



Review Article

Novel positioning of *Nigella sativa* L. (Black seed) from farm to pharma indexed in pharmacopeia

Afreen Usmani¹, Rania I.M. Almoselhy^{2*}

¹MESCO Institute of Pharmacy, Uttar Pradesh, India

²Oils and Fats Research Department - Food Technology Research Institute - Agricultural Research Center, Giza, Egypt



ARTICLE INFO

Article history:

Received 10-12-2023

Accepted 20-01-2024

Available online 01-02-2024

Keywords:

Nigella sativa L

Black seed

Black cumin

Medicinal plants

Pharmacopeia

Herbal monograph

Egyptian Drug Authority (EDA)

Traditional medicine

Therapeutic nutrition 1

ABSTRACT

The current study examines the regulatory status and inclusion of *Nigella sativa* L. (*N. sativa*) in pharmacopeias across diverse regions. The regulatory landscape varies globally, with some countries recognizing it as a traditional medicine in pharmacopeias, while others impose restrictions due to safety and efficacy concerns. The lack of standardized guidelines complicates its status, ranging from dietary supplement to traditional herbal medicine in different regions. A pivotal shift is observed in the Egyptian Herbal Monograph Volume 3, marking Black Seed's evolution from traditional medicinal use to a recognized pharmaceutical preparation in the pharmacopeia. This transition signifies a move towards evidence-based medicine, emphasizing rigorous scientific scrutiny and standardization. The integration of Black Seed underscores growing recognition of its efficacy and safety, transforming it into a pharmaceutical product and consolidating its position in mainstream healthcare. The inclusion not only enhances patient accessibility but also instills confidence among healthcare practitioners, solidifying Black Seed as a trusted therapeutic agent. The debate around *N. sativa*'s inclusion continues, with traditional medicine systems endorsing its value, while modern pharmacopeias grapple with standardization and quality control. *N. sativa* emerges as a promising natural resource, necessitating comprehensive documentation for its prospective inclusion in evidence-based healthcare practices and official guidelines.

This is an Open Access (OA) journal, and articles are distributed under the terms of the [Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License](https://creativecommons.org/licenses/by-nc-sa/4.0/), which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: reprint@ipinnovative.com

1. Introduction

Nigella sativa L. (*N. sativa*), also known as black cumin or black seeds, is an annual flowering plant of the Ranunculaceae family. It is characterized by its delicate pale blue and white flowers and small, angular black seeds. The seeds of *N. sativa* are the most commonly used part of the plant and are known for their strong aromatic fragrance.¹⁻⁴ The chemical profile of *N. sativa* seeds is quite complex. It has been widely used in traditional medical systems such as Unani, Ayurveda, and Siddha. They contain various bioactive compounds such as thymoquinone, nigellidine,

nigellimine, dithymoquinone, thymohydroquinone, and thymol. The main active component responsible for its pharmacological properties is thymoquinone, found in the essential oil. The plant has a low degree of toxicity and has been used in food, pharmaceutical, and cosmetic industries.^{5,6}

These seeds have a significant historical and cultural significance, with documented use in various civilizations throughout history. They have been used as a traditional remedy for various ailments and as a culinary spice in many cultures:

1. *Ancient Egypt*: *N. sativa* seeds were found in the tomb of King Tutankhamun, emphasizing their historical use in ancient Egypt. They were used for culinary

* Corresponding author.

E-mail address: rania_almoselhy@outlook.com (R. I. M. Almoselhy).

purposes and were also recognized for their medicinal properties.

2. *Traditional Ayurveda*: In traditional Indian medicine, known as Ayurveda, *N. sativa* seeds were used to treat various ailments, including digestive issues, respiratory conditions, and skin disorders.
3. *Traditional Chinese Medicine*: These seeds have a history of use in traditional Chinese medicine, where they were employed for their anti-inflammatory, diuretic, and digestive properties.
4. *Greco-Roman Civilization*: *N. sativa* seeds were also recognized in Greco-Roman civilization for their medicinal properties, with references in the works of Dioscorides, a renowned Greek physician and botanist.
5. *Islamic Medicine*: *N. sativa* seeds have been extensively used in traditional Islamic medicine for various therapeutic purposes. They are mentioned in the Hadith (sayings of Prophet Muhammad) as a remedy for a range of ailments.
6. *Contemporary Research*: In recent years, there has been a growing interest in the scientific community to study the potential health benefits of *N. sativa* seeds. Research has focused on their antioxidant, anti-inflammatory, and antimicrobial properties, as well as their potential role in the management of various chronic diseases.⁷⁻⁹

2. Plant Profile of *N. sativa*

1. *Botanical Name*: *N. sativa* Linn.
2. *Family*: Ranunculaceae
3. *Vernacular names*
4. *English*: Black cumin
5. *Hindi*: Kalonji
6. *Arabic*: Habat Al-Barakah
7. *Sanskrit*: Krishana Jiraka¹⁰

3. Distribution

N. sativa is cultivated in various countries in the world such as India, Pakistan, Saudi Arabia, South Europe, Turkey, Syria and Middle Eastern Mediterranean region whereas it is native to North Africa, Southern Europe and Southwest Asia.¹¹

4. Phytochemical Composition of *N sativa*

The main active chemical constituents are thymoquinone (25-50%), dithymoquinone, thymohydroquinone, p-cymene (5-15%), carvacrol (6-10%), 4-terpineol (2-6%), sesquiterpene, longifolene (1-7%), tanethol (1-5%), α -pinene and thymol etc. *N. sativa* seeds contain two types of alkaloids; i.e. isoquinoline alkaloids e.g. nigellimine-N-oxide, nigellimine and pyrazol alkaloids or indazole ring containing alkaloids which include nigellicine and nigellidine. Furthermore, *N. sativa*

seeds have alpha-hederin, a saponin and water soluble pentacyclic triterpene, a potent anticancer agent.¹² The pharmacological actions of *N. sativa* are mainly due to quinone constituents in which thymoquinone is the most active constituents. The seeds of *N. sativa* consist of fat (28.5%), protein (26.7%), carbohydrates (24.9%), crude fibre (8.4%) and total ash (4.8 %), vitamins, minerals (Fe, Cu, Zn and P etc) and unsaturated fatty acids, mainly linoleic acid, oleic acid, dihomolinoleic acid, eicodadienoic acid, saturated fatty acids such as palmitic and stearic acid. α - sitosterol is also contained as major sterol (6.57-20.92% of total sterols).¹³ Other reported chemical constituents are nigellone, avenasterol-7-ene, avenasterol-5-ene, stigmastanol, stigmasterol-7-ene, campesterol, citrostadienol, obtusifoliol, lophenol, β -amyryn, butyro-spermol, cycloartenol, 24-methylene-cycloartanol, taraxerol, tirucallol, cholesterol, volatile oil (0.5-1.6%), fatty oil (35.6-41.6%), oleic acid, esters of unsaturated fatty acids, esters of dehydrostearic and linoleic acid, melanthin, melanthigenin, aliphatic alcohol, tannin, resin, reducing sugar and glycosidal saponin.^{1-3,14} Analytical techniques, such as high-performance liquid chromatography (HPLC) and gas chromatography-mass spectrometry (GC-MS), have been extensively employed for the identification and quantification of these bioactive constituents.

5. Extraction and Formulation Techniques of *N. sativa*

5.1. Extraction techniques

1. *Traditional Extraction Methods*: The traditional methods for *N. sativa* extraction involve processes such as maceration, percolation, and distillation. These methods have been used for centuries and are known for their simplicity and cost-effectiveness. However, they often yield lower extraction efficiencies and may lead to the degradation of certain bioactive compounds.
2. *Modern Extraction Approaches*: Modern extraction techniques of *N. sativa* (Figures 1 and 2), including solvent extraction, supercritical fluid extraction, and microwave-assisted extraction, have gained prominence for their ability to improve extraction yields and preserve the integrity of bioactive compounds. Supercritical fluid extraction, in particular, has shown promise in maximizing the extraction of volatile compounds while minimizing the use of organic solvents.¹⁵

It is noteworthy to mention that the oil yield of *N. sativa* has superior quality and safety compared with many vegetable and seed oils which require further refining, bleaching, and deodorizing (RBD)¹⁶ which may result in hazardous thermal processing contaminants such as 3-MCPD.¹⁷

6. Formulation Strategies

1. **Encapsulation Techniques:** Encapsulation techniques, such as nanoemulsion, microencapsulation, and solid lipid nanoparticles, have been employed to enhance the stability and bioavailability of *N. sativa* extracts. These approaches protect the bioactive components from degradation and improve their targeted delivery, thereby maximizing their therapeutic efficacy.¹⁸
2. **Combination Formulations:** Formulating *N. sativa* extracts with other natural compounds or pharmaceutical agents has been explored to amplify their therapeutic effects. Synergistic combinations have been studied for their potential in addressing various health conditions, including inflammation, oxidative stress, and microbial infections.¹⁹



Figure 1: *N. sativa* whole plant, flower and seed¹⁵



Figure 2: Experimental design of *Nigella sativa* L. from Farm to Pharma

7. Pharmacological Properties of *N sativa*

Research (Table 1) has shown that *N. sativa* exhibits potential in the treatment of various types of cancers.^{20–23} cardiovascular system disorders,²⁴ gastrointestinal diseases.^{25,26} liver diseases.²⁷ asthma.²⁸ depression.^{29–31} headache, migraine.³² analgesic,¹⁵ rheumatoid arthritis,²⁴ infertility,³³ wound healing,³⁴ neurological³⁵ and nephrological disorders.³⁶ Studies have also demonstrated its antimicrobial,³⁷ antifungal,³⁸ immunomodulatory, anti-inflammatory³⁹ and antioxidant properties,^{40,41} *N. sativa* has also shown potential as a natural remedy for COVID-19, with studies reporting its positive effects on immune function and viral clearance.^{42–44}

Additionally, *N. sativa* has been investigated for its potential in managing diabetes, with studies demonstrating its hypoglycemic activity and improvement in blood glucose levels.^{45–46} Furthermore, *N. sativa* has been reported to have antiviral efficacy against various viruses, and could be used as an adjuvant therapy in the management of monkeypox infection.^{46,47} Overall, *N. sativa* shows promise in various therapeutic applications and further research is needed to explore its mechanisms of action and clinical use.

8. Clinical Studies and Efficacy of *N sativa*

1. **Anti-inflammatory and Immunomodulatory Effects:** Several studies have highlighted the anti-inflammatory and immunomodulatory properties of *N. sativa*. In a randomized, double-blind, placebo-controlled trial, it was found that supplementation with *N. sativa* significantly reduced markers of inflammation in patients with rheumatoid arthritis. Additionally, a systematic review by Butt et al. demonstrated the immunomodulatory effects of *N. sativa*, suggesting its potential use in immune-related disorders.^{48,49}
2. **Anticancer Potential:** Research has suggested that *N. sativa* may exhibit anticancer properties through various mechanisms, including apoptosis induction, cell cycle arrest, and anti-proliferative effects. For instance, a study by Gali-Muhtasib et al. reported the potential of thymoquinone, a key component of *N. sativa*, in suppressing tumor growth and enhancing the efficacy of conventional cancer therapies.⁵⁰
3. **Cardioprotective Effects:** Several clinical trials have explored the cardioprotective effects of *N. sativa*. For instance, a study by Dehkordi et al. demonstrated the beneficial effects of *N. sativa* supplementation in reducing cardiovascular risk factors, including blood pressure and lipid profiles, in patients with mild hypertension.⁵¹
4. **Antimicrobial Activity:** *N. sativa* has exhibited promising antimicrobial properties against various pathogens, including bacteria, viruses, and fungi. In a study by Ali and Blunden, the essential oil extracted from *N. sativa* seeds demonstrated significant antimicrobial activity against a range of pathogens, suggesting its potential application in combating infectious diseases.⁵²

9. Quality Control and Standardization of *N. sativa*

1. **Authentication Techniques for *N. Sativa*:** Due to the rising concerns regarding adulteration and misidentification of herbal products, various authentication techniques have been developed to ensure the purity and authenticity of *N. sativa*. These include DNA barcoding, thin-layer chromatography (TLC) fingerprinting, and nuclear magnetic resonance

Table 1: Pharmacological activities of *N. sativa* and their respective mechanisms of action:

Pharmacological Activities	Mechanism of Action	Reference
Anticancer	Induction of apoptosis in cancer cells Suppression of tumor cell proliferation Inhibition of angiogenesis	20–23
Cardiovascular effects	Regulation of lipid profile Improvement of endothelial function	24
Gastroprotective	Enhancement of gastric mucosal defense Reduction of gastric ulcer formation	25,26
Hepatoprotective	Attenuating oxidative stress in the liver Restoring liver function	27
Respiratory health	Bronchodilatory effects Reduction of airway inflammation	28
Antidepressant	Regulation of neurotransmitter levels Modulation of neuroendocrine factors	29–31
Analgesic and antipyretic	Inhibition of pain mediators Modulation of pain signaling pathways	15
Anti-arthritic	Reduction of joint inflammation Modulation of immune responses in arthritis	24
Reproductive health	Regulation of reproductive hormone levels Enhancement of fertility parameters	33
Wound healing	Promotion of cell proliferation and migration Stimulation of collagen synthesis	34
Neuroprotective	Antioxidant protection against neurotoxic insults Modulation of neuroinflammation	35
Nephroprotective	Reduction of oxidative stress in the kidneys Preservation of renal function	36
Antimicrobial	Disruption of microbial cell membranes Inhibition of microbial growth	37
Antifungal	Disruption of fungal cell membranes Inhibition of fungal growth	38
Immunomodulatory	Regulation of immune responses Modulation of cytokine production	39
Anti-inflammatory	Inhibition of pro-inflammatory cytokines Modulation of NF- κ B signaling pathway	39
Antioxidant	Scavenging reactive oxygen species Enhancing endogenous antioxidant enzymes	40,41
Antiviral	Inhibition of viral replication Stimulation of immune responses	42–44
Anti-diabetic	Improving insulin sensitivity Modulating glucose metabolism	53
Anti-allergic	Modulation of histamine release Inhibition of allergic inflammatory mediators	28
Bone health	Enhancement of bone mineral density Promotion of osteoblast activity	15
Diuretic	Enhanced renal excretion of water and electrolytes Modulation of kidney function	34

(NMR) spectroscopy. These methods play a crucial role in verifying the identity and quality of *N. sativa* and its derived products.¹⁵

2. **Regulatory Guidelines and Standardization:** The lack of standardized guidelines poses a significant challenge in maintaining the quality and consistency of *N. sativa* based products. International regulatory authorities, including the World Health Organization (WHO) and the United States Pharmacopeia (USP), have emphasized the necessity of establishing comprehensive quality control standards for herbal medicines. Harmonization of these guidelines could facilitate the development of uniform protocols for the quality assessment and standardization of *N. Sativa*.^{10,11}

10. Regulatory Status and Inclusion in Pharmacopeia of *N. sativa*

1. **Regulatory Status of *N. Sativa*:** The regulatory status of *N. sativa* varies across different regions and countries. While some countries have included it in their pharmacopeia as a traditional medicine, others have imposed restrictions on its use due to concerns regarding its safety and efficacy. The lack of standardized guidelines for the cultivation, processing, and quality control of *N. sativa*-based products has further complicated its regulatory status. In some regions, it is categorized as a dietary supplement, whereas in others, it falls under the domain of traditional herbal medicine.^{54–56}
2. **Inclusion in Pharmacopeia:** The Egyptian Herbal Monograph Volume 3, published by the Egyptian Drug Authority (EDA) in 2022, marks a significant shift in the status of Black Seed, moving it beyond its traditional use as a medicinal plant to a prominent position in the pharmacopeia as a recognized pharmaceutical preparation. This transition signifies a notable evolution, as Black Seed is now treated as a drug available in pharmacies, thereby acknowledging its therapeutic potential and solidifying its place in mainstream healthcare practices.

Moreover, the inclusion of Black Seed in the pharmacopeia underscores the growing recognition of its efficacy and safety, backed by rigorous scientific scrutiny and standardization. The transformation of Black Seed into a pharmaceutical product reflects a shift towards evidence-based medicine and a departure from its previous status solely within the realm of traditional medicine. This paradigm shift emphasizes the need for standardized dosages, clear administration protocols, and adherence to pharmaceutical guidelines, ensuring consistent quality and efficacy of the Black Seed preparations available in pharmacies.

Furthermore, the integration of Black Seed into the pharmacopeia highlights the growing acceptance and endorsement of its medicinal properties by the mainstream healthcare community. This inclusion not only enhances accessibility for patients but also instills confidence among healthcare practitioners in prescribing Black Seed-based pharmaceuticals, thereby consolidating its position as a recognized and trusted therapeutic agent.

In summary, the repositioning of Black Seed from its historical usage in traditional medicine to its newfound status in the pharmacopeia as a pharmaceutical preparation available in pharmacies represents a significant advancement in the integration of traditional and modern healthcare systems. This transition not only underscores the transformative power of scientific validation but also serves as a testament to the growing acceptance of traditional herbal remedies within contemporary healthcare practices.⁵⁷

The inclusion of *N. sativa* in pharmacopeia has been a topic of debate among regulatory authorities and healthcare professionals. Some traditional medicine systems, such as the Unani and Ayurvedic systems, have long recognized the therapeutic value of *N. sativa* and have included it in their respective pharmacopeia. However, its inclusion in modern pharmacopeia remains limited, with ongoing discussions regarding its standardization, quality control, and clinical evidence.⁵⁴

11. Challenges and Opportunities

The standardization of *N. sativa*-based products poses significant challenges, including variability in active compound content, adulteration, and lack of robust clinical data. Developing standardized protocols for cultivation, extraction, and quality assessment is crucial to ensure the safety and efficacy of *N. sativa*-based formulations. Collaboration between regulatory authorities, research institutions, and herbal medicine practitioners is essential to establish comprehensive guidelines for the use of *N. sativa* in healthcare practices.

12. Safety and Side Effects Of *N sativa*

N. sativa has been used traditionally for its medicinal properties for centuries. Various studies have explored its potential health benefits, but it is essential to consider the safety aspects and potential side effects associated with its use.

12.1. Safety Profile

N. sativa is generally considered safe for consumption and has been used as a culinary and medicinal herb for its potential health benefits. According to a review published in the Asian Pacific Journal of Tropical Biomedicine, the safety profile of *N. sativa* is favorable, with a long history

of use in traditional medicine without significant reported toxicity or adverse effects.⁵⁸

12.2. Adverse Reactions

Despite its generally favorable safety profile, some individuals may experience adverse reactions or side effects. Common reported side effects associated with the consumption of *N. sativa* include:

12.2.1. Allergic Reactions

In rare cases, allergic reactions, such as skin rashes, itching, and difficulty breathing, have been reported following the ingestion or topical application of *N. sativa*. Individuals with known allergies to plants in the Ranunculaceae family should exercise caution when using *N. sativa*.

12.2.2. Gastrointestinal Disturbances

Some individuals may experience mild gastrointestinal disturbances, such as nausea, vomiting, or an upset stomach, particularly when consuming *N. sativa* in higher doses or in concentrated forms. However, these effects are typically mild and transient.⁵⁹

12.2.3. Drug Interactions

It is important to consider potential interactions between *N. sativa* and certain medications. *N. sativa* may interact with certain medications due to its potential to affect metabolic enzymes and drug transporters. Individuals taking medications should consult a healthcare professional before incorporating *N. sativa* into their regimen to avoid potential interactions and adverse effects.⁶⁰

12.2.4. Pregnancy and lactation

Limited research is available on the safety of *N. sativa* during pregnancy and lactation. As a precautionary measure, pregnant and lactating women are advised to avoid the use of *N. sativa* due to the lack of sufficient evidence regarding its safety during these stages.

13. Future Directions and Challenges in Harnessing the Potential of *N. sativa*

13.1. Future directions

1. *Clinical Trials and Standardization*: To fully unlock the potential of *N. sativa*, rigorous clinical trials are imperative. Establishing standardized protocols for dosage and administration is crucial in determining its efficacy and safety across diverse patient populations.
2. *Mechanistic Understanding*: Elucidating the precise molecular mechanisms underlying the therapeutic effects of *N. sativa* will provide insights into its mode of action and aid in the development of targeted therapies for specific ailments.

3. *Formulation Development*: Exploring innovative delivery systems and formulations, such as nanoparticles, liposomes, and nanoemulsions, can enhance the bioavailability and stability of bioactive compounds, thereby improving its therapeutic efficacy.
4. *Drug Interactions and Safety Profile*: Investigating potential drug interactions and evaluating the long-term safety profile of *N. sativa* is essential for its integration into mainstream medicine and ensuring patient well-being.^{25,26}

13.2. Challenges

1. *Quality Control and Standardization*: The lack of standardized procedures for cultivation, harvesting, and extraction poses a significant challenge in ensuring consistent quality and potency of *N. sativa*-based products.
2. *Bioavailability Issues*: The poor bioavailability of certain bioactive compounds in *N. sativa* limits its therapeutic effectiveness, necessitating innovative strategies to enhance absorption and systemic delivery.
3. *Regulatory Hurdles*: Establishing regulatory frameworks and guidelines for the commercialization of *N. sativa*-based products is critical in ensuring their quality, safety, and efficacy for consumer use.
4. *Global Awareness and Accessibility*: Enhancing public awareness regarding the potential health benefits of *N. sativa* and ensuring its accessibility, especially in resource-constrained regions, remains a significant challenge for widespread adoption and utilization.

14. Conclusions

In conclusion, *N. sativa* represents a valuable natural resource with diverse pharmacological properties and immense therapeutic potential. Its botanical and chemical profile, traditional uses, pharmacological activities, extraction and formulation techniques, quality control measures, regulatory status, clinical efficacy, safety profile, and future research directions collectively contribute to its growing significance in modern medicine and nutraceutical industries. Its inclusion in pharmacopeias is limited, highlighting the need for comprehensive documentation of its botanical characteristics, chemical composition, and pharmacological properties to facilitate its integration into official monographs and guidelines. Comprehensive efforts are warranted to bridge the gap between traditional knowledge and contemporary scientific advancements, thereby facilitating the integration of *N. sativa* into evidence-based healthcare practices.

15. Author Contribution

“Conceptualization, A.U. and R.I.M.A.; methodology, A.U. and R.I.M.A.; data curation, A.U. and R.I.M.A.;

writing—original draft preparation, A.U. and R.I.M.A.; writing—review and editing, A.U. and R.I.M.A.”

16. Data Availability

All data generated or analyzed during this study are included in this published article.

17. Source of Funding

None.

18. Conflict of Interest

None.

References

- Ahmed N. Nigella sativa: A Potent Secondary Metabolite. *Pak BioMed J.* 2022;5(9):1–2.
- Khan S, Ali M, Albratty MM, Najmi AY, Azeem U, Khan SA. Nigella sativa: From chemistry to medicine. *Pharmacol Therap Appl.* 2022;3(5):29–62.
- Ahmad MF, Ahmad FA, Ashraf SA, Saad HH, Wahab S. An updated knowledge of Black seed (Nigella sativa Linn.): Review of phytochemical constituents and pharmacological properties. *J Herb Med.* 2021;25:100404.
- Smail LB, Achat S, Brahmi F, Bey MB, Arab R. Biological Properties, Phenolic Profile, and Botanical Aspect of Nigella sativa L. and Nigella damascena L. Seeds: A Comparative Study. *Molecules.* 2023;28(2):571.
- Mahmud NM, Paraoan L, Khaliddin N, Kamalden TA. Thymoquinone in Ocular Neurodegeneration: Modulation of Pathological Mechanisms via Multiple Pathways. *Front Cell Neurosci.* 2022;16:786926.
- Usmani A, Mishra A, Jafri A, Arshad M, Siddiqui MA. Green Synthesis of Silver Nanocomposites of Nigella sativa Seeds Extract for Hepatocellular Carcinoma. *Current Nanomaterials.* 2019;4(3):191–200.
- Nyemb JN, Shaheen H, Wasef L, Nyamota R, Segueni N, Batiha GES, et al. Black Cumin: A Review of its Pharmacological Effects and its Main Active Constituent. *Pharmacognosy Rev.* 2022;16(32):107–25.
- Mogharbel GH, Badawi AS, Zaman AY, Elmoniem MA, Abdel-Rahman IM. Therapeutic benefits of prophetic medicine remedies in treating hematological diseases (A review article). *Am J Blood Res.* 2023;13(4):130–42.
- Heshmati J, Namazi N. Effects of black seed (Nigella sativa) on metabolic parameters in diabetes mellitus: A systematic review. *Complement Therap Med.* 2015;23(2):275–82.
- Chevallier A. Encyclopedia of medicinal plants. New York, NY: DK Publishing; 1996. p. 237.
- Khare CP. Encyclopedia of Indian Medicinal Plants: Rational Western Therapy, Ayurvedic and Other Traditional Usage. Botany: Springer; 2004. p. 523.
- Mehta BK, Pandit V, Gupta M. New principles from seeds of Nigella sativa. *Natural product research.* 2009;23(2):138–148.
- Kooti W, Hasanzadeh-Noohi Z, Sharafi-Ahvazi N, Asadi-Samani M, Ashtary-Larky D. Phytochemistry, pharmacology, and therapeutic uses of black seed (Nigella sativa). *Chinese J Natural Med.* 2016;14(10):30088–95.
- Al-Jassir MS. Chemical composition and microflora of black cumin (N. sativa L.) seeds growing in Saudi Arabia. *Food Chem.* 1992;45(4):239–42.
- Ahmad A, Husain A, Mujeeb M, Khan SA, Najmi AK. A review on therapeutic potential of Nigella sativa: A miracle herb. *Asian Pac J Trop Biomed.* 2013;3(5):60075–6.
- Almoselhy RIM, Eid MM, Abd-Elmageed SMM, Youness RA. Using Nanotechnology in Bleaching Vegetable Oils. *Egyptian Journal of Chemistry.* 2020;63(7):2699–2706.
- Almoselhy RIM, Eid MM, El-Baset A, Aboelhassan WS. Determination of 3-MCPD in Some Edible Oils using GC-MS/MS. *Egyptian J Chem.* 2021;64(3):1639–52.
- Kanter M. Nigella sativa and derived thymoquinone prevents hippocampal neurodegeneration after chronic toluene exposure in rats. *Neurochem Res.* 2008;33(3):579–88.
- Khader M, Bresgen N, Eckl PM. In vitro toxicological properties of thymoquinone. *Food Chem Toxicol.* 2009;47(1):129–33.
- Al-Seeni MN, Rabey HE, Zamzami MA, Alnefayee AM. The hepatoprotective activity of olive oil and Nigella sativa oil against CCl4 induced hepatotoxicity in male rats. *BMC Complement Alternat Med.* 2016;16:1–14.
- Majdalawieh AF, Fayyad MW. Recent advances on the anti-cancer properties of Nigella sativa, a widely used food additive. *J Ayurveda Integrat Med.* 2016;7(3):173–80.
- Mohamed HA, El-Sayed IH, Moawad M. Protective effect of N. sativa seeds against dimethylaminoazobenzene (DAB) induced liver carcinogenesis. *Nat Sci.* 2010;8(6):80–7.
- Khan MA, Tania M, Fu S, Fu J. Thymoquinone, as an anticancer molecule: from basic research to clinical investigation. *Oncotarget.* 2017;8(31):51907.
- Hadi V, Pahlavani N, Malekhamadi M, Eshtivani EN, Navashenaq JG, Hadi S, et al. N. sativa in controlling Type 2 diabetes, cardiovascular, and rheumatoid arthritis diseases: molecular aspects. *J Res Med Sci.* 2021;26:1–20.
- Pandey N, Shri P, Pandey H, Tripathi YB. radiation Induced Gastrointestinal damage and Protection: N. sativa seed extract and thymoquinone. *Def Life Sci J.* 2017;2(3):264–9.
- Bukar MA, Ishaya HB, Dibal NI, Attah MO. Gastroprotective effect of N. sativa seed on ethanol-induced gastric ulcer in rats. *Libyan J Med Sci.* 2017;1(3):63–7.
- Adam GO, Rahman MM, Lee SJ, Kim GB, Kang HS, Kim JS, et al. Hepatoprotective effects of N. sativa seed extract against acetaminophen-induced oxidative stress. *Asian Pacific J Trop Med.* 2016;9(3):221–7.
- Koshak A, Koshak E, Heinrich M. Medicinal benefits of N. sativa in bronchial asthma: A literature review. *Saudi Pharma J.* 2017;25(8):1130–6.
- Elkhatay ES, Alorainy MS, El-Ashmawy IM, Fat'hi S. Potential antidepressant constituents of N. sativa seeds. *Pharmacogn Magazine.* 2016;12(1):27–31.
- Perveen T, Haider S, Zuberi NA, Saleem S, Sadaf S, Batool Z. Increased 5-HT levels following repeated administration of N. sativa L.(black seed) oil produce antidepressant effects in rats. *Scientia Pharmaceutica.* 2014;82(1):16–70.
- Akbar A. Antidepressant and anti-nociceptive effects of N. sativa and its main constituent, thymoquinone: A literature review. *Asian Pacific J Trop Biomed.* 2022;12:495.
- Boroujeni HR, Samani MA, Moradi MT. A review of the medicinal plants effective on headache based on the ethnobotanical documents of Iran. *Der Pharm Lett.* 2016;8(3):37–42.
- Marbat MM, Ali M, Hadi AM. The use of N. sativa as a single agent in treatment of male infertility. *Tikrit J Pharma Sci.* 2013;9(1):19–29.
- Sallehuddin N, Nordin A, Idrus R, Fauzi MB. N. sativa and its active compound, thymoquinone, accelerate wound healing in an in vivo animal model: a comprehensive review. *Int J Environ Res Pub Health.* 2020;17(11):4160.
- Islam MH, Ahmad IZ, Salman MT. Neuroprotective effects of N. sativa extracts during germination on central nervous system. *Pharmacogn Magazine.* 2015;11:182.
- Hayatdavoudi P, Rad AK, Rajaei Z, Mousa AL. Renal injury, nephrolithiasis and N. sativa: A mini review. *Avicenna J Phytomed.* 2016;6(1):1–8.
- Hanafy MSM, Hatem ME. Studies on the antimicrobial activity of N. sativa seed (black cumin). *J Ethnopharmacol.* 1991;34(2-3):275–8.
- Khan MAU, Ashfaq MK, Zuberi HS, Mahmood MS, Gilani AH. The in vivo antifungal activity of the aqueous extract from N. sativa seeds.

