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AN EXHAUSTIVE REVIEW ON *NIGELLA SATIVA* SEEDS (KALONJI) WITH SPECIAL FOCUS ON ITS THERAPEUTIC POTENTIAL

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ABSTRACT

Nigella sativa is a commonly used medicinal plant all over the world. *Nigella sativa* seed, sometimes known as black seed, has been used as a natural cure for a variety of diseases in various cultures for ages. Thymoquinone, thymohydroquinone, dithymoquinone, thymol, carvacrol, nigellimine, nigellicine, nigellidine, and alphahederin are among the active ingredients. It was discovered to have a variety of pharmacological effects on various body organs. It is being used as antihypertensive, liver tonics, diuretics, digestive, anti-diarrheal, appetite stimulant, analgesics, anti-bacterial, and in skin problems, it has been widely utilized. Various researchers have conducted extensive research on *N.Sativa* , and a wide range of its pharmacological actions have been investigated, including antidiabetic, anticancer, immunomodulator, analgesic, antimicrobial, anti-inflammatory, spasmolytic, bronchodilator, hepato-protective, renal protective, gastro-protective, antioxidant properties, and so on. The medical effects of *Nigella sativa* have been noted in ancient systems such as Unani, Chinese traditional medicine, and Ayurveda. It also has antiviral, antioxidant, anti-inflammatory, anticoagulant, immunomodulatory, bronchodilatory, antihistaminic, antitussive, antipyretic, and analgesic properties, according to recent pharmacological investigations. The active compounds of *N.Sativa* , such as nigellidine and -hederin, have been identified as potential SARS CoV-2 inhibitors; this activity might be tested clinically in COVID-19 patients.

Keywords- Immunomodulator, Kalonji, *Nigella sativa*, Unani

INTRODUCTION

Nigella sativa (black seed or black cumin) is a perennial herb in the Ranunculaceae family **[1]**. India, Pakistan, Syria, Lebanon, and Afghanistan are among the Middle Eastern and Western Asian countries where the *N.Sativa* plant is widely farmed **[2]**. It produces delicate flowers with 5 to 10 petals in white, yellow, pink, and purplish colours **[3]**. When the fruits are pulled apart, they reveal a great quantity of black seeds and an inflated big capsule. Black cumin seeds are sometimes known as black cumin seeds **[4]**. Black seeds and their oil have been utilized for a variety of health conditions, including respiratory, digestive, kidney, and liver functions, cardiovascular, and immune system functions, as well as general well-being. It has a long history of use in Indian and Arabian civilizations as traditional medicine **[5, 6]**. *N.Sativa* is considered an important substance in Asian and Middle Eastern traditional medicine **[7, 8]** and its frequent use is also suggested in Tibb-e-Nabwi (Prophetic Medicine) **[9]**. It includes a variety of active ingredients, including thymoquinone (TQ), alkaloids (nigellicines and nigelledine), saponins (alpha-hederin), flavonoids, proteins, fatty acids, and many more, all of which have been shown to have beneficial benefits in the treatment of a variety of disorders **[10, 11]**. TQ is the most prevalent compound in *Nigella sativa* seeds. Anti-cancer **[10, 12-13]**, antimicrobial **[14, 15]**, analgesic **[16, 17]**, antipyretic **[18]**, contraceptive and anti-fertility, anti-oxytocic **[4]**, anti-tussive **[19]**, anti-inflammatory **[16, 20]**, and anti-oxidant potentials for black seed and its active component TQ have been found in cell culture studies and animal models.

Taxonomical Classification: [24]

Kingdom : Plantae
Division : Magnoliophyta
Class : Magnoliopsida
Order : Ranunculales
Family : Ranunculaceae
Genus : *Nigella*
Species : *sativa*

Vernacular names: [25-33]

Afghanistan - *Shewadaru, Siyahdaru*
Arabic - *Habbatussuda*
Bengali - *Kalijira, Kalzira, Mungrela*
Burma - *Samonne*
Deccan - *Kulanjan*
Egypt - *Hubsindee*
English - Black cumin, Nutmeg Flower, Small Fennel
Persian - *Shuniz, Siyahdana, Shunoz*
French - *Cumin noir, Faux cumin, Gith, Nielle de Crete, Nielle romaine, NigelleCultivee, Nigelle romaine*

German - *Schwarzkuemmel, GemeinerSchwarzkuemmel, RoemischerSchwarzkuemmel*
Gujrati - *Kalonji-jirum*
Hebrew -*Qesah*
Hindi - *Kamoon, Kalonji, Magrela, kaladana, kalajaji, Mangrela, krishanjirak*
Italian -*Cinnamonea, Cuminella, Erbaspezie*
Kanad -*Karejirage*
Kannar -*Karijirigi*
Malayalam - *karunchirakam, karunshiragam*
Marathi - *Kalaunjijire*
Persian - *Shuniz, Siahdanah, Siyahbiranj*
Russian -*Tchernushka*
Sanskrit -*Kunchi, Bashpika, Kalajaji, Karava, Krishnajiraka, Kunchika, Kunjika, Musavi, Prathvika, prithvi, Prithu, Prithuka, Sthulajiraka, Sushavi, Upakunchiraka, Upakuncika, Karavi, Krsnajiraka*
Sindhi - *Kalodi*
Tamil - *Karun jiragam, Karun Shiragam, Karumciragam*
Turkey - *Nellajeelakaira, Nullajilakara*
Telgu - *QurachorakAodi*
Urdu - *Kalonji*

Pharmacognostical Description of Plant:

Nigella sativa is a perennial plant. It reaches a height of 45cm. It has linear-lanceolate leaves that are 2.5-5.0 cm long. Flowers are pale blue in colour, solitary on long peduncles, 2.0-2.5cm across, capsule 1.2cm long, and seeds are flattened, rectangular, angular, funnel shaped, tiny, 0.2 cm long and 0.1 cm wide, black in colour. The *Nigella sativa* plant flowers and fruits from January through April. It is typically grown in dry soil from November to April, and seeds take 10 to 15 days to germinate. It can also be determined aseptically from established seedling callus cultured in vitro from leaf stem and root explants. The seeds are small dicotyledonous, trigonus, angular, regulose tubercular 2-3.5 X 1-2mm, black on the outside and white on the inside, dicotyledonous, trigonus and angular. The smell is slightly aromatic, and the flavour is unpleasant **[34-38]**.

Figure 1: *Nigella sativa* PlantFigure

2: *Nigella sativa* Seeds

Character of seed: They are little dicotyledonous, trigonus, angular, regulose-tubercular, dicotyledonous, trigonus, angular, regulose-tubercular, 2-3.5 x1-2 It seems white on the inside and black on the outside. It has a mildly fragrant odour and a bitter flavour. A single layered epidermis comprised of elliptical, thick-walled cells covered externally by a papillose cuticle and filled with dark brown contents was visible in a transverse section of the seed. After the epidermis, there are 2-4 layers of thick walled tangentially elongated parenchymatous cells, followed by a reddish-brown pigmented layer made up of thick-walled rectangle elongated cells. A layer of thick walled rectangular elongated or nearly columnar elongated cells exists within the pigment layer **[37, 38]**.

Description in Unani System of Medicine:

Avicenna mentions black seeds in "The Cannon of Medicine." He mentioned that black seeds can increase physiological energy. It alleviates weariness and general weakness. In Arabian and Indian civilizations, it is employed as a folkloric medicine. Black seeds and their oil have also been used to treat disorders of the respiratory system, digestive system, kidney and liver functions, cardiovascular system, and immune system, as well as for general health **[39, 40]**. Nigella is known in Arabia as *'Habbat-ul-Barakah*,' which means seed of blessing. Loss of appetite, indigestion, diarrhea, dropsy, amenorrhea, dysmenorrhea, and skin eruptions can all benefit from a modest number of seeds. Seeds are roasted and given internally to treat vomiting. Externally, black seed oil is used as a local anesthetic and antiseptic **[39-42]**.

***Mizaj* (Temperament)**

Hot and Dry in second degree **[29, 32]**

Hot and Dry in third degree **[28, 43]**

***Muzir* (Adverse effect)**

Kalonji causes diphtheria and coma when taken in big dosages. It harms the kidneys, urinary system organs, lungs, and liver, as well as causing headaches **[32]**.

***Musleh* (Correctives)**

It can be corrected by mixing vinegar or water of *Kasni (Cichoriumintybus)/ Khurfa (Portulacaoleracea)* **[32]**. *Kateera (Sterculiaurens)/ Bansalochan (Bambusaarundinaceae Retz.)/ Kasni (Cichoriumintybus)*are also used as correctives.

***Afa'al* (Pharmacological actions of seeds in Unani System of Medicine)**

1. *Mukhrij-e-sang-e-gurda wa masana* (Excretes stone from kidney and bladder) **[44]**
2. *Musakkin-e-alam* (Analgesic) **[44]**
3. *Tiryaq-e- zaharsard* (Antidote) **[44]**
4. *Dafe humma* (Anti-pyretic) **[44]**

Pharmacological actions of oil in Unani System of Medicine-

1. *Muqawwi bah* (Sexual stimulant) **[44]**
2. *Munaffis-e-balgham* (Expectorant) **[29, 34]**
3. *Muhallil wa Kasir-e-riyah* (Resolvent and carminative) **[29, 34]**
4. *Muqawwi-e-meda* (Stomachic) **[29, 34]**
5. *Mulayyan* (Laxative) **[29, 34]**
6. *Qatil kiram-e-shikam* (Vermicide/Anti- helminthic) **[29, 34]**
7. *Musakkin-e-awja* (Analgesic) **[29, 34]**
8. *Mudir-e-baul* (Diuretic**[29, 34]**
9. *Mudir-e-haiz* (Emmenagogue) **[32]**
10. *Mudirr-e-sheer* (Lactogogue) **[32]**
11. *Mukhrij-e-janeen* (Abortifacient) **[32]**
12. *Mohallil-e-awram* (Anti-inflammatory) **[32]**
13. *Mukhrij deedan-e-shikam* (Vermifuge) **[32]**
14. *Jali, Jazib* (Detergent, Desiccant) **[32]**
15. *Munzij* (Concoctive) **[32]**
16. *Muqawwi-e-dimagh* (Brain tonic) **[45]**
17. *Muqawwi-e-asab* (Nervine tonic) **[45]**
18. *Mufatteh-e-sudad* (Deobstruent) **[46]**
19. *Muqawwi-e-jigar* (Liver tonic) **[46]**
20. *Habis al dam* (Styptic/ hemostatic) **[46]**

Table1: Therapeutic uses of Tukhme Kalonji (*Nigella sativa* .)

***Mawaq e Istemal* (Therapeutic uses)**	**References (Unani)**
***Bawaseer* (Piles)**	**44**
***Yarqan* (Jaundice)**	**44**
***Sardi, zukam, sua'al, Dard-e-seena* (cold, cough, chest pain)**	**44**
***Matli, Istisqa, Qaulanj reehi* (Nausea, ascites, colic due to flatulence)**	**44**
***Sang e gurda wa masana* (Kidney and bladder stone)**	**44**
***Laqwa, Nuzul-ul-ma* (facial palsy, cataract)**	**44**

Dard e sar **(Headache)**	**44**
Dad, kharish **(Tinea, Itching)**	**44**
Waja al mafasil **(Rheumatoid arthritis)**	**44**
Ihtabas-e-tams, Qilat-e-Laban **(Amenorrhea, hypogalactorrhea)**	**44**
Zoaf-e-Dimag **(cerebral asthenia),** ***Nisyan*** **(amnesia)**	**45**
Nafakh-e- shikam **(flatulence),** ***Dard-e-shikam*** **(Pain Abdomen)**	**45**
Dard-e-kamar **(Backache)**	**31**
Amraz-e-balghami **(phlegmatic ailments)**	**31**
Falij, Suzak, Sra'a **(Paralysis, Gonorrhea, Epilepsy)**	**46**

Pharmacological Activities:

Anti-Inflammatory and analgesic activity:

Carrageenan-induced paw edema in rats and croton oil-induced ear edema in mice were used to test anti-inflammatory efficacy. Acetic acid induced writhing, formalin, and light tail flick tests were utilized to determine analgesic activity. In acetic acid induced writhing, formalin, and light tail flick tests, black cumin seed essential oil was found to have a considerable analgesic effect. The analgesic effect seen in the formalin test was not prevented by naloxone or opioid antagonists. Carrageenan induced paw edema was considerably (p0.001) reduced by intraperitoneal injection of the same dosages **[47]**.

Effects on Central Nervous System

The potential positive effect of *Nigella sativa* on experimental spinal cord damage in rats was examined in comparison to methylprednisolone. The fact that neurons in the methylprednisolone and *Nigella sativa* treated groups had similar morphologies showed that *Nigella sativa* could help protect spinal cord tissue **[48]**.

The central nervous system and analgesic activities of aqueous and methanol extracts of defatted *Nigella sativa* seeds were studied. The findings of the study revealed that both extracts have CNS depressive and analgesic properties **[49]**. *Nigella sativa* seeds oil was discovered to increase pentobarbitone-induced sleeping time in a study **[50]**.

Another study found that aqueous and methanol extracts of *Nigella sativa* seeds caused changes in general behavior, significant reductions in spontaneous motility, normal body temperature, and analgesic activity against a hot plate, implying that the seeds have CNS depressant effect **[51]**.

Anticonvulsant activity:

In pentylenetetrazol-induced epileptic convulsions, intra-cerebroventricular injections of thymoquinone at doses of 200 and 400 m delayed the time until start and reduced the length of tonic-clonic seizures. The findings suggest that thymoquinone may have anticonvulsant properties, most

likely through an increase in GABAergic tone mediated by opioid receptors **[52]**.

The anticonvulsant and antioxidant properties of *Nigella sativa* oil were investigated in mice with pentylenetetrazol (PTZ) kindling seizures. The findings revealed that *Nigella sativa* oil has anti-epileptogenic capabilities, since it lessens the sensitivity of kindled mice to convulsions and the deadly effects of PTZ on the brain **[53]**.

Antioxidant activity:

The diphenylpicrylhydracyl test was used to assess the putative antioxidant activity of *Nigella sativa* essential oil. Using two TLC screening methods, thymoquinone and its components carvacrol, amethole, and 4-terpineol were found to have decent radical scavenging properties **[54]**.

Using chemiluminescence and spectrophotometric methods, the free radical scavenging effects of thymol, thymoquinone, and dithymoquinone on reaction generating reactive oxygen species such as superoxide anion radical, hydroxyl radical, and singlet oxygen were investigated **[55]**.

Antinociceptive activity:

The antinociceptive impact of a watery solution of *Nigella sativa* seeds was assessed using a formalin test, which assesses the potency and duration of the response to a standardized stimulus. The behavioral alterations generated by acute nociceptive stimuli were considerably reduced by *Nigella sativa* (hot plate, early phase and late phase of formalin test). The findings show that the antinociceptive action of *Nigella sativa* seeds in water is related to the seeds' inhibitory influence on nociceptive systems and/or inflammatory mediators. This could indicate that *Nigella sativa* seed components, particularly thymoquinone, have opioid action. **[56]**.

The antinociceptive effects of *Nigella sativa* oil and thymoquinone were investigated in mice in an experimental investigation. In the hot-plate test, tail-pinch test, and acetic acid-induced writhing test, as well as the early phase of the formalin test, oral treatment of *Nigella sativa* oil (50-400 mg/kg) decreased the nociceptive response in a dose-dependent manner **[57]**.

Antispasmolytic activity

Nigella sativa volatile oil and ethanolic extract prevented spontaneous rabbit jejunum movements **[58]**. The seed aqueous extract induced mild to moderate dose-dependent relaxation, enhanced ileum cholinergic sensitivity, and interacted with serotonin in a dose-dependent manner **[59]**. It also demonstrated spasmolytic action mediated by a calcium antagonist effect, supporting its application in diarrhea **[60]**.

Contraceptive activity

Nigella sativa volatile oil and ethanolic extract prevented spontaneous rabbit

jejunum movements **[58]**. The seed aqueous extract induced mild to moderate dose-dependent relaxation, enhanced ileum cholinergic sensitivity, and interacted with serotonin in a dose-dependent manner **[59]**. It also demonstrated spasmolytic action mediated by a calcium antagonist effect, supporting its application in diarrhoea **[64]**.

Anti-asthmatic activity

The possible effect of thymoquinone, a seed component of *Nigella sativa* , on airway-induced hypersensitivity was investigated in a study. The finding revealed that thymoquinone has potent anti-allergic and anti-asthmatic properties, suggesting that it could be useful in the prevention or treatment of a variety of allergic illnesses **[65]**.

Antimicrobial activity

The antimicrobial activity of *Nigella sativa* seed extracts was tested against three Gram positive bacteria: *Bacillus subtalis*, *Entereococcus faecalis*, and *Staphylococcus aureus*, as well as two Gram negative bacteria: Pseudomonas aeruginosa and Salmonella typhi. This plant's methanolic, hot water, and cold-water extracts were used in an antibacterial assay using the disc agar diffusion technique. Plant extracts had a better and broader spectrum of antimicrobial activity against a variety of food-borne germs, according to the findings **[66]**.

A clinical trial was undertaken to explore the activity of *Nigella sativa* seed for the eradication of Helicobacter pylori in non-ulcer dyspeptic patients, and it was found to have anti H. pylori activity comparable to the conventional triple therapy **[67]**.

Black seed oil has a significant antibacterial activity against gram-positive bacteria and yeasts, but no sporicidal action, according to data from an antimicrobial investigation. Oil can thus be advised for use as a flavouring agent in food and as an antibacterial agent in topical medicinal formulations **[68]**.

Another study used the disc diffusion method to measure antibacterial activity. The antibacterial activity of *Nigella sativa* oil was compared to the standard, and the efficacy of the volatile oil was significantly higher than the standard **[69]**.

Antibacterial activity was investigated in *Nigella sativa* seed essential oil derived by hydrodistillation, dry steam distillation, steam distillation of crude oils obtained by solvent extraction, and supercritical fluid extraction. Gram-positive bacteria were much more active against all oil samples than Gram-negative bacteria **[70]**.

At a concentration of 4 mg/disc, an ethanolic extract of seeds inhibited the growth of Methicillin-resistant *Staphylococcus aureus* with a MIC range of 0.2-0.5 mg/ml **[71]**. The methanol extract of the seed was discovered to have anti-

plaque properties, inhibiting Streptococcus mutants and so avoiding tooth cavities **[72]**. Antibacterial activity was seen against *Micrococcus pyogenes var. aureus, Shigella dysenteriae, Shigella sonnei, Shigella boydii, Vibrio cholerae, and E. coli* **[73]**. It was discovered to have antibacterial efficacy against *Bacillus pumilus*, *Bacillus subilis, Streptococcus mutants, Staphylococcus aureus, S. lutea, and Pseudomonas aeruginosa* in another investigation **[74]**.

Anti-arthritic activity

Using an inflammation-induced oxidative stress and tissue damage model, the aqueous methanolic extract of *Nigella sativa* was tested for rheumatoid arthritis in Wistar rats. The mice were given collagen vaccines, and illness appeared 13+1 days following induction. The study's findings revealed that the plant has promising anti-rheumatoid arthritis properties **[75]**.

Immunomodulatory activity

In rats, the immunomodulating and cytotoxic effects of *Nigella sativa* seed volatile oil were examined. The findings suggest that the oil could be an immunosuppressive cytotoxic agent **[76]**.

The radioprotective potential of Nigella savita crude oil against the hemopoietic effects of gamma irradiation was examined. Oral administration of *Nigella sativa* seed oil before irradiation significantly reduced plasma glutathione peroxidase, catalase, and erythrocyte superoxide dismutase activities, indicating that *Nigella sativa* seed oil is a promising natural radioprotective agent against the immunosuppressive and oxidative effects of ionizing radiation **[77]**.

Anti-SARS-CoV Activity-

N.Sativa 's medicinal effects have been documented in the Unani System of Medicine, Chinese Traditional Medicine, Ayurveda, and other healing systems **[5]**. *N.Sativa* contains terpenes, flavonoids, phytosterols, tannins, coumarins, phenolic compounds, alkaloids, cardiac glycosides, saponins, fatty acids, and volatile oils, according to phytochemical screening. Terpenes like thymoquinone (TQ), dithymoquinone (DTQ), carvone, limonine, trans-anethol, and p-cymene, indazole alkaloids like nigellidine and nigellicine, and isoquinoline alkaloids like nigellicimine, nigellicimine-N-oxide, and -hederin are among the bioactive componds of *N.Sativa* **[78]**. *N.Sativa* could be used to treat COVID-19 patients since it has antiviral, antioxidant, anti-inflammatory, anticoagulant, immunomodulatory, bronchodilatory, antihistaminic, antitussive, antipyretic, and analgesic properties. N. sativa has also been demonstrated to have anti-hypertensive, anti-obesity, anti-diabetic, anti-hyperlipidemic, anti-ulcer, and antineoplastic properties, all of which

could benefit COVID-19 patients with co-morbid diseases **[79]**. Furthermore, active components of *N.Sativa* , including as nigellidine and -hederin, have been identified as potential SARS CoV-2 inhibitors **[80]**.

CONCLUSION:

Herbal medications are widely used as a supplemental therapy, and their popularity is growing worldwide. Many medications are chemically modified natural compounds, while others are obtained straight from plants. In the Unani System of Medicine, *N.Sativa* has a long history of use for different neurological and GIT illnesses. Recent scientific investigations have also established that *N.Sativa* seeds, oil, and extracts, as well as some of its active components, including TQ and alpha-hedrin, have outstanding in vitro and in vivo pharmacological activity against a wide range of disorders and are generally safe. Furthermore, active components of *N.Sativa* , including as nigellidine and alpha-hedrin, have been identified as potential SARS CoV-2 inhibitors. Because the medicine in question has significant therapeutic potential, more scientific data should be obtained in order to fully investigate it.

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