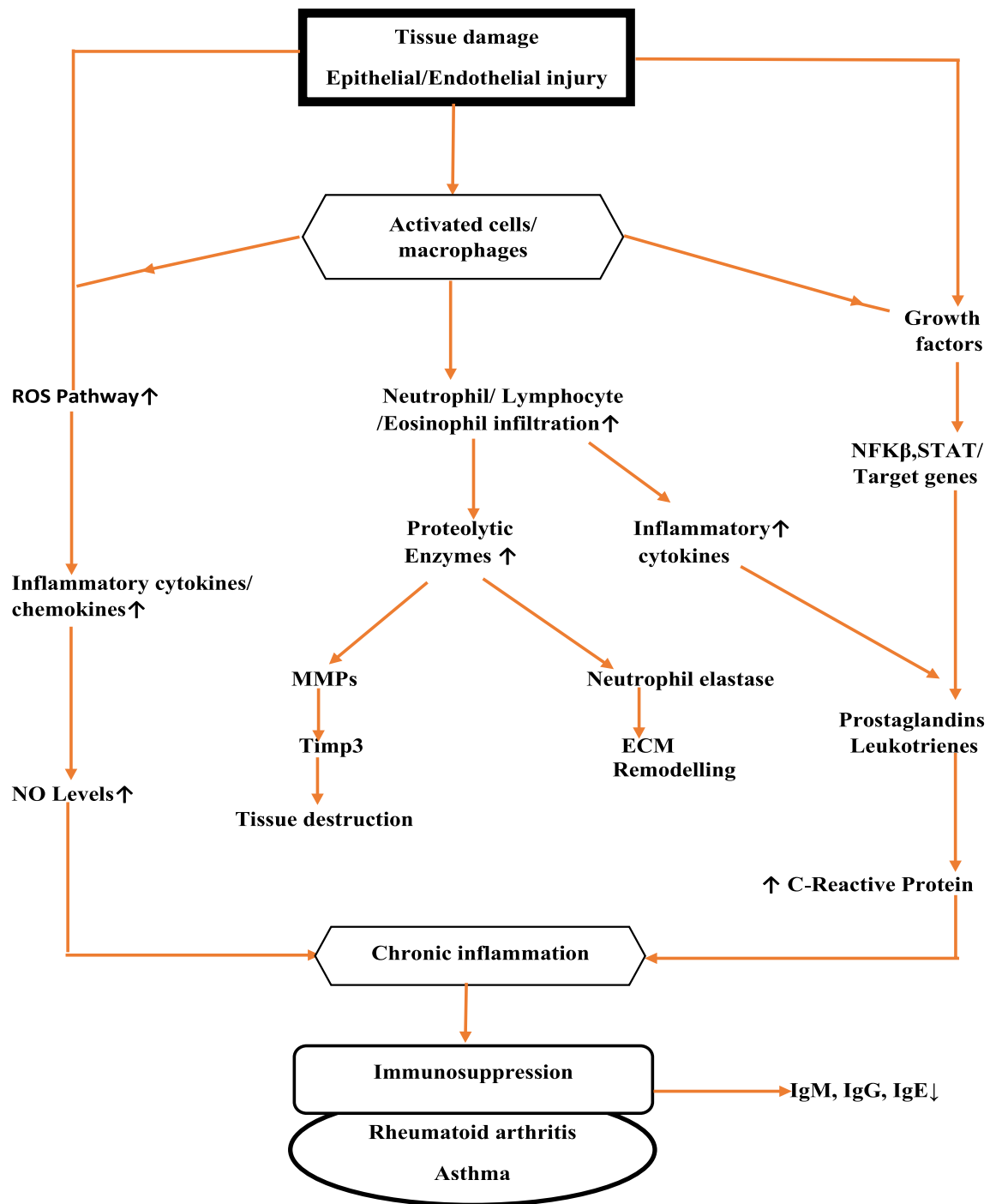


Fig. 5 The initial step of the inflammatory cascade entails the identification of tissue or endothelial injury. Macrophages become activated as a result of tissue damage triggering a complex series of cellular and inflammatory responses and greatly affected as a result of the magnitude, nature, and duration of the injury. The activated neutrophils, lymphocytes, eosinophils, inflammatory mediators [including cytokines, C-reactive protein (CRP), ROS, Nuclear factor kappa B (NF- κ B), growth factors, prostaglandins, leukotrienes, and nitric

oxide (NO)] are involved in inflammatory and immune response. Neutrophils induce proteolytic enzymes. These specific set of enzymes are implicated in extracellular matrix damage (ECM). Neutrophils mediate ECM remodeling by producing specific remodeling enzyme including matrix metalloproteinases (MMPs) and neutrophil elastase, leading to myriad of inflammatory and immune system dysfunction such as rheumatoid arthritis and asthma

pathogenic organisms. However, natural therapy might be advantageous compared to synthetic drugs. *N. sativa* seeds and their purified bioactive ingredients have been extensively utilized in the treatment and prevention of several immune system disorders. *N. sativa* has a potentiating ability on the cellular immunity mediated by T cells which are connected to immune response (Fig. 5) (Salem, 2005). A particular study revealed that *N. sativa* oil decreases the anti-islet cell antibodies level, and the principal antibodies generated in autoimmune process and brought about significant reduction of immunological markers {Pan B-lymphocytes (CD19), Pan innate cells (CD 11b), and Pan T- lymphocytes (CD90)} in Streptozotocin-Induced type I diabetes rat model (Hmza et al., 2013). Paarakh reported that *N. sativa* oil enhances immune resistance in the geriatrics and T lymphocytes' cell production (Paarakh, 2010). *N. sativa* significantly elevated total white blood cells (leukocytes) count and hemoglobin levels induced by cisplatin in mice model as well as stimulating the production of T-lymphocytes cells. Approximately 3% increase was observed in the total leukocyte count of mice treated with *N. sativa* (Tutuncu, 2020). Studies have shown that *N. sativa* stimulates T cells synthesis, thus, aiding the secretion of IL-3 but no stimulatory ability on IL-2 production. *N. sativa* protein elevated absolute lymphocytes count and, in this regard, possesses immunomodulatory ability in the biological system (Randhawa and Alghamdi, 2011; Salama, 2010). Some studies revealed that *N. sativa* elevated T-lymphocyte cell production, clusters of differentiation (CD3, CD4, CD8) surface antigens, and some immune cells. Due to this elevation, *N. sativa* and thymoquinone were observed to activate blood cellular component (hematopoiesis) and modulate immune-related cells formation (Rahmani and Aly, 2015; Tutuncu, 2020). This is consistent with a particular study which revealed that *N. sativa* enhances the total leukocytes and hemoglobin count induced by cisplatin in mice model. Also, this seed increased (cluster of differentiation 3) plus T-lymphocyte cells; (cluster of differentiation 4) plus helper T-lymphocyte cells; (cluster of differentiation 8) plus suppressor to cytotoxic T lymphocyte cells (Mills and Bone, 2010). Alsamarai et al. reported that the allergic rhinitis patients going through allergen-specific immunotherapy for a month combined with the consumption of *N. sativa* (2 g/day) along with immunotherapy experienced better progress (polymorphonuclear leukocytes functions (PMNs) and cluster of differentiation 8 (CD8 counts) than patients who received only immunotherapy for 2 months (Alsamarai et al., 2009). He concluded that administration of *N. sativa* contributed toward more effective immunotherapy.

The level of immunoglobulins (IgM and IgA) and complements (C3 and C4) revealed no notable differences in the control and *N. sativa*-treated groups of immunosuppressed rabbit induced with dexamethasone. However, the IgG level was significantly elevated in the immune-suppressed mice

treated with *N. sativa* and remarkably suppressed in the untreated rabbits. *N. sativa* demonstrated a potent immune modulatory effect, thus enhancing cellular immunity in normal and immune-suppressed rabbits (Al-Saaidi et al., 2012). Furthermore, a notable increase in the weight of the kidney, lymph node, and liver were observed in the immunosuppressed rabbits. Also, there was reduction in the total white blood cell count, monocytes eosinophils, and lymphocytes but elevation in their neutrophil levels. Conversely, *N. sativa* seed reversed this effect by elevating lymphocyte and suppressing neutrophil levels. This finding is consistent with some studies which reported the effect of dexamethasone to stimulate high degranulation and aggregation of the inflammatory focus of the white blood cells (Salem and Hussain, 2000; Jeklova et al., 2008). This could be as a result of the secretion and translocation of white blood cells differentials (with the exception of neutrophils) from circulation to lymphatic tissue or hypergenesis. A particular finding by Al-Saaidi et al. revealed elevation in the phagocytic ability of male rabbits treated with *N. sativa*, which could be due to its immune's regulatory potential (Al-Saaidi et al., 2012). This result also proved the elevated leukocytes inflammatory core degranulation by dexamethasone. The administration of lipopolysaccharide (LPS) elevated the total leukocyte, neutrophils, monocytes' eosinophils, and basophils' count and reduced lymphocytes count. However, treatment with the extract of *N. sativa* (200, 400 mg/kg) on LPS-induced lung injury in rats significantly reversed the effect in dose-dependent manner (Mokhtari-Zaer et al., 2020). Immunoglobulins (IgG and IgM) play a pivotal part in reducing parasitemia levels and ameliorating the enervating effect of Plasmodium parasites. Interestingly, our findings revealed that *N. sativa* supplemented diet enhanced IgG and IgM antibody levels in the serum of Plasmodium berghei-infected mice (Ojueromi et al., 2022).

The immune stimulating property of *N. sativa* on cell line of murine macrophage (J774A.1) was evaluated by Sheik et al. The result showed that *N. sativa* extract modulated immune function by elevating the rate of proliferation of macrophage population and stimulating phagocytic activity (Sheik et al., 2017; Dalli et al., 2022). The anti-oxidative and anti-inflammatory ability of the *N. sativa* may enhance its function in stimulating the immune and phagocytic cells (Salem, 2005; Abdulelah, 2007), its activity on the synthesis of DNA during cell proliferation, and scavenging ability of superoxide radicals (Musa, 2004). A particular study carried out by Salem et al. recorded the ability of *N. sativa* to decrease the deleterious side effects of dexamethasone which may be associated with the ability of the *N. sativa* proteins to regulate the production of IL-1 and IL-3 by lymphocytes, as it has been demonstrated when cultured with or without allogenic cell (Salem et al., 2005). The oral administration of encapsulated *N. sativa* oil (dosage of 40–80 mg/kg per day)

in individuals diagnosed with asthma, eczema, and allergic rhinitis significantly suppressed the immunoglobulin levels (IgE), eosinophil count, and endogenous cortisol in the urine and blood plasma when compared with the control (Kalus et al. 2003). In addition, ovalbumin-induced asthmatic mice revealed significant decrease in T helper 2 cytokines, leukotrienes-B₄, C₄, and eosinophils in BALF. Interestingly, another study reveals that TQ mitigated ovalbumin-induced airway inflammation by preventing the expression of COX-2 and prostaglandin D₂ production. This preventive effect on prostaglandins production is enhanced by a notable reduction in T helper type 2 cytokines, goblet cell hypergenesis, immunoglobulins, and activated eosinophils in OVA-induced mice (El Mezayen et al., 2006). Intriguingly, TQ was reported to inhibit IL-4, and suppress activated eosinophils in the airway and IgE level in the serum of murine allergen-induced mice (Renz et al., 1995).

Immunopathogenesis of asthma and the dietary intervention of black seed (*Nigella sativa*)

Asthma is characterized by prolonged inflammatory disorder of the respiratory system connected to a specific pattern of network of mutually interacting cytokines, inflammatory cells (mast cells, plasma cells, lymphocytes, eosinophils, neutrophils, etc.), and excessive synthesis of mucus. Asthma statistics worldwide revealed that approximately 300 million (300,000,000) individuals are affected around the globe and it is probable that additional 100 million (100,000,000) may be vulnerable by the year 2025 (Afzal et al., 2022). Asthma is prevalent in both children and adult. The use of glucocorticosteroids, a core anti-inflammatory therapy for asthma, gives rise to adverse reaction (reduced bone metabolism, stunted growth, and adrenal suppression) with non-specificity in their mechanism of action (Ora et al., 2020). More so, patients diagnosed of asthma react unsatisfactorily or appallingly to steroid therapy (Henderson et al., 2020). Therefore, efforts are channeled towards the need to invent and advance specific and safe therapeutic anti-asthmatic drugs made from natural products. Research findings suggest that some natural plant seeds which include *N. sativa* in folklore possess remarkable effect in decreasing the intensity of respiratory disorder Koshak et al., 2018; Ikhsan et al., 2018). The pathophysiology of asthma originates from diverse interconnection between cells and mediators of inflammatory and immune system disorder. The principal immune cells implicated in asthma-related inflammation were mast cells, dendritic cells, T helper cells (namely Th1, Th2, and Th9 cells, etc.), B cells, innate lymphoid cells, neutrophils, eosinophils, basophils, macrophages, and epithelial cells (Koshak et al., 2018; Ikhsan et al., 2018), and they function in the pathophysiology of airway and lung inflammation

in asthma progression. Actually, Th2 cells also performs a pertinent function in the pathophysiology of allergic airway inflammation via the proliferation of cytokines (Chang et al., 2022; Chen et al., 2022). The result obtained from the study buttressed the point that Th2 inflammatory activity are majorly caused by the cytokines proliferation. In asthmatic condition, the pro-inflammatory mediators released by Th2 cells which include, IL-4, IL-5 and IL-13 as well as IFN- γ and IL-6 (Th1 cells-secreted cytokines) were observed to be the key cytokines stimulated in asthma (Beasley et al., 2019) (Fig. 5 & 6). Interleukin-6 (IL-6), a core pro-inflammatory mediator was significantly elevated in the bronchial epithelial cells, BALF, stimulated sputum in the serum of patients diagnosed of asthma (Ilmarinen et al., 2016; Neveu et al., 2010). Interleukin 6 also performs a central role in the adaptive immune response via the induction of Th2 cells development (Matucci et al., 2021). Pre-clinical and clinical studies demonstrated that *N. sativa* exhibits bronchodilatory and anti-allergic properties. Diverse research findings have assessed the effect of *N. sativa* and its bioactive constituents on the anti-inflammatory and immunomodulatory markers associated with asthma (Balaha et al., 2012; Saadat et al., 2015; Shahzad et al., 2009; El Gazzar et al., 2006). The mice treated with *N. sativa* was reported to potentially suppress IL-4, IL-5, IL-13, and MUC5, a gene expression in OVA-induced asthmatic mice (Azimi et al., 2016). Azimi et al. also revealed that *N. sativa* possessed anti-inflammatory, immunomodulatory and mucus hypersecretion potential as a result of eosinophil infiltration, inhibition of Th2 cytokine and also suppressed the overproduction in the airways of asthmatic mice (Azimi et al., 2016). Koshak et al. recorded that *N. sativa* and TQ enhanced immune function and decreased asthma-associated inflammatory mediators such as IL-2, IL-6, and PGE₂ in primary human T-lymphocytes, monocytes, and A549 human lung epithelial cells (Koshak et al., 2018) This is in concordance with the study conducted by Shahzad et al. who investigated the immunomodulatory ability of *N. sativa* oil in allergic airway inflammation using rat model (Shahzad et al., 2009). It was observed that *N. sativa* mitigated OVA-induced airway inflammation via the suppression of T cells causing a remarkable reduction in Th2 cells, goblet cell hyperplasia, NO generation, cytokines (IL-4, IL-5, IL-6 and TGF- β 1), immunoglobulin, and lung eosinophil level in OVA-induced rats. The TGF- β has been reported to stimulate the proliferation of goblet cells and excessive secretion of the mucus (Young et al., 2021). The elevation in eosinophil production as well as Immunoglobulins (IgG and IgE) levels can be traced to increased synthesis of interleukins (IL 4 & 5) levels in the rats (Shahzad et al., 2009). Dajani et al. revealed that the asthmatic symptoms (night wheezing, night coughing, and chest wheezing) decreased significantly after 45 days of treatment with the *N. sativa* extract (15 ml/kg/day) compared to the control

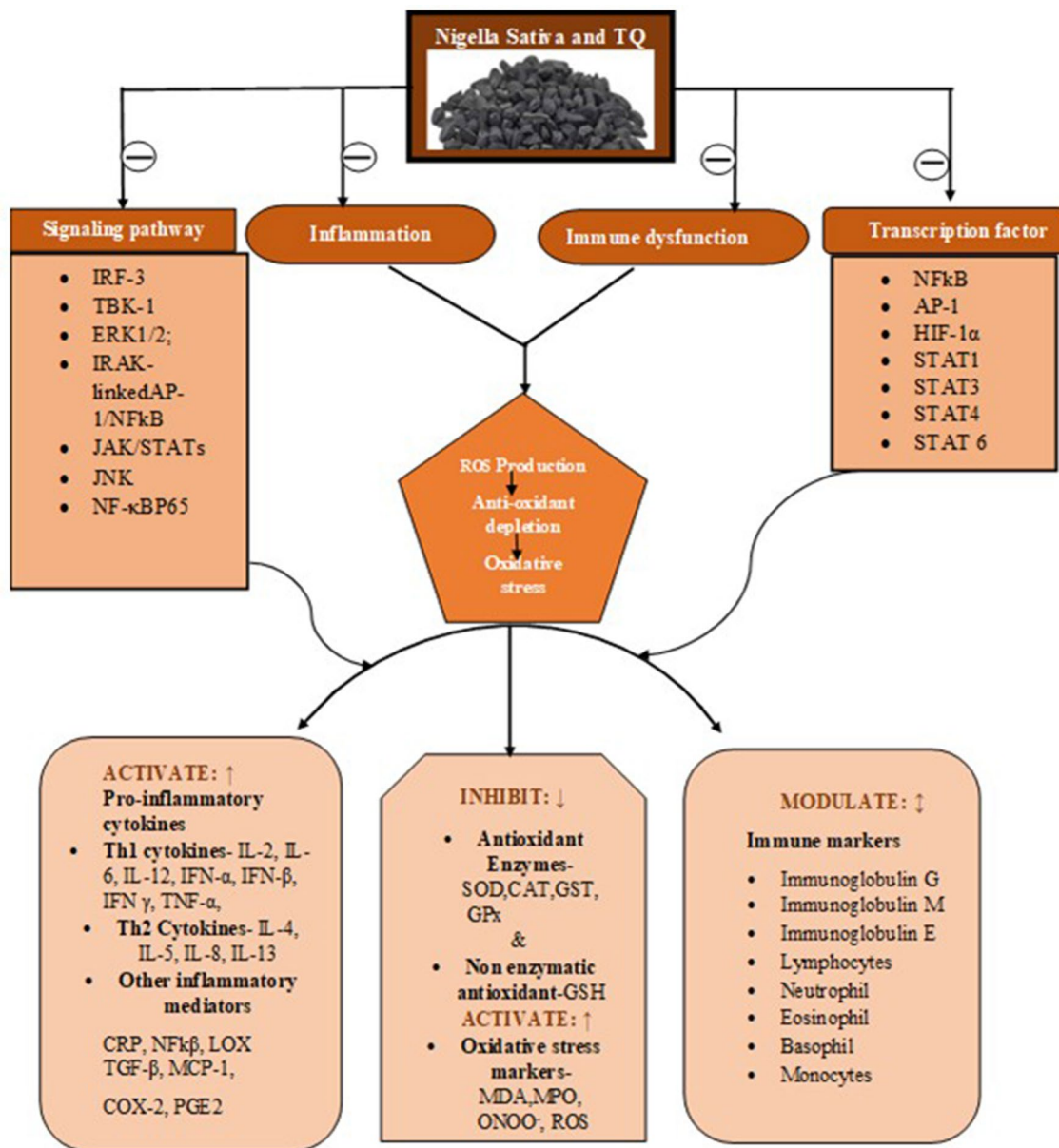


Fig. 6 *N. sativa* downregulates inflammatory and immune signaling pathways [IRF 3 (Interferon regulatory factor 3); TBK-1 (TANK-binding kinase-1); ERK1/2 (Extracellular signal-regulated kinase 1/2); IRAK-linked AP1 (Interleukin-1 Receptor Associated Kinase Activator Protein-1); JAK/STAT (Janus kinase-signal transducer and activator of transcription) and JNK (c-Jun *N*-terminal kinase phosphorylation) and transcription factor {NF-κB (Nuclear factor kappa B); HIF-1α (hypoxia-inducible factor 1); STAT1, STAT3, STAT4, STAT 6 (Signal transducer and activator of transcription 1, 3, 4,

and 6), respectively]. During inflammatory and immune response, the excessive ROS generated inhibit antioxidant enzymes, modulate immune markers, and activate inflammatory mediators [interleukins (IL-2, 4, 5, 6, 8, 12, 13), TNF-α (tumor necrosis factor-alpha), CRP (C-reactive protein), MCP-1 (monocyte chemoattractant protein-1), LOX (lipooxygenase), PGE2 (prostaglandin E2) NF-κB] and oxidative stress markers {Malondialdehyde (MDA) Myeloperoxidase (MPO), Peroxynitrite (ONOO⁻)}

(placebo) group (Dajani et al., 2018). Koshak, et al. carried out a randomized, double-blind, placebo-controlled trial in which *N. sativa* oil (500 mg twice daily) was utilized as a supplementary treatment in eighty (80) asthmatic patients. The *N. sativa*-treated group revealed remarkable improvement in asthma test scores and pulmonary function tests

(PFTs) when compared with the placebo group after four (4) weeks of treatment. (Koshak et al., 2017) Remarkably, observed improvement was connected to a significant normalization of blood eosinophilia in the patients. Intriguingly, Boskabady et al. also reported a randomized double-blinded clinical trial that revealed a short bronchodilator activity in

asthmatic patients after administration of a single dose of *N. sativa* (50 mg/kg) (Boskabady et al., 2010).

Nitric oxide, a biomarker of lung inflammation, and elevated exhaled NO levels have been observed in asthmatic patients (Heaney et al., 2019; Duong-Quy et al., 2019). It was observed that the treatment with *N. sativa* oil remarkably suppressed NO generation in OVA-induced rats. Previous studies have shown the important alkaloid components (nigellidine, nigellimine, and nigellicine) present in *N. sativa* could alter NO production (Khaldi et al., 2017; Nayeem et al., 2022). The inhibitory ability of *N. sativa* oil on the inflammation of the airway could be as a result of the reduction in Th2 cytokine level and consequent mitigation of inflammatory mediators. Hence, *N. sativa* can be endorsed as a pharmacological substance for the treatment of allergic asthma.

Immunopathogenesis of rheumatoid arthritis and the dietary intervention of black seed (*Nigella sativa*)

Rheumatoid arthritis is a prolonged inflammatory disorder that affects the joint of synovial-lined diarthrodial, as well as joints of the hand and the wrist, and it lacks effective cure. Rheumatoid arthritis was first initiated in the year, 1859, by Garrod and stated as a systemic inflammatory disorder that is predominant in the female gender associated with rheumatoid factor and dayspring inflexibility which could lead to moderate or critical disability (Christian and Paget, 1978). Although there is dearth of information as regards the pathogenesis of rheumatoid arthritis, but the activation of broad range of the humoral and cellular components of the immune system contributes to its pathology. It is believed that immense activation of the B- and T-lymphocyte antigens as well as macrophage interactivity in the inflamed synovial membrane results in lymphocytes' release from T cells and antibodies (immunoglobulins) from plasma cells. Immune dysfunction is one of the major factors that contributes to the progression of rheumatoid arthritis via the discovery of rheumatoid factors including anti-immunoglobulin antibodies (IgM, IgG, IgA, and IgE) formerly by Erik Waaler in the 1940s and later explicitly described by Devi and his colleagues (Devi et al., 2021; Sieghart Waaler, 2018). Bandilla et al. investigated the core antibody in rheumatoid arthritis patients in response to three antigens (sheep cell stroma and Brucellin) (Bandilla et al., 1970). A probable description for deficiency in IgM level by rheumatoid arthritis patients is the aspect of antigenic competition. This term has been used by Adler to describe the inhibition of production of antibody to a second antigen by a host intensively immunized with a prior antigen (Adler, 1964). Increased levels of immunoglobulins, high titers of rheumatoid factors, and low levels of complement in synovial fluid in patients with

rheumatoid arthritis suggest that the patients are making an intense immune response to an unidentified antigenic stimulus. A significant suppression in the IgM response to Brucellin than sheep cell stroma was observed in rheumatoid arthritis patients (Bandilla et al., 1970). Oxidative stress and pro-inflammatory cytokines, such as IL-1, IL-6, IFN- γ , CRP, TNF- α , and GM-CSF, has been linked to the pathogenesis of rheumatoid arthritis (Lucas et al., 2020; Kim et al. 2019). However, the excessive production of TNF- α is proposed to be the core contributor to elevated release of ROS in patients diagnosed with rheumatoid arthritis. Conversely, Regulatory T cells (Tregs) suppressed immune response overactivity via the generation of anti-inflammatory cytokines of TGF- β and IL-10 and prevented exaggerated inflammatory states (Lucas et al., 2020). The findings by Kril et al. revealed that neutrophils and monocytes as the key target cells of the innate immune system that regulate the development and progression of inflammatory rheumatic diseases (Kril et al., 2020). Hadi et al. reported the supplementation *N. sativa* seed for eight weeks notably suppressed the pro-inflammatory cytokine (TNF α) and increased anti-inflammatory cytokine (IL-10) of patients diagnosed with rheumatoid arthritis (Hadi et al., 2016). A particular study on rheumatoid arthritis showed that administration of *N. sativa* orally significantly reduced TNF- α , NF-k β , IL-6, MDA, NO, and increased IL-10 levels in animal model (Zielińska et al., 2021; Mahboubi et al., 2018; Khabbazi et al., 2020).

Signaling pathway associated with inflammation and immune system disorders

Various findings have been carried out to unravel the signal transduction mechanism utilized by *N. sativa* and its bioactive constituents to demonstrate their anti-inflammatory and immunomodulatory abilities. Inflammatory disorders develop as a result of the elevation of pro-inflammatory cytokines (IL-1, TNF, IFN, NF-kB), granulocyte-macrophage-colony-stimulating factor and the suppression of anti-inflammatory cytokines including IL-10 and TGF- β . *N. sativa* was shown to activate the synthesis of T-lymphocytes and macrophages, thus, aiding the secretion of interleukin (Haq et al., 1995). The stimulatory and suppressive abilities of *N. sativa* on cultured lymphocytes to modulate the inflammatory cytokines levels including interleukins were also observed (Haq et al., 1999). In the biological system, the signal transduction pathways must have sufficient regulatory steps in a physiological state. The anti-inflammatory ability of *N. sativa* and their active constituents can be linked to various signaling pathways. *N. sativa* and bioactive phytochemicals, known for their immune modulatory ability, transduce their effect by targeting some specific signaling pathways. Nuclear Factor kappa-light-chain-enhancer of activated B cells (NF-KB) is a principal dimeric eukaryotic

transcription factor that regulates genes crucially associated with several biological processes including immune and inflammatory response. The NF- κ B proteins activation performs a main role in inflammation via the modulation of genes encoding pro-inflammatory mediators, and inducible enzymes including NO synthase and COX-2 (Ingawale and Mandlik, 2020). Hossen et al. revealed that *N. sativa* and TQ suppressed pro-inflammatory cytokines, including TNF- α , IL-1 β , IL-6, NO, iNOS, and COX-2 in lipopolysaccharide (LPS)-induced murine macrophage-like RAW264.7 cells, via an inhibition mediated by interleukin-1 receptor-associated kinase 1 (IRAK)-linked AP-1/NF- κ B signaling pathways (Hossen et al., 2017). The study also utilized a kinase activity experiment to investigate the effect of TQ on the enzymatic ability of IRAKs. TQ lowered the inflammatory responses by targeting the activity of the enzyme and break down of IRAK 1, thus suppressing the downstream ability of NF- κ B and Activator protein 1 (AP-1) transcription factor (in vitro and in vivo) (Fig. 6). TQ blocked the activation of NF- κ B and 5-LOX by attenuating the effect of these inflammatory agents (El Mezayen et al., 2006). The TNF- α -activated I κ - β phosphorylation and degradation brought about the suppression of NF- κ B (Sethi et al., 2008). The stimulation of inflammatory signaling cascades in the cell caused the activation of some specific immune cells including, mast cell, macrophage and NK-cell and also affected inflammatory response (Kotowski et al., 2017; Ismail et al., 2016). NF- κ BP65 is a core biochemical pathway responsible for the pro-inflammatory biomarkers' expression induced by LPS. In a recent finding, there was a notable elevation in expression of NF- κ BP65 in the LPS- induced group when compared with the normal control group; p-cymene (bioactive compound of *N. sativa*) was found to downregulate NF- κ BP65 (Hossen et al., 2017; Chen et al., 2014). Chen et al. assessed the effect of p-cymene on the inhibition of TNF- α and IL-6 by interfering with the activation of NF- κ B. The NF- κ B signaling has been observed to function in the pathogenesis of acute lung injury (ALI) (Chen et al., 2014). The extracellular signal-regulated kinase (ERK1/2) signaling performs a crucial function in inflammation and is not only limited to NF- κ B up-regulation but also involved in inflammatory burst, leading to the activation of phagocytosis (Monick et al., 2008). Carvacrol, a phenolic monoterpene compound, identified in *N. sativa* demonstrated potent anti-inflammatory ability by suppressing ERK1/2 and NF- κ B signaling pathway as well as decreasing NO generation in LPS- activated macrophages. However, carvacrol inhibited the activity of LPS on the translocation of NF- κ B (p65) from the cytoplasm to nucleus. The attenuation of the transactivation by carvacrol with or without LPS was able to suppress the basal activation of NF- κ B in RAW 264.7 macrophages.

Also, in the cells of LPS-induced murine macrophage-like RAW264.7, *N. sativa* and TQ suppressed IRF-3 signaling, enhanced TANK-binding kinase autophosphorylation and decreased mRNA expression of interferons (IFN- α , β) (Aziz et al., 2018). The suppression of IRF-3 activation plays a central role in innate immune responses via the modulation of type one interferon synthesis (Aziz and Cho 2018). Interferon (IFN) utilizes the Janus kinase (JAK, a non-receptor tyrosine kinases family that transmits signals effected by cytokines through the JAK-STAT pathway) and majorly activates signal transducer and activator of transcription 1 (STAT 1). Intriguingly, IL-10 in turn activates STAT 3, STAT 4, and STAT 6 which are important for Th1 and Th2 progression. The STATs proteins are downstream signaling target of the Janus Kinase 2 required for the modulation of broad spectrum of cytokines, growth factors, as well as various cellular activity including immune response, cell proliferation, and death (Xin et al., 2020). It performs a central function in inflammation and are critical mediators of immunity against pathogens, and progression of inflammatory disease (Habel et al., 2020). It functions through the JAK/STAT signaling pathway modulating genes expression associated with inflammatory and immune response. STAT 1, 3, and 4 was observed in inflammatory bowel disease, colitis, Crohn's disease, and rheumatoid arthritis elevating IL-6 level in mice model (Parrello et al., 2000; Hanada and Yoshimura, 2002). STAT-4-driven Th1 responses have been revealed to be paramount in human Crohn's disease. Activation of STAT 1 and 5 were also noticed in epithelial cells of asthmatic patients (Zhu et al., 2021). STAT 3 is involved in inflammation via the activation of T helper cells, inflamed epithelial cells, and fibroblast stimulating the production of inflammatory cytokines. Some studies showed that conditional knockout of STAT 3 in macrophages and neutrophils caused prolonged enterocolitis (Gonzalez et al., 2022; Takeda et al., 1999) This knockout might be due to Th1 stimulation via the inhibition of Interleukin-10 (a potent anti-inflammatory cytokine) signaling, which uses STAT3. Some findings have revealed the preventive effect of TQ in the pathogenesis of cancer (Imran et al., 2015; Shanmugam, et al., 2018). TQ prevented the constitutive and IL-6 inducible STAT3 phosphorylation in multiple myeloma cells (Li et al., 2010). More so, TQ significantly reduced JAK 2 effect in the gastric cells of patients diagnosed with cancer and also suppressed the expression STAT3-regulated gene (Zhu, et al., 2016). The Janus Kinase 2 and STAT 3 functions as important signaling pathway in inflammation (Zhu et al., 2016). STAT 5 also functions in the pathophysiology of leukemia and cancer (Dalgıç et al., 2015). A study conducted by Al-Rawashde et al. revealed that TQ notably suppressed the proliferation of chronic myeloid leukemia cells (K562)

through JAK2/STAT3 and STAT5 gene downregulation and decreasing the level of STAT 5 and JAK 2 proteins (Al-Rawashde et al., 2021).

Conclusion

The therapeutic potential of *N. sativa* has been reported by several researchers promoting its utility in folklore to suppress the biological markers that have been implicated in the pathogenesis of inflammatory and immune system disorder. Intriguingly, the most remarkable signaling pathways targeted at *N. sativa* and its compounds were those connected to anti-inflammatory, immunomodulatory, and the antioxidant defense system. However, the bioactive components present in *N. sativa* have often been attributed to its pharmacological properties, but there is dearth of information on the molecular and cellular mechanism underlying the immunomodulatory and anti-inflammatory effect of some other active component of *N. sativa*. Despite the fact that the fundamental mechanism of action of these bioactive components of these seeds was carefully demonstrated, some are still incipient, hence, needs additional clarification. Noteworthy, outstanding development as regards the antioxidant, anti-inflammatory, and immunomodulatory abilities of *N. sativa* have been reported, yet, there is still limited clinical implementation and application. Majority of the findings in this review were carried out at the pre-clinical stage; therefore, it is necessary to perform more clinical trial of these studies for translation into clinical usage, most especially to abate chronic inflammatory and immune system disorders.

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Declarations

Conflict of interest The authors have no conflict of interest to declare.

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