Chapter 41

Nigella sativa: A Promising Alternative to Antimicrobials

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ABSTRACT

The *Nigella sativa*, also referred to as black seed, has long been utilized for medical purposes. *Nigella sativa* is a promising alternative to antibiotics due to the rising incidence of antibiotic-resistant illnesses. In exploring *Nigella sativa*'s nutritive and chemical profiles, this chapter highlights the plant's many medicinal uses, such as its antibacterial, antiviral, antifungal, and antiparasitic properties. Important active ingredients with strong antibacterial activity against a range of diseases include thymoquinone. The effects of *Nigella sativa* are discussed, including how it inhibits microbial development and interferes with microbial defense mechanisms. The study also examines the safety guidelines for using *Nigella sativa* and how it might develop as a complementary therapy, providing a viable natural defense against antibiotic resistance.

KEYWORDS		
Thymoquinone, Anti-inflammatory, Antimicrobial resistance, , Black seed, Therapy	Received: 25-Jun-2024 Revised: 12-Jul-2024 Accepted: 29-Aug-2024	A Publication of Unique Scientific Publishers

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INTRODUCTION

The kingdom of plants, apart from supplying oxygen necessary for life and preserving environmental equilibrium, is also vital to human and animal nutrition and an indispensable source of contemporary pharmaceuticals. Diets composed of plants fulfill the body's fundamental nutritional needs, maintain bodily health, and strengthen the immune system to fight off an array of diseases. Because there is a direct correlation between a healthy diet and an average life expectancy, the terms, nutraceuticals, and functional foods have gained popularity in recent decades among those who are health-conscious (Qadir and Raja, 2021). Spices and herbs, which are usually employed as flavoring additives and preservatives, are minor but essential components that include an extensive number of bio-functional molecules among the range of functional food elements. Due to their great potential for supporting health, most of these culinary herbs and spices are also widely recognized for their pharmaceutical properties. The increasing prevalence of bacterial infections and the growing threat of antibiotic resistance in most parts of the world have drawn the attention of physicians, dietitians, nutritionists, food scientists, and the food and pharmaceutical industries to these alternatives in recent times (Msomi and Simelane, 2019).

One of the top ten most dangerous diseases in the world is Infectious disease, and the threat of increasing antimicrobial resistance (AMR) has made most conventional medications less effective including most clinical antibiotics. Antibiotic overuse drives up the rate of antimicrobial resistance (AMR), which raises the number of AMR-related fatalities worldwide (Arbune et al., 2021). Patients with methicillin-resistant Staphylococcus aureus (MRSA) infection, for instance, have a 64% higher mortality rate than those with drug-sensitive forms of the infection (Carey et al., 2023). Furthermore, AMR has grown remarkably globally due to the reasons of changes in host vulnerability as well as genetic modifications in bacteria and other microbes with the advancement of science. Compounds and molecules derived from plant sources are naturally multi-targeting as they battle against various predators, including bacteria, fungi, viruses, insects, and herbivores, throughout their life cycle, from germination to maturity, and must withstand difficult defense mechanisms to survive (Dhandge and Deshmukh, 2023). Therefore, it is more practical and economical to investigate possible antibacterial compounds derived from plant sources as an alternative to creating new antibiotics. Furthermore, it is easy and secure to obtain plant sources because traditional medicine, particularly in the world's less industrialized and developing nations, provides healthcare for 75 to 80% of the worldwide population (Jamal, 2023).

Historically, medicinal plants have served as essential natural factories to produce phytochemicals with biological activity, including steroids, alkaloids, terpenoids, tannins, and flavonoids. The seeds of *Nigella sativa (N. sativa)*, commonly referred to as black seeds, are highly concentrated in phytoconstituents and have made the plant popular for a variety of therapeutic benefits (Abbas and Banno, 2020). Because of their chemical structure, *N. sativa* seeds have been shown to provide pharmacological qualities such as analgesic, appetizer, antidiabetic, antioxidant, anti-inflammatory, radical scavenger, and antibacterial activities. It has been evident that the extract and oil of black seed been widely used for the treatment and prevention of multiple disorders is both animal and human models. These disorders include asthma, oxidative stress, diabetes, ulcers, inflammatory disorders, hypertension, epilepsies, cancer, fatty liver and arthritis (Ara et al., 2020). Thymoquinone is the major component of black seed and had been extensively used for its pharmaceutical properties and applications. It promotes health due to its ability to cope with different ailments, here in Pakistan it has been extensively used in traditional and Unani medications for a long time (Shafodino et al., 2022). Besides all other activities the antimicrobial properties and potential of black seed is of great importance and it will be discussed in this chapter.

Overview of *N. sativa*

N. sativa is cultivated in different parts of the world, mainly in damp and moist areas. The general height of the plant to which it grows is 20-60 cm with aspects of leaves having the appearance of thread-like structures and very attractive flowers. The plant is an upright, branching herb with divided leaves, a tap root system, and attractive yellow-to-white blooms (M. T. Islam et al., 2017). Except for its many stamens, the plant is typically pentamerous. A wide area of the eastern Mediterranean, northern Africa, the Indian subcontinent, and Southwest Asia is home to the black cumin plant, which is grown in various nations such as Egypt, Iran, Greece, Syria, Albania, Turkey, Saudi Arabia, India, and Pakistan (Hannan et al., 2021).

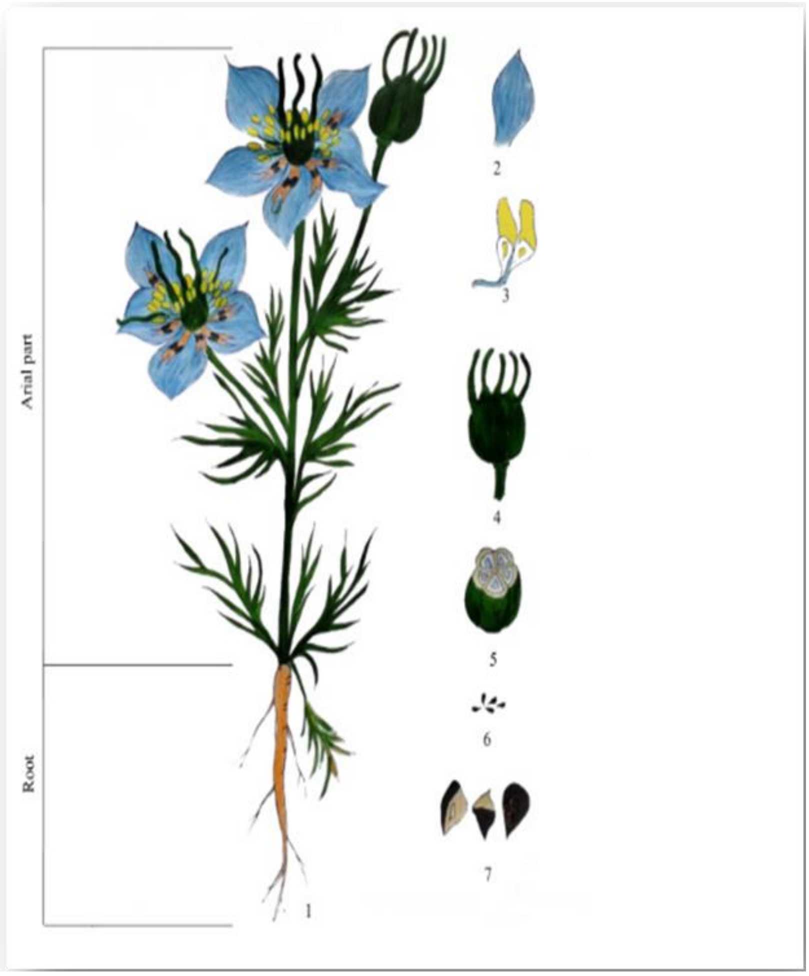

Fig. 1: Flower of *N. sativa* and its different Parts, 1; Habit, 2; Petal, 3; Stamen, 4; Fruit, 5; Transverse section of Fruit, 6; Seed, 7; Transverse section of seed. Source: (Hossain et al., 2021)

N. sativa is frequently referred to as *black seed* in English because, when exposed to air, the seeds typically turn black. In the Muslim community, it is also known by the names *Alhabahat Alsawda*, *Habbatus Sauda*, and *Alkamoun Alaswad*, depending on the color of the seeds (Thakur et al., 2021). The vernacular names of this significant black seed are shown in the figure below. Its seeds are a rich source of phytochemicals with a wide range of pharmacological potential, including steroids, alkaloids, terpenes, flavonoids, and polyphenols. Black cumin is a panacea used in traditional medicine to treat various illnesses and ailments and is also available as an essential oil, paste, powder, and extract. Some of these include eczema, hypertension, rheumatism, headaches, back pain, anorexia, amenorrhea, paralysis, inflammation, and asthma

(Dabeer et al., 2022).

English	Fennel Flower, Nutmeg Flower, Raman coriander, Blaxkseed, black caraway, black sesame
Hindi/Urdu	Kalaunji/Mangrail
Russian	Chernushka, Herbrew, Ketzakh
Turkish	Corek out
Arabic	Habbat ak-barkah
Indonesian	Jintan hitam
Bosnian	Curekor
French	Nigelle de Crete, toute epice
Germany	Schwarzkummel
Portuguese	Cominho-negro
Spanish	Ajenuz, aranuel
Swedish	svartkummin
Assamese	Kaljeera, kolajeera
Bengali	Kalo jeeray
Kannada	Krishna Jeeriage
Tamil	Karum, jeerakam

Fig. 2: Vernacular Names of *N. sativa*, Source: (Thakur et al., 2021)

Nutritional Profile of *N. sativa*

A small percentage of essential oils of 0.4 to 1.49%, fixed oils of 30 to 45%, and other chemicals are present in *N. sativa* seed. The other chemicals vary in concentration. Proteins, carbohydrates, amino acids, and bioactive compounds are all present in *N. sativa*. The protein percentage of 26.7%, fat at about 28.5%, carbs at 24.9%, crude fiber at 8.4%, total ash at 4.8%, volatile oil at 0.5 to 1.6%, fatty oil about 35.6 to 41.5%, cellulose at 6.8 to 7.4%, and moisture of 8.1 to 11.6% are all present in the black seeds of *N. sativa* (Albakry et al., 2022). Furthermore, the seeds are abundant in minerals including Ca, K, Se, Cu, P, Zn, Fe, and several vitamins particularly A, B1, B2, B3, and C. Its seeds, roots, and shoots have also been reported to contain beta-carotene and vanillic acid, respectively. The primary unsaturated fatty acids found in fat components are linolic acid at 50 to 60%, oleic acid at 20%, dihomo-γ-linoleic acid at 10%, and eicosadienoic acid at 3%. The two primary saturated fatty acids that palmitic acid and stearic acid are a part of are α-sitosterol at 44 to 54% and stigmasterol at 6.57 to 20.92%. It has also been claimed that *N. sativa* contains certain additional fatty acids, including myristic acid, palmitoleic acid, linoleic acid, linolenic acid, arachidonic acid, cholesterol, campesterol, β-sitosterol, 5-avenasterol, 7-stigmasterol, and 7-avenasterol (Mazaheri et al., 2019).

N. sativa's Chemical Constituents

The main chemical constituents of *N. sativa* and the main substances that make the chemical profile of Black seed include α-phellandrene, oleic acid, thymol, thymoquinone, carbohydrates, and proteins. As per the past literature, the main composition of *N. sativa* is comprised of linoleic acid, trans-anethole, palmitic acid, and oleic acid. Quinones (thymoquinone, thymol, di-thymoquinone, and thymohydroquinone) and phenolics were present in the plant. Monoterpene hydrocarbons dominated the chemicals that were extracted from *N. sativa* seeds. shown that *N. sativa* seeds contain proteins, oils, phenols, and alkaloids (Dalli, Bekkouch, et al., 2021). It has also been reported more recently that the plant contained a variety of biochemical compounds, primarily flavonoids, terpenes, and phenols. Alkaloids, fatty acids, polyphenols, phytosterol, terpenes, terpenoids, and other compounds are among the phytocompounds found in the plant (Imran et al., 2022).

Therapeutic Applications of *N. sativa*

The main ingredients that give black cumin seed its pharmacological and therapeutic actions are thymoquinone, thymohydroquinone, thymol, carvacrol, nigellidine, nigellicine, and α-hederin, especially in its essential oil. The Unani system lists *N. sativa* seeds as having stomachic, laxative, carminative, and galactagogue properties in addition to being used to treat paralysis, tertian fever, piles, inflammation, ascites, and eye disorders. It is also used to treat kidney stones and treat headaches, coughs, and asthma (Hosni et al., 2023). Moreover, *N. sativa* seeds have been utilized as an emmenagogue, stomachic, diaphoretic, diuretic, liver tonic, and parasite infection preventive. When mixed with other components, *N. sativa* can treat dyspepsia, reflux, obesity, and dyspnea, and improve breath. Relentless hiccups, anorexia, vomiting, edema, and puerperal illnesses are all treated with the seeds taken with buttermilk. They can be used to treat skin eruptions, amenorrhea, dysmenorrhea, leprosy, and polio in addition to being effective against mercury toxicity. It has been demonstrated that a tincture made from *N. sativa* seeds is beneficial. It has been employed as the anti-parasitic drench with its oils utilized as the oral dose, because of its immune-stimulant qualities (Ojueromi et al., 2022).

The oil is often used to treat skin ailments like boils, psoriasis, and eczema. Additionally, burns, joint pain alleviation, moisturizers, and anti-wrinkle agents can be treated using a mixture of beeswax and black seed oil. The oil can be used externally and possesses antibacterial qualities as well. Dried pods of *N. sativa* are sniffed to revive a sense of smell lost in time. By distributing them in between fabric folds, they prevent insects from damaging woolen textiles and act as insect repellents like mothballs (Abd-Rabou and Edris, 2021).

Antimicrobial Properties of *N. sativa*

Thymoquinone serve as the major and most important anti-microbial chemical constituent of the *N. sativa* that is responsible for the properties of anti-bacterial, anti-fungal and anti-parasitic aspects of this plant. Along with this substance, another chemical demonstrating anti-microbial properties for *N. sativa* involves the α-pinene, possessing both bactericidal and antimicrobial actions. Also, thymohydroquinone chemical of this plant also contains anti-bacterial and antifungal properties as per (Perera et al., 2021).

Thymoquinone's Role as an Active Chemical

A remarkable and significant anti-septic property is demonstrated by the active chemical, thymoquinone, at a specific dose rate. Along with this, the major active chemical fighting against the coronavirus and the virus of avian influenza in the *N. sativa* is the Thymoquinone as postulated by (Fatima Shad et al., 2021). Similarly, the research by (Al-Khalifa et al., 2021) evaluates that the consumption of *N. sativa* routinely has the capacity to block the multiplication and growth properties of coronavirus. Through this action, Nigella prevents the virus from entering the cell, thereby acting as the inhibiting agent against the corona infection. Besides, the analgesic, antioxidant, anti-inflammatory and anticancer properties are also manifested by Thymoquinone in the recent studies (Al-Khalifa et al., 2021).

Thymoquinone can inhibit the nuclear factor kappa beta (NF-κβ), mitogen-activated protein kinase (MAPK), Janus kinase/signal transduction, and activator of transcription (JAK-STAT) signaling pathways. Myeloperoxidase, cyclooxygenase (COX), lipo-oxygenase (LOX) enzymes, pro-inflammatory cytokines, reactive oxygen species (ROS), and elastase are all disrupted by thymoquinone (Khazdair et al., 2021).

Reported Anti-Bacterial Effects of *N. sativa*

It has been documented that *N. sativa* inhibits both Gram-negative (Pseudomonas aeruginosa and Escherichia coli) and Gram-positive (Staphylococcus aureus) microorganisms (Dalli, Azizi, et al., 2021). Along with beneficial effects when combined with spectinomycin, erythromycin, tobramycin, doxycycline, chloramphenicol, nalidixic acid, ampicillin, lincomycin, and co-trimoxazole, it demonstrated synergistic benefits with streptomycin and gentamycin (Al-Saedi, 2023). Additionally, it demonstrates actions like topical mupirocin. It has the potential to combat resistant pathogens, such as numerous multi-drug resistant gram-positive and gram-negative bacteria (Forouzanfar et al., 2014). In S. aureus, thymoquinone from *N. sativa* essential oils exhibited anti-methicillin-resistant action. The bactericidal potential of *N. sativa* was demonstrated by several studies (Dhahir Mansour Al Sultani et al., 2021). A study by (Arici et al., 2005) that used method of agar diffusion in the twenty four bacteria, including the spoilage, lactic acid and virulent bacteria, and then used *N. sativa* oil at doses of 0.5%, 1.0%, and 2.0%. 2.0% was the more effective concentration. 0.5% was the lowest active concentration of NS oil. When tested against Escherichia coli, E. Coli O157:H7, Pseudomonas aeruginosa, Yersinia enterocolitica, Lb. casei ssp. casei, Leu. pseudomesenteroides, or *Weissella paramesenteroides*, the concentration showed no activity. *Aeromonas hydrophila* was the most susceptible species of bacteria to all concentrations of *N. sativa* oils, whereas Y. enterocolitis was the most resistant. On average, fixed oils in *N. sativa* samples had more antibacterial activity than Lactic Acid Bacteria against pathogenic bacteria and spoiling. Another study by (A. R. Khan and Kour, 2016) used the agar-well diffusion method to examine the antibacterial activity of ethanol and hexane extracts of *N. sativa*. The extract's concentrations of 1.5, 3.0, 4.5, and 6.0 mg/ml were examined and compared with regular antibiotics (tetracycline, erythromycin, ciprofloxacin, and ampicillin). The ethanol extract demonstrated strong and notable action against *S. epidermidis* and *K. pneumonia*, followed by *Bacillus cereus*, *Bacillus subtilis*, *E. coli*, and *Salmonella typhimurium*. The extract had an antibacterial impact against both Gram-positive and Gram-negative bacteria. Methicillin-resistant Staphylococcus aureus (MRSA), the most frequent bacterium identified in clinics and laboratories, is also effectively prevented by *N. sativa*. MRSA has grown to be a significant global health issue (Badger-Emeka et al., 2021).

Mechanism of Action of *N. sativa* Against Bacteria

Multidrug efflux pumps are found in both Gram-positive and Gram-negative bacteria. These pumps play their role in the promotion of bacterial immunity and protection against the external antimicrobial substances. By origin, they act as the protein transporters playing their major role in the removal of the antimicrobial drugs and other molecules, harmful for the growth of bacteria and transport it outside the bacterial cell, thereby acting as the major root source of resistance of bacteria from anti-microbial and other multi-drugs (Randhawa et al., 2017). Listeria Monocytogenes has been examined to contain two to these major efflux pumps. These two pumps, recognized as the MdrL and Lde have been effective in removing several drug substances being MdrL in the removal of Ethidium Bromide, cefotaxime, macrolides and some heavy metals. The second efflux pump have been successful in the removal of acridine organe, flouroquinone and Ethidium Bromide as asserted by (Mosolygó et al., 2019). Such multi-drug antibiotic resistance can be effectively managed by the *N. sativa*. The active chemical of this plant, thymoquinone makes accumulation of these antibiotics possible through the blockage of the efflux pumps. This mechanism makes the antibiotics effective even at minimal dose rates. By generating reactive oxygen species (ROS), thymoquinone also interferes with its antibacterial action by inducing oxidative stress and cell death. P-cymene, on the other hand, has no antibacterial properties. However, it does so by making the membrane more permeable, which encourages the entry of antimicrobial compounds (Sicak and Eliuz, 2019).

Reported Anti-Viral Effects of *N. sativa*

As an herbal antiviral drug against novel coronavirus, *N. sativa* offers a great deal of potential, according to recent research (Shamim Molla et al., 2019). One significant phytochemical with potent antiviral properties that is present in *N. sativa* is DL-Arabinose. According to a study by (Basurra et al., 2021), *N. sativa* contains various bioactive ingredients, including Thymoquinone, dithymoquinone, thymohydroquinone, and nigellimine activity, which is enhanced by a zinc supplement, therefore, it may be regarded as a natural alternative to chloroquine. In another in-silico study using molecular docking (Bouchentouf and Missoum, 2020), the primary *N. sativa* compounds protecting the corona virus infection with the identical or higher potency as compared to the medications undergoing research experiments such as nigerlidine and α-hederin. Also, (Maiti et al., 2020) conducted an in-silico investigation and revealed that nigellidine had the strongest binding affinity of −7.61 to both nucleocapsid and N terminus protease, the primary protease required for viral maturation in terms of protein structures, RNA packaging, and other functions. Additionally, after viral infection, attaching to Interleulin-1 and Tumor Necrosis Factor-α receptors may lessen the surge of cytokines. The human system's ACE2 receptors, which are important for virus entry, have been found to bind well to α-hederin with a binding affinity of −6.265 kcal/mol) and thymohydroquinone with a binding affinity of −5.466 kcal/mol as asserted by (Jakhmola Mani et al., 2022). Dithymoquinone (DTQ), often described as nigellone, is one of the chemicals that exhibits a promising capacity to bind at the junction of ACES and SARS-CoV-2 and disturb contact of the virus and the host. It shows −8.6 kcal/mol after comparing to the chloroquine binding affinity as the positive control, with a binding affinity of −7.2 kcal/mol as postulated by (Ahmad et al., 2021).

When honey and *N. sativa* were taken orally, COVID-19 patients experienced a reduction in mortality, a rapid viral clearance, and a severity reduction in clinical symptoms. For COVID-19 treatment, Taibah University launched TaibUVID, a cutting-edge evidence-based treatment. Oil of *N. sativa* in one spoon and crushed anthemis hyaline of 1g along with the addition of honey makes up the dose of TaibUVID. For COVID-19 close contacts and patients, this mixture should be chewed in the mouth and eaten orally. This evidence-based strategy is encouraging for reducing deaths and quickly bringing the COVID-19 outbreak to a stop (El Sayed et al., 2020).

***N. sativa*'s Mode of Action Against Viruses**

Natural killer (NK) cells and the ratio of suppressor T cells (T4 and T8) are both increased by *N. sativa*. It has a suppressive effect against the human immune deficiency virus protease because it improves immunity. Moreover, it has been found to function against the murine cytomegalovirus and the protease of HIV. It was revealed that in the second scenario, the production of interferon-gamma (INF-γ) was associated with an increase in the number and effectiveness of CD4+ve T cells. Anti-influenza virus action is demonstrated by *N. sativa* (M. N. Islam et al., 2021). Through the induction of effective immunological responses, it has its effects in reducing the virulent actions of the virus. When *N. sativa* seed oil was used, patients with hepatitis C virus (HCV) infection showed a significant improvement in their HCV viral load. Patients with HIV can use *N. sativa* seeds to achieve sero-reversion and regain their health. It has been suggested that *N. sativa* oil interacts with murine cytomegalovirus, which in a rat model inhibited viral proliferation (Perera et al., 2021). The Newcastle disease virus was effectively inhibited by the ethanolic extracts of *N. sativa* in terms of both viral load and egg mortality in embryonic chicken embryos (Raheem et al., 2021).

Reported Anti-fungal Effects of *N. sativa*

Higher anti-dermatophytic action is present in *N. sativa* essential oil. In research conducted by b (Aljabre et al., 2005) some antifungal activity against dermatophytes, four species of Trichophyton rubrum and one each of *T. interdigitale*, *T. mentagrophytes*, *Microsporum cani*, and *Epidermophyton floccosum* was demonstrated by an ether extract of *N. sativa* seed and its active ingredient, Thymoquinone. Further, The *N. sativa* and Thymoquinone ether extracts had minimum inhibitory concentrations of 10 to 40 mg/ml and 0.125 to 0.25 mg/ml, respectively, which prevented 80 to 100% of the development of fungi. When applied at concentrations of 0.1% and 0.15%, *N. sativa* oil completely suppressed non-dermatophytic filamentous fungi including *F. moniliform*, *Alternaria alternative*, along with *Drechslera hawiinesis* as postulated by (Sitara et al., 2008).

Researchers found that *N. sativa* was able to inhibit *Macrophomina phaseolina*, one of the most harmful phytopathogenic fungi that cause charcoal rot disease, to the fullest extent possible at a concentration of 10% (Iqbal et al., 2014). Isolated from N. sativa seeds, Ns-D1 and Ns-D2, two new antifungal defensins, show strong, varying antifungal activity against a variety of phytopathogenic fungi (Rogozhin et al., 2011). Aflatoxin and mycelia formation in *Aspergillus parasiticus* are both inhibited by the essential oil of 67.4% of *N. sativa* @1.5 mg/ml. In Aspergillus flavus and Aspergillus fumigates, *N. sativa* oils @2 mg/ml caused the fibrillar layer of the cell wall to break down, as per the study by (Khosravi et al., 2011). It has been observed that the black seed hinders the growth of fungus causing aflatoxin, moreover it damages the cytoplasm of fungus causing less growth and disruption in cellular activity (Khosravi et al., 2011).

Anti-fungal activity of *N. sativa*

Black seed can decrease the activity of numerous disease-causing yeasts. It is believed that *N. sativa*'s antifungal effect stems from the presence of oleic acid and β-sitosterol in its oil composition. Furthermore, some constituents of natural spice oil, like stigmasterol and β-sitosterol, exhibit antifungal characteristics against certain pathogenic yeasts like *Geotrichum candidum*, *Candida tropicalis*, and *Candida albicans* (Shokri, 2016). A study conducted in vivo on mice demonstrated the antifungal efficacy of the aqueous extract from *N. sativa* seeds against candidiasis-causing *Candida albicans* (M. A. U. Khan et al., 2003). Nitric oxide (NO) is required for the candidacidal pathway in mouse neutrophils, according to another study. Potentially, the plant extract's active ingredient(s) could induce nitric oxide synthesis in monocytes and granulocytes, which would have strong antifungal effects and ultimately kill Candida albicans. At pH 7 and 30°C, *N. sativa* seed extract has its highest anti-yeast activity (Nadaf et al., 2015).

Anti-Parasitic Effects of *N. sativa*

N. sativa has been revealed to have strong anti-parasitic (anti-helminth, anti-cestodal, and anti-schistosomal) effects. *N. sativa* seeds demonstrate significant anti-cestodal actions. These locally available, inexpensive, and easily grown plant-based medications are suitable for use in treating roundworm and tapeworm infestations in children. With no severe side effects, the dose rate of 40 and 50mg/kg were the mostly effective and efficient doses (Akhtar and Riffat, 1991). While the major medication having synthetic origin, chloroquinone, had a suppression rate of 86 percent, the methanolic extract of *N. sativa* seeds at 1250 mg/kg had a 94% suppression rate against *Plasmodium yoelii* infection (Francis et al., 2023). To treat coccidiosis in rabbits, aqueous suspensions and oil emulsions containing 400 mg/kg of *N. sativa* seeds were utilized. The alkaloid nigellicine, which is lethal to parasites, is present in higher concentrations in the emulsion. The number of Schistosoma mansoni worms were also found to be reduced in the liver through the *N. sativa* oil action other than the decrease in the quantity of ova that were present in the liver and intestines. Besides this, the efficacy against the helminths were also examined such as, *Hymenolepis nana*. The potency of *N. sativa* was additionally tested against the adult worms of *Schistosoma mansoni*, miracidia and cercariae. It has shown significant biocidal action against every stage of the parasite and has an impact on the adult female worms' ability to produce eggs (Forouzanfar et al., 2014). The exact mechanism of action underlying *N. sativa*'s anti-parasitic properties, however, is yet unknown and needs more research.

Safety Standards of *N. sativa* Utilization

Thymoquinone is the primary ingredient in the volatile oil found in *N. sativa* seeds. There doesn't seem to be much toxicity in its seed extract or its components. The level of established toxicity following oral ingestion of Thymoquinone was insignificant (Hannan et al., 2021). Oral Thymoquinone is either bio-transformed in the gastrointestinal system into more modest toxic metabolites or converted into dihydro-thymoquinone in the liver. Because Thymoquinone is fully absorbed into the systemic circulation after injection, the toxicity increases. When male albino rats were given intraperitoneal injections of 200 mg/kg cyclophosphamide or phosphate-buffered saline (PBS) and then intragastric injections of *N. sativa* oil or Thymoquinone every other day for the period of twelve days, starting six hours prior and later to the injection of chemical cyclophosphamide, it was observed that the cyclophosphamide medication resulted in a substantial increase in overall pathogenicity, however the *N. sativa* oil or Thymoquinone treatment caused a significant decrease in overall toxicity as per (Alenzi et al., 2010). When administered sub-chronically in drinking water at levels around twelve times the cytoprotective dose, Thymoquinone has comparatively low acute toxicity and is often well tolerated. There were no alterations in the levels of liver enzymes or harmful effects on liver function after 28 days of *N. sativa* supplementation up to 1 g/kg (Burdock, 2022). In rodents, Thymoquinone can shield against and prevent cisplatin nephrotoxicity. Additionally, cisplatin-induced nephrotoxicity was significantly reduced by the intake of Thymoquinone orally @ 50 mg/L mixed in drinking water in the routine of 5 days before and 5 days with the follow up of a single cisplatin injection @ 5 mg/L in rats and 7 or 14 mg/l in mice (Zaoui et al., 2002).

Opportunities for advancement as an Alternative medicine

Modern medications, also often known as chemical medicines, pharmaceuticals, pharmaceutical products, and conventional medicines, more especially, antimicrobial drugs have been utilized extensively to effectively treat a variety of illnesses. However, the side effects of using these medications have drawn millions of individuals worldwide to turn to herbal and natural therapies as alternatives for pharmaceuticals in medical treatment. Most patients prefer to prevent the negative consequences of long-term use of modern medicine for chronic illnesses, which is why they turn to herbal medicine. Given the established benefits of various herbal medicines, the modern medical system must fully utilize this valuable plant as an efficient replacement for antimicrobials on a large scale, thereby directing the aspirational role of *N. sativa* in a variety of medical conditions within the anti-microbial universe (Bhat et al., 2019). Synthetic medicine formulations go through numerous stages, from the first assessment of the drug's effectiveness in model organisms to the assessment of toxicity and tolerance, human trials, and ultimately, production. Modern medical systems may use the same stages for *N. sativa*, considering the affectivity trials and toxicity assessment. The current pharmaceutical system has the ability to produce *N. sativa* seed extract, pills, and capsules, which could be used as alternative medicines (Bhikha and Glynn, 2019).

Conclusion

In a nutshell, an insightful understanding and in-depth discussion on the overall description of *N. sativa* and its role in the therapeutic world, along with the brief understanding of the anti-microbial effects of *N. sativa* thereby, demanding the critical and clinical experimentation in the contemporary medicine. Through this discussion, it was evaluated that the antifungal, anti-bacterial, anti-parasitic and anti-viral effects were reported by the various active chemical substances of this plant. This plant, *N. sativa* belonging to the family of Ranunculaceae, has been found effective and proficient against various antimicrobial infections and restoration of health from these infections through the therapeutic action against various microbes. Various forms of this plant have been utilized for therapeutic effects including the oils, seeds along with the extracts of seeds and oils. The major active chemical in this plant, known as thymoquinone has been evaluated to possess the anti-cancer, anti-microbial, anti-diabetic and hepatoprotective function. Many other active chemicals are also present in *N. sativa* manifesting the therapeutic properties. Major active chemical substances against the antimicrobial resistant bacteria are found to be thymoquinone, carvacoal, and many others as apparent by the discussion from this chapter. The mechanism by which these active chemical acts involved the accumulation of anti-bacterial molecules by the inhibition of the efflux pumps. Bacteria eventually develop sensitivities and die. Even at smaller dosages, this activity may be effective. Thymoquinone stimulates oxidative stress and the generation of reactive oxygen species (ROS), which leads to cell death. P-cymene, a more powerful *N. sativa* compound, enhances the permeability of bacterial membranes, which facilitates the entry of antimicrobial agents. Potential antibacterial agents include *N. sativa* oil, carvacrol, p-cymene, and thymoquinone. When processed and utilized appropriately, phytochemicals, nutritionally essential components, polyunsaturated fatty acids, and highly active volatile compounds like p-cymene, Thymoquinone, α-thujene, carvacrol, β-pinene, limonene, methyl linoleate, sabinene, d-limonene, 4,5-epoxy-1-isopropyl-4-methyl-1-cyclohexene, and 4-terpineol found in *N. sativa* may have medicinal value. It is recommended that *N. sativa* be widely used in both conventional and modern medication systems due to its broad range of therapeutic potential as an antimicrobial.

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