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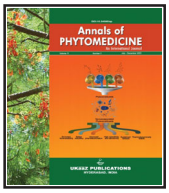

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Traditional and modern usage of *Nigella sativa* L. (Black cumin)

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Abstract

Since ancient times, herbs have been used as natural treatments and form the foundation of the Indian medical system. Most of the world's population relies on herbal therapy for health-related issues. *Nigella sativa* L., commonly referred to as black cumin, has been widely used as a remedy for many ailments. Seeds and oil of black cumin are used in food as well as medicine and have a long tradition of folklore applications in Indian traditional medicine systems (Unani and Ayurveda), Chinese medicine, Malay medicine, Arabic, and Islamic medicine. It consists of several bioactive substances, including carvacrol, thymoquinone, p-cymene, thymol, thymohydroquinone, dithymoquinone, 4-terpineol, t-anethole, sesquiterpene longifolene, and a-pinene. Among them, TQ plays a crucial role in the treatment of various diseases. Comprehensive research on the *N. sativa* plant suggests various biological activities, including antibacterial, bronchodilator, digestive, antioxidant, antidiabetic, antiglycation, diuretic, liver tonic, anti-inflammatory, renal protective, appetite stimulant, antihypertensive, analgesic antimicrobial, anticancer, immunomodulator, and hepatoprotective. The present study focuses on highlighting the traditional and modern medicinal significance of *N. sativa*.

1. Introduction

A healthy diet and average life expectancy are closely related, so the ideas of “nutraceuticals” and “functional foods” have gained popularity among those who are concerned about their health in recent decades. Nutritionists, dietitians, doctors, food scientists, and pharmaceutical companies have all expressed interest in these ideas. Extensive studies are being done to discover traditional foods with potential health advantages as the worldwide market for functional meals grows. Herbs and spices are primarily employed as preservatives and flavoring additives and are among the diverse functional foods that include a wealth of bio-functional molecules (El-Sayed and Youssef, 2019). Traditional herbal medicine has always been used, despite all the tremendous developments in modern medicine. Plants have organized the fundamental principles of complex conventional medical systems, giving rise to some significant medications that are still used today (Sofowora, 2013). Although, many plants are used today, we do not fully understand their potential mechanisms of action, therapeutic qualities, toxicological investigations, or safety evaluations.

One of these plants, *N. sativa*, also known as Kalonji, black seed, black cumin, Love-in-a-Mist, Barakah, Habatut, Sauda, Songz, Jiraka, Krishana, and Sidadanah in different languages, has been widely used in different cultures for many centuries (Ismail and Yaheya, 2009). In addition to being well known for its culinary uses, it has a long history of use in traditional medicine. Albania, Egypt, Greece, India, Iran, Pakistan, Saudi Arabia, Syria, and Turkey cultivate black cumin. It is native to the Indian subcontinent, eastern Mediterranean, northern Africa, and Southwest Asia (Dabeer *et al.*, 2022). In traditional medicine, *N. sativa* has been recommended for a variety of illnesses and disorders like hypertension, anorexia, amenorrhea, paralysis, dermatitis, and bronchitis (Chaudhry *et al.*, 2020). These conventional applications of *N. sativa* are largely attributable to its various medicinal benefits like antidiabetic, anti-inflammatory, antihypertensive, antioxidant, antimicrobial, immunomodulatory, cardioprotective, anticancer, neuroprotective, nephroprotective, hepatoprotective, and gastroprotective properties (Yimer *et al.*, 2019).

Thymoquinone (TQ), carvacrol, thymol, thymohydroquinone, nigellidine, nigellicine, and α-hederin are the main compounds in black cumin seed, which are mostly accountable for its therapeutic potential and pharmaceutical advantages (Randhawa and Alghamdi, 2011). Thymoquinone, a significant chemical constituent of *N. sativa* is responsible for most of its medicinal properties (Shad *et al.*, 2021; Balyan *et al.*, 2022). Because black seeds have a low level of toxicity, they are utilized in food as a flavour component in pickles and bread. This review makes an effort to summarize the extensive traditional and modern usage of *N. sativa* into a concise, understandable narrative so that researchers can appreciate the pharmacological properties, effects, and chemical structure of *N. sativa*.

2. *Nigella sativa* L. and its constituents

This miraculous herb has already been used in worldwide folkloric traditional medicine before the development of modern medicine to heal a wide range of illnesses and disorders. Ayurveda, Greek-Roman, Jewish, Malay, Siddha, Tibb-e-Nabawi, and Unani all include it in their well-documented traditional medicinal works (Ahmad *et al.*, 2013). Numerous active substances have been isolated, recognized, and reported from various black seed types. Since ancient times,

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people have used *N. sativa* oil and seeds extensively to treat a wide range of illnesses.

2.1 Botanical description

Nigella sativa L. is a native angiosperm from Asia and the Middle East of the Ranunculaceae family (Taleuzzaman *et al.*, 2022). It is a branched and erect herb with alternate leaves, terminal white flowers, and capsule-like fruits (Figure 1). The leaves of this plant are tapering green, while the flowers are usually white, pink, yellow, pale purple, green, or blue, with 5-10 petals. Seeds are small, black, rugulose-tubercular, dicotyledonous, and trigonous. Fruit is an enormous, inflated capsule made up of three to seven united follicles, each of which has many black triangular seeds, with a length ranging from 2.5-3.5 mm and a width of 1.5-2 mm (Goreja, 2003). This plant possesses a wide range of pharmacological effects like antimicrobial, nephroprotection, analgesic, antidiabetic, anti-inflammatory, hepatoprotection, bronchodilation, and contraceptive effects (Padhye *et al.*, 2008).

Figure 1: *Nigella sativa* L. plant, flower, and seeds (Adapted from Sharma *et al.*, 2009).

2.2 *Nigella sativa* L. in different languages

The common names for *N. sativa* differ from language-to-language and country-to-country. *N. sativa* seed is known as kalonji (Urdu), Kalonji, Kalajira, Mangraila (Hindi), Habbat-albarakah or habbatus-sauda (Arabic), Heizhongcao (Chinese), Black caraway, black cumin, fennel flower, black coriander (English), Mangrela, Kala Zeera (Bengali), Kalaunji Jirum, Kadujeeroo (Gujarati), Karijirige (Kannada), Karinchirakam (Malayalam), Tukhme Gandana (Kashmiri), Kalerjire, Kalaunji-jire (Marathi), Karunjarakam, Karunjiragam (Tamil), Kavanji (Punjabi), Peeajila Kara, Nalla Jilakara (Telugu), Susavi, Sthula Jiraka, Krishna jeeraka, Karvi, Upakuncika, (Sanskrit), Kalodi (Sindhi) Sheenon, Sino, Kamaazaruus (Unani), Schwarzkummel (German), Carvi (French), Ketzah (Hebrew), Siyahdaneh (Persian), Chernushka (Russian), Krishnajira (Sanskrit), and Kara çörekotu or siyahkimyon (Turkish) (Nandkarni, 1982; Anonymous, 2007; Anonymous, 1992; Anonymous, 1987; Das and Kumar, 2005; Khare, 2007; Nandkarni, 2005; Pullaiah, 2006).

2.3 Chemical constituents of *N. sativa*

The most intriguing plant portion of *N. sativa*, *i.e.*, the seeds, is composed of alkaloids, terpenes, and phenolic chemicals in terms of their phytochemical compounds, as shown in Figure 2. The most significant active substances include dithymoquinone, thymoquinone (30%-48%), thymohydroquinone, p-cymene (7%-15%), carvacrol (6%-12%), 4-terpineol (2%-7%), sesquiterpene longifolene (1%-8%), t-anethol (1%-4%), α-pinene, and thymol, among others (Sahak *et al.*, 2021). The bioactive phytoconstituents of *N. sativa*, which include several secondary metabolites, have been classified into distinct chemical classes, which are as follows:

2.3.1 Fixed oil

Numerous studies on the oil of black cumin seeds revealed that the principal fatty acids present in it are linoleic acid (50-60%), oleic acid (20%), myristic acid (30%), and palmitic acid (12.5%) (Ali *et al.*, 2020).

2.3.2 Volatile oil

The volatile oil from black cumin seeds, ranging from 0.5% to 1.5%, had high abundances of thymoquinone (30%-48%), and other phenolic derivatives for example, carvacrol, dithymoquinone (nigellone), p-cymene, thymohydroquinone, t-anethol, α-pinene and thymol (El-Naggar *et al.,* 2017).

2.3.3 Alkaloids

Alkaloids in plants can serve as a source for the development of new drugs. The alkaloids found in *N. sativa* seeds are nigellimine, nigellimine-N-oxide, nigericin, and nigellidine-4-O-sulfite. In addition, the black cumin seeds were found to contain nigellidine, methyl nigellidine, higenamine, and nigeglanine too. Among these alkaloids,

methyl nigellidine, nigelloside, and nigeglanoside serve as markers for species differentiation (Yun *et al.*, 2014).

2.3.4 Saponins

The heterogeneous class of glycosides known as saponins consists of one or more hydrophilic moieties coupled with a lipophilic triterpene or steroid derivative. The specific saponins in *Nigella* seeds are particularly triterpene saponins. Other related saponins to alpha-hederin include: 3-O-[d-xylopyranosyl-(1 → 3) -α-l-rhamnopyranosyl-(1 → 2)-α-l-arabinpyranosyl] -28-O-[-α-l-rhamnopyranosyl-(1 → 4) -β-d-glucopyranosyl-(1 → 6) -β-d-glucopyranosyl] 3-O-[d-xylopyranosyl-(1-3)]hederagenin, -α-l-rhamnopyranosyl-(1 → 2)-α-l-arabinpyranosyl 28-O-d-glucopyranosyl hederagenin, 3-O-[l-rhamnopyranosyl-(12)-l-arabinpyranosyl] -28-O-[β-d-glucopyranosyl-(1 → 6)-β-d-glucopyranosyl] 3-O-[d-xylopyranosyl-(1-3)]hederagenin, -α-l-rhamnopyranosyl-(1 → 2)-α-l-arabinpyranosyl -28-O-[-α-l-rhamnopyranosyl-(1 → 4)-β-d-glucopyranosyl-(1 → 6)-β-d-glucopyranosyl] Hederagenin (Boubertakh *et al.*, 2013).

2.3.5 Phenolic compounds

Small molecules that include at least one phenol unit are known as phenolic compounds. Some of the phenols that have been discovered in the *N. sativa* seeds include quercetin, kaempferol, salicylic acid, rutin, methyl-4-hydroxybenzoate, pyrogallol, and p-hydroxybenzoic acid (Xin *et al.*, 2008).

2.3.6 Miscellaneous compounds

Other identified terpene compounds include phytosterols like β-sitosterol, 5-avenasterol, and stanols like cycloartenol. Other triterpenes include butyrospermol and β-amyrin as well as α-tocopherol, β-carotene and γ-tocopherol (Ramadan and Mörsel, 2002; Ijaz *et al.*, 2017).

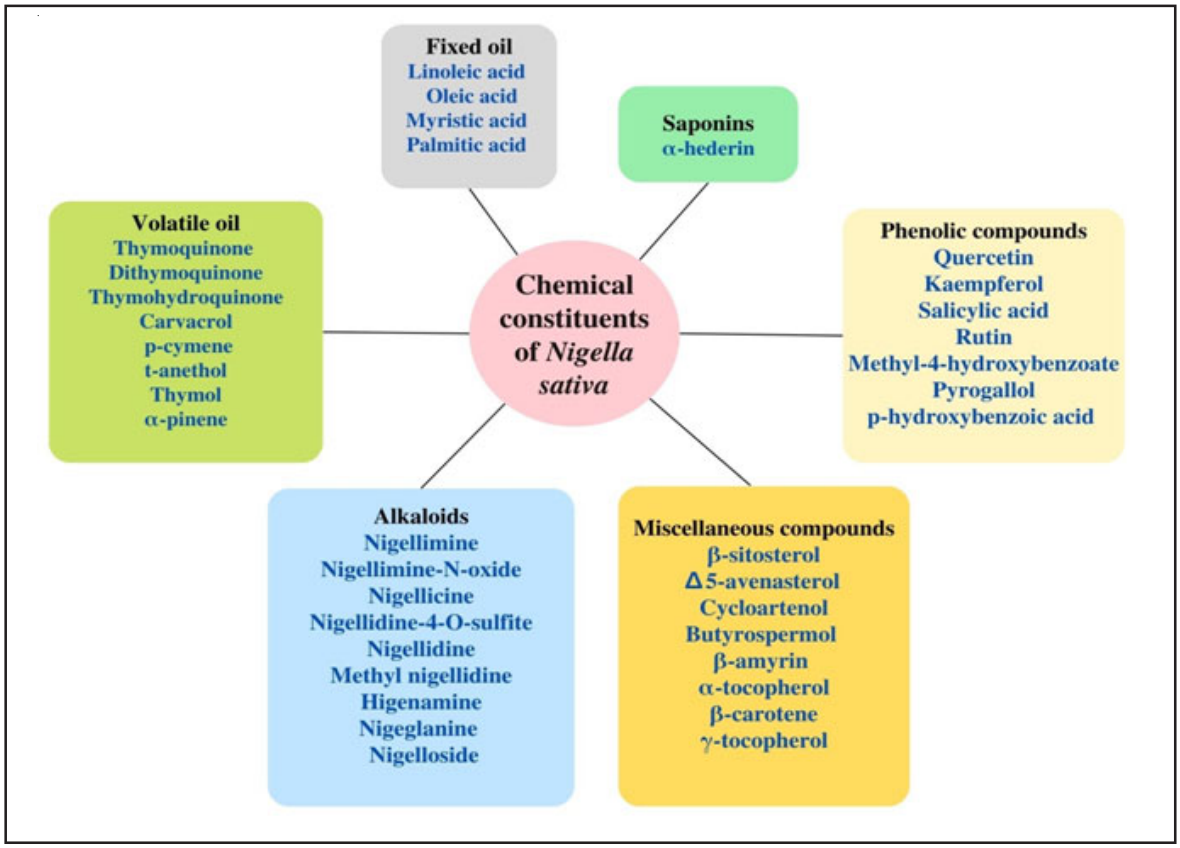

Figure 2: Chemical constituents of *Nigella sativa* L. seeds.

3. Traditional usage of *N. sativa* in different cultures

More than 2000 years ago, *N. sativa* seeds were used for the first time in Middle Eastern traditional medicine to treat a range of diseasesas shown in Table 2. Over the last decade, there has been an increase in the use of traditional medicine worldwide. According to evidence, traditional medicine is becoming more common in nations where allopathic medicine predominates in the healthcare system, rather than just being utilized to treat the poor (Kala, 2017). Traditional medicine is described by the World Health Organization (WHO) as the "total of knowledge, skills, and practices based on the theories, beliefs, and experiences indigenous to different cultures, whether explicable or not, used in the maintenance of health as well as in the prevention, diagnosis, improvement, or treatment of physical and mental illness" (WHO, 2000). Because they are impacted by things like culture, history, personal attitudes, and philosophy, traditional medical practices differ considerably from country to country and area to region.The plant has been extensively discussed and prescribed for a variety of ailments and as a general tonic in Tibb-e-Nabvi (Sarwar and Latif, 2015), Unani medicines (Zaidi *et al.*, 2015), African and Eastern medicines (Meddah *et al.*, 2009), Arabic, Chinese, and Ayurvedic medicines (Rehmani *et al.*, 2014).

N. sativa seeds have been used in traditional Arabic herbal medicine for the treatment of various illnesses like Zeeq Un Nafs (asthma), Ziabetus (diabetes), Siman-e-Murit (obesity), Sartan (cancer), Sual Muzmin (chronic cough), Zagatuddam Qawi (hypertension), Tayammum-e-Dam (dyslipidemia), and others. Early herbalists referred to *N. sativa* as "the herb from heaven" and characterized it as a miraculous plant. Because of its multiple applications, *Nigella sativa* has been given the Arabic name "Habbatul barakah," which means the seed of blessing. Additionally, it is mentioned as a curative black seed in the "Holy Bible" and is also known as Melanthion by Dioscorides and Hippocrates (Worthen *et al.*, 1998). Black seed oil, found in Egypt's Pharaoh Tutankhamen tomb, played an important role in ancient Egyptian practices (Corneanu and Corneanu, 2011). The fact that Queen Nefertiti, who was admired for her flawless complexion, was a devoted consumer of NS oil, has made it known as a beauty secret from the dawn of time.

Archaeologists also discovered black seeds combined with honey and beeswax in a pilgrim flask from the Old Hittite Period level of BoyalHöyük (Mound) in north-central Turkey, dating from around 1650 BC. Citing *N. sativa* as a heavenly herb that can be used to treat cases of "ghost possession," An old Hittite pilgrim's flask from 1650 BCE was found at the Anatolian BoyalHöyük archaeological site in Corum, Turkey. It contained a stash of *N. sativa* seeds mixed with bee propolis and beeswax. The use of *N. sativa*in this region can be traced back to this (Salih *et al.*, 2009).Cuneiform tablets discovered in ancient Assyria describe it as a method of fumigation using a concoction produced from black cumin seed (Thompson, 1949; Heiss *et al.*, 2012).

Avicenna, also known as Ibn Sina (in Persian) a renowned physician from the 10th century, advised using *Nigella* seeds to boost the body's energy and aid in the recovery from exhaustion and depression in his book "The Canon of Medicine." He also advised using it to treat fungus, wounds, fever, skin conditions, worms, and parasites, as well as to protect against the stings and bites of venomous animals. In his renowned medical treatise "Canon of Medicine," which is regarded as a milestone in human medicinal history and was utilized as the primary medical text until the 17th century in Europe. He claimed in his works that *N. sativa* has preventative and therapeutic properties because it boosts the body's energy and aids in the recovery from exhaustion or dejection (Warrier and Nambiar, 2004).

The usage of *N. sativa* seeds as currency in Levanto-Aegean trade during the Bronze Age has also been confirmed. These seeds were discovered in Canaanite amphorae jars at the ancient shipwreck site of Uluburun, which is located off the Mediterranean coast in modern-day Turkey (1350 BCE-1300 BCE) (Pulak, 2010). Excavation sites in Egypt's Eastern Desert have revealed cultivated black cumin ruminants in the form of carbonized and dried seeds have been found (Van der Veen, 2007).

For the followers of Prophet Muhammad, its long-lasting usage is primarily due to the authentic prophetic statement that "Hold on to this black seed, as it has a remedy for every illness except death"(Bhatti *et al.*, 2013). In addition, numerous Arab thinkers also emphasized the value of these seeds in the tradition of "Prophetic medicine" and its therapeutic benefits.

It has been used for thousands of years in Northern Africa to cure headaches, asthma, bronchitis, rheumatism, fever, cough, influenza, and eczema. The *N. sativa* seed crude extract and its refined components have been linked to several medicinal effects (Al-Ghamdi, 2001; Ali and Blunden, 2003; Ahmed *et al.*, 2015).

Table 1: Uses of *N. sativa* in the treatment of various diseases

S.No.	Model/system	Part of the plant used	Disease	Effect observed	References
1.	Rats	Thymoquinone	Hypertension	Anti-hypertensive effects	Enayatfard *et al*., 2018
2.	Rats	Seed extract	Hyperglycemia, hyperlipidemia, and vasoreactivity	ameliorates the induced changes of VCAM-1, eNOS, and LOX-1 mRNA expressions	Abbasnezhad *et al*., 2019
3.	Rats	Seeds	Diabetes	enhancing gene expressions of catalase (CAT), glutathione-s-transferase (GST) and B-cell CLL/ lymphoma 2(Bcl-2)	Althnaian *et al*., 2019
4.	Humans	Seed	Diabetes	reducing MDA as well as NO among people with T2D	Hadi *et al*., 2018
5.	Rats	Ethanol extract	Hepatocellular carcinoma	Anticancer effects	Bumidin *et al*., 2018
6.	Rats	Ethanol extract	Asthma	Histamine production decrease	Ikhsan *et al*., 2018
7.	Essential oil and TQ	Carcinogenic bacteria	Bacterial toxicity	Antimicrobial and cytotoxic activity	Harzallah *et al*., 2011
8.	Seed oil	Humans	Hepatitis C	Decreased oxidative stress and viral load	Barakat *et al*., 2013
9.	Polyphenols	Rats/mice	Inflammation	Analgesic and anti-inflammatory responses	Ghannadi *et al*., 2005
10.	Seed oil	Humans	Fatty liver (non-alcoholic)	Reduced hepatic steatosis and improve liver performance	Khonche *et al*., 2018
11.	Oil capsule	Humans	Menstrual irregularities	Significant improvement in menstrual cycle	Naeimi *et al*., 2020
12.	Alcoholic extracts	Rats	Liver disorders	Hepato-protection	Hosseini *et al*., 2020

4. Potential health benefits and modern usage of *N. sativa*

N. sativa has a long history of folklore use across civilizations, where it has been hailed as a "wonder remedy" for its capacity to treat a wide range of illnesses and aid the body's natural healing process (Ahmad *et al.*, 2013). NS has been cited as a renowned healer for a variety of illnesses in ancient literature and historical archives.

Figure 3: Potential health benefits of *N. sativa* (Adapted from Balyan *et al.*, 2021).

4.1 Cardiovascular effect

The term "cardiovascular disease" (CVD) refers to several conditions affecting the heart and blood vessels. There are many different causes of cardiovascular disorders. Among the leading causes of CVD are excessive blood pressure, atherosclerosis, and high LDL and cholesterol levels for the prevention and treatment of cardiovascular disorders, *N. sativa* offers a great deal of potential (Shakeri *et al.*, 2018). According to research on how TQ consumption of rabbits affected their serum lipid profile, it has been reported that TQ significantly decreased total cholesterol, triglyceride, low-density lipoprotein (LDL), and thiobarbituric acid-reactive substance concentrations while significantly increasing high-density lipoprotein (HDL) cholesterol concentrations (Nader *et al.*, 2010). Also, it was noticed that continuous therapy with *N. sativa* fixed oil had a positive impact on rat blood homeostasis. While the haematocrit and haemoglobin concentrations increased dramatically, the levels of serum lipids, glucose, leukocytes, and platelets were significantly reduced. The administration of the oil (800 mg/kg) for four weeks resulted in a significant decrease in serum total cholesterol, triglycerides, and LDL as well as a significant increase in serum HDL levels (El-Dakhakhny *et al.*, 2000). *N. sativa* oil demonstrated a favourable effect on the serum lipid pattern. In human investigations, promising outcomes were also noted. In hypercholesterolemic patients, it was found that a daily intake of 1 g of black cumin seed powder for two months would result in significant drops in triglyceride and LDL cholesterol levels, as well as an increase in HDL cholesterol levels (Zaoui *et al.*, 2002). Similar findings were also made in another study on hypercholesterolemic individuals, where it was discovered that *N. sativa* ingestion was linked to a reduction in bad cholesterol, helping to normalize patients' lipid profiles and averting heart problems (Tasawar *et al.*, 2011). It was thought that several components, including phenols, flavonoids, sterols, and TQ, worked together to affect the lipid profile of black cumin rather than any single one of them.

4.2 Antidiabetic effect

N. sativa seeds and their essential oil, which are components of traditional remedies, have enormous potential as antidiabetic

substances. Plant extracts have been proven to improve the course of diabetes in either streptozotocin-induced or alloxan-induced diabetic rats or mice. The mechanism involves regulating blood lipid profiles (Bensiameur-Touati *et al.*, 2017), reducing oxidative stress (Widodo *et al.*, 2016), improving endothelial dysfunction (Abbasnezhad *et al.*, 2019), and enhancing tissue regeneration and wound healing (Nourbar *et al.*, 2019). Both the aqueous extract and oil of *N. sativa* are effective at regulating insulin response and serum glucose levels. The main ingredient thought to be responsible for the herb's antidiabetic properties is the TQ (Younus, 2018). It was discovered that supplementing *N. sativa* with L-carnitine and α-lipoic acid increases its efficacy in treating diabetic patients. In STZ-induced diabetic rats, it was demonstrated that combining all three of them, had a significant impact on glucose metabolism, and its ingestion was observed to increase insulin production and C-peptide levels (Salama *et al.*, 2011).

4.3 Antiglycating effect

Glycation refers to a complicated set of processes wherein carbohydrates and biomolecules like lipids, DNA, or proteins are linked together. Nevertheless, the antiglycation potential of *N. sativa* is not very well understood. According to the researchers, it was discovered that the antioxidant and antiglycation capabilities of the plant were correlated. Researchers have also reported the concentration-dependent activity of *N. sativa* against early and late advanced glycation products (Zafar *et al.*, 2013). In 2011, Losso and his colleagues (2011) identified the *N. sativa* plant's ability to block several glycation stages. As more data mounts, it appears that *N. sativa*-incubated samples produced considerably less AGE than untreated samples (Ahmad, 2013). A lot of studies indicate that TQ is crucial to the inhibitory potential of *N. sativa*. *N. sativa* stops the oxidation of glucose, which limits the production of ketamine linked to the development of AGE (Mahmood *et al.*, 2013). According to another report, considerable inhibition was allegedly observed with the addition of protein (bovine serum albumin) and sugar (fructose) to *N. sativa* plant extract (Pandey *et al,* 2018). Additionally, they discovered that the aqueous extract of black cumin seeds showed a greater capacity to inhibit AGE than their methanolic extract. Kumar and Ali (2019) reported the effectiveness of TQ in the inhibition of glycation and aggregation. They showed that both the early, intermediate, and late stages of AGEs' production were strongly inhibited. The results presented in a recent study by Rubab *et al.* (2021) also showed that the black cumin seed extracts (aqueous and methanolic) possess the substantial antiglycation potential and the inhibitory effect was more prominent at the late glycation stage.

4.4 Anticancer properties

About 8.2 million deaths worldwide were attributed to cancer, and that number is expected to increase to 22 million over the next 20 years, making it the second-leading cause of death globally. Modern research on *N. sativa* ability to combat cancer may have begun when researchers noticed an increase in natural killer cell activity in patients receiving a multimodal immunotherapy regimen that included this plant as one of its components (Peng *et al.*, 2013). Studies on cell lines have revealed that the injection of seed oil, nanoemulsions, and alcoholic seed extracts from *N. sativa* significantly decreased cell viability, changed the shape of the cells, and triggered apoptotic cell death (Salehi *et al.*, 2021). Regarding *in vivo* studies, supplementation of various doses of ethanolic extract of *N. sativa* (150, 250, and 350 mg/kg), silymarin (100 mg/kg), and thymoquinone (20 mg/kg), daily prevented the proliferation of hepatocellular carcinoma induced by diethyl nitrosamine through several pathways like: Increase in antioxidant enzyme levels, deactivation of EGFR/ERK1/2 signalling, suppression of cell proliferation, reduction in p-EGFR and p-ERK1/2, reduction in alpha-fetoprotein (AFP) and hepatic enzymes, and downregulation of target genes (c-fos, PCNA, and Bcl-2) (Shahin *et al.*, 2018).

4.5 Antiobesity effect

In vivo and *in vitro* investigations on *N. sativa* demonstrated the anti-obesity potential of its oil, fruit, and seed extracts. The following mechanisms are involved in this effect: (a) the inhibition of digestive enzymes, *i.e.*, pancreatic α-amylase and α-glucosidase (Sellami *et al.*, 2016); (b) proinflammatory cytokine production in pre-adipocytes (Namazi *et al.*, 2018); and (c) weight loss by favourably influencing the uncoupling protein-1 (UCP-1), the index protein of brown adipose tissue (Bordoni *et al.*, 2019).

4.6 Immunomodulatory activity

Since 1959, various investigations on the pharmacological efficacy of *N. sativa* and its main bioactive components have been studied, providing evidence of its immunomodulatory action. Numerous *in vivo* and *in vitro* studies support the use of *N. sativa* in modifying the humoral and cellular immune response in a variety of illness situations (Khan *et al.*, 2022). In an experiment with guinea pigs sensitized by ovalbumin, Boskabady *et al.* (2011) found that *N. sativa* extract can reduce lung inflammation. In mice's intestines and plasma, the extracts demonstrated an anti-inflammatory effect by reducing the number of mast cells and mast cell protease-1, respectively (Duncker *et al.*, 2012). In a similar study, rats with arthritis caused by collagen injection were given thymoquinone, which was shown to reduce inflammatory mediators and boost the immune system (Ahmad *et al.*, 2013). Rats have been used as models to study the effectiveness of *N. sativa* in the treatment of hyperoxia-induced lung damage (Tayman *et al.*, 2012). Both trials showed that the use of *N. sativa* essential oils significantly lessened the severity of lung damage.

4.7 Neuroprotection effect

Recent reviews have examined the potential of phytoconstituentsof *N. sativa* plant as neuropharmacological agents that support learning and memory (Sahak *et al.*, 2016). For 14 days, 1 ml/kg of oil of *N. sativa* in rats reduced NO and ROS levels, improved acetylcholinesterase (AChE) activities, and increased neurogenic proteins. It also decreased levels of neuro-cognitive markers in rats exposed to chlorpyrifos (Oskouei *et al.*, 2018). The extracts (hydroalcoholic) of *N. sativa* seeds (200 and 400 mg/kg) for five days increased antioxidant effects in the rat brain and had positive effects on learning and memory deficits (Behesti *et al.*, 2015).

4.8 Anti-inflammatory and analgesic properties

The primary molecule responsible for black cumin's anti-inflammatory properties is TQ. TQ down regulated IRF-3 signalling pathways, increased the autophosphorylation of TANK-binding kinase 1 (TBK1), and decreased the mRNA expression of interferons, and in LPS-stimulated murine macrophage-like RAW264.7 cells (Aziz *et al.*, 2018). Hossen *et al.*(2017) also reported that TQ suppressed pro-inflammatory factors like IL-1, IL-6, nitric oxide (NO), TNF,

cyclooxygenase (COX) 2, and nitric oxide synthase (iNOS) through a mechanism involving the suppression of IRAK-linked AP-1 and NF-κB pathways in LPS-stimulated murine macrophage-like RAW 264.7 cells. In another study, it was shown that *N. sativa* oil (NSO) reduced IL-6 and IL-1 levels in low-grade inflammation in human preadipocytes (Bordoni *et al.*, 2019). NSO administration (400 mg/kg) in the paw exudates and sera of rats with carrageenan-induced paw edema significantly decreased the levels of pro-inflammatory cytokines like tumour necrosis factor (TNF), IL-6, and IL-12 (Attia *et al.*, 2016).

4.9 Hepatoprotective effects

One of the main causes of hepatic illness is oxidative stress, which results in lipid peroxidation (Noorbakhsh *et al.*, 2018). However, adding black cumin extract and its bioactives to a diet lowers lipid peroxidation, reduces oxidative stress, lengthens the lifespan of laboratory animals, stimulates cellular antioxidant systems, and increases the CAT, SOD, GPx, and GSH activity levels. Inflammation brought on by chronic hepatitis, hepatotropic viral infections, carcinogen exposure, and cirrhosis are additional possible causes of hepatic illness (Matsuzaki *et al.,* 2007). Studies have shown that toxicants increase the levels of liver apoptotic markers including caspase 12, Bax, cytochrome c, caspase 3, and caspase 9, as well as excessive inflammatory markers like TNF-α, IL-6, TGF-α, NF-κB, and Hs-CRP (Hosseini *et al.*, 2020).

A powerful signalling molecule that is essential for liver health is nitric oxide (NO) (Iwakiri *et al.*, 2015). By modifying the activity of nitrite reductase, *N. sativa* extract and its constituents have been found to lower NO levels, suggesting that itcan protect against NO-mediated hepatic problems (Behesti *et al.*, 2018). When too much fat accumulates in the liver, it leads to fatty liver, often referred to as non-alcoholic steatohepatitis (NASH) or non-alcoholic fatty liver disease (NAFLD) (Benedict and Zhang, 2017). This condition makes liver cirrhosis, or HCC, more likely. In contrast to the placebo group, patients with NAFLD who received 2.5 ml of black cumin seed oil every 12 h for three months saw a significant reduction in aminotransferases, LDL, and blood triglycerides, as well as an increase in HDL levels, while their body mass index, serum creatinine, blood urea nitrogen, and blood cell counts, remained unaffected (Khonche *et al.*, 2019).

4.10 Reproprotective and contraceptive effects

The levels of estrogen, progesterone, and other reproductive hormones, as well as ovarian function in females and the quantity and quality of sperm in males, influence the soundness of the reproductive system. Numerous preclinical and clinical investigations have shown that *N. sativa* seed, notably its oil and primary ingredient TQ, positively alters key fertility indices and, as a result, improves reproductive success (Gholamnezhad *et al.,* 2016). Rats have dramatically increased semen parameters, seminal vesicle development, and testicular spermatogenesis after 45 days of oral administration of *N. sativa* oil (NSO). NSO may directly affect the reproductive cells' and tissues' antioxidant defense mechanisms by increasing the activity of antioxidant enzymes such as catalase, glutathione peroxidase, and superoxide dismutase. In consequence, these putative antioxidant actions reduce the production of lipid peroxidation and ROS in reproductive cells and tissues, which in turn encourage pregnancy and childbirth (Mosbah *et al.*, 2012).

Numerous toxico-pharmacological and clinical studies have reported black cumin's probable function in female reproduction, which is consistent with the impact it has on male reproduction. In 12-week observational research, Latiff and colleagues (2014) examined whether giving perimenopausal Iranian women *N. sativa* powder (1600 mg/day) reduced the severity and frequency of menopausal symptoms or not. A randomized double-blind clinical trial showed that women who received a 500 mg black cumin tablet along with a 250 mg dose of mefenamic acid, an NSAID commonly used to treat mild or moderate pain, reported significantly less postpartum pain than women who received only mefenamic acid (Chananeh *et al.*, 2018).

5. Conclusion

In the Ranunculaceae family, *N. sativa* is a significant medicinal plant with several health advantages and proven therapeutic effects against a variety of illnesses. Since ancient times, the seeds, in extracted forms, in powder form, and their oils, have been utilized to treat many ailments. Thymoquinone, one of its many active components, has been shown in numerous studies to have anticancer, hepato-protective, and antidiabetic properties. The reports in the literature suggest that asthma, analgesia, ulcers, gastritis, obesity, wound healing, hypertension, and cardiovascular problems can all benefit from *N. sativa*. Considering the wide range of therapeutic possibilities, extensive *N. sativa* is recommended for both conventional and contemporary drug systems.

Future perspectives

The main pharmacological characteristics of *N. sativa* and TQ include antioxidant, anti-inflammatory, antiapoptotic, and immuno-modulatory capabilities, which together results in potential health benefits against a variety of illness situations. *N. sativa* and its components can remove a wide range of toxins that are frequently tainted or adulterated in food due to their strong chelating abilities. *N. sativa* and TQ both serve as effective natural antidotes, defending against toxins in various organs like, brain, liver, heart, lung kidney,gastrointestinal tracts, and reproductive system. Additionally, *N. sativa* and TQ may be able to lessen the negative effects of various types of cancer and other human disease-treatment medications. Even though research has mostly focused on the health advantages of black cumin, TQ has frequently been held responsible for the pharmacological effects of the herb. However, other research has revealed significant results on the essential health advantages brought about by other phytoconstituents, including carvacrol, thymol, and thymohydroquinone, indicating that substances other than TQ also merit study.

Black cumin may adhere to the "multidrug, multitarget" idea since it targets numerous cells signalling systems and has pharmacological effects. To gain a thorough understanding of the pharmacological effects of *N. sativa* and TQ, particularly against diseases that are interconnected, such as chronic metabolic diseases. Neuro-degenerative disorders, and cancer, a computational and an integrated system pharmacology approach can be used. In addition to their benefits, *N. sativa* or TQ enhances the biological activity of other substances or natural products when combined with them. This synergy reduces the dosage required for other medications to be administered concurrently and lessens their potential toxicity.

Despite substantial advancements in the pharmacological effects of *N. sativa* seeds, the therapeutic use of this traditional medication is

still a long way off. TQ has a low bioavailability, which restricts its therapeutic usage. However, there are ways to increase bioavailability, such as by purposefully altering the structure of TQ without impairing its biological function. To increase their absorption and pharmacological effects, *N. sativa* and TQ were synthesized as nanoparticles in several recent investigations. However, because most ofthe research was done at the preclinical level, a human study must be conducted to apply the findings in the clinic. Although, *N. sativa* and TQ exhibit little to no toxicity; most of this knowledge was derived from preclinical investigations. A thorough human trial is necessary to validate the toxicological and pharmacological profiles for potential clinical use.

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Conflict of interest

The authors declare no conflicts of interest relevant to this artic

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