

# An Elaborate Pictographic Monograph On Black Cumin: The Miracle Herb

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## Abstract

*Nigella sativa* L. of family Ranunculaceae has been used as a treatment for various diseases, in ancient times. The seeds of *N. sativa* show extensive pharmacological properties, that include immune potentiating, anti-histaminic, anti-diabetic, anti-hypertensive, anti-inflammatory, and anti-bacterial effects. It is efficacious against various varieties of diseases, including Eczema, Jaundice, Conjunctivitis, Diabetes, Dyspepsia, Hypertension, Paralysis, intrinsic Hemorrhage, Anorexia, Cough, Asthma, Bronchitis, Fever, Headache, and Influenza. The seed of *Nigella sativa* L. contains important fatty acids such Linolenic and Linoleic acid. Other pharmacologically active chemical substances found in it include Phyosterols, Flavonoids, Tocopherols, Nigellone, Carvacrol, Dihydrothymoquinone, and pinene. Thymoquinone, Thymohydroquinone, Dithymoquinone, Thymol, Carvacrol, Nigellimine, Nigellidine, and Alphahederin are only a few of the many active substances it contains. One of the most active constituents of the Thymoquinone (TQ), is therapeutically effective against wide range of bacteria, parasites, viruses, fungus, and Schistosoma.

Though the exact mechanism is un-identified, the theory is that the anti-inflammatory and anti-oxidative properties could be useful in treating osteoporosis, as both conditions are linked to inflammation and oxidative stress. Neuroprotective, Nephroprotective, Cardioprotective, Gastroprotective, Hepatoprotective and anti-cancer effects are some important pharmacological properties of *Nigella sativa*. To verify the safety and efficacy of *Nigella sativa* L. in treating HFMD patients, further randomized controlled clinical trials are required. This paper is a comprehensive review of the pharmacognostic profile and pharmacological activity of Black Seeds. This information will be valuable for healthcare professionals, researchers, and scientists who work with this plant and need to be informed about it.

**Keywords:** Kalvangi, *Nigella sativa*, Magical drug, Kala Dana, Immunity Booster

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## 1. INTRODUCTION

Kalonji, also widely known as *Nigella sativa* L. family Ranunculaceae, Black Seed, and Black Cumin, is a flowering plant [1, 2]. The seeds of Black Cumin have a past long history of usage in many herbal medicines to treat a different diseases and situations varying from diabetes mellitus to arthritis [1, 3].

*Nigella sativa* L. is a spicy herb that is known for its medicinal properties. It has been used for culinary purposes and traditional medicine for a long time [4-6]. *Nigella sativa* L. is an indigenous plant of the Indian Subcontinent, Southwest Asia, northern Africa and eastern Mediterranean. It is cultivated in countries like Egypt, Greece, Iran, Syria, Turkey, Saudi Arabia, Albania, Pakistan and India [1, 3]. *Nigella sativa* L., As a universal remedy is available in the form of seeds, oil, paste, extract and powder [1, 4].

The plant is well-known for its tiny, black seeds, which have a characteristic smell and a mildly acrid flavor. *Nigella sativa* is a plant with a rich historical and cultural significance, having been used for thousands of years [7]. It was found/ disclosed in the Tutankhamen tomb in ancient Egypt, and both the Bible and Islamic literature mention to it [8-10].

*Nigella sativa* has been used for its prospective health benefits in Allopathic or modern medicines. Anti-inflammatory, antioxidant, antibacterial, and immunomodulatory effects have all been noted. Different studies show, Black Seed extract may be beneficial in treating different gastrointestinal problems, diabetes, hypertension, asthma, and allergies [1, 3].

*Nigella sativa* seeds are used in preparing food/cooking and therapeutically. Especially, in Middle Eastern and South Asian culinary traditions, they are regularly used as a spice and flavoring agent. Foods like bread, pastries, curries, and pickles, the seeds can be added whole or crushed form and spice blends to boost flavor and aroma [2].

The seeds of *Nigella sativa* are nutritionally rich and include a variety of advantageous compounds, including essential fatty acids, amino acids, vitamins (such as Thiamine, Riboflavin, and Niacin), minerals (such as Calcium, Iron, and Potassium), and antioxidants. One of the important active components of *Nigella sativa* L. is Thymoquinone, which is thought to have numerous therapeutic characteristics [4]. *Nigella sativa* seeds are thought to contain about 45% fat, 20% carbohydrates, and 20% protein, according to one research/study. Furthermore, even though specific amounts aren't mentioned, they seem to give some Calcium, Magnesium, Phosphorus, and Potassium. *Nigella sativa* may also contain trace amounts of the vitamins A, C, and E as well as few B vitamins [1-3, 10, 11].

*Nigella sativa* L. has a long history of traditional use in treating various ailments and conditions affecting the digestive, respiratory, kidney, and liver systems, as well as cardiovascular health, immune function, and overall well-being. Avicenna mentioned black seeds in "The Canon of Medicine" for their energizing properties and ability to aid recovery from fatigue and low mood. Indian and Arabian civilizations have also used black seeds and their oil as both food and medicine throughout history [12]. Due to its versatile uses, it has been referred to as "Habbatulbarakah" in Arabic, meaning the seed of blessing [13].

In Southeast Asian and Middle Eastern countries, traditional medicine often employs *Nigella sativa* L. seeds to address rheumatism, skin rashes, and other inflammatory conditions. Ether extract of *Nigella sativa* L. and TQ inhibits few clinically isolated dermatophytes, i.e. *Trichophyton mentagrophytes*, *Trichophyton rubrum*, *Microsporum cani*, *Trichophyton interdigitale* and *Epidermophyton floccosum*. Research findings suggest that the anti-dermatophyte activity of *Nigella sativa* L. is primarily attributed to its active compound, TQ. The therapeutic potential of *Nigella sativa* L. and TQ seed extracts was evaluated for treating vitiligo skin disorders and understanding the cellular mechanisms involved in skin darkening [2]. Treatment with the extracts and TQ resulted in skin darkening by displacing melanin within the pigment cells known as Melanophores. 52 patients with the Vitiligo skin lesions in a double-blind trial used *Nigella sativa* L. oil twice daily [9].

Interactions between co-administered medications and *Nigella sativa* L. can be expected, distressing the drugs' intestinal bioavailability and therapeutic actions. Extracts of *Nigella sativa* L. have confirmed to Inhibit P450, 2C9, 3A5, 3A4 of Human Cytochrome with the 3A7-mediated metabolism of marker substrates in in-vitro tests, which infers that they may manipulate or hinder the metabolism of a wide range of medication. Literature confirms the pharmacological and therapeutic potential of seeds, oil, extracts, and active compounds like TQ and Alpha-Hederin of *Nigella sativa* L. These substances have demonstrated safety and significant pharmacological activities in laboratory and animal studies against various diseases [4, 14].

## **2. Plant description**

*Nigella sativa* L. is an erect, herbaceous, blooming plant with a well-developed taproot and a stiff, multi-branched stem. The agro-morphological characteristics of *Nigella sativa* L, set it apart from other herbaceous plants and other *Nigella sativa* L. accessions [8].



Figure 1. Black Cumin with Ingredients for cooking and Ayurveda treatments



Flour, oil and Seeds of *Nigella sativa*



Seeds of *Nigella sativa*

Figure 2

### 2.1. Vernaculars

Vernaculars of *Nigella sativa* are illustrated as under in Table 1.

Table 1. Vernaculars of *Nigella sativa* [13, 15, 16]

Language	Name
	Black seed
	Black cumin
Amharic	Tikurazmud
Arabic	Kamuneswid (“black cumin”), Habbat al Barakah (“seed of blessing”)
Assamese	Kaljeera

Hindi	Kalonji, Mangrail
Hebrew	Ketzakh
Malayalam	Karimjerrakam
Persian	Siyah Daneh
Russian	Chernushka
Tamil	Karum cheerakam
Turkish	Cörek out
English	Black Cumin, Small Fennel, Love-in-a-mist
French	Cumin noir, Nigelle cultivée, Toute-épice
Indonesia	Jintenheim
Malaysia	Jintanhitam
Medicinal	Habbat us Sauda/ السوداء الحبة/ دانه سياه
Punjabi	Kala Bee
Urdu	Kala Dana/ كلونجی

### 2.2 Part used

Seeds of Black Cumin are used medicinally, leaves are also used in culinary arts and as food [13].



**Figure 3.** Black cumin oil seeds and flower

### 2.3. Habit

*Nigella sativa* L. is a small shrub almost 20–90cm tall. It possess green leaves and rosaceous white, pink, yellow, pale or purplish flowers with 5–10 corolla. The fruit is capsule with 3–7 united follicles, also contains several minute seeds, sharp black in color [16, 17].

### 2.4. Distribution

The species is grown and spread throughout the Sub-Continent, but is particularly abundant in Punjab, Himachal Pradesh, the Ganges lowlands, Bihar, Bengal, Assam, and Maharashtra. In addition to Sub-Continent, the plant is grown in Bangladesh, Turkey, the Middle East, and the Mediterranean region. It is also grown in Syria, Lebanon, Israel, and South Europe [6, 18, 19].

### 2.5. Temperament

*Nigella sativa* L. has Hot & Dry temperament according to Tibb-e-Unani [16] and ghudi uzlati temperament in Simple Organ Theory [20].

### 2.6. Morphological Description

Morphological traits of *Nigella Sativa* are illustrated in table 2 and by figures (4-6) as under

**Table 2.** Morphological traits of *Nigella Sativa* [6, 18, 19]

Trait	Value/Characteristics
Plant Height	30–70 cm
<b>Stem</b>	
Diameter	0.65–0.98 cm

Shape	Angular
<b>Leaves</b>	
Arrangement	Alternate
Length	2.5–5.0 cm
Width	2.0–2.5 cm
Shape	Linear to lanceolate
Phyllotaxis	1-2
Pinna/rachis	5-6
<b>Root</b>	
Length	12.74 - 15.08 cm
<b>Flower</b>	
Color	Pink, white, yellow, pale blue, or pale purple color
Size	2.74 cm × 2.78 cm
Number of petals	5-10
Number of sepals	4-6
<b>Seed</b>	
Capsule size	0.4–1.7 cm
Seed/capsule	59.29 ± 3.2
Color	Black
Size	2.33 mm ± 0.1 × 1.14 mm ± 0.02
Shape	Acute, angles sharp, ovate, tetra-angular, more tapering at the end.
Flowering and Fruiting Time	January to April



Blue flower of *Nigella sativa*



Capsules of *Nigella sativa*

**Figure 4.** Parts of Black Cumin



**Figure 5.** Real Black Cumin - *Nigella sativa*



**Figure 6.** Close up photography (selective focus) on Seeds, Flowers and Capsule of *Nigella sativa*

### 3. Cultivation

In Sub-Continent, *N. sativa* is typically grown only once per year as a rabi crop in the plains during the months of October (late) - November to March-April, and sporadically in the hills during the months of May-June [6].



**Figure 7.** Growth stages of plant from seed to flower and fruit

### 3.1. Habitat

It grows well in warm, humid environments to cool, dry locations with light snowfall. Flowering and seed germination are encouraged by cool, humid conditions [6, 18, 19].

### 3.2. Soil

The best soil for cultivation is a sandy, microbial active loam. Both the flat and well-drained soils in places with moderate rainfall and the sloppy soil in heavy rainfall regions are quite suited for farming. A good soil pH range for cultivation is 7.0 to 7.5 [6, 15, 18, 19].

### 3.3. Preparation of Land

One furrowing taken after by 2-3 nerve racking and leveling will be reasonable [6, 15, 18, 19].

### 3.4. Method of Sowing

Planting seeds or transferring plants from the previous year's roots. The process of planting seeds is done in October or November. It can be done by scattering the seeds over the land (using 1.5 kg of seeds per hectare), using a seed drill machine, or by planting seeds in straight lines with gaps between them (30, 40, or 50 cm apart) and burying them 2 cm deep in the soil. After planting for 20 days, the plants are spaced out by removing some so they are 20 cm apart. Planting bulbs from the previous year's root stock can be done when the soil has enough moisture for deep ploughing not too wet or too dry [6, 18, 19].



Figure 8. Crop of Black Cumin



Figure 9. Landscape view of Blooming *Nigella sativa* flowers in the field

### 3.5. Weed Control

Weeding often helps reduce competition from weeds and creates a good environment for plants to grow and develop. It is suggested to do weeding by hand hoe or Khurpi every 20 to 25 days, around 3 to 5 time [6, 18, 19].

### 3.6. Irrigation

Watering the plants one or two times when they are flowering and forming seeds can help make the grains bigger and contain more oil [6, 18, 19].

### 3.7. Harvesting

Black cumin is usually harvested in late March or the first week of April. Harvesting the crop when it is still at a young green stage, results in a higher amount of fragrant oil. This attracts more buyers and is beneficial for the market [15]. Black Cumin seeds stay alive longer if they are fully ripe. It is really important to harvest before the fruit falls off (which is a big problem). So, we can do 2 to 3 or more rounds of picking to prevent seeds from being lost because of the falling fruits. The collected plants are left in the sun to dry and then are hit with a stick to separate the grain [6, 18, 19].

### 3.8. Post-Harvest Management

*N. Sativa* plants need a lot of work to be collected and harvested because the capsules (fruit) often break apart when they are fully grown. After the fruits are picked one by one by hand, they are stored in a dry place until they naturally open up [15]. The fully grown fruits don't need a lot of care because they can



protect themselves from fungus, insects, and rodents with their natural oil [6, 18, 19].

**Figure 10.** Post-Harvest Management

## 4. Pharmacogenetic Characteristics

### 4.1. Macroscopic features

### 4.2. Microscopic features

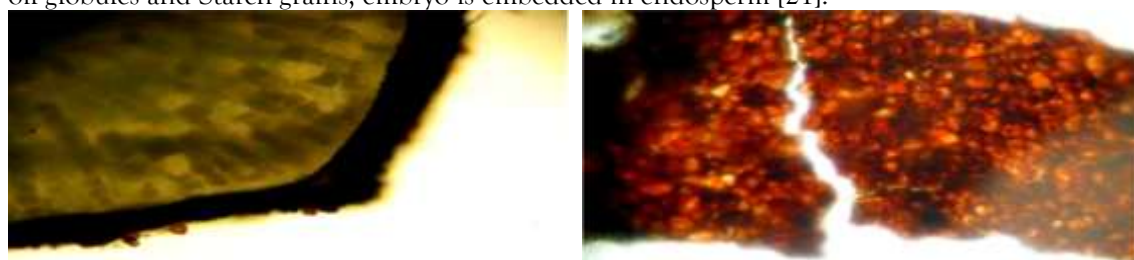
Microscopic examination of transverse section of seed showed epidermis and endosperm [21].

#### 4.2.1. Epidermis

Epidermis consists of single layers of thick walled, elliptical cells that are covered by a papilla's cuticle externally, it is filled with reddish to brown content; epidermis is also followed by two to four layers of tangentially elongated and thick walled Parenchymatous cells which is followed by a pigmented layer of cylindrical thick walled and tangentially elongated cells filled with reddish brown pigment. Beneath the pigmented layer is Parenchyma that is comprised of the rectangular, radially elongated, thick walled cells in the form of a layer [21].

#### 4.2.2. Endosperm

It consists of moderately polygonal to rectangular, thick walled cells, few of which are crammed with the oil globules and Starch grains; embryo is embedded in endosperm [21].



**Figure 13.** Cross-sections of the external tegument of *N. sativa* [22]

## 5. Preliminary Phytochemical Analysis

Preliminary Phytochemical Analysis is illustrated in Table 3 as under.

**Table 4.** Phytochemical Analysis [23-25]

Test Perform	Chemical Test	Observation	Result
Test for Alkaloids	Saturated solution of picric acid+ filtrate	Yellow colour precipitate	Positive
Test for fixed oil	Drops of filtrate on Filter paper	Stain on filter paper	Positive
Test for volatile oil	1.Drops of filtrate on Filter paper 2. Filtrate+ Sudan III dye	Permanent stain on filter paper Red colour obtained	Positive
Test for Tannins	5% solution of FeCl <sub>3</sub> + filtrate	Green colour or yellow obtained	Positive
Test for Flavonoids	NaOH solution+ filtrate	Yellow colour obtained	Positive
Test for Glycoside	Dilute H <sub>2</sub> SO <sub>4</sub> +filtrate + 5% solution of NaOH + add Fehling solution (A+B)	Red colour produced	Positive
Test for Steroids	Conc. Sulphuric acid+ filtrate	Yellow colour on top	Positive
Test for Triterpenes	Conc. Sulphuric acid+ filtrate	Green colour on bottom produced	Positive

## 6. Chemical Constituents

*Nigella. sativa* possess crude fibers (8.4%), carbohydrates (24.9%), fats (28.5%), proteins (26.7%) and total ash (4.8 %). Several vitamins and minerals i.e. Fe, Zn, P and Cu etc. Carotenes which are converted to vitamin A by liver are also present in Black Cumin. Unsaturated fatty acids like Eicodadienoic acid (3%), Dihomolinoleic acid (10%), oleic acid (20%) and Linoleic acid (50-60%) are contained in seeds along with Palmitic, Stearic acid which are Saturated fatty acids about 30%. A major Sterol  $\alpha$ -sitosterol, accounts for 44% in Tunisian and 54% in Iranian varieties [2, 23, 24].

Two types of alkaloids; i.e. Isoquinoline alkaloids ( Nigellcimimine and Nigellcimimine-N-oxide) and Pyrazol or Indazole ring containing alkaloids (Nigellcicine and Nigellidine) [2, 21, 23]. Some other compounds e.g. Citronellol, Carvone and Limonene, are present in trace the amounts [2, 23, 24]. The Seeds also contain a water soluble compound Alpha-Hederin (pentacyclic Triterpene and Saponin) which is a potent anticancer agent [2, 23, 24]. Vanillic acid is also reported in roots and shoots [2, 23, 24].

Various other compounds reported to be present includes Tirucallol, Avenasterol-7-ene, Avenasterol-5-ene, Nigellone, Citrosteradienol, Campesterol, Cycloeucalenol, Cholesterol, Gramisterol, Lophenol, Obtusifoliol, Stigmastanol, Stigmasterol-7-ene, Butyrospermol, Taraxerol, 24- Methylene-Cycloartanol, Cycloartenol and  $\beta$ -amyrin etc [2, 13, 23].

### 6.1. Bioactive Constituents

Important bioactive phytochemicals of Black Cumin include  $\alpha$ -Pinene, Thymol, Carvacrol (6%-12%), Thymoquinone (30%-48%), Dithymoquinone, Thymohydroquinone, 4-Terpeneol (2%-7%), p-cymene (7%-15%),  $\iota$ -Anethol (1%-4%), Longifolene (1%-8%) and Sesquiterpene etc [2, 21, 23]. Black Cumin also contains a water soluble compound Alpha-Hederin (pentacyclic Triterpene and Saponin) which is a potent anticancer agent [2, 23, 24]. Most of the pharmacological features of Black Cumin are essentially credited to Quinine compounds, among which Thymoquinone (TQ) is most prolific [2, 23].

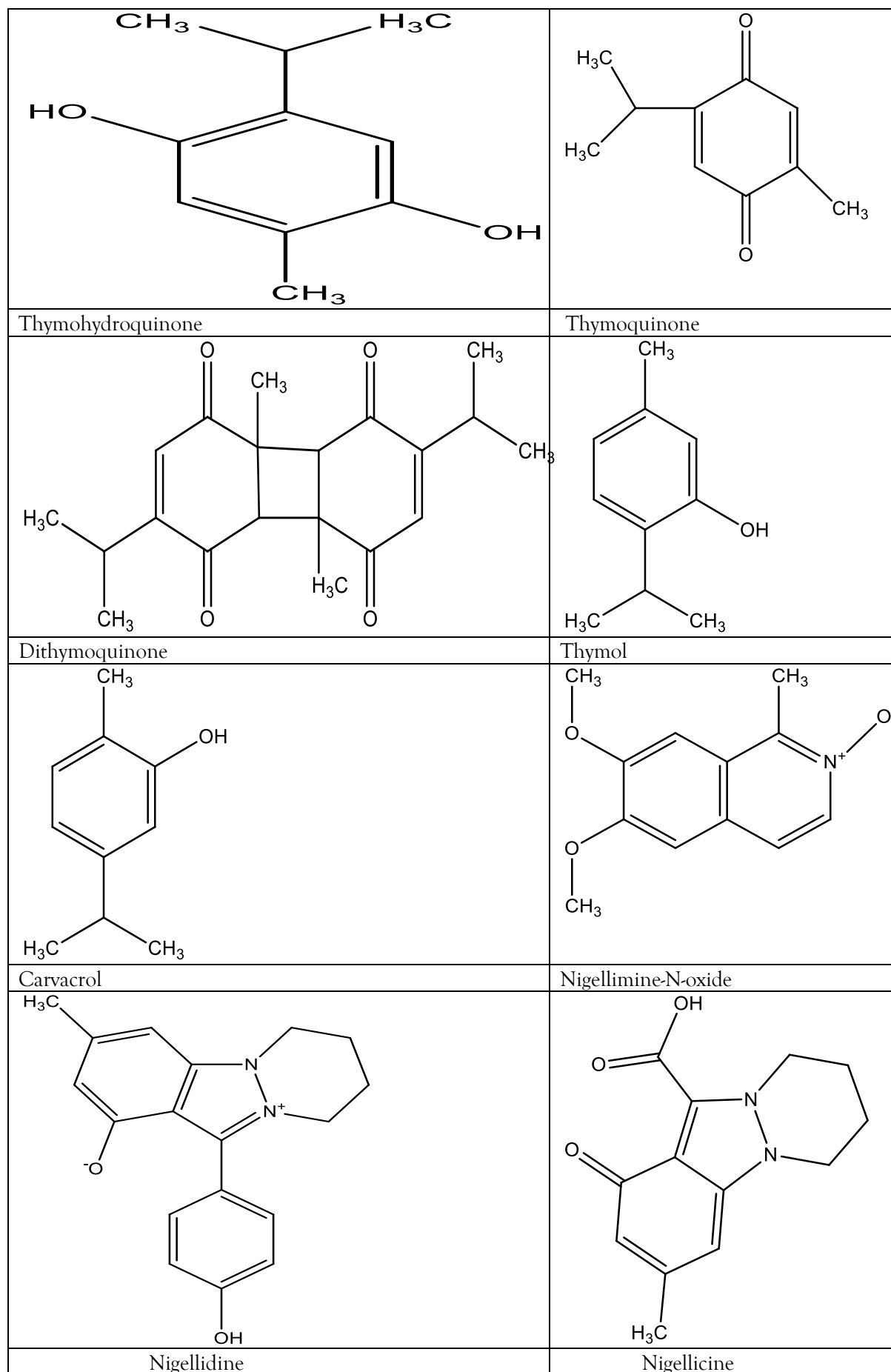
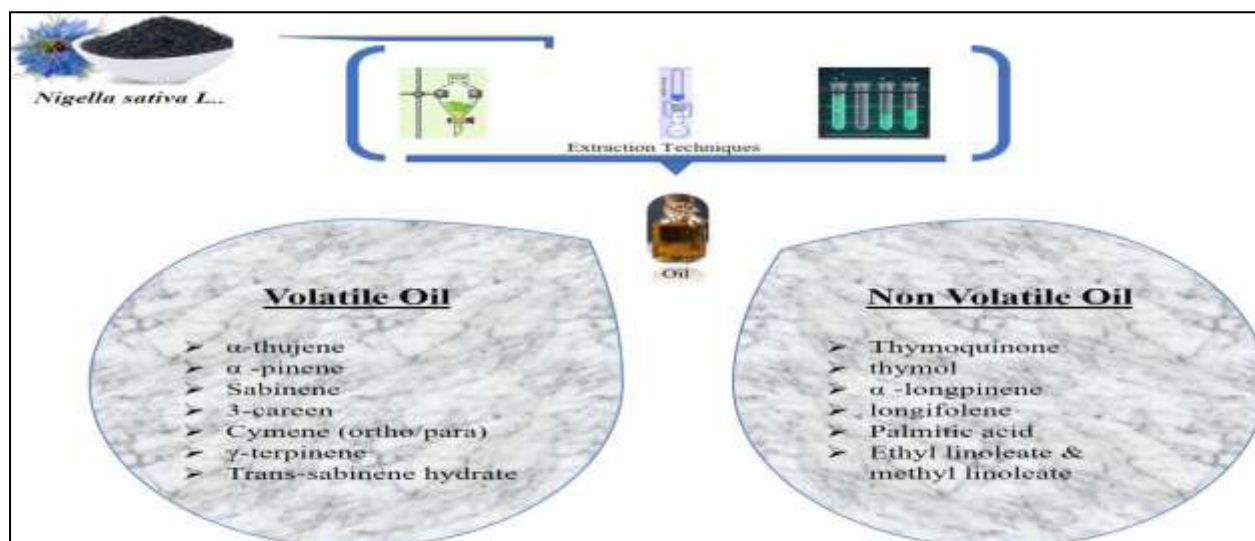


Figure 14. Bioactive compounds in Black Cumin



**Figure 15.** Black Cumin Oil composition

### 6.1. Determination of total ash

Accurately measured 2 to 3 grams of powder is placed on a crucible. It is cared that temperature does not go over 450 degrees Celsius. It is then cooled down and then its weight is measured. We can't get ash without Carbon. The content is moistened with 2 ml of distilled water and dried on water bath or hot plate. It is then ignited till constant weight. The percentage of total ash is calculated [23, 25, 26].

### 6.2. Determination of acid insoluble ash

To determine the percentage of acid insoluble ash, the ash is boiled with dilute Hydrochloric acid for 5 minutes. The insoluble matter is collected on ash less filter paper, washed with hot water, and then ignited until a constant weight is achieved [25, 26].

### 6.3. Extractive values

The powder is extracted using the hot maceration method with 500 ml of alcohol. The extractive values are determined following the method described in the Ayurvedic Pharmacopoeia of India [25, 26].

#### 6.3.1. Alcohol soluble extractive

To prepare the alcoholic extract, 5 grams of coarsely powdered drug is taken in 100 ml of alcohol in a closed flask. The flask is shook frequently for 6 hours and then let it stand for 18 hours. The mixture is filtered carefully. 25 ml of the filtrate is taken and evaporated in a flat-bottomed Petri dish at 105 degrees Celsius until a constant weight is achieved. Finally, percentage weight of the dried extract is weighed and percentage yield is calculated [25, 26].

#### 6.3.2. Water soluble extractive

To prepare the water extract, 5 grams of coarsely powdered drug is taken in 100 ml of water in a closed flask. The flask is shook frequently for 6 hours and then let it stand for 18 hours. The mixture is filtered carefully. 25 ml of the filtrate is taken and evaporated in a flat-bottomed Petri dish at 105 degrees Celsius until a constant weight is achieved. Finally, percentage weight of the dried extract is weighed and percentage yield is calculated [25, 26].

### 7. Dosing

For therapeutic purposes, *Nigella sativa* extract has been used at doses of 100 mg, black seed oil at doses of 5 mL, and black seed powder at doses of 1.5 to 3 grams daily for up to 3 months. A study found that taking 1000 mg of black seed oil capsules daily for 4 months was safe and effective as a supplementary treatment for asthma [27]. In the context of weight loss and reducing blood sugar levels, research suggests that higher doses of 2-3 grams of black seed oil per day for 8-12 weeks have been found to be the most effective [28-31].

### 8. Folkloric uses

As per the teachings of Prophetic Medicines, Black Seed is highly beneficial and can combat all diseases in the human body except death. In Islamic, Ayurvedic, Unani, traditional, and indigenous medicine, Black Seed seeds or its oil are traditionally used alone or in combination with ingredients like Honey, Butter, and astringents [8, 13, 31, 32].

Black Seed or oil are utilized to treat a wide range of diseases including abdominal disorders, abscesses, Anorexia, worm infections, Asthma, Bronchitis, chronic headache, cardiovascular disease, Colic,

Coughs, Coryza, Diabetes, Dermatoses, Diarrhoea, eye infections, fatigue, dispiritedness, Fever, Galactopoiesis, Haemorrhoids, Hypertension, Jaundice, nasal ulcers, liver ailments, Pulmonosis, metabolic syndrome, Orchitis, Obesity, reproductive disorders, Rheumatism, respiratory infections, Sinusitis and sore eyes, and also as a booster for body energy [8, 13, 28-33].

#### 10. Religious significance of *Nigella sativa*

Black Cumin has a rich spiritual and chronological significance as is referenced in several religious textual content. In the Bible's Old Testament, it is mentioned as "Ketzah" and described as a versatile spice for bread and cake. It is also referred to as Melanthoin and Githin in ancient literature. The *Nigella sativa* is extensively narrated in Traditional Arab and Islamic Medicine (TAIM) as "Habb-e-Sauda." It holds the title of prophetic medicine due to its mention by Prophet Muhammad (SAW) [28-31]. According to the teachings of Prophet Muhammad (SAW), black seed is highly beneficial and can combat all diseases in the human body except death. It has also been discussed in the book of Bukhari as "*Nigella sativa* is healing of all the diseases" [33, 34]. Avicenna mentioned black cumin seed in his book the Canon of Medicine [33].

The Prophet Muhammad (P.B.U.H) who is seen as one of the most influential figures in history, reportedly said that "There is a cure for every disease in Black Seeds except death and black seeds are Shooneez." Salim Bin Abdullah narrates with reference to his father Hazrat Abdullah Bin Omar that Prophet Muhammad (PBUH) said, "Let fall these Black Seeds upon you, these contain a cure for all diseases except death. The historical importance of Black Seeds in Islamic culture highlights their healing and protective properties, underscoring the remarkable potential of this remarkable plant to positively impact on the human body [32]. Black seed is referred to as 'Habbatulbarakah' in Arabic, meaning the seed of blessing, due to its numerous beneficial uses [13, 32, 33].

#### 11. Pharmacological Uses

*Nigella sativa* seeds are reported to have a broad range of pharmacological efficacy as anti-oxidant, gastro-protective, anti-tussive, anti-anxiety, anti-ulcer, anti-asthmatic, anti-cancer, immune-modulatory, anti-inflammatory and anti-tumor potentials as discussed below [13, 32, 33].



Figure 16. Pharmacological activities

It also has hepato-protective effects, promote gastric ulcer healing, suppress tumor growth, improve male infertility, address cardiovascular disorders, enhance memory, stimulate milk production, protect against lipid peroxidation, exhibit antibacterial and antiviral activity against Cytomegalovirus, and have anti-dermatophyte properties [13, 23, 32].



**Figure 1.** Pharmacological uses

### 11.1. Testicular-protective activity

The protective role of Thymoquinone (TQ) on the Methotrexate' testicular toxicity of in male mice was examined. Thymoquinone therapy lowered TAC and prohibited the increasing the activity of Myeloperoxidase. When mice were given Methotrexate, microscopic examination revealed dilated interstitial spaces, edema, noteworthy distraction of Seminiferous epithelium with a decrease in diameter of the Seminiferous tubules. Administration of Thymoquinone (TQ) significantly overturned the histological variations caused by Methotrexate. It is recommended that using Thymoquinone possibly reduce the harmful effects of the Methotrexate on testicular tissue of the patients [13].

### 11.2. Anti-microbial activity

Experimental research has shown that extracts from *Nigella sativa* have anti-microbial properties against various microbes, including antibiotic-resistant bacteria. The antimicrobial effects have been observed in the Gram-positive bacteria and the Gram negative bacteria along with pathogenic fungus *Candida albicans*. The active compounds in *Nigella sativa*, such as Thymohydroquinone and Melanin, are responsible for these antimicrobial properties. The antimicrobial activity was tested against various targets, including yeast strain, three Gram positive bacteria and two Gram negative bacteria. Thymoquinone, p-cymene, and Carvacrol contribute to the anti-microbial properties of (HS), while Oleic, Linoleic, and Palmitic acid derivatives are responsible for the anti-bacterial activity. This integration aimed to leverage the herb's significant anti-bacterial properties, thereby enhancing the effectiveness of the composite material as a safe implant [3, 35].

The anti-bacterial properties of ground *Nigella sativa* were tested using a modified paper disc diffusion assay. A significant inhibition of *Staphylococcus aureus* was observed at a dosage of 300 mg/mL, compared to the control using distilled water. Azithromycin, as the positive control, also confirmed this inhibition. TQ and Melanin which are key photochemicals are attributed to show positive inhibition [3].

Anti-bacterial activity of Black Cumin extract against Methicillin resistant *Staphylococcus aureus* (MRSA) was found to be positive at a concentration of 4 mg/disc. An (MIC) range of 0.2-0.5 mg/mL minimum inhibitory concentration was observed [36].

### 11.3. Antioxidant activity

*Nigella sativa* is a traditional and natural source of antioxidants. It can inhibit free radicals and effectively reduce oxidative stress. Its extract contains various antioxidant compounds, such as TQ, Carvacrol,  $\alpha$ -anethole, and 4-terpineol. TQ, in particular, possesses strong anti-oxidant properties, which indirectly suppresses the generation of reactive oxygen species and inhibits lipid peroxidation [35].

*Nigella sativa* is a valuable source of bioactive compounds known for their enhanced antioxidant activities. It helps lower total Triglycerides, total Cholesterol, and LDL-cholesterol levels while increasing HDL-cholesterol levels. Additionally, *Nigella sativa* administration has demonstrated significant anti-hypertensive effects, attributed to its hypoglycemic, hypolipidemic, anti-oxidant, cardiac depressant, Calcium channel blockade, and diuretic properties [37].

#### 11.4. Anti-inflammatory activity

The fixed oil of *Nigella sativa* seed and its phytochemicals exhibit anti-inflammatory effects by inhibiting the production of compounds involved in inflammation, such as Eosinophils, Oxidants, Cytokines, and inflammatory Macrophages and Neutrophils. These components play a role in creating an inflammatory state in the body. *Nigella sativa* oil and Thymoquinone have strong anti-inflammatory properties, as shown in different disease models including Encephalomyelitis, Colitis, Peritonitis, Edema, and Arthritis. They work by suppressing inflammatory mediators like Prostaglandins and Leukotrienes. In a study on rats, oral administration of 4 mL/kg/day *Nigella sativa* oil for 31 days resulted in reduced production of IL-4 and NO. At a dose of 10 mg/kg in rats, Thymoquinone exhibits anti-inflammatory effects by inhibiting the COX and 5-LPO pathways. At a dose of 5 mg/kg in rats, it can reduce TNF- $\alpha$  and IL-1 $\beta$  levels in Arthritis. The anti-inflammatory properties of [38, 39]. In a study, *Nigella sativa* Silver Nanoparticles (AgNPs) were administered. A significant anti-inflammatory activity [39].

#### 11.5. Anti-cancer activity

*Nigella sativa* seed, its essential oil, and certain active compounds like TQ and  $\alpha$ -Hederin have demonstrated notable anti-cancer effects against different types of tumors. These effects involve various mechanisms such as targeting free radicals, influencing enzyme activity, inhibiting cell growth, altering intracellular Glutathione levels, acting as anti-oxidants, capturing free radicals, and inducing Apoptosis in cancer cells [38, 39].

TQ has been found to inhibit the growth of Colon Cancer cells, induce morphological changes, and increase apoptosis in these cells. Additionally, the topical application of *Nigella sativa* extract has shown inhibitory effects on early stages of skin Cancer. The development of functionalized Nanoparticles for biomedical applications has become a significant challenge [40, 41].

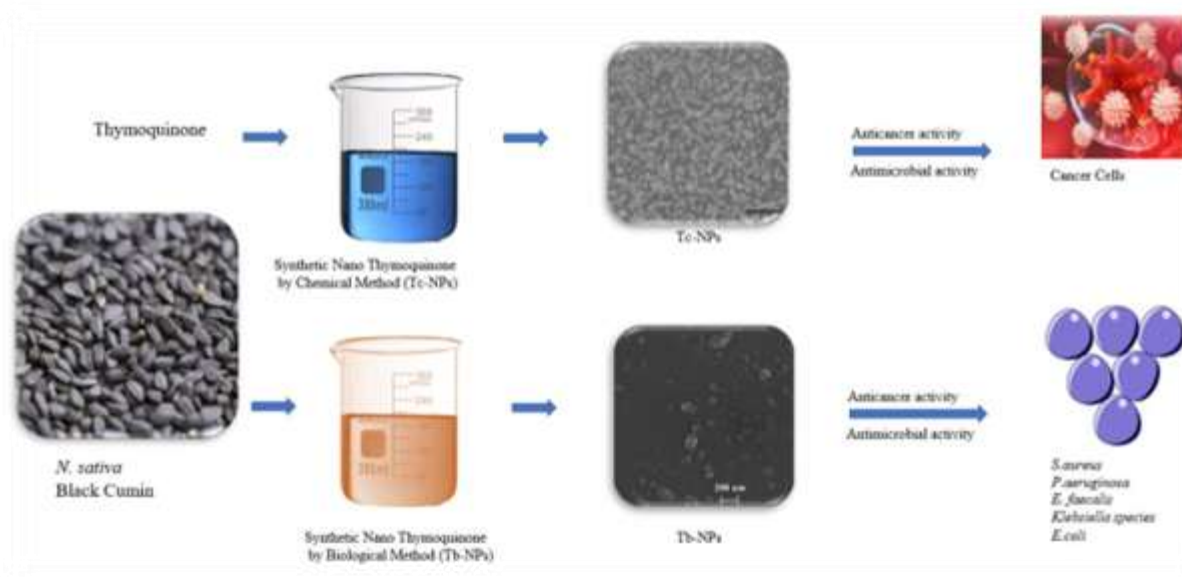
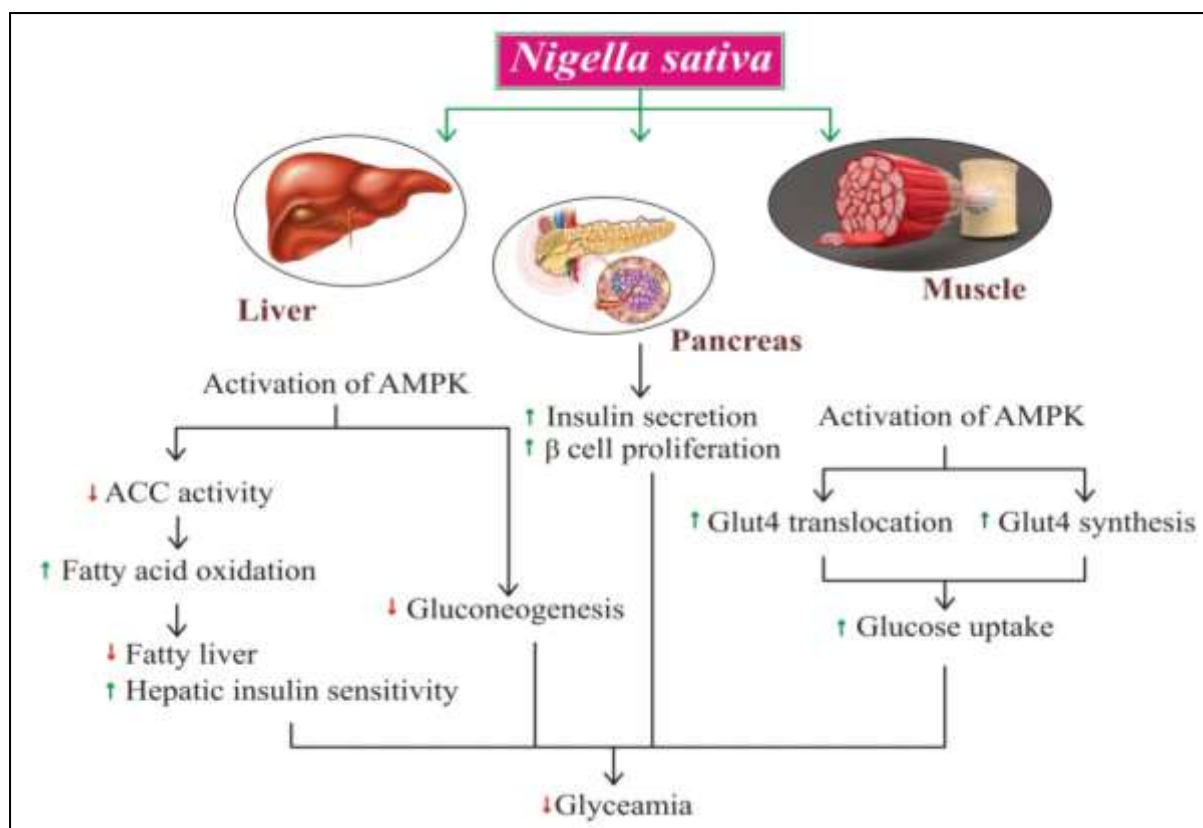


Figure 2. Pathway of anticancer activity of *Nigella sativa*

#### 11.6. Anti-diabetic activity

The presence of essential oil in *Nigella sativa* has shown to have significant effects on reducing blood sugar levels. These anti-diabetic properties are believed to be linked to the activation of Adenosine Monophosphate Kinase (AMPK), which affects the cellular uptake of proteins with hypolipidemic and anti-diabetic properties. Both oral administration and intra-peritoneal injection of *Nigella sativa* oil have demonstrated notable hypoglycemic effects in reducing blood glucose levels [42].

Numerous clinical studies have shown that *Nigella sativa* has anti-diabetic properties. In a study involving 46 patients with type 2 Diabetes, the administration of powdered *Nigella sativa* seeds for 40 days led to significant reductions in fasting blood glucose, total Cholesterol, LDL-Cholesterol, and Triglycerides, while increasing Insulin and HDL-cholesterol levels. Another observational study found that the daily administration of 2.5 mL of *Nigella sativa* oil, along with Atorvastatin and Metformin, for 6 weeks resulted in significant improvements in fasting blood glucose, LDL-Cholesterol, and total Cholesterol levels [43].



**Figure 19.** Mechanism of Hypoglycemia of *Nigella sativa*

#### 11.7. Anti-oxytotic activity

*Nigella sativa* seeds have been found to inhibit the contraction of smooth uterus muscle started by Oxytocin stimulation. Volatile oil derived from *Nigella sativa* not only inhibits unprompted muscle movements but also reduces contractions induced by Oxytocin. This suggests that *Nigella sativa* seeds oil has potential anti-oxytotic properties. Prostaglandins, which are produced by COX-1 and COX-2 in the uterine wall, are powerful pro-inflammatory mediators. Prostaglandins, specifically PGE2 and PGF2 $\alpha$ , have been shown to play a role in the development of Dysmenorrhea, causing increased Myometrial contraction and resulting in pain. Elevated levels of these mediators can also lead to symptoms such as headache, nausea and vomiting, backache, and diarrhea. Thymoquinone demonstrated anti-inflammatory effects against allergic airway inflammation in a mouse model [44].

#### 11.8. Anti-fertility and Contraceptive activity

Hexane extract from *Nigella sativa* seeds prohibited pregnancy in rats on Oral administration. Hexane extract also had significant anti-fertility effects. The active Hexane extract had mild effects on uterine growth at Contraceptive doses. In male rats The Ethanol extract of *Nigella sativa* seeds showed anti-fertility activity. Possibly it was due to its Estrogenic properties [21].

#### 11.9. Neuro-pharmacological activity

Aqueous and methanolic extracts of Black Cumin seeds without fat had strong effects on the central nervous system and pain relief; particularly the Methanol extract had a depressant effect. Anxiolytic drugs work by rising Serotonin (5-HT) level and lessening Hydroxyindoleacetic acid (5-HIAA) levels in the brain. Long-term use of *Nigella sativa* increases 5-HT level in the CNS, leading to CNS stimulation. frequent use of Black Cumin reduces the yield of serotonin (5-HT) and has anxiety-reducing effects in rats [21].

The drug demonstrated antiolytic effects in rats. Oral use elevated Serotonin (5-HT) levels in the brain, while decreasing level of Hydroxyindoleacetic acid (5-HIAA). Additionally, it significantly increased Tryptophan levels in the brain and plasma after repeated oral administration. 10 and 20 mg/kg dosage of TQ showed a significant anti-anxiety activity in undisturbed mice without changing the nitrite levels. In stressed mice, 20 mg/kg of TQ resulted anxiolytic activity, with a noteworthy decline in plasma nitrite and reverse of the little brain GABA content [13].

#### 11.10. Wound healing activity

*Nigella sativa* seeds and oil have been shown to enhance wound healing in animals. Topical application of *Nigella sativa* seed extract on infected skin reduces inflammation, infection, and tissue damage. *Nigella sativa* essential oil can also speed up the healing process of worsening wounds. Using *Nigella sativa* L.

essential oil topically can be an effective alternative for improving wound healing. It may help reduce oxidative stress, lipid peroxidation, and related complications, making it useful for treating Diabetic wounds [45].

#### 11.11. Hepato-protective activity

*Nigella sativa* has been found to alleviate the harmful effects of Ischemia-Reperfusion injury on the liver. Treatment with *Nigella sativa* protects the liver from damage caused by hepatic Ischemia-Reperfusion. TQ protective function in the hepatotoxicity caused by Cd<sup>++</sup> particularly with regards to its fortification against perturbation of non-enzymatic and enzymatic antioxidants has been inferred. Pretreatment with TQ (10 μmol·L<sup>-1</sup>) results in a noteworthy fortification by decline in protein oxidation and the washed-out antioxidants rejuvenation of cellular fraction. Using dried and powdered Kalonji seeds in milk, along with Ajwain extract and Kalonji oil can provide fast relief for liver problems and jaundice. Thymoquinone, a potent hepatoprotective compound, has been identified in these remedies [46].

#### 11.12. Anti-malarial activity

Different extracts of *Nigella sativa* have demonstrated anti-plasmodial activity against both in vivo and in vitro infections caused by Plasmodia. At a concentration of 50 ug/ml, it exhibited 100% inhibition of parasite growth, specifically against *Plasmodium falciparum*. The activity of *Nigella sativa* against the parasite was found to be dependent on the dosage administered. Its potential as an anti-malarial agent has not been reported in Nigeria. Exploring the anti-malarial properties of these plants could greatly contribute to addressing the challenges of anti-malarial resistance [46].

#### 11.13. Gastroprotective activity

The aqueous extract of *Nigella sativa* seeds demonstrated a 36% reduction in the ulcer index caused by Aspirin. Another study found that the oil derived from *Nigella sativa* seeds had protective effects against stress Gastritis in rats with Hypothyroidism. *Nigella sativa* can have a notable impact in the treatment of gastric ulcers caused by Indomethacin and Ethanol. The release of Pepsinogen pro-enzyme from stomach cells combines with Hydrochloric acid in gastric juice and converts into Pepsin. TQ, found in *Nigella sativa*, stimulates the activation of Pepsinogen into Pepsin enzyme in gastric juice, providing a protective effect against ulcers. Additionally, the antioxidant properties of TQ contribute to its impact on gastrointestinal disorders by scavenging free radicals and exhibiting antioxidant activity [47].

In a study comparing *Nigella sativa* to a Triple Therapy (Omeprazole, Clarithromycin and Amoxicillin) was found that *Nigella sativa* was effective against *Helicobacter pylori* [48]. Bioactive constituents of Black Cumin affective in GIT are shown in Table 6.

**Table 5.** Bioactive constituents of Black Cumin affective in GIT [48]

Class	Constituents	Proposed Mechanism
	Thymoquinone	Carminative, Cyto-protection, Immune boosting Hydroxyl radical scavenging, Digestive
Fatty acids	Eicosadienoic acid, Palmitic acid, Stearic acid, Myristic acid, Oleic acid, Linoleic acid, Arachidonic acid and Linolenic acid	Immunity boosting, maintain skin moisture and anti-inflammatory
Alkaloids	Triterpene-alpha-Hederin, Nigelline-N-oxide, Nigellimine, Nigellone	anti-cancer, Antihistamine and anti-leishmanial property
Saponin	tocopherols (α, β and γ)	Antioxidant, immune boosting
Minerals	Iron, Copper, Calcium, Phosphorous, Zinc	reticence of free radicals by stabilizing transition metals, so sinking free radicals damage
Vitamins	Niacin, Carotene, Folic acid Thiamine, Riboflavin	Immune boosting, anti-oxidant and free radical scavenger

#### 11.14. Effect on nervous system

*Nigella sativa* seeds showed potential narcotic analgesic activity initiated probably by Opioid receptors. The seeds oil exhibited CNS depressant and possible analgesic effect. It was known to potentiate Pentobarbitone induced sleeping time too. It showed that there is increase in GABA activity while discharge of Glutamate, Aspartate and Glycine was observed to decline. All the results illustrated the

sedative and suppressive effects of Black Cumin extract. *Nigella sativa* has been found to decrease 5HT turnover and has anxiolytic effects when used repeatedly. *Nigella sativa* seeds and TQ proved their therapeutic potential against a wide range of neurologic conditions (Schizophrenia, Neurodegenerative, acute brain injury, Ischemic stroke, depression, anxiety and Epilepsy). *Nigella sativa* and TQ have been found to provide protection against chemical-induced neuronal damage in experiments. Their Neuro-protective effects are mainly attributed to their anti-oxidative and anti-inflammatory properties [2].

### 11.15. Effect on immune system

*Nigella sativa* seeds and oil are believed to promote good health and may be used for preventing common Cold and Asthma [49]. A study found that *Nigella sativa* has immune-enhancing properties in Human T-cells, stimulating the secretion of Interleukin-3 (IL-3) and Interleukin-1B (IL-1B) [50, 51].

### 11.16. Anti-dyslipidemic activity

Kalonji proved to be a potential source of treatment of Dyslipidemia at the dosage of 1gm in powder form BID for sixty days in almost twenty patients. Another study exposed that Black Cumin apply anti-atherogenic action by lessening LDL Cholesterol level; it also increases the HDL level. Black Cumin of 500 mg dosage along with Statins (10-20mg) shows significant properties [52].

### 11.17. Hypoglycemic activity

In a study with Wistar rats, the Aqueous extract of Kalonji powder at a concentration of 500 mg/kg resulted in a significant 61.3% reduction in fasting blood glucose levels after 14 days of treatment. Another study suggested that *Nigella sativa* can be used as an additional drug therapy for metabolic syndrome patients with poor Glycemic control. The study concluded that *Nigella sativa* is safe and effective in treating patients with metabolic syndrome [53-57]. In another study, treatment with *Nigella sativa* at a concentration of 5 mg/kg resulted in significant weight gain and reduced fasting blood glucose levels compared to the control group. Histopathological examination revealed that *Nigella sativa* partially restored Hepatic Glycogen content and protected a significant portion of Pancreatic Islet cells [52, 58-60].



Figure 3. Pharmacological uses of Black Cumin

## 12. Famous formulations of Black Seeds

The most famous Unani formulations of Black seed are Shoneez, Itreefal Qanbeel, Roghan Kameela, Safoof-e- Haka, Habb-e-Huleet and Maajoon Kulkulaj [61-66].

## 13. Adverse Effects

### 13.1. Oral use

Consuming *Nigella sativa* in food is generally safe. Black Seed oil and powder are considered safe when taken in larger amounts for up to 3 months. However, it's still important to use them in moderation and follow recommended guidelines [67]. The safety of using larger amounts of black seed for more than 3

months is uncertain due to limited reliable information [67-73]. Some individuals may experience allergic rashes, stomach upset, vomiting, or constipation when consuming *Nigella sativa*. It's important to be aware of these potential side effects [74].

### 13.2. Topical use

Using *Nigella sativa* oil or gel for a short period of time is potentially safe. However, it's important to note that some individuals may experience allergic rashes when using black seed products [74].

### 14. Toxicological studies

Numerous toxicity studies have been conducted on *Nigella sativa*. These studies showed that there was no toxicity found in *Nigella sativa* fixed oil orally. In a sub-acute toxicity study did not result in any changes in important LFT levels (Gamma-glutamyl-Transferase, Aspartate-Aminotransferase and Alanine-Aminotransferase) [67-73]. Additionally, Histopathological examination revealed normal tissue conditions for the Heart, Liver, Kidneys, and Pancreas [13].

The high LD50 values, stable hepatic enzyme levels, and intact organ condition indicate that *Nigella sativa* fixed oil has low toxicity and a wide safety margin for therapeutic doses. Another study resulted that LD50 of TQ was 104.7 mg/kg and 870.9 mg/kg intra-Peritoneal and oral, respectively, in mice. For rats, the LD50 was found to be 57.5 mg/kg and 794.3 mg/kg through intra-Peritoneal injection and oral ingestion, respectively. These findings suggest TQ as a relatively safe compound, especially when administered orally to lab animals [3, 13].

TQ, similar to other Quinone compounds, can undergo Redox cycling in the body. This means that it can be metabolized by cellular Oxidoreductases, resulting in the formation of Hydroquinones or Semiquinone radicals and the generation of reactive Oxygen species. Through this mechanism, Thymoquinone has the potential to cause adverse effects and may contribute to the observed effects of Aqueous extracts of *Nigella sativa* in primary rat Hepatocytes [75].

The LD50 values were calculated using the MPD program. Both oral and intraperitoneal administration of all doses resulted in immediate agitation and behavioral disturbances, accompanied by temporary wasting. This was followed by a period of calmness and sedation. In general, the mice exhibited diarrhea and succumbed to death within 12 hours of receiving the fixed oil. Autopsies revealed congested Lungs and Hearts that had stopped in diastole. However, the surviving mice showed a rapid recovery in terms of their normal activity and growth. The duration of this recovery period varied, ranging from 4 to 8 days, depending on the dose and method of administration [76].

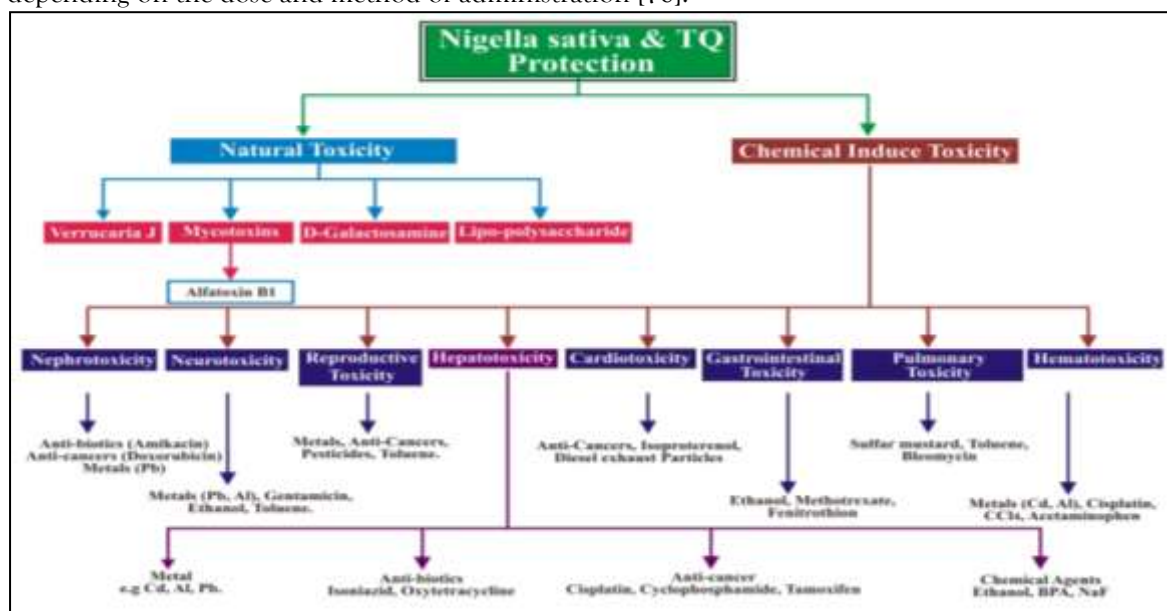


Figure 4. Toxicity of Black Cumin

### 15. Drug Interactions

There is possibility that Black Cumin may interact with co-administered drugs and influence their bioavailability and therapeutic effects. In vitro studies showed that Black Cumin inhibit cDNA-expressed Human Cytochrome (P-450, 3A4, 3A5, 2C9 and 3A7-mediated metabolism) of substrates marker for that reason may influence or inhibit the metabolism of medications as shown in figure 21 [13].



Figure 22. Drugs interactions with Black Seeds

#### 15.1. Anti-Diabetes drugs

Black seed has the potential to lower blood sugar levels. If you are taking Diabetes medications, combining them with black seed consequently lower the excessive Blood sugar level. It's important to closely monitor your blood sugar levels [13].

#### 15.2. Immuno-suppressants

Black seed could enhance Immune system activity. However, certain medications, like those used post-transplant, suppress the immune system. Combining *Nigella sativa* with these medications can lower their efficacy [13].

#### 15.3. Anti-Coagulant / Anti-platelet drugs

*Nigella sativa* has the potential to slow down blood clotting. If you are taking medications that also slow blood clotting, combining them with black seed may enhance the danger of bruising and also the bleeding [13].

#### 15.4. Anti-Hypertensive drugs

Black Seed has the potential to lower blood pressure. If you are taking medications that also lower blood pressure, combining them with black seeds may cause excessive hypotension. It's important to closely monitor your blood pressure levels [13].

#### 15.5. Sedative medications (CNS depressants)

Black Seed can induce sleepiness and slow down breathing. Sedative medications can also have these effects. Combining black seed with sedatives may cause difficulties in breathing and too much sleepiness [13, 77].

#### 15.6. Cyclosporine

Black Seed may decrease in the blood the levels of Cyclosporine, potentially reducing its effectiveness [13].

#### 15.7. Diuretic drugs

Black Seed has the potential to lower Potassium levels. "Water Pills" can also have this effect. Combining black seed with "Water Pills" may cause severe drop in potassium levels [13].

#### 15.8. Amlodipine

Amlodipine and black seed both lower blood pressure. Combining them may severely decrease blood pressure. It's important for people taking both to monitor their blood pressure [13, 33].

#### 15.9. Serotonergic Drugs

Black Seed can increase Serotonin levels in the brain, like certain medications. Combining *Nigella sativa* with these medications may lead to excessive Serotonin levels, which can cause serious adverse effects e.g. Seizures, heart problems and Vomiting [13].



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