Therapeutic uses of Nigella Sativa: a wonder seed

Abdel-Aziz A. A. El-Sayed*

Biology Department, Faculty of Science, Islamic University of Madinah, Madinah, Saudi Arabia.

*Correspondent author Email: abosharaf63@iu.edu.sa

Abstract

Owing to its unique results and minimal harmful properties, herbal medicines are recently generating a lot of interest across the world in the therapy of several ailments. Nigella sativa is a popular medicinal herb used all over the world. The abundance of bioactive components, particularly thymoquinone, thymol, α hederin and their antioxidant properties for other potential health benefits is credited with Nigella sativa's pharmacological activities. Previous studies exhibited that Nigella sativa has various potential therapeutic and natural activities like antidiabetic, anti-inflammation, antimicrobial, anticancer, antibacterial, antifungal, antihypertensive, wound therapeutic influences, renal protective and antioxidant properties besides its various other potential health benefits. In conclusion, our findings have enhanced the medical, pharmacological, cultural value, and healing practices of N. sativa, which perhaps aid researchers in approaching the utility, efficacy, and effectiveness of this herb. However, the incorporation of these plants in development and creation of new medications for treating several diseases has not yet been fully exploited. Hereby, this review provides a detailed survey on the scientific literature regarding pharmacological properties, chemical constituents and biological influences of the seeds of this herb.

Key words: Nigella sativa, appearance, structural, medicinal value, toxicities.

الاستخدامات العلاجية لحبة البركة: بذرة عجيبة

الملخص: نظرًا لنتائجها الفريدة والحد الأدنى من الخصائص الضارة ، تولد الأدوية العشبية مؤخرًا الكثير من الاهتمام في جميع أنحاء العالم في علاج العديد من الأمراض. حبة البركة هي عشب طبي مشهور يستخدم في جميع أنحاء العالم. إن وفرة المكونات النشطة بيولوجيًا ، وخاصة ثيموكينون ، ثيمول ، ألفا هيديرين وخصائصها المضادة للأكسدة لفوائد صحية محتملة أخرى تُنسب إلى الأنشطة الدوائية لـ Nigella sativa. أظهرت الدراسات السابقة أن حبة البركة لها العديد من الأنشطة العلاجية والطبيعية المحتملة مثل مضادات السكر ، ومضادة للالتهابات ، ومضادات الميكروبات ، ومضادات السرطان ، ومضادات الجراثيم ، ومضادات الفطريات ، ومضادة لارتفاع ضغط الدم ، والتأثيرات العلاجية للجروح ، وخصائص الحماية الكلوية ومضادات الأكسدة إلى جانب العديد من الفوائد الصحية المحتملة الأخرى. في الختام ، عززت النتائج التي توصلنا إليها القيمة الطبية والدوائية والثقافية والممارسات العلاجية لـ N. sativa ، والتي ربما تساعد الباحثين في الاقتراب من فائدة وفعالية وفعالية هذه العشبة. ومع ذلك ، فإن دمج هذه النباتات في تطوير وإنشاء أدوية جديدة لعلاج العديد من الأمراض لم يتم استغلاله بالكامل بعد. بموجب هذا ، تقدم هذه المراجعة مسحًا تفصيليًا للأدبيات العلمية المتعلقة بالخصائص الدوائية والمكونات الكيميائية والتأثيرات البيولوجية لبذور هذه العشبة.

1. Introduction:

In recent years, literature on the therapy of many ailments using natural products has been increasing lengthily owing to their promising results as well as uncommon negative effects (Al-Attass et al., 2016). Recently is a huge rise in the use of medicinal herbs, compared to chemical medications. This can be attributed to many considerations, such as ease of over-the-counter access, low price, no need to speak to healthcare specialists, in addition to belief in diminishing side effects of natural herbal remedies. Herbal therapies that have been proven to work, which rank greatly as a "wonder seed" is Nigella (Ahmad et al., 2013; Yimer et al., 2019). The significance of *Nigella sativa* to the Islamic culture came from saying "In the black seed is the remedy for each ailment except death," according to the Prophet Mohammed's holy teaching (Ghaznavi, 1991). It is exactly the same sort of black cumin that the Messenger of god Muhammad described as a treatment for all illnesses, but it does not prevent old age or death. *Nigella sativa* is a well-known medicinal plant with a wide range of therapeutic properties, like antidiabetic, anti-microbial, anti-inflammation, anti-tumor influences, besides many other various diseases in Middle East, little Asian countries, Southern Europe to many decades (Gholamnezhad et al., 2016). Medicinal influences of Nigella might be due to its numerous active constituents, like thymoquinone, thymol, and Nigellone (Gholamnezhad et al., 2016; Majdalawieh AF, and Fayyad MW. 2015). However, thymoquinone is the most biologically active ingredient isolated from the seeds of Nigella sativa. In recent centuries, Nigella sativa has become a major research area, and it has a number of traditional applications, so it has already been studied a lot for its bioactive constituents and medicinal uses.

2. Plant's morphology:

Nigella sativa is a tiny yearly herb that produces to a tallness of fifty to sixty cm. Its leaves are alienated into 2 to 3 cm long linear segments that grow on both sides of the stem that develop in pairs. It has long upper leaves and short, petiolate below leaves. Flowers on solitary long peduncles are fragile, light, and blue. Nigella sativa reproduces by forming a capsule containing a large number of white trigonal seeds.

When the capsule has developed, it releases up and the seeds inside are opened to the air, turning dark in color. The seeds have a strong pungent flavor and are triangular in shape (Chevallier, 1996).

Figure 1: Nigella sativa (B. whole plant, A, D. flowers and C, E. seeds) adopted from internet.

3. Scientific Classification

Kingdom: Plantae

Division: Magnoliophyta

Order: Ranunculales

Family: Ranunculaceae

Genus: Nigella

Species: sativa (Kooti et al., 2016)

4. Chemical constituents

Nigella sativa seed involves: proteins, saponin, alkaloid, and oil like fatty acids that aren't saturated such as almitoleic, sterol esters, linolenic, sterol glucosides, stearic and myristic acid like linoleic, oleic, beta-sitosterol, palmitic, eicosadienoic, cycloartenol, arachidonic, and cycloeucalenol (Tembhurne et al., 2014; Ahmad et

al., 2013; Staphylakis PK, and Gegiou D. 1986). Oil is a highly volatile commodity (0.4-0.45 %) comprises saturated fatty acids which comprises: Thymoquinone (TQ), thymohydroquinone (THQ), The nigellone which consider the single part of the carbonyl chain of the oil, limonene, dithymoquinone, alpha and beta pinene, thymol, carvacrol, citronellol, and cymene instable oil of the seed that include: longifoline, carvacrol, p-cymene, 4-terpineol and t-anethole (Tembhurne et al., 2014; Ahmad et al., 2013; Enomoto et al., 2001). Nigella sativa seed possess two various types of alkaloids: isoquinoline type that comprises: nigellicimine, nigellicimine n-oxide and pyrazol type that contains: nigellidine and nigellicine (Tembhurne et al., 2014; Ahmad et al., 2013). Carbohydrates, lipids, vitamins, essential salts, also proteins that including eight or nine necessary amino acids, are all nutritious components of N. sativa. Furthermore, N. sativa seeds comprise alpha hederine, saponin, and trace quantities of limonene, citronellol and carvone, as well as a variety of minerals like Ca, Zn, Cu, Fe, P, K and vitamins (Tembhurne et al., 2014; Ahmad et al., 2013).

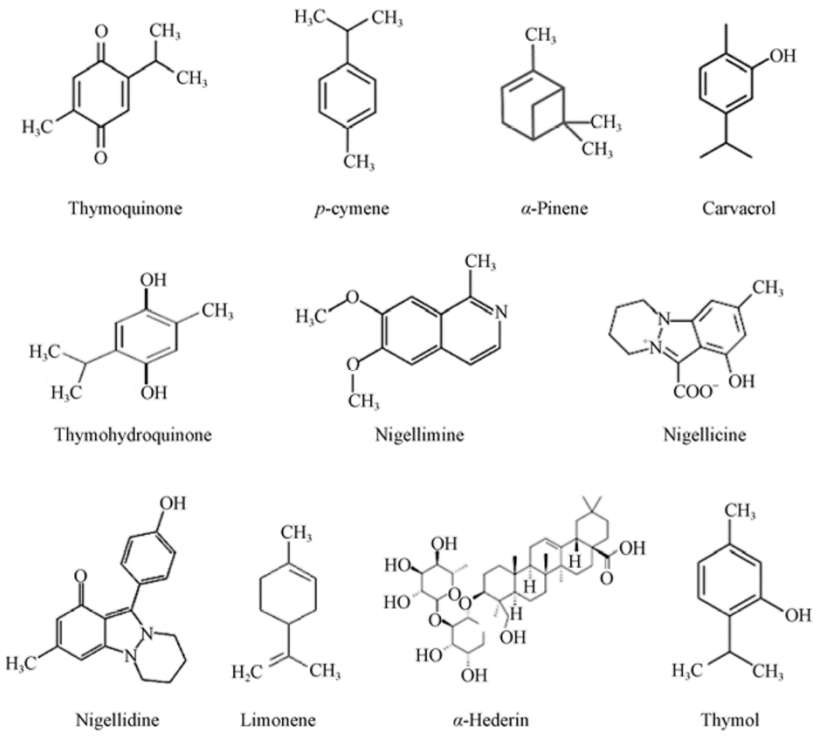

Figure 2: Some of the main components of Nigella sativa seeds' chemical structures

(Adopted from Kooti et al., 2016).

Table 1: vital component and elements separated from Nigella sativa seeds and their percentages (Ahmad et al., 2013; Shomar, B. 2012) adopted from (Mohamed et al., 2020).

Nr.	Compound and elements	Percentages
1	Thymoquinone	30 up to 48%
2	Thymohydroquinone, dithymoquinone, *p*-cymene	7 up to 15%
3	Carvacrol	6 up to 12%
4	4-Terpineol	2 up to 7%
5	*t*-Anethol	1 up to 4%
6	Longifolene (a sequiterpene)	1 up to 8%
7	nigellicimine n-oxide, nigellicimine, nigellicine, nigellidine, alpha hederine, saponin , limonene, carvone, citronellol	Less than 1% (trace quantities)
8	Minerals (calcium, manganese, phosphorus, potassium, magnesium, aluminum, copper, zinc, iron,)	Less than 1% (trace quantities)

Table 2: Common components of *Nigella sativa* seeds (adopted from Hamid M. and Hossein H.

2014):

Component	% Range (w/w)
Oil	31 up to 35.5
Protein	16 up to 19.9
Carbohydrate	33 up to 34
Fiber	4.5 up to 6.5
Saponin	0.013
Moisture	5 up to 7

Table 3: Common components of *Nigella sativa* oils (adopted from Hamid M. and Hossein H.

2014):

Component	% Range (w/w)
Linoleic acid	44.7 up to 56
Oleic acid	20.7 up to 24.6
Linolenic acid	0.6 up to 1.8
Arachidic acid	2 up to 3
Palmitoleic acid	3
Eicosadienoic acid	2 up to 2.5
Palmitic acid	12 up to 14.3
Stearic acid	2.7 up to 3
Myristic acid	0.16
Stroles	0.5

1. **long history of uses in folk remedies:**

Nigella sativa seeds were used in traditional Arabic herbal medication in middle eastern for thousands of years as a spices and food preserving and also for the resistant and therapeutic of various diseases (e.g., headaches, gastrointestinal problems, bronchitis, asthma, skin diseases, influenza, dizziness, conjunctivitis, infections, inflammation, jaundice, anorexia, paralysis, rheumatism, dyspepsia, diabetes, cough, obesity, dysentery, amenorrhea, intrinsic hemorrhage, fever, eczema and hypertension) in Northern Africa, South Asia and Middle East (Bakathir HA and Abbas NA. 2011), (Phillips JD. 1992; Sayed MD. 1982; Burits M and Bucar F. 2000; Rajsekhar S and Kuldeep B. 2011; Merfort et al., 1997; Aboutabl et al., 1986; Warrier et al., 2004; New Delhi. 1989), (Salem, 2005; Ali and Blunden, 2003). A solution extracted from the seeds is beneficial in dropsy, anorexia, dysmenorrhea, indigestion, diarrhea and amenorrhea and use as anti-worms as well as in the therapy of skin rashes. The roasted pills also used to arrest

vomiting (El-Tahir K E and Bakeet DM. 2006; Hosseinzadeh et al., 2007; Ziaee et al., 2012). In this regards, in his famous treatise, Canon of Medicine, Avicenna has mention various Nigella sativa's features, such as energy recovery and weakness enhancement. This herb's health characteristics have also been recognized in Islamic medicine. (Sharma et al., 2009).

2. **Biological activities and pharmacological properties**:

The current article, include some reviewed effects of Nigella sativa on different diseases particularly during the last two decades.

6.1. Anti-cancer activity:

Since 428H, Ibn-Sina recognized the anticancer activities of Nigella sativa (Al-Jishi, 2000) and used Nigella sativa for the therapy of tumors, mainly hard spleen tumor. During recent science, perhaps for the first time, the anti-tumor influences of Nigella sativa were observed, when a development of the natural killer cell action, ranging from 200–300%, was showed in advanced cancer patients receiving multi-modality immunotherapy program in which Nigella sativa seed was one of the components (El-Kadi and Kandil, 1986). Recently, several researchers indicate the antineoplastic activities of Nigella sativa seed and its extracts through in vivo using animal models and in vitro using cancer cell lines. According to Salomi et al. (1992), the raw methanolic extract of Black seed had a substantial cytotoxic activity on Elrich ascites carinoma, Dalton's ascites lymphoma, and sarcoma 180, but had no effect on normal lymphocytes. Another study found that the ethyl acetate phase chromatographic component (CC-5) of Nigella sativa ethanolic extract had cytotoxic capabilities against a variety of cancer cell lines, including P388, Hep G2, Molt4, and Lewis lung carcinoma cells (Swamy and Tan, 2000). Furthermore, Nigella sativa seeds given orally protect 80 % of rats from methylnitrosourea-induced oxidative stress and carcinogenesis, and Nigella sativa seeds combined with honey protect 100 % of rats from methylnitrosourea-induced oxidative stress and carcinogenesis. (Mabrouk et al., 2002). Nigella sativa extracts, both aqueous and ethanolic, were found to destroy MCF-7 breast cancer cells (Farah and Begum, 2003). The aqueous extract had a significantly higher

cytotoxic activity than the ethanolic extract, whereas Nigella sativa oil given orally to rats inhibited the induction and improvement of 1,2-dimethylhydrazine-induced abnormal crypt foci, which are putative preneoplastic lesions for colon cancer, without causing any pathological injury to the liver, kidneys, spleen, or other organs (Salim and Fukushima, 2003). The volatile oil of N. sativa is also cytotoxic to human cancer cell lines (SCL, SCl-6, NUGC-4) and the 3T6 fibroblast line (Islam et al., 2004). Worthen et al. (1998) tested the cytotoxicity of a raw gum, a fixed oil, and two purified constituents of the seeds, thymoquinone (TQ) and dithymoquinone (DTM), on numerous parental and multidrug resilient cancer cell lines in vitro. Furthermore, thymoquinone, a cytotoxic molecule separated from Nigella sativa seeds, was previously exclusively found in the ethanolic extract. Consequently, other constituents beyond thymoquinone are likely to have mediated the cytotoxicity of this many herbal preparation's aqueous extract (Samarakoon et al., 2010). In another study, addition to cytotoxic activity of vital oil and extracts of ethyl acetate of Nigella sativa against several tumor cell lines, in vivo animal model (DBA2/P815), the injection of necessary oil into the tumor tissue significantly reduced tumor growth, stopped liver metastasis, and improved the mice's survival chances (Ait Mbarek et al., 2007). Thymoquinone and associated fat soluble compounds have been thoroughly researched and described as having anticancer potential in Nigella sativa extracts with organic solvents. However, as mentioned above in some investigations, the aqueous extract of N. sativa seed presented antitumor influence, suggesting the presence of water soluble active ingredients. This effect was recently confirmed when Nigella sativa aqueous extract significantly increased NK cytotoxic action against YAC-1 cancer cells (Majdalawieh et al., 2010).

6.2. Antioxidant activity:

Several previous studies have identified the anti-oxidant capabilities of Nigella sativa seeds. Nigella sativa may be useful in the fight against and treatment of brain ischemia and neurodegenerative illnesses due to its anti-oxidant characteristics (Mahmoud et al., 2002). Free radical production could be at least partially to blame for various human sicknesses and disorders. As a result, Nigella

sativa's antioxidant properties may have contributed to its usage in traditional medication. The antioxidant properties of Nigella sativa crude extract were investigated. The vital extracts, thymoquinone, and other compounds such as anethole, carvacrol, and 4-terpineol all showed promising radical scavenging abilities. The chemiluminescence and spectrophotometer procedures were used to test the free radical scavenging impact of thymoquinone, dithymoquinone, and thymol on reactions producing reactive oxygen species such as superoxide anion radical, hydroxyl radical, and singlet oxygen (Kruk et al., 2000). In addition, thymoquinone inhibits iron-dependent lipid peroxidation in a concentration-dependent manner (Nagi MN and Mansour MA. 2000). As a result, thymoquinone can lower oxidative stress and promote antioxidant defenses in the body. Therapy with thymoquinone results in a decrease in malondialdehyde and other oxidative stress indicators, as well as a rise in total thiol content and glutathione levels (Seronello et al., 2007; Mohamed et al., 2005; El-Tawil O and Moussa SZ. 2006). Protein deactivation, protein oxidation, calcium balance disturbances, lipid peroxidation, and consequent loss of cell viability can all be induced by oxidative stress reduction (El-Tawil O and Moussa SZ. 2006). Moreover, reduction of free radicals with thymoquinone can also reduce the chance of free radicals damaging DNA and causing cancer (Burits M and Bucar F. 2000; Fouda et al., 2014). By boosting the capabilities of quinone reductase and glutathione transferase, oral injection of thymoquinone is a prospective preventive drug against hepatocarcinogenesis and damage in liver tissues (Sayed-Ahmed et al., 2010).

6.3. Anti-inflammatory activity:

Many acute and chronic disorders include inflammation as one of their key pathophysiological features (Zahra et al., 2016). Contagion and oxidative stress increase the expression of inflammatory genes, which leads to an increase in inflammatory mediators such as cytokines, eicosanoids, oxidants, and lytic enzymes. As a result, introducing a multipotential and preventive agent in the therapy of inflammatory illnesses is promising (Zahra et al., 2016). Also, thymoquinone and other fixed oil from the seeds were found to treat skin rashes,

rheumatism and back pain (Umar et al., 2012) and a considerable reduction in rat paw edema and granuloma pouch weight, as well as reduced membrane fat peroxidation and eicosanoid production in leucocytes (Sharma et al., 2009). Moreover, thymoquinone has anti-inflammatory properties in a variety of inflammatory illnesses. (Mansour M and Tornhamre S. 2004; Mahgoub A. 2003; Tekeoglu et al., 2007). Inflammatory cytokines can also activate signaling pathways in hepatocellular that cause cell injury. By reducing the enzymes cyclooxygenase and lipoxygenase, thymoquinone is an efficient reduction of eicosanoid synthesis, specifically thromboxane B2 and leukotriene B4. One of most significant mediators are the development of bleb in hepatocyte cell membranes and the promotion of free radical generation (El-Tawil O and Moussa SZ. 2006). Thymoquinone reduces inflammation by lowering malondialdehyde level, fat peroxidation products and reducing cytokines by suppressing NF-B activity, and decreasing cytochrome c synthesis from mitochondria by preventing the creation of reactive oxygen species (ROS) in the liver (Badary et al., 2000).

6.4. Antidiabetic activity:

Several traditional medicine experts recommended by Nigella sativa to treatment diabetes (Ali B and Blunden G. 2003). Previous research has shown that Nigella sativa has therapeutic properties for fat and carbohydrate metabolism disturbances. Nigella sativa has been demonstrated to have a therapeutic influence on metabolic parameters in diabetes in a number of animal and clinical investigations (Heshmati and Namazi. 2015). Nigella sativa has been shown to have significant blood glucose lowering properties, this could be owing to the presence of essential oil (Al Yahya M. 1986). The antidiabetic effects of Nigella sativa are assumed to be caused by the stimulation of (AMPK), which affects cellular absorption from hypolipidemic and antidiabetic proteins. In this context, the evidence and traditional use of Nigella sativa's hypolipidemic and hypoglycemic effects among diabetic's patients and those with metabolic syndrome have been explored in several clinical research (Bamosa, 2010; Sabzghabaee, 2012). Similarly, a clinical trial of Nigella sativa on sixty diabetic individuals revealed significant enhancements in total cholesterol, it is active as an

add-on medication in patients with insulin resistance syndrome, as measured by little density lipoprotein cholesterol (LDL- C) and fasting blood sugar levels. (Najmi et al., 2008). In a study conducted by Nadia and Taha (2009), they analyzed the effects of Nigella sativa essential oils and thymoquinone on oxidative stress and neuropathy in Streptozotocin-caused diabetic animals. The results demonstrated a large rise in norepinephrine and dopamine levels, as well as a significant drop in serotonin content, as compared to the control group. Oral Nigella sativa oil or TQ injections partially reversed these effects (Tembhurne et al., 2011). According to the findings, total antioxidant capacity (TAC), catalase (CAT), glutathione (GSH), and superoxide dismutase (SOD) all increased significantly after Nigella sativa intake, as did the level of thiobarbituric acid-reactive substances (TBARS). There were no important variations in liver and renal function among the two groups, and the blood picture analysis was normal. As a result, continuing Nigella sativa treatment improved blood sugar level and antioxidant equilibrium in type 2 diabetes cases taking oral hypoglycemic medications (Kaatabi et al., 2015). In streptozotocin-diabetic rats, Nigella sativa extract resulted in beta cell regeneration and relative proliferation, as well as a reduction in free radical creation (Benhaddou-Andaloussi et al., 2011; Ramadan et al., 2003). Supplementing rats with Nigella sativa extract and oil, as well as TQ, lowers tissue MDA and blood glucose while increasing serum insulin and tissue SOD level. These results imply that Nigella sativa and TQ may be effective in the therapy of diabetes and the prevention of oxidative stress in β-cells (Kanter et al., 2003). TQ (in drinking water) and Nigella sativa powder (matched with edible food) were administrated to rats over a period of 25 days, and the studied hematology indicators revealed that TQ and Nigella sativa caused a important reduction in blood glucose. (Abdelmeguid et al., 2010). In rabbits, Nigella sativa extract reduces blood glucose and ceruloplasm and recovers biochemical as well as histological markers of damage liver after two months of treatment. Its antioxidant activities are responsible for these beneficial properties. (Yaman I and Balikci E. 2010). Nigella sativa inhibits gluconeogenesis by regulating the activity of liver enzymes include glucose metabolism. It inhibits the gluconeogenesis enzymes glucose 6-phosphatase and fructose 1.6 bisphosphatase. Also it increases levels of

the glucose 6-phosphate enzyme, which is important in the pentose phosphate circus in cells. (Wienkötter et al., 2008; Pari L and Sankaranarayanan C. 2009).

Table 4: N. sativa and its components have anti-inflammatory and immunomodulatory properties. (adopted from, Zahra et al., 2016).

Plant extract & doses	Study case	influences	Ref.
Anti-inflammatory			
Oil of Nigella sativa (500 mg twice a day)	Patients with rheumatoid arthritis	↓ disease activity score, swollen joints, and morning stiffness length	(Gheita and Kenawy, 2012)
Thymoquinone	Cells of human blood	Both 5-lipoxygenase and LTC4 synthase pathways are inhibited.	(Mansour and Tornhamre, 2004)
Immunomodulatory			
Nigella sativa (1g b.i.d. for 4 weeks)	Volunteers from human	↑ CD4+/CD8+ Natural killer (NK) cell function and T cell ratio	(El Kadi et al., 1990)
Nigella sativa (whole plant) and its refined proteins	Mononuclear cells from human peripheral blood (PBMC)	mixed lymphocyte cultures, stimulatory and suppressive effects	(Haq et al., 1999)
Nigella sativa (whole plant) and its refined proteins	PBMCs were activated by the pokeweed mitogen (PWM)	Effects on lymphocytes that are suppressive, ↑IL-8, and TNFα	(Haq et al., 1999)
Nigella sativa (whole plant)	PBMCs that have not been activated	↑IL-1beta secretion and TNFα, ↓IL-8	(Haq et al., 1999)
RPMI seed solution of Nigella sativa	PBMC of Human	Mitogen-stimulated T cells and macrophages are inhibited.	(Winkler et al., 2008)

Nigella sativa oil (40–80 mg/kg/day)	Atopic eczema, bronchial asthma, and allergic rhinitis patients	↓IgE and eosinophil count, ↓in plasma T and ↑ no change in HDL cholesterol, lymphocyte subpopulations, endogenous cortisol levels, or ACTH release.	(Kalus et al., 2003)
Ointments containing Nigella sativa	Patients with eczema on their hands	Hand eczema has improved, ↓ dermatology life quality index I scores.	(Yousefi et al., 2013)
30 days of Nigella sativa oil	Patients suffering from allergic rhinitis	↓ Nasal mucosal congestion, itching, runny nose, sneezing bouts, turbinate hypertrophy, and mucosal pallor	(Nikakhlagh et al., 2011)
30 days of Nigella sativa seed (2 g/day orally)	Patients suffering from allergic rhinitis	↑PMN functions, ↑ CD8 counts	(Isik et al., 2010)
For 6 months, use Nigella sativa oil twice daily on lesions.	Vitiligo patients have vitiligo lesions on their skin.	↓ The size of the lesions on the patient's body	(Ghorbanibirgani et al., 2014)

6.5. Antimicrobial activity:

Nigella sativa oil and extracts have been demonstrated in numerous studies to exhibit antimicrobial activity against a wide range of microbes, including those resistant to antibiotics (Kamil ZH. 2013; Toama et al., 1974). Nigella sativa extracts were tested for antimicrobial influence against Staphylococcus aureus, Pseudomonas aeruginosa and E. coli, and Candida albicans, a harmful fungi (Morsi NM. 2000). Nigella sativa's antimicrobial properties are attributed to active components such as melanin and thymohydroquinone (Al Yahya M. 1986). In vitro

antimicrobial influence of Nigella sativa oil on various types of bacteria including eleven gram-negative, three gram-positive, and C. albicans yeast revealed that all species were very sensitive (Hanafy M, Hatem M. 199). Morsi NM. (2000) showed that, after subcutaneous injection, Nigella sativa extract successfully destroyed harmfull staphylococcal contagion in mice. Several studies have found that Nigella sativa extracts work in tandem with gentamicin and other antibiotics, cephalexin, terbinafine, chloramphenicol, nalidixic acid, streptomycin, doxycycline and ampicillin to eradicate E. coli. (Morsi NM. 2000; Ara et al., 2005). Additionally, Yersinia enterocolitica, Pasteurella multocida, Trueperella pyogenes, Corynebacterium pseudotuberculosis, Listeria monocytogenes, Corynebacterium renale, Mannheimia haemolytica, Brucella abortus, E. coli, and S. aureus are among the bacteria that Nigella sativa inhibits. (Namjoo et al., 2013). According to another study, NSO has anti-bacterial activity similar to antibiotics like ceftazidime, cefaclor, cefamandol, and cefuroxime (Gharibi et al., 2012). Likewise, Nigella sativa's antifungal properties for methanolic extraction is demonstrated. In mice, it had an inhibiting effect on candidiasis. (Niakan et al., 2006). In a study, the antidermatophyte effectiveness of Nigella sativa thymoquinone and other extracts were evaluated beside eight fungal infections: 4 Trichophyton rubrum types and one each of Microsporum canis Trichophyton mentagrophytes, Trichophyton interdigitale, and Epidermophyton floccosum (Bita et al., 2012). Garlic extracts and NSO both have oxidative and antischistosomal properties that investigated in several studies. The findings show that GE and NSO protection considerably improves the oxidant resistant properties of schistosomiasis mice compared to non-treated infected mice and prevents the majority of biochemical and blood abnormalities. (Aljabre et al., 2005). Similarly, the actions of NSO in injury hepatocytes produced by the infection of mice with S. mansoni were observed by Mahmoud et al. Infection with S. mansoni causes a important rise in serum ALP, ALT and GGT activity, with a minor rise in ALP quantity, however decreasing the level of albumin. Injection of NSO enhances the alterations in GGT, ALT, and AP action, in addition to the albumin level (Shenawy et al., 2008). Moreover, the antibacterial properties of TQ at low doses suggested the need for more in vivo research. As a result, future research should focus on isolating and

formulating novel antibacterial elements from this herb, as well as conducting more clinical trials.

Table 5: Antitumor influences of Nigella sativa and its components (adopted from, Zahra et al., 2016).

Plant extract & doses	Study case	Influences	Ref.
Nigella sativa seed oil and extract	Lung cancer cell line from a human	↓ Cancer cell viability and alterations in cellular morphology	(Al-Sheddi et al., 2014)
Nigella sativa oil	Monocytes and macrophages from humans	In monocytes and monocyte-derived macrophages, there is a regulatory influence on cell proliferation and differentiation.	(Mat et al., 2011)
N. sativa seed extracts' lipid fraction	MCF-7 human breast cancer cells	At low doses, cytotoxic to MCF-7 cells	(Mahmoud and Torchilin, 2013)
Nigella sativa seed aqueous extract	MCF-7 human breast cancer cells	Aqueous extract cytotoxicity at high concentrations and hormetic impact at low concentrations	(Mahmoud and Torchilin, 2013)
Oil nanoemulsion adjuvant treatment	MCF-7 human breast cancer cells	↑ Doxorubicin's antitumor action	(Mahmoud and Torchilin, 2013)
Nigella sativa hydroalcoholic extract, n-hexane, and ethyl acetate fractions	Human renal adenocarcinoma (ACHN) and normal renal epithelial (GP-293) cell lines	↓ ACHN cell viability is affected by dose and time. Total extract caused more significant morphological alterations and apoptotic effect in ACHN cells than in GP-293 cells.	(Shahraki et al., 2015)

Thymoquinone	Human colon cancer cells HCT-116	TQ induces apoptosis in HCT-116 cells (through Bcl-2 protein and p53 mRNA expression).	(Gali-Muhtasib et al., 2004)
Thymoquinone	Osteosarcoma cell line from a human (SaOS-2)	Apoptotic impact (↓ inhibition of tumor angiogenesis and growth via inhibiting NF-B)	(Peng et al., 2013)
Thymoquinone	Endothelial cell of the human umbilical vein	Apoptotic impact (↓ inhibition of tumor angiogenesis and growth via inhibiting NF-B)	(Peng et al., 2013)
Thymoquinone	cell lines of Human osteosaroma	In human osteosarcoma cells, p53-independent apoptosis occurs.	(Roepke et al., 2007)
Thymoquinone	Cervical squamous cancer cells of humans	Effect on the cells (elevation of p53 and downregulation of the antiapoptotic Bcl-2 protein)	(Ng et al., 2011)

6.6. Antibacterial activity:

Different previous investigation have showed the antibacterial activities of Nigella sativa and TQ on numerous types of bacterial species (Goyal et al., 2017). In many studies TQ and Nigella sativa constituents have revealed a substantial bactericidal effect in contradiction of Gram-positive bacteria and Gram-negative and prevent bacterial production (Kapil et al., 2018; Goel et al., 2018), promising the usage of TQ as a microbial resistant drug in various illnesses (Maideen, N.M.P. 2020; Ahmad et al., 2020). Nigella sativa was studied for bacterial resistant action beside Staphylococcus aureus, Klebsiella pneumoniae, Proteus species, Staphylococcus epidermidis, Enterococcus faecalis, Streptococcus pneumoniae, Porphyromonas species, Acinetobacter baumannii/calcoaceticus, and Veillonella species. (Kiari et al., 2018). The analysis accomplished via the microdilution process showed great antiseptic influences of the vital oil extract of Nigella sativa beside all the examined types of bacteria and mainly *Porphyromonas* sp. And *Staphylococcus*

epidermidis. As a result, the agar well diffusion process did not yield perfect findings, indicating that a variety of factors may influence the antibacterial activity of NS extracts. (Kiari et al., 2018). Nigella sativa and its extracts contain antibacterial characteristics that have been recognized since antiquity, and laboratory tries to explain these properties goes back to the early 19th century. (Dorman HJ and Deans SG. 2000). In this regard, the enhancement of resistant bacteria to a number of regularly used antibiotics encourages more research into novel antimicrobial medication to eliminate illness and overcome the challenges of resistance and adverse effects associated with currently used antimicrobial treatments. (Morsi NM. 2000; Hannan et al., 2008). Although the resistant method of Nigella sativa seeds' antimicrobial influence has yet to be determined, its microbial resistant properties might be related to the vital components, mainly the melanin and TQ (Bakathir HA and Abbas NA. 2011). The influence important processes of organisms must be due to the broad scope of their activity (Monika et al., 2013). Furthermore, an additive antibacterial activity with erythromycin, nalidixic acid, doxycycline, spectinomycin, tobramycin, lincomycin, chloramphenicol, ampicillin, and sulfa-methoxazole trimethoprim. (Hanafy MS and Hatem ME. 1991). Many bacterial isolates, including 6 Gram- positive and 16 Gram- negative types of bacteria, were used to estimate the bacterial resistant properties of raw extraction of N. sativa. These separates, notably Gram-negative bacteria, demonstrated multiple antibiotic resistance. The most active fragments were raw alkaloid and a queous extracts, which remained particularly effective against Gram-negative isolates. (Morsi NM. 2000). Beside all species of L monocytogenes, N. sativa extracts demonstrated powerful antibacterial influences, resulting in a substantially larger inhibition zone than gentamicin (P0.01). N. sativa and gentamicin formed mean inhibition zones of 31.50 ±1.0 and 14.80 ± 0.50 mm, respectively. (Nair et al., 2005). MRSA, or methicillin resistant Staph. aureus, is consider the greatest common diseases found in laboratories and clinics. The ethanolic extract at a dose 4 mg/discs was shown to be sensitive to the majority of MRSA strains tested; the extract had a lowest inhibitory concentration (MIC) range of 0.2-0.5 mg/ml. (Hannan et al., 2008). Antibiotics may enhance TQ's antibacterial activities, particularly with Staph. aureus. TQ and HQ were found to

have antibacterial properties against E. coli, Salmonella typhimurium, Pseudobacterium aeruginosa, Shigella flexneri, Salmonella enteritidis, and Staph. aureus in a study. TQ was found to be particularly effective against Staph. aureus, with concentrations of three and six g/ml being enough to prevent and destroy the organism, respectively. Compared to methanol extract, N. sativa aqueous extracts showed less antibacterial activity.

6.7. Antiparasitic activity:

In other studies, the antiparasitic properties of Nigella sativa seeds were investigated. Nigella sativa is thought to be a beneficial ingredient for preventing and treating parasitic illnesses. However, Nigella sativa oil has been shown to have antinematodal and anticestodal activities. Moreover, Nigella sativa oil was found to be beneficial in decreasing the quantity of Schistosoma mansoni worms inside hepatic duct as well as the overall amount of ova placed in hepatic duct and gut. (Mahmoud et al., 2002; El-Shenawy et al., 2008). Other parasitic worms, such as Hymenolepis nana, have lately been found to be resistant to Nigella sativa (Ayaz et al., 2007). It accomplishes this by boosting the host's immunity. Other worms, such as Trichinella spiralis and Aspiculuris, were studied for similar defensive benefits. (AbuElEzz, 2005). The influences of N. sativa seeds were studied in youngsters who were commonly infested with cestode worms. At the levels examined, oral treatment of a dose (40 mg/kg) N. sativa ethanolic extract decreased the ratio of fecal ova (Akhtar MS and Riffat S. 1991). Moreover, the antimalarial activities is attributed to MENS having an antioxidant influence in mice infested with *Plasmodium*, which improves the oxidative state in erythrocytes, and liver cells of infected mice were also seen (Okeola et al., 2011). Rabbits were given 400 mg/kg of aqueous extracts and seeds oil emulsification to treat coccidiosis. Both treatments had anticoccidial effects, although the N. sativa oil emulsion had a faster antiparasite effect. Both treatments improved the histology of the liver tissue and promoted weight increase and a reduction in the detaching of fecal ova. The improvements involved a substantial decrease in inflammatory cell penetration in portal area, as well as a reduction in several phases of worms in the biliary canals, as well as hemorrhage among liver lobules,

hepatic cells returning to their normal circular preparation, as well as totally intense indicators disappearing. Alkaloid nigellicine, which own a fatal effect on worms, is found in higher concentrations in the N. sativa oil emulsion (Baghdadi HB and Al-Mathal EM. 2011). The efficacy of NSO and TQ to decrease the cytogenetic harm induced by schistosomiasis infection also contributes to the protection (Aboul-Ela EI. 2002).

Table 6: N. sativa and its constituents have anti-diabetic, anti-hyperlipidemic, hepatoprotective, and other effects on metabolic syndrome. (Adopted from, Zahra et al., 2016).

Plant extract & doses	Study case	Influences	Ref.
For 12 weeks, take 2mg of Nigella sativa seed every day.	Adjuvant treatment for patients with type 2 diabetes	↓ Insulin resistance, FBS, 2hPG, HbAlc, and FBS	(Bamosa et al., 2010)
2 grams of Nigella sativa seed each day for a year	Adjuvant treatment for patients with type 2 diabetes	↓ Insulin resistance, FBG, and HbA1c; ↑β-cell activity; ↑ all antioxidants: TAC, SOD, CAT, and glutathione, ↓TBARS	(Kaatabi et al., 2015)
3 months of Nigella sativa oil (2.5 ml)	Adjuvant treatment for patients with type 2 diabetes	↓ (BMI), HbA1C, FBS, 2hPG and lipid profile	(Hosseini et al., 2013)
12 weeks of Nigella sativa oil (3g/day)	Adjuvant treatment for patients with type 2 diabetes	↓ NS changes in TC, HDL-C, insulin secretion; NS changes in weight and BMI FBS, HbA1c, TG, and LDL-C	(Heshmati et al., 2015)
Nigella sativa seed + Trigonella foenum-graecum (250 mg)	Adjuvant treatment for patients with type 2 diabetes	↑ HDL-C; NS triglyceride and creatinine changes	(Memon et al., 2012)

Nigella sativa seed powder (500 mg/day)	Patients suffering from metabolic syndrome	↓ Blood sugar levels: FBG, PPBG, HbA1c, and LDL-C.	(Najmi et al., 2012)
6 weeks of Nigella sativa oil (2.5 mL twice daily)	Patients suffering from metabolic syndrome	↓FBG, LDL-C and TC.	(Haque et al., 2011)
Treatment with Nigella sativa (2mg/day)	Patients with hyperlipidemia	↓ NS changes in FBS, HDL-C; TC, and LDL-C	(Sabzghabaee et al., 2012)
2 months of Nigella sativa powder (1g/day)	Patients with high cholesterol levels are called hypercholesterolemics.	↓TC, TG, HDL-C and LDL-C	(Bhatti et al., 2009)
8 weeks of Nigella sativa powder (2 g/day)	Females that are overweight	↓TC, TG, LDL-C, and ↑ HDL-C	(Farzaneh et al., 2014)
2 months of Nigella sativa powder (1g/day)	Women who have reached menopause	↓TC, TG LDL and ↑HDL-C	(Ibrahim et al., 2014b)
12 weeks of Nigella sativa seed (1.6 g/day)	Premenopausal ladies are women who have not yet reached menopause.	↓ NS changes in TC, TG, and HDL-C; BG and LDL	(Latiff et al., 2014)
Allium Sativum oil + Nigella sativa seed (500 mg-250 mg)	Dylipidemia caused by psoriasis	↓Non-HDL, LDL, TG and cholesterol, and ↑HDL	(Ahmad Alobaidi, 2014)
Extract of ethanol (10–100 mg/ml)	Microsomes from human liver (in vitro)	↓ Metabolites of CYP2D6 and CYP3A4 formation	(Al-Jenoobi et al., 2010)
7 days of ethanolic extract (2.5 g twice daily)	Volunteers who are in good health	↓ DEX/DOR and DEX/3- MM urinary metabolic ratios	(Al-Jenoobi et al., 2010)
N. sativa oil (80 mg/kg/day)	ALL children should receive methotrexate treatment.	↓ Direct, and indirect serum bilirubin; serum ALT, AST, and ALP levels; and prothrombin time	(Hagag et al., 2013)

HbAlc (glycosylated hemoglobin), CAT (catalase), AST (aspartate transaminase), TAC (total antioxidant capacity), 3-MM (3-methoxymorphinan), SOD (superoxide dismutase), DEX (dextromethorphan), TBARS (thiobarbituric acid reactive substances), NS (Not Significant), DOR (dextrorphan) and ALT (alanine transaminase).

6.8. Antiviral effects:

Viral infections produce apoptosis, which results in a loss of lymphocytes in the recipient cell. Antioxidants be able to prevent viral apoptosis as well as inhibit viral repetition in target cells, therefore antiviral and antioxidant actions can be related. (Peterhans E. 1997). Murine cytomegalovirus (MCMV) was employed as a model to assess the antiviral properties of Nigella Sativa oil. On the third day of infestation, mice were given an intraperitoneal injection of Nigella Sativa oil, which revealed viral titers in the liver and spleen. The viral burden in the liver and spleen of control mice was 45×104 vs. 7×104 and 23×103 vs. 31×03, respectively, compared to Nigella Sativa oil treated mice. This antiviral activity was accompanied by a rise in interferon-gamma levels in blood, in addition to a rise in the number of CD4+ helper T cells, suppressor function, and macrophage quantities. On the 10th day following infection, the viral level in the liver and spleen of NSO-treated mice was undetectable, while it was visible in animals treated, indicating that in vivo therapy with N. sativa oil elicited strong antiviral influences against MCMV infection (Salem ML and Hossain MS. 2000). The NSO's antiviral actions are linked to an increase in CD4 cell responsiveness (Salem ML and Hossain MS. 2000).

6.9. Antifungal activity:

Different studies showed that, against numerous strains of Candida albicans, methanolic extracts of Nigella sativa show the greatest antifungal activity, followed by chloroform extracts. There was no antifungal activity for aqueous extracts. Candida albicans colonies were developed in the liver, kidneys, and spleen after an intravenous inoculum was given. Administration of mice with N. sativa extract 24 hours after injection had a strong decreasing effect on the organism's development in all organs tested. In 2003, Khan et al. discovered that an aqueous extract of Nigella sativa seeds had a decreasing activity on candida infection in mice. In the

groups that injected with the N. sativa extract, there was a five-fold drop in Candida in the kidneys, an eight-fold decrease in the liver, and an 11-fold decrease in the spleen. Histopathological testing of the various organs supported these findings (Bita et al., 2012). These findings support the use of N. sativa in folk medicine for the therapy of fungal skin infections due to its influence as a source of antidermatophyte medicines (Aljabre et al., 2005). The anti-yeast properties of dithymoquinone, TQ, quinines, and thymohydroquinone from N. sativa seeds were established in vitro in contradiction of six dairy spoilage yeast types using a broth microdilution process. At two pH levels (4.0 and 5.5), the antifungal activities of the quinones were in comparison to the usual preservatives used in milk yields (calcium propionate, potassium sorbate and natamycin), while thymohydroquinone and TQ have significant antiyeast effects. (Halamova et al., 2010). Ns-D1 and Ns-D2, two novel antifungal defensins, were isolated and sequenced from N. sativa seeds. The antifungal actions of the Ns-D1 and Ns-D2 defensins against a variety of phytopathogenic fungi were quite different (Rogozhin et al., 2011). The mechanism is thought to be because to defenses interacting with certain sphingolipids on fungal membranes (Rogozhin et al., 2011).

6.10. Antifertility activity:

The antifertility effects of Nigella sativa among male rats were investigated. Sperm production was inhibited, and the sialic acid concentration of prostate, vesicula seminals, epididymis, and the testis, was significantly reduced. (Sharma et al., 2009). Oral injection of Hexane extract of N. sativa seeds L. at a dose of 2 g/kg daily on days 1 -10 postcoitum stopped pregnancy in rats. While Hexane extract of N. sativa seeds showed substantial anti-fertility effects in column fractions and sub-fractions. The active hexane extract had only a moderate uterotrophic effect at contraceptive doses, similar to 0.002 mg/kg doses of 17 varies; is directly related to-ethinylestradiol, nonetheless had no estrogenicity in the young rat bioassay (Keshri et al., 1995). In male rats, an alcoholic extract of Nigella sativa seeds was reported to have anti-fertility influences, possibly due to Nigella sativa's innate estrogenic properties. (Agarwal et al., 1990).

6.11. Antimalarial activity:

Several Nigella sativa extracts have been found to have antiplasmodial properties in each in vivo and in vitro plasmodia pathogens. At a dosage of 50 ug/ml, it completely inhibits parasite growth (Plasmodium falciparum). Nigella sativa has antiparasitic action that is dose dependent (Abdulelah et al., 2007; El-Hadi et al., 2010).

6.12. Anti-ulcer activity:

Nigella sativa seeds, aqueous extract was found to be efficient in lowering the ulcer rate produced by aspirin by 36% (Rajkapoor et al., 1996). In another investigation, NSO was discovered to own a protective influence against the development of stress gastritis in hypothyroidal rats (Khaled et al., 2009). The elimination of Helicobacter pylori in individuals with non-ulcer dyspepsia also supports the recent clinical investigation (Salem et al., 2010).

Cardiovascular-protective activity:

Nigella sativa has been shown to protect against diabetes, platelet aggregation, blood pressure disorder, heart rate lipid levels alteration, endothelial malfunction, metabolic syndrome, atherogenesis, heart mass and muscle contraction irregularity and cardiotoxicity in numerous in vitro and in vivo experimental animal studies. As a result, N. sativa able to employed as a defensive and helpful mediator in cardiovascular illnesses as a harmless multi-properties herb with effective antioxidant and anti-inflammatory effects (Shabana et al., 2013). A little studies have looked at the cardio-protective properties of Nigella sativa and its components in both animal and human studies, with mixed results. Dehkordi et al. (2008) discovered that a two-month oral injection of N. sativa seed extract had a decreasing blood pressure influence in individuals with moderate hypertensive. When compared to the baseline, systolic pressure (SBP) and diastolic pressure (DBP) were considerably lower after administration with 2.7 and 5.3 mg/kg/day of the herb extracts. Furthermore, when compared to baseline data, N. sativa administration considerably lowered complete and LDL-C amounts (Zahra et al.,

2016). The preventive effect of N. sativa on the thorax aorta contractile response is examined in a model in rats of diabetes mellitus. The results reveal that treating diabetic rats with this plant reduces the contractile response to non-specific KCL agonist and specific adrenergic receptors agonist to the greatest extent possible. Long-term oral N. sativa injections may lower arterial contractile reactivity and the amount of heart problems in diabetics (Fararh et al., 2004). Previous research has revealed that the actions of N. sativa have been documented on cardiac effects in diabetic rabbits, with the findings showing that N. sativa extract moderates unbalanced heart influence in diabetic rats (Roughani et al., 2006). TQ's protective activities and the severe (at 4 and 18 h) impact of diesel exhaust particles (DEP) on cardiovascular and pulmonary factors in mice were also studied, with the findings revealing that TQ therapy lowers systolic pressure, inhibits leukocytosis and IL-6 production, and reduces plasma SOD effects. As well as prevents the numbers of platelets from dwindling and prothrombotic proceedings from occurring (Meral et al., 2004). In addition, the influence of NSO on cholesterol, blood glucose levels, and homeostatic balance in rats have been investigated, with the results indicating a decrease in cholesterol, glucose, TG and an increase in white blood cells, hematocrit, platelets, and hemoglobin. Nigella sativa extract injection at 800 mg kg-1 for 3 months reduced heart tissue injury induced by ischemia reperfusion, which was likely related to Nigella sativa's anti-oxidant activity (Nemmar et al., 2011). In anesthetized rats, injection of a required oil ingredient at 4–32 μg·mL–1 resulted in a dose-dependent decreasing in blood pressure and heart contraction, which was reduced by anticholinergics (Amarouch et al., 2002). Another study indicated that dichloromethane N. sativa extract (0.6 mL·kg–1·d–1) lowers mean blood pressure in spontaneously hypertensive rats (El Tahir et al., 1993). N. sativa is used to treat hypertension alone or in conjunction with honey or garlic, which prompted El-Tahir et al. (1993) to examine the effects of the instable oil of N. sativa and its essential ingredient thymoquinone on the blood pressure and heart contraction of anaesthetized rats. The heart contraction and blood pressure are reduced by both drugs by the dose-dependent method. Cyproheptadiene, atropine, and hexamethonium greatly inhibited these actions. This indicated that these actions were mostly inhibited centrally via 5-hydroxy

tryptaminergic and muscarinic mechanisms. In spontaneously hypertensive rats, an oral injection dose of 0.6 ml/kg/day of N. sativa extract showed considerable hypotension effects. These findings were equivalent to those of the conventional anti-hypertension medication nifedipine (Zaoui et al., 2002). The drug's influence was attributed in part to its diuretic action, which was associated to 0.5 mg/kg/day furosemide.

Gastro-protective activity:

In rats with induced stomach ulcers and gastric basal secretion, the aqueous extract of Nigella sativa exhibits anti-ulcer activities, according to numerous studies. The aqueous extract of Nigella sativa reduced the formation of induced stomach ulcers, according to the findings. In pylorus-ligated Shay rats, this compound also decreased the severity of the ulcer and the amount of acid produced by the stomach during rest. The anti-ulcer influences of Nigella sativa extract are most likely attributable to prostaglandin interactions as well as antioxidant and anti-secretory properties (Zaoui et al., 2000). Furthermore, in rats with aspirin-induced stomach ulcers, Nigella sativa aqueous extract reduces indices by up to 36% (Al Mofleh et al., 2008). Two weeks of supplementation with Nigella sativa extraction at a dose of 0/88 g·kg−1·d−1 raises glutathione and mucin amount in the gut while lowering histamine levels. Hydroalcoholic extract has been researched for its protective effects on the stomach mucosa. (Akhtar et al., 1996). Furthermore, doses of 50 and 100 mg·kg−1 of TQ and Nigella sativa revealed to have a defensive effect on stomach ulcer in rats, reducing ischemia-reperfusion injury and gastric ulcer through their anti-oxidant effects (El-Dakhakhny et al., 2000). TQ therapy can also help to avoided and enhance ulcer, which can be used to treat patients with inflammatory bowel disease (IBD) (El-Abhar et al., 2003). In addition, Mohtashemi et al. show that injecting a honey-based NS oil composition (5 mL NS oil each day) for 8 weeks, compared to placebo, improved indications like dyspepsia intensity and reduced the risk of H. pylori contagion in patients with useful dyspepsia (Mohtashami et al., 2015).

Hepato-protective activity:

The influences of ischemia reperfusion damage (CRI) on the liver have been shown to be reduced when given Nigella sativa (0.2 ml/kg) intraperitoneally. Biochemical markers like as aspartate aminotransferase, lactate dehydrogenase, CAT, alanine aminotransferase, oxidative stress index (OSI), TOS, total antioxidant capacity (TAC), and MPO were investigated in hepatic tissues of rats having liver ischemia. According to the findings, Nigella sativa medication keeps the liver of rat from ischemia reperfusion damage (Yildiz et al., 2008). Nigella sativa prevents liver tissues from toxic elements such as lead, as well as reducing hepatic lipid oxidation after exposure to poisons like carbon tetrachloride (Kapoor S. 2009). Cadmium (Cd++) disturbs tissue homeostasis and produces free radicals. The defensive effects of TQ on C d++ liver injury were investigated, with a focus on enzymatic and non-enzymatic antioxidant damage prevention. Under in vitro settings, the protective effects of TQ pretreatment were assessed in post-nuclear supernatant produced from the liver of mice. The antioxidant enzymatic effects were significantly increased after injection with CdCl2 (5 mmol/L). It also resulted in an important rise ($P < 0.001$) in protein carbonyl and a decrease in glutathione concentration. TQ (10 mol/L) pretreatment provided considerable prevention, as shown by decreased protein oxidation and regenerated of cellular fraction-depleted antioxidants. These results support the theory that TQ has a modifying effect on the antioxidant defense system when it is exposed to a toxic shock (Zafeer et al., 2012). Hepatotoxicity is linked to changes in the concentration and effects of enzymes including glutamic-pyruvic transaminase (SGPT), glutamic-oxaloacetic transaminase (SGOT) and the system of oxidative scavenger enzymes like glutathione (GSH), catalase (CAT) and superoxide dismutase (SOD). Using isolated rat hepatocytes, the protective efficacy of thymoquinone against hepatotoxin: terbutyl hydroperoxide was investigated (Daba and Abdel-Rahman, 1998). The hepatoprotective effects of thymoquinone (TQ) were compared to those of silybin, a well-known hepatoprotective drug, in this study. TQ's hepatoprotective mechanism is unknown, although it is likely connected to the protection of intracellular glutathione (GSH), which is recognized to enhance the

vulnerability of cells to irreparable harm when depleted by oxidative stress. It was also discovered that pre-treating rats with Nigella sativa oil for four weeks protected them from CCl4 and D-galactosamine-induced liver damage. When green oil was administered orally with a dose of 100 mg/kg/day for four weeks, no harmful impact on liver function were seen. Thymoquinone with a dose of 8 mg/kg/day for 5 days before and 1 day after CCl4 therapy protected mice from liver histological and biochemical markers impairment (Nagi et al., 1999). It has recently been discovered to have protective properties against ischemia reperfusion damage to the liver (Fahrettin et al., 2008).

Nephroprotective activity:

In rabbits, the nephroprotective influences of Nigella sativa oil and vitamin C against gentamicin (GM)-caused nephrotoxicity were studied. For all rabbit groups, blood urea nitrogen, creatinine, and antioxidant effects were examined as indications of kidney injury. When compared to the GM control group, Nigella sativa oil and vitamin C have been demonstrated to have a protective impact on the kidneys by lowering antioxidant influences, blood urea nitrogen and serum creatinine. These two forms of antioxidants have been shown to have synergistic nephroprotective effects when given simultaneously (Saleem et al., 2012). In albino rats, the defensive effects of Nigella sativa oil on kidney toxicity caused by methotrexate were investigated, and this study confirmed the prevention activities of Nigella sativa oil on kidney injury caused by methotrexate (Abul-Nasr et al., 2001). It has been shown that Nigella sativa can protect kidney tissues from ischemia-perfusion injury. MPO, TAC, CAT, OSI, and TOS levels in blood and tissues of kidney were examined. The amounts of blood urea and blood creatinine were also measured. The histology of kidney tissues was also examined. Nigella sativa was found to be beneficial in lowering the amounts of blood urea and creatinine and lowering tubular necrosis scores. Therapy with Nigella sativa lowered TOS and OSI levels while increasing TAC levels in renal tissue and blood. The findings revealed that Nigella sativa had a prevention activity in the rat kidneys against renal I/R damage (Yildiz et al., 2010). The preventive properties of Nigella sativa oil were tested in rats to see if they might prevent cyclosporine A (CsA)-

induced nephrotoxicity. Nigella sativa oil enhanced functional and histological indicators while reducing oxidative stress caused by CsA. Nigella sativa oil defends kidney tissues from oxygen free radicals, which reduces renal damage and morphological irregularities caused by continuous CsA injection (Uz et al., 2008). Nigella sativa in combination with intraperitoneal GM When compared to the GM group, there was a substantial decrease in urea, MDA, NO, creatinine and an increase in SOD and GSH-Px effects, indicating a nephro-protective impact. Nigella sativa inhibits the harmful effects of GM on biochemical and histopathological parameters by acting as a potent free radical scavenger (Yaman I and Balikci E. 2010). Nigella sativa seeds have no effect on biochemical measures of cisplatin-induced nephrotoxicity, despite the fact that the kidneys' histopathologic features have improved after Nigella sativa use (Hadjzadeh et al., 2012). Pretreatment with Nigella sativa oil (5.0 mL·kg−1) reduced plasma transaminase activity, MDA, and TG levels, and improved liver histological alterations in another investigation (Slim et al, 2012).

Testicular-protective activity:

Among male C57BL/6 mice, the preventive influence of thymoquinone (TQ) on damage testes caused by methotrexate were investigated. TQ therapy reduced TAC and prevented myeloperoxidase effect from increasing. Mice given methotrexate had interstitial space dilation, a reduction in the diameter of the seminiferous tubules, severe disruption of the seminiferous epithelium, and edema according to light microscopy. TQ may minimize the harmful influences of methotrexate on testes tissues in individuals taking this medication, according to several studies (Gokce et al., 2011).

Wound healing activity:

Black seed and oil have been shown to help farm animals recover wounds (Ghonime et al., 2011). In addition, applying a topical therapy ether extract of Nigella sativa seed to staphylococcus-diseased skin in mice promotes therapeutic by lowering total and difference WBC numbers, local contagion and inflammation,

tissue damage and bacterial proliferation (Ahmed et al., 1995). When the activities of cream of silver sulfadiazine (SSD) and Nigella sativa on burn wound therapeutic in an animal model were evaluated, it was discovered that recovering from burns was enhanced in the Nigella sativa and SSD groups in comparison to the control group on the 4, 9, and 14 days (Durmus and Ceribasi, 2010). However, among the 4th, 9th, and 14th days, however, wound curative differed considerably between groups. (Abu-Al-Basal MA. 2011). Despite its non-substantial effects on collagen production, Nigella sativa extracts show greater proliferation of human gingival fibroblasts and faster treatment when comparing to Piper Sarmentosum extracts, Pluchea indica, and Melastoma malabathricum. In addition to boosting bFGF levels until 15% at 100 μg·mL−1 of Nigella sativa, a somewhat healthier activity on TGF-expression was seen. Therefore, N. sativa exhibits hopeful healing effects on wounds, demonstrating its historic usage in the treatment of oral wounds (Osama Abu Zinada, 2009).

Effect on respiratory system:

The antispasmodic effects of Nigellone and TQ on the trachea, as well as their activity on the respiratory system, have been studied (Wienkotter et al., 2008). The micro dialysis technique was used to investigate the effects of B a ++ carbachol and leukotriene on tracheal contractions and the transfer of the fluorescent dye rhodamine B in relation to activity of the cilia in the trachea. When the trachea was contracted by the depolarizing impact of Ba2+, Nigellone and great doses of TQ had an inhibitory action that is concentration dependent. The tracheal contractions generated by leukotriene-d (4) LT4 were reduced by nigellone and TQ. In addition, nigellone possesses antispasmodic properties and increases mucociliary clearance, whereas TQ does not. As a result, nigellone not TQ, may be effective in the therapy of certain respiratory disorders (Wienkotter et al., 2008). Relaxant influences of four total concentrations of methanol, n-hexane, aqueous fractions and dichloromethane of Nigella sativa (0.8, 2.0, 1.6 and 1.2 g%) compared to saline solution as a negative control and four total concentrations of theophylline (0.2, 0.4, 0.6 and 0 .8 mmol/L) their sedative properties was tested on guinea pig tracheal chains that had been pre-contracted with 60 mmol/L

potassium chloride (group 1) and 10 μM methacholine (group 2). The findings revealed that most fractions of Nigella sativa have relaxant properties on the guinea pigs' bronchial chains, with the dichloromethane fractions and methanol being more effective (Boskabady et al., 2008). The preventive effect of Nigella sativa on tracheal response (TR) and pulmonary disease in guinea pigs subjected to sulfur mustard was investigated. With n = 6, guinea pigs were administered a dilute solution (ethanol, control group), 100 mg/m3 sulfur mustard breathing (SME group), and SME administered with Nigella sativa, 0.08 g a day (SME + N). TR to methacholine, total lung lavage WBC count, and differential WBC were performed 14 days following exposure. The results propose that Nigella sativa has a protective influence on the TR of guinea pigs exposed to sulfur mustard gas (Hossein et al., 2008). Furthermore, Nigella sativa medication may be effective in the treatment of lung injuries and has therapeutic potential (Kanter M. 2009). The protective effect of NSO was assessed in rats with hyperoxia-induced pulmonary damage, which is expected to promote bronchopulmonary dysplasia in preterm newborns. Chakravarty et al. (1993) demonstrated that nigellone, a thymoquinone carbon polymer derived from Nigella sativa seeds, effectively reduced histamine produce from mast cells in an in vitro investigation, demonstrating the rationale for its traditional usage in asthma. Another study found that giving 15 ml/kg of 0.1 % NS decoction extract for three months resulted in better improvements in PFT parameters and a reduction in asthma symptoms than giving a placebo. (Boskabady et al, 2007). Ahmed et al. studied LRTI patients with wheeze aged 5 to 15 years and found that conventional therapy alone versus conventional treatment with Nigella sativa oil had favorable effects (Ahmad et al., 2009). As a result, conventional treatment with NS oil (0.1 mg/kg) intended for 14 days was found to have greater favorable effects in lowering pulmonic index and rising peak respiration flow rate (Ahmad et al., 2009). Another study found that, daily injections of 0.375 mL/kg of a heated water extract of 50% NS, for two months, when compared to a placebo, there were significant enhancements in PFT and respiratory symptoms for chemical warfare victims. NS was found to have a protective impact on chemical warfare victims, indicating that it was used to protect them (Boskabady MH and Farhadi J. 2008).

Effect on nervous system:

The central nervous system (CNS) has been demonstrated to be protected by Nigella sativa seeds, and the most promising narcotic effect perhaps mediated by opioid receptors (Khanna et al., 1993). Neuronal degeneration is reduced by TQ produced from Nigella sativa extract (Houcher et al., 2007). The central nervous system (CNS) is analgesic when using Nigella sativa seed oil. Seizures that are uncontrollable are treated in children with a water extract of Nigella sativa seed (40 mg/kg/8 h) against placebo as therapeutic antiepileptic medication treatment considerably reduced the mean seizure frequency, according to Akhondian et al (Akhondian et al, 2007). While TQ (1 mg/kg) was injected as an adjuvant medication in place of a water extract of Nigella sativa seed in alike medical trial carried out by the same author, the outcomes were comparable (Akhondian et al., 2011). In the LPS-induced depression type, Nigella sativa (200-400 mg·kg−1) caused a reduction in depression in both the forced swim test and the open field test. (Hosseini et al., 2012). NSO has been shown to protect mice from tramadol tolerance and dependence, according to Abdel-Zahir et al. NSO has therapeutic potential by reducing nitric oxide overproduction and oxidative stress caused by drugs (Parvardeh et al., 2005). It has also been shown to enhance the effects of pentobarbitone-induced sleep. The influence of neurotransmitter release on cultured cortical neurons indicated that they imply enhanced neurotransmitter secretion. In cultured neurons, it also controls the release of amino acids. There was an increase in GABA effect, however there was a reduction in glutamate, aspartate and glycine excretion. N. sativa seed extract has relaxing and depression properties which represented in all of the results (Tariq et al., 2010). Intake of Nigella sativa on a regular basis was also shown to lower 5HT turnover and have an anxiolytic influences (Perveen et al., 2009). The major component of nigella seeds is thymoquinone. Thymoquinone was found to have an anticonvulsant action in mice in one investigation (Hosseinzadeh et al., 2004; Hosseinzadeh et al., 2005).

Effect on the immune system:

Individuals gain Nigella sativa seeds or oil as a natural medicine to improve their health and avoid colds and Asthama. Several studies have linked Nigella sativa and TQ to immune system activation (Garah et al., 2012; Abdelzaher et al., 2011; Haq et al., 1995). El-Kadi et al. (1986) demonstrated that the effects of Nigella sativa on the immune response, finding that the herb had immuno-potentiating activities in human T-cells in vitro. This was corroborated by Haq et al. (1995), who discovered that Nigella sativa seeds cause T cells to release interleukin-3 and IL-1B. Other research has found that α-linolenic acid, steridonic acid, and other chemicals found in the herb seed improve immune system, notably in T cells (Swamy S and Tan B. 2000; Yehuda S and Carasso RL.1993). Nigella sativa raises the activity of natural killer cells while suppressing T helper cells (Abdel-Zaher et al., 2011). Nigella sativa also has an anti-inflammation and pro-inflammatory cytokine discharge regulating effect. Nigella sativa also affects Th1/Th2 balance and decreases Th2 levels (Işık et al., 2010). The influences of Nigella sativa on immuno-hematological indicators in rainbow trout were investigated in another study, and the results revealed a considerable rising in serum immunoglobulin contents in the therapeutic group (Gholamnezhad et al., 2014). In addition, the immunomodulating properties of a range of medicinal plants, including N. sativa, were tested in BALB/c mice. The findings revealed that N. sativa has an immunoreactive impact and may have treated effects in the protection of opportunistic contagions as well as supportive therapy in neoplastic diseases (Dorucu et al., 2009).

Reproductive system effect:

The reproductive organs' weight, as well as the motility and amount of sperm in the caudal epididymis and testicular ducts, are all increased by Nigella sativa seeds. The amount of primary and secondary spermatocytes increases during spermatogenesis. Furthermore, the number of pregnant female rats is increasing (Makhled et al., 2009; Al-Saidi et al., 2009). Infertile men have also been studied for other positive activities of Nigella sativa on Leydig cells, reproductive systems,

and sex hormones (Awad E and Binder B. 2005). Furthermore, when Nigella sativa oil is compared to nicotine on sperm and testes parameters in rats, nicotine reduces the motility and morphology of normal and living sperm, as well as affecting testes tissues, but Nigella sativa oil raises sperm quality and exhibits better testes characteristics of histology (Al- Sa'aidi et al., 2009). In male rats, when comparing the lower and upper dose groups to the control group, the impacts of N. sativa extract on fertility possibility, pituitary-testicular axis hormones, and testosterone showed an important difference in testes and epididymis weight, ESR, sperm count, LH, serum testosterone concentration, DSP and fertility indicator (Ng et al., 2014).

Table 7: The anti-infertility characteristics of Nigella sativa and its components, as well as their effects on neurological, cardiovascular, and respiratory diseases (adopted from, Zahra et al., 2016).

Plant extract & doses	Study case	Effects	References
Effects on the nervous system			
Seeds of N. sativa (500 mg twice a day for 9 weeks)	Volunteers who are over the age of 65 are needed.	All neuropsychological tests have improved.	(Bin Sayeed et al., 2014)
4 weeks of N. sativa oil	Children with uncontrollable epilepsy	Seizure frequency, intensity, or oxidative stress markers did not vary significantly (TAC and MDA)	(Shawki et al., 2013)
(1 mg/kg) thymoquinone	Children with uncontrollable epilepsy	Anti-epileptic properties	(Akhondian et al., 2011)
Effects on the cardiovascular system			
2 months of N. sativa seed extract	Patient suffers from mild hypertension.	↓ DBP and SBP; ↓ LDL and TC	(Dehkordi and Kamkhah, 2008)

(100/200 mg twice a day)			
Seeds of Nigella sativa	Patients over the age of eighteen	There was no discernible reduction in serum lipids, blood sugar, blood pressure, or body weight.	(Qidwai et al., 2009)
8 weeks of N. sativa oil (2.5 ml twice a day)	Volunteers who are in good health	↓ DBP and SBP	(Fallah Huseini et al., 2013)
Effects on the lungs			
Immunotherapy using N. sativa powder	Mild asthmatic children	There is no influence on the number of Th17 cells. Clinical symptoms have improved.	(Kardani et al., 2013)
Immunotherapy using N. sativa powder	Mild asthmatic children	CD4+CD25+ foxp3+Treg and CD4+ IL-10+Treg had no effect. Clinical symptoms are becoming better.	(Susanti et al., 2013)
aqueous extract that has been boiled	Patients with asthma	All asthmatic symptoms, asthma symptom/week, chest wheeze, and PFT levels have improved. Inhaler and oral -agonists, oral corticosteroid, oral theophylline, and inhaler corticosteroid usage are all being reduced.	(Boskabady et al., 2007)
aqueous extract that has been boiled	Victims of chemical warfare	Inhaler and oral β-agonists, as well as oral corticosteroids, were used less frequently in the study group.	(Boskabady and Farhadi, 2008)
aqueous extract that has been boiled	Patients with asthma	Less effective than theophylline in terms of FEV1, PEF, MMEF, MEF75, MEF50, MEF25, and sGaw.	(Boskabady Et al., 2010)
Oil of N. sativa	Patients with asthma	PEFR improvement PI decrease	(Ahmad et al., 2010)
Infertility-preventative characteristics			

2 months of N. sativa oil (5 ml/12 h)	Men who are unable to conceive	Improves sperm count, motility, morphology, and volume of sperm, as well as pH and roundness of cells.	(Kolahdooz Et al., 2014)

Effect on Blood:

When comparing total time of blood clotting, plasma clotting, and kaolin-cephalin clotting in male rabbits, petroleum ether extract from Nigella sativa was found to reduce total time of blood clotting, plasma clotting, and kaolin-cephalin clotting. Additionally, rats showed a considerable reduction in bleeding time. Although there were no notable changes on prothrombin or thrombin time, the partial time of thromboplastin was reduced while the time of euglobulin was extended (Ghoneim et al., 1982).

Infertility effect:

The traditional treatment of Nigella sativa for infertility was established. About 68 infertile males with defective sperm activity were selected based on presence criteria such as aberrant sperm morphology (< 30%), the count of sperm under 20×106/ml, or category A and B motility < 25% and 50%, respectively. Persons were randomly allocated to one of two groups: Nigella sativa oil (n = 34) or placebo (n = 34) and were given the medicine twice a day for two months. At the start and completion of the trial, the major outcomes were sperm count, semen volume, pH, morphology and motility and round cells. The results revealed that ingesting 5 ml of Nigella sativa oil (60 mg/kg/day) for two months enhanced the a count of sperm, appearance, locomotion, pH, the volume of semen, and round cells much more than the control group, with no negative activities. This study determined and presented the fatty acid constituents of the fixed oil and the chemical structure of the volatile oil constituents of the herbal oil. TQ, unsaturated fatty acid, vitamin E, and selenium levels in Nigella sativa oil perhaps accountable for the herb's antioxidant properties (Kolahdooz et al., 2014).

Conclusion:

Nigella sativa seeds and their extracts are utilized as a natural cure for a variety of ailments all over the world. The constituents of Nigella sativa particularly TQ, have a wide range of health benefits. Studies show that the plant has anti-inflammatory, antidiabetic, anticancer, antimicrobial, antiparasitic, antibacterial, antioxidant, and hepato-renal protective properties, as well as antidiabetic, anticancer, antimicrobial, antiparasitic, antibacterial, and antioxidant properties. Moreover, different studies have looked into its impact on the digestive system, immune system, and nervous system. Further research on the plant's composition and therapeutic capabilities, as well as other unknown traits, is needed before it may be employed as a plant-derived medicine to treat a variety of ailments.

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