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Black cumin (*Nigella sativa* L.), from traditional medicine to modern therapeutics: A comprehensive review

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Abstract

Nigella sativa or black cumin has a long history of use in traditional medicine in various cultures across the globe more particularly in India, Egypt and Turkey. Numerous studies have demonstrated its therapeutic efficacy against a wide range of chronic ailments such as neurological and mental disorders, diabetes, cardiovascular disease, cancer, inflammatory disorders, allergies and various infectious diseases. Its significant antioxidant qualities also make it a possible dietary supplement. While limited research has been conducted on *N. sativa* yet studies suggest its effects on COVID-19 and HIV/AIDS. The results suggested that this plant may be used as an alternate therapy for the same. However, further research is required to confirm its medicinal potential. These studies might improve the way *N. sativa* is used to treat a variety of illnesses and explore some of its undiscovered properties. This review offers a detailed analysis of the medicinal applications of black cumin (*N. sativa*) oilseeds along with potential anti-diabetic, anti-inflammatory, antioxidant, and anti-cancer pathways.

Key words : AIDS, COVID-19, HIV,*N. sativa*, Therapeutic, Thymoquinone.

Black cumin (*Nigella sativa* L.), commonly known as black seed, is native to the Mediterranean region[38]. Due to its medicinal and culinary properties it has been cultivated globally[102]. Egypt, India, and Turkey are the highest producers of *N. sativa* however; India ranks the second-largest significant black cumin producer with an estimated 20,000 tons of annual production[8,72]. In many regions of India, particularly the states of Gujarat,

Rajasthan, and Uttar Pradesh, *N. sativa* is extensively grown along with other places like Kashmir, Punjab and Haryana[93,112]. *Kalonji, Kalojeera,* and *Mangraila* are some of the local names of *N. sativa* widely used in India[131]. *N. sativa* may grow well in these areas due to the climatic and soil characteristics and it is frequently produced as a secondary crop in a rotation with other plants including wheat, maize, and sugarcane[114]. Due to the unfavorable climatic and soil characteristics of Northeast India, *N. sativa* is not commonly grown here, as it requires a hot and dry climate with well-drained soil[43,44]. To boost revenue, some farmers in the area have started growing *N. sativa* as an alternative crop using drip irrigation and other modern techniques[20]. In some parts of Assam, especially in the Barak Valley, *N. sativa* is grown in modest amounts[115]. In Manipur it is known as "ngari" and is a common spice in regional dishes[117]. In Nagaland, *N. sativa* is not commonly grown, however the seeds are occasionally used in traditional medicine and similarly in Arunachal Pradesh, and it is not widely cultivated[113].

It is known for its possible health advantage due to the abundance of various bioactive compounds (Table-1). For medicinal purpose the most frequently used plant parts are leaves, roots, flowers and seeds, the seed oil[9]. Oil of *N. sativa* contains several important components like thymoquinone, thymol, nigellone, carvacrol and alpha-pinene which contribute to its potential health benefits such as antioxidant, boosting immune response, anti-inflammatory, anti-cancer, anti-diabetic, antiviral, antifungal, anti-parasitic and antibacterial properties[12,58,77] (Figure 1). Due to their multiple health advantages, these seeds have been utilized for centuries in traditional medicine[28]. *N. sativa* has attracted interest in recent years for its medicinal properties and various researches have been carried out to investigate its possible therapeutic applications. In a study researchers discovered that *N. sativa* oil could boost the activity of natural killer cells which concluded that *N. sativa* can be used as a medication for immunological disorders and infectious diseases[4,34]. Its application on animal body revealed enhanced sensitivity to insulin as well as reduces blood glucose levels. *N. sativa* has also been linked to lipid-lowering properties, which can aid in lowering blood cholesterol and triglyceride level[75,85].

The government and various non-government organizations have initiated many programs to promote the cultivation of *N. sativa* in the north eastern regions of India[90,92]. If its cultivation is promoted and developed further, the crop has the potentiality to become a new income source for farmers in the area. The production of *N. sativa* in North Eastern regions of India may be enhanced with proper planning and investment which will help the farmers consequently contributing to the economy of the states as a whole. Additionally, through promoting the use of natural treatments helping small-scale farmers and expanding access to wholesome foods, research on *N. sativa* can assist sustainable developmental goals.

In recent times, there has been a global rise in antimicrobial resistance in pathogenic microorganisms, posing an ever-increasing threat to public health[65,129]. This has necessitated the search for novel solutions, including those derived from natural products

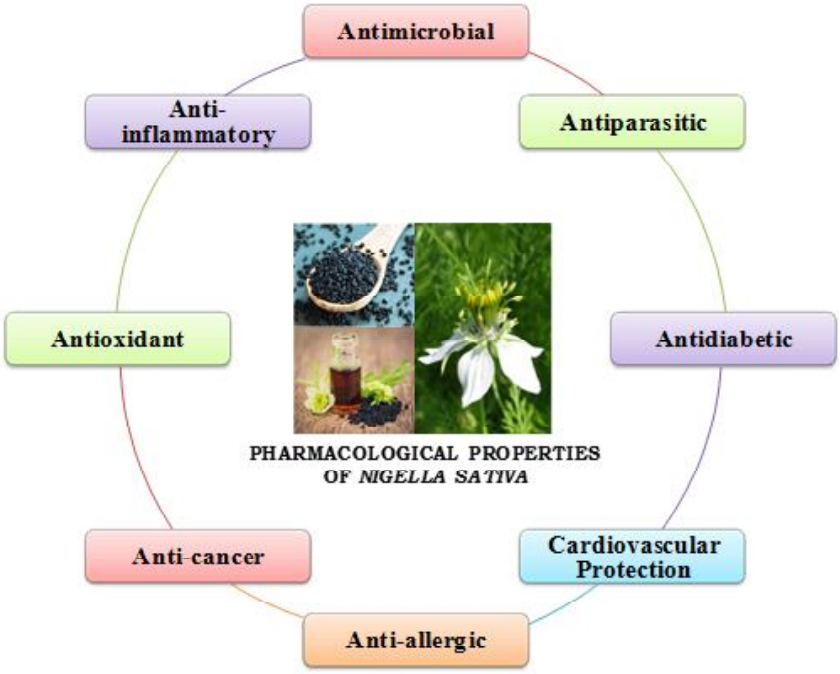
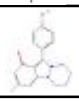
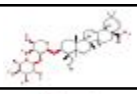
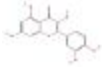
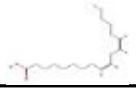
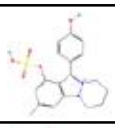
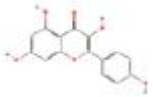
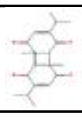
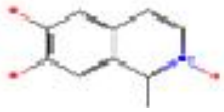


Figure 1. Various pharmacological properties of *Nigella sativa*

Table-1. Major compounds of *N. sativa*, types and their structures

Sl No.	Name of thecompound	Type	Structure	References
1	Thymoquinone	Terpene		Ali & Meitei[10]
2	Thymohydroquinone	Terpene		Sonmez *et al*.,[119]
3	Nigellidine	Alkaloid		Khan *et al*.,[59]
Pharmacological Properties				
4	α-Hederin	Terpene		Woo *et al*.,[133]
5	Quercetin	Flavonoid		Kaur *et al*.,[61]
6	Linoleicacid	Fattyacid		Khader & Eckl[57]

7	Nigellidine-4'-O-sulfite	Alkaloid		Khan *et al*.,[61]
8	Kaempferol	Flavonoid		Khattak *et al*.,[62]
9	Palmiticacid	Fattyacid		Balbaa *et al*.,[19]
10	Dithymoquinone	Terpene		Nickavar *et al*.,[79]
11	NigellimineN-oxide	Alkaloid		Liu *et al*.,[68]

Antimicrobial activity :

such as plants based on their traditional use in ethnomedicine[14,124]. *N. sativa* is a plant having medicinal attributes demonstrated potent antiviral, antibacterial, antifungal and antiparasitic properties making it a promising candidate for further exploration as a potential source of novel antimicrobial agents.

Antiviral Activity :

Recent scientific studies have investigated the antiviral properties of *N. sativa* as well as its bioactive components with promising results. Thymoquinone is one of the primary bioactive components and is believed to have antiviral activity against a range of viruses including hepatitis C virus, HIV and corona viruses such as MERS-CoV and SARS-CoV. This compound is thought to interfere with the replication and assembly of the viruses thereby inhibiting their growth and spread[7]. Human immunodeficiency virus (HIV) continues to pose a significant challenge to the public health worldwide, which can progress to acquire immunodeficiency syndrome (AIDS). The virus attacks CD4 cells and weakens the immune system and makes it challenging to recover from minor infections. Despite the absence of a preventive vaccine and fully effective treatments for the virus, recent studies have examined the potential of combining *N. sativa* and pure extracts of honey in treating HIV patients and these studies have reported various effects on HIV including lowering viral load and possibly increasing CD4 count[82,83]. In a study it was found that *N. sativa* seed extracts were able to suppress HIV replication in human T cells *in vitro*[60]. Similarly, a study found that a compound isolated from the seeds of *N. sativa* was able to suppress the activity of HIV-1 protease, an important enzyme for the replication of the virus[122]. The researchers

suggested that this compound may be a promising lead for developing new anti-HIV drugs. In addition to thymoquinone other bioactive compounds in *N. sativa*such as thymohydroquinone, dithymoquinone and thymol have also been found to have antiviral effects against various viruses and these compounds work by inhibiting different stages of the viral life cycle such as viral entry, replication and release[121].

With the recent emergence of COVID-19 antiviral properties of *N. sativa* have become one of the most hopeful areas of research. Studies have shown that extract from *N. sativa* can inhibit the replication of the SARS-CoV-2 virus, the causative agent of COVID- 19[108]. This is due to the occurrence of several bioactive components in *N. sativa* including thymoquinone that has potent antiviral activity. The emergence of COVID-19 has highlighted the need for effective treatments that can specifically target this virus. COVID-19 is known to cause an overreaction of the immune system, which can lead to a cytokine storm and severe inflammation. *N. sativa* may help to regulate the immune response and prevent excessive inflammation[107]. COVID-19 primarily affects the respiratory system, and *N. sativa* may help to alleviate symptoms such as coughing and shortness of breath. Inflammation is a key feature of COVID-19 and reducing inflammation may help to improve outcomes for individuals with the disease[64,70].

Computational docking studies have suggested that TQ may inhibit SARS-CoV-2 replication by disrupting viral binding to ACE-2 receptors. Consequently, it can block the virus from entering host cells and prevent its replication, establishing itself as a potent antiviral agent (Figure 2). This compound can be harnessed through the human cell-surface receptor HSPA5 and demonstrates efficacy in combating the virus particularly in high-risk patients thereby reducing the threat of SARS-CoV-2[21,36]. TQ's interaction with key residues at the interface can potentially inhibit host recognition offering a potential avenue for treating viral infections. Its antiviral activity is further underscored by its ability to regulate nitric oxide (NO) and reactive oxygen species (ROS) production[95,99,118]. Moreover, it mitigates cytokine storm-induced endothelial dysfunction and to inhibit viral infections thereby improving multiple organ dysfunction syndrome complications by restoring redox and immune balance[8]. This effect is probably influenced by a redox mechanism which could help reduce inflammatory responses and systemic oxidative stress. Moreover, TQ's interference with nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) activation known to contribute to oxidative stress induced by virus-activated phagocytes shows a significant role in immune cell activation and reducing inflammation safeguarding tissues and organs from damage[5,67,98].

Antibacterial Activity :

Thymoquinone showed extensive antibacterial activity against various strains of gram-positive and gram-negative bacteria such as *Listeria, Bacillus*, *Staphylococcus, Enterococcus*, *Micrococcus*, *Salmonella, Pseudomonas*, *Escherichia*, *Serovar*, and *Vibrio parahaemolyticus*[2]. The methyl alcoholic extract of the *N. sativa* seeds also

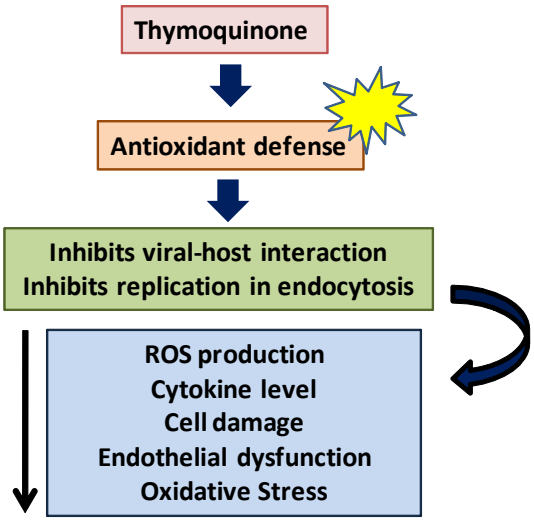


Figure 2. Antiviral pathway of thymoquinone, a constituent of *N. sativa*.

showed a greater inhibition zone on gram-positive bacteria over gram-negative bacteria[45,101]. Various concentrations of *N. sativa* oils showed a significantly higher zone of inhibition against different strains of methicillin-resistant *S. aureus*[74]. Thymoquinone also demonstrated substantial bactericidal activity against gram-positive *cocci* with a minimum biofilm inhibition concentration for both *S. epidermidis* and *S. aureus*[29]. The anti *Helicobacter pylori* effects of *N. sativa* were found to have notable clinical value, comparable to that of triple therapy making it a potential treatment option for *H. pylori*-induced gastric ulcers[105]. These studies provide a scientific basis for further exploration of *N. sativa* as a source of novel antimicrobial agents.

Antifungal Activity :

The essential oil derived from *N. sativa* has been found to demonstrate a moderate inhibitory effect against pathogenic strains of yeast, namely, dermatophytes and non-dermatophytic filamentous fungi which includes fungi that produce aflatoxin. This therapeutic approach focused on the different components of the fungal cell including the cell wall, plasma membrane and various membranous organelles primarily within the nuclei and mitochondria[111]. Additionally, *N. sativa* extracts have showed potent fungicidal activity against dermatophyte strains such as *Microsporum gypseum, Fusarium solani,Aspergillus niger* and *Trichophyton mentagrophytes* similar to Amphotericin-B which is effective against *Candida tropicalis*, *C. albicans* and *C. krusei*[11,71,86]. Moreover, the active compounds of *N. sativa* including Thymoquinone, thymol, and thymohydroquinone exhibited strong antifungal effects against various strains of clinically isolated fungi such as molds, dermatophytes and yeasts[120]. Hence, there is potential for utilizing *N. sativa* as a food additive and natural preservative to safeguard foods from spoilage due to its multiple antimicrobial activities.

Antiparasitic Activity :

Recent studies have shown that *N. sativa* seeds exhibit significant potential as an antiparasitic agent. *In vitro* experiments indicate that the seeds exhibit inhibitory effect against *Schistosoma mansoni* with a potent ability to eliminate various developmental stages of the parasite and hinder the egg-lying process in adult female worms[1,15,50]. Furthermore, a topical ointment containing the seeds of *N. sativa* effectively reduced inflammation caused by cutaneous leishmaniasis in mice[17]. In experiments involving mice infected with

Plasmodium yoelii it was observed that extract of *N. sativa* at adose of 1.25 g/kg lowered infection rates by 94% with higher efficacy in eliminating parasite and the ability to restore altered biochemical indicators compared to chloroquine[80]. Further investigation is necessary to fully evaluate the curative, prophylactic and chemo preventive potential of *N. sativa* as an anti-parasitic agent, particularly in light of emerging anti-malarial drug resistance.

Antidiabetic Activity :

N. sativa is also used as a remedy for diabetes. The activation of adenosine monophosphate kinase (AMPK) triggers the anti-diabetic properties of *N. sativa* affecting the cellular absorption of proteins known for their hypolipidemic and anti-diabetic properties[41,128]. Administering the volatile oil of *N. sativa* orally at a dose of 2 $mg \cdot kg^{-1}$. BW^{-1} showed a significant decrease in blood glucose levels in Balb/c mice[18]. The abdominal injection of *N. sativa* oil (50 $mg \cdot kg^{-1}$) resulted in a significant reduction in blood glucose levels for both fasting normal rabbits and alloxan-diabetic rabbits. *N. sativa* reduces blood glucose levels by an insulin-independent mechanism without changing basal insulin levels[24]. Additionally, the extract of *N. sativa* causes regeneration and relative growth of beta cells and reduces the generation of free radical in rats with streptozotocin-induced diabetes[23,91]. *N. sativa* oil and thymoquinone led to a notable reduction of malondialdehyde (MDA) and superoxide dismutase (SOD) levels in tissue and serum glucose levels along with an increase in serum insulin levels in rats, proving its potential clinical use in treating diabetes and protecting beta cells from oxidative stress[52] as illustrated in Figure 3. The MAPK signaling pathway appears to be involved during such conditions. Furthermore in a study conducted where rats were provided with a mixture of *N. sativa* powder and edible food, while thymoquinone was incorporated into their drinking water all administered for a period of 25 days. Analysis of hematological parameters revealed that both thymoquinone and *N. sativa* caused a significant reduction in blood sugar level in normal rats[3]. *N. sativa* regulates the activity of liver enzymes which are involved in glucose metabolism and reduce gluconeogenesis, inhibiting the function of glucose-6-phosphatase and fructose 1,6-bisphosphatase. Besides, it enhanced the glucose-6-phospate enzyme activity that is associated with the pentose phosphate pathway within cells[84,132]. The antioxidant, antimicrobial, cytotoxic, and anti-inflammatory activities of *N. sativa* may also contribute to the antidiabetic properties. The reduced level of HbA1c is particularly beneficial for preventing nephropathy, retinopathy, neuropathy and cardiovascular disease[48].

Cardiovascular Protective Activity :

N. sativa is also known for its potential in cardiovascular protective activities. Thymoquinone, a bioactive compound in *N. sativa* has anti-inflammatory and antioxidant properties that protect the heart and blood vessels from damage[109]. Several studies have examined the effects of *N. sativa* and its bioactive compounds on various aspects of cardiovascular health. These studies show that *N. sativa* increases HDL cholesterol and reduces total LDL cholesterol and triglycerides[7].

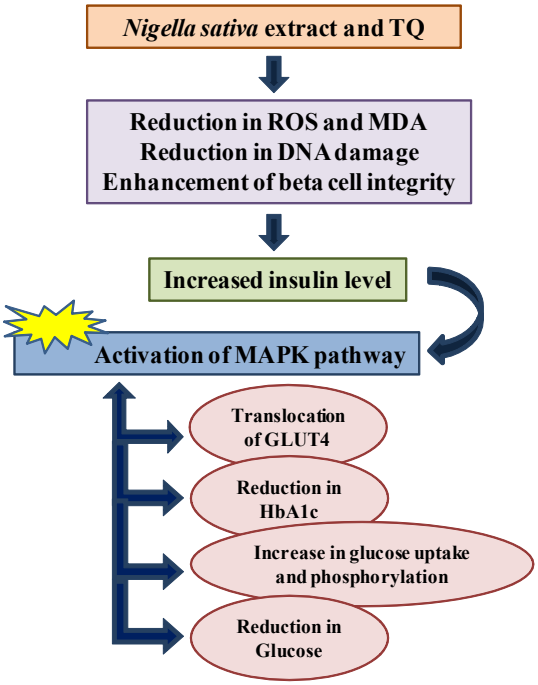


Figure 3. Anti-diabetic pathways of *N. sativa*

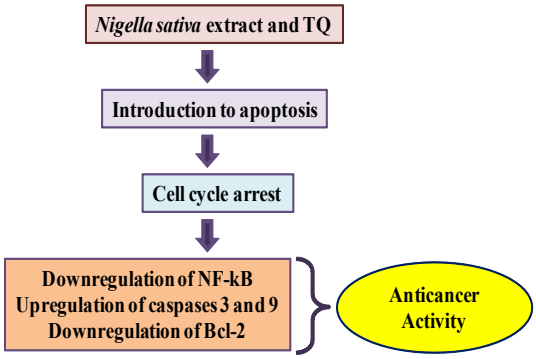


Figure 4. Anti-cancer pathway of *N. sativa*

Additionally, *N. sativa* has a significant effect on reducing both diastolic and systolic blood pressure[103]. Moreover, *N. sativa* increases antioxidants level and reduces markers associated with oxidative stress both of which are important factors in the development of cardiovascular diseases. According to these findings it can be suggested that *N. sativa* and its bioactive compounds may be beneficial for maintaining cardiovascular health. A study was conducted to examine the potential protective effects of *N. sativa* on vascular and cardiac activity in diabetic rats. The essential oil component of *N. sativa* reduced heart rate and blood pressure in a dose-dependent manner in anesthetized rats[13,89]. The study provides evidence for the possible therapeutic benefits of *N. sativa* in the management of cardiovascular complications associated with diabetes and hypertension.

Anti-allergic Activity :

Thymoquinone has been studied for its potential anti-allergic properties. Its ability to inhibit the production of chemokines and pro-inflammatory cytokines shows anti-inflammatory effects that help to reduce allergic responses[33]. Other compounds such as thymohydroquinone and dithymoquinone also have anti-inflammatory effects that may be beneficial for reducing allergic responses. *N. sativa* is also effective in reducing the symptoms of various allergic conditions such as rhinitis, asthma and atopic dermatitis. A study revealed the effects of *N. sativa* oil (NSO) on asthma symptoms in asthmatic

patients[26,104]. The results demonstrated that NSO notably improved lung function and reduced asthma symptoms suggesting that it has the potential to be a promising natural treatment for asthma. Another study examined the effects of *N. sativa* oil supplementation on oxidative stress and inflammatory markers among individuals diagnosed with rheumatoid arthritis. The results showed that NSO significantly reduced markers associated with oxidative stress and inflammation suggesting that it can have potential as a natural treatment for rheumatoid arthritis[76]. These findings highlight the traditional application of *N. sativa* for its therapeutic properties and suggested that it may be a promising natural treatment option for individuals with allergic diseases.

Anti-cancer Activity :

N. sativa has been utilized in traditional medicinal practices for its potential anti-cancer properties. Recent scientific studies have investigated thymoquinone for its potential anti-cancer benefits. The potential pathway for the anti-cancer activity of *N. sativa* involves the alteration of multiple molecular and cellular pathways (Figure 4). The active compound thymoquinone induces apoptosis in cancer cells via enhancement of pro-apoptotic Bcl-2 family proteins, lowering of anti-apoptotic Bcl-2 proteins and induction of caspases consequently inhibiting their proliferation making it effective against various cancer types such as lung cancer, prostate cancer, colon cancer, breast cancer and pancreatic cancer[51]. TQ induces cell cycle arrest by upregulating cyclin-dependent kinase inhibitors p16INK4A and p21WAF1/Cip1 leading to the arrest of G0/G1 phase cell cycle in wide range of cancer cells[133]. *N. sativa* extract and its active compound TQ have been reported to inhibit tumor angiogenesis by suppressing vascular endothelial growth factor (VEGF) production and expression. Additionally, they have also been reported to inhibit the signal transducer and activator of transcription 3 (STAT3) and nuclear factor kappa B (NF-κB), both of which are over expressed in many cancers and have been involved in cancer development and progression (Table-2).The inhibition of the NF-κB pathway results down regulation of various genes associated in cell cycle regulation, angiogenesis and inflammation. *N. sativa* induces autophagy in cancer cells, a process that results degradation of intracellular components to maintain cellular homeostasis. It sensitizes cancer cells to chemotherapy and radiotherapy leading to enhanced cancer cell death. Moreover, thymoquinone has antioxidant and anti-inflammatory propertieswhich can help against chronic inflammation and oxidative stress, both of which contribute to cancer development and progression[46,54].

Anti-oxidant Activity :

The *N. sativa* extract contains several antioxidant components such as thymoquinone, t- anethole, carvacrol, and 4-terpineol. TQ indirectly lowers the production of reactive oxygen species and inhibits lipid peroxidation. Injection of *N. sativa* oil or thymoquinone during the ischemia phase induces reperfusion enhancing the performance and elevating the level of superoxide dismutase and glutathione peroxidase in rats[110]. Thymoquinone enhances enzymatic (CAT, SOD, GST and GPX) and non-enzymatic (vitamin C and glutathione) antioxidant activities and reduces malondialdehyde levels in the mouse brain. Additional

constituents include 4-terpineol, carvacrol and quinone exhibit efficacy in linking free radicals together to facilitate their neutralization[22,97,127]. Presence of glycones and flavonol glycosides, which have higher antioxidant effects act as a detector of superoxide radicals in the bloodstream effectively neutralizing free radicals and inhibit the oxidative processes within cells[31,100]. Furthermore, the antioxidant activities of *N. sativa* seeds make it a potential compound for the treatment and prevention of cerebral ischemic and neurodegenerative diseases. The combined application of *N. sativa* and cisplatin in male rats has been found to improve oxidative stress in the testicles induced by cisplatin[123]. *N. sativa* and its derived compounds possess strong radical scavenging and oxidative stress inhibitory properties. Thymoquinone has a significant impact on adenosine deaminase (ADA), lipid peroxidase (LPO), catalase (CAT), myeloperoxidase (MPO), glutathione-S-transferase (GSH-ST), reduced glutathione (GSH), glutathione peroxidase (GPX), nitric oxide (NO) and superoxide dismutase (SOD) which helps to reduce oxidative stress. Additionally, thymoquinone was found to decrease the levels of conjugated diene (CGD), interferon-gamma (IFN-γ), tumor necrosis factor-alpha (TNF-α), malondialdehyde (MDA), prostaglandin (PGE2) and pro-inflammatory mediators interleukin (IL)-1-beta, IL-6 while increasing IL-10[6,37,96] (Figure 5).

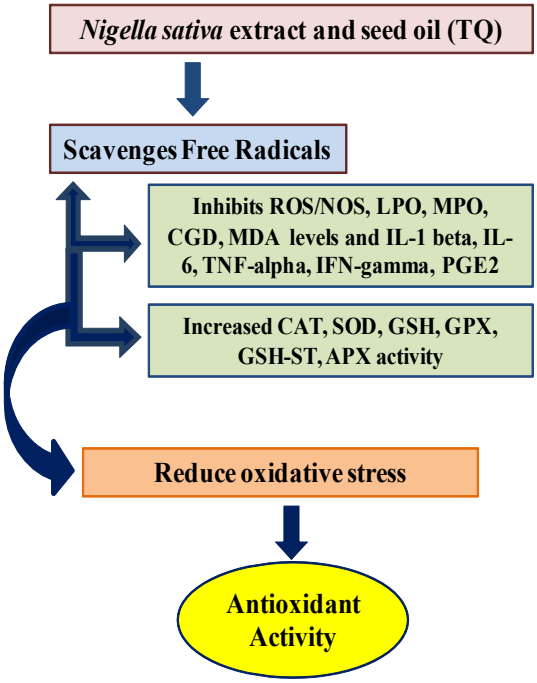


Figure 5. Anti-oxidant pathway of *N. sativa* and its constituents

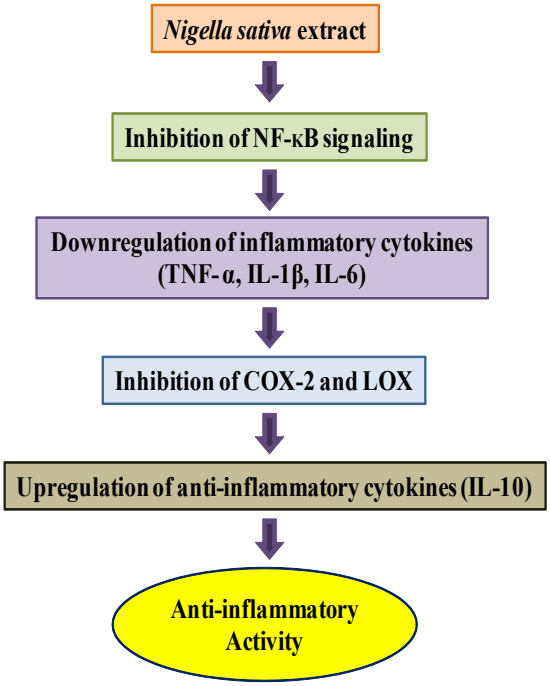


Figure 6. Anti-inflammatory pathways of *N. sativa* andits constituents

Anti-inflammatory Activity :

Thymohydroquinone, thymoquinone and thymol have potent anti-inflammatory effects. These compounds exhibit their functions by inhibiting the production of pro-inflammatory cytokines such as tumor necrosis factor-α, interleukin-6 and interleukin-1β which are responsible for promoting inflammation in the body[108] (Fig. 6.). *N. sativa* extract and thymoquinone have been reported to suppress the activity of inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2) that leads to reduced production of nitric oxide and prostaglandins respectively. Additionally, *N. sativa* upregulates the expression of antioxidant enzymes such as glutathione peroxidase (GPx) and superoxide dismutase (SOD) which protects from oxidative stress induced inflammation[37,42]. The fixed oil of *N. sativa* seed has been used in traditional medicine for the treatment of different inflammatory diseases. Recent studies have shown that *N. sativa* seed oil and its active component thymoquinone have anti-inflammatory effects. Administration of *N. sativa* seed extract has been shown to inhibit the production of 5-lipooxigenase in calcium ionophore-stimulated neutrophils which helps to reduce inflammation[42]. Numerous experimental models of inflammatory diseases such as peritonitis, colitis, arthritis, edema and encephalomyelitis have shown the anti-inflammatory effects of *N. sativa* seed oil and thymoquinone. TQ and *N. sativa* seed oil also inhibit nitric oxide production by glial cells and macrophages likely through the inhibition of iNOS[69,106]. Furthermore, TQ affects adenosine receptors suggesting that its anti-inflammatory properties might result from its interaction with these receptors[30]. In many medical conditions like cystic fibrosis, allergies, rheumatoid arthritis, asthma, osteoarthritis and cancer inflammation is a contributing factor. Current anti-inflammatory agents have severe adverse effects resulting from prolonged use[32,73]. Therefore, medicinal herbs such as *N. sativa* seed may offer a significant source of novel biological components with fewer side effects.

Table-2. Major genes and transcription factors associated with various signaling pathways of *N sativa* and their functions

Sl. No.	Gene/Transcription factor (s)	Function (s)	Reference (s)
1	MMP9 (Matrix Metallopeptidase 9)	Degrades extracellular matrix components, facilitating the clearance of microbial infections and tissue remodeling.	Lee & Kim[66]
2	IL1β (Interleukin 1 Beta)	Encodes IL-1β, a cytokine involved in the inflammatory response against microbial infections.	Rebe & Ghiringhelli[94]
3	IL6 (Interleukin 6)	Encodes IL-6, a cytokine that plays a role in the immune response to infections and inflammation.	Uciechowski & Dempke[126]

4	GLUT4 (Glucose Transporter Type 4)	Facilitates glucose uptake in muscle and adipose tissue, regulating blood sugar levels.	Wang *et al*.,[130]
5	AMPK (AMP-activated protein kinase)	Regulates energy balance and glucose metabolism.	Grahame Hardie[40]
6	TP53 (Tumor Protein p53)	Acts as a tumor suppressor by regulating cell cycle and promoting apoptosis in cancer cells.	Aubrey *et al*.,[16]
7	BAX (Bcl-2 Associated X Protein)	Promotes apoptosis, helping to eliminate cancerous cells.	Qian *et al*.,[88]
8	BCL2 (B-cell lymphoma 2)	Regulates cell death by inhibiting apoptosis, providing a survival advantage to cells.	Kapoor *et al*.,[53]
9	CASP3 (Caspase 3)	Encodes a protein involved in the execution-phase of cell apoptosis.	Boice & Bouchier-Hayes[25]
10	CASP8 (Caspase 8)	Involved in the initiation of apoptosis through death receptors.	Tummers & Green[125]
11	NOS3 (Nitric Oxide Synthase 3)	Produces nitric oxide, which helps in vasodilation and blood pressure regulation.	Oliveira-Paula *et al*.,[81]
12	ACE (Angiotensin-Converting Enzyme)	Regulates blood pressure by controlling the volume of fluids in the body.	Khurana & Goswami[63]
13	IL4 (Interleukin 4)	Encodes IL-4, a cytokine that promotes differentiation of naive helper T cells to Th2 cells, involved in allergic responses.	Keegan *et al*.,[56]
14	IL5 (Interleukin 5)	Encodes IL-5, a cytokine that stimulates the growth and differentiation of eosinophils, which are involved in allergic reactions.	Yanagibashi *et al*.,[134]
15	IL10 (Interleukin 10)	Encodes IL-10, an anti-inflammatory cytokine that helps suppress allergic reactions and inflammation.	Nagata & Nishiyama[78]
16	SOD1 (Superoxide Dismutase 1)	Encodes an enzyme that catalyzes the dismutation of superoxide radicals to oxygen and hydrogen	Eleutherio *et al*.,[35]

		peroxide, protecting cells from oxidative stress.	
17	GPX1 (Glutathione Peroxidase 1)	Reduces hydrogen peroxide to water, preventing oxidative damage.	Ighodaro & Akinloye[47]
18	NFkB1 (Nuclear Factor Kappa B Subunit 1)	Encodes a protein complex that controls the transcription of DNA, playing a crucial role in regulating immune response and inflammation.	Singh & Singh[116]
19	PTGS2 (Prostaglandin-Endoperoxide Synthase 2)	Involved in the synthesis of pro-inflammatory prostaglandins.	Jaén *et al.*,[49]
20	STAT3 (Signal Transducer and Activator of Transcription 3)	Mediates the expression of various genes in response to cytokines and growth factors.	Gao *et al.*,[39]
21	FOXO1 (Forkhead Box O1)	Transcription factor involved in regulating the expression of genes involved in apoptosis, cell cycle control, and oxidative stress response.	Yang *et al.*,[135]
22	TNF (Tumor Necrosis Factor)	Encodes a cytokine involved in systemic inflammation, stimulating the acute phase reaction.	Postal & Appenzeller[87]

Conclusion and Future Prospects :

N. sativa has been extensively used in traditional medicine for centuries. It has shown to have a potential herbal remedy for numerous conditions due to its wider safety margins and significant efficacy against a broad range of illnesses. However, the exact cellular and molecular mechanisms responsible for the antimicrobial effects of *N. sativa*, either alone or in combination with other drugs are not yet fully understood, indicating a research gap in this area. Further research is needed to evaluate the safety and efficacy of *N. sativa* as a phytomedicine and to isolate novel bioactive elements from both the plant itself and its oil. These studies could help to optimize the use of *N. sativa* in the treatment of several diseases and explore its unknown features. Therefore, *N. sativa* could be a significant agent for microbial diseases. Its composition as well as medicinal properties requires additional exploration on other valuable and undiscovered features. Clinical trials and studies using targeted clinical models are recommended to assess the medicinal benefits of *N. sativa* along with its isolated components.

Authors' contributions

MR conceived and designed the

research. All authors were involved in the survey. KS wrote the manuscript. SYJ, IAR and PKM reviewed the manuscript. All authors read and approved the manuscript.

Conflict of Interest

None.

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