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Mini Review

Could *Nigella sativa* Extract be a Promising Anticancer Agent?

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Abstract

Nigella sativa, commonly known as black seed, has a long history of traditional use in folk medicine. Recent scientific investigations have highlighted its significant therapeutic potential, particularly in cancer treatment. Thymoquinone, the primary bioactive compound in *N. sativa*, has demonstrated promising anticancer properties in numerous preclinical studies. This review comprehensively examines the current understanding of *N. sativa*'s anticancer potential, focusing on the pharmacological actions of thymoquinone. We analyzed high-quality research articles from various databases to assess the efficacy of *N. sativa* and its constituents in cancer treatment. Furthermore, we explored the potential of *N. sativa* as an adjunct therapy within existing cancer treatment guidelines. Finally, we discuss the safety profile of *N. sativa* and propose future research directions to fully realize its therapeutic potential in cancer management.

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INTRODUCTION

Nigella sativa, widely recognized as black seed, particularly in Egypt and the Middle East, possesses a rich historical and cultural significance[1]. Known by a variety of common names, including black cumin, black caraway, blessed seed, and fennel flower, this plant belongs to the Ranunculaceae family, generally regarded for its relatively safe profile and fewer reported adverse effects[2]. *Nigella sativa* thrives in hot subtropical and tropical climates, with cultivation prevalent in regions such as Egypt, the Middle East, India, Mexico, the southern United States (Florida), and the West Indies[3]. For centuries, *N. sativa* has been an integral component of traditional folk medicine, often employed to alleviate a diverse range of symptoms and support conventional drug therapies in managing various diseases[4].

The therapeutic potential of *N. sativa* is largely attributed to its complex phytochemical composition, with thymoquinone representing approximately 50% of the key active constituents within its essential oil[5]. Thymoquinone has demonstrated a broad spectrum of pharmacological activities, including significant anti-proapoptotic, anti-inflammatory, antioxidant, anti-carcinogenic, and anti-fibrotic effects[6]. In addition to thymoquinone, other notable bioactive compounds present in *N. sativa* include dithymoquinone (nigellone), thymohydroquinone, p-cymene, carvacrol, 4-terpineol, t-anethol, the sesquiterpene longifolene, α-pinene, thymol, the saponin α-hederin, as well as isoquinoline and pyrazol alkaloids[7,8]. The synergistic or individual actions of these constituents contribute to the diverse pharmacological properties observed in *N. sativa*.

A substantial body of scientific literature has indicated that *N. sativa* and its isolated bioactive constituents exhibit a considerable role in the prevention and management of numerous human diseases[9-11]. This mini-review will specifically focus on elucidating the efficacy of *N. sativa* and its key components in suppressing carcinogenesis. By examining the existing preclinical and clinical evidence, this article aims to provide a concise yet comprehensive overview of the potential of *N. sativa* as a complementary or alternative therapeutic strategy in the context of cancer prevention and treatment.

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DATA COLLECTION METHODOLOGY

A comprehensive literature search was conducted to identify high-quality articles and clinical trials evaluating the anticancer potential of *N. sativa*. The following electronic databases were systematically searched up to July 2024: PubMed, Google Scholar, Wiley Online Library, Scopus, and ScienceDirect. The search strategy employed the following keywords and their combinations: "Medicinal plants", "Nigella sativa", "Thymoquinone", "Herbal medicine", "anticancer", and "cancer". To ensure a thorough and inclusive review, the reference lists of identified articles were also manually screened for potentially relevant publications. This iterative search process was repeated to capture additional pertinent studies that met the inclusion criteria for this mini-review[12].

The selection and interpretation of the included literature were based on a critical evaluation of the experimental results reported by the original authors. Particular attention was paid to studies investigating the effects of thymoquinone, the primary bioactive compound of *N. sativa*, across various cancer types. The extracted data encompassed study design, experimental models, treatment regimens, and reported anticancer effects.

Finally, to visually represent the trends in research output related to the anticancer potential of *N. sativa*, data on the number of publications over time were compiled. Microsoft Office Excel was utilized to generate the accompanying chart (**Figure 1**), illustrating the evolving research landscape in this field. This trend analysis highlights the growing scientific interest in *N. sativa*, particularly concerning the anticancer activities of thymoquinone against a spectrum of malignancies, including breast, prostate, and lung cancers. The observed increase in research activity underscores the expanding recognition of *N. sativa* as a promising candidate for complementary and alternative medicine in oncology.

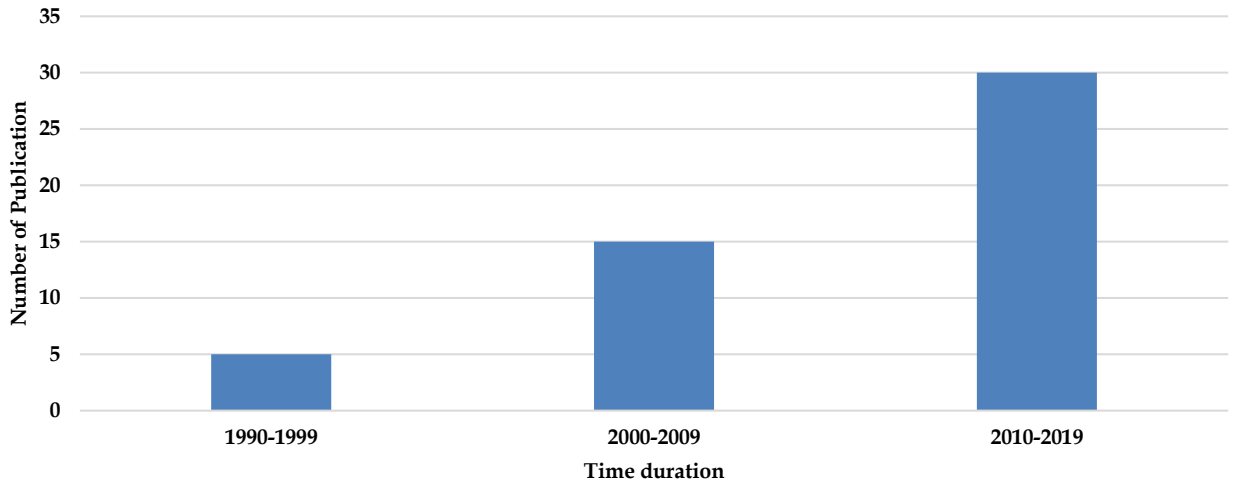

Figure 1. The number of publications illustrating the potential anti-cancer activity of *N. sativa*.

NIGELLA SATIVA AS AN ANTICANCER AGENT

Thymoquinone, a prominent bioactive compound derived from *N. sativa*, has garnered significant attention for its diverse anticancer potential across various malignancies. Its therapeutic efficacy stems from its ability to modulate multiple oncogenic pathways[13,14]. Mechanistically, thymoquinone exhibits a range of anti-cancer activities, including the inhibition of angiogenesis and metastasis, the prevention of oxidative stress and inflammation, and the induction of apoptosis[15,16]. Furthermore, thymoquinone influences gene expression by upregulating tumor suppressor genes and downregulating tumor-promoting genes, highlighting its multifaceted role in controlling cancer development and progression[17,18].

A key aspect of thymoquinone's anticancer action involves the disruption of cancer cell proliferation through cell cycle modulation and interference with essential cellular machinery[15,19]. Studies have demonstrated that thymoquinone can induce cell cycle arrest at different phases depending on the cancer type and drug concentration[20,21]. For instance, thymoquinone triggers G1 phase arrest in breast, osteosarcoma, and colon cancer cells by modulating the expression of cyclins (E and D) and cyclin-dependent kinase (CDK) inhibitors (p21 and p27). Notably, the concentration of thymoquinone

dictates its specific cell cycle target, with higher concentrations leading to G2 arrest and lower concentrations inducing S phase arrest, underscoring the importance of dosage in its therapeutic application[16,22,23]. Additionally, thymoquinone disrupts microtubule dynamics and downregulates proteins crucial for cancer cell survival, further contributing to its antiproliferative effects[24].

Beyond its direct anticancer effects, thymoquinone demonstrates promising synergistic potential when combined with conventional chemotherapeutic agents, offering a strategy to overcome drug resistance and enhance treatment efficacy[25,26]. Preclinical studies have shown that thymoquinone can potentiate the effects of drugs like doxorubicin, gemcitabine, oxaliplatin, ifosfamide, cisplatin, 5-fluorouracil, thalidomide, and bortezomib in various cancer cell lines and animal models[27-32]. This chemosensitizing effect is often attributed to thymoquinone's ability to modulate key molecular targets involved in cancer progression and drug resistance, including PTEN, PPAR-γ, p73, p53, NF-κB signaling, STAT3 pathways, and the activation of caspases[33-36]. Moreover, encapsulation of thymoquinone into nanoparticles has shown promise in enhancing its bioavailability and anticancer activity, highlighting a potential avenue for future therapeutic development[37].

NIGELLA SATIVA REDUCES ADVERSE REACTIONS OF SOME ANTICANCER AGENTS

Preclinical evidence derived from animal studies suggests a promising role for thymoquinone in mitigating the adverse effects associated with certain chemotherapeutic agents. Specifically, findings indicate that thymoquinone exhibits a protective effect against cisplatin-induced nephrotoxicity, as well as potentially counteracting deleterious drug-related alterations in hemoglobin levels and leucocyte count[38,39]. Furthermore, animal model investigations propose that thymoquinone may also offer protection against doxorubicin-induced renal toxicity. These consistent observations across different animal models and chemotherapeutic agents highlight the potential of thymoquinone as a supportive therapeutic strategy to ameliorate chemotherapy-related toxicities[40]. However, it is crucial to acknowledge that these findings are based on preclinical research, and further rigorous investigation, including human clinical trials, is warranted to validate these protective effects and establish their clinical relevance.

NIGELLA SATIVA SAFETY

Based on its extensive historical use as both a food source and within traditional medicine, *N. sativa* is generally regarded as possessing a favorable safety profile. However, a comprehensive understanding of its safety at therapeutic dosages necessitates further rigorous scientific investigation. While dietary consumption appears to be well-tolerated, caution is advised in individuals with pre-existing immune disorders[41]. Furthermore, individuals with a known allergy or hypersensitivity to plants belonging to the Ranunculaceae family should avoid *N. sativa* preparations. Notably, case study reports have documented instances of allergic contact dermatitis following the topical application of *N. sativa* oil, highlighting the potential for localized hypersensitivity reactions[42]. Therefore, while its historical use suggests a general safety, ongoing research at therapeutic levels and awareness of potential allergic reactions are crucial for establishing a complete safety profile of *N. sativa*.

FUTURE PERSPECTIVES

Despite the growing body of evidence supporting the therapeutic potential of *N. sativa*, several critical areas warrant further rigorous scientific investigation. Notably, comprehensive and reliable data regarding the full spectrum of adverse reactions associated with *N. sativa* consumption, particularly at supranutritional doses, remains limited and necessitates systematic evaluation. Furthermore, the considerable preclinical interest in *N. sativa* as a novel anticancer therapeutic agent presents a compelling avenue for ongoing and future research. While current evidence suggests that *N. sativa* is likely safe when consumed in typical dietary amounts, the safety profile of higher doses, potentially relevant for therapeutic applications, has not been adequately characterized through robust scientific inquiry. Addressing these knowledge gaps through well-designed clinical and toxicological studies is crucial for a comprehensive understanding of *N. sativa*'s therapeutic utility and for translating its potential benefits into safe and effective clinical practice.

CONCLUSION

In summary, *N. sativa* demonstrates promising moderate to potent anticancer potential across a spectrum of tumor types. Its multifaceted pharmacological actions and diverse mechanisms of action contribute to its ability to combat cancerous cells. Notably, *N. sativa* exhibits a favorable safety profile at reported dosages, with the primary contraindication being known hypersensitivity. Given its preclinical efficacy and safety profile, physicians and clinical practitioners may consider incorporating thymoquinone, a key bioactive constituent of *N. sativa*, as an adjunct therapy within clinical guidelines and treatment protocols for both the prevention and management of carcinogenesis and its associated complications. Furthermore, the diverse array of *N. sativa* phytoconstituents presents significant opportunities for the development of novel commercial pharmaceutical and cosmeceutical products.

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AUTHORS' CONTRIBUTION

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Writing - original draft: Mennatallah Shabana, Ahmed Abd El-Moniem Amer
Writing - review & editing: Ahmed Abd El-Moniem Amer

DATA AVAILABILITY

All data supporting the findings of this mini-review are presented within the article itself. For any further clarification or specific datasets, the authors are available for reasonable requests.

CONFLICT OF INTEREST

The authors declare no conflicts of interest related to this study.

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