REVIEW
Pharmacology Discovery 2025;5(1):2. https://doi.org/10.53388/PD202505002

The impact of black seeds (*Nigella sativa*) on inflammatory biomarkers – an aspect on insights of clinical and preclinical data

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Author contributions
Maideen NMP collected, analyzed the research literature, drafted the paper and prepared the artwork. The author has read and approved the final version of the manuscript.
Competing interests
The authors declare no conflicts of interest.
Acknowledgments
The author thanks Dubai Health for their continuous support.
Peer review information
Pharmacology Discovery thanks all anonymous reviewers for their contribution to the peer review of this paper.
Abbreviations
N. Sativa, *Nigella sativa*; PRRs, pattern recognition receptors; COPD, chronic obstructive pulmonary disease; MAPK, mitogen-activated protein kinase; NF-kB, nuclear factor kappa B; iNOS, inducible nitric oxide synthase; IL-6, interleukin-6; IFN-γ, interferon-γ; TNF-α, tumor necrosis factor-α; hs-CRP, high sensitivity C-reactive protein; MDA, malondialdehyde; TAC, total antioxidant capacity; LDL, low-density lipoprotein; TC, total cholesterol; HbA1c, glycosylated hemoglobin; FBS, fasting blood sugar; TGs, triglycerides; NAFLD, non-alcoholic fatty liver disease; ALT, alanine aminotransferase; AST, aspartate aminotransferase; RCTs, randomized controlled clinical trials; SOD, superoxide dismutase; OVA, ovalbumin; PGE2, prostaglandin E2; LPS, lipopolysaccharide; MMP, matrix metalloproteinases; LD 50, lethal dose; AP-1, activator protein-1.

Citation
Maideen NMP. The Impact of black seeds (Nigella sativa) on inflammatory biomarkers – an aspect on insights of clinical and preclinical data. Pharmacol Discov. 2025;5(1):2. doi: 10.53388/PD202505002

Executive editor: Yu-Tong Liu.
Received: 30 October 2024; **Revised:** 09 December 2024; **Accepted:** 10 January 2025; **Available online:** 15 January 2025.

Abstract
The immune system's reaction to harmful stimuli, such as radiation, poisonous substances, tissue damage, pathogenic microbes, and damaged cells, is termed as inflammation. This review focuses on black seeds (*Nigella sativa*)'s anti-inflammatory properties, which have been shown in a number of clinical and preclinical studies. Online resources like Medline/PMC/PubMed, Google Scholar, Science Direct, Web of Science, reference lists, Embase, and EBSCO were used to search the literature for pertinent papers. Several clinical, in vitro, and in vivo investigations demonstrated the potentials of *Nigella sativa* (*N. sativa*) against inflammation. There are several mechanisms in which *N. sativa* may have anti-inflammatory properties.

Keywords: black seeds; *Nigella sativa*; anti-inflammatory; inflammatory conditions; inflammatory biomarkers

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Introduction

Immune systems trigger inflammation as a vital, healthy reaction to preserve tissue homeostasis and guarantee survival in the face of infection and tissue damage. The immune systems reaction to harmful stimuli, such as radiation, poisonous substances, tissue damage, pathogenic microbes, and damaged cells, is termed as inflammation [1]. Swelling, discomfort, redness, heat, and loss of function are all signs of inflammation, which is brought on by increased blood flow, vascular permeability, lymphocyte and macrophage infiltration, cytokine buildup, and tissue damage [2].

Migration of different leukocytes including neutrophils, monocytes, basophils, and eosinophils at inflammation site and the release of mediators like leukotrienes, histamine, prostaglandins, serotonin, and free radicals, immune defense cells induce inflammation. Vasodilation brought on by tissue damage or microbial infection increases permeability, allows inflammatory mediators to enter, and causes interstitial edema [3].

Inflammation is categorized as acute inflammation (aids defense against harmful microbes), and chronic inflammation (results from an inappropriate, long-term, uncontrolled inflammatory response) [4].

The self-limiting process of acute inflammation lasts anywhere from a few hours to a few days. Neutrophils are recruited first at the location of acute inflammation. Toll-like receptors and other pattern recognition receptors (PRRs) are involved in the initiation of acute inflammation. Resident immune cells such as dendritic cells, mast cells and macrophages contain toll-like receptors and PRRs on their cell surface. Pathogen-associated molecular patterns or damage-associated molecular patterns liberate inflammatory mediators that cause swelling, increased permeability of blood vessels (edema), and vasodilation (increased blood flow that causes redness and heat), when PRRs are attached to them. On the other hand, chronic inflammation may result from prolonged exposure to damaging stimuli and their failure to be removed. Chronic inflammation is caused by immunological cells such as lymphocytes and macrophages [5].

Numerous chronic diseases, including multiple sclerosis, arthritis, cardiovascular disease, obesity, cancer, chronic obstructive pulmonary disease (COPD), and neurodegenerative diseases are associated with inflammation on their onset, progression, and maintenance. Various chronic pathological conditions including cardiovascular disease (atherosclerosis, cardiomyopathy), metabolic disorders (diabetes, fatty liver), lung and colon cancers, chronic inflammatory diseases (arthritis, pancreatitis), neurological disorders (Parkinson's, Alzheimer's), and many more are associated with chronic inflammation [6].

Inflammatory reactions frequently begin, when PRRs pick up foreign stimuli on cell surface. Numerous inflammatory pathways are triggered by this, including mitogen-activated protein kinase (MAPK) pathway, Janus kinase-signal transducer and activator of transcription pathway, and nuclear factor kappa B (NF-κB) pathway. Activation of these pathways results in recruitment of inflammatory cells, production of inflammatory mediators, and the release of inflammatory cytokines and chemokines [1, 7].

Innate immune cells with PRRs that bind to Pathogen-associated molecular patterns or damage-associated molecular patterns include neutrophils, mast cells, macrophages, monocytes, eosinophils, basophils, natural killer cells, and dendritic cells.

Innate immune system is induced by PRRs to produce pro-inflammatory mediators like cyclooxygenase 2, prostaglandins, NF-kB, inducible nitric oxide synthase (iNOS), and chemokines (chemotactic cytokines), in addition to pro-inflammatory cytokines like interleukin-6 (IL-6), interleukin-1, interferon-γ (IFN-γ), and tumor necrosis factor-α (TNF-α) [8]. Adhesion molecules like intercellular adhesion molecule-1, and vascular cell adhesion molecule-1 drive T-cell-mediated immune response by rolling, stopping, and transmigrating circulating T cells at an inflammatory location [9].

Numerous phytochemicals with anti-inflammatory properties have been found, including flavonoids, terpenoids, alkaloids, tannins, saponins, anthraquinones, and essential oils. Therefore, the potentials of *N. sativa* against inflammation which have been demonstrated in a number of clinical and preclinical investigations, are the main focus of our current review.

Methods

In order to locate relevant publications, the literature was searched using keywords like *Nigella sativa*, black seeds, black cumin seeds, inflammation, cytokines, chemokines, anti-inflammatory, pro-inflammatory cytokines, pro-inflammatory mediators, and inflammatory pathways in online databases such as Medline/PMC/PubMed, Google Scholar, Web of Science, Embase, EBSCO, Science Direct, and reference lists. Duplicate articles were not included in this review; only English-language publications were.

Results and discussion

Black seeds (*Nigella sativa*) is a medicinal herb that belongs to Ranunculaceae family. "In the black cumin, there is a cure for every disease except death," according to Prophet Muhammad, which is why *N. sativa* is referred to as prophetic medicine. Additionally, the Bible calls black cumin "Curative black seed" and cites Hippocrates, Dioscorides, and the "Gith of Pliny" as describing it as "Melanthion" [10, 11].

Numerous phytochemical analyses have revealed that *N. sativa* contains a variety of bioactive phytoconstituents, such as phytosterols (β-sitosterol), fibers, vitamins, minerals, amino acids, alkaloids (nigellidine, nigellicine, nigellicimine, and nigellicimine-N-oxide), polyphenols (quercetin, kaempferol, and rutin), terpenes and terpenoids (thymoquinone), thymoquinone, dithymoquinone, thymol, carvacrol, α-pinene, and others) [12].

Nigella sativa (*N. sativa*) was analyzed using gas chromatography-mass spectrometry and identified with several bioactive phytoconstituents including Thymoquinone, β-Pinene, O-Cymene, 6-DL-Arabinose, D-Glucose, O-α-Dgalactopyranosyl, Thujane trans-4-methoxy, α-D-glucopyranoside, 2-isopropylidene-5-methylhex-4-enal Pivalate, Longifolene, Limonen-6-ol, ß-Bisabolene, 2-(4-Nitrobutyryl) cyclooctanone, Phenol, 1,1-Diphenyl-4-phenylthiobut-3-en-1-ol, 4-trimethyl-2, 3, 6-methoxy, Propanoic acid, methyl ester, 5-methylene-4α, cholestan-3-ol, 2-methylene-, (3ß, 5α), 2, 6-dihexadecanoate, 1-Heptatriacotanol, 2H-Benzo [f] oxireno [2, 3-E], 10, 13-Eicosadienoic acid, methyl ester, E, E, Z-1, 3, 12-Nonadecatriene-5, 14-diol, and 9-Octadecenamide Phthalic acid, decyl oct-3-yl ester, 1, 2-Benzenedicarboxylic acid, bis (8-methylnonyl) ester, benzofuran8 (9H)-one, 9-[2-(dimethylar), and stigmasterol [13].

The presence of several bioactive phytoconstituents, including octanoic acid (m/z 144.21), capric acid (m/z 172.26), benzene, 1, 3-bis (1, 1-dimethyl ethyl) (m/z 190.32), maculosin (m/z 260.1), 3-ketosphingoshine (m/z 297.3), ethyl ester (m/z 256.42), hygrine (m/z 141.1), tetra decanoic acid, and 2-monomyristin (m/z 302.4) were also detected in *N. sativa* oil by Gas chromatography-mass spectrometry and liquid chromatography-mass spectrometry analyses [14]. The potentials of *N. sativa* against inflammation were demonstrated in a number of clinical, in vitro, and in vivo studies.

Clinical studies that explored anti-inflammatory activity of *N. sativa*

Black seeds, or *N. sativa*, have been shown in numerous clinical studies to possess anti-inflammatory properties (Table 1). Supplementation of 2 g/day of *N. sativa* for 8 weeks ensued in significant reduction of serum levels of IL-6, and IL-1β, as well as serum leptin and serum insulin, were observed in a recent crossover design, placebo-controlled, randomized, clinical trial (RCT) of 46 women with overweight and obesity [15]. Furthermore, a placebo-controlled, parallel, double-blind, triple-arm, RCT of 45 patients with knee osteoarthritis demonstrated that the oral administration of 2.5

milliliters of *N. sativa* oil 2-3 times daily for six weeks ensued in a significant improvement in serum levels of high sensitivity C-reactive protein (hs-CRP), malondialdehyde (MDA), and total antioxidant capacity (TAC) [16]. Furthermore, oral administration of two capsules containing 500 mg of *N. sativa* oil daily for eight weeks dramatically decreased mean serum levels of hs-CRP, MDA, low-density lipoprotein (LDL)-cholesterol and total cholesterol (TC), according to a double-blind, placebo-controlled RCT involving 50 hemodialysis patients [17]. Additionally, oral administration of two grams of *N. sativa* oil a day consecutively for 12 weeks dramatically decreased levels of hs-CRP, MDA, glycosylated hemoglobin (HbA1c), and fasting blood sugar (FBS) in a double-blind, placebo-controlled RCT with 46 diabetic hemodialysis patients [18].

Table 1 Clinical studies that explored anti-inflammatory activity of *N. sativa*

S.No	Type of study	Participants	Treatment	Outcome	Reference
1	Crossover design, randomized, placebo-controlled, clinical trial	46 women with overweight and obesity	2 g/day of *N. sativa* for 8 weeks	Significant reduction of serum levels of IL-1β, IL-6, along with the reduction of serum leptin and serum insulin	[15]
2	Randomized, double-blind, parallel, triple-arm, placebo-controlled, clinical trial	45 patients with knee osteoarthritis	2.5 mL of *N. sativa* oil twice/thrice daily for 6 weeks	Significant reduction of serum levels of high sensitivity C-reactive protein (hs-CRP) along with a significant increase in total antioxidant capacity (TAC) levels and a significant decline in serum malondialdehyde (MDA) levels	[16]
3	Randomized, double-blind, placebo-controlled, clinical trial	50 patients who underwent hemodialysis	2 capsules of *N. sativa* oil (1000 mg/day) for 8 weeks	Significant decline of mean serum levels of hs-CRP along with a significant decrease in mean serum levels of MDA, total cholesterol (TC), and low-density lipoprotein (LDL)-cholesterol	[17]
4	Randomized, double-blind, placebo-controlled, clinical trial	46 diabetic hemodialysis patients	2 g/day of *N. sativa* oil for 12 weeks	Significant reduction of hs-CRP along with a significant reduction of MDA, glycosylated hemoglobin (HbA1c) and fasting blood sugar (FBS) levels	[18]
5	Prospective, randomized, double-blind, placebo-controlled, clinical trial	56 patients with type 2 diabetes mellitus (type 2 DM)	1800 mg/day of *N. sativa* oil for 12 weeks	Significant reduction of hs-CRP along with a significant decrease in serum levels of HbA1c, intercellular adhesion molecule-1, TC, and TGs	[19]
6	Comparative clinical study	117 obese prediabetic subjects	Metformin 500 mg twice daily and *N. sativa* oil soft gelatin 450 mg capsules twice daily for 8 weeks	Significant reduction of TNF-α, and Castelli risk index-I in comparison of other interventions	[20]
7	Double-blind, placebo-controlled, randomized clinical trial	50 patients with type 2 DM	*N. sativa* oil soft gelatin 1000 mg capsules twice daily for 8 weeks	Significant reduction of serum hs-CRP along with a significant decline of FBS, low-density lipoprotein (LDL) cholesterol, total cholesterol (TC), triglycerides (TGs), and MDA levels and a significant increase in high-density lipoprotein cholesterol	[21]
8	Prospective double-blind, placebo-controlled, randomized clinical trial	100 patients with mild-moderate COPD	1 g of *N. sativa* oil soft gelatin capsules twice daily for 3 months	Significant reduction of serum levels of TNF-α, and IL-6 along with a significant increase in antioxidants like SOD, CAT, GPx, vitamin C and vitamin E	[22]
9	Double-blind, placebo-controlled, clinical trial	51 patients with Helicobacter pylori infection	2 g/day of *N. sativa* for 8 weeks	Non-significant reduction of serum levels of IL-8 and hs-CRP along with a significant improvement in patients' quality of life, and more Helicobacter pylori eradication	[23]
10	Double-blind, placebo-controlled, randomized clinical trial	89 patients with Behcet's disease	*N. sativa* oil soft gelatin 1000 mg capsules for 8 weeks	Non-significant reduction of serum levels of TNF-α, IL-10, hs-CRP along with a significant reduction of serum MDA levels and a significant increase total antioxidant capacity (TAC) level	[24]

Table 1 Clinical studies that explored anti-inflammatory activity of *N. sativa* (*continued*)

S.No	Type of study	Participants	Treatment	Outcome	Reference
11	Double-blind, placebo-controlled, randomized clinical trial	44 patients with non-alcoholic fatty liver disease (NAFLD)	1 g/day of *N. sativa* oil for 8 weeks	Diminished levels of hs-CRP, IL-6, TNF-α along with a reduction of FBS, TC, LDL, VLDL, TGs, aspartate aminotransferase (AST), and alanine aminotransferase (ALT) levels	[25]
12	Double-blind, placebo-controlled, randomized clinical trial	50 patients with NAFLD	2 g/day of *N. sativa* seeds for 12 weeks	Significant reduction of hs-CRP levels, nuclear factor kappa-B (NF-kB) activity, and TNF-α levels in addition to significant reduction of hepatic steatosis percentage	[26]
13	Clinical study	46 patients with mild to moderate ulcerative colitis	2 g/day of powdered *N. sativa* seeds for 6 weeks	Significant reduction of serum levels of hs-CRP and TNF-α along with a significant decrease in stool frequency score	[27]
14	Double-blind, placebo-controlled, randomized clinical trial	43 patients with type 2 DM	500 mg of *N. sativa* capsules twice daily for 8 weeks	Non-significant decline in serum levels of IL-1β, and TNF-α	[28]
15	Double-blind, placebo-controlled, randomized clinical trial	28 children aged 6-15 years with asthma	15-30 mg/kg/day of *N. sativa* oil for 8 weeks	Significant reduction of IL-4 and a significant elevation of IFN-γ along with improved asthma control test (ACT) score	[29]
16	Participant-blinded, placebo-controlled, randomized clinical trial	76 patients with partly controlled asthma	1 g and 2 g daily of *N. sativa* along with maintenance inhaled therapy for 12 weeks	Non-significant changes in IL-4, IL-10, and IL-17A levels	[30]
17	Double-blind, placebo-controlled, randomized clinical trial	90 obese women	3 g daily of *N. sativa* oil	Diminished serum levels of hs-CRP and TNF-α	[31]
18	Double-blind, placebo-controlled, randomized, parallel-group clinical trial	43 female patients with rheumatoid arthritis	500 mg capsules of *N. sativa* oil 2 times daily for 8 weeks	Significant reduction of serum levels of hs-CRP in addition to a significant reduction of disease activity scores of 28 joints and an improved number of swollen joints	[32]
19	Double-blind, cross-over, placebo-controlled, randomized clinical trial	51 patients with metabolic syndrome	Bread with 3 g daily of *N. sativa* powder and wheat bran for 2 months	Non-significant changes in serum levels of hs-CRP and other parameters including LDL, high-density lipoprotein, and TGs	[33]
20	Double-blind, cross-over, placebo-controlled, randomized clinical trial	42 patients with rheumatoid arthritis	2 capsules of 500 mg of *N. sativa* oil daily for 8 weeks	Significant increase in serum levels of IL-10 and non-significant decrease in serum levels of TNF-α	[34]
21	Placebo-controlled, randomized, clinical trial	40 female patients with rheumatoid arthritis	500 mg capsules of *N. sativa* oil 2 times daily for 1 month	Significant reduction of disease activity scores of 28 joints and improvements in number of swollen joints, pain and morning stiffness	[35]

N. Sativa, *Nigella sativa*; TNF-α, tumor necrosis factor-α; IFN-γ, interferon-γ.

The results of a prospective, double-blind, and placebo-controlled RCT involving 56 type 2 diabetes mellitus patients showed a significant decrease in the serum levels of hs-CRP, intercellular adhesion molecule-1, HbA1c, TC, and triglycerides (TGs), after taking 1800 mg of *N. sativa* oil daily for 12 weeks [19]. Furthermore, 117 obese prediabetic participants were divided into several groups for a comparative clinical trial. The *N. sativa* group consumed soft gelatin capsules containing 450 mg of *N. sativa* oil two times daily for the study period of 8 weeks. Lifestyle changes group followed a strict diet and exercise plan. The metformin group took 500 mg of metformin twice daily. The study found that *N. sativa* intake significantly reduced TNF-α and Castelli risk index-I when compared to other therapies [20]. Furthermore, in a double-blind, placebo-controlled, RCT of 50 type 2 diabetes mellitus patients, oral administration of soft gelatin capsules containing *N. sativa* oil 1000 mg two times a day for 8 weeks resulted in a significant improvement in serum levels of hs-CRP, high-density lipoprotein-cholesterol, FBS, LDL-cholesterol, TC, TGs, and MDA levels [21]. Additionally, a prospective double-blind, placebo-controlled, RCT of 100 patients with mild-to-moderate COPD found that the oral administration of soft gelatin capsules containing 1000 mg of *N. sativa* oil 2 times a day for the study period of three months, in addition to standard COPD medications, significant improvement in serum levels of IL-6, TNF-α, SOD, CAT, GPx [22].

Quadruple therapy with 2 g of *N. sativa* daily for 8 weeks resulted in more Helicobacter pylori eradication, quality of life of patients improved significantly, and a non-significant reduction of serum levels of hs-CRP, and IL-8, according to a double-blind, placebo-controlled RCT of 51 patients with Helicobacter pylori infection [23].

Furthermore, supplementation of soft gelatin capsules containing 1000 mg of *N. sativa* oil for the study period of 8 weeks ensued in significant reduction of serum levels of hs-CRP, TNF-α, and IL-10 and significant elevation of TAC levels, according to a double-blind, placebo-controlled RCT involving 89 patients with Bechet's disease [24]. *N. sativa* oil capsules may not be enough to significantly lower inflammation markers when taken daily. Furthermore, following an 8-week course of 1 g/day of *N. sativa* oil, 44 non-alcoholic fatty liver disease (NAFLD) patients experienced decreases in their levels of TNF-α, hs-CRP, and IL-6 along with FBS, TC, LDL, VLDL, TGs, and both alanine aminotransferase (ALT) and aspartate aminotransferase (AST) [25]. Furthermore, a double-blind, placebo-controlled RCT of 50 NAFLD patients showed that consuming 2 g/day of *N. sativa* seeds for the study period of 12 weeks resulted in significant reduction of percentage of hepatic steatosis, hs-CRP, and TNF-α levels and NF-kB activity [26].

Taking 2 g of powdered *N. sativa* seeds daily for 6 weeks resulted in a significant drop in serum levels of hs-CRP and TNF-α as well as a notable decrease in stool frequency score in a clinical study with 46 participants who had mild to moderate ulcerative colitis [27]. A double-blind, placebo-controlled RCT also found that taking 500 mg of *N. sativa* capsules twice a day for eight weeks resulted in a statistically insignificant reduction in serum levels of TNF-α and IL-1β in 43 individuals with type 2 diabetes [28]. Additionally, administering 15-30 mg/kg of *N. sativa* oil daily for the study period of 8 weeks resulted in a significant improvement in serum levels of IL-4 and IFN-γ, along with an improved asthma control test score, according to a double-blind, placebo-controlled RCT that included 28 asthmatic children aged 6–15 years [29]. Furthermore, in a participant-blinded, placebo-controlled RCT of 76 people with partially controlled asthma showed non-significant changes in IL-4, IL-10, and IL-17A levels after taking 1 g and 2 g/day of *N. sativa* for the study period of 12 weeks in addition to continuing inhaled treatment [30].

In a double-blind, placebo-controlled RCT of 90 obese women showed reduced serum levels of hs-CRP and TNF-α following the consumption of 3 g/day of *N. sativa* oil in conjunction with a low-calorie diet [31]. Consumption of *N. sativa* oil 500 mg capsules two times daily for the study period of 8 weeks resulted in significant improvements in 28-joint disease activity scores, number of swollen joints, and serum hs-CRP levels in a double-blind, placebo-controlled RCT that involved 43 women with rheumatoid arthritis [32]. Additionally, eating bread containing 3 g of *N. sativa* powder and wheat bran every day for two months did not significantly alter serum levels of hs-CRP or other metrics like LDL, high-density lipoprotein, and TGs, according to a cross-over, double-blind, placebo-controlled RCT involving 51 patients with metabolic syndrome [33]. Furthermore, according to a cross-over, double-blind, placebo-controlled RCT involving 42 rheumatoid arthritis patients, taking two capsules of *N. sativa* oil 500 mg every day for the study period of eight weeks led to a non-significant decrease in TNF-α levels and a notable increase in serum IL-10 levels [34]. Taking capsules of *N. sativa* oil 500 mg two times a day for the study period of one month resulted in significant improvements in 28-joint disease activity scores, counts of swollen joints, pain levels, and morning stiffness in a placebo-controlled RCT with 40 female patients with rheumatoid arthritis [35].

Meta-analyses that determined anti-inflammatory activity of *N. sativa*

Numerous meta-analyses have shown that *N. sativa* may have anti-inflammatory properties (Table 2). *N. sativa* supplementation dramatically decreased serum levels of TNF-α, C-reactive protein (CRP), and IL-6 according to a meta-analysis that analyzed 16 randomized controlled clinical trials (RCTs) with 1033 participants suffering from metabolic syndrome and related conditions [36]. Additionally, a meta-analysis that analyzed 20 RCTs involving 1086 participants revealed that taking *N. sativa* supplements led to a significant drop in serum levels of CRP, and TNF-α and a non-significant drop in IL-6 levels [37]. Additionally, *N. sativa* supplementation significantly reduced serum levels of CRP, IL-6, and TNF-α in addition to significantly lowering the grade of hepatic steatosis, according to a thorough analysis of four RCTs involving patients with nonalcoholic fatty liver disease and hepatic enzymes [38]. Additionally, taking *N. sativa* supplements dramatically decreased serum levels of CRP, FPG, HbA1c, TC, LDL-cholesterol, and MDA, according to a meta-analysis that analyzed 11 RCTs. When the dosage exceeded 1 g/day and the duration exceeded 8 weeks, participants in the *N. sativa* group had lower body mass indices than those in the control group [39].

N. sativa supplementation dramatically reduced serum levels of TNF-α and significantly raised levels of the enzyme superoxide dismutase (SOD) and TAC, according to a meta-analysis that analyzed 11 RCTs involving 710 participants [40]. Additionally, taking *N. sativa* supplements significantly raised SOD and TAC levels, decreased MDA levels, and significantly decreased serum levels of hs-CRP and TNF-α according to a meta-analysis that analyzed ten RCTs [41]. Additionally, *N. sativa* supplementation raised serum levels of hs-CRP, ALT, AST, and FPG, according to a meta-analysis that analyzed RCTs involving 358 NAFLD patients [42]. Furthermore, a meta-analysis that analyzed 12 RCTs revealed that taking *N. sativa* supplements raised TAC and decreased MDA levels while also significantly lowering serum levels of CRP [43].

Supplementing with *N. sativa* led to a significant reduction of serum levels of TC, TGs, LDL-cholesterol, FPG, and HbA1c l, but it also insignificantly decreased serum levels of TNF-α, according to a meta-analysis that analyzed 50 RCTs [44]. Additionally, *N. sativa* supplementation enhanced the functions of the immune, cardiac, renal, and hepatic systems, decreased inflammatory biomarkers, and inhibited the production of pro-inflammatory mediators while raising antioxidant enzymes, according to a thorough review of RCTs. Supplementing with 2 g of powdered *N. sativa* daily improved the glycemic indices and lipid profiles for a minimum of 12 weeks [45]. Furthermore, taking *N. sativa* supplements dramatically lowered serum levels of CRP, according to a meta-analysis of five RCTs [46].

In-vivo studies that determined anti-inflammatory activity of *N. sativa*

The anti-inflammatory properties of *N. sativa* have also been confirmed by a number of *in-vivo* studies (Table 3). In a study of 25 male white Wistar rats given a high-fat diet, the injection of 3 milliliters per kilogram and 4 milliliters per kilogram of *N. sativa* led to a significant drop in CRP levels and a significant rise in IL-10 levels [47]. Additionally, dose-dependent reduction of volume of paw edema was observed in Long-Evans rats with carrageenan-induced paw edema by the administration of 400 and 800 mg/kg of *N. sativa* extract [48]. Furthermore, 50 mg/kg of *N. sativa* oil thymoquinone supplementation reversed the rise in pro-inflammatory cytokines like IL-6, TNF-α, and others in a study involving Wistar rats with paw edema brought on by carrageenan [49]. Furthermore, in a rat experiment, adding 2 and 4 milliliters per kilogram of *N. sativa* oil to the diet reduced the acute inflammation caused by carrageenan and sub-acute inflammation caused by complete Freund's adjuvant [50].

An experimental study on 50 male albino rats with diabetic neuropathy found that supplementing *N. sativa* extract with silver nanoparticles improved elevated levels of inflammatory biomarkers like TNF-α and NF-kB [51]. Additionally, an experimental study using a rat model of arthritis found that a 25-day oral supplementation of 1.82 milliliters per kilogram of *N. sativa* oil significantly reduced IL-6, and CRP levels and had anti-inflammatory and anti-arthritic effects [52]. Additionally, an experimental study using a rat model of arthritis found that thymoquinone intake for 25 days decreased serum CRP levels, bone erosion, synovial inflammation, and the macroscopic arthritic score in addition to mRNA levels of IL-1, NF-kB, and TNF-α [53].

Table 2 Meta-analyses that determined anti-inflammatory activity of *N. sativa*

S.No	Number of RCTs	Participants	Outcome	Reference
1	16 RCTs	1033 patients with metabolic syndrome and related disorders	Significant reduction of serum levels of TNF-α, IL-6, and CRP	[36]
2	20 RCTs	1086 participants	Significant reduction of serum levels of TNF-α, and CRP and a non-significant reduction of IL-6	[37]
3	4 RCTs	324 patients with NAFLD	Significant reduction of serum levels of TNF-α, IL-6, and CRP in addition to significant decrease in hepatic steatosis grade and significant reduction of hepatic enzymes	[38]
4	11 RCTs	666 participants with prediabetes and type 2 DM	Significant reduction of serum levels of CRP along with a reduction of FPG, HbA1c, TC, LDL-cholesterol, and MDA levels	[39]
5	11 RCTs	710 participants	Significant reduction of serum levels of TNF-α, in addition to significant increase in superoxide dismutase (SOD) enzyme, and total antioxidant capacity (TAC) levels	[40]
6	10 RCTs		Significant reduction of serum levels of TNF-α, and hs-CRP along with a significant elevation of SOD and TAC levels and a significant decrease in MDA levels	[41]
7	5 RCTs	358 patients with NAFLD	Improvement in serum levels of hs-CRP, in addition to improvement in ALT, AST, and FPG levels	[42]
8	12 RCTs		Significant reduction of serum levels of CRP along with an elevation of TAC levels and a reduction of MDA levels	[43]
9	50 RCTs		Insignificant reduction of serum levels of TNF-α in addition to significant reduction of TC, TGs, LDL-cholesterol, FPG, and HbA1c levels	[44]
10	7 RCTs	439 participants with NAFLD, obesity, ulcerative colitis, or rheumatoid arthritis	Significant reduction of serum levels of CRP	[46]

N. Sativa, *Nigella sativa*; TNF-α, tumor necrosis factor-α; IL-6, interleukin-6; NAFLD, non-alcoholic fatty liver disease; hs-CRP, high sensitivity C-reactive protein; CRP, C-reactive protein; HbA1c, glycosylated hemoglobin; TC, total cholesterol; TGs, triglycerides; LDL, low-density lipoprotein; RCTs, randomized controlled clinical trials.

Table 3 In-vivo studies that determined anti-inflammatory activity of *N. sativa*

S.No	Type of animals	Treatment	Outcome	Reference
1	25 male white Wistar rats fed with high-fat diet	3 mL/kg and 4 mL/kg of *N. sativa*	Significant reduction of CRP levels and a significant increase in IL-10 levels	[47]
2	Long-Evans rats with carrageenan-induced paw edema	400 and 800 mg/kg of *N. sativa* extract	Dose-dependent reduction of paw edema volume	[48]
3	Wistar rats with carrageenan-induced paw edema	50 mg/kg of thyoquinone of *N. sativa* oil	Reversal of elevated pro-inflammatory cytokines such as TNF-α, IL-6 and others	[49]
4	Experimental study of rats	2 and 4 mL/kg of *N. sativa* oil	Anti-inflammatory effect comparable to diclofenac on carrageenan-induced acute inflammation and complete Freund's adjuvant induced sub-acute inflammation	[50]
5	50 male albino rats with diabetic neuropathy	*N. sativa* extract with silver nanoparticles	Amelioration of enhanced levels of inflammatory biomarkers including TNF-α, and NF-kB	[51]
6	Rat model of arthritis	1.82 mL/kg *N. sativa* oil for 25 days	significant anti-inflammatory and anti-arthritic effects along with a reduction of CRP, and IL-6 levels	[52]
7	Rat model of arthritis	Thymoquinone of *N. sativa* oil for 25 days	Reduction of serum CRP levels, and mRNA levels of IL-1, TNF-α, and NF-kB, synovial inflammation, macroscopic arthritic score, and bone erosion	[53]
8	Experimental study of rats	Topical application of simple balm sticks of 10% *N. sativa* oil in rats	Notable reduction of TNF-α levels, high inhibition of carrageenan-induced paw edema, and lower leukocytes count	[54]

Table 3 In-vivo studies that determined anti-inflammatory activity of *N. sativa* (*continued*)

S.No	Type of animals	Treatment	Outcome	Reference
9	Stroke prone spontaneously hypertensive (SHRsp) rats	Thymoquinone of *N. sativa*	Remarkable reduction of mRNA expression of IL-6, IL-1β, MCP-1, COX-2 in the brain of SHRsp rats	[55]
10	Wistar rats sensitized with ovalbumin and exposed to smokeless tobacco	4 mL/kg/day of *N. sativa* oil	Reduced IL-4 and NO production, restoration of antioxidant status, reduced lipid peroxidation, and improved histopathological alterations	[56]
11	Albino Wistar rats with carrageenan-induced paw edema, cotton pellet granuloma, and formaldehyde-induced arthritis	*N. sativa* oil	Significant lowering of inflammation in carrageenan-induced paw edema and significant decrease in formation of granulomatous tissue in cotton pellet granuloma, and significant reduction of inflammation in formaldehyde-induced arthritis	[57]
12	Ovalbumin (OVA)-sensitized mice	Thymoquinone of *N. sativa*	Inhibition of production of inflammatory factors (IL-4, and IL-5)	[58]
13	Male Wistar albino rats with cerulein-induced acute pancreatitis	Thymoquinone of *N. sativa*	Significant reduction serum levels of IL-1β	[59]
14	Male albino Wistar rats with pancreatitis fed with ethanol and high-fat diet	Thymoquinone of *N. sativa*	Significant reduction of mRNA expression of IL-1β, IL-18, and TNF-α	[60]
15	Female Sprague-Dawley rats with pristane-induced arthritis	Intraperitoneal injection of 2 mg/kg of thymoquinone of *N. sativa* daily for 15 days	Reduced arthritis score	[61]
16	Streptozotocin-induced diabetic pregnant mice	Thymoquinone of *N. sativa*	Marked reduction of plasma levels of cytokines including IL-2, IL-4, and IL-7 in macrosomic offspring born to diabetic mice	[62]
17	Wistar rats with collagen-induced arthritis	5 mg/kg of thymoquinone of *N. sativa* once daily for 21 days	Significant reduction of levels of pro-inflammatory mediators (IL-6, IL-1β, TNF-α, interferon-γ (IFN-γ), and prostaglandin E2 (PGE2) and increased levels of IL-10	[63]
18	Rat model of arthritis	2.5 mg/kg and 3.5 mg/kg of thymoquinone of *N. sativa*	Reduction of IL-1β, TNF-α levels	[64]
19	Ovalbumin (OVA)-sensitized mice	Intraperitoneal injection of thymoquinone of *N. sativa* for 5 days before OVA challenge	Significant reduction of Th2 cytokines, lung eosinophilia, and goblet cell hyperplasia	[65]
20	Ovalbumin (OVA)-sensitized mice	Intraperitoneal injection of thymoquinone of *N. sativa*	Significant inhibition of IL-4, IL-5, and IL-13 along with a reduction of lung eosinophilia and a reduction of elevated serum levels of OVA-specific immunoglobulin E (IgE) and IgG1	[66]
21	Ovalbumin (OVA)-sensitized mice	Intraperitoneal injection of thymoquinone of *N. sativa*	Significant reduction of leukotrienes (LTB4, and LTC4) along with a marked reduction of bronchoalveolar (BAL) fluid and lung tissue eosinophilia	[67]

N. Sativa, *Nigella sativa*; TNF-α, tumor necrosis factor-α; CRP, C-reactive protein; IL-6, interleukin-6; NF-kB, nuclear factor kappa B.

Rats in an experimental trial showed a significant reduction in TNF-α levels, a high prevention of carrageenan-induced paw edema, and a decreased leukocyte count when simple balm sticks containing 10% *N. sativa* oil were applied topically [54]. Additionally, an experimental study revealed that the thymoquinone reduced the mRNA expression of COX-2, IL-6, IL-1β, and MCP-1 levels significantly in the brain of stroke-prone spontaneously hypertensive rats [55]. Additionally, in an experimental study of Wistar rats sensitized with ovalbumin and exposed to smokeless tobacco, daily oral administration of 4 milliliters per kilogram of *N. sativa* oil led to improved histopathological alterations, decreased lipid peroxidation, restored antioxidant status, and decreased production of IL-4 and NO [56]. Furthermore, an experimental study of Albino Wistar rats with formaldehyde-induced arthritis, cotton pellet granuloma, and carrageenan-induced paw edema found that supplementing with *N. sativa* oil significantly reduced inflammation in these conditions, as well as the formation of granulomatous tissue in these conditions [57].

In an experimental study, thymoquinone was found to reduce the synthesis of inflammatory factors (IL-4 and IL-5) in mice that were ovalbumin (OVA) sensitized [58]. Additionally, in an experimental trial of male Wistar albino rats with cerulein-induced acute pancreatitis, thymoquinone therapy led to a significant reduction in serum levels of IL-1β [59]. Additionally, significant reduction of IL-1β, TNF-α, and IL-18 were observed in mRNA of male albino Wistar rats with pancreatitis that were fed ethanol and a high-fat diet, by thymoquinone supplementation [60].

An intraperitoneal injection of 2 milligrams per kilogram of thymoquinone daily for 15 days resulted in a lower arthritis score in female Sprague-Dawley rats with pristane-induced arthritis [61]. Additionally, in an experimental study of pregnant mice with diabetes

brought on by streptozotocin, thymoquinone was demonstrated to significantly lower plasma levels of cytokines such as IL-2, IL-4, and IL-7 in macrosomic offspring born to diabetic mice [62]. Additionally, in a study of wistar rats with collagen-induced arthritis, pro-inflammatory mediators (TNF-α, IFN-γ, IL-1β, IL-6, and prostaglandin E2 (PGE2) were significantly reduced and IL-10 was increased when 5 mg/kg of thymoquinone was given once daily for 21 days [63]. Furthermore, supplementing with 2.5 milligrams per kilogram and 3.5 milligrams per kilogram of thymoquinone reduced TNF-α and IL-1β levels in a study employing a rat model of arthritis [64].

Thymoquinone was administered intraperitoneally five days prior to the OVA challenge in an experimental study of mice sensitized to ovalbumin OVA. This led to a notable decrease in Th2 cytokines, lung eosinophilia, and goblet cell hyperplasia [65]. Additionally, in an experimental study of ovalbumin OVA-sensitized mice, thymoquinone given intraperitoneally led to a significant inhibition of IL-4, IL-5, and IL-13, as well as a decrease in lung eosinophilia and elevated serum levels of OVA-specific IgG1, and immunoglobulin E [66]. Furthermore, thymoquinone of *N. sativa* administered intraperitoneally resulted in a significant decrease in leukotrienes (LTB4 and LTC4) as well as a marked decrease in bronchoalveolar fluid and lung tissue eosinophilia, according to an experimental study conducted on ovalbumin OVA-sensitized mice [67].

Table 4 In-vitro studies that determined Anti-inflammatory activity of *N. sativa*

S.No	Type of cells	Treatment	Outcome	Reference
1	3T3-L1 adipocytes and Raw264.7 macrophages	*N. sativa* seed extract	Significant reduction of mRNA expression levels of key pro-inflammatory mediators (IL-6, IL-1β, TNF-α), inhibition of lipopolysaccharide-induced production of PGE2, and NO, diminished levels of MCP-1, iNOS, and COX-2, and significant attenuation of lipid accumulation	[68]
2	Lipopolysaccharide (LPS)-induced inflammation on microglial cells	10-40 μg/mL of *N. sativa* seed oil	Significant reduction of TNF-α, IL-6, IL-1β, PGE2 levels	[69]
3	Red blood cells	Water soluble extract of *N. sativa* seeds	Protection against lysis of red blood cells (RBCs)	[70]
4	Bone marrow mesenchymal stem cells (BM-MSCs) derived from patients with osteoarthritis	Thymoquinone of *N. sativa*	Upregulation of anti-inflammatory genes (IL-4, and IL-10) and downregulation of pro-inflammatory genes (TNF-α, IL-6, IL-8, IL-16, IL-12A, COX-2, and IFN-γ)	[71]
5	Simpson-Golani-Behmel syndrome human pre-adipocytes with low-grade inflammation	Fresh extracted *N. sativa* oil	Significant reduction of IL-6 levels	[72]
6	Primary human T-lymphocytes, monocytes, and A549 human lung epithelial cells	*N. sativa* oily preparations extracts	Significant suppression of IL-6, IL-2, and PGE2 in T-lymphocytes and IL-6 and PGE2 in monocytes	[73]
7	LPS-stimulated murine macrophage-like RAW264.7 cells and human monocyte-like U937 cells	Thymoquinone of *N. sativa*	Strong inhibition of production of TNF-α, IL-6, IL-1β, and COX-2 in LPS-stimulated RAW264.7 cells	[74]
8	Human osteoarthritis chondrocytes	Thymoquinone of *N. sativa*	Dose-dependent inhibition of IL-1β-induced production of TNF-α, IL-1β, NO, COX-2, iNOS, NO, and PGE2, and inhibition of IL-1β-induced NF-kB activation	[75]
9	LPS-stimulated BV-2 murine microglial cells	Thymoquinone of *N. sativa*	Lowering of pro-inflammatory cytokines including IL-6, and IL-12	[76]
10	TNF-α-induced rheumatoid arthritis synovial fibroblasts	Thymoquinone of *N. sativa*	Inhibition of TNF-α-induced IL-6 and IL-8 production	[77]
11	LPS-stimulated BV2 microglial cells	Thymoquinone of *N. sativa*	Dose-dependent inhibition of LPS-induced production of TNF-α, IL-1β, NO and PGE2, and inhibition of activation of NF-kB	[78]
12	LPS-stimulated BV2 microglial cells	Thymoquinone of *N. sativa*	Downregulation of matrix metalloproteinases (MMP) such as MMP-1, MMP-3, and MMP-13	[79]

N. Sativa, *Nigella sativa*; TNF-α, tumor necrosis factor-α; IL-6, interleukin-6; PGE2, prostaglandin E2; NF-kB, nuclear factor kappa B.

Pharmacology Discovery 2025;5(1):2. https://doi.org/10.53388/PD202505002

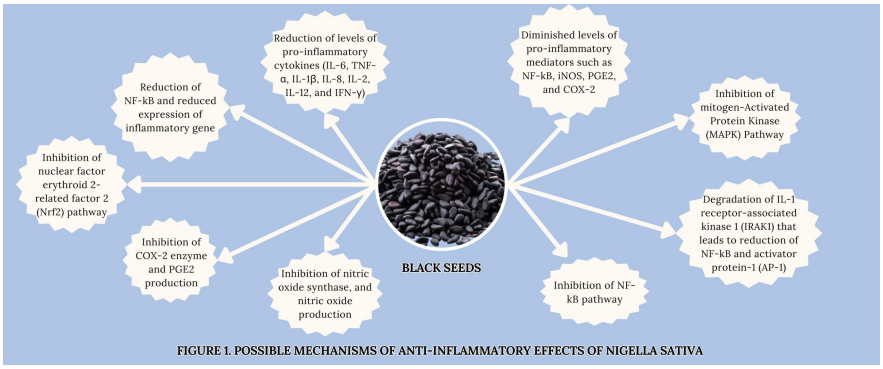

Figure 1 Possible mechanisms of anti-inflammatory effects of *N. sativa*. *N. Sativa*, *Nigella sativa*; NF-kB, nuclear factor kappa B; iNOS, inducible nitric oxide synthase; MAPK, mitogen-activated protein kinase; PGE2, prostaglandin E2; TNF-α, tumor necrosis factor-α; IL-6, interleukin-6.

In-vitro studies that determined anti-inflammatory activity of *N. sativa*

N. sativa may have anti-inflammatory properties, according to a number of *in-vitro* studies (Table 4). When 3T3-L1 adipocytes and Raw264.7 macrophages were treated with *N. sativa* seed extract, the lipid accumulation was significantly reduced, MCP-1, iNOS, and COX-2 levels were lowered, lipopolysaccharide-induced production of PGE2 and NO was inhibited, and the mRNA expression levels of important pro-inflammatory mediators (TNF-α, IL-6, and IL-1β) were significantly reduced [68]. In addition, an *in vitro* study of lipopolysaccharide (LPS)-induced inflammation in microglial cells revealed that 10–40 μg/mL of *N. sativa* seed oil significantly reduced PGE2, TNF-α, IL-6, IL-1β levels [69]. Breakdown of red blood cells was also inhibited by a water-soluble extract of *N. sativa* seeds, according to an in vitro study of Red blood cells [70]. Furthermore, in an in vitro study of bone marrow mesenchymal stem cells derived from patients with osteoarthritis, thymoquinone treatment led to elevation of anti-inflammatory genes (IL-4, IL-10) and reduction of pro-inflammatory genes (IFN-γ, COX-2, TNF-α, IL-6, IL-8, IL-16, and IL-12A) [71].

Freshly extracted *N. sativa* oil significantly reduced IL-6 levels in human pre-adipocytes with low-grade inflammation in Simpson-Golani-Behmel syndrome [72]. Additionally, an in vitro study using primary human T-lymphocytes, monocytes, and A549 human lung epithelial cells determined that the treatment with extracts of *N. sativa* oil significantly suppressed PGE2, IL-2, and IL-6 in T-lymphocytes and PGE2 and IL-6 in monocytes [73]. Additionally, thymoquinone was found to reduce the production of COX-2, TNF-α, IL-6, and IL-1β significantly in LPS-stimulated RAW264.7 cells in an in vitro study using human monocyte-like U937 cells and LPS-stimulated murine macrophage-like RAW264.7 cells [74]. Furthermore, in an *in vitro* study using human osteoarthritis chondrocytes, thymoquinone was found to support dose-dependent suppression of IL-1β-induced NF-kB activation and IL-1β-induced generation of iNOS, NO, COX-2, PGE2, TNF-α, and IL-1β [75].

In an in vitro study using LPS-stimulated BV-2 murine microglial cells, thymoquinone was found to decrease pro-inflammatory cytokines like IL-6 and IL-12 [76]. Additionally, in an in vitro study using TNF-α-induced rheumatoid arthritis synovial fibroblasts, thymoquinone was found to reduce TNF-α-induced IL-6 and IL-8 production [77]. Additionally, in an in vitro study using LPS-stimulated BV2 microglial cells, thymoquinone was found to induce dose-dependent inhibition of LPS-induced generation of PGE2, NO, TNF-α, and IL-1β along with the inhibition of activation of NF-κB [78]. Furthermore, an in vitro study using rabbit chondrocytes demonstrated that thymoquinone treatment suppressed matrix metalloproteinases (MMP) including MMP-1, MMP-3, and MMP-13 [79].

Proposed mechanisms of anti-inflammatory activity of *N. sativa*

It is anticipated that *N. sativa* will have anti-inflammatory effects through a number of mechanisms (Figure 1), including reduction of pro-inflammatory mediators such as iNOS, COX-2, PGE2, and NF-kB levels [80, 81], inhibition of the MAPK, NF-κB, and Nrf2 pathways [82], inhibition of NOS enzyme and NO production, inhibition of the COX-2 enzyme and PGE2 production, degradation of interleukin-1 receptor-associated kinase 1, which lowers AP-1, and diminishes NF-κB and inflammatory gene expression [74].

Safety and effectiveness of use of *N. sativa*

Many *N. sativa* extracts, oil, and bioactive compounds are thought to have a broad margin of safety. It was discovered that the median lethal dose (LD50) of *N. sativa* fixed oil given orally to mice was 28.8 mL/kg body weight. However, it was discovered that the LD50 of intraperitoneal *N. sativa* fixed oil was 2.06 mL/kg of mice's body weight [83]. Furthermore, in male Swiss albino mice, the LD50 of intraperitoneal *N. sativa*'s aqueous extract, volatile oil, and fixed oil were determined to be 3020 mg/kg, 1853 mg/kg, and 3371 mg/kg respectively [84]. Additionally, no mortality was observed in mice treated with a single oral administration of 14, 9, and 21 g/kg of methanol, aqueous, and chloroform extracts of *N. sativa* [85]. Similarly, zero mortality was observed in Wistar rats and albino mice following administration of 0.2, 0.4, 0.6, 0.8, and 1.0 mg/kg of *N. sativa*oil [86].

Oral administration of 6 g/kg of chloroform, methanol, and aqueous extracts of *N. sativa* daily for 14 consecutive days did not alter plasma concentrations of alkaline phosphatase, ALT, and AST in the subacute toxicity study of *N. sativa* [85]. Additionally, *N. sativa*'s subchronic toxicity study revealed that oral administration of higher doses (20 and 100 g/kg) of powdered *N. sativa* seeds in Hibro broiler chicks for seven weeks ensued in elevation of AST and ALT levels [87]. Furthermore, a 12-week oral administration of 2 mL/kg of *N. sativa* fixed oil to rats did not alter AST and ALT levels, and histopathological changes in liver, heart, pancreas, and kidneys according to a chronic toxicity study of the plant [83].

Variety of ailments have been treated using *N. sativa* for many decades in different traditional medical systems, such as Siddha, Ayurveda, and Unani. Several human studies have shown that *N. sativa* is effective in the management of diabetes [88], hypertension [89], dyslipidemia [90], obesity and overweight people [91], and other chronic conditions.

Conclusion

Various clinical, in vitro, and in vivo investigations established the potentials of *N. sativa* against inflammation. The anti-inflammatory properties of *N. sativa* may be attributed to their ability to decrease pro-inflammatory cytokine levels (IFN-γ, TNF-α, IL-6, IL-1β, IL-2, IL-8, IL-12), reduction of pro-inflammatory mediators (COX-2, PGE2, NF-kB, and iNOS), inhibition of MAPK pathway, Nrf2 pathway and NF-kB pathway, inhibition of iNOS and the production of NO, and degradation of IL-1 receptor-associated kinase 1 interleukin-1 receptor-associated kinase 1, which lowers NF-kB, AP-1 and

inflammatory gene expression.

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