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MEDICINAL SIGNIFICANCE OF NIGELLA SATIVA AND ITS SEEDS: RECENT UPDATES

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ABSTRACT: *N. sativa* (black cumin seed) is popularly known for its medicinal significance such as Anticancer, Antioxidant, Anti-microbial, Anti-inflammatory, Anti-ulcer, Anti-parasitic, Anti-histamine, Analgesic, for skin rashes, hair treatment and also used as a flavoring agent. Recent reports reveal that the *Nigella sativa* seeds exhibit a potent effect on the Covid-19 virus. Further, *N. sativa* seed can be used to reduce weight as well as increase digestion. In this manuscript, the recent medicinal updates are highlighted. Finally, this review may attract the young researcher to further design and development of the drug.

INTRODUCTION: The *Nigella sativa* medicinal plant has various traditional medicinal potential ¹ (Ahmad *et al.* 2013). *N. sativa* very common spice used in Indian kitchens. *N. sativa* plant will grow 50 to 60 cm tall with different colour of flowers in different parts of the world ² (Tembhurne SV *et al.* 2014). *N. sativa* popularly known for its medicinal significance such as Anti (cancer, diabetic, bacterial, fungal, viral, inflammatory, oxidative, histaminic, tumor, fibrotic, infertility, convulsant), analgesic, cardiovascular, neuro-protective effect, kidney protection, wound healing, dermatological effects, for skin rashes, for hair treatment and also used as flavoring agent. Recently observed the *Nigella sativa* seeds showed some potent effect on the Covid-19 virus.

Medicinal Significance of *N. sativa*:

Anti-cancer Activity: Selma Dagtas *et al.* 2021 observed that the oral cancer can be treated or managed by consuming whole seed or aqueous seed extract ³. Swamy S. M. *et al.* 2000 reported the cytotoxicity activity of *N. sativa* ethyl acetate seed extract against cancer cell lines (P388, Molt4, Wehi 164, HepG2, SW620 and J82). The experimental result reveals that CC-5 showed higher cytotoxic effect ⁴. Majdalawieh A. F. *et al.* 2016 reported that the various *in-vitro* and *in-vivo* models of *N. sativa* studied for anti-cancer potential due to its properties of anti-proliferative, pro-apoptotic, anti-oxidant, anti-metastatic.

The results showed the *N. sativa* with combination with other drug highly effective to protect the growth of the tumour ⁵. Arshad H. Rahmani *et al.* 2014 observed the thymoquinone is the major constituent to prevent or treat the cancer. The major constituent of *N. sativa* has many therapeutic benefits including controlling cancer by suppressing the tumor genes and carcinogens ⁶.

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Anti-diabetic Activity: Kaur G *et al.* 2018. reported that the combination of *Nigella sativa* and *C. cassia* extract mixture were effective for decreasing the blood glucose levels along with the other medication and also reduced lipid profile. Extracts of *Nigella sativa* has the capacity to regenerate the beta cells of pancreas which induce insulin secretion ⁷.

Abdelrazek H. M. *et al.* 2008 reported that the oil of *N. sativa* showed high potential against various diabetic complications. The experimental study reveals that thymoquinone is the key role for minimizing the diabetic complications ⁸.

Anti-bacterial Activity: Grzegorz Gawron *et al.* 2019 observed the antibacterial activity of seed extract of *N. sativa* showed high potential against all used bacterial strain with a concentration of 4-16 µg/ml ⁹. Shabina Ishtiaq *et al.* 2013 reported the the antibacterial activity of various extracts of the *N. sativa* of different concentration on different strains of bacteria. The most effective extracts were methanolic, ethanolic, chloroform, acetonetic and n-hexane. This study shows that most of the bacterial strains common to human diseases can be controlled by using extracts of *N. sativa* ¹⁰.

Mohamed shohayeb *et al.* 2012 observed the volatile oil and its fractions of *Nigella sativa* showed potent antibacterial activity against different types of bacteria and fungi. The seed of *N. sativa* phenol extract effective against *Esherichia coli*, *Bacillus subtilis* and *Streptococcus faecalis* ¹¹.

Mohammad H Islam *et al.* 2012 reported the distilled methanolic extract was very effective in inhibition of gram positive as well as gram negative bacteria. The extracts of the germination phase had a better inhibitory activity than many other antibiotics due to presence of metabolites in the methanolic extracts ¹².

Anti-fungal Activity: The *N. sativa* medicinal plant showed its potential in many diseases. Shah S B *et al.* 2018 observed the methanol, ethanol and aqueous extract of *N. sativa* seed extract effective against all used fungal strains ¹³. Sheik Noor Mohamed *et al.* 2015 reported the *Nigella sativa* seed extract contains more bioactive compounds and all are highly effective against fungal strains ¹⁴. Katerina Halamova *et al.* 2010 observed that dairy

industry is affected by the growth of various types of yeast and other fungus. The *N. sativa* extracts can be used for the inhibition of growth of microorganisms without harming the chemical characteristic of the product ¹⁵.

Anti-viral Activity: Badary O. A. *et al.* 2021 observed the antiviral activity against a SARS CoV-2 and also the molecular docking studies results showed that the important constituent of *N. sativa*, thymoquinone can inhibit the COVID-19. The whole world is fighting against the covid-19 virus and there is no treatment found for it. The researchers and scientist are trying out different combination of various anti-viral and antibiotics. The *N. sativa* plant constituent can be (Thymoquinone) used in the past to treat avian influenza virus ¹⁶. Ajaz Ahmad *et al.* 2020. reported that for corona virus infection if the cells are treated with black seed extracts the replication and virus load decreases ¹⁷.

Alam Kulyar M *et al.* 2020 observed the important composition of *N. sativa* are the evidence for its medicinal significance and docking study results reveal that *N. sativa* give more or similar effect against COVID-19 virus ¹⁸.

Umar *et al.* 2015 conducted experiment on turkey's infected by H9N2 avian influenza virus. The birds treated with extracts of *N. sativa* had higher antibody and immunomodulatory nature. Suppose it is used with 3% amount with dietary supplements enhances immunity and suppress pathogenicity of the influenza virus ¹⁹. A. A. Onifade *et al.* 2015 reported the black cumin and honey mixture highly effective against HIV infection if it is used for a year ²⁰.

Anti-inflammatory and Analgesic Activity: Harshal N Pise *et al.* 2017 conducted a test for comparing the effect of *N. saliva* along with other drugs. The steroidal anti-inflammatory can be used for long term as it has toxins and other side effects. The experimental observations of *N. sativa* oil showed potent anti-inflammatory properties ²¹.

Alireza Ghannadi *et al.* 2005. reported the *N. sativa* seed exhibited potent anti-inflammatory and analgesic effects studied in mice and rats by using tail flick and carrageenan induced paw edema method ²².

Antioxidative and Anti-histaminic Activity:

Kanter Metal *et al.* 2006. Observed the thymoquinone is the important constituent of *N. sativa* has more medicinal significance such as antioxidant and antihistaminic properties²³. M. H. Boskabady *et al.* 2002 reported the *N. sativa* extract highly effective to prevent the lung inflammation in guinea pigs²⁴.

Cardiovascular Effects: Cardiovascular diseases are a class of heart problems (diseased vessels, structural problems and blood clots). Hypertension is a major cause of cardiovascular disease in the world. Enayatfard L *et al.* 2019. found that a hydroalcoholic extract of *N. sativa* and TQ considerably reduced the cardiovascular responses. The Wistar rats were separated into groups and pre-treated with three doses of *N. sativa* (200, 400, and 600 mg/kg) administered intraperitoneally. After which the angiotensin II was injected. The experimental results reveal that *N. sativa* exhibits well anti cardiovascular effects²⁵.

Ahmed M *et al.* 2013. carried out a study to evaluate the cardio-protective effect of *Nigella sativa* oil. *Nigella sativa* oil administration resulted in considerable stabilization of physiological parameters, regeneration of histological structure, and suppression of cyclooxygenase-2 expression in the heart when compared to the Pb group. In lead-induced cardio toxicity²⁶.

Anti-tumor Effect: The present evidence strongly suggests that *N. sativa* could be used alone or with the combination to suppress tumor genesis, growth, and metastasis. The main constituent of *N. sativa* is Thymoquinone (TQ) which has a major action in anti-tumour effect²⁷. Tabasi N *et al.* 2014 observed that the TQ oral administration resulted in suppression of stomach tumor in mice²⁸.

Linjawi and his co-workers reported the effects of Thymoquinone (TQ) and black cumin seed oil on tumor markers. Parenteral TQ (1–10 mg/kg) or *N. sativa* oil (three times a week for four months) protected female rats from developing breast cancer²⁹. Black cumin seed has also been shown to protect and limit the growth and spread of cancer-causing neoplastic cells.

Anti-fibrotic Effect: Al-Gayyar *et al.* 2016 reported the effects of oral sodium nitrite on kidney

function in rats as well as the possible protective benefits of NSO. Based on their findings, NSO when injected in sodium nitrite treated rats in a dose-dependent manner of 2.5, 5 and 10 ml/kg for 12 weeks, showed progressive development of tubulointerstitial fibrosis³⁰.

Elmowafy M *et al.* 2016 reported the TQ's antifibrotic properties are mainly due to its antioxidant action, which results in less hepatocyte damage and hence less hepatic stellate cell transactivation (HSCs). TQ's role in directly suppressing the fibro genic activity of HSCs, in particular, has not been investigated yet³¹.

Neuro-protective Effect: TQ has a good safety profile and is well tolerated for the treatment of neurological illnesses. TQ's neuroprotective impact was tested in a temporal lobe epileptic diseased brain model. Landucci E *et al.* 2021 observed in his experiment conducted that TQ increases the PSD95 levels in basal conditions. Its neuroprotective effects may be mediated by antioxidant, free radical quenching, and anti-inflammatory activities³².

Tabeshpour *et al.* 2019. treated rats with ACR for 11 consecutive days which showed limb amputation. TQ was dissolved in 0.9% NaCl solution in the experiment. Wistar rats exposed to ACR (50 mg/kg, intraperitoneal, for 11 days) showed behavioral changes and weight loss.

Whereas rats that were administered with TQ (5 and 10 mg/kg, i.p., for 11 days) along with ACR, showed reduced or no evidence of paralysis in their limbs³³. Asiaei F *et al.* 2017. observed the effect of *Nigella sativa* alcoholic extract on hippocampal volume, number of dark neurons, and apoptotic cells in hypothyroidism rats' hippocampus during the neonatal and juvenile period. The rats of experimental groups that included propylthiouracil (PTU) + *N. sativa* extract. Different doses of *N. sativa* hydro alcoholic extract reduced hypothyroidism-induced hippocampus neuronal damage³⁴.

Kidney Protection: Kidney protection includes acute renal failure, acute kidney injury, kidney stones, and kidney damage due to effect of drugs. Kidney toxicity is caused by increased free radical production, suppression of antioxidant defense mechanisms and acute renal tubular cell necrosis,

which leads to kidney failure and a reduced glomerular filtration rate³⁵. Hannan et al. 2021. reviewed that Thymoquinone, a bioactive component of Black Cumin (*Nigella sativa*), protects against Kidney Injury by harmful pesticides, heavy metals and some drugs. Black cumin seed oil is used to normalize the blood and urine parameters³⁶.

Benhelima A et al. 2016. studied the outcome of treating lithiasic Wistar rats with *N. sativa* extract for nephroprotective and diuretic effect. The study mainly focused on calcium oxalate urolithiasis. The study found that giving 5 ml/kg body weight/dose/day for 28 days has a protective impact by lowering urine and serum calcium, phosphate, and oxalate levels considerably. This preventive diet was also observed to increase the amount of urine output³⁷.

Jaswal A et al. 2022. investigated defensive role of *N. sativa* against antituberculosis drugs induced renal toxicity. It was found that kidney can be protected from drug induced renal disorder or nephrotoxicity by using ethanolic extract of *N. sativa*. It indicates a reduction in serum urea, creatinine, uric acid, urea nitrogen levels, whereas improvement in histological tubular and glomerular damage. This is found to be very useful during anti TB treatment³⁸.

The effectiveness of black seed in the treatment of kidney stones was investigated by Ardakani Movaghati et al 2019. Based on the results of preclinical studies it reveals that consuming *N. sativa* seeds prevents formation of renal stones and eliminate early-stage stones. Based on experimental observations *N. sativa* powder capsules 500 mg made & given to the patients twice a day for 10 weeks and the results showed 44.4% patient excreted the stone and 51.8% the size of the stone decreased meanwhile 3.1% the stone remained unchanged and also they reported for treating larger stones concentrated solution of the seed extract can be used an Alcoholic extract of *N. sativa* reduces calcium oxalate deposition in kidney as well as in the urine³⁹.

Wound Healing: Healing of wound refers to a series of events that result in the replacement of missing tissue to the greatest extent possible⁴⁰.

In diabetic male rats, the effect of hydroethanolic *Nigella sativa* L. extract on skin wound healing was investigated by Nourbar E et al. 2016.

The experimental study involved diabetic and non-diabetic rats treated with phenytoin and hydroethanolic extract of *N. sativa* 20% and 40%. According to the observations diabetic untreated group cured in 27 days, diabetic phenytoin treated group cured in 24 days⁴¹.

Sarkhail P et al. 2011. studied burn healing potential of *N. sativa* seed oil in rats. The experimental study reveals that n-hexane extract of *N. sativa* seeds external application on burn wound increases the healing rate as compared with control group. After 16 days of application of the extract 96% of wound was cured. It was also reported that Silver sulfadiazine shows better wound contraction (97% after 16 days) but excessive use can lead to toxicity⁴².

Anti-Infertility: Infertility, which leads to unintentional childlessness, is a social and clinical issue that affects couples all over the world. Male factors make up more than half of over all cases of infertility in infertile couples. M. Kollahdooz et al 2014 studied the effects of *Nigella sativa* L. seed oil on infertile men's aberrant semen quality were investigated.

Fatty acid content and chemical composition of *N. sativa* oil was examined. In the study the infertile men were given 2.5ml of *N. sativa* oil twice a day and it was observed that the sperm count increased from 43.53 ± 4.94 to 60.18 ± 5.16 . Also, the other semen parameters were improved as compared to placebo effect (treated with 5ml mineral oil)⁴³.

Anti-convulsant: Chemically induced seizures in albino rats were used to test the anticonvulsant efficacy of a volatile oil extract of *Nigella sativa* seeds by Bepari A et al. 2016.

Different dosage of *N. sativa* oil was studied and compared with conventional treatment using sodium valproate. The experimental study concluded that the use of sodium valproate in epilepsy treatment can be reduced by combining it with *N. sativa* oil and thus can reduce the adverse effect of Sodium Valproate⁴⁴.

Dermatological Effects:

Sun Protection: Shantanu *et al* 2010. studied the sun protection effect of *N. sativa* oil. In the experimental study *N. sativa* oil was extracted by petroleum ether in 40-60°C and sunscreen was formulated using this oil. Sunscreen with an SPF of more than 2 is considered to have good sunscreen action. In this investigation, designed sunscreen cream was determined to be in the middle of the range. As a result, *Nigella sativa* has a high level of sunscreen action. Seed oil has the potential to be a viable option for use as a sunscreen or cosmeceutical⁴⁵.

Acne Treatment: One of the most prominent skin problems is acne vulgaris, which is a chronic inflammatory multifactorial condition of the pilosebaceous follicles. It is most usually linked with adolescence, when androgen production is at its highest, but it can affect individuals of any age or ethnicity⁴⁶. Soleymani S *et al.* 2020. performed a preclinical trial on the effect of a hydrogel. According to preclinical studies the hydroethanolic extract of *N. sativa* was used to prepare the hydrogel. Based on the results of the preclinical studies the treatment essentially decreased the check of skin break out injuries counting comedowns, papules and pustules. Also, this formulation is well suited in most of the patient and can be considered as a natural remedy⁴⁷.

Vitiligo: In vitiligo, the skin's melanocytes (pigment-producing cells), mucous membrane and retina are damaged, resulting in white spots in various places of the skin⁴⁸. Ghorbanibirgani A *et al.* 2014. studied comparison between *N. sativa* and fish oil in treating vitiligo. Based on the clinical trial 96% ethanol was used to extract *N. sativa* oil and it was made alcohol free by evaporation. The recovery of skin lesions was found to be more significant as compared to fish oil.

Patients who used topical *Nigella sativa* saw a decrease in their VASI score from 4.98 to 3.75 after six months, while those who used topical fish oil saw a decrease from 4.98 to 4.62. *N. sativa* can also distribute melanin pigment across the skin by enhancing the sensitivity of cholinergic receptors in the melanopsin, that is also found on the lizard's skin. So, it can be used as a treatment for skin pigmentation⁴⁹.

Anti Hair-fall: Mahmoudvand H. *et al.* 2014. studied the effect of various *N. sativa* seeds extracts on dermatitis. One of the main reasons from hair-fall is dermatitis. Dermatophytes are one of the most important genera of fungi that cause illnesses in humans and animals all over the world. They have the potential to infect keratinized tissues like hair, skin and nails, causing an ailment known as ringworm. According to the study essential oil, methanolic extract, aqueous extract of Thymoquinone Fluconazole and Ketoconazole were used against pathogenic dermatophyte strains *T. mentagrophytes*, *M. canis* and *M. gypseum*. Based on the results thymoquinone had the lowest MIC and shows more significant results as compared to control group⁵⁰.

Other Effect of *N. sativa* Seed: The seeds of *N. sativa* if taken in small quantities as flavoring agent in food or as medicine it generally does not have any side effects for most of the humans. But people who consume other medicines might see some side effects due to reactions with some chemical compound.

Some of the rare side effects of *N. sativa*:

1. Allergic rashes when the black seed oil is applied on the skin.
2. Stops uterus from contracting if taken in large amount so should be avoided during pregnancy.
3. Lower blood sugar and blood pressure, hence the consumption should be monitored.

These side effects occur when the consumption is more than dietary level and when the person is under other medications. The biological potential of other versatile molecules like Coumarin & Pyrimidine acting as CNS depressants, antimicrobial agents, natural product extraction and its biological potential & also our previous group contribution⁵¹⁻⁶⁶.

CONCLUSION: The *N. sativa* has much therapeutic potential with no or least side effects. Many studies have shown positive results of treating many diseases using these seed as well as the oil (Anticancer, Antioxidant, Antimicrobial, Anti-inflammatory, Antiulcer, Antiparasitic, Antihistamine, Analgesic, for skin rashes, for hair

treatment and also used as Flavoring agent). Further, the extracts of seed also used in the food preservative industries. Especially in the case of the diseases like cancer and diabetes which has treatments with a lot of side effects. Finally, a lot of study is being done to synthesize these compounds with better improvements to enhance the medicinal uses as natural remedies.

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