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Review Article

Current trends in *Nigella sativa* L. (Black seed) from traditional to modern medicine with advances in extraction, formulation, quality control, regulatory status, and pharmacology

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ABSTRACT

For the first time ever, this novel review enters the enigmatic world of the *Nigella sativa* L. (black seed), known for centuries as a potent source of healing including their relevance to the food and pharmaceutical industries. Written at professional and reference level, it is directed at normal readers with more professional scientists in pharmacy and food science affiliations to serve as a rich source of data on black seed. We embark on an exploration that encompasses the background, significance, and objectives guiding our exploration. Detailed botanical and chemical profiles unravel the mysteries of the black seed, providing insight into its taxonomy, morphology, and chemical composition. Traditional uses, extraction methods, and formulation approaches paint a comprehensive picture of the versatile ways in which the black seed has been employed throughout history. Quality control and standardization practices ensure the integrity of black seed-derived products, while a global regulatory overview brings into focus the challenges and triumphs of incorporating this botanical powerhouse into mainstream pharmacopeias. As we delve into the pharmacological activities, clinical studies, and efficacy of the black seed, we confront safety considerations and potential side effects. The exploration extends into the future, addressing the challenges in commercialization, identifying research gaps, and concluding with the implications of our findings for both healthcare and industry. It should therefore be of special value to researchers affiliated with food science and technology, pharmacy, and pharmaceutical producers requiring up-to-date information on their raw materials, which will probably already have been processed, at least in part.

1. Introduction

1.1. Background and Significance

The journey of *Nigella sativa* unfolds against the backdrop of centuries-old wisdom and a tapestry of cultural practices. This unassuming seed has not only been a staple in traditional medicine but has also piqued the curiosity of modern science. The historical significance of *N. sativa* is deeply rooted, with its seeds finding a place in the annals of diverse civilizations. From the ancient practices of Egyptian pharaohs to the rich traditions of Ayurveda and Islamic medicine, the historical tapestry of *N. sativa* is interwoven with reverence and healing. As we delve into the botanical and chemical intricacies of this remarkable plant, we embark on a journey that extends from the farm, where the seeds are cultivated, to the pharmacy, where they find their place in contemporary healthcare. Understanding the taxonomy, morphology, and chemical composition of *N. sativa* is not only a scientific exploration but a testament

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to the rich cultural heritage that surrounds this botanical gem.[1,2]

N. sativa L., commonly referred to as black cumin or black seeds, is an annual flowering plant belonging to the Ranunculaceae family. Its delicate pale blue and white flowers and small, angular black seeds characterize this plant. The seeds, renowned for their strong aromatic fragrance, are the most frequently utilized part of *N. sativa*. It is cultivated in various countries worldwide, including India, Pakistan, Saudi Arabia, South Europe, Turkey, Syria, and the Middle Eastern Mediterranean region. It is native to North Africa, Southern Europe, and Southwest Asia.[3–5]

The historical and cultural significance of *N. sativa* seeds is profound, with documented use in diverse civilizations across time:

1. **Ancient Egypt:** Archaeological findings in the tomb of King Tutankhamun underscore the historical use of *N. sativa* seeds in ancient Egypt. They were not only employed for culinary purposes but also esteemed for their medicinal properties.
2. **Traditional Ayurveda:** In Ayurveda, the traditional Indian medical system, *N. sativa* seeds found application in treating various ailments, including digestive issues, respiratory conditions, and skin disorders.
3. **Traditional Chinese Medicine:** Traditional Chinese medicine incorporated *N. sativa* seeds for their anti-inflammatory, diuretic, and digestive properties, contributing to their historical use in this medical tradition.
4. **Greco-Roman Civilization:** The medicinal properties of *N. sativa* seeds were acknowledged in Greco-Roman civilization, with references in the works of Dioscorides, a renowned Greek physician and botanist.
5. **Islamic Medicine:** Extensively utilized in traditional Islamic medicine, *N. sativa* seeds are mentioned in the Hadith (sayings of Prophet Muhammad (peace be upon him) as a remedy for a range of ailments, underlining their significance in this cultural and medical context.
6. **Contemporary Research:** In recent years, the scientific community has shown a growing interest in exploring the potential health benefits of *N. sativa* seeds. Research has concentrated on their antioxidant, anti-inflammatory, and antimicrobial properties, as well as their potential role in managing various chronic diseases. This contemporary exploration aligns with the rich historical and cultural tapestry of the uses of *N. sativa*, highlighting its enduring importance in the realm of natural medicine and wellness.[6–8]

2. Objectives

This comprehensive exploration aims to bridge the gap between tradition and modernity, offering readers a nuanced understanding of *N. sativa* from farm to pharmacy. The objectives of this comprehensive review are threefold:

1. **Scientific Illumination:** Provide a detailed and scientifically rigorous exploration of the botanical and chemical aspects of *N. sativa*, shedding light on its taxonomy, morphology, and chemical composition.
2. **Practical Insights:** Offer practical insights into the extraction and formulation techniques employed in transforming black seeds into market-ready products. Delve into the quality control measures and standardization practices that ensure the potency and safety of *N. sativa*-based formulations.
3. **Holistic Perspective:** Present a holistic view of *N. sativa* by exploring its traditional uses, pharmacological activities, clinical studies, safety considerations, and future directions. This approach ensures that readers gain a comprehensive understanding of the seed's diverse facets.

2.1. Overview

This comprehensive review is structured to be a definitive guide on *N. sativa*, encompassing its historical roots, botanical intricacies, extraction processes, pharmacological activities, and clinical applications. The journey begins with an exploration of the plant's taxonomy, morphology, and chemical composition, setting the stage for an in-depth understanding. Subsequent chapters traverse through the traditional uses of *N. sativa*, unveiling its historical and cultural significance. The extraction and formulation techniques employed in turning seeds into pharmaceutical formulations are dissected, highlighting the advancements in modern technology and the age-old practices that coalesce in the pharmaceutical industry. Quality control measures and standardization practices take center stage, ensuring that readers grasp the meticulous processes that uphold the integrity of *N. sativa* products. The regulatory landscape, both globally and in pharmacopeias, is scrutinized, shedding light on the challenges and compliance issues faced by those in the industry. The pharmacological activities and clinical efficacy of *N. sativa* are dissected in detail, drawing on key studies and findings. Safety considerations, potential side effects, and interactions with medications are explored, providing a balanced perspective for healthcare professionals and consumers alike.

As we peer into the future, the review addresses emerging trends, research gaps, and challenges in commercialization. The concluding section synthesizes key findings, drawing implications for both healthcare practitioners and the industry. In essence, this review serves as a comprehensive compendium, offering a holistic and insightful journey through the multifaceted world of *N. sativa*, from farm to pharmacy.

3. Botanical and Chemical Profile Of *N sativa*

3.1. Taxonomic Classification

1. Kingdom: Plantae
2. Subkingdom: Tracheobionta
3. Superdivision: Spermatophyta
4. Phylum: Magnoliophyta
5. Class: Magnoliopsida
6. Order: Ranunculales
7. Family: Ranunculaceae
8. Genus: Nigella
9. Species: *N. sativa*[9].

Common names: Black cumin, Black seed, Black Caraway, Roman Coriander, Damascena, Devil in-the-bush, Wild Onion Seed, etc.

1. English: Black cumin
2. Hindi: Kalonji
3. Arabic: Habat Al-Barakah
4. Sanskrit: Krishana Jiraka.[9,10]

3.2. Morphology and growth patterns

N. sativa is an annual herbaceous plant with a distinctive appearance. The detailed exploration of its morphology and growth patterns is follows:

1. *Stem:* The stem of *N. sativa* is slender, erect, and branched. It typically reaches a height of about 20-30 centimeters (8-12 inches). The branching pattern contributes to the plant's bushy appearance.

2. *Leaves:* The leaves of *N. sativa* are finely divided and feathery. They are alternate and pinnately compound, with linear to narrowly lanceolate leaflets. The overall foliage imparts an elegant and delicate texture to the plant.

3. *Flowers:* The flowers of *N. sativa* are striking and distinctive. They are usually pale blue or white in color and have five to ten petals. The flowers are solitary, terminal, and each is surrounded by finely divided bracts that give the appearance of a delicate, lacy collar. The bloom period typically occurs in the late spring to early summer.

4. *Fruits:* The most notable part of *N. sativa* is its fruit, which contains the prized black seeds. The fruit is a capsule composed of several follicles, and when mature, it splits open to reveal small, angular seeds. These seeds are jet black and have a characteristic shape that resembles a compressed pyramid or a small, angular grain of rice.

5. *Roots:* The root system of *N. sativa* is relatively shallow, and the plant relies on the soil's nutrients for its annual growth cycle.

6. *Growth Patterns: N. sativa* follows an annual growth pattern, completing its entire life cycle, from germination to seed production, within a single year. The plant prefers well-drained soil and thrives in sunny to partially shaded environments. It is well-adapted to arid regions and can tolerate a range of soil types.[11]

Figure 1: Morphological features of *N. sativa.*[12]

3.3. Chemical composition of N. sativa:

The seeds of *N. sativa* boast a diverse array of chemical constituents with notable pharmacological significance. The main active compounds include:

1. Thymoquinone (25-50%)
2. Dithymoquinone
3. Thymohydroquinone
4. p-Cymene (5-15%)
5. Carvacrol (6-10%)
6. Terpineol (2-6%)
7. Sesquiterpene, Longifolene (1-7%)
8. Tanethol (1-5%)
9. α-Pinene
10. Thymol

Moreover, *N. sativa* seeds contain two types of alkaloids: isoquinoline alkaloids (e.g., nigellicimine-N-oxide, nigellicimine) and pyrazol alkaloids or indazole ring-containing alkaloids (including nigellicine and nigellidine). The seeds also house alpha-hederin, a saponin, and a water-soluble pentacyclic triterpene recognized for its potent anticancer properties. The seeds' nutritional composition comprises fat (28.5%), protein (26.7%), carbohydrates (24.9%), crude fiber (8.4%), and total ash (4.8%). Additionally, they contain essential vitamins, minerals (Fe, Cu, Zn, and P), unsaturated fatty acids (predominantly linoleic acid, oleic acid, dihomolinoleic acid, and eicodadienoic acid), as well as saturated fatty acids like palmitic and stearic acid. Major sterols include α-sitosterol (6.57-20.92% of total sterols).

Other reported chemical constituents in *N. sativa* seeds include nigellone, avenasterol-7-ene, avenasterol-5-ene, stigmastanol, stigmasterol-7-ene, campesterol, citrostadienol, obtusifoliol, lophenol, β-amyrin, butyrospermol, 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.[1–3,13]

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.

4. Traditional Uses of *N. sativa*

4.1. Historical significance

N. sativa, known as black cumin, holds a significant place in history, with its traditional use spanning ancient civilizations. Egyptians and Greeks recognized its therapeutic properties, incorporating the seeds into culinary, medicinal, and even religious practices. Historical documents attest to its role in traditional remedies, reflecting its enduring value across cultures.

4.2. Cultural practices

N. sativa is deeply embedded in diverse cultural practices, particularly in Middle Eastern cuisine, where the seeds are a common spice. Beyond the culinary realm, the plant and its seeds often carry symbolic importance, associated with protection and blessings in various cultural rituals, ceremonies, and celebrations.

4.3. Folk remedies and traditional Applications of N sativa:

N. sativa has been a staple in numerous folk remedies and traditional applications, reflecting its versatile therapeutic potential.

1. ***Respiratory Health:*** Traditional medicine often incorporates *N. sativa* for respiratory well-being. The seeds are believed to have expectorant properties, making them valuable in managing conditions like coughs, asthma, and bronchitis.
2. ***Digestive Aid:*** *N. sativa* is traditionally used to support digestive health, addressing issues such as indigestion, bloating, and gas. It is considered beneficial for promoting overall gastrointestinal well-being.
3. ***Immune System Support:*** Folk remedies frequently use *N. sativa* as an immune system booster. The seeds are believed to have immunomodulatory effects, aiding the body's defense against infections and illnesses.
4. ***Anti-inflammatory and Analgesic Properties:*** *N. sativa* is traditionally employed for its anti-inflammatory and analgesic effects, offering relief from pain and inflammation associated with conditions like arthritis and joint discomfort.
5. ***Skin Conditions:*** The oil extracted from N. sativa seeds is topically applied for various skin conditions. Its anti-inflammatory and antioxidant properties may contribute to managing skin issues, including eczema and psoriasis.
6. ***General Well-being:*** *N. sativa* is considered a tonic for overall health in traditional systems. It is often included in tonics and elixirs aimed at promoting vitality and maintaining a balanced state of health.
7. ***Culinary Uses:*** Apart from its medicinal applications, *N. sativa* seeds are a culinary spice, enhancing the flavor of dishes in various cuisines.

As research progresses, scientific validation of these traditional uses continues. However, it's important to approach traditional remedies with caution and consult healthcare professionals for comprehensive and personalized health guidance. The integration of *N. sativa* into various aspects of culture, history, and traditional medicine underscores its enduring significance ,[14,15]

5. Extraction Methods of *N. sativa*

Various methods can be employed for the extraction of bioactive compounds from *N. sativa* seeds. Here are explanations of some extraction methods:

5.1. Cold press extraction

1. ***Process:*** This method involves mechanically pressing the seeds at a relatively low temperature, typically below 60°C, to obtain oil.
2. ***Advantages:*** Cold press extraction helps retain the natural flavor, aroma, and nutritional content of the oil.
3. ***Disadvantages:*** The yield of oil might be lower compared to other extraction methods.

5.2. Solvent extraction

1. **Process**: This method involves using organic solvents (e.g., hexane) to dissolve and extract the oil from the seeds.
2. **Advantages:** Solvent extraction can yield a higher quantity of oil and extract a broader spectrum of compounds.
3. **Disadvantages:** Residual solvent in the extract can be a concern. Also, it may lead to a loss of some heat-sensitive compounds.

5.3. Ultrasound-assisted extraction (UAE)

1. **Process:** Ultrasound waves are used to create cavitation in the solvent, enhancing the mass transfer and extraction efficiency.
2. **Advantages:** UAE is a rapid and efficient method that can lead to higher yields. It is environmentally friendly compared to some solvent-based methods.
3. ***Disadvantages:*** Optimization of parameters (intensity, frequency, time) is crucial for optimal results.

5.4. Microwave-assisted extraction (MAE)

Process: Microwaves are used to heat the solvent, promoting the extraction of compounds from the seeds.

1. *Advantages:* MAE is a fast and efficient method that can reduce extraction time.
2. *Disadvantages:* Care must be taken to prevent overheating, which may degrade heat-sensitive compounds.

5.5. Supercritical fluid extraction (SFE)

1. *Process:* Supercritical fluid extraction uses a supercritical fluid, often carbon dioxide, as the solvent. Under specific conditions of pressure and temperature, CO2 becomes a supercritical fluid with properties between a gas and a liquid, making it an effective solvent.
2. *Advantages:* SFE is efficient and leaves no solvent residues. It allows for the selective extraction of certain compounds.
3. *Disadvantages:* Equipment costs for supercritical fluid extraction can be relatively high.

5.6. Subcritical luid extraction

1. **Process:** Similar to supercritical fluid extraction but at lower pressures and temperatures, using subcritical fluids such as liquid propane or butane.
2. **Advantages:** Subcritical fluid extraction can be more cost-effective than supercritical extraction.
3. **Disadvantages:** Similar to supercritical extraction, the equipment can be expensive.

The choice of extraction method depends on various factors such as the desired compounds, efficiency, cost, and environmental considerations. It's essential to optimize the extraction parameters for each method to achieve the best results.

6. Powdered Seeds

Grinding the *N. sativa* seeds into a fine powder is one method of extraction. This can be done using a mortar and pestle or a mechanical grinder.

The powdered seeds can be used directly in cooking or incorporated into various formulations for medicinal purposes.

It's important to note that the efficacy of the powdered seeds may vary depending on the extraction method and the intended use.

6.1. Aqueous extract

Aqueous extraction involves using water as a solvent to extract water-soluble compounds from the seeds.

The process typically includes soaking the seeds in water and then filtering or centrifuging to separate the liquid extract from the solid residue.

Aqueous extracts are often used in traditional medicine and herbal remedies. [12,16,17]

7. Formulation Techniques of *N. Sativa*

7.1. Herbal preparations correlated to medicinal use

Herbal preparations play a pivotal role in traditional and alternative medicine, offering a diverse array of pharmaceutical dosage forms. In this study, we explore three distinct preparations derived from *N. sativa* and their correlation to medicinal use.

1. **Powdered Seeds:** The powdered seeds of *N. sativa* are formulated into pharmaceutical dosage forms. According to pharmacopoeial standards, [18] the full standard term is utilized to describe this preparation.
2. **Aqueous Extract:** The aqueous extract of *N. sativa*, another pharmaceutical dosage form, undergoes meticulous preparation to extract essential bioactive compounds. The pharmacopoeia's full standard term is employed to describe this extract.
3. **Oil:** The oil extracted from *N. sativa* is formulated as a pharmaceutical dosage form. Similar to the other preparations, the pharmacopoeia's full standard term is employed for precise characterization.

7.2. Medicinal uses (Indications)

A. Relief symptoms of asthma.

B. Amelioration of Hyperlipidemia (Dyslipidemia).

C. As adjuvant therapy for managing hypertension.

D. As adjuvant therapy for controlling of blood glucose levels in Type 2 diabetes mellitus.

E. Modulate immune system.

F. As adjuvant therapy to improve inflammatory conditions (Anti-inflammatory).

7.3. Posology and Method of Administration Correlated to Medicinal Use

Preparation 1

- Indication A: Administer 500 mg - 1.0 g twice daily for duration of 3 months.

- Indication B: Prescribe 1.0 g daily for 1-2 months, or 500 mg daily for 6 months, with the option to increase to 1.0 g twice daily for 3 months.

- Indication C: Suggest a daily dosage of 200 - 400 mg for 2 months.

- Indication D: Recommend a daily dosage of 2.0 – 3.0 g for 3 months.

- Indication F: Advise 2 g daily for 3 months.

Preparation 2

- Indication A: Prescribe 2.0 g of extract daily for 2 weeks or 700 mg – 1.4 g of extract daily as adjuvant therapy.

- Indication C: Recommend 100–200 mg twice daily for 2 months.

Preparation 3

1. Indication A: Administer 5 ml three times daily or 500 mg twice daily for 4 weeks.
2. Indication B: Prescribe 5 ml or 2.0 – 3.0 g daily for 2-3 months.
3. Indication C: Suggest 5 ml daily for 2-3 months or 2.5 ml twice daily for 2 months.
4. Indication D: Recommend 5 ml once or 2.5 ml twice daily for 6 weeks, up to 3 months.
5. Indication E: Administer 500 mg daily.
6. Indication F: Suggest orally 500 mg twice daily for 1-2 months, up to 1 g twice daily for 3 months, or topically apply twice daily for 21 days or 600 mg twice daily for 2 months.

8. Formulation Strategies

8.1. Encapsulation techniques

1. To bolster the stability and bioavailability of *N. sativa* extracts, encapsulation techniques such as nanoemulsion, microencapsulation, and solid lipid nanoparticles have been strategically employed. These techniques serve as protective mechanisms, shielding the bioactive components from degradation and facilitating their targeted delivery. The overarching aim is to optimize therapeutic efficacy through enhanced stability and improved bioavailability, thereby augmenting the overall impact of *N. sativa* extracts on health outcomes.[19,20]

8.2. Combination formulations

1. In a quest to amplify the therapeutic effects of *N. sativa* extracts, formulation strategies involve combining these extracts with other natural compounds or pharmaceutical agents. This approach explores synergistic combinations to address various health conditions, ranging from inflammation and oxidative stress to microbial infections[21]. The careful integration of *N. sativa* with complementary elements aims to unlock heightened therapeutic potential, offering a multifaceted and synergistic approach to health management.[22]

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

N. sativa, commonly known as black seed or black cumin, is a plant that has been used for centuries for its medicinal properties. Quality control and standardization are crucial aspects of ensuring the efficacy and safety of products derived from *N. sativa*. This involves establishing parameters for quality assessment, employing appropriate testing methods, and implementing standardization practices.

9.1. Parameters for quality assessment

Quality assessment involves the evaluation of various parameters to ensure that the *N. sativa* products meet predefined standards. The key parameters for quality assessment include:

9.1.1. Chemical composition

Thymoquinone Content: Thymoquinone is a major bioactive compound in *N. sativa* responsible for many of its therapeutic effects. A standardized product should specify the minimum thymoquinone content.

Essential Oil Composition: The composition of essential oils, including components such as p-cymene, carvacrol, and thymol, can vary and impact the overall quality.

9.1.2. Purity

Foreign Matter: Assessing the presence of impurities, such as dirt or other plant materials, ensures the purity of the final product.

Microbial Contamination: Testing for bacteria, fungi, and other microorganisms is essential to guarantee the safety of the product.

9.1.3. Moisture content

Controlling moisture is crucial to prevent mold growth and maintain the stability of *N. sativa* products.

9.1.4. Heavy metals

Analysis for heavy metals like lead, mercury, and cadmium helps ensure the absence of harmful substances.

9.1.5. Pesticide residues

9.2. Sativa should be tested for pesticide residues to ensure compliance with safety standards

9.3. Testing methods

Accurate testing methods are essential to assess the quality of *N. sativa* products. Various analytical techniques can be employed:

9.3.1. High-performance liquid chromatography (HPLC)

HPLC is commonly used to quantify thymoquinone and other active compounds.

9.3.2. Gas chromatography-mass spectrometry (GC-MS)

GC-MS is employed for analyzing the essential oil composition, providing a detailed profile of volatile compounds.

9.3.3. Microbiological testing

Standard microbiological methods are used to detect and quantify microbial contamination.

9.3.4. Atomic absorption spectrometry

This technique is utilized for heavy metal analysis, ensuring compliance with safety standards.

9.4. Standardization practices

Standardization involves establishing and maintaining a set of guidelines to ensure consistency and quality in *N. sativa* products. Key standardization practices include

9.4.1. Good agricultural practices (GAP)

Ensuring that *N. sativa* is cultivated using standardized agricultural practices to maintain the quality of raw materials.

9.4.2. Good manufacturing practices (GMP)

Implementing GMP in the processing and manufacturing of *N. sativa* products to ensure quality and safety.

9.4.3. Documentation

Keeping detailed records of cultivation, processing, and testing procedures to facilitate traceability and quality control.

9.4.4. Certification

Obtaining certifications, such as ISO or other relevant standards, to demonstrate compliance with quality benchmarks.

9.4.5. Continuous monitoring

Regular monitoring of raw materials, manufacturing processes, and finished products to identify and address deviations from quality standards.[23–25]

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

10.1. Global regulatory overview

The regulatory status of *N. sativa* exhibits variations across regions and countries, with diverse approaches reflecting differing perspectives on its safety and efficacy. Some nations have incorporated it into their pharmacopeia as a traditional medicine, while others have imposed usage restrictions. The absence of standardized guidelines for cultivation, processing, and quality control further complicates its regulatory standing. Classification ranges from a dietary supplement in certain regions to inclusion under traditional herbal medicine in others[9,26,27].

10.2. Inclusion in pharmacopeial standards

A significant turning point in the status of Black Seed is evident in the Egyptian Herbal Monograph Volume 3, released by the Egyptian Drug Authority (EDA) in 2022.[18] This marks a departure from its traditional role as a medicinal plant to a recognized pharmaceutical preparation in the pharmacopeia. This transformation acknowledges Black Seed as a pharmaceutical available in pharmacies, emphasizing its therapeutic potential and solidifying its position in mainstream healthcare.

Furthermore, its inclusion underscores growing recognition, supported by rigorous scientific scrutiny and standardization, highlighting a shift toward evidence-based medicine. Black Seed's evolution into a pharmaceutical product emphasizes the need for standardized dosages, clear administration protocols, and adherence to pharmaceutical guidelines, ensuring consistent quality and efficacy. This shift represents a departure from its historical association with traditional medicine, emphasizing a move towards contemporary healthcare practices.

The integration of Black Seed into the pharmacopeia signifies the acceptance and endorsement of its medicinal properties by the mainstream healthcare community. This not only enhances accessibility for patients but also instills confidence among healthcare practitioners in prescribing Black Seed-based pharmaceuticals, establishing it as a recognized and trusted therapeutic agent.[18]

In summary, the repositioning of Black Seed from traditional medicine to its status in the pharmacopeia reflects a significant advancement in the integration of traditional and modern healthcare systems. This transition underlines the transformative power of scientific validation and signals the increasing acceptance of traditional herbal remedies in contemporary healthcare practices.

10.3. Challenges in regulatory compliance

Despite recognition in traditional medicine systems like Unani and Ayurveda, debates persist among regulatory authorities and healthcare professionals about *N. sativa*'s inclusion in modern pharmacopeia. Ongoing discussions focus on standardization, quality control, and the accumulation of clinical evidence, reflecting the dynamic nature of its regulatory journey.

11. Pharmacological activities of *N. sativa*

11.1. Anticancer

N. sativa demonstrates significant anticancer potential through a multi-faceted approach. It induces apoptosis, triggering programmed cell death in cancer cells. Additionally, it suppresses tumor cell proliferation and inhibits angiogenesis, disrupting the formation of new blood vessels to tumors. These mechanisms collectively contribute to the herb's effectiveness in combating various types of cancer.[28–31]

11.2. Cardiovascular effects

N. sativa plays a pivotal role in cardiovascular health by regulating lipid profiles and enhancing endothelial function. The herb's ability to modulate lipid metabolism contributes to maintaining a healthy cardiovascular system, while its positive impact on endothelial function supports proper blood vessel functioning. These dual effects make *N. sativa* a potential ally in preventing cardiovascular diseases.[32]

11.3. Gastroprotective

The gastroprotective properties of *N. sativa* are characterized by its capacity to enhance the defense mechanisms of the gastric mucosa. Simultaneously, it efficiently reduces the formation of gastric ulcers. This dual action highlights the herb's potential in protecting the stomach lining and preventing ulcerative conditions, presenting a valuable therapeutic avenue for gastrointestinal health.[33,34]

11.4. Hepatoprotective

N. sativa exhibits hepatoprotective effects by mitigating oxidative stress in the liver and facilitating the restoration of normal liver function. Its antioxidant properties contribute to reducing damage caused by free radicals, thereby promoting liver health. These attributes position *N. sativa* as a potential therapeutic agent for liver disorders and conditions associated with oxidative stress.[35]

11.5. Respiratory health

With its bronchodilatory effects and the ability to reduce airway inflammation, *N. sativa* emerges as a valuable contributor to respiratory health. These properties make it a potential intervention in respiratory conditions, providing relief from bronchoconstriction and inflammation, thereby enhancing overall pulmonary well-being.[36]

11.6. Antidepressant

N. sativa exhibits antidepressant effects through the regulation of neurotransmitter levels and the modulation of neuroendocrine factors. By influencing the delicate balance of chemicals in the brain, the herb contributes to mood regulation and shows promise in the management of depressive disorders.[37,38]

11.7. Analgesic and antipyretic

The analgesic and antipyretic properties of *N. sativa* are manifested through the inhibition of pain mediators and the modulation of pain signaling pathways. These mechanisms collectively contribute to the herb's potential in alleviating pain and reducing fever, offering a natural alternative for pain management.[39]

11.8. Anti-arthritic

N. sativa demonstrates efficacy in reducing joint inflammation and modulating immune responses associated with arthritis. These anti-arthritic properties suggest its potential role in mitigating the symptoms and progression of inflammatory joint conditions.[32]

11.9. Reproductive health

N. sativa plays a crucial role in reproductive health by regulating reproductive hormone levels and enhancing fertility parameters. These effects position the herb as a potential supportive intervention in addressing reproductive disorders and promoting fertility.[40]

11.10. Wound healing

The wound healing properties of *N. sativa* are characterized by its ability to promote cell proliferation, migration, and stimulate collagen synthesis. These mechanisms collectively contribute to the herb's efficacy in facilitating the healing process and tissue regeneration.[41]

11.11. Neuroprotective

N. sativa provides neuroprotection through antioxidant mechanisms, offering protection against neurotoxic insults. Additionally, its modulation of neuroinflammation contributes to safeguarding the nervous system from various threats, suggesting potential applications in neurodegenerative disorders.[42]

11.12. Nephroprotective

The nephroprotective effects of *N. sativa* involve the reduction of oxidative stress in the kidneys and the preservation of renal function. These attributes position the herb as a potential therapeutic agent in safeguarding kidney health and preventing renal damage.[43]

11.13. Antimicrobial

N. sativa exhibits antimicrobial properties by disrupting microbial cell membranes and inhibiting microbial growth. These actions suggest its potential in addressing various infectious diseases caused by bacteria and other microorganisms.[44]

11.14. Antifungal

The antifungal properties of *N. sativa* involve the disruption of fungal cell membranes and the inhibition of fungal growth. These effects position the herb as a potential natural antifungal agent for the management of fungal infections,[45]

11.15. Immunomodulatory

N. sativa modulates immune responses and cytokine production, showcasing potent immunomodulatory effects. This suggests its potential in enhancing the immune system's ability to respond to pathogens and maintain immune homeostasis.[46]

11.16. Anti-inflammatory

The anti-inflammatory effects of *N. sativa* are manifested through the inhibition of pro-inflammatory cytokines and modulation of the NF-κB signaling pathway. These actions highlight the herb's potential in managing inflammatory conditions and associated diseases.[46]

11.17. Antioxidant

N. sativa acts as an antioxidant by scavenging reactive oxygen species and enhancing endogenous antioxidant enzymes. These antioxidative properties contribute to cellular protection and suggest potential applications in preventing oxidative stress-related diseases.[47,48]

11.18. Antiviral

N. sativa exhibits antiviral effects by inhibiting viral replication and stimulating immune responses. These properties position the herb as a potential natural intervention in combating viral infections and enhancing the body's antiviral defenses.[49]

11.19. Anti-diabetic

The anti-diabetic properties of *N. sativa* involve improving insulin sensitivity and modulating glucose metabolism. These effects suggest its potential role in managing diabetes and related metabolic disorders.[50]

11.20. Anti-allergic

N. sativa demonstrates anti-allergic effects through the modulation of histamine release and the inhibition of allergic inflammatory mediators. These actions position the herb as a potential natural remedy for allergic conditions.[36]

11.21. Bone Health

N. sativa positively impacts bone health by enhancing bone mineral density and promoting osteoblast activity. These effects suggest its potential in supporting bone growth and preventing conditions associated with bone density loss.[12]

11.22. Diuretic

The diuretic effects of *N. sativa* involve enhanced renal excretion of water and electrolytes, along with the modulation of kidney function. These actions suggest its potential in managing conditions related to fluid retention and kidney function.[41]

12. Clinical Investigations and Efficacy of *N. sativa*

12.1. Clinical investigations and efficacy of N. sativa

In the realm of clinical research, N. sativa has been a subject of substantial interest and scrutiny. Various studies have delved into its therapeutic potential, aiming to unravel the diverse health benefits associated with this natural substance.

1. **Anti-Inflammatory and Immunomodulatory Effects:** Numerous studies have emphasized the anti-inflammatory and immunomodulatory attributes of N. sativa. In a randomized, double-blind, placebo-controlled trial, supplementation with *N. sativa* was observed to notably diminish markers of inflammation in rheumatoid arthritis patients. Moreover, a systematic review conducted by Butt et al. illustrated the immunomodulatory effects of *N. sativa*, indicating its potential utility in immune-related disorders.[51,52]
2. **Potential Anticancer Properties:** Research suggests that *N. sativa* may possess anticancer properties through diverse mechanisms, such as apoptosis induction, cell cycle arrest, and anti-proliferative effects. For instance, Gali-Muhtasib et al.'s study reported the potential of thymoquinone, a key component of *N. sativa*, in inhibiting tumor growth and enhancing the effectiveness of conventional cancer therapies.[53]
3. **Cardioprotective Effects:** Numerous clinical trials have investigated the cardioprotective effects of *N. sativa*. Dehkordi et al.'s study, for instance, demonstrated the favorable impacts of *N. sativa* supplementation in reducing cardiovascular risk factors, including blood pressure and lipid profiles, in individuals with mild hypertension.[54]
4. **Antimicrobial Activity:** *N. sativa* has exhibited promising antimicrobial properties against various pathogens, encompassing bacteria, viruses, and fungi. In a study by Ali and Blunden, the essential oil extracted from *N. sativa* seeds showcased significant antimicrobial activity against a spectrum of pathogens, suggesting its potential application in addressing infectious diseases.[55]

12.2. Key studies and findings

Several pivotal studies have contributed significantly to our understanding of *N. sativa*'s efficacy. These investigations have explored its anti-inflammatory and immunomodulatory effects, potential anticancer properties, and cardioprotective benefits. Notably, research has highlighted the role of thymoquinone, a key component

of *N. sativa*, in inhibiting tumor growth and enhancing conventional cancer therapies. Additionally, clinical trials have showcased the cardioprotective impact of *N. sativa* supplementation, particularly in reducing cardiovascular risk factors such as blood pressure and lipid profiles.

12.3. Challenges in clinical trials

Despite the promising findings, clinical trials involving *N. sativa* face certain challenges. These may include methodological complexities, variability in study designs, and the need for larger sample sizes to establish more robust evidence. Addressing these challenges is crucial to ensure the reliability and applicability of the results obtained from clinical investigations involving *N. sativa*.

13. Safety and Adverse Effects of *N. sativa*

N. sativa, an herb with a centuries-old tradition of medicinal use, has garnered attention for its potential health benefits. Despite the exploration of its positive attributes, it is imperative to delve into the safety considerations and potential side effects associated with its utilization.

13.1. Safety profile

Generally acknowledged as safe for consumption, *N. sativa* has served as both a culinary and medicinal herb, offering potential health benefits. A review featured in the Asian Pacific Journal of Tropical Biomedicine attests to the favorable safety profile of *N. sativa*. Its extensive use in traditional medicine has not been significantly linked to reported toxicity or adverse effects.[56]

13.2. Adverse reactions

While the safety profile remains favorable, there exist reported instances of adverse reactions or side effects for some individuals. Common side effects linked to the consumption of *N. sativa* include:

1. **Allergic Reactions:** In rare cases, individuals have reported allergic reactions such as skin rashes, itching, and difficulty breathing following the ingestion or topical application of *N. sativa*. Those with known allergies to plants in the Ranunculaceae family should exercise caution when using *N. sativa*.
2. **Gastrointestinal Disturbances:** Some individuals may experience mild gastrointestinal disturbances, like nausea, vomiting, or an upset stomach, especially when consuming *N. sativa* in higher doses or concentrated forms. However, these effects are typically mild and transient.[55]
3. **Interaction with Medication :** Careful consideration of potential interactions between *N. sativa* and certain medications is essential. *N. sativa*'s impact on metabolic enzymes and drug transporters may lead to interactions with specific medications. Individuals taking medications should consult healthcare professionals before incorporating *N. sativa* into their regimen to prevent potential adverse effects.[57]

13.3. Safety considerations in special populations

Limited research on the safety of *N. sativa* during pregnancy and lactation warrants caution. As a preventive measure, pregnant and lactating women are advised to avoid using *N. sativa* due to insufficient evidence regarding its safety during these stages.

14. Future Directions and Challenges in Unleashing the Potential of *N. sativa*

14.1. Future directions

1. **Advancements in Clinical Trials and Standardization:** Unveiling the full potential of *N. sativa* requires rigorous clinical trials. Establishing standardized protocols for dosage and administration is essential to ascertain its efficacy and safety across diverse patient populations.
2. **Comprehensive Mechanistic Understanding:** Illuminating the precise molecular mechanisms driving the therapeutic effects of *N. sativa* will offer insights into its mode of action, paving the way for the development of targeted therapies for specific ailments.
3. **Innovation in Formulation Development:** Exploring cutting-edge delivery systems and formulations, such as nanoparticles, liposomes, and nanoemulsions, can enhance the bioavailability and stability of bioactive compounds, ultimately improving therapeutic efficacy.
4. **Scrutiny of Drug Interactions and Safety Profile:** Investigating potential drug interactions and evaluating the long-term safety profile of *N. sativa* is crucial for its integration into mainstream medicine, ensuring patient well-being.

14.2. Challenges in commercialization

1. **Quality Control and Standardization Dilemmas:** The absence of standardized procedures for cultivation, harvesting, and extraction poses a substantial challenge in ensuring consistent quality and potency of *N. sativa*-based products.
2. **Bioavailability Challenges:** The suboptimal bioavailability of certain bioactive compounds in N. sativa restricts its therapeutic effectiveness, prompting the need for innovative strategies to enhance absorption and systemic delivery.
3. **Regulatory Obstacles:** Establishing robust regulatory frameworks and guidelines for the commercialization

of *N. sativa*-based products is critical to ensuring their quality, safety, and efficacy for consumer use.

4. ***Global Awareness and Accessibility Struggles:*** Amplifying public awareness about the potential health benefits of *N. sativa* and ensuring its accessibility, particularly in resource-constrained regions, remains a significant challenge for widespread adoption and utilization.

14.3. Research Gaps

1. **Limited Clinical Trials:** While there has been significant interest in the potential therapeutic properties of *N. sativa*, there may be a gap in the number and scope of well-designed clinical trials. Clinical trials provide crucial insights into the efficacy and safety of interventions and are essential for translating preclinical findings into applicable knowledge for human health.
2. **Mechanistic Understanding:** Despite the known traditional uses and some identified bioactive components, there might be gaps in the understanding of the precise molecular mechanisms by which *N. sativa* exerts its therapeutic effects. Elucidating these mechanisms could provide a more targeted approach to its applications.
3. **Long-term Safety Profile:** Although *N. sativa* is generally considered safe, there may be a gap in long-term safety data, especially with prolonged and diverse usage patterns. More research on potential adverse effects and interactions, particularly with chronic use, could contribute to a more comprehensive safety profile.
4. **Standardization and Quality Control:** Standardization of cultivation, harvesting, and extraction processes for *N. sativa* can be an area that needs attention. Ensuring consistent quality and potency of *N. sativa*-based products is crucial for both research and practical applications.
5. **Population-specific Studies:** Research gaps may exist in terms of understanding how the effects of *N. sativa* may vary across different populations, including diverse ethnicities, age groups, and individuals with specific health conditions.
6. **Combination Therapies:** Investigating the potential synergies or conflicts between *N. sativa* and conventional therapies could be an area of research. Understanding how *N. sativa* interacts with other medications or treatments is essential for its safe integration into healthcare practices.

15. Key Findings and Implications for Healthcare and Industry

1. ***Botanical and Chemical Profile:*** The taxonomic classification, morphological insights, and chemical composition of *N. sativa* have been meticulously examined, providing a foundational understanding of its biological characteristics.
2. **Traditional Uses:** The historical significance, cultural practices, and folk remedies associated with *N. sativa* have been explored, shedding light on the rich tapestry of its traditional applications.
3. ***Extraction and Formulation Techniques:*** Various extraction methods and formulation approaches have been discussed, offering insights into the diverse ways in which *N. sativa* can be processed for medicinal use.
4. **Quality Control and Standardization:** Parameters for quality assessment, testing methods, and standardization practices have been outlined, emphasizing the importance of maintaining consistent quality in *N. sativa*-based products.
5. **Regulatory Status:** An overview of the global regulatory landscape and challenges in regulatory compliance has been presented, underscoring the need for a standardized framework for the commercialization of *N. sativa*.
6. **Pharmacological Activities:** The pharmacological activities of *N. sativa*, including anti-inflammatory, antioxidant, immunomodulatory, and antimicrobial effects, have been thoroughly examined, highlighting its potential therapeutic applications.
7. **Clinical Studies and Efficacy:** An overview of clinical research, key studies, and the challenges encountered in clinical trials has been discussed, emphasizing the need for rigorous investigation to establish the efficacy of *N. sativa* in diverse patient populations.
8. **Safety and Side Effects:** Adverse effects, interactions with medications, and safety considerations in special populations have been outlined, providing a balanced perspective on the potential risks associated with *N. sativa* use.
9. **Future Directions and Challenges**: Emerging trends, research gaps, and challenges in commercialization have been identified, guiding future endeavors in the exploration and utilization of *N. sativa*.
10. **Implications for Healthcare and Industry:** The implications of the findings presented in this comprehensive exploration of N. sativa are profound and far-reaching. In healthcare, the identified pharmacological activities suggest a potential role for *N. sativa* in the management of inflammatory, oxidative stress-related, infectious conditions, etc. However, careful consideration of safety aspects, interactions, and regulatory standards is imperative for

its responsible integration into healthcare practices.

In the realm of industry, the diverse extraction and formulation techniques discussed open avenues for the development of innovative *N. sativa*-based products. The emphasis on quality control, standardization, and regulatory compliance underscores the importance of maintaining product integrity for consumer safety and trust.

16. Conclusions

In the culmination of this comprehensive exploration into the multifaceted aspects of N. sativa, it is evident that this natural remedy holds substantial promise for various applications in healthcare and industry. The journey through the intricate layers of *N. sativa*, from its botanical and chemical profile to its traditional uses and contemporary pharmacological activities, has unraveled a wealth of knowledge. In summary, *N. sativa* stands as a valuable natural reservoir endowed with diverse pharmacological attributes and considerable therapeutic promise. Its botanical and chemical makeup, historical applications, pharmacological effects, extraction methods, quality control protocols, regulatory standing, clinical effectiveness, safety profile, and future research trajectories collectively underscore its escalating importance in both modern medicine and the nutraceutical sector. Despite its recognized potential, the limited inclusion of *N. sativa* in pharmacopeias emphasizes the necessity for comprehensive documentation pertaining to its botanical characteristics, chemical composition, and pharmacological properties. Such documentation is pivotal to facilitate its formal incorporation into official monographs and guidelines. Addressing this gap between traditional wisdom and contemporary scientific advancements is crucial, paving the way for the integration of *N. sativa* into evidence-based healthcare practices.

17. 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."

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None.

References

1. Ahmed N. Nigella sativa: A Potent Secondary Metabolite. *Pak Bio Med J*. 2022;5(9):1–2.
2. Khan S, Ali M, Albratty MMA, Najmi AY, Azeem U. Chapter 2 - Nigella sativa: From chemistry to medicine. Elsevier; 2022. Available from: https://doi.org/10.1016/B978-0-12-824462-3.00014-7.
3. 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.
4. Benazzouz-Smail L, Achat S, Brahmi F, Bachir-Bey M, Arab R. Biological Properties, Phenolic Profile, and Botanical Aspect of Nigella sativa L. and Nigella damascena L. Seeds: A Comparative Study. *Molecules*. 2022;28(2):571–571.
5. Khare CP. Encyclopedia of Indian Medicinal Plants: Rational Western Therapy, Ayurvedic and Other Traditional Usage. Botany: Springer; 2004. Available from: https://search.worldcat.org/en/title/56324397.
6. Nyemb JN, Shaheen H, Wasef L, Nyamota R, Segueni N. Black Cumin: A Review of its Pharmacological Effects and its Main Active Constituent. *Pharmacognosy Reviews*. 2022;16(32):107–125.
7. Mogharbel GH, Badawi AS, Zaman AY, Elmoniem MMA, Abdel-Rahman IM. Therapeutic benefits of prophetic medicine remedies in treating hematological diseases (A review article). *American Journal of Blood Research*. 2023;13(4):130–142.
8. Heshmati J, Namazi N. Effects of black seed (Nigella sativa) on metabolic parameters in diabetes mellitus: A systematic review. *Complementary Therapies in Medicine*. 2015;23(2):275–282.
9. Sultana S, Asif HM, Akhtar N, Iqbal A, Nazar H. Nigella sativa: Monograph. *Journal of Pharmacognosy and Phytochemistry*. 2015;4(4):103–106.
10. Chevallier A. The Encyclopedia of Medicinal Plants. vol. 237. New York, NY: DK Publishing; 1996. Available from: https://search.worldcat.org/title/34513394.
11. Hosseini SS, Nadjafi F, Asareh MH, Rezadoost H. Morphological and yield related traits, essential oil and oil production of different landraces of black cumin (Nigella sativa) in Iran. *Scientia Horticulturae*. 2018;233:1–8.
12. Ahmad A, Husain A, Mujeeb M, Khan SA, Najmi AK. A review on therapeutic potential of N. sativa: A miracle herb. *Asian Pac J Trop Biomed*. 2013;3(5):60075–60076.
13. Mahmud NM, Paraoan L, Khaliddin N, Kamalden TA. Thymoquinone in Ocular Neurodegeneration: Modulation of Pathological Mechanisms via Multiple Pathways. Front. *Cell Neurosci*. 2022;16:786926–786926.
14. Majeed A, Muhammad Z, Ahmad H, Hayat SSS, Inayat N. Nigella sativa L.: Uses in traditional and contemporary medicines - An overview. *Acta Ecologica Sinica*. 2021;41(4):253–258.
15. Srinivasan K. 2018. Available from: https://doi.org/10.1093/fqsafe/fyx031.
16. Khoddami A, Ghazali HM, Yassoralipour A, Ramakrishnan Y, Ganjloo A. Physicochemical Characteristics of Nigella Seed (Nigella sativa L.) Oil as Affected by Different Extraction Methods. *Journal of the American Oil Chemists' Society*. 2011;88:533–540.
17. Mazaheri Y, Torbati M, Azadmard-Damirchi S, Savage GP. A comprehensive review of the physicochemical, quality and nutritional properties of Nigella sativa oil. *Food Reviews International*. 2019;35(4):342–362.
18. Monograph EH. 2022. Available from: https://edaegypt.gov.eg/media/qmgijjsm/nigella-sativa-l----.pdf.
19. Kanter M. Nigella sativa and Derived Thymoquinone Prevents Hippocampal Neurodegeneration After Chronic Toluene Exposure in Rats. *Neurochem Res*. 2008;33:579–88.
20. Rathore C, Hemrajani C, Sharma AK, Gupta PK, Jha NK. Self-nanoemulsifying drug delivery system (SNEDDS) mediated improved oral bioavailability of thymoquinone: Optimization, characterization, pharmacokinetic, and hepatotoxicity studies. *Drug Deliv Transl Res*. 2023;13:292–307.
21. Khader M, Bresgen N, Eckl PM. In vitro toxicological properties of thymoquinone. *Food Chem Toxicol*. 2009;47(1):129–33.
22. Chowdhury MA, Shuvho MA, Kashem MA, Shahid MA, Hossain N. Conceptual Analysis of Microbial Processes and Drug Delivery System by the Active Ingredients of Nigella sativa. *Biointerface Res Appl Chem*. 2023;13(1):1–13.

23. Pachaiappan R, Nagasathiya K, Singh PK, Gopalakrishnan AV, Velusamy P. Phytochemical profile of black cumin (Nigella sativa L.) seed oil: identification of bioactive anti-pathogenic compounds for traditional Siddha formulation. *Biomass Conv Bioref*. 2023;13:14683–14695.
24. Sharma NK, Ahirwar D, Gupta S, Jhade D. Pharmacognostic standardization, physico and phytochemical evaluation of Nigella sativa Linn. seed. *International Journal of Pharmaceutical Sciences and Research*. 2011;2(3):712–718.
25. Ahmad R, Ahmad N, Amir M, Aljhisi F, Alamer MH. Variation in Nigella sativa quality and its standardization via instrumental analysis: A study based on geographical origin. *Notulae Botanicae Horti Agrobotanici Cluj-Napoca*. 2020;48(3):1141–1154.
26. Yimer EM, Tuem KB, Karim A, Ur-Rehman N, Anwar F. Nigella sativa L. (Black Cumin): A Promising Natural Remedy for Wide Rrange of Illnesses. Evid Based Complement Alternat Med. *Article ID 1528635*. 2019;.
27. Tariq M. Nigella sativa seeds: Folklore Treatment in Modern Day Medicine. *Saudi J Gastroenterol*. 2008;14(3):105–106.
28. Al-Seeni MN, Rabey HAE, Zamzami MA, Alnefayee AM. The hepatoprotective activity of olive oil and Nigella sativa oil against CCl4 induced hepatotoxicity in male rats. *BMC Complementary and Alternative Medicine*. 2016;16:438–438.
29. Majdalawieh AF, Fayyad MW. Recent advances on the anti-cancer properties of Nigella sativa, a widely used food additive. *Journal of Ayurveda and Iintegrative Medicine*. 2016;7(3):173–180.
30. Mohamed HA, El-Sayed IH, Moawad M. Protective effect of Nigella sativa seeds against dimethylaminoazobenzene (DAB) induced liver carcinogenesis. *Nat Sci*. 2010;8(6):80–87.
31. Khan MA, Tania M, Fu S, Fu J. Thymoquinone, as an anticancer molecule: from basic research to clinical investigation. *Oncotarget*. 2017;8(31):51907–51919.
32. Hadi V, Pahlavani N, Malekahmadi M, Nattagh-Eshtivani E, Navashenaq JG. Nigella sativa in controlling Type 2 diabetes, cardiovascular, and rheumatoid arthritis diseases: Molecular aspects. *Journal of Research in Medical Sciences: the official journal of Isfahan University of Medical Sciences*. 2021;26(1):20–20.
33. Pandey N, Shri P, Pandey H, Tripathi YB. Radiation Induced Gastrointestinal Damage and Protection: Nigella Sativa Seed Extract and Thymoquinone. *Def Life Sci J*. 2017;2(3):264–269.
34. Bukar MA, Ishaya HB, Dibal NI, Attah MOO. Gastroprotective Effect of Nigella sativa Seed on Ethanol-induced Gastric Ulcer in Rats. *Libyan Journal of Medical Sciences*. 2017;1(3):63–67.
35. Adam GO, Rahman MM, Lee SJ, Kim GB, Kang HS. Hepatoprotective effects of Nigella sativa seed extract against acetaminophen-induced oxidative stress. *Asian Pacific Journal of Tropical Medicine*. 2016;9(3):221–227.
36. Koshak A, Koshak E, Heinrich M. Medicinal benefits of N. sativa in bronchial asthma: A literature review. *Saudi Pharmaceutical Journal*. 2017;25(8):1130–1136.
37. Perveen T, Haider S, Zuberi NA, Saleem S, Sadaf S. Increased 5-HT Levels Following Repeated Administration of Nigella sativa L. (Black Seed) Oil Produce Aantidepressant Effects in Rats. *Sci Pharm*. 2014;82(1):161–170.
38. Akbar A. Antidepressant and anti-nociceptive effects of Nigella sativa and its main constituent, thymoquinone: A literature review. *Asian pacific Journal of Tropical Biomedicine*. 2022;12(12):495–503.
39. Rouhi-Boroujeni H, Asadi-Samani M, 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.
40. Marbat MM, Ali MA, Hadi AM. The use of Nigella sativa as a single agent in treatment of male infertility. *Tikrit Journal of Pharmaceutical Sciences*. 2013;9(1):19–29.
41. Sallehuddin N, Nordin A, Idrus RBH, Fauzi MB. Nigella sativa and Its Active Compound, Thymoquinone, Accelerate Wound Healing in an In Vivo Animal Model: A Comprehensive Review. *Int J Environ Res Public Health*. 2020;17(11).
42. Islam MH, Ahmad IZ, Salman MT. Neuroprotective effects of Nigella sativa extracts during germination on central nervous system. *Pharmacogn Mag*. 2015;11(1):182–189.
43. Hayatdavoudi P, Rad AK, Rajaei Z, Hadjzadeh MA. Renal injury, nephrolithiasis and Nigella sativa: A mini review. *Avicenna J Phytomed*. 2016;6(1):1–8.
44. Hanafy MS, Hatem ME. Studies on the antimicrobial activity of Nigella sativa seed (black cumin). *J Ethnopharmacol*. 1991;34(2-3).
45. Khan MAU, Ashfaq MK, Zuberi HS, Mahmood MS, Gilani AH. The in vivo antifungal activity of the aqueous extract from Nigella sativa seeds. *Phytotherapy Research: An International Journal Devoted to Pharmacological and Toxicological Evaluation of Natural Product Derivatives*. 2003;17(2):183–186.
46. Majdalawieh AF, Fayyad MW. Immunomodulatory and anti-inflammatory action of Nigella sativa and thymoquinone: A comprehensive review. *Int Immunopharmacol*. 2015;28(1):295–304.
47. Kavyani Z, Musazadeh V, Golpour-Hamedani S, Moridpour AH, Vajdi M. The effect of Nigella sativa (black seed) on biomarkers of inflammation and oxidative stress: an updated systematic review and meta-analysis of randomized controlled trials. *Inflammopharmacology*. 2023;31(3):1149–1165.
48. Tiji S, Benayad O, Berrabah M, Mounsi IE, Mimouni M. Phytochemical Profile and Antioxidant Activity of Nigella sativa L Growing in Morocco. *The Scientific World Journal*. 2021;.
49. Usmani H, Malik S, Arya A, Mahto P, Kant R, Dua R, et al. Effects of Active Compounds of Nigella sativa in COVID-19: A Narrative Review. *Recent Adv Antiinfect Drug Discov*. 2023;.
50. Bamosa AO, Kaatabi H, Lebdaa FM, Elq A, Al-Sultanb A. Effect of Nigella sativa seeds on the glycemic control of patients with type 2 diabetes mellitus. *Indian J Physiol Pharmacol*. 2010;54(4):344–54.
51. Akhondian J, Kianifar H, Raoofziaee M, Moayedpour A, Toosi MB. The effect of thymoquinone on intractable pediatric seizures (pilot study). *Epilepsy Res*. 2011;93(1):39–43.
52. Dhaheri A, Wali Y, Akbar AF, Rasool I, Razmpoor S. Chapter 3 - Nigella sativa, a cure for every disease: Phytochemistry, biological activities, and clinical trials. and others, editor. Elsevier; 2022. p. 63–90. Available from: https://doi.org/10.1016/B978-0-12-824462-3.00011-1.
53. Gali-Muhtasib H, Assaf MD, Boltze C, Al-Hmaira J, Hartig R. Thymoquinone extracted from black seed triggers apoptotic cell death in human colorectal cancer cells via a p53-dependent mechanism. *Int J Oncol*. 2004;25(4):857–66.
54. Dehkordi FR, Kamkhah AF. Antihypertensive effect of Nigella sativa seed extract in patients with mild hypertension. *Fundamental Clin Pharmacol*. 2008;22:447–52.
55. Ali BH, Blunden G. Pharmacological and toxicological properties of Nigella sativa. *Phytotherapy Res*. 2003;17(4):299–305.
56. Ahmed JH, Ibraheem AY, Al-Hamdi KI. Evaluation of efficacy, safety and antioxidant effect of Nigella sativa in patients with psoriasis: A randomized clinical trial. *Journal of Clinical and Experimental Investigation*. 2014;5(2):186–193.
57. Joseph L, Puthillath RE, Rao SN. Drug Interaction analysis - Nigella sativa L. seed (Black Cumin) ethanolic extract on antiseizure activity of Phenobarbitone sodium. *Asian Journal of Medical Sciences*. 2020;11(2):18–20.

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