Chapter 43

Nigella Sativa: A Natural Remedy for Sepsis Amelioration

Huma Qayyum[1], Aamina Jamil[2], Fatima Zahra Naqvi[3], Nawal Fatima[1], Muhammad Farhan Rahim[1], Syed Zain-Ul-Abideen Sherazi[1], Riaz Hussain Pasha[4], Muhammad Nadeem Shahzad[1], Adnan Hassan Tahir[1*] and Muhammad Arif Zafar[1*]

[1]Department of Clinical Studies, [2]Department of Veterinary Pathology, [4]Department of Veterinary Biomedical Sciences, Faculty of Veterinary and Animal Sciences, Pir Mehr Ali Shah-Arid Agriculture University, 46300, Rawalpindi-Pakistan
[3]Senior Veterinary Officer, Garden City Zoo, Bahria Town Phase-7, Rawalpindi-Pakistan
*Corresponding author: dr.mazafar@uaar.edu.pk and adnan.tahir@uaar.edu.pk

ABSTRACT

Current medicine always faces sepsis as one of the most threatening issues that requires unparalleled and unique treatment to enhance the chances of adequate patients' recovery. Originally known as Blacks seeds other name is *Nigella sativa* being used over a long time as medicinal plant due to the positive results in the treatment of many diseases including sepsis. In this chapter, the *Nigella sativa* has been described with regards to its biochemical and pharmacological Profile, its significance and the constituents participating in the alleviation of sepsis. Additionally, it also reviews the rising research publications in preclinical and clinical research outlining the anti-inflammatory, antioxidant and organ protective effects of *Nigella sativa* in sepsis. The other things discussed in the chapter include antibacterial properties, immunomodulating effects and what may be the additive action of *Nigella sativa* with conventional treatment. More studies should be done to determine black seed's benefits on sepsis where more intense research is required to prove its use as an adjuvant therapy.

KEYWORDS
Black seed, Immunomodulation, Amelioration, Thymoquinone, Sepsis

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INTRODUCTION

Popularly referred to as ''black cumin'' or ''black seed''.' *Nigella sativa* belongs to the Ranunculaceae family, is an annual herb that is found in Asia, North Africa, Europe and the Middle East among other regions (Dalli et al., 2022). It has been applied for centuries to cure different human and animal diseases in the numerous civilizations of the globe. Thus far, a multitude of studies have shown that *Nigella sativa* seeds and thymoquinone, the primary active ingredient, are highly effective medicinally against a wide range of illnesses, including but not limited to a variety of chronic conditions, inflammatory illnesses, cancer, diabetes, neurological and mental disorders, cardiovascular disorders, and infections caused by bacteria, fungi, parasites, and viruses (Yimer et al., 2019). It has proven efficacy in ameliorating sepsis. It is the saying of Holy Prophet Mohammed (peace be upon him), "*Nigella sativa* seeds treats all diseases and ailments excluding death" (Al-Bhukhaari, 5688). The scientist Ibn Sina, who wrote "The Canon of Medicine" and is better known in the West as Avicenna, gave advice on the use of *Nigella sativa*. It increases the body's energy and aids in the body's recovery from exhaustion and depression. More times than any other plant, NS is referenced in the Bible. It is used for both birth control and cancer cure. Pliny refers to it as Gith while Hippocrates and Dioscorides refer to it as Melanthion. According to Pedanius Dioscorides, NS seeds can be consumed and used medicinally to heal leprosy, eye disorders, toothaches, and for diuresis and repel snakes. The NS plant was used both internally to cure stomach issues and externally to alleviate bruising and swelling in Babylonia. It also functioned as a medicinal ingredient that protected against the venomous species' poisons and stings (Hossain et al., 2021). This chapter is focused to explore how *Nigella sativa* helps alleviating sepsis. So firstly, we are going to have a look at what sepsis is, and what is its pathophysiology.

Sepsis can be defined as a life-threatening condition which results when our immune system shows a dysregulated response against various infections. This dysregulation in response may lead to tissue and organ injuries and death. Though a considerable set of advances are evident in how to manage this condition but it is still a major healthcare problem globally (Esposito et al., 2017). We can also define sepsis as a severe systemic condition as a result of an increased inflammatory response to infections caused by microbes which usually results in high death rate (Alkharfy et al. 2018).

Sepsis is usually dealt in Intensive Care Units (ICUs), and the database of National Hospital Discharge Survey analyzed by Martin et al. shows that there was an annual increase in the incidence of sepsis of 8.7% between 1979 to 2000 in USA, which means every 83 to 240 people per 100,000 population gets sepsis. A recent review that attempted to quantify the global incidence of sepsis concluded that the total incidence rate is 288 for sepsis and 148 for severe sepsis per 100,000 person/years, even though epidemiological data are still lacking, particularly for low- and middle-income countries. In summary, throughout the past few decades, there has been a noticeable increase in the occurrence of sepsis syndromes (Esposito et al., 2017). Sepsis is thought to be the cause of about 5 million fatalities worldwide each year, accounting for over half of all hospital deaths in the United States (Alkharfy et al., 2018). Sepsis still claims the lives of up to 25% of people worldwide, despite the fact that general mortality rates seem to be declining (Jarczak et al., 2021). Keeping in view the statistics mentioned above, sepsis is a foremost challenge to deal with. Given how quickly sepsis can cause septic shock or a serious infection, prompt medical attention is necessary. Many of the components of plants have received less recognition and appreciation despite having been shown to have significant advantages. *Nigella sativa* seeds and their contents are not a fresh discovery, given the nature and significance of the seeds; rather, they have long been used in traditional nutritional and therapeutic purposes. Results show that these seeds have a wide range of uses, especially in the food and pharmaceutical sectors. Researchers have been attempting to offer a thorough comprehension of the historical and contemporary experimental many applications of *Nigella sativa* seeds (Msibi, 2023). The purpose of this chapter is to look over how *Nigella sativa* seeds have been used evolutionarily to treat sepsis.

Pathophysiology of Sepsis

Before going through the role of *Nigella sativa* in amelioration of sepsis, let us discuss its pathophysiology first. Despite all the experimental and clinical research conducted over the past three decades, there is still little that can be done to positively affect the course and outcome of sepsis. Prompt fluid resuscitation and early administration of broad-spectrum antibiotics are the only proven strategies to reduce death rates. A crucial factor is the time of the correct diagnosis and the initiation of the supportive, adjunctive, and causal therapy (Jarczak et al., 2021).

Depending on the strength of the host reaction, the pathophysiological mechanisms underlying sepsis may begin as protective and adaptive but eventually turn maladaptive and destructive (Arina & Singer 2021). However, a significant body of research on the molecular mechanisms of sepsis has demonstrated that the host and the infectious agent interact in a much more complex and nuanced way, which ultimately results in the numerous symptoms of sepsis (Gyawali et al., 2019).

Innate Immunity and Inflammatory Mediators

Sepsis is not a simple infectious process involving the immune defense systems as an inflammation-on/anti-inflammation off switch but is a complex dysregulation of the human immune response to infection. Both pro-inflammatory and anti-inflammatory messages are produced systematically in terms of cytokines and other mediators and pathogen-related collections that activate the complement and coagulant sequences. The first alarm is an identification of the pathogen-associated molecular patterns (PAMPs including endo- and exotoxins, lipids, or DNA fragments) or endogenous host-derived danger signals (damage-associated molecular patterns, DAMPs). It becomes apparent that these substances bind to certain receptors on the surface of such immune cells as APC's and monocytes, triggering the clinical picture of sepsis via the genes' transcription, which are implicated in inflammation, cell metabolism, and immune adaptation (Jarczak et al., 2021).

Even while pro- and anti-inflammatory pathways are both upregulated, the ensuing inflammation eventually results in gradual tissue damage that compromises multiple organs. In many patients, concurrent immunosuppression might result in "immunoparalysis" later in the illness course because of increased immune cell death, T cell fatigue, and downregulation of activating cell surface chemicals. This makes people more vulnerable to opportunistic infections, viral reactivation, and nosocomial infections. The process of signal transduction occurs when PAMPs and DAMPs bind to TLRs on APCs and monocytes. This results in the translocation of NF-κB, also referred to as nuclear factor-kappa light chain enhancer of activated B cells, into the cell nucleus. Among the "early activation genes" that are expressed as a result are tumor necrosis factor alpha (TNF-α), interferons (IFNs), and pro-inflammatory interleukins (IL) such IL-1, IL-12, IL-18, and others. These subsequently cause the downregulation of elements of the adaptive immune system because of negative feedback, as well as the activation of complement, coagulation, and other cytokines (including IFN-y, IL-6, and IL-8). The presence of these pathways is indicated by the upregulation of pro- and anti-inflammatory cytokines in the early stages of septic disease. The immunological phenotype (hypo- vs. hyper-responsiveness) is still highly individualized overall, which greatly complicates diagnosis (Jarczak et al., 2021).

Furthermore, some PRRs like the NOD-like receptor group can assemble into big protein structures called inflammasomes and they are involved in synthesis of caspases involved in apoptosis and cytokines like IL-1β and IL-18. The effects of proinflammatory cytokines include chemokine synthesis and endothelial adhesion protein expression, leukocyte activation, complement activation, tissue factor production, and stimulation of hepatic acute phase proteins. Sepsis increases the hitherto described immunological effect which comes with a 'collateral damage', accompanied by host cell/tissue demise (Gyawali et al., 2019).

Dysregulation of Hemostasis

Hemostasis and inflammatory pathways interact intricately in sepsis, with both cascades being active at the same time. Mild thrombocytopenia to severe disseminated intravascular coagulation (DIC) are examples of this interaction. Sepsis-related dysregulation of coagulation is caused by several causes. Hypercoagulability is brought on by the release of tissue factor, which is mostly produced by damaged endothelium cells. Tissue factor blocking reduces the amount of thrombin produced in response to inflammation, according to experimental models. Tissue hypoxia and organ dysfunction result from tissue factor's stimulation of the coagulation cascade, which in turn triggers the synthesis of thrombin, platelet activation, and microthrombi (Gyawali et al., 2019).

Moreover, sepsis inhibits the coagulation cascade's normal regulation by proteins C and antithrombin, which have anticoagulant properties. Low levels of protein S, downregulated thrombomodulin, and lowered plasma levels of protein C are all indicators of severe inflammation, including sepsis, and they all contribute to the uncontrollably proliferating coagulation cascade. Fibrinolysis is also inhibited by sepsis. Tissue plasminogen activators are released more often in response to elevated levels of TNFα and IL-1β. Persistently high levels of plasminogen activator inhibitor type 1 (PAI-1) mitigate this by reducing fibrinolysis and extending the duration of microvascular thrombosis (Gyawali et al., 2019).

Immunosuppression

At the commencement of sepsis, a proinflammatory state eases the way for a longer period of immunosuppression. This shift is characterized by a decrease in T cells due to apoptosis and a decreased sensitivity to inflammatory cytokines. When sepsis-related ICU patients are examined after they die, a significant loss of CD4+ and CD8+ T cells is seen, particularly in lymphoid organs like the spleen. Moreover, neutrophils in severe patients react to IL-8 by showing reduced chemokine receptor expression and chemotaxis (Gyawali et al., 2019).

These findings imply that sepsis patients' immunological responses to ensuing bacterial, viral, or fungal infections are impaired. Low lymphocyte counts, a sign of early lymphopenia around the fourth day following the diagnosis of sepsis, have been found to be a predictive biomarker for both short-term (28 days) and long-term (one year) mortality. This highlights how crucial it is to identify immunosuppression in order to improve patient outcomes when treating sepsis (Gyawali et al., 2019).

Function Impairment at Cellular, Tissue and Organ Level

Sepsis primarily results in tissue and organ failure due to hypoperfusion brought on by impaired circulatory function. Septic cardiomyopathy, which is brought on by mitochondrial malfunction and cytokine-mediated ventricular depression, affects between 18% and 60% of patients. Due to venous and arterial dilatation, this disease results in distributive shock, altered hemodynamics, and systolic and diastolic dysfunction. It is distinguished by reversible left ventricular dysfunction and an abrupt onset (Gyawali et al., 2019).

Endothelial dysfunction, which is defined by reduced barrier function, vasodilation, and a procoagulant state, has a significant impact on the pathophysiology of sepsis. Interstitial edema, acute renal damage, hepatic cholestasis, gastrointestinal mucosal permeability, and central nervous system dysfunction are the outcomes of this. In addition, muscle breakdown for amino acids to sustain immunological function and insulin resistance, which results in hyperglycemia, are signs of a catabolic condition brought on by sepsis. All of these complex changes add up to the morbidity and mortality that come with sepsis (Gyawali et al., 2019).

Bioactive Compounds in *Nigella sativa*

Every illness has a cure in the domain of plants. There were either very few or no synthetic medications available 250 years ago. Most of the world's population used to get their medications from these plants. The impoverished three-fourths of the world's population, or 75% of the total, still use these herbs and other traditional medical instruments. Novel medicinal molecules have been inspired by plants, as the health and well-being of people have benefited from plant-derived medicines. The World Health Organization (WHO) has proposed that the greatest source for a wide range of medications would be medicinal plants. The health of individuals and communities is deemed to be impacted by the usage of therapeutic plant-based medications, as they have few or no adverse effects. Based on estimates from the World Health Organization, traditional medicine provides primary medical treatment to 80% of people in developing countries. About 85% of these cases involve the use of plant extracts. This indicates that between 3.5 and 4 billion people worldwide get their medication from plants (Yessuf, 2015).

It is proven from studies that Black Cumin (*Nigella sativa*) has over 100 components, and the synergistic interaction between them promotes the immune system and are supportive to the body, better than any other single substance. It is a critical source of proteins, carbs, and other vitamins and minerals in addition to crucial fatty acids. The seeds are rich in sterols, particularly beta sitosterol, which is well-known for its anti-carcinogenic properties (Tabassum et al., 2018). *N. sativa* seeds have saponins, essential oils, alkaloids, fixed oils and proteins. As far as the unsaturated fatty acids portion is concerned, it has myristic acid, linoleic acid, arachidonic acid, palmitic acid, palmitoleic acid, eicosadienoic acid and stearic acid. It also has relatively a good amounts of Copper (Cu), Iron (Fe), Potassium (K), Phosphorus (P), Calcium (Ca), and Zinc (Zn) (Qayyum et al., 2020). Most of the black cumin is composed of non-volatile components such as flavonoids, phenolic acids, tannins, and a volatile fraction of terpene compounds. Many biological activities, particularly those connected to

antioxidants, anti-inflammatory, antihepatotoxic, analgesics, anti-tumor necrosis, immunostimulants, anti-ulcer, antimicrobial, and antiparasitic properties, are attributed to a number of bioactive compounds and extracts from the seeds, particularly the essential oil and its primary constituent thymoquinone (Dalli et al., 2022).

Volatile Compounds of *N. sativa*

Research analyzing the essential oil of *Nigella sativa* has identified several different molecules with different characteristics. They consist of ketone, sesquiterpenes, monoterpenoid alcohols, diterpenes, and monoterpenes. We list carvacrol, α-pinene, β-pinene, thymol, thymoquinone, thymohydroquinone, and thymol among them (Dalli et al., 2022). Many of these compounds possess pharmacological effects and have therapeutic potential in humans. A primary component of *N. sativa*, thymoquinone, has been shown by researchers to possess anti-inflammatory, antibacterial, and anticancer as well as asthma relieving properties (Kabir et al., 2020). Thymoquinone is the main active ingredient in the *N. sativa* seeds (Cheikh-Rouhou et al. 2007). It is the main ingredient of *Nigella sativa*'s volatile oil (Kabir et al., 2020). Among other tautomeric forms, this chemical is present in mixtures, the enol form, and the keto form. Thin layer chromatography (TLC) and high-performance liquid chromatography (HPLC) assays reveal that the pharmacological activities of thymoquinone are attributed to its keto form, which constitutes approximately 90% of the compound. Its effects on the heart, lungs, immune system, cytotoxicity, and inflammation have all been researched. In a research experiment, sepsis was induced in mice via lipopolysaccharide (LPS) and live E. Coli challenge. Then, they were given thymoquinone at the dose of 0.75-2mg/kg intra-peritoneally, which resulted in the reduced mortality up to 80-90%. By measuring the level of creatinine and ALT, it was also evident that thymoquinone resulted in protection of kidney and liver function, respectively. Serum creatinine, BUN, ALT, LDH, albumin, and CK elevations are indicative of induced sepsis, which damages and impairs the liver and kidney, among other organs. Thymoquinone therapy was shown to improve these indicators, supporting previous research that used animal models. Oxidative cellular damage can result from the prolonged generation of reactive oxygen species, such as superoxide anion and nitric oxide, during sepsis. At least in part, thymoquinone's protective benefits in sepsis can be ascribed to its antioxidant properties during the redox cycle between quinine (the keto form) and hydroquinone (the enol form) in biology. (Alkharfy et al., 2011). Thymohydroquinone isolated from the volatile oil of *Nigella sativa* was proved to have a high activity against gram positive organisms (Randhawa & Al-Ghamidi, 2002) .

Phenolic Acids and Flavonoids in *N. sativa*

Among the extracted phenolic compounds, gallic acid, ferulic acid, vanillic acid, p-coumaric acid, chlorogenic acid, catechin, quercetin, apigenin, flavone, nigelflavonoside B and rutin are worth mentioning. All these compounds inherit antioxidant properties which protect an organism against free radicals (Dalli et al., 2022). According to a phytochemical investigation, N. sativa has polyphenols in various sections of the plant. Vanillic acid was the main component in the mixture of phenolic acids, and phenolic acids were identified in the highest concentration (Cheikh-Rouhou et al., 2007; Topcagic et al. 2017). Topcagic et al. (2017) was the first to report the antibacterial effect of phenolic portion of *N. sativa* oil. There have been reports of a wide range of action against various bacteria by both the oil and the extract. Even at 1:1000 dilutions, the essential oil's in vitro antibacterial activities shown strong effectiveness against several species, including Vibrio cholera, Salmonella typhi, E. coli, and Staphylococcus albus. It was discovered that the oil exhibited outstanding antifungal action, especially against Aspergillus species (Tembhurne et al., 2014). Flavonoids mostly show antidiabetic activity (Parveen et al., 2020).

Alkaloids

Different *Nigella sativa* alkaloids were extracted and identified between 1985 and 1995. Examples are nigellimine, an isoquinoline molecule, nigellimine N-oxide, and nigellidine, an indazole molecule. nigellicine is made up of an indazole nucleus. Recently, a chemical known as magnoflorine has been discovered (Dalli et al., 2022). *N. sativa* and honey have synergistic antibacterial properties when treating P. aeruginosa infections. For bacterial infections, mouthwash containing chlorhexidine gluconate is used as a germicidal agent. Research has demonstrated that *N. sativa* oil extract is more effective than chlorhexidine gluconate in treating S. mutans infections and other common dental diseases (Ahmad et al. 2021). In one trial reported by Barakat et al. (2013), patients with hepatitis C virus were given 450 mg capsules of *N. sativa* oil three times a day for three months. Overall, there was a notable decrease in viral load, a notable improvement in oxidative stress, and notable increases in albumin, total protein, platelet, and red blood cell levels. The reduction in membrane lipid peroxidation and the likelihood of hemolysis are aided by the increase in RBC count (Ahmad et al. 2021). Nigellidine suppresses the development of viruses by binding to nucleocapsid and N-terminus protease (Hossain et al., 2021).

Saponins

The secondary metabolites of black cumin include saponins. Numerous saponins were found in NS in a study, however nigelloside, kaempferol 3-O-rutinoside, and flaccidoside are the most prevalent ones (Dalli et al., 2022). Thanks to medicinal plants and the compounds they produce, significant drugs like quinine, morphine, digoxin, and vincristine that treat life-threatening conditions like diabetes, cancer, coronary heart disease, HIV/AIDS, and neurological disorders have been developed for modern medicine (Parveen et al., 2020).

Fatty Acids

Through the GC MS analysis of the Qualitative Analysis of active constituents of *Nigella sativa*, it was realized that it contains several fatty acids. Thus, the analysis of the fatty acid composition of *NS* seeds showed that linoleic acid amounted to 55. 6% of the total fatty acids; oleic acid was 23. 4%; and palmitic acid comprised 12. 5%. Concentration of stearic acid, lauric acid (myristic acid), linolenic acids and eicosadienoic acids are labelled in trace quantities as they are between 0. 5% to 3. 4% (Dalli et al., 2022). Any disruption of this finely tuned concept of homeostasis whether through sepsis following an infection/trauma, or through more extreme inflammatory responses, often results in very dangerous consequences including organ failure, shock or death (Körner et al., 2018). The supplement value of *N. sativa* is attributed to the presence of several phytochemicals, nutritionally essential components, and polyunsaturated fatty acids (PUFA) which makes it possible to reverse sepsis (Hossain et al., 2021).

Biological Activities of *N. sativa*

The Immunomodulatory Effect

The properties like the splenocyte proliferation, macrophage function and NK anti-tumor activity make it clear that nigella seeds comprise of strong immunomodulatory compounds. Moreover, nigella oil has hepatoprotective activity against humoral immune responses, non-cellular immune responses and hypervitaminosis A. Immunomodulatory effect of *Nigella sativa* is mainly through head-on stimulation of phagocytic activity of macrophages, or via lymphocyte activation (Khan and Afzal, 2016).

Nigella sativa is a well know immune stimulant having a protective role against various pathological conditions. Nigella compounds like Thymoquinone and other terpenoid compounds like carvacrol, trans-anethole and 4-terpeneol have antioxidant properties. Carvacol inhibits neutrophil elastase enzyme and thus may prove a useful agent for phytotherapy of injuries like chronic obstructive pulmonary disease and emphysema (Khan and Afzal, 2016). In a study conducted to investigate the effects of *N. sativa* on immune system, it was proved that use of its seeds or oil improved helper T cell (T4) to suppressor ratio and also enhanced the activity of Natural Killer cell (Randhawa & Al-Ghamidi, 2002).

Anti-Microbial and Anti-Parasitic Actions

Since the latter part of the 20th century, antimicrobials have formed the cornerstone of clinical medicine and have prevented several cases of deadly microbial infections. However, it has been observed that antibiotic resistance in pathogenic bacteria has emerged and expanded globally in the late 20th and early 21st centuries. An international effort is required to find creative answers to the growing threat of microbial diseases and antibiotic-resistant bacteria. One potential source of these remedies could be natural goods like plants, which are chosen for their well-established ethnomedicinal uses. Black cumin (*N. sativa*) is one of the most inspiring medicinal plants; it exhibited potent antiviral, antibacterial, antifungal, and antiparasitic properties (Yimer et al., 2019).

In the study conducted by Hanafi and Hatem the anti-microbial effect of *N. sativa* Di-ethyl Ether Extract was looked into. It was also found out that the extract of the plant affected growth of both gram positive bacteria Staphylococcus aureus and gram-negative bacteria Pseudomonas aerogenosa and Escherichia coli through concentration. When used together with Gentamycin and Streptomycin, probability of synergism was found out; while in using it together with Spectinomycin, Erythromycin, Tobramycin, Doxycycline, Chloramphenicol, Nalidixic acid, Ampicillin, Lincomycin, and Co-Trimoxazole the chance of an additive was found out. In the same study, it was also identified that it had an inhibitory effect against Candida albicans, which is a pathogenic yeast and this effect was dose dependent. In prospective research, it has been shown that the extract of *N. sativa* has a favorable impact on multi-antibiotic resistance on organisms including both gram-positive and gram-negative bacteria (Randhawa & Al-Ghamidi, 2002).

In another study, mice with murine cytomegalovirus received intraperitoneal injection with *N. sativa* oil and the level of virus titer in the organs liver and spleen were found significantly lowered. This activity may have transpired due to higher recruitment of M and Phi numbers and functions, and also due to augmentation of IFN-γ production (Randhawa & Al-Ghamidi, 2002). The aqueous extract of *N. sativa* which was prepared by boiling of it seeds when used at the concentration of 100ug/L showed anti-microbial activity against both the gram-positive bacterial isolates such as Bacillus subtilis, S. aureus, Micrococcus luteus and the gram-negative bacterial isolates like Salmonella Setubal, Enterobacter aerogenes and Agrobacteria tumefaciens. A study that contrasted thymoquinone to the escorted counselling of microorganisms proved that the compound is oriented towards the inhibition of the escalation of distinguishable categories of bacteria. Experimenting with the formation of biofilm using different concentration of the same substance helped to know that the formation of the biofilm decreases. Besides, the compound studies shown here provided evidences that the chemical indeed compounded with the antibiotics and enhanced the effect in case of both gram-positive and gram-negative bacterial species. Thus, the n-butanol extract from the NS seeds LH demonstrated a very high antibacterial effectiveness against P. aeruginosa, K. pneumoniae, and A. baumannii, with the least inhibitory zones at 0. 25 to 1 µL/mL (Dalli et al., 2022).

The activities of thymoquinone isolated from seeds of *N. sativa* were found to be broader with most gram-negative and positive bacterial strains including Salmonella Serovar, Bacillus, Listeria, Enterococcus, Micrococcus, Staphylococcus, Pseudomonas and Vibrio parahaemolyticus. It not only inhibited bacterial biofilms, but also inhibited their growth a part from having potent anti-bacterial effect (Yimer et al., 2019).

El-Sayed et al., in their research work published in 2019 mentioned that out of all the parasites i.e., *Theileria equi*, *Babesia caballi*, *Babesia bigemina*, *Babesia divergens* and *Babesia bovis* are some of the parasites that are effectively inhibited by Thymoquinone in vitro. Interaction between Thymoquinone and the diminazen aceturate on the parasites Babesia and Theileria was very satisfactory. *Babesia microti* growth suppression was induced in mice by intraperitoneal injection of Thymoquinone at a dose of 50 and 70 mg/kg and by oral treatment (Dalli et al., 2022)

Antiviral Activity

Using female rats immunized against Candida albicans-thought to be the main cause of vulvovaginal candidiasis—the therapeutic potential of black cumin was validated in vivo. The results showed that after giving *NS* extract at a dose of 6.6 mL/kg, the number of fungal colonies dramatically dropped (Dalli et al., 2022).

Antioxidant Activity

Oxidative stress and elevated amounts of free radicals are two of the most significant critical markers associated with numerous progressive pathological conditions, including cancer, aging, neurological disorders, and endocrine disorders. The utilization of therapeutic plants as natural antioxidants is growing in importance now. Among the many naturally occurring medicinal plants, *N. sativa* has been demonstrated to have strong antioxidant qualities in both in vitro as well as in vivo studies. Antioxidant measures improved dramatically in a study where Wistar rats received *N. sativa* and nanosized clinoptilolite separately (Yimer et al., 2019).

Anti-Inflammatory Properties

Thymoquinone, an important component of *N. sativa* oil, and its extracted form demonstrate their mode of action through a variety of mechanisms, including cytoprotective, immunomodulatory, antioxidant, and inflammatory mediator inhibitory actions. Thymoquinone activates lymphocytes, macrophages, mast cells, neutrophils, and eosinophils in cases of auto-immune and infectious disorders due to antigen exposure or host cell damage. The most crucial components of an immune response are an increase in T cell and Natural Killer Cell-mediated immunity, regulation of the CD4(+) and CD8(+) ratios, and improvement of the oxidant scavenger system (Alkharfy et al., 2011).

Conclusions and Future Perspectives

Given the overwhelming scientific information we got, it is evident that the claim by Prophet Muhammad (PBUH) over 1400 years ago that "*Nigella sativa* (Black seed) can cure all illnesses except death" is true and acceptable. Numerous studies conducted to date have demonstrated the remarkable natural therapy properties of black seed and its component thymoquinone for the treatment of a wide range of illnesses, including both infectious (bacterial, fungal, viral, and parasitic infections) as well as chronic noninfectious diseases (neurological disorders, diabetes, hypertension, dyslipidemia, inflammatory disorders, cancer, and so forth). This review chapter was meant for exploring the use of *Nigella sativa* for amelioration of sepsis. As mentioned above, it is evident that *Nigella sativa* seeds and oil have plenty of useful compounds including sterols, essential oils, phenolic acids, flavonoids, alkaloids, saponins and fatty acids. Keeping in view the chemical composition of *N. sativa* and its biological activity, we have seen that these compounds have immunomodulatory, antimicrobial, antiparasitic and antiviral effects. Immunomodulatory activity enhances the immune system's ability to tackle sepsis, while antimicrobial activity adds another layer of power for this purpose i.e. to fight sepsis. It is also clear that when used in combination with antibiotics, *N. sativa* either has synergistic or additive effect which is also a plus point for amelioration of sepsis. Keeping in view the above discussion, it is evident that *N. sativa* has a promising potential in ameliorating the sepsis given its ability to inhibit various gram positive and gram-negative bacteria as well as making positive changes for enhanced immune activity.

A limited literature is available on the use of *N. sativa* for amelioration of sepsis and more research needs to be conducted to have a clear understanding of its role in controlling the sepsis so that it may be used as a complementary medicine to tackle this condition. Moreover, it may also prove a great support in decreasing the dose of antibiotics and help control the antibiotic resistance development.

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