

## Black Seeds (*Nigella Satival.*) - kalonji: A Brief Review of its Anti-Cancer and Anti-Tumour Qualities

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### Abstract

*Nigella Sativa* belongs to genus of the *Ranunculaceae* family and is famous for its various traditional uses in Tibb and Unani medicine. The seeds and oil of *N. sativa* are greatly used in treating different diseases and ailments. In Islamic literature, our beloved Prophet Muhammad, has recommended it in many ailments due to its healing properties, hence, is advised to use it on regular basis. It has different names such as *seeds of blessing*, *black cumin*, *black seed*, *Al-Habba Al-Sauda*, *Al- Habba Al-Barakah*, *Siyahdaneh* and *Kalonji*. The seeds are found all over the world, especially in the Middle East. *N. sativa* contains some chief constituents such as thymoquinone (TQ), dithymoquinone (DTQ), thymol-hydroquinone (THQ), and thymol (THY); p-cymene, 4-terpineol, and t-anethol. Its most essential component i.e., thymoquinone has remarkably proved its activity as hepatoprotective, anti-inflammatory, antioxidant, cytotoxic and anti-cancer agents. Thymoquinone is an active pharmacological component which is responsible

to fight human breast and ovarian cancers by arresting the cell cycle.

In this paper, an effort has been made to prove that how various constituents of *N. sativa* can help in preventing different types of carcinomas, by mentioning the individual functions and effects of these constituents. Since in Muslim countries, the seeds are used due to their religious importance, not many researches have been done in other countries of the world, thus studies showing its medicinal value are very limited.

However, further researches and clinical trials are still required in order to ensure the correct usage of this plant to treat cancers and other diseases. This article has reviewed researches done in a span of last two decades on this miraculous plant and found different works and studies that proved the beneficial therapeutic qualities of this plant for future treatment of diseases. A lot of work is still required as the existing literature does not provide enough proof to recommend it as an applicable treatment of

various diseases, especially cancer, the world over.

### Keywords

Black seeds, *Nigella sativa*, cancer, thymoquinone, gene, drugs, chemotherapy.

## 1. INTRODUCTION

Hazrat Aisha (R.A) has narrated that she heard the Prophet (PBUH) Saying, ‘This black cumin is healing for all diseases except As-Sam.’ Aisha said, ‘What is As-Sam?’ He said, ‘Death.’ (Sahih Al-Bukhari, 5687).

The scientific name of Black Seed is *Nigella sativa* which is a derivative of the Latin “Niger” (black). It has a variety of other names in English such as black cumin, fennel flower or Roman coriander (Nasir and Irshad, 2015). It is called ‘Al-Habba Al-Sauda’ or ‘Al- Habba Al-Barakah’ or Al-JattulSaudain Arabic and ‘Kalvanji/Kalonji’ in Urdu and few local languages of the Indian Sub-continent. It is a well-known natural remedy for many ailments and a flavouring agent used in bread and pickles, in the Middle East, Middle Asia and Far East (Randhawa, 2008). It is known as “siyahdaneh” in Persian (Nasir and Irshad, 2015) and also as the “seeds of blessing” (Khan *et al.*, 2011).

Belonging to the family *Ranunculaceae*, *Nigella sativa* (NS), is an annual flowering native to the Mediterranean and the neighbouring countries of Pakistan and India (Agbaria, 2015). It is a plant, which attains a height of 0.5 meter, and bears blue / whitish coloured flowers (Ghaznavi, 1995). Its seeds contain more than hundred valuable nutrients, including fatty acids, volatile oils, proteins, carbohydrates, saponins, alkaloids, tannins, flavonoids, sterols and trace elements..

Thymoquinone, nigellone and beta-sisterolare some of the active constituents found in this remarkable herbal ingredient (Ahmad, *et al.*, 2013). Due to its Thymoquinone content, having qualities like hepatoprotective, anti-inflammatory, antioxidant, cytotoxic and anti-cancer chemical, it provides support to an idea of a compound which can serve as an emerging drug (Khader and Eckl, 2014). Many current researches carried out in Muslim countries have shown that *N. sativa* is commonly used by cancer patients as dietary supplement (DS) as Complementary and Alternative Medicine (CAM) along with chemotherapy (Khader and Eckl, 2014).

**Table 1. Botanical Classification of *N. Sativa***

Kingdom:	Plantae
Clade:	Tracheophytes
Clade:	Angiosperms
Clade:	Eudicots
Order:	Ranunculales
Family:	Ranunculaceae
Genus:	<i>Nigella</i>
Species:	<i>N. sativa</i>

Cancer could also be represented as a group of diseases for which the cells of the structure associate in nurse mines which increase and divide perpetually and by fault (Mathews, *et al.*, 2021). Defined in the aftermath of this century’s plague, “most cancers” could be a complex of sophisticated pathologies and diseases character-

ized by “out of control” mobile increase, to uncontrollable mobile proliferation or the inability of cells to go through apoptotic mobile death” (Kus G, et al., 2018).

In 1971, the Chief Executive of the President of the United States declared the “fight for most cancers”, predicting that it will end within 5 years. Despite a period of over forty years, most cancers continued to be the main cause of death in economically developed countries and also the second main reason for disappearance in the growing nations of the international. Despite key advances, the cures for most cancers that have evolved so far have not reached the expected peak and most cancer studies are now at crossroads, calling for a change in the way which most cancers are studied and treated (Kaiser, 2021). World Health Organization (WHO) reviews in 2021 identified most cancers as the leading cause of death worldwide, accounting for nearly ten million deaths in 2020 world wide. Cancer is perhaps the most terrible for humanity and the main danger to health in the world. The irony is that the precise purpose of most cancers and even the method by which the progress are

not always fully known, but “it was thought to be due to altered genetic and epigenetic pathways” (Rahmani, et al., 2014).

## 2. MATERIAL AND METHODS

### 2.1. Chief Components of *Nigella Sativa*

*Nigella sativa* is known as the miraculous plant due to its unique constitution (Ahmad et al., 2013). Major constituents of *N. sativa* are thymoquinone (TQ), Di-thymoquinone (DTQ), thymol-hydroquinone (THQ), and thymol (THY); p-cymene, 4-terpineol, and t-anethol (Rahmani, et al., 2014). Thymoquinone (TQ) is the most essential constituent of *N. sativa* seeds on which an intensive research section has been dedicated, including 406 researches, on the “PubMed” database since 1960 (Khader and Eckl, 2014). TQ’s medicinal role includes treating diseases like cancers, for example, pancreatic, osteosarcoma, bladder, breast, colon, skin and lung cancer. Multiple biological activities like modulation of antineoplastic, antioxidant, antitumor, and antimicrobial are known to be done by this essential ingredient (Rahmani et al., 2014).

**Table 2. Bioactive Compound of *N. sativa***

Class	Subclasses	Bioactive Compound	Reference
Fixed oil	Unsaturated fatty acids	Oleic acid, Linoleic acid, dihomolinoleic acid, eicodadienoic acid	(Naz, 2011; Nickavar et al., 2003; Ramadan and Morsel, 2002)
	Saturated fatty acids	Palmitic acid, stearic acid	(Naz, 2011)
Terpenes	Aliphatic	Thymoquinone, p-cymene, $\alpha$ -pinene, dithymoquinone, thymohydroquinone, Carvacrol, carvone, limonene, 4-terpineol, citronellol, anethol	(Ghosheh et al., 1999; Naz, 2011)

<b>Alkaloids</b>	Isoquinoline alkaloids	Nigellicimine, Nigellicimine N-oxide	(Naz, 2011)
	Pyrazole alkaloids	Nigellidine, nigellicine	(Naz, 2011)
<b>Coumarins</b>	Methoxycoumarin	6-methoxy-coumarin	(Tembhurne <i>et al.</i> , 2014)
	Hydroxycoumarin	7-hydroxy-coumarin	(Tembhurne <i>et al.</i> , 2014)
	Oxy coumarin	7-oxy-coumarin	(Tembhurne <i>et al.</i> , 2014)
<b>Saponins</b>	Steroidal	Alpha hedrin	(Randhawa and Al-Ghamdi, 2002)
	Triterpenes	Sterylglucosides, Acetyl-steryl-glucoside	(Randhawa and Al-Ghamdi, 2002)
<b>Flavonoids</b>	Flavonoidal pigment	Quercetin	(Merfort <i>et al.</i> , 1997)
	Flavonoidal glycoside	Kaempferol 3-glucosyl galactosylglucoside, quercetin 3-galactosyl glucoside, trigillin quercetin-3-glucoside	(Merfort <i>et al.</i> , 1997; Raj Kapoor <i>et al.</i> , 2002)
<b>Phenolics</b>	Acidic phenolics	Vanillic acid, hydroxybenzoic acid, syringic acid, p-cumaric acids	(Bourgou <i>et al.</i> , 2008; Mariod <i>et al.</i> , 2009)
<b>Amino acids</b>	Essential amino acids	Valine, phenylalanine, threonine, methionine, histidine, tryptophan, leucine, isoleucine, lysine	(Babayan <i>et al.</i> , 1978)
<b>Metals and trace elements</b>		Calcium, iron, and potassium, phosphorus, zinc	(Al-Gaby, 1998)

An attraction for healers in ancient civilisation as well as for researchers in current era, *Nigella sativa* has been used traditionally in different forms to treat many diseases including asthma, hypertension, diabetes, inflammation, cough, bron-

chitis, headache, eczema, fever, dizziness and influenza (Khader and Eckl, 2014). Though it doesn't make a significant part of the human diet, yet it has been used since long as a spice and preservative on a daily basis in the Middle East.

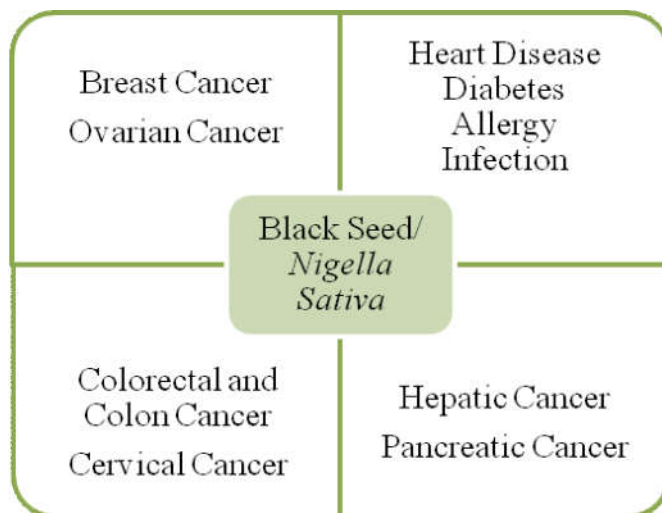


Fig- 1. Types of major diseases known to be treated with Black seeds (Kalonji)

## 2.2. CANCER

Cancer is known as ‘Sartan’ in Unani system of medicine. According to Unani medicine, cancer is due to ‘Sawda’ (black bile) and ‘SawdiMada’ develop into two as; ‘TabayeeMadaSawda’ (normal black bile) which develops as ‘warm e sulb’ (hard swelling) and if the ‘abayeeMadaSawda’ develops burning, it causes ‘Sartan’ (Farzana, *et al.*, 2017). As Kaiser in 2021 also said that cancer is a family of diseases unique to multicellular animals that are characterized by the uncontrolled cell growth and proliferation. Normally, cell division is strictly controlled by multiple evolutionarily conserved cell cycle control mechanisms, so that the production of two genetically identical cells is ensured. There are cell cycle check points too which operate as DNA surveillance mechanisms preventing the accumulation and propagation of genetic errors during cell division. Cancer-associated mutations that perturb cell cycle con-

trol allow continuous cell division chiefly by compromising the ability of cells to exit the cell cycle (Mathews, *et al.*, 2021).

### 2.2.1. Anti-Cancer and Anti-Tumour Activities

Thymoquinone (TQ), a constituent found most abundantly in black seed essential oil, is said to be primarily contributing to many of the seed’s beneficial effects (Muhtasib, *et al.*, 2004). TQ is known to have free radical scavenging activity as well as it acts in anti-lipid peroxidation. Similarly, a combination of TQ with ifosfamide improve the therapeutic index and saves non tumour tissues from chemotherapy-induced damage (Edris, 2009). Researcher revealed TQ’s therapeutic qualities in the health management/human health while preventing cancer via modulation of genetic cascades. Hence, compounds which may trigger

cancer cell apoptosis may lead to promising future drugs for the treatment of cancer (Kus G, *et al.*, 2018).

TQ contributes to inhibit cancer cell growth and apoptosis induction and has been reported to be active against many multidrug-resistant variants of different human cancer cell lines. The same study also indicated that TQ could be used as a dietary supplement to augment the impact of other anti-cancer drugs. A clinical trial of using a combination of TQ with anti-cancer drugs may decrease side effects and enhance the performance of these drugs (Edris 2009).

Other than thymoquinone, several other active constituents are present in *N. sativa*, which help in tumour prevention. These include both fixed and essential oils, proteins, alkaloids, and saponin. Earlier studies have revealed the precise mechanism of tumour inhibition by *N. sativa* volatile oil (Rahmani *et al.*, 2014). "Antioxidant and anti-inflammatory activities, coupled with an enhancement of detoxification processes" serve as a possible mechanism of the chemo-preventive actions of TQ" (Edris, 2009).

### 2.2.2. Genetic of Cancer

Cancer is a multifactorial disease, inclusive of alteration in genetic pathways. Mutation or alteration of tumour suppressor genes make a contribution to the improvement of most cancers through inactivating the inhibitory functions. *N. sativa* and its parts assist save you most cancers via the activation of tumour suppressor gene (Rahmani *et al.*, 2014).

PTEN gene is a multifunctional phosphatase, whose essential substrate is phosphatidylinositol-3,4,5-trisphosphate (PIP3). Lipid phosphatase hobby of PTEN performs a k-

ey function in dephosphorylation of PIP3 (a form of phospholipid that is living at the plasma membrane). Altered movement of PTEN has been found in most cancers, thus, upregulation of PTEN attains significance in most cancers prevention. Rahmani's observation confirmed the time-structured growth of PTEN in cells. He found that TQ remedy prompted the growth in PTEN mRNA through 1.8-, 2.0-, 3.8-, 5.9-, and 7.9-fold after 1, 2, 4, 8, and 24 hours, respectively.

p53 is taken into consideration because the father or mother of genes and research display that the characteristic of p53 is altered in about 50% of cancers (Rahmani *et al.*, 2014). Cells can reply to the activation of the tumour suppressor protein p53 through present process mobile cycle arrest or apoptosis (Muhtasib, *et al.*, 2004). Studies favouring TQ confirmed that it acts inside the modulation of p53 and in the end suppresses improvement and development of tumour. *Nigella sativa* and its parts TQ confirmed that each of one its anticancer-energetic derivatives assist inside the induction of apoptosis related to DNA laddering, "a lower in mitochondrial membrane capping potential and additionally growth in reactive oxygen species" (Rahmani, *et al.*, 2014).

Active p53 stimulates the transcription of quite a few genes inclusive of p21 Waf1, that is a well-known inhibitor of the cyclin-structured kinases, and is needed to arrest cells on the G1 and G2 checkpoints of the mobile cycle after DNA damage (Muhtasib, *et al.*, 2004).

In comparison to p21 Waf1, the overexpression of Bcl-2 protein has been proven to inhibit p53-mediated apoptosis in addition to p53-mediated transcriptional activation. Cell boom inhibition executed through TQ remedy became correlated with G1 section arrest of the mobile cycle accompanied through apoptosis. TQ exten-

sively up-regulated p53 and p21 Waf1 expression and extensively reduced Bcl-2 protein.

p53 reputation of HCT-116 cells has a full-size effect at the reaction of those tumour cells to TQ remedy; p53 null cells are much less touchy to boom arrest and apoptosis induction through TQ. (Muhtasib, *et al.*, 2004)

### 2.2.3. Colon Cancer:

TQ has the capacity to limit the boom of colon most cancers cells through G/S arrest induction. It results in apoptosis via p53-structured mechanisms (Muhtasib, *et al.*, 2004). Another observe has additionally installed that TQ would possibly play a function in colon most cancers mobileular dying that could bring about fantastic final result for reinforcing the immune system's reaction to chemotherapy whilst treating this most cancers (Zhang, *et al.*, 2016).

Beside its shielding hobby for the inner

### 2.2.4. Skin Cancer

organs, TQ has proved to be a cappotential pores and skin chemo-preventive agent, specially early on-set of pores and skin tumorigenesis. Particularly, the entire important oil of *N. sativa* has chemo-preventive results in opposition to carcinogenesis, if administrated orally. Research confirmed that the oil inhibited the colon carcinogenesis with inside the post-initiation degree in rats, having no damaging facet results (Edris, 2009).

### 2.2.5. Pancreatic Cancer

Chehl *et al.* (2009) pointed out that TQ from the *N. sativa* oil extract induced apoptosis and inhibited proliferation in PDA (pancreatic ductal adenocarcinoma) cells. Its antineoplastic activities were proven against human pancreatic adenocarcinoma, uterine sarcoma, Ehrlich ascites carcinoma, Dalton's ascites lymphoma, with less or no exerting cytotoxicity seen in normal lymphocytes (Muhtasib, *et al.*, 2004).

**Table 4: Thymoquinone and cancer cell types**

Constituent	Cancer type	mechanism	References
Thymoquinone	Pancreatic	Induced apoptosis Inhibit proliferation	(Muhtasib, <i>et al.</i> , 2004).
	Hepatic	Increase reductase and glutathione transferase Decrease chemical carcinogenesis	Nagi and Almakki (2009)
	Cervical	reduces the viability	(Ichwan, <i>et al.</i> , 2014).
	Breast cancer	Anti-proliferative and pro-apoptotic effects	(Ichwan, <i>et al.</i> , 2014

### 2.2.6. Hepatic Cancer:

Nagi and Almakki (2009) described the effective increase in the activities of Quinone reductase and glutathione transferase through oral administration of TQ making it a promising prophylactic agent which functions against chemical carcinogenesis and toxicity in hepatic cancer.

### 2.2.7. Cervical Cancer:

Practically speaking, all malignant tumours are caused by HPV infections, with HPV types 16 and 18 responsible for about 70% of all types of cervical cinomas. Researches have revealed that TQ significantly reduces the viability of both the C33A and Siha cells (one of the HPV-positive cell lines) (Ichwan, *et al.*, 2014).

### 2.2.8. Breast Cancer:

Thymoquinone is an active pharmacological component of the volatile oil which is found to fight human breast and ovarian cancer by arresting the cell cycle (Nasir and Irshad, 2015). In breast cancer cells, TQ was able to increase peroxisome proliferator-activated receptor gamma (PPAR- $\alpha$ ) activity and to down-regulate the expression of the genes for Bcl-2, Bcl-xL and survivin. Treatment of human breast carcinoma in both *in vitro* and *in vivo* models demonstrated antiproliferative and proapoptotic effects of TQ, which are mediated by its inductive effect on p38 and ROS signalling (Khader and eckl, 2014).

## 3. RESULTS AND DISCUSSION

The irritation and the potent allergenic effect of TQ should be taken into consideration when testing on the skin (Edris, 2009). TQ possesses a high selectivity for inhibiting proliferation and viability of cancerous, but not non-cancerous, prostate epithelial cells.

The selective anti-tumour activity of TQ compared with that of 5-fluorouracil suggests that this compound may be a safe alternative for the treatment of human colon cancer. Sustained delivery of TQ produced significant cellular destruction and interference of cellular metabolic functions of certain human colon cancer cells, which was comparable to the effect of 5-fluorouracil (Edris, 2009).

After going through all these studies and researches, we infer that while keeping in mind the factors relating to the treatment of cancer, one of the most important factors about the anti-cancer qualities of black seeds, is environment. The environment influences the quantity and quality of the compound in more than one way. Environment not only means the biodiversity and the ecosystem where this compound is grown, but it also includes the methods and the chemicals used during its farming, for example, the type of fertilizer/s used, irrigation process, and the most important of all is the climatic changes, like temperature, humidity, type of land, latitude and altitude, etc.

## 4. CONCLUSION

In conclusion, *Nigella sativa* should be medicinally used worldwide due to its beneficial characteristics. Currently, it is used widely in the Muslim countries especially in the Middle East as well as in rest of the world, but more research is required at multiple levels to prove its medicinal value for various diseases, starting from common illness such as allergy and inflammation to the major ones like cancer. The plant is proved to have so many usages for many illnesses through its seeds as well as oil and extracts. All we need is its correct and proper use to cure these illnesses. Its essential component, thymoquinone, alters gene's function and provides an alternative to th-



erapeutic drugs, thus lessening the side-effects of chemotherapy against major cancers like breast, ovarian, hepatic, cervical, etc.

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