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Bioactive Constituents of Nigella sativa: Dual Regulation of Oxidative Stress and Inflammatory Responses

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Abstract:

Nigella sativa (black seed) is a medicinal herb recognized for its diverse pharmacological properties, primarily attributed to thymoquinone and related bioactive. Chronic diseases such as cardiovascular disorders, diabetes, neurodegeneration, and cancer share underlying mechanisms of oxidative stress and inflammation. This review critically examines the phytochemical composition of *N. sativa* and highlights its dual role in regulating oxidative stress and inflammatory responses. The antioxidant actions include free radical scavenging, enhancement of enzymatic defense systems, lipid peroxidation inhibition, and mitochondrial protection via Nrf2 activation. Anti-inflammatory effects involve suppression of NF-κB, MAPK, and JAK/STAT pathways, modulation of cytokine release, and inhibition of COX/LOX-derived eicosanoids. The synergistic interplay of these mechanisms positions *N. sativa* as a promising therapeutic candidate across a spectrum of oxidative-inflammatory disorders. Preclinical and clinical studies substantiate its efficacy, yet challenges remain regarding standardization, bioavailability, and long-term safety. Future translational research integrating multi-omics approaches may establish *N. sativa* as a viable adjunct in personalized medicine.

Keywords: *Nigella sativa*, thymoquinone, oxidative stress, inflammation, NF-κB, Nrf2, phytochemistry

1. Introduction

Chronic diseases are the leading cause of global mortality, accounting for nearly 71% of deaths worldwide (WHO, 2020). Among the underlying mechanisms, oxidative stress and inflammation play pivotal roles. Oxidative stress arises from an imbalance between the production of reactive oxygen/nitrogen species (ROS/RNS) and the body's antioxidant defense systems [1]. Persistent oxidative damage contributes to DNA mutations, lipid peroxidation, and protein dysfunction, thereby fueling pathological processes. In parallel, chronic inflammation mediated by cytokines, prostaglandins, and immune cell infiltration—drives tissue damage and fibrosis [2]. Together, oxidative stress and inflammation establish a vicious cycle, exacerbating conditions such as cardiovascular disease, diabetes, neurodegeneration, arthritis, and cancer.

A. Global burden of oxidative stress and inflammation

Cardiovascular disorders, including atherosclerosis and myocardial infarction, are linked to ROS-induced endothelial dysfunction and inflammatory cytokine release. Similarly, diabetes mellitus is characterized by oxidative pancreatic β-cell damage and chronic low-grade inflammation, resulting in insulin resistance. Neurodegenerative conditions such as Alzheimer's and Parkinson's disease are associated with mitochondrial ROS production and microglial activation [3]. This underscores the urgent need for therapeutic agents that target both oxidative and inflammatory pathways.

B. Ethnopharmacological relevance of *Nigella sativa*

Nigella sativa (Ranunculaceae), known as black seed or kalonji, has been revered for its medicinal value for over 2,000 years. Traditional systems such

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as Unani, Ayurveda, and Arabic medicine describe its use in respiratory ailments, digestive disturbances, and inflammatory disorders [4]. The Prophet Muhammad reportedly referred to it as "a cure for every disease except death," highlighting its cultural and spiritual significance. The seeds and their oil remain integral in Middle Eastern and South Asian ethnomedicine, often consumed as tonics or applied topically.

C. Rationale for exploring antioxidant and anti-inflammatory properties

Modern pharmacological research has validated traditional claims, identifying *N. sativa*'s diverse bioactive constituents with potent antioxidant and anti-inflammatory properties. Central among these is thymoquinone (TQ), a monoterpene quinone with free radical scavenging ability and regulatory effects on transcription factors like NF-κB and Nrf2 [5]. Other compounds such as nigellone, alkaloids, flavonoids, and saponins contribute synergistically to pharmacological activity. Given the overlapping pathophysiology of oxidative stress and inflammation in chronic disease, understanding how *N. sativa* modulates these processes has substantial therapeutic implications.[4]

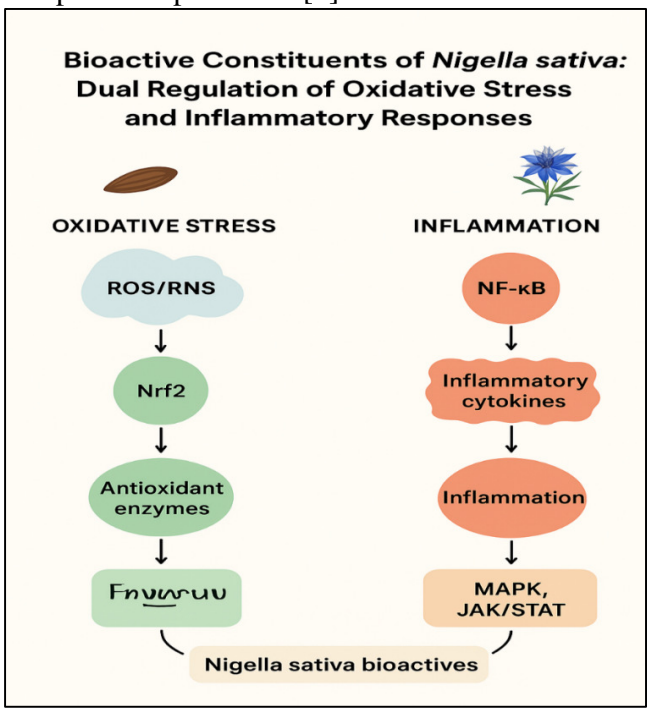

Figure 1. Graphical abstract showing mechanisms of *Nigella sativa* bioactives in modulating oxidative and inflammatory pathways.

Figure 1 illustrates the dual mechanisms through which bioactive constituents of *Nigella sativa*, particularly thymoquinone, nigellone, flavonoids, and saponins, regulate oxidative stress and inflammation. On the oxidative stress side, reactive oxygen and nitrogen species (ROS/RNS) generated during cellular metabolism or pathological conditions activate the Nrf2 pathway. Bioactive from *N. sativa* promote Nrf2 translocation into the nucleus, where it enhances the expression of antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), and heme oxygenase-1 (HO-1). This results in reduced oxidative damage, inhibition of lipid peroxidation, and protection of mitochondrial function. On the inflammation side, *N. sativa* suppresses the activation of nuclear factor kappa B (NF-κB), a key transcription factor in inflammatory responses. This leads to downregulation of pro-inflammatory cytokines like TNF-α, IL-1β, and IL-6, alongside upregulation of the anti-inflammatory cytokine IL-10. Additionally, modulation of MAPK and JAK/STAT pathways further suppresses inflammatory mediator synthesis, including prostaglandins and nitric oxide. Collectively, these actions demonstrate how *N. sativa* bioactive enhance antioxidant defenses while simultaneously inhibiting inflammatory cascades, thereby breaking the vicious cycle where oxidative stress and inflammation reinforce one another.[6]

2. Phytochemical Profile of *Nigella sativa*

The seeds of *N. sativa* contain more than 100 bioactive compounds.

Major constituents

- **Thymoquinone (TQ):** The principal bioactive molecule, accounting for 30–48% of volatile oil.
- **Nigellone:** Exhibits bronchodilator and antioxidant effects.
- **Alkaloids:** Nigellidine, nigellicine, and isoquinoline derivatives with immune-modulatory actions.
- **Flavonoids and phenolics:** Provide radical scavenging and metal chelation.
- **Saponins (α-hederin):** Contribute cytotoxic and immunomodulatory activities.
- **Fatty acids:** Linoleic and oleic acid improve membrane stability and modulate lipid metabolism.

Extraction methods and analytical approaches

Extraction methods influence yield and composition:

- **Cold-pressing:** Preserves fixed oils but may yield less TQ.
- **Soxhlet extraction with ethanol/methanol:** Concentrates polar compounds.
- **Supercritical CO_2 extraction:** Yields high-purity volatile oils.

Analytical methods include HPLC, LC-MS/MS, GC-MS, and NMR spectroscopy for quantification and structural elucidation.

Structure–activity relationship (SAR)

Thymoquinone's quinone structure allows electron donation to neutralize radicals, while hydrophobicity ensures membrane integration. Structural modifications of TQ analogues aim to enhance solubility and potency.

Table 1. Major phytochemicals of *Nigella sativa*, their chemical structures, and pharmacological activities

Constituent/Class	Representative Compound	Simplified Structure Description*	Pharmacological Activities	References
Quinones (Volatile oil)	Thymoquinone (TQ)	Monoterpene benzoquinone with two keto groups on aromatic ring	Antioxidant (ROS scavenging, Nrf2 activation), anti-inflammatory (NF-κB inhibition), anticancer (apoptosis induction), hepatoprotective, neuroprotective	[4,5,7]
	Thymohydroquinone	Reduced form of TQ (hydroxyl groups replacing keto groups)	Potent antioxidant, antimicrobial, synergistic with TQ	[4]
	Nigellone (polymer of TQ)	Dimeric carbonyl quinone	Bronchodilator, anti-asthmatic, antioxidant	[4]
Alkaloids	Nigellidine	Indazole-type alkaloid	Analgesic, anti-inflammatory, immune-modulatory	[8]
	Nigellicine	Isoquinoline-type alkaloid	Antimicrobial, potential CNS effects	[4]
Flavonoids/Phenolics	Kaempferol, Quercetin derivatives	Polyphenolic C6–C3–C6 structures with hydroxyl substitutions	Radical scavenging, metal chelation, anti-inflammatory, anticancer	[4]
Saponins	α-Hederin	Triterpenoid saponin with sugar moiety	Cytotoxic (apoptosis induction), immunomodulatory, anticancer	[9]
Fixed oils (fatty acids)	Linoleic acid (C18:2), Oleic acid (C18:1), Palmitic acid (C16:0)	Long-chain fatty acids with unsaturated/saturated bonds	Anti-atherogenic, hypolipidemic, membrane stabilization, anti-inflammatory	[10]
Essential amino acids & minor compounds	Arginine, aspartic acid, sterols (β-sitosterol)	Amino acid residues, sterol skeleton	Nutritional support, cholesterol-lowering, antioxidant	[4]

3. Antioxidant Mechanisms of *Nigella sativa*

N. sativa combats oxidative stress via multiple pathways.

Free radical scavenging

TQ directly scavenges superoxide anion, hydroxyl radical, and peroxynitrite. Seed extracts show DPPH and ABTS radical scavenging activity comparable to vitamin C.

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Modulation of antioxidant enzymes

- Upregulation of SOD, CAT, GPx restores redox balance.
- Nrf2 activation: TQ disrupts Keap1 binding, enabling Nrf2 nuclear translocation, enhancing HO-1 and NAD(P)H quinone oxidoreductase 1 (NQO1) expression.

Lipid peroxidation inhibition

Animal studies demonstrate reduced MDA levels and improved glutathione redox status.

Mitochondrial protection

TQ preserves mitochondrial membrane potential and prevents ROS leakage, reducing apoptotic signaling.

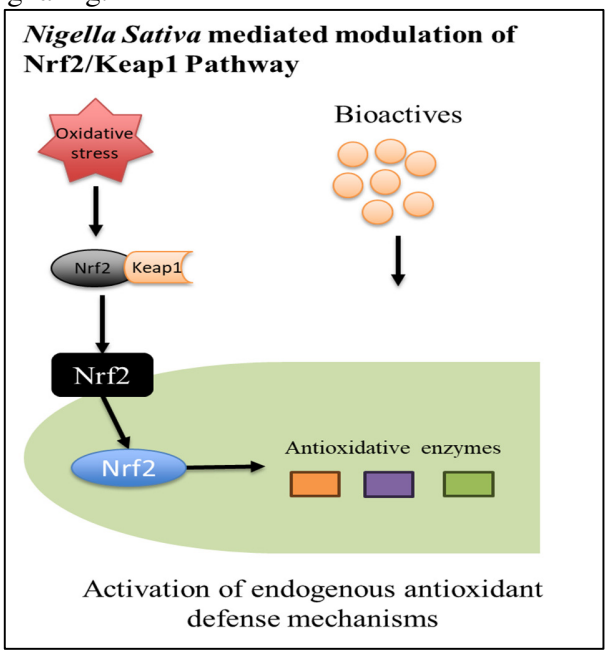

Figure 2. Schematic representation of *N. sativa*-mediated modulation of Nrf2/Keap1 pathway. Figure 2 depicts the modulation of the Nrf2/Keap1 signaling pathway by bioactive constituents of *Nigella sativa*. Under normal conditions, Nrf2 is bound to its cytoplasmic inhibitor Keap1, leading to its ubiquitination and proteasomal degradation. During oxidative stress, excessive reactive oxygen species disrupt the Nrf2–Keap1 complex, allowing Nrf2 to dissociate and translocate into the nucleus. Bioactive compounds of *N. sativa*, particularly thymoquinone, further enhance this dissociation by directly interacting with Keap1 cysteine residues and stabilizing Nrf2 activation. Once inside the nucleus, Nrf2 binds to antioxidant response elements (ARE) on DNA, promoting the transcription of phase II antioxidant and detoxifying enzymes such as heme oxygenase-1 (HO-1), superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), and NAD(P)H quinone oxidoreductase 1 (NQO1). This cascade amplifies the cell's endogenous defense system, counteracts oxidative injury, and restores redox homeostasis. Through this mechanism, *N. sativa* bioactive provide cytoprotection against oxidative stress–related tissue damage.

Table 2. Experimental evidence of antioxidant activity of *Nigella sativa* in in vitro and in vivo models

Model Type	Study/Experimental Design	Preparation/Compound Used	Key Findings on Antioxidant Activity	Reference
In vitro	DPPH, ABTS, FRAP assays (seed extract)	Ethanolic/methanolic seed extracts	Significant free radical scavenging comparable to ascorbic acid; dose-dependent activity	[4]
	Lipid peroxidation inhibition assay	Thymoquinone (TQ)	Inhibited Fe^{2+}-induced lipid peroxidation in rat liver microsomes	[11]
	DNA protection assay	Seed oil and TQ	Protected plasmid DNA from oxidative damage induced by H_2O_2	[12]
In vivo	CCl_4-induced	TQ and seed oil	Reduced malondialdehyde	[13]

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(rodent models)	hepatotoxicity in rats		(MDA) levels, restored SOD, CAT, and GPx activity	
	Streptozotocin (STZ)-induced diabetes in rats	Seed extract, TQ	Increased GSH, SOD, CAT; reduced lipid peroxidation and hyperglycemia	[14]
	Ischemia-reperfusion injury in rats	TQ pre-treatment	Preserved mitochondrial function, reduced oxidative stress markers	[15]
	Gentamicin-induced nephrotoxicity in rats	Nigella sativa oil	Attenuated oxidative damage, lowered MDA, restored antioxidant enzyme levels	[16]
	Cisplatin-induced cardiotoxicity in rats	TQ supplementation	Reduced oxidative stress, enhanced antioxidant defense enzymes	[17]
Ex vivo / Cell culture	Human lymphocyte oxidative stress model	TQ	Decreased ROS production, increased antioxidant enzyme activity	[18]

4. Anti-inflammatory Mechanisms of *Nigella sativa*

Regulation of NF-κB, MAPK, and JAK/STAT

TQ inhibits phosphorylation of IκB kinase, preventing NF-κB activation. It downregulates p38 MAPK and JAK/STAT pathways, reducing cytokine gene expression.

Cytokine modulation

TQ decreases TNF-α, IL-1β, IL-6, while increasing IL-10, balancing pro- and anti-inflammatory responses.

COX, LOX, and prostaglandin inhibition

Seed extracts inhibit COX-2 and 5-LOX, reducing PGE_2 and leukotrienes involved in inflammation and asthma.

Immunomodulatory perspectives

N. sativa enhances T-cell mediated immunity and modulates macrophage polarization from M1 (pro-inflammatory) to M2 (anti-inflammatory).

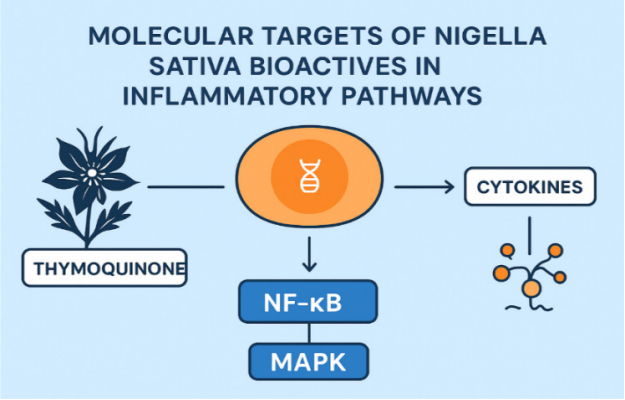

Figure 3. Molecular targets of *Nigella sativa* bioactives in inflammatory pathways.

Figure 3 illustrates the molecular targets of *Nigella sativa* bioactives, particularly thymoquinone, in modulating inflammatory pathways. Thymoquinone interferes with the activation of nuclear factor-kappa B (NF-κB), a central transcription factor that regulates the expression of pro-inflammatory genes. By preventing NF-κB nuclear translocation, *N. sativa* reduces the production of key cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-1

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beta (IL-1β), and interleukin-6 (IL-6). Additionally, thymoquinone modulates the mitogen-activated protein kinase (MAPK) pathway, thereby attenuating signal transduction that drives cytokine release and inflammatory mediator synthesis. This dual targeting of NF-κB and MAPK results in the downregulation of inflammatory cascades, decreased leukocyte recruitment, and restoration of immune balance. Consequently, *N. sativa* bioactives exert broad anti-inflammatory effects, offering therapeutic potential in conditions like arthritis, asthma, colitis, and autoimmune diseases where these pathways are dysregulated.

Table 3. Preclinical and clinical findings on anti-inflammatory activity of *Nigella sativa*

Model/Study Type	Experimental Design / Clinical Condition	Preparation/Compound Used	Key Anti-inflammatory Outcomes	Reference
Preclinical (in vivo)	Carrageenan-induced paw edema in rats	TQ, seed extract	Significant reduction in paw swelling; suppression of COX-2 and iNOS	[19]
	Freund's adjuvant-induced arthritis in rats	TQ	Decreased joint swelling, reduced TNF-α and IL-1β levels	[13]
	DSS-induced colitis in mice	TQ	Reduced colonic inflammation, decreased MPO activity and cytokine expression	[9]
	LPS-stimulated lung inflammation in mice	Nigella sativa oil	Lowered IL-6, TNF-α, reduced leukocyte infiltration in bronchoalveolar fluid	[20]
	Asthma model (ovalbumin-induced) in guinea pigs	Nigellone	Bronchodilator effect, decreased airway inflammation, lowered eosinophil counts	[21]
Cell culture (in vitro)	LPS-stimulated RAW 264.7 macrophages	TQ	Inhibited NF-κB activation; reduced IL-6, TNF-α, and NO production	[5]
	Human peripheral blood mononuclear cells (PBMCs)	Seed oil	Suppressed pro-inflammatory cytokines, enhanced IL-10 production	[22]
Clinical evidence	Rheumatoid arthritis patients (n=40)	*N. sativa* oil capsules (500 mg/day)	Reduced joint pain, morning stiffness, and serum TNF-α levels	[23]
	Allergic rhinitis patients (n=68)	*N. sativa* oil (daily oral dose for 4 weeks)	Significant reduction in nasal congestion, itching, sneezing; improved eosinophil counts	[24]
	Asthma patients (n=29, randomized	Seed oil supplementation	Improved pulmonary function (FEV_1),	[25]

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	trial)		decreased serum IgE and eosinophils	
	Metabolic syndrome (n=88)	*N. sativa* supplementation	Lowered CRP and IL-6 levels, improved antioxidant status	[26]

5. Interplay Between Oxidative Stress and Inflammation

Oxidative stress and inflammation reinforce each other: ROS activate NF-κB, which enhances cytokine expression, while cytokines stimulate immune cells to generate more ROS. *N. sativa* interrupts this cycle by simultaneously activating antioxidant defenses (via Nrf2) and suppressing inflammatory mediators (via NF-κB inhibition). This bidirectional regulation breaks the vicious cycle, explaining its broad pharmacological spectrum [27].

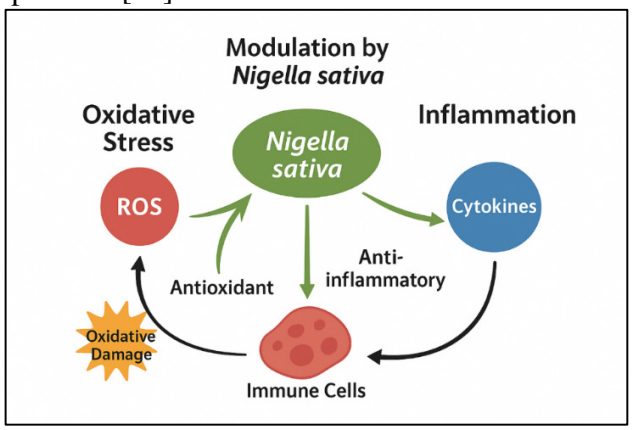

Figure 4. Oxidative stress–inflammation axis and modulation by *Nigella sativa.*

Figure 4 demonstrates the oxidative stress–inflammation axis and how *Nigella sativa* bioactive modulate this bidirectional relationship. Under pathological conditions, excessive reactive oxygen species (ROS) cause oxidative damage to cellular macromolecules, which activates immune cells and initiates inflammatory responses. Activated immune cells, in turn, release pro-inflammatory cytokines and generate additional ROS, thereby sustaining a vicious cycle of oxidative stress and inflammation. Bioactive compounds from *N. sativa*, particularly thymoquinone, interrupt this cycle through two complementary actions. First, they enhance antioxidant defenses by scavenging ROS and upregulating endogenous antioxidant enzymes, which minimizes oxidative damage. Second, they exert anti-inflammatory effects by suppressing cytokine release and inhibiting key inflammatory pathways such as NF-κB and MAPK. Through this dual regulation, *N. sativa* restores redox balance, attenuates chronic inflammation, and protects tissues from progressive oxidative–inflammatory injury.

6. Therapeutic Applications and Clinical Evidence

Neurodegenerative disorders

Animal studies show TQ reduces amyloid-β accumulation and dopaminergic neuron loss. Small clinical trials suggest cognitive benefits in elderly subjects.

Cardiovascular and metabolic diseases

TQ lowers LDL, triglycerides, and improves endothelial function. Trials in diabetic patients demonstrate improved glycemic control and antioxidant status.

Respiratory and gastrointestinal conditions

Nigellone exhibits bronchodilator activity in asthma. Seed oil reduces gastric ulceration through antioxidant protection.

Autoimmune and inflammatory diseases

Animal models of rheumatoid arthritis and colitis show reduced inflammatory scores.

Clinical evidence

Meta-analyses report significant reductions in fasting glucose, HbA1c, and CRP levels in patients supplemented with *N. sativa.* However, studies are limited by small cohorts and variability in formulations.

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Table 4. Clinical studies on *Nigella sativa* and therapeutic outcomes

Clinical Condition / Population	Study Design / Sample Size	Preparation / Dose	Therapeutic Outcomes	Reference
Type 2 Diabetes Mellitus	Randomized controlled trial, n=94	*N. sativa* seed powder, 2 g/day for 12 weeks	Improved fasting glucose, HbA1c, lipid profile, and antioxidant markers	[28]
Metabolic Syndrome	Double-blind RCT, n=88	*N. sativa* oil capsules, 3 g/day for 8 weeks	Reduced CRP and IL-6; improved HDL and insulin sensitivity	[26]
Hypertension	Open-label clinical trial, n=70	*N. sativa* oil, 2.5 mL twice daily for 8 weeks	Significant reduction in systolic and diastolic blood pressure	[29]
Asthma	Randomized trial, n=29	*N. sativa* oil capsules, 500 mg twice daily for 4 weeks	Improved pulmonary function (FEV_1, PEF), decreased serum IgE and eosinophils	[25]
Allergic Rhinitis	Clinical trial, n=68	*N. sativa* oil, daily oral dose for 4 weeks	Reduction in nasal congestion, sneezing, itching, improved quality of life	[24]
Rheumatoid Arthritis	Randomized controlled trial, n=40	*N. sativa* oil capsules, 500 mg/day for 8 weeks	Decreased disease activity score (DAS-28), reduced TNF-α and CRP	[23]
Obesity	Clinical trial, n=90	*N. sativa* oil, 2 g/day for 12 weeks	Reduced body weight, waist circumference, BMI, and appetite scores	[30]
Dyslipidemia	Randomized placebo-controlled trial, n=72	*N. sativa* seed powder, 2 g/day for 6 weeks	Lowered total cholesterol, LDL, triglycerides; raised HDL	[31]
Children with Epilepsy (drug-resistant)	Pilot study, n=22	*N. sativa* oil, 40 mg/kg/day	Reduced seizure frequency in partial cases	[32]
COVID-19 (adjunct therapy)	RCT, n=313	*N. sativa* oil + honey for 13 days	Faster symptom recovery, reduced viral clearance time	[33]

7. Limitations, Challenges, and Future Directions

- **Variability in phytochemical composition:** Cultivar, geography, and extraction methods affect bioactive content.[5]
- **Bioavailability issues:** Poor aqueous solubility and rapid metabolism of TQ limit clinical translation.
- **Pharmacokinetics:** Short half-life necessitates novel delivery systems (nanoformulations, liposomes).[34]
- **Standardization:** Lack of uniform dosage hampers reproducibility across trials.
- **Future approaches:** Multi-omics integration (genomics, proteomics, metabolomics) could identify biomarkers of response. Personalized medicine approaches may optimize therapeutic use.

8. Conclusion

Nigella sativa represents a promising medicinal plant with dual antioxidant and anti-inflammatory properties. Its bioactive constituents, particularly thymoquinone, modulate redox balance and

inflammatory signaling via Nrf2 activation and NF-κB inhibition. Evidence from preclinical studies is robust, while clinical trials demonstrate modest benefits in metabolic, cardiovascular, and inflammatory diseases. Nevertheless, challenges of standardization, bioavailability, and long-term safety remain. Future research must employ well-designed randomized controlled trials, standardized extracts, and advanced delivery systems. Integrating pharmacogenomics and systems biology may further clarify its role in precision medicine. Ultimately, *N. sativa* offers therapeutic potential as an adjunctive agent in chronic diseases driven by oxidative stress and inflammation, bridging the gap between ethnomedicine and modern pharmacology.

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