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NIGELLA SATIVA LINN AND ITS COMPREHENSIVE ACTIVITY AGAINST VARIOUS MICROBES AND CANCER: A MINI REVIEW

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ABSTRACT

Nigella sativa (Black seed) is an annual flowering plant, native to south and southwest Asia. It is cultivated different countries of the world including Syria, Lebanon, Israel and Southern Europe.In India it is mostly cultivated in the Gangetic plains and different provinces including Punjab, Himachal Pradesh and Bihar. The popularity of the plant was highly enhanced by the ideological belief in the herb as a cure for multiple diseases. Traditionally the seeds and its oil are used in several diseases.Various researchers conducted extensive research on N. sativa and revealed a wide spectrum of its pharmacological actions those include antimicrobial, antidiabetic, anticancer, antiinflammatory, immunomodulator, analgesic, bronchodilator, hepatoprotective, spasmolytic, gastroprotective, renal protective, and antioxidant properties.N. sativa, has been widely used as antihypertensive, liver tonics, diuretics, digestive, anti-diarrheal, appetite stimulant, analgesics, antibacterial and in skin disorders due to its miraculous power of healing. Theanti microbial and anti cancer activities of this seed is found to be the ray of hope to fight against cancer and the currently evolved multidrug resistant (MDR) microbes. In this mini review the major activities of N. sativa seeds and it's by products on microbes and cancers were extensively highlighted.

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INTRODUCTION

Since ancient civilization and nowadays, natural sources especially plants are used as medicinal therapy because they contain several components which are believed to cure various infectious diseases. The biodiversity of plants provides an important source of chemical compounds, which have many therapeutic applications such as antiviral, antibacterial, antifungal and anticancer activities [1- 3].

Nigella sativa is commonly known as black seed, has been used in traditional medicine to treat many diseases.It has been used for centuries for the treatment of various ailments, including infectious diseases.(4) The seeds, commonly used in recipes in Asian countries are reported to possess several medicinal properties.The methanol extract of *Nigella sativa* are used for the treatment of some bacterial and fungal diseases [5]. Different crude extracts of *N. sativa* tested for antimicrobial activity against different bacterial isolates, viz. Gram negative and Gram positive bacteria and antifungal activities [3, 6,7].

N. sativa has regarded as a valuable remedy for number of diseases. Now a days, black seed is used for treating digestive tract conditions including gas, colic, diarrhoea, dysentery, constipation, and haemorrhoids. It is also used for respiratory conditions including asthma, allergies, cough, bronchitis, emphysema, flu, swine flu and congestion. It has uses in various traditional activities i.e., ascites, cough, jaundice, hydrophobia, fever, paralysis, conjunctivitis, piles, skin diseases, anorexia, dyspepsia, flatulence, abdominal disorders, diarrohoea, dysentery, intrinsic

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hemorrhage and amenorrhea. The most effective extracts were the crude alkaloid and water extracts. Gram negative isolates were affected more than the Gram positive bacteria [4, 8, 9].

Nigella sativa (black seed) has active substances particularly thymoquinone and longifolene possess invitro activities against a large variety of cancers. *Nigella sativa* seed, its oil, thymoquinone or their analogs could be used in suitable combinations with already established as chemotherapeutic agents. Seed extract and seed oil of N sativa has found the anticancer activity on human lung cancer cell line and reduce the viability significantly. Both in vivo and in vitro studies showed that *N. sativa*is rich source of different biologically active compounds and are found effective in controlling number of various cancers and cardiovascular diseases.It is found effective inatitumor, antidiabetic, Cardiovascular, Gastroprotective, Nephroprotective, Heparoprotective, Anti-inflamatory, Immunomodulatory, Central nervous system For breast cancertherapy it could be potentially used as an alternative source of medicine as *Nigella sativa* has ability to kill cancer cells such as HeLa, PC3, and hepatoma cells [10 -12].

MEDICINAL PROPERTY OF NIGELLA SATIVA

The Greek physician Dioskorides used black seed to treat headaches, nasal congestion, toothache and intestinal parasites. Hippocrates, the grandfather today's scientific medicine regarded *Nigella Sativa* as a valuable remedy in hepatic and digestive disorders. Recently independent clinical studies published in the archives of Aids also established some astonishing effects of black seed on the defense system by improving the ration between helper t-cells and suppressor t-cells by a significant amount while also enhancing the natural killer cell activity [13].
Oxidation reactions are crucial for life, they can also be damaging; plants and animals maintain complex systems of multiple types of antioxidants, such as glutathione, vitamin C, vitamin A, and vitamin E. The antioxidant and free radical scavenging properties of manyplants have been found to play an important role in theirmedicinal property[14]. It was reported that about 70% of pollen and dust allergies, asthma and neuro-dermitis were cured by *Nigella Sativa*. It is widely used as natural remedy and the seeds are extensively used as spice, carminative, condiment and aromatic [15,16]. Traditionally, the seeds were used as diuretic, diaphoretic, stomachic, liver tonic and digestive. As a confection with other ingredients, they are used in diarrhea, indigestion, dyspepsia and sour belching; they also remove foul breath and watering from the mouth. It has antibilious property and is administered internally in intermittent fevers [17,18].
Thymoquinone, found in the seed oil extract of *Nigella sativa*, has been shown to have antineoplastic effects in rats and mice and in cultured human cells from several types of cancer, including pancreatic ductal adenocarcinoma. It has protective antioxidant and anti-inflammatory effects, and promotes apoptosis (cell death) of the cancer cells [19].
The oil of *Nigella sativa* is so beneficial due to its content of over a hundred components such as aromatic oils, trace elements, vitamins and enzymes. It contains 58% of essential fatty acids including omega 6 and omega 3 which are necessary for the forming of Prostaglandin E1 which balances and strengthens the immune system giving it the power to prevent infections and allergies and control chronic illnesses [20]. Healthy cells are protected from viruses thus inhibiting tumors. Black seed oil also contains about 0.5 – 1.5% volatile oils including nigellone and thymochinone which are responsible for its anti-histamine, anti-oxidant, anti-infective and broncho-dilating effect [21].The dried seeds of *Nigella sativa* are used as astringent, bitter, diuretic, emmemagogue; stimulant and antihelminthic. It is useful in paralysis, jaundice, intermittent fever, dyspepsia, piles and skin diseases [22].
The fixed oil of *Nigella Sativa* had both antioxidant and anti-eicosanoid effect greater than thymoquinone which is its active constituent. The results of extensive pharmacological studies justify the broad, traditional therapeutic value of Black Seeds [23]. These studies found black Seed to have analgesic, antilipemic, postcoital, contraceptive, diuretic and antihypertensive, bronchodilator and calcium antagonist, histamine release inhibitor, hepatoprotective, antihelminthic, antifungal, antimicrobial (against a wide range of organisms), anticancer and anti-inflammatory activities [24]. The black seeds contain 36–38% fixed oil, with proteins, alkaloids, saponins and essential oils making up the rest of the composition [14]. Although black seed extract or oil has been reported to possess antimicrobial activity (antioxidant activity antitumor activity and a stimulatory effect on the immune system its full potential as an antimicrobial agent has not been exploited [4, 26, 27].

EFFECTS OF NIGELLA SATIVA ON MICROBES

Systematic investigation has been carried out to evaluate the anticancer and antimicrobial properties of plants as they have vast potentiality in traditional medication. So scientists start looking for anticancer and antimicrobial property of selected medicinal plants of Ayurveda by in-vitro evaluation. Some microorganisms like, *E.coli*,

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P.vulgaris can cause not only diarrhea but more serious diseases such as hemorrhagic colitis and hemolytic uremic syndrome leads to ulceration and finally in cancer [28]. *Nigella sativa* seeds caused concentration-dependent inhibition of Gram-positive Staphylococcus aureus and Gram-negative Pseudomonas aeruginosaand E.coli and a pathogenic yeast Candida albicans. The extract showed antibacterial synergism with streptomycin and gentamicin and showed additive antibacterial action with spectinomycin, erythromycin, tobramycin, doxycycline, chloramphenicol, nalidixic acid, ampicillin, lincomycin and sulfamethoxyzole–trimethoprim combination. Interestingly, the extract successfully eradicated a non-fatal subcutaneous staphylococcal infection in mice when injected at the site of infection [6, 31].

The essential oil and chloroform, n- Hexane, ethyl acetate and methanol extracts of a *Nigella sativa* were found to contain remarkable antibacterial effects against food borne and spoilage bacteria, *Bacillus subtilis, Salmonellatyphimurium, Pseudomonas aeruginosa, Enterobactoraerogensand Staphylococcus aureus* [32, 33]. The scanning electron microscopic studies also investigated the inhibitory effect of essential oil on the morphology of *Bacillus subtilis* at the minimum inhibitory concentration [35, 33]. The dried seeds of *Nigella sativa* exhibited bactericidal activity against Pseudomonas aeruginosa [6, 25, 34]. Antifungal activities of the oils of *Nigella sativa* seeds has been also established [3].

IMPORTANT ROLE OF NIGELLA SATIVA AGAINST CANCER

Cancer is a major public health burden in both developed and developing countries. Occurs due to some molecular changes within the cell. The major cause of cancer are smoking, dietary imbalances, hormones and chronic infections leading to chronic inflammation. *Nigella sativa* seeds as a natural remedy for a variety of complaints including liver diseases. The hepatoprotective effects of TQ have been well documented and have been found to be related to its strong antioxidant potentials [36, 18].

Nigella sativa can be compared to *Echinacea*, the well-known immune booster but works in a very different way, which makes it even suitable for diseases of the immunesystem itself, eg., Allergies, MS, TB, cancer, aids etc., where Echinacea could have detrimental effects [37]. Enzymes such as catalase, Superoxide dismutase and various peroxidise. Insufficient levels of antioxidants, or inhibition of the antioxidant enzymes, cause oxidative stress and may damage or kill cells (38). Recently, the presence of TQ, TQ2 and TOH in *Nigella sativa* seed was confirmed using thin layer chromatography (TLC) and normal phase high-performance liquid chromatography (HPLC) methods. The content of TQ in *Nigella sativa* seed oil samples, obtained from different origins, was measured by gas chromatography (GC) analysis and found to be in the range of 0.13–0.17% w/v of the oil [23]. GC-MS analysis of the essential oil obtained from different samples of *Nigella sativa* seeds and from a commercial fixed oil showed that the qualitative composition of the volatile compounds was almost identical. *Nigella sativa* seed contain high amount of volatile compounds were identified and their differences were mainly restricted to the quantitative composition [14].

Nigella sativa has a greater effect against HepG2. It is a human liver carcinoma cell line (Hepatocellular carcinoma) [16, 18]. The high degree of morphological and functional differentiation in vitro, HepG2 cells are a suitable model to study the intracellular trafficking and dynamics of bile canalicular and sinusoidal membrane proteins and lipids in human hepatocytes in vitro. This can be important for the study of human liver diseases that are caused by an incorrect sub cellular distribution of cell surface proteins [16, 18, 39]. HepG2 cells and their derivatives are also used as a model system for studies of liver metabolism and toxicity of xenobiotics, the detection of environmental and dietary cytotoxic and genotoxic (and thus cytoprotective, anti-genotoxic, and cogenotoxic) agent, understanding hepatocarcinogenesis, and for drug targeting studies. HepG2 cells are also employed in trials with bio-artificial liver devices [16, 18].

Nowadays *Nigella sativa* is used to cure MCF-7 cell line. It invades breast ductal carcinoma. Tumour necrosis factor alpha (TNF alpha) inhibits the growth of MCF-7 breast cancer cells. Treatment with anti-estrogens can modulate the secretion of insulin like growth factor binding protein. In *Nigella sativa* seeds contain thymoquinone (TQ) it will inhibit the growth of MCF-7 cell line [40,51].

Even after introduction of new antimicrobial agents for clinical use an alarming increase in bacterial resistance to existing agent's demands that a renewed effort be made to seek antibacterial agents effective against pathogenic bacteria resistant to current antimicrobials *Nigella sativa* Linn. *Nigella sativa* seed oil has anti-inflammatory properties and effective in chronic pancreatitis also several other groups with risk of development or recurrence of pancreatic cancer, such as high risk family members and post - surgical patients. These potent effects show promise

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for the herb as a potential preventive and therapeutic strategy for pancreatic cancer. Researchers need to further examine if thymoquinone extract, as a preventative approach against the re-occurrence of cancer after surgery and chemotherapy.

Table: 1. Beneficial effects of *N. sativa* on various Microorganisms

Diseases	Organisms associated	Ref
1. Bacterial	***Staphylococcus aureus, Pseudomonas aeruginosa, Escherichia coli, Salmonella typhi, Bacillus subtilis, Micrococcus lysodeikticus,*** **Helicobacter pylori**	6, 41, 42, 26
2. Fungal	***Candida albicans, Trichophytonrubrum, Trichodermaspp, Fusariumspp***	41, 7
3. Viral	**Cytotomegalovirus (CMV)**	26

Table: 2. Beneficial effects of *N. sativa* on various Cancer diseases

Cancer Diseases	Benificial effects	Ref
Cervical cancer	Thymoquinone is the main constituent of black seed essential oil has in vitro and in vivo anti-neoplastic activities in different tumor cell lines. Methanolic extract of *Nigella sativa* using SiHa human cervical has the potential anti-cancer effects on cancer cells which showed an 88.3% inhibition of proliferation of SiHa human cervical cancer. It could potentially be an alternative source of medicine for cervical cancer therapy.	43
Blood cancer	TQ exhibits anti-proliferative effect in human myeloblastic leukemia HL-60 cells. Derivatives of TQ bearing terpene-terminated 6-alkyl residues were tested in HL-60 cells and 518A2 melanoma and found that the derivatives induce apoptosis associated with DNA laddering, a decrease in mitochondrial membrane potential and a slight increase in reactive oxygen species.	52
Hepatic cancer	The cytotoxic activity of *N. sativa* seed was tested on the human hepatoma HepG2 cell line and 88% inhibitory effect on HepG2 was found after 24-hr incubation with different concentrations (0-50 mg/ml) of the *N. sativa* extract. It is also reported that oral administration of TQ is effective in increasing the activities of quinonereductase and glutathione transferase and makes TQ a promising prophylactic agent against chemical carcinogenesis and toxicity in hepatic cancer	16
Colon cancer	It was demonstrated that the volatile oil of *N. sativa* has the ability to inhibit colon carcinogenesis of rats in the post-initiation stage, with no evident adverse side effects.	45
Renal cancer	It was reported that the chemo-preventive effect of *N. sativa* against ferric nitrilotriacetate (Fe-NTA)- induced renal oxidative stress, hyper-proliferative response and renal carcinogenesis.	46
Skin cancer	Topical application of *N. sativa* extract inhibited two-stage initiation/promotion [dimethylbenz[a]anthracene (DMBA)/croton oil] skin carcinogenesis in mice.	47
Fibrosarcoma	TQ from *N. sativa* was administrated (0.01% in drinking water) one week before and after MCA treatment significantly inhibited the tumor incidence (fibrosarcoma) and tumor burden by 43% and 34%, respectively. Moreover, TQ delayed the onset of MCA-induced fibrosarcoma tumors. In vitro studies showed that TQ inhibited the survival of fibrosarcoma cells with IC50 of 15 mM Oil of *N. sativa* also decreased the fibrinolytic potential of the human fibrosarcoma cell line (HT1080).	48, 13.
Pancreatic cancer	TQ, the major constituent of *N. sativa* oil extract, induced apoptosis and inhibited proliferation in PDA (pancreatic ductal adenocarcinoma) cells. TQ also can abrogate gemcitabine- or oxaliplatin-induced activation of NF-kappa B, resulting in the chemosensitization of pancreatic tumors to conventional therapeutics .	19, 44

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Breast cancers	Aqueous and alcohol extracts of *N. sativa* were found to be effective in vitro in inactivating MCF-7 breast cancer cells (Farah and Begum, 2003). *N. sativa*, in combination with melatonin and retinoic acid reduced the carcinogenic effects of DMBA (7, 12-di-methylbenz(a)anthracene) in mammary carcinoma of rats.	40
Lung cancer	The antitumor activity of α-hederin from *N. sativa* against LL/2 (Lewis Lung carcinoma) in BDF1 mice . Supplementation of diet with honey and *N. sativa* has a protective effect against MNU (methylnitrosourea)-induced oxidative stress, inflammatory response and carcinogenesis in lung, skin and colon.	49

DISCUSSION

The molecular mechanisms behind its anticancer role is still not clearly understood, however, some studies showed that TQ has antioxidant role and improves body's defense system, induces apoptosis and controls Akt pathway [23]. Although the anti-cancer activity of *N. sativa* components was recognized thousands of years ago but proper scientific research with this important traditional medicine is a history of last 2~3 decades. Serious diseases such as hemorrhagic colitis and haemolytic uremic syndrome leads to ulceration and finally in cancer [2, 28]. Because of high death rate associated with cancer and serious side effect of chemotherapy and radiation therapy, many cancer patients seek alternative and complementary method of treatment [28].

The anti-cancer activities of *N. sativa* components were recognized thousands of years ago but proper scientific research with this important traditional medicine is a very recent story. More research works should be emphasized behind this because it is a safe and promising anticancer agent. Specially, researchers should investigate the active ingredients more broadly, because, there is very few authentic reports about the chemical composition of seeds or oil of *N. sativa* exist [32]. Also, the exact molecular mechanisms of thymoquinone and other components on different cancers should be investigated with more emphasis because current understandings are mostly unclear. It is reported that *N. sativa* oil can protect cells from radiation, but the molecular mechanisms behind this is not properly understood [31, 50].

CONCLUSION

Currently, in some parts of the world, there is a renaissance of interest in traditional remedies. Many investigators now believe that traditional medicine is a promising source of new therapeutics against cancer (33). Towards the end of the 20th century, plant based products, neutraceuticals and food supplements comprising the complementary and alternative therapies have gained a big share in the drug market in the developed countries. Further investigations are required to study the mechanism of actions of *N. sativa* seeds and its constituents by which they exert their therapeutic effects. Chemical modifications in the molecular structure of TQ, alpha-hederin and other constituents of *N. sativa* seeds could lead to more effective and safer drugs for the treatment of wide variety of diseases in the future. Aljabre SH 2005.*N. sativa* seeds, its oil, constituents of *N. sativa* seeds like TQ, alpha-hederin or others could be used in suitable combinations with existing chemotherapeutic agents for an effective treatment of many infectious diseases and to overcome the resistance problem. Moreover, further researches should focus and explore the specific cellular and molecular targets of various constituents of *N. sativa*, particularly TQ. Extensive research with *N. sativa* may contribute to the discovery of new anticancer strategies.

CONFLICT OF INTEREST

There is no conflict of interest.

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