

## Review article

A Review On *Nigella sativa* (Kalonji) Seeds: A Universal HealerAnjum Areefa<sup>1\*</sup>, Aslam Mohd<sup>2</sup>, Chaudhary Shahid Shah<sup>3</sup><sup>1</sup>MD. Scholar, Dept of Ilmul Advia, Jamia Hamdard, India, <sup>2</sup>Professor, Head, Dept of Ilmul Advia, Jamia Hamdard, India,<sup>3</sup>Assistant Professor, Dept of Ilmul Saidla, Jamia Hamdard, India

## ABSTRACT

*Nigella sativa* commonly known as Black seed, Black cumin or Kalonji (Family Ranunculaceae) is a widely used for its miraculous healing power. Use of *N. sativa* seeds and oil has splendid historical past in diverse traditional systems of medicine and food. In Tibb-e-Nabwi (Prophetic Medicine), it is considered as one of the greatest forms of healing medicine. Phytochemically; it contains fixed oil, protein, alkaloids saponin and essential oil. Therapeutic properties of this plant are due to the presence of thymoquinone which is one of major active component and has different beneficial properties. In Unani System of Medicine the diseases are treated with nontoxic herbal drugs. As per Unani classical literature *N. sativa* perform various pharmacological actions like carminative, anti-inflammatory, analgesic, diuretic, emmenagogue, galactagogue, expectorant etc. Ample of phytochemical, pharmacological and clinical researches has been executed on *N. sativa*, which may include antidiabetic, anticancer, immunomodulator, analgesic, antimicrobial, anti-inflammatory, bronchodilator, hepato-protective, renal protective, gastro-protective, antioxidant properties, etc. This review is an effort to summarize the literature on scientific researches of pharmacognostical characteristics, chemical composition and pharmacological activities of the kalonji seeds

**Keywords** *Nigella sativa* (*N. sativa*), Healing Medicine, Thymoquinone (TQ), Prophetic Medicine.

## INTRODUCTION

Medicinal plants have been used for treating diseases for several decades in various indigenous and traditional systems of medicine. Among the various potential medicinal plants, *N. sativa* is a dicotyledonous miraculous herb of ranunculaceae with a strong historical and religious background (Ahmad *et al.*, 2013). The seeds of *N. sativa* are the sources of the active ingredient which have been utilized for thousand years as a spice and food preservative, as well as a defending and therapeutic remedy for several disorders (Sultana *et al.*, 2015). Historical use of *N. sativa* has been mentioned in various religious and ethnic books (Tembhure *et al.*, 2014). In Islam, it is considered as one of the greatest form of healing medicine existed as a remedy for all diseases except death in one of the saying of Prophet Muhammad It is also commended for use on consistent basis in Tibb-e-Nabwi (Prophetic Medicine) (Ahmad *et al.*, 2013; Tembure *et al.*, 2014; Paarakh, 2010). *N. sativa* seeds are identified as the curative black cumin in the holy bible; it is also described as the melanthon (little black seed) by Hippocrates and Dioscorides. In the Greco Arab/ Unani-Tibb system of medicine which construct from the work Hippocrates and others Unani physician, his contemporary Galen and Ibn- Sina has regarded *N. sativa* as a valuable remedy in hepatic and digestive

disorder. The famous book of medicine by Ibn-Sina "The cannon of medicine (980-1037) revealed historical importance of *N. sativa* as seeds that stimulates the body's energy and help recovery from fatigue and dispiritedness" (Tembhure *et al.*, 2014; Paarakh, 2010). In ayurvedic medicine, the seeds are employed for action like astringent, bitter, stimulant, diuretic, emmenagogue, anti-helminthic and used in jaundice, intermittent fever, dyspepsia, paralysis, piles and skin diseases etc (Paarakh, 2010). The aim of current review is to emphasize the traditional uses, pharmacological investigations that has been carried out on the plant so that the therapeutic potential of the said herb can be further explored for the betterment of humanity. Further study should be performed to investigate its aptitude.

## Taxonomic classification

|                |                   |
|----------------|-------------------|
| Kingdom        | Plantae           |
| Subkingdom     | Tracheobionta     |
| Super division | Spermatophyta     |
| Division       | Magnoliophyta     |
| Class          | Magnoliopsida     |
| Order          | Ranunculales      |
| Family         | Ranunculaceae     |
| Genus          | <i>Nigella</i> L. |
| Species        | <i>N. sativa</i>  |

Synonym of *N. sativa* in various languages

(Tembhure *et al.*, 2014; Dymock *et al.*, 2005; Anonymous, 1992; Satyavati *et al.*, 1987)

English: Black cumin, Love-in-a-mist, Fennel flower, Nutmeg

\*Correspondence: Anjum Areefa

E-mail: ariareefa@gmail.com

Received Jan 09, 2020; Accepted Mar 05, 2020; Published May 29, 2020

doi: <http://dx.doi.org/10.5667/CellMed.2020.0011>

©2020 by CellMed Orthocellular Medicine Pharmaceutical Association

This is an open access article under the CC BY-NC license.

<http://creativecommons.org/licenses/by-nc/3.0/>

flower, Damascena, Devil in the Bush; Arabic: Habatut Barakah; Shuneez; Habbat-us-sauda; Kamune-asvad; Persian: Siyadanah; Hindi: Kalonji, Kalajira; Sanskrit: Krishana – Jiraka, Upakunchika, Kaalaajajee, Sushavee, Ajaji, Kalvanjika, Kalika; Bengali: Mungrela; Malayalam: Karun shiragani; Tamil: Karun shiragam; Telugu: Nillajila; Kannar: Karijirigi

### Habitat

*N. sativa* is a small elegant herb, mostly attained and cultivated in India, Southern Europe, Pakistan, Syria, Turkey, Saudi Arabia and is a native of Southern Europe, North Africa and South West Asia. In India, it is found in Punjab, Himachal Pradesh, Gangetic plains, Bihar, Bengal, Assam, Maharashtra (Sultana *et al.*, 2015; Paarakh, 2010).

## PHARMACOGNISTAL DESCRIPTION

### Macroscopic feature of plant

It is an annual flowering plant ascending upto 30-60cm with linear-lanceolate leaves and has tap root; the flowers are white, yellow, pink or pale purple color, 5-10 petals on solitary long peduncle; sepals are ovate, acute and clawed. A fruit capsule comprise of 3-7 united follicles, each enclosing black seeds of size 0.2cm x 0.1cm are dicotyledonous, flattened, oblong, tubercular having rough testa containing white oily kernel; slightly aromatic in odor, taste bitter and takes about 10-15 days to germinate. Flowering and fruiting occur from January to April and is cultivated in dry soil in month of November till April (Forounzafar *et al.*, 2014; Phulwaria *et al.*, 2014; Ahmad *et al.*, 2013; Paarakh, 2010; Dymock *et al.*, 2005; Anonymous., 1992; Kirtikar *et al.*, 1987).

### Microscopic feature of seed

Transverse section of seed demonstrate single layer of epidermis comprising of elliptical, thick-walled cells covered externally by papillose cuticle. 2-3 layers of parenchymatous cells, a reddish-brown pigmented layer composed of tangentially elongated cells, followed by rectangular, radially elongated cells. Endosperm consists of moderately thick-walled polygonal cells, numerous oil filled globules and embryo entrenched in it (Paarakh, 2010; Ahmad *et al.*, 2013; Anonymous, YNM).



Fig. A & B. Flowers and Seeds of *Nigella sativa*

## UNANI DESCRIPTION

### Properties

Temperament (Mizaj): Hot<sup>2</sup>, Dry<sup>2</sup> (Khan, 2014; Ghani, YNM; Kabiruddin, YNM; Anonymous, 1992) Hot<sup>3</sup>, Dry<sup>3</sup> (Ghani, YNM; Hakeem, YNM).

Taste (Maza): Slightly bitter (Khan, 2014; Kabiruddin, YNM;

Anonymous, 1992; Hakeem, YNM), Acrid in taste (Ghani, YNM)

Odour (Boo): Pleasant odour like a lemon (Dymock *et al.*, 2005), strong smell (Hakeem, YNM; Khan, 2014).

Adverse Effect (Muzir): It affect liver (Khan, 2014; Ghani, YNM), cause diphteria (Kabiruddin, YNM; Hakeem, YNM), harms kidney (Hakeem, YNM; Ghani, YNM), lungs and patient with headache (Ghani, YNM).

Main Function (Nafa-e-Khas): Diuretic and Emmenagogue (*Mudir-e-Baul wa Haiz*) and Jaundice (*Yarqaan*) (Kabiruddin, YNM; Hakeem, YNM), Abortifacient (Mukhrij-e-Janeen), Haemorrhoids (*Bawaseer*) (Hakeem, YNM).

Corrective (*Musleh*): *Cucumis sativus* (*Tukhme Khyaar*) (Khan., 2014; Ghani, YNM), *Sterculia urens* (*Kateera*) (Ghani, YNM; Kabiruddin, YNM; Anonymous, 1992; Hakeem, YNM), Drugs of cold temperament (*Sard Ashiyaa*) (Kabiruddin, YNM; Hakeem, YNM), *Bumusa arundinacea* (*Banslochan*) (Ghani, YNM; Anonymous, 1992), Vinegar (*Sirka*) (Ghani, YNM; Anonymous, 1992; Hakeem, YNM), *Cichorium intybus* (*Kasni*) (Ghani, YNM)

Substitute (*Badl*): *Olea europae* (*Samaghe zaitoon*) (Khan, 2014; Ghani, YNM), *Lepidium sativum* (*Tukhme Rashaad*) (Khan, 2014; Ghani, YNM), *Pimpinella anisum* (*Anisoon*) (Kabiruddin, YNM; Khan, 2014; Ghani, YNM; Hakeem, YNM), *Anethum sowa* (*Sowa Seed*) (Khan, 2014; Hakeem, YNM), *Hyoscyamus niger* (*Ajwain Khurasani Seed*) (Ghani, YNM; Anonymous, 1992; Khan, 2014)

Important Unani formulations:

Habb-e-Hilteet, Jawarish Shoneez, Majoon Kalkalanaj (Kabiruddin, YNM; Anonymous, 1992; Anonymous, YNM); Majoon Fanjnosh, Majoon Kundur (Anonymous, YNM)

### Special Use of *N. sativa* by Ancient Unani Physician:

Externally:

- ♦ Jaundice (*Yarqaan*) - Use as nasal drop (*qutoor*) by mixing kalonji with mother milk (Kabiruddin, YNM; Ghani, YNM; Khan, 2014; Kirtikar *et al.*, 1987; Anonymous, YNM)
- ♦ Migraine (*Shaqeeqa*) and Chronic headache - used as nasal drop (*sauoot*) by mixing paste of kalonji in vinegar (Kabiruddin, YNM; Hakeem, YNM; Anonymous, 1992; Anonymous, YNM)
- ♦ Poison (*Samoom-e-Barida*) - Used as paste (*Zamad*); Tumours (*Sulaa*), Ptylosis (*Intishare Shaar*) - Used as liniment. (Khan, 2014)

### Ayurvedic description (Satyavati *et al.*, 1987)

- ♦ Properties

Taste (*Rasa*): Bitter (*Kattu*), Pungent (*Tikta*); Properties (*Guna*): Lightness (*Laghu*), Dryness (*Rooksha*), Sharp (*Teekshna*); Potency (*Veerya*): Hot (*Ushna*).

- ♦ Action/ use-

*Appetizer* (*Rochana*), *Carminative* (*Deepana*), *Digestive* (*Paachana*), *Pacifier* (*Vaatakaphahara*), *Eliminate foul smell* (*Daurgandhya-naashana*), *Brass* (*Pittala*), *Nootropic drug* (*Medhya*), *Purify uterus* (*Garbhaashayashodhaka*), *Beneficial for eye* (*Chakshushya*), *Phantom tumour* (*Gulmahara*), *Decrease*

emesis (*Chardihara*), Helps in diarrhoea (*Atisaarahara*) (vitiated condition of vata and kapha).

#### Afaal (Pharmacological Action) and Mawaqae istimal (Indications)

| Pharmacological Action (Afaal)                                 | Uses (Mawaqae istimal)                                                                                                                                                                                                               | Classical References                                        | Ethnobotanical References                                                                         |
|----------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------|---------------------------------------------------------------------------------------------------|
| Expectorant (Munafis-e-Balgham)                                | Asthma ( <i>Zeequn Nafas</i> )<br>Pleural Effusion ( <i>Zatul Janab</i> )<br>Cold ( <i>Nazla</i> ) and Cough ( <i>Sual</i> )<br>Chest pain ( <i>Dard e Sadar</i> )                                                                   | Kabiruddin, YNM;<br>Ghani, YNM<br>Khan, 2014<br>Hakeem, YNM | Kirtikar <i>et al.</i> , 1987<br>Anonymous, YNM                                                   |
| Phlegmatic diseases (Balgami Amraz)                            | <b>Externally:</b><br>Coryza ( <i>Zukaam</i> )- snuffing of roast seed or as nasal drop by mixing its powder with olive oil<br><b>Internally:</b> Cold ( <i>Nazla</i> ) and Cough ( <i>Saul</i> )                                    | Kabiruddin, YNM<br>Ghani, YNM<br>Khan, 2014                 | Dymock <i>et al.</i> , 2005<br>Anonymous, 1992                                                    |
| Anti-flatulence (Muhallil e Riyah)                             | Flatulence ( <i>Nafkhe Shikam</i> )<br>Colic ( <i>Qoolinj Reehi</i> )<br>Stomachache ( <i>Dard-e-Shikam</i> )                                                                                                                        | Kabiruddin, YNM<br>Khan, 2014<br>Hakeem, YNM<br>Ghani, YNM  | Kirtikar <i>et al.</i> , 1987<br>Anonymous, YNM<br>Anonymous, 1992                                |
| Stomach tonic (Muqawwi-e-Meda)                                 | Weakening of Stomach ( <i>Zauf-e-meda</i> )                                                                                                                                                                                          | Kabiruddin, YNM                                             | Anonymous, YNM<br>Dymock <i>et al.</i> , 2005                                                     |
| Laxative ( <i>Mulaiyin</i> ) and Purgative ( <i>Mushil</i> )   | Chronic constipation ( <i>Qabz Daimi</i> )                                                                                                                                                                                           | Kabiruddin, YNM                                             | Kirtikar <i>et al.</i> , 1987                                                                     |
| Liver tonic (Muqawwi-e-Jigar)                                  | Weakening of liver ( <i>Zauf-e-Jigar</i> ),<br>Jaundice ( <i>Yarqaan</i> ), Hepatitis ( <i>Warm-e-Jigar</i> )                                                                                                                        | Khan, 2014                                                  |                                                                                                   |
| Antihelminthic ( <i>Qatil-e-Kirmu-shikam</i> )                 | Helminthiasis ( <i>Kirm-e-Shikam</i> )                                                                                                                                                                                               | Kabiruddin, YNM<br>Khan, 2014<br>Hakeem, YNM                | Kirtikar <i>et al.</i> , 1987<br>Dymock <i>et al.</i> , 2005<br>Anonymous, YNM                    |
| Emmenagogue ( <i>Mudir-e-Haiz</i> )                            | Amenorrhoea ( <i>Ehteabas-e-Haiz</i> )                                                                                                                                                                                               | Kabiruddin, YNM<br>Ghani, YNM<br>Hakeem, YNM<br>Khan, 2014  | Anonymous, 1992<br>Dymock <i>et al.</i> , 2005<br>Kirtikar <i>et al.</i> , 1987<br>Anonymous, YNM |
| Diuretic ( <i>Mudir-e-Baul</i> )                               | Dysuria ( <i>Ushrul Baul</i> )<br>Kidney and Bladder stone ( <i>Hisate Kuliya wa Masana</i> )-Paste of kalonji when used with honey help in excretion of stones from kidney and bladder<br>Renal colic ( <i>Waj'a ul Gurda</i> )     | Ghani, YNM<br>Hakeem, YNM                                   | Dymock <i>et al.</i> , 2005<br>Kirtikar <i>et al.</i> , 1987                                      |
| Galactagogue ( <i>Mudir-e-Labn</i> )                           | Increase Lactation ( <i>Idra-e-Sheer</i> )-Intake of kalonji for longer time helpful in increasing maternal milk                                                                                                                     | Ghani, YNM<br>Khan, 2014                                    | Anonymous, 1992<br>Dymock <i>et al.</i> , 2005<br>Kirtikar <i>et al.</i> , 1987                   |
| Analgesic ( <i>Musakkin-e-Alam</i> )                           | Renal colic ( <i>Waj'a ul-Gurda</i> )<br>Backache ( <i>Dard e kamar</i> )<br>Dysmenorrhoea ( <i>Ushr ul Tams</i> )<br>Pain in uterus ( <i>Waj'a ul Reham</i> )<br>Headache ( <i>Sudaa</i> )                                          | Kabiruddin, YNM<br>Khan, 2014                               | Anonymous, YNM                                                                                    |
| Detergent ( <i>Jali</i> ) (Externally)                         | Scald ( <i>Bahek</i> ), Vitiligo ( <i>Bars</i> ), Tinea ( <i>Da'ad</i> ), Alopecia ( <i>Da-us-salab</i> ), Acne ( <i>Basoorlabn</i> )-used as liniment by using kalonji alone or by mixing with vinegar along with appropriate drug. | Kabiruddin, YNM<br>Khan, 2014                               | Anonymous, 1992<br>Dymock <i>et al.</i> , 2005<br>Anonymous, YNM                                  |
| Styptic ( <i>Habis e Dam</i> ) (Externally)                    | <b>Externally:</b> Haemorrhage ( <i>Jiryaa-e-Dam</i> ), Hemorrhoids ( <i>Bawaseer</i> )                                                                                                                                              | Kabiruddin, YNM<br>Hakeem, YNM                              |                                                                                                   |
| Coctive ( <i>Munziji</i> ) and Desiccative ( <i>Mujaffif</i> ) | Wound healing ( <i>Mudammil-e-qurooh</i> ), Ascites ( <i>Istisqaa</i> )                                                                                                                                                              | Ghani, YNM<br>Hakeem, YNM<br>Khan, 2014                     | Anonymous, 1992                                                                                   |
| Nervine tonic (Muqawwi-e-Asaab)                                | <b>Externally:</b><br>Paralysis ( <i>Falij</i> ) - massage with kalonji oil, Bell's palsy ( <i>Laqwa</i> ) -massage with kalonji oil, Tetanus ( <i>Kuzaz</i> )                                                                       | Kabiruddin, YNM;<br>Khan, 2014                              | Kirtikar <i>et al.</i> , 1987<br>Anonymous, YNM                                                   |
| Abortifacient ( <i>Musqit-e-Janeen</i> )- in high dose         | Abortion ( <i>Istiqrar-e-Hamal</i> )                                                                                                                                                                                                 |                                                             | Anonymous, 1992<br>Dymock <i>et al.</i> , 2005                                                    |
| Anti-inflammatory ( <i>Muhallil-e-awram</i> )                  | Arthritis ( <i>Waj'a ul-mufasil</i> )                                                                                                                                                                                                | Kabiruddin, YNM<br>Hakeem, YNM                              | Anonymous, 1992<br>Anonymous, YNM                                                                 |
| Emetic ( <i>Muqui</i> )                                        | Nausea ( <i>Gisyaan</i> ) & Vomiting ( <i>Qai</i> )                                                                                                                                                                                  | Khan, 2014                                                  |                                                                                                   |

|                                               |                                                                                                                                                                                                                                        |                               |                               |
|-----------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------|-------------------------------|
| Rubefacient<br>( <i>Mushakhin</i> )           | Baldness ( <i>Sa'afa</i> ) - mix kalonji with oil, wax and is apply on bald portion of head.<br>Ringworm ( <i>Qooba</i> ) - used as liniment by mixing it with vinegar.                                                                | Khan, 2014<br>Kabiruddin, YNM |                               |
| Antipyretic<br>( <i>Da'afae Humma</i> )       | Tertian Fever                                                                                                                                                                                                                          |                               | Kirtikar <i>et al.</i> , 1987 |
| Anti-microbial<br>( <i>Qatil-e-Jaraseem</i> ) | <b>Externally :</b><br>Scald ( <i>Bahak</i> ), Scabies ( <i>Jarb</i> ) - used as liniment by making a paste with seed and vinegar and mix it with rose oil.<br>Ringworm ( <i>Qooba</i> ) - used as liniment by mixing it with vinegar. | Khan, 2014<br>Kabiruddin, YNM |                               |

## PHYTOCHEMICAL STUDY OF *N. sativa*

Extensive phytochemical studies has been done to isolate and identify the chemical composition of *N. sativa*. Seeds include 36 to 28% fixed oil, proteins, alkaloid, saponin and 0.4 to 2.5% essential oil (Forouzanfar *et al.*, 2014; Tembhurne *et al.*, 2014). Pharmacological properties of black cummin is mainly due to presence of Thymoquinone (TQ). Important active volatile constituents of *N. sativa* are thymoquinone (30%-48%), thymohydroquinone, dithymoquinone, nigellone that is the only component of the carbonyl fraction of the oil (Ahmad *et al.*, 2013),  $\alpha$  and  $\beta$ -pinene, d-limonene, d-citronellol, p-cymene and thymol (Forouzanfar *et al.*, 2014). Other component present in it are p-cymene (7%-15%), carvacrol (6%-12%), 4-terpineol (2%-7%), t-anethol (1%-4%), sesquiterpene longifolene (1%-8%) (Ahmad *et al.*, 2013; Tembhurne *et al.*, 2014).

Seeds contain two different types of alkaloids i.e. isoquinoline alkaloids e.g. nigellicimine and nigellicimine-N-oxide and pyrazol alkaloids or indazole ring bearing alkaloids which include nigellidine and nigellicine. Moreover, it also contain alpha-hederin, a water soluble pentacyclic triterpene and saponin, a potential anticancer agent (Sultana *et al.*, 2015; Ahmad *et al.*, 2013). Flavonoids present in seed are quercetin and kaempferol 3-glucosyl (1-2) galactosyl (1-2) glucoside and quercetin-3-(6-feruloyl glucosyl) (1-2) galactosyl (1-2) glucoside (Merfort *et al.*, 1997). Other than those triglycoside quercetin 3-glucoside, kaempferol 3-glucoside and rutin were also isolated from the seeds of *N. sativa* (Tembhurne *et al.*, 2014). The nutritional component of seeds contain protein (26.7%), fat (28.5%), carbohydrates (24.9%), crude fibre (8.4%) and total ash (4.8 %), vitamins and minerals like potassium, phosphorus, sodium, iron are main element and Copper, Magnesium, Manganese. Zinc and Calcium found at low levels (Al-Jassir., 1992; Sultana *et al.*, 2015). The seeds contain carotene which is

converted by the liver to vitamin A. Root and shoot are reported to contain vanillic acid (Ahmad *et al.*, 2013).

The fixed oil comprise of unsaturated fatty acids which includes: arachidonic, eicosadienoic (3%), linoleic (50-60%), linolenic, oleic (20%) (Sultana *et al.*, 2015) and saturated fatty acid comprise of palmitic (12.5%), stearic and myristic acid (Tembhurne *et al.*, 2014; Nickavara *et al.*, 2003). Beta-sitosterol, cycloartenol, cycloartenol, sterol esters and sterol glucosides are also found (Forouzanfar *et al.*, 2104).  $\alpha$ -sitosterol is a major sterol, which accounts for 44% and 54% of the total sterols in Tunisian and Iranian varieties of *N. sativa* oils, pursued by stigmasterol (6.57-20.92% of total sterols) (Sultana *et al.*, 2015).

Numerous chemical components reported are nigellone, avenasterol-5-ene, nigellone, nigellicine, nigellimine, nigellimine-N-oxide, avenasterol-7-ene, campesterol, cholesterol, citrostadienol, lophenol, obtusifoliol, stigmastanol, stigmasterol-7-ene,  $\beta$ -amyrin, butyro- spermol, cycloartenol, 24-methylene-cycloartanol, taraxerol, tirucallol, 3-O-[ $\beta$ -D-xylopyranosyl-(1 $\rightarrow$ 3)- $\alpha$ -L-rhamnopyranosyl-(1 $\rightarrow$ 2)- $\alpha$ -L-arabinopyranosyl]-28-O-[ $\alpha$ -L-rhamnopyranosyl-(1 $\rightarrow$ 4)- $\beta$ -D-glucopyranosyl-(1 $\rightarrow$ 6)- $\beta$ -D-glucopyranosyl] hederagenin, volatile oil (0.5-1.6%), fatty oil (35.6-41.6%), oleic acid, esters of unsaturated fatty acids with C-15 and higher terpenoids, esters of dehydrostearic and linoleic acid, aliphatic alcohol, melanthin, melanthigenin, bitter principle, tannin, resin, protein, reducing sugar, glycosidal saponin, 3-O-[ $\beta$ -D-xylopyranosyl-(1 $\rightarrow$ 2)- $\alpha$ -L-rhamno-pyranosyl-(1 $\rightarrow$ 2)- $\beta$ -D-glucopyranosyl]-11-methoxy-16, 23-dihydroxy-28-methylolean-12-enoate, stigma-5, 22-dien- 3- $\beta$ -D-glucopyranoside, cycloart-23-methyl-7, 20, 22- triene-3 $\beta$ , 25-diol, nigellidine-4-O-sulfite, N. mines A3, A4, A5, C, N. mines A1, A2, B1, and B2 (Sultana *et al.*, 2015; Ahmad *et al.*, 2013; Paarakh *et al.*, 2010).

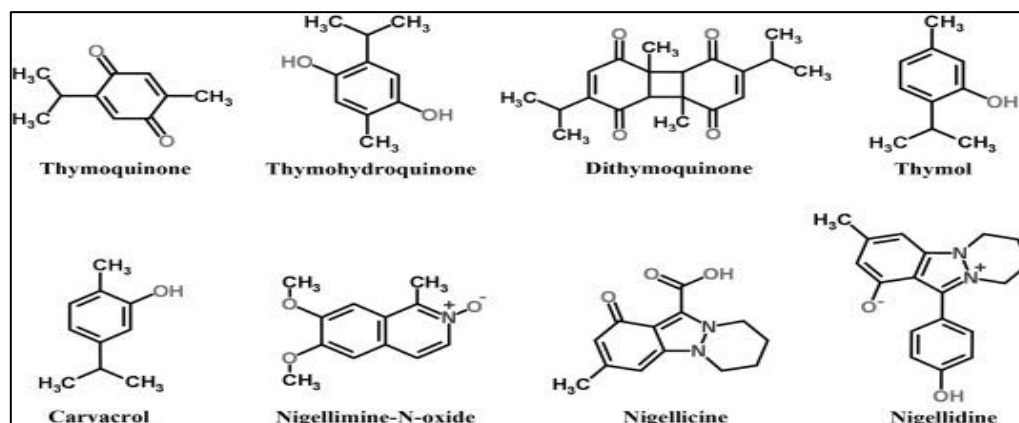


Fig. c Chemical Constituents Of *Nigella sativa*

**ETHANOPHARMACOLOGICAL USES OF *N. sativa***

Traditionally seed of *N. sativa* are used in middle-eastern folk medicine for treating several diseases for more than 2000 years (Forouzanfar *et al.*, 2014). There is extensive historical description of folklore usage of *N. sativa* seeds and their oil in Indian and Arabian civilization as food and medicine (Ahmad *et al.*, 2013). The seeds were used as pungent appetizer, aromatic, thermogenic, diuretic, expectorant, purgative, anthelmintic, emmenagogue, antibacterial, anti-inflammatory, anodyne, febrifuge, galactagogue stimulant, sudoriferous, sedative and carminative (Sala, 1997). It is used for treatment of wide range of disease conditions related to respiratory system, digestive tract, kidney and liver function, cardiovascular system, skin care, fertility and immune system as well as for general health (Ahmad *et al.*, 2013; Aklaque, 2018; Phulwaria, 2018). Roasted seeds are given internally to stop the vomiting (Ahmad *et al.*, 2013; Sultana *et al.*, 2015).

In Indian and Arabian system of medicine, seeds are used for skin diseases, jaundice, gastrointestinal problems, anorexia,

conjunctivitis, diarrhea, dyspepsia, rheumatism, diabetes, hemorrhoids, helminthiasis, hypertension, halitosis, intrinsic hemorrhage, paralysis, amenorrhea, dysmenorrhea anorexia, asthma, cough, bronchitis, headache, fever, influenza and eczema (Forouzanfar *et al.*, 2014; Sala, 1997; Kirtikar, 1987). It is also traditionally used by Iranian therapists as a treatment for mastalgia (Aklaque, 2018).

In case of skin eruptions, seeds powder are mixed with sesame oil for local application (Kirtikar, 1987). Externally the oil is used as an antiseptic and local anesthetic. Due to its countless uses *nigella* has earned the Arabic approbation of '*Habbat ul Barakah*', meaning the seed of blessing (Ahmad *et al.*, 2013; Phulwaria, 2018).

It is generally used to increase lactation in nursing mothers, to fight against parasitic infections, and to boost their immune system. Since they have very low level of toxicity seeds are also used in food like flavoring additive in the breads and pickles (Sultana *et al.*, 2015).

| Pharmacological Activity             | Conclusion of the study                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | References                                                                                                                                                                                                                                                                                                                                                                                                                  |
|--------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Antibacterial activity</b>        | <ul style="list-style-type: none"> <li>Antibacterial effect against G +ve and G -ve bacteria is shown by various crude extract of <i>N. sativa</i> seed, essential oil and due to presence of Thymoquinone (TQ), Thymohydroquinone and Melanin.</li> <li>Ethanol extract of <i>N. sativa</i> seed, oil, Thymoquinone and Carvacrol exhibit antibacterial and resistant modifying activity against Mithicilin Resistant <i>Staphylococcus aureus</i> and <i>Listeria monocytogens</i> respectively.</li> <li>Furthermore, <i>N. sativa</i> oil alone shows this activity against <i>Mycoplasma mycoides subsp mycoides</i> and <i>Schistosoma mansoni</i>. Methanolic, ethanolic and aqueous extract of <i>N. sativa</i> work against gallbladder and infantile septicemia pathogen.</li> </ul>                                                                                                                                                                                                                                                                                    | Bakathir <i>et al.</i> , 2011<br>Chaieb <i>et al.</i> , 2011<br>Mechraoui <i>et al.</i> , 2018<br>Reddy <i>et al.</i> , 2018<br>Hosseinzadeh <i>et al.</i> , 2007<br>Salem <i>et al.</i> , 2010<br>Mouwakeh <i>et al.</i> , 2019<br>Halawani, 2009<br>Morsi, 2000<br>Hannan <i>et al.</i> , 2008<br>Mouwakeh <i>et al.</i> , 2018<br>Onsa <i>et al.</i> , 2019<br>Abououf <i>et al.</i> , 2018<br>Shah <i>et al.</i> , 2018 |
| <b>Antifungal activity</b>           | <ul style="list-style-type: none"> <li>Methanolic extracts, chloroform extracts and bioactive compound like Quinines, Dithymoquinone, Thymohydroquinone, and Thymoquinone of <i>N. sativa</i> and nano-particulated drugs-<i>Amphotericin-B</i>, <i>Ketoconazole</i> and <i>Thymoquinone</i> have the strongest antifungal effect against different strains of <i>Candida albicans</i> and dairy spoilage yeast specie and their biofilm respectively.</li> <li>Antidermatophyte activity of essential oil, various extract of <i>N. sativa</i> and Thymoquinone was tested against eight species of dermatophytes like <i>T. mentagrophytes</i>, <i>M. canis</i> and <i>M. gypseum</i> etc.</li> <li>Two antifungal defensins named Ns-D1 and Ns-D2 isolated from its seeds displayed antifungal activity towards phytopathogenic fungi. Fractioned methanolic extract and essential oil of <i>N. sativa</i> against <i>F. oxysporum</i>, <i>M. phaseolina</i> and <i>Aspergillus</i> species respectively show complete inhibition of the fungal biomass production.</li> </ul> | Khan <i>et al.</i> , 2003<br>Halamova <i>et al.</i> , 2010<br>Randhawa <i>et al.</i> , 2015<br>Aljabre <i>et al.</i> , 2005<br>Mahmoudvand, 2014<br>Rogozhin <i>et al.</i> , 2011<br>Aftab <i>et al.</i> , 2019<br>Khosravi, 2011                                                                                                                                                                                           |
| <b>Anti-schistosomiasis activity</b> | <ul style="list-style-type: none"> <li>The effect of <i>Nigella sativa</i> Oil (NSO) and Anti-schistosomal activities of the Garlic Extract (AGE) against the liver damage induced by <i>Schistosoma mansoni</i> infection in mice shows its strong biocidal effects against all stages of the parasite and an inhibitory effect on egg laying of female worms.</li> <li>AGE and NSO prevent most of the hematological and biochemical changes and markedly improved the antioxidant capacity of schistosomiasis mice and disturbing the antioxidant enzymes of adult worms using <i>N. sativa</i> seeds play a role in the anti-schistosomal potency.</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                 | Mohamed <i>et al.</i> , 2005<br>El Shenawy <i>et al.</i> , 2008                                                                                                                                                                                                                                                                                                                                                             |
| <b>Antioxidant activity</b>          | <ul style="list-style-type: none"> <li>TQ and methanolic extract of seed shows significant antioxidant activity along with anti-inflammatory, anticancer, antibacterial and antiarthritic activity in vivo and in vitro. Extract of <i>N. sativa</i> and <i>C. angustifolia</i> exhibit potential anti-oxidant activity. TQ also suppress the Fe-NTA-induced oxidative stress, and renal carcinogenesis in rats.</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | Umar <i>et al.</i> , 2012<br>Bourgou <i>et al.</i> , 2012<br>Khan <i>et al.</i> , 2005<br>Mariod <i>et al.</i> , 2009<br>Reddy <i>et al.</i> , 2018<br>Al-Othmanetal., 2006                                                                                                                                                                                                                                                 |

|                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|----------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                  | <ul style="list-style-type: none"> <li>Dietary supplementation of its powder inhibits the oxidative stress alone thus very helpful in a patient of ulcerative colitis and hepatocarcinogens induced rats.</li> <li>The <i>N. sativa</i> oil, its hydroalcoholic extract and TQ have protective effects on oxidative enzymes during ischemia-reperfusion injury (IRI) and play beneficial role in cerebrovascular insufficiency state and alter the oxidative activity in rat model.</li> <li>Broiler chicks was treated with seed for 6 weeks prevented the liver from oxidative stress.</li> <li>Pretreatment with TQ in colon carcinogenesis of Wistar rat have modulatory effect on erythrocyte lipid peroxidation and antioxidant status. <i>N. sativa</i> suppress the oxidative stress and enzyme activity induced by Nanoparticle (Cu and CdS).</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | Gendy <i>et al.</i> , 2007<br>Bodaghi <i>et al.</i> , 2019<br>Hosseinzadeh <i>et al.</i> , 2007<br>Fanoudi <i>et al.</i> , 2019<br>Sogut <i>et al.</i> , 2008<br>Harzallah <i>et al.</i> , 2012<br>Kumbhakara <i>et al.</i> , 2019                                                                                                                                                                                                                                                                                                                                      |
| <b>Antidiabetic activity</b>     | <ul style="list-style-type: none"> <li>The therapeutic potentials of <math>\alpha</math>-lipoic acid (<math>\alpha</math>-LA), L-carnitine or <i>N. sativa</i> combinedly contribute significant reduce in the elevated blood glucose level in diabetic rats.</li> <li><i>N. sativa</i> seeds, its extract, oil and TQ show significant reduce in the elevated blood glucose level, it emphasizes on glucose-induced secretion of insulin, preserve pancreatic <math>\beta</math>-cell integrity and altered carbohydrate metabolic enzymes activity were restored to normal. It also show synergistic effect with human parathyroid hormone. Its extract is capable of producing insulin producing cell.</li> <li>Clinically <i>N. sativa</i> oil shows effective adjuvant effect on the patient of insulin resistance syndrome and use of oil also decrease Fasting Blood Glucose and increase insulin levels in diabetic rats. Oral dose of 2 gm/day of its seed is a beneficial adjuvant to oral hypoglycemic agents in type 2 diabetic patients.</li> <li>The in vivo antidiabetic activity of ethanolic extract <i>N. sativa</i> seed in diabetic Merionesshawii demonstrate insulin-sensitizing action by AMPK signaling pathway and by enhancing muscle Glut4 (Glucose transporter type4) content.</li> <li><i>N. sativa</i> and propolis methanol extract, <i>N. sativa</i> and <i>Cinnamomum cassia</i> and methanolic Extract of <i>N. sativa</i> and <i>Brassica alba</i> seeds exhibit its combinatorial antidiabetic capability.</li> <li>The antihyperglycemic effect of <i>N. sativa</i> oil was more effective than <i>N. sativa</i> powder in reduction of glycemic status. It was observed that <i>N. sativa</i> seed reduced the higher blood glucose level and revealed overexpression to CAT, GST and Bcl2 (B-cell Lymphoma) genes and also to SOD, GPX and IGF-1 (Insulin like growth factor-1) by higher quantitative PCR in diabetic rats.</li> <li>Furthermore use of <i>N. sativa</i> has been shown to increase the activity of rat parotid gland for insulin and glucagon that was markedly diminished with advance of age there by decreasing the incidence of diabetes.</li> <li>Thymoquinone(TQ) nano-capsules (actually containing half of the doses of thymoquinone) produced better antihyperglycemic effect in type-2 diabetic rats as compared to thymoquinone alone.</li> </ul> | Salama., 2015<br>Kanter <i>et al.</i> , 2009<br>Kapoor., 2009<br>Andaloussi <i>et al.</i> , 2008<br>Younus., 2018<br>Pari <i>et al.</i> , 2009<br>Altan <i>et al.</i> , 2007<br>Najmi <i>et al.</i> , 2008<br>Ranjbaran <i>et al.</i> , 2018<br>Abdelrazek <i>et al.</i> , 2018<br>Bamosa <i>et al.</i> , 2010<br>Andaloussi <i>et al.</i> , 2011<br>Rabey <i>et al.</i> , 2017<br>Kaur <i>et al.</i> , 2018<br>Arefin <i>et al.</i> , 2018<br>Askari <i>et al.</i> , 2019<br>Althnaian <i>et al.</i> , 2019<br>Kamal <i>et al.</i> , 2012<br>Rani <i>et al.</i> , 2018 |
| <b>Anticancer activity</b>       | <ul style="list-style-type: none"> <li>TQ has a beneficial effect in conditioning T cells in vitro for adoptive T-cell therapy against cancer and infectious disease. <i>N. sativa</i> seed and extracts has cytotoxic effect in human breast cancer cells.</li> <li>TQ and ethanolic extract of <i>N. sativa</i> has antitumor and anti-angiogenic effects.</li> <li>TQ was cytotoxic towards human cervical squamous carcinoma cells which was determined by MTT assay and trypan blue dye exclusion test.</li> <li>TQ exert antiproliferative effect in breast cancer cells and gastric cancer cell. TQ isolated from extract of <i>N. sativa</i> and <i>Thymus vulgaris</i> exerts a dose-dependent anti-proliferative effect on HeLa cancer cells.</li> <li><i>N. sativa</i> oil administration exerts potent inhibitory effects on rat tumor development and on cellular proliferation in multiple organ sites with no evidence of clinical side effects.</li> <li>The aqueous extract of <i>N. sativa</i> significantly enhances splenocyte proliferation and NK (Natural Killer cell) cytotoxic activity against tumor cells.</li> <li>TQ exerts antimetastatic activity on pancreatic cancer both in vitro and in vivo. <i>N. sativa</i> nano emulsion reduced the cell viability against human liver carcinoma cells.</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | Salem <i>et al.</i> , 2011<br>Mahmoud <i>et al.</i> , 2012<br>Shafi <i>et al.</i> , 2008<br>Peng <i>et al.</i> , 2013<br>Fathy <i>et al.</i> , 2018<br>Ng <i>et al.</i> , 2011<br>Woo <i>et al.</i> , 2011<br>Lei <i>et al.</i> , 2012<br>Butt <i>et al.</i> , 2019<br>Salim <i>et al.</i> , 2010<br>Majdalwieh <i>et al.</i> , 2010<br>Wu <i>et al.</i> , 2011<br>Torres <i>et al.</i> , 2010<br>Tabassum <i>et al.</i> , 2019                                                                                                                                         |
| <b>Immunomodulatory activity</b> | <ul style="list-style-type: none"> <li>The potential immunomodulatory effects of aqueous extract, methanolic extract and volatile oil of <i>N. sativa</i> seed boost splenocyte proliferation, enhance WBC count, suppress primary macrophage and enhances NK cytotoxic activity against tumor cells and lethal infections.</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | Majdalaweih <i>et al.</i> , 2010<br>Ghonime <i>et al.</i> , 2011<br>Torres <i>et al.</i> , 2010<br>Abel-Salam., 2012<br>Mohamed <i>et al.</i> , 2009<br>Assayed., 2010                                                                                                                                                                                                                                                                                                                                                                                                  |

|                                                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                                                                                                                                                                                                                                                                                                                           |
|-----------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                                 | <ul style="list-style-type: none"> <li>It has immunomodulatory activity in prophylactic treatment of opportunistic infections and as supportive treatment.</li> <li>When seed are co-administered with Oxytetracycline produce immunostimulant effect in pigeon.</li> <li>TQ is 90% preventive in experimental autoimmune encephalomyelitis and 50% curative in chronic relapsing due to its antioxidant effect.</li> <li><i>N. sativa</i> oil is radioprotective agent against immunosuppressive and oxidative effects of ionizing radiation.</li> <li>Extract of <i>N. sativa</i> show potential immunomodulation effect on lung inflammation of ova-albumin sensitized guinea pigs and significantly improves symptoms and immune parameters in murine OVA-induced allergic diarrhea.</li> </ul>                                                                                                                                                                                                                                                                                                                                                             | Boskabady <i>et al.</i> , 2011<br>Duncker <i>et al.</i> , 2012                                                                                                                                                                                                                                                                            |
| <b>Anti-inflammatory and Analgesic activity</b>                 | <ul style="list-style-type: none"> <li>The aqueous extract of <i>N. sativa</i> was found to possess anti-inflammatory and analgesic activity.</li> <li>Extract of <i>N. sativa</i> and TQ significantly reduced pancreatic ductal adenocarcinoma (PDA) cell synthesis.</li> <li>TQ has an anti-inflammatory effect during the allergic response in the lung by inhibiting immune response. The shoots, roots and seeds methanol extracts of <i>N. sativa</i> has antioxidant, anti-inflammatory, anticancer and antibacterial activities.</li> <li><i>N. sativa</i> oil reduces allergic rhinitis. It is also could be used for prevention and for asthma therapy.</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | Alemi <i>et al.</i> , 2012<br>Al-Ghamdi., 2001<br>Chehl <i>et al.</i> , 2009<br>El-Mezayen <i>et al.</i> , 2006<br>Pichette <i>et al.</i> , 2012<br>Nikakhlagh <i>et al.</i> , 2011<br>Ikhsan <i>et al.</i> , 2018                                                                                                                        |
| <b>Cardiovascular activity</b>                                  | <ul style="list-style-type: none"> <li>TQ prevents decrease in platelet numbers and prothrombotic events and has cardio protective effect.</li> <li>Pretreatment with <i>N. sativa</i> oil reduces heart injury, normalizes cardiac histopathology, improve antioxidant enzyme status and cellular protein oxidation.</li> <li><i>N. sativa</i> protect against hypertension-induced tissue damage and enhance cardiovascular function by its antioxidant and antihypertensive effects.</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | Nemmar <i>et al.</i> , 2011<br>Nagi <i>et al.</i> , 2011<br>Ebru <i>et al.</i> , 2008<br>Tasar <i>et al.</i> , 2012                                                                                                                                                                                                                       |
| <b>Gastro-protective activity</b>                               | <ul style="list-style-type: none"> <li>TQ has gastroprotective mechanisms via inhibiting proton pump, acid secretion and neutrophil infiltration, while enhancing mucin secretion, and nitric oxide production.</li> <li>It has anti-ulcer effect which is either prostaglandin-mediated or through its antioxidant and anti-secretory activities.</li> <li><i>N. sativa</i> Oil and TQ possess gastroprotective effect against gastric lesions.</li> <li>TQ protects gastric mucosa against the ulcerating effect of alcohol and alleviate most of the biochemical harmful effects induced by alcohol in gastric mucosa. It can prevent and improve induced colitis and is also used for treating inflammatory bowel disease.</li> <li><i>N. sativa</i> Oil significantly reduces the severity of intestinal damage in necrotizing enterocolitis.</li> </ul>                                                                                                                                                                                                                                                                                                   | Magdy <i>et al.</i> , 2012<br>Al Mofleh <i>et al.</i> , 2008<br>El-Abhar <i>et al.</i> , 2003<br>Khaled, 2009<br>Lei <i>et al.</i> , 2012<br>Tayman <i>et al.</i> , 2012                                                                                                                                                                  |
| <b>Hepato-protective activity</b>                               | <ul style="list-style-type: none"> <li><i>N. sativa</i> intraperitoneally relieves the adverse effects of ischemia reperfusion injury on liver.</li> <li><i>N. sativa</i> protects hepatic tissue from harmful effects of toxic metals and reduce hepatic lipid peroxidation.</li> <li>TQ has modulatory influence on the antioxidant defense system and it also act as hepatoprotective by prevention of SOD suppression mediated by paraquat.</li> <li><i>N. sativa</i> hydroalcoholic extract improves liver function during neonatal and juvenile growth.</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | Yildiz <i>et al.</i> , 2008<br>Kapoor., 2009<br>Zafeeretal., 2012<br>Lorestani <i>et al.</i> , 2018<br>Hosseinia <i>et al.</i> , 2018                                                                                                                                                                                                     |
| <b>Nephroprotective activity</b>                                | <ul style="list-style-type: none"> <li>Vitamin C and <i>N. sativa</i> oil when given in combination have synergistic nephroprotective effect.</li> <li>TQ synergizes with its nephroprotective effect against cisplatin-induced and Gentamicin induced acute kidney injury by preventing degenerative changes in renal tissues of rats.</li> <li><i>N. sativa</i> oil has protective effect in methotrexate-induced and Gentamicin induced nephrotoxicity. It also protects renal tissue against oxygen free radicals, percluding renal dysfunction and morphological abnormalities related to cyclosporin an administration.</li> <li><i>N. sativa</i> also has protective effect against renal injury. It hinder the toxic effects of Gentamicin both in the biochemical and histopathological parameters.</li> <li>Therapeutic administration of <i>N. sativa</i> reduces the toxic effects of paracetamol on kidneys by preventing oxidative stress changes.</li> <li><i>N. sativa</i> extract has antioxidant and anti-inflammatory effect and it also act as therapeutic agent to treat unilateral ureteral obstruction induced kidney damage.</li> </ul> | Saleem <i>et al.</i> , 2012<br>Ulu <i>et al.</i> , 2012<br>Sayed-Ahmad <i>et al.</i> , 2007<br>Abul-Nasr <i>et al.</i> , 2001<br>Ali, 2004<br>Uz <i>et al.</i> , 2008<br>Yildiz <i>et al.</i> , 2010<br>Yaman <i>et al.</i> , 2010<br>Hadjzadeh <i>et al.</i> , 2012<br>Canayakin <i>et al.</i> , 2016<br>Hosseinian <i>et al.</i> , 2018 |
| <b>Pulmonary-protective activity and anti-asthmatic effects</b> | <ul style="list-style-type: none"> <li>Nigellone possess anti-spasmodic effect and is useful in treatment of different respiratory diseases.</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | Wienkotter <i>et al.</i> , 2008<br>Boskabady <i>et al.</i> , 2008<br>Hossein <i>et al.</i> , 2008                                                                                                                                                                                                                                         |

|                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                                                                                                                                                                                                                                                |
|--------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                  | <ul style="list-style-type: none"> <li>♦ Methanol and dichloromethane fraction of <i>N. sativa</i> have relaxant effect on pre contracted tracheal chains.</li> <li>♦ <i>N. sativa</i> has protective effect on tracheal responsiveness and lung inflammation which was exposed sulfur mustard gas in guinea pigs. It is useful in lung injury and in clinical use.</li> <li>♦ <i>N. sativa</i> oil reduces severity of lung damage due to hyperoxia.</li> <li>♦ <i>N. sativa</i> has prophylactic effect on asthma disease and has anti-asthmatic effect on asthmatic airways although boiled extract has less effect than theophylline.</li> </ul>                                                                                                                    | Kanter, 2009<br>Tayman <i>et al.</i> , 2012<br>Boskabady <i>et al.</i> , 2007<br>Boskabady <i>et al.</i> , 2010                                                                                                                                                |
| <b>Anti-osteoporotic activity</b>                | <ul style="list-style-type: none"> <li>♦ <i>N. sativa</i> and TQ were shown to inhibit inflammatory cytokines such as interleukin-1 and 6 and the transcription factor, nuclear factor <math>\kappa</math>B. Both NS and TQ have shown potential as anti-osteoporotic agent.</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | Shuid <i>et al.</i> , 2012                                                                                                                                                                                                                                     |
| <b>Testicular-protective activity</b>            | <ul style="list-style-type: none"> <li>♦ TQ decrease the destructive effects of methotrexate on testicular tissue of patients.</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | Gokce <i>et al.</i> , 2011                                                                                                                                                                                                                                     |
| <b>Neuro-pharmacological activities</b>          | <ul style="list-style-type: none"> <li>♦ The aqueous and methanol extracts of defatted <i>N. sativa</i> L. seeds were shown to hold a potent anti-depressant and analgesic activities.</li> <li>♦ Long term administration of <i>N. sativa</i> enhance learning and memory. Its oil and TQ is used for treatment of anxiety.</li> <li>♦ <i>N. sativa</i> oil appears to have a therapeutic potential in tramadol tolerance and dependence.</li> <li>♦ Aqueous and hydroalcoholic extracts of <i>N. sativa</i> have neuroprotective effects in cerebral ischemia.</li> <li>♦ <i>N. sativa</i> supplementation improves Pb-induced neurotoxicity and antioxidant potentials.</li> <li>♦ TQ has protective activity against chemotherapy-induced neurotoxicity.</li> </ul> | AL-Naggar <i>et al.</i> , 2003<br>Perveen <i>et al.</i> , 2008<br>Perveen <i>et al.</i> , 2009<br>Gilhotra <i>et al.</i> , 2011<br>Abdel-Zaher <i>et al.</i> , 2011<br>Akhtar <i>et al.</i> , 2012<br>Butt <i>et al.</i> , 2018<br>Ustuna <i>et al.</i> , 2018 |
| <b>Anticonvulsant activity</b>                   | <ul style="list-style-type: none"> <li>♦ Curcumin and <i>N. sativa</i> oil has anti- convulsant and antioxidative effect by reducing oxidative stress, excitability and the induction of seizures in epileptic animals and it also recovers from some of the adverse effects of antiepileptic drugs.</li> <li>♦ Aqueous extract, fixed oil, volatile oil of <i>N. sativa</i> seeds and TQ has antiepileptic effect when pass through maximal electroshock (MES)-induced convulsions and minimal neurological deficit (MND) test.</li> </ul>                                                                                                                                                                                                                             | Ezz <i>et al.</i> , 2011<br>Raza <i>et al.</i> , 2008                                                                                                                                                                                                          |
| <b>Contraceptive and anti-fertility activity</b> | <ul style="list-style-type: none"> <li>♦ Hexane extract and ethanolic extract of <i>N. sativa</i> seeds exhibit antifertility activity due to its inherent estrogenic activity</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | Keshri <i>et al.</i> , 1995<br>Agarwal <i>et al.</i> , 1990                                                                                                                                                                                                    |
| <b>Anti-oxytocic activity</b>                    | <ul style="list-style-type: none"> <li>♦ <i>N. sativa</i> seeds and oil helps in inhibition of smooth muscle contraction of uterus induced by oxytocin stimulations and has anti- oxytocic effect.</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | Aqel <i>et al.</i> , 1996                                                                                                                                                                                                                                      |
| <b>Toxicological studies</b>                     | <ul style="list-style-type: none"> <li>♦ The low toxicity of <i>N. sativa</i> fixed oil has wide margin of safety for therapeutic doses.</li> <li>♦ TQ is a safe compound, particularly when given orally to experimental animals.</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | Zaoui <i>et al.</i> , 2002<br>Al-Ali <i>et al.</i> , 2008<br>Khader <i>et al.</i> , 2009                                                                                                                                                                       |

## CONCLUSION

There is a prevalent use of herbal drug as traditional medicine and is gaining global popularity. One of them is *N. sativa* which have been used since antiquity as a natural therapy for various diseases and also their use were stated in Bible, *Tibb-e-Nabwi*, Cannon of Medicine and Ayurvedic literature. A lot of studies validate its significance in folk medicine as antihypertensive, anti-inflammatory, immune stimulant, analgesic, anti-microbial, anti-fungal, anti-oxidant, and as an anti-cancer. Further work can be desired to discover the pharmacokinetics, biochemical and therapeutic activities of active constituents and their collaboration with modern drugs. Cellular and molecular target of various constituent of *N. sativa* seed may be explored to get more effective and safer drug. Further thorough Clinical studies on *N. sativa* should be done so that humanity can be benefited.

## ACKNOWLEDGEMENTS

None

## CONFLICT OF INTEREST

No conflict of interest is involved in writing of this article

## REFERENCES

- Abdelrazek HMA, Kilany OE, Muhammad MAA, Tag HM, Abdelazim AM. Black Seed Thymoquinone Improved Insulin Secretion, Hepatic Glycogen Storage, and Oxidative Stress in Streptozotocin-Induced Diabetic Male Wistar Rats. *Oxidative Medicine and Cellular Longevity* Volume, pp.1-10, 2018
- Abdel-Zaher AO, Abdel-Rahman MS, Elwasei FM. Protective effect of *Nigella sativa* oil against tramadol-induced tolerance and dependence in mice: role of nitric oxide and oxidative stress. *Neurotoxicology*, 2011;32(6):725–733
- Abel-Salam BK. Immunomodulatory effects of black seeds and garlic on alloxan-induced diabetes in albino rat. *Allergologica et Immunopathologica*, 2012;40(6):336–340.

- Abououf EA, Elhamshary AMS, Nagati IM, Eraky MA, Elkholy AA, Ibrahim AN, Omar GH. Effect Of *Nigella sativa* Oil On Schistosoma Mansonii Mature Worms In Experimentally Infected Mice. *Journal of the Egyptian Society of Parasitology*, 2018; 48(1): 55-66
- Abul-Nasr SM, El-Shafey MDM, Osfor MMH. Amelioration by *Nigella sativa* of methotrexate induced toxicity in male albino rats: a biochemical, haematological and histological study. *Scintia Agriculturae Bohemica*, 2001;32:123-160.
- Aftab A, Yousaf Z, Javaid A, Riaz N, Younas A, Rashid M, Shamsheer HB, Chahel AA. Antifungal Activity of Vegetative Methanolic Extracts of *Nigella sativa* against Fusarium oxysporum and Macrophomina phaseolina and its Phytochemical Profiling by GC-MS Analysis. *International journal of agriculture & biology*, 2019; 21: 569-576
- Agarwal C, Narula A, Vyas DK, Jacob D. Effect of seeds of kalaunji on fertility and sialic acid content of the reproductive organs of male rat. *Geo Bios*, 1990;17:269-272.
- Ahmad A, Husain A, Mujeeb M, Khan SA, Najmi AK, Siddique NA, Zoheir A, Damanhoury ZA, Anwar F. A review on therapeutic potential of *Nigella sativa*: A miracle herb. *Asian Pacific Journal of Tropical Biomedicine*, 2013;3(5): 337-352
- Al-Jassir SM. Chemical composition and microflora of black cumin (*Nigella sativa* L.) seeds growing in Saudi Arabia. *Food Chemistry*, 1992;45: 239-242
- Akhtar M, Maikiyo AM, Khanam R, Mujeeb M, Aqil M, Najmi AK. Ameliorating effects of two extracts of *Nigella sativa* in middle cerebral artery occluded rat. *Journal of Pharmacy and Bioallied Science*, 2012;4(1):70-75.
- Aktaque N, Begum W. Therapeutic & pharmacological potential of *Nigella sativa* linn. In unani system of medicine: a review. *World Journal of Pharmaceutical Research*, 2018;7(12):153-158
- Al Mofleh IA, Alhaider AA, Mossa JS, Al-Sohaibani MO, Al-Yahya MA, Rafatullah S, et al. et al. Gastroprotective effect of an aqueous suspension of black cumin *Nigella sativa* on necrotizing agents-induced gastric injury in experimental animals. *Saudi Journal of Gastroenterology*, 2008;14(3):128-134.
- Al-Ali A, Alkhawajah AA, Randhawa MA, Shaikh NA. Oral and intraperitoneal LD50 of thymoquinone, an active principle of *Nigella sativa*, in mice and rats. *Journal of Ayub Medical College Abbottabad*, 2008;20(2):25-27.
- Alemi M, Sabouni F, Sanjarian F, Haghbeen K, Ansari S. Anti-inflammatory effect of seeds and callus of *Nigella sativa* L. extracts on mix glial cells with regard to their thymoquinone content. *AAPS Pharm Sci Tech*, 2012
- Al-Ghamdi MS. The anti-inflammatory, analgesic and antipyretic activity of *Nigella sativa*. *Journal of Ethnopharmacology*, 2001;76:45-48
- Ali BH. The effect of *Nigella sativa* oil on gentamicin nephrotoxicity in rats. *American Journal of Chinese Medicine*, 2004;32(1):49-55
- Aljabre SH, Randhawa MA, Akhtar N, Alakloby OM, Alqurashi AM, Aldossary A. Antidermatophyte activity of ether extract of *Nigella sativa* and its active principle, thymoquinone. *Journal of Ethnopharmacology*, 2005; 101(1-3): 116-119.
- Al-Naggar TB, Gomez-Serranillos MP, Carretero ME, Villar AM. Neuropharmacological activity of *Nigella sativa* L. extracts. *Journal of Ethnopharmacology*, 2003;88(1):63-68.
- Al-Othman A M, Ahmad F, Al-Orf S, Al-Murshed KS, Ariff Z. Effect of dietary supplementation of Ellataria cardamun and *Nigella sativa* on the toxicity of rancid corn oil in rats. *International Journal of Pharmacology*, 2006; 2(1): 60-65.
- Altan MF, Kanter M, Donmez S, Kartal ME, Buyukbas S. Combination therapy *Nigella sativa* and human parathyroid hormone on bone mass, biomechanical behavior and structure in streptozotocin-induced diabetic rats. *Acta Histochemica*, 2007;109(4):304-314.
- Althnaian T, Albokhadaim I, El-Bahr SM. Hepatic Gene Expression, Antioxidant Enzymes and Anti-diabetic Effect of *Nigella sativa* in Diabetic Rats. *International Journal of Pharmacology*, 2019; 15(2): 265-273.
- Andaloussi AB, Martineau LC, Spoor D, Vuong T, Leduc C, Joly E, Burt A, Meddah B, Settaf A, Arnason JT, Prentki M, Haddad PS. Antidiabetic Activity of *Nigella sativa*. Seed Extract in Cultured Pancreatic  $\beta$ -cells, Skeletal Muscle Cells, and Adipocytes. *Pharmaceutical Biology*, 2008;46(1-2): 96-104.
- Andaloussi AB, Martineau L, Vuong T, Meddah B, Madiraju P, Settaf A, Haddad PS. The in vivo antidiabetic activity of *Nigella sativa* is mediated through activation of the AMPK pathway and increased muscle glut4 content. *Evidence- Based Complementary and Alternative Medicine*, 2011; 2011:538671.
- Anonymous. Standardization of Single Drugs Of Unani Medicine. CCRUM, 1992; II:196-200
- Anonymous. The Unani Pharmacopoeia Of India (First Edition) .Ministry Of Health & Family Welfare Government Of India. YNM
- Aqel M, Shaheen R. Effects of the volatile oil of *Nigella sativa* seeds on the uterine smooth muscle of rat and guinea pig. *Journal of Ethnopharmacology*, 1996;52(1):23-26.
- Arefin Z, Hossain MN, Rahmatullah M. Oral glucose tolerance test (OGTT) with a polyherbal formulation of *Nigella sativa* and Brassica alba seeds. *World Journal of Pharmaceutical Research*, 2018;7(13):1200-1206
- Askari G, Rouhani MH, Ghaedi E, Ghavami A, Nouri M, Mohammadi H. Effect of *Nigella sativa* (black seed) supplementation on glycemic control: A systematic review and meta-analysis of clinical trials. *Phytotherapy Research*, 2019; 33(5):1341-1352

- Assayed ME. Radioprotective effects of black seed (*Nigella sativa*) oil against hemopoietic damage and immunosuppression in gamma-irradiated rats. *Immunopharmacology and Immunotoxicology*, 2010;32(2):284-296.
- Bakathir HA, Abbas NA. Detection of the antibacterial effect of *Nigella sativa* ground seeds with water. *African Journal of Traditional, Complementary and Alternative Medicine*, 2011; 8(2): 159-164
- Bamosa AO, Kaatabi H, Lebdaa FM, Elq AM, Al-Sultanb A. Effect of *Nigella sativa* seeds on the glycemic control of patients with type 2 diabetes mellitus. *Indian Journal of Physiology and Pharmacology*, 2010; 54(4):344-354.
- Bodaghi MN, Darabi Z, Agah S, Hekmatdoost A. The effects of *Nigella sativa* on quality of life, disease activity index, and some of inflammatory and oxidative stress factors in patients with ulcerative colitis. *Phytotherapy Research*, pp.1-6, 2009
- Boskabady MH, Javan H, Sajady M, Rakhshandeh H. The possible prophylactic effect of *Nigella sativa* seed extract in asthmatic patients. *Fundamental and Clinical Pharmacology*, 2007;21(5):559–566.
- Boskabady MH, Keyhanmanesh R, Khameneh S, Doostdar Y, Khakzad MR. Potential immunomodulation effect of the extract of *Nigella sativa* on ovalbumin sensitized guinea pigs. *Journal of Zhejiang University Science B*, 2011;12(3):201–209.
- Boskabady MH, Keyhanmanesh R, Saadatloo MA. Relaxant effects of different fractions from *Nigella sativa* L. on guinea pig tracheal chains and its possible mechanism(s). *Indian Journal of Experimental Biology*, 2008;46(12):805–810.
- Boskabady MH, Mohsenpoor N, Takaloo L. Antiasthmatic effect of *Nigella sativa* in airways of asthmatic patients. *Phytomedicine*, 2010;17(10):707–713
- Bourgou S, Pichette A, Marzouk B, Legault J. Antioxidant, antiinflammatory, anticancer and antibacterial activities of extracts from *Nigella sativa* (Black Cumin) plant parts. *Journal of Food Biochemistry*, 2012; 36(5): 539-546.
- Butt AS, Nisar N, Ghani N, Altaf I, Mughal TA. Isolation of thymoquinone from *Nigella sativa* L. and *Thymus vulgaris* L., and its anti-proliferative effect on HeLa cancer cell lines. *Tropical Journal of Pharmaceutical Research*, 2019;18(1): 37-42
- Butt UJ, Shah SAA, Ahmed T, Zahid S. Protective effects of *Nigella sativa* L. seed extract on lead induced neurotoxicity during development and early life in mouse models. *Toxicology Research*, 2018; 7: 32-40
- Canayakin D, Bayir Y, Baygatalp NK, Karaoglan ES, Atmaca HT, Ozgeris FBK, Keles MS, Halici Z. Paracetamol-induced nephrotoxicity and oxidative stress in rats: the protective role of *Nigella sativa*. *Pharmaceutical Biology*, 2016;54(10):2082-91
- Chaieb K, Kouidhi B, Jrah H, Mahdouani K, Bakhrouf A. Antibacterial activity of Thymoquinone, an active principle of *Nigella sativa* and its potency to prevent bacterial biofilm formation. *BMC Complementary and Alternative Medicine*, 2011;11:29.
- Chehl N, Chipitsyna G, Gong Q, Yeo CJ, Arafat HA. Anti-inflammatory effects of the *Nigella sativa* seed extract, thymoquinone, in pancreatic cancer cells. *HPB (Oxford)* 2009;11(5):373-381.
- Duncker SC, Philippe D, Martin-Paschoud C, Moser M, Mercenier A, Nutten S. *Nigella sativa* (Black Cumin) seed extract alleviates symptoms of allergic diarrhea in mice, involving opioid receptors. *PLoS One*. 2012;7(6):e39841.
- Dymock W, Warden C.J.H, Hooper D. *Pharmacographia Indica*. Srishti Book Distributors, pp.28, 2005
- Ebru U, Burak U, Yusuf S, Reyhan B, Arif K, Faruk TH, *et al*. Cardioprotective effects of *Nigella sativa* oil on cyclosporine A-induced cardiotoxicity in rats. *Basic and Clinical Pharmacology and Toxicology*, 2008;103:574-80
- El Mezayen R, El Gazzar M, Nicolls MR, Marecki JC, Dreskin SC, Nomiyama H. Effect of thymoquinone on cyclooxygenase expression and prostaglandin production in a mouse model of allergic airway inflammation. *Immunology Letter*, 2006; 106(1):72–81.
- El Shenawy NS, Soliman MF, Reyad SI. The effect of antioxidant properties of aqueous garlic extract and *Nigella sativa* as anti schistosomiasis agents in mice. *Revista do Instituto de Medicina Tropical de Sao Paulo*, 2008; 50(1): 29-36.
- El-Abhar HS, Abdallah DM, Saleh S. Gastroprotective activity of *Nigella sativa* oil and its constituent, thymoquinone, against gastric mucosal injury induced by ischaemia/reperfusion in rats. *Journal of Ethnopharmacology*, 2003;84(2-3):251-258.
- El-Rabey HA, Al-Seen MN, Bakhshwain AS. The Antidiabetic Activity of *Nigella sativa* and Propolis on Streptozotocin-Induced Diabetes and Diabetic Nephropathy in Male Rats. *Evidence-Based Complementary and Alternative Medicine*, 2017
- Ezz HS, Khadrawy YA, Noor NA. The neuroprotective effect of curcumin and *Nigella sativa* oil against oxidative stress in the pilocarpine model of epilepsy: a comparison with valproate. *Neurochemical Research*, 2011;36(11):2195-2204.
- Fanoudi S, Alavi MS, Hosseini M, Sadeghnia HR. *Nigella sativa* and thymoquinone attenuate oxidative stress and cognitive impairment following cerebral hypoperfusion in rats. *Metabolic Brain Disease*, 2019
- Fathy M, Nikaido T. In vivo attenuation of angiogenesis in hepatocellular carcinoma by *Nigella sativa*. *Turkish Journal of Medical Sciences*, 2018;48:178-186
- Forouzanfar F, Bazzaz BSF, Hosseinzadeh H. Black cumin (*Nigella sativa*) and its constituent (thymoquinone): a review on antimicrobial effects. *Iranian Journal of Basic Medical Sciences*, 2014;17(12)
- Gendy E, Hessien M, Abdel Salamm I, Moradm MEL, Magrabym K, Ibrahim HA, *et al*. Evaluation of the possible

- antioxidant effects of Soybean and *Nigella sativa* during experimental hepatocarcinogenesis by nitrosamine precursors. *Turkish Journal of Biochemistry*, 2007;32(1):5-11.
- Ghani MN. Khazainul -advia. Aijaz Publication House, YNM; 3: 389-390
- Ghonime M, Eldomany R, Abdelaziz A, Soliman H. Evaluation of immunomodulatory effect of three herbal plants growing in Egypt. *Immunopharmacology and Immunotoxicology*, 2011; 33(1):141-145.
- Gilhotra N, Dhingra D. Thymoquinone produced antianxiety-like effects in mice through modulation of GABA and NO levels. *Pharmacological Reports*. 2011;63(3):660-669.
- Gokce A, Oktar S, Koc A, Yonden Z. Protective effects of thymoquinone against methotrexate-induced testicular injury. *Human and Experimental Toxicology*, 2011;30(8):897-903.
- Hadjzadeh MA, Keshavarzi Z, Yazdi TSA, Ghasem SM, Rajaei Z, Khajavi Rad A. Effect of alcoholic extract of *Nigella sativa* on cisplatin-induced toxicity in rat. *Iranian Journal of Kidney Diseases*, 2012;6(2):99-104.
- Hakeem AH. Bustanul Muffradat. pp. 258, YNM
- Halamova K, Kokoska L, Flesar J, Sklenickova O, Svobodova B, Marsik P. In vitro antifungal effect of black cumin seed quinones against dairy spoilage yeasts effect of black cumin seed quinones against dairy spoilage yeasts at different acidity levels. *Journal of Food protection*, 2010;73(12):2291-2295
- Halawani E. Antibacterial Activity of Thymoquinone and Thymohydroquinone of *Nigella sativa* L. and Their Interaction with Some Antibiotics. *Advances in Biological Research*, 2009; 3(5-6):148-152
- Hannan A, Saleem S, Chaudhary S, Barka M, Arshad MU. Antibacterial activity of *Nigella sativa* against clinical isolates of methicillin resistant *Staphylococcus aureus*. *Journal of Ayub Medical College Abbottabad*, 2008;20(3):72-74.
- Harzallah HJ, Grayaa R, Kharoubi W, Maaloul A, Hammami M, Mahjoub T. Thymoquinone, the *Nigella sativa* bioactive compound, prevents circulatory oxidative stress caused by 1,2-dimethylhydrazine in erythrocyte during colon post initiation carcinogenesis. *Oxidative Medicine and Cellular Longevity*, 2012; 854065.
- Hossein BM, Nasim V, Sediqa A. The protective effect of *Nigella sativa* on lung injury of sulfur mustard-exposed Guinea pigs. *Experimental Lung Research*, 2008;34(4):183-194.
- Hosseinia M, Ghasemia S, Hadjzadehb MR, Ghorbanic A, Aghilib S, Aghaeic A, Soukhtanlood M, Beheshtie F. Administration of *Nigella sativa* during neonatal and juvenile growth period improved liver function of propylthiouracil-induced hypothyroid rats. *The Journal of Maternal-Fetal & Neonatal Medicine*, pp.1476-4954, 2018
- Hosseinian S, Bideskan AE, Shafei1 MN, Sadeghnia HR, Soukhtanloo M, Shahraki S, Noshahr ZS, Rad AK. *Nigella sativa* extract is a potent therapeutic agent for renal inflammation, apoptosis, and oxidative stress in a rat model of unilateral ureteral obstruction. *Phytotherapy Research*, pp.1-9, 2018
- Hosseinzadeh H, Bazzaz BSF, Haghi MM. Antibacterial Activity of Total Extracts and Essential oil of *Nigella sativa* L. Seeds in Mice. *Pharmacolgyonline*, 2007;2:429-435
- Hosseinzadeh H, Parvardeh S, Asl MN, Sadeghnia HR, Ziaee T. Effect of thymoquinone and *Nigella sativa* seeds oil on lipid peroxidation level during global cerebral ischemia-reperfusion injury in rat hippocampus. *Phytomedicine*, 2007;14(9):621-627.
- Ikhsan M, Hiedayati N, Maeyama K, Nurwidya F. *Nigella sativa* as an anti-inflammatory agent in asthma. *BMC Research Notes*, 2018;11:744
- Kabirruddin H. Makhaznul Muffradat. pp. 460-461, YNM
- Kamal SM, Lsharkawy RTE, Abdelmoneim RA. Effect of *Nigella sativa* on the integrity of parotid salivary gland of albino rats and its activity for insulin and glucagon. *Journal of American Science*, 2012;8(12):1168-1172.
- Kanter M, Akpolat M, Aktas C. Protective effects of the volatile oil of *Nigella sativa* seeds on beta-cell damage in streptozotocin-induced diabetic rats: a light and electron microscopic study. *Journal of Molecular Histology*, 2009; 40(5-6):379-385.
- Kanter M. Effects of *Nigella sativa* seed extract on ameliorating lung tissue damage in rats after experimental pulmonary aspirations. *Acta Histochemical*, 2009;111(5):393-403
- Kapoor S. Emerging clinical and therapeutic applications of *Nigella sativa* in gastroenterology. *World Journal of Gastroenterology*, 2009;7:2170-217153.
- Kaur G, Invally M, Khan MK, Jadhav P. A nutraceutical combination of Cinnamomum cassia & *Nigella sativa* for Type 1 diabetes mellitus. *Journal of Ayurveda and Integrative Medicine*, 2018; 9: 27-37
- Keshri G, Singh MM, Lakshmi V, Kamboj VP. Post-coital contraceptive efficacy of the seeds of *Nigella sativa* in rats. *Indian Journal of Physiology and Pharmacology*. 1995; 39(1):59-62.
- Khader M, Bresgen N, Eckl PM. In vitro toxicological properties of thymoquinone. *Food and Chemical Toxicology*, 2009;47(1):129-133.
- Khaled AAS. Gastroprotective effects of *Nigella sativa* oil on the formation of stress gastritis in hypothyroidal rats. *International Journal of Physiology, Pathophysiology and Pharmacology*, 2009;1:143-149.
- Khan MA. Muheete- Azam. CCRUM, 2014;3:382-385
- Khan MAU, Ashfaq MK, Zuberi HS, Mahmood MS, Gilani AH. The In Vivo Antifungal Activity of the Aqueous Extract from *Nigella sativa* Seeds. *Phytotherapy Research*, 2003;17:183-186
- Khan N, Sultana S. Inhibition of two stage renal carcinogenesis, oxidative damage and hyperproliferative response by *Nigella*

- sativa*. *European journal of Cancer Prevention*, 2005;14(2): 159-168.
- Khosravi AR, Minooeianhaghighi MH, Shokri H, Emami SA, Alavi SM, Asili J. The potential inhibitory effect of cuminum cyminum, ziziphora linopodioides and *Nigella sativa* essential oils on the growth of aspergillus fumigatus and aspergillus flavus. *Brazilian Journal of Microbiology*, 2011;42: 216-224
- Kirtikar KR, Basu BD. Indian Medicinal Plant. *International Book Distributor*, 1987;1(2):11-12
- Kumbhakara DV, Dattaa AK, Dasa D, Ghosha B, Pramanika A, Gupta S. Assessment of oxidative stress, antioxidant enzyme activity and cellular apoptosis in a plant based system (*Nigella sativa* L.; black cumin) induced by copper and cadmium sulphide nanomaterials. *Environmental Nanotechnology, Monitoring & Management*, 2019;11
- Lei X, Liu M, Yang Z, Ji M, Guo X, Dong W. Thymoquinone Prevents and ameliorates dextran sulfate sodium-induced colitis in mice. *Digestive Disease and Science*, 2012;57(9):2296-2303.
- Lei X, Lv X, Liu M, Yang Z, Ji M, Guo X. Thymoquinone inhibits growth and augments 5-fluorouracil-induced apoptosis in gastric cancer cells both in vitro and in vivo. *Biochemical and Biophysical Research Communication*, 2012; 417(2):864-868
- LorestaniHZ, Ahmadabadi AN, Balak F, Hasanzadeh G, Sabzevari O. Protective role of thymoquinone against paraquat-induced hepatotoxicity in mice. *Pesticide Biochemistry and Physiology*, 2018;148:16-21
- Magdy MA, Hanan el-A, Nabila el-M. Thymoquinone: Novel gastroprotective mechanisms. *European Journal of Pharmacology*, 2012;697(1-3):126-131.
- Mahmoud SS, Torchilin VP. Hormetic/cytotoxic effects of *Nigella sativa* seed alcoholic and aqueous extracts on MCF-7 breast cancer cells alone or in combination with doxorubicin. *Cell Biochemistry and Biophysics*, 2012; 25(7):1392-1398
- Mahmoudvand H, Sepahvand A, Jahanbakhsh S, Ezatpour B, Mousavi SAA. Evaluation of antifungal activities of the essential oil and various extracts of *Nigella sativa* and its main component, thymoquinone against pathogenic dermatophyte strains. *Journal de Mycologie Médicale*, 2014; 482: 7
- Majdalawieh AF, Hmaidan R, Carr RI. *Nigella sativa* modulates splenocyte proliferation, Th1/T2 cytokine profile, macrophage function and NK anti-tumor activity. *Journal of Ethnopharmacology*, 2010; 131(2):268–275.
- Mariod AA, Ibrahim RM, Ismail M, Ismail N. Antioxidant activity and phenolic content of phenolic rich fractions obtained from black cumin (*Nigella sativa*) seedcake. *Food Chemistry*, 2009; 116(1): 306-312.
- Mechraoui O, Ladjel S, Nedjimi MS, Belfar ML, Moussaoui Y. Determination of polyphenols content, antioxidant and antibacterial activity of *Nigella sativa* L. seed phenolic extracts. *Scientific study & research-Chemistry & chemical engineering, biotechnology, food industry*, 2018;19(4): 411 – 421
- Merfort I, Wray V, Barakat HH, Hussein SAM, Nawwar M, Willuhn G. Flavonol triglycosides from seeds of *Nigella sativa*. *Phytochemistry*, 1997;46(2):359-363
- Mohamed A, Waris HM, Ramadan H, Quereschi M, Kalra J. Amelioration of chronic relapsing experimental autoimmune encephalomyelitis (cr-eae) using thymoquinone-biomed 2009. *Biomedical Science Instrumentation*, 2009; 45:274-279.
- Mohamed AM, Metwally NM, Mahmoud SS, *Nigella sativa* seeds against Schistosoma mansoni different stages. *Memorias do Instituto Oswaldo Cruz*, 2005; 100(2): 205-211.
- Morsi NM. Antimicrobial effect of crude extracts of *Nigella sativa* on multiple antibiotics-resistant bacteria. *Acta Microbiologica Polonica*, 2000; 49(1): 63-74.
- Mouwakeh A, Kincses A, Nové M, MosolygóT, Farkas CM, Kiskó G, Spengler G. *Nigella sativa* essential oil and its bioactive compounds as resistance modifiers against Staphylococcus aureus. *Phytotherapy Research*, 2019;3:1010-1018
- Mouwakeh A, Telbisz A, Spengler G, Farkas CM, Kiskó G. Antibacterial and Resistance Modifying Activities of *Nigella sativa* Essential Oil and its Active Compounds Against Listeria monocytogenes. In vivo, 2018;32: 737-743
- Nagi MN, Al-Shabanah OA, Hafez MM, Sayed-Ahmed MM. Thymoquinone supplementation attenuates cyclophosphamide-induced cardiotoxicity in rats. *Journal of Biochemical and Molecular Toxicology*, 2011;25:135-42
- Najmi A, Haque SF, Naseeruddin M, Khan RA. Effect of *Nigella sativa* oil on various Clinical and biochemical parameters of metabolic syndrome. *International Journal of Diabetes in Developing Countries*, 2008; 16:85-87
- Nemmar A, Al-Salam S, Zia S, Marzouqi F, Al-Dhaheri A, Subramaniyan D, et al. et al. Contrasting actions of diesel exhaust particles on the pulmonary and cardiovascular systems and the effects of thymoquinone. *British Journal of Pharmacology*, 2011;164(7):1871-1882.
- Ng WK, Yazan LS, Ismail M. Thymoquinone from *Nigella sativa* was more potent than cisplatin in eliminating of SiHa cells via apoptosis with down-regulation of Bcl-2 protein. *Toxicology In vitro*, 2011;25(7):1392-1398.
- Nickavara B, Mojaba F, Javidniab K, Amolia MAR. Chemical Composition of the Fixed and Volatile Oils of *Nigella sativa* L. from Iran. *Z. Naturforsch*, 2003;58c: 629-631
- Nikakhlagh S, Rahim F, Aryani FH, Syahpoush A, Brougerdnya MG, Saki N. Herbal treatment of allergic rhinitis: the use of *Nigella sativa*. *American Journal of Otolaryngology*, 2011; 32(5):402-407.
- Onsa RAH, Muna EA, Hassan SAA. Detection of Antibacterial Activity of the Black Cumin (*Nigella sativa*) Seed Extract against Mycoplasma mycoides subsp mycoides (Mmm). *International Journal of Pathogen Research*, 2019; 2(1): 1-6

- Paarakh MP. *Nigella sativa* Linn- A Comprehensive Review. *Indian journal of natural product and resources*, 2010;1(4):409-429
- Pari L, Sankaranarayanan C. Beneficial effects of thymoquinone on hepatic key enzymes in streptozotocin-nicotinamide induced diabetic rats. *Life Science*, 2009; 85(23-26):830-834.
- Peng L, Liu A, Shen Y, Xu HZ, Yang SZ, Ying XZ, et al. et al. Antitumor and anti-angiogenesis effects of thymoquinone on osteosarcoma through the NF- $\kappa$ B pathway. *Oncology Reports*, 2013; 29(2):571-578.
- Perveen T, Abdullah A, Haider S, Sonia B, Munawar AS, Haleem DJ. Long-term administration of *Nigella sativa* effects nociception and improves learning and memory in rats. *Pakistan Journal of Biochemistry and Molecular Biology*, 2008; 41(3):141–143
- Perveen T, Haider S, Kanwal S, Haleem DJ. Repeated administration of *Nigella sativa* decreases 5-HT turnover and produces anxiolytic effects in rats. *Pakistan Journal of Pharmaceutical Science*, 2009;22(2):139–144.
- Phulwaria R, Kaushal K, Sharma AK, Mishra RC, Soni P. A review on folklore uses and therapeutic indications of *Nigella sativa* - a miracle herb. *World Journal of Pharmaceutical Research*, 2019; 8(1):1369-1379.
- Pichette A, Marzouk B, Legault J. Antioxidant, anti-inflammatory, anticancer and antibacterial activities of extracts from *Nigella sativa* (black cumin) plant parts. *Journal of Food Biochemistry*, 2012; 36(5):539–546
- Randhawa MA, Gondal MA, Al-Zahrani AHJ, Rashid SG, Ali A. Synthesis, morphology and antifungal activity of nano-particulated amphotericin-B, ketoconazole and thymoquinone against *Candida albicans* yeasts and *Candida* biofilm. *J Environ Sci Health A Tox Hazard Subst Environ Eng*, 2015;50:119-24
- Rani R, Dahiya S, Dhingra D, Dilbaghi N, Kim KH, Kumar S. Improvement of antihyperglycemic activity of nano-thymoquinone in rat model of type-2 diabetes. *Chemico-Biological Interactions*, 2018; 295:119-132
- Ranjbaran H, Abediankenari S, Amiri MM. Enhanced Differentiation of Wharton's Jelly-Derived Mesenchymal Stem Cells in Insulin-Producing Cells by the Extract of *Nigella sativa* Seeds. *Iran Red Crescent Medical Journal*, 2018; 20(3): 62111
- Raza M, Alghasham AA, Alorainy MS, El-Hadiyah TM. Potentiation of valproate-induced anticonvulsant response by *Nigella sativa* seed constituents: the role of GABA receptors. *International Journal of Health Sciences*, 2008;2(1):15–25
- Reddy SH, Al-Kalbani AS, Al-Rawahi AS. Studies on phytochemical screening - GC-MS characterization, antimicrobial and antioxidant assay of black cumin seeds (*Nigella sativa*) and senna alexandria (*Cassia angustifolia*) solvent extracts. *International Journal of Pharmaceutical Sciences and Research*, 2018;9(2):490-497
- Rogozhin EA, Oshchepkova YI, Odintsova TI, Khadeeva NV, Veshkurova ON, Egorov TA, Grishin EV, Salikhov SI. Novel antifungal defensins from *Nigella sativa* L. seeds. *Plant Physiology and Biochemistry*, 2011;49:131-137
- Sala AV. Indian medicinal plant. *Orient Longman Ltd*, 1997; 4:139
- Salama RH. Hypoglycemic effect of lipoic acid, carnitine and *Nigella sativa* in diabetic rat model. *International Journal of Health Science*, 2011;5(2):126-134
- Saleem U, Ahmad B, Rehman K, Mahmood S, Alam M, Erum A. Nephro-protective effect of vitamin C and *Nigella sativa* oil on gentamicin associated nephrotoxicity in rabbits. *Pakistan Journal of Pharmaceutical Science*, 2012;25(4):727–730.
- Salem EM, Yar T, Bamosa AO, Al-Quorain A, Yasawy MI, Alsulaiman RM, et al. Comparative study of *Nigella sativa* and triple therapy in eradication of *Helicobacter Pylori* in patients with non-ulcer dyspepsia. *Saudi Journal of Gastroenterology*, 2010;16(3):207-214.
- Salem ML, Alenzi FQ, Attia WY. Thymoquinone, the active ingredient of *Nigella sativa* seeds, enhances survival and activity of antigen-specific CD8-positive T cells in vitro. *British Journal of Biomedical Science*, 2011; 68(3):131-137.
- Salim EI. Cancer chemopreventive potential of volatile oil from black cumin seeds, *Nigella sativa* L., in a rat multi-organ carcinogenesis bioassay. *Oncology Letters*, 2010;1(5):913–924
- Satyavati GV, Gupta AK. Medicinal Plants of India. *Indian Council of Medical Research*, 1987; 2: 337-342
- Sayed-Ahmed MM, Nagi MN. Thymoquinone supplementation prevents the development of gentamicin-induced acute renal toxicity in rats. *Clinical and Experimental Pharmacology and Physiology*, 2007;34(5-6):399-405
- Shafi G, Hasan TN, Sayed NA. Methanolic extracts of *Nigella sativa* seed as potent onogenic inhibitor of PC-3 cells. *International Journal of Pharmacology*, 2008;4(6):477-481.
- Shah SB, Shah SIA, Sartaj L, Zaman S, Bilal M, Salman M. Effect of *Nigella sativa* seeds extracts on clinically important bacterial and fungal species. *MOJ Bioequivalence & Bioavailability*, 2018; 5(4)
- Shuid AN, Mohamed N, Mohamed IN, Othman F, Suhaimi F, Mohd Ramli ES, Mohamed N, Soelaiman IM. *Nigella sativa*: A potential antiosteoporotic agent. *Evidence- Based Complementary and Alternative Medicine*, 2012; 2012:696230
- Sogut B, Celik I, Tuluce Y. The effects of diet supplemented with the black Cumin (*Nigella sativa* L.) upon immune potential and antioxidant marker enzymes and lipid peroxidation in broiler chicks. *Journal of Animal and Veterinary Advances*, 2008; 7(10): 1196-1199.
- Sultana S, Asif HM, Akhtar N, Iqbal A, Nazar H, Rehman R. *Nigella sativa*: Monograph. *Journal of Pharmacognosy and Phytochemistry*, 2015;4(4):103-106
- Tabassum H, Ahmad IZ. Evaluation of the Anticancer Activity of Sprout Extract-Loaded Nanoemulsion of N.sativa against

- Hepatocellular Carcinoma. *Journal of Microencapsulation*, 2019;35(7-8): 643-656
- Tasar N, Sehirlı O, Yiginer O, Soleymanoglu S, Yoksel M, Yegen B, *et al.* Protective effects of *Nigella sativa* against hypertension-induced oxidative stress and cardiovascular dysfunction in rats. *Journal of Research in Pharmacy*, 2012;16:141-9.
- Tayman C, Cekmez F, Kafa IM, Canpolat FE, Cetinkaya M, Tonbul A. Protective effects of *Nigella sativa* oil in hyperoxia-induced lung injury. *Archivos de Bronconeumologica*, 2012;49(1):15-21.
- Tayman C, Cekmez F, Kafa IM, Canpolat FE, Cetinkaya M, Uysal S. Beneficial effects of *Nigella sativa* oil on intestinal damage in necrotizing enterocolitis. *Journal of Investigative Surgery*, 2012;25(5):286-294.
- Tembhurne SV, Feroz S, More BH, Sakarkar DM. A review on therapeutic potential of *Nigella sativa* (kalonji) seeds. *Journal of Medicinal Plants Research*, 2014;8(3):167-177
- Torres MP, Ponnusamy MP, Chakraborty S, Smith LM, Das S, Arafat HA. Effects of thymoquinone in the expression of mucin 4 in pancreatic cancer cells: implications for the development of novel cancer therapies. *Molecular Cancer Therapeutics*, 2010; 9(5):1419-1431.
- Ulu R, Dogukan A, Tuzcu M, Gencoglu H, Ulas M, Ilhan N. Regulation of renal organic anion and cation transporters by thymoquinone in cisplatin induced kidney injury. *Food and Chemical Toxicology*, 2012;50(5):1675-1679
- Umar S, Zargan J, Umar K, Ahmad S, Katiyar CK, Khan HA. Modulation of the oxidative stress and inflammatory cytokine response by thymoquinone in the collagen induced arthritis in Wistar rats. *Chemico- Biological Interaction*, 2012;197(1):40-46.
- Ustuna R, Oguzb EK, Şekera A, Korkaya H. Thymoquinone prevents cisplatin neurotoxicity in primary DRG neurons. *Neurotoxicology*, 2018;69: 68-76
- Uz E, Bayrak O, Uz E, Kaya A, Bayrak R, Uz B, *et al.* *Nigella sativa* oil for prevention of chronic cyclosporine nephrotoxicity: an experimental model. *American Journal of Nephrology*, 2008;28(3):517-522.
- Wienkotter N, Höpner D, Schütte U, Bauer K, Begrow F, El-Dakhakhny M, *et al.* The effect of nigellone & thymoquinone on inhibiting trachea contraction and mucociliary clearance. *Plant Medicine*, 2008;74(2):105-108.
- Woo CC, Loo SY, Gee V, Yap CW, Sethi G, Kumar AP, *et al.* Anticancer activity of thymoquinone in breast cancer cells: possible involvement of PPAR- $\gamma$  pathway. *Biochemical Pharmacology*, 2011;82(5):464-475
- Wu ZH, Chen Z, Shen Y, Huang LL, Jiang P. Anti-metastasis effect of thymoquinone on human pancreatic cancer. *Yao Xue Xue Bao*, 2011; 46(8):910-914.
- Yaman I, Balıkcı E. Protective effects of *Nigella sativa* against gentamicin-induced nephrotoxicity in rats. *Experimental and Toxicologic Pathology*, 2010;62(2):183-190.
- Yildiz F, Coban S, Terzi A, Ates M, Aksoy N, Cakir H, *et al.* *Nigella sativa* relieves the deleterious effects of ischemia reperfusion injury on liver. *World Journal of Gastroenterology*, 2008;14(33):5204-520952.
- Yildiz F, Coban S, Terzi A, Savas M, Bitiren M, Celik H. Protective effects of *Nigella sativa* against ischemia-reperfusion injury of kidneys. *Renal Failure*, 2010;32(1):126-131
- Younus H. Antidiabetic Action of Thymoquinone. Molecular and Therapeutic actions of Thymoquinone. (Singapore: Springer), pp.7-17. 2018
- Zafeer MF, Waseem M, Chaudhary S, Parvez S. Cadmium-induced hepatotoxicity and its abrogation by thymoquinone. *Journal of Biochemical and Molecular Toxicology*, 2012;26(5):199-205.
- Zaoui A, Cherrah Y, Mahassini N, Alaoui K, Amarouch H, Hassar M. Acute and chronic toxicity of *Nigella sativa* fixed oil. *Phytomedicine*, 2002;9(1):69-74.