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Review article

Application of Thymoquinone in scaffold-based wound healing strategies: Current advances and future perspectives

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Abstract

Objective: Wound healing is a complex, multi-phase process that can be impaired by factors such as diabetes, infection, and oxidative stress. Among natural bioactive compounds, thymoquinone has shown considerable therapeutic potential. Therefore, this review aims to comprehensively evaluate the application of thymoquinone in scaffold-based wound healing strategies, with particular emphasis on its incorporation into biomaterial scaffolds, underlying mechanisms of action, therapeutic potential, and recent advances in tissue regeneration.

Materials and Methods: In the present study, studies on the relationship between *Nigella sativa* and its most important and main bioactive component, thymoquinone, in wound healing were conducted by searching Google scholar, PubMed, Science Direct and Medline Plus databases for articles published between 2001 and 2024.

Results: The evaluation of the data indicated that thymoquinone has anti-inflammatory, antioxidant and antibacterial properties and helps to improve the wound healing process.

Conclusion: The use of this substance alone or in combination with other natural healing agents is a promising approach for healing wounds, especially in conditions such as diabetes and chronic infections.

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Introduction

Wound healing is affected by several intrinsic and extrinsic factors including age, nutrition, underlying medical conditions, and infection presence. In clinical practice, chronic wounds which deviate from the usual healing phases—cause great challenges that lead to longer disease and more expensive treatment (Khazaei et al. 2024b). Thus, treatments that might enhance the wound-healing process and get over the limitations of current treatment modalities are much needed. One area of research showing promise is the use of natural chemicals—more especially, those derived from medicinal plants—which have shown ability to improve wound healing process (Alizadeh et al. 2022; El-Ashram et al. 2021).

Originally from South Asia and the Mediterranean, *Nigella sativa*—also known as black seed or black cumin—is a flowering plant. Because of its claimed therapeutic benefits—anti-inflammatory, antioxidant, and antibacterial—the seeds of this plant have been used for millennia in traditional medicine. The major active component of *N. sativa*, thymoquinone, has attracted attention lately because of its therapeutic effects in curing many medical conditions, including wound healing. Thymoquinone has shown the capacity to control several fundamental biological processes linked with wound healing, including the development of new blood vessels, fibroblast growth and migration, and modification of inflammatory responses (Sallehuddin et al. 2020a).

A new study on thymoquinone effect on wound healing shows that it may help the healing process in more than one way. Collagen production, angiogenesis, and oxidative stress reduction are all important for wound healing, and thymoquinone has been shown to help with all of them. Another new way to improve the medical benefits of thymoquinone is to combine it with different kinds of support materials (Selçuk et al. 2013). Three-dimensional structures called scaffolds help cells stick together, grow, and change into different types of cells, which allows tissues to grow back. Thymoquinone can attach to different types of scaffolds including natural polymers, manmade polymers, and hybrid materials, to create a targeted delivery system that makes the drugs more bioavailable and effective at the wound site. The use of thymoquinone-loaded supports has made huge progress in the field of wound treatment. These structures give thymoquinone a managed way to get to the right places and give cells a place to work, which improves the mending process as a whole (Rahmani-Moghadam et al. 2021) (Figure 1).

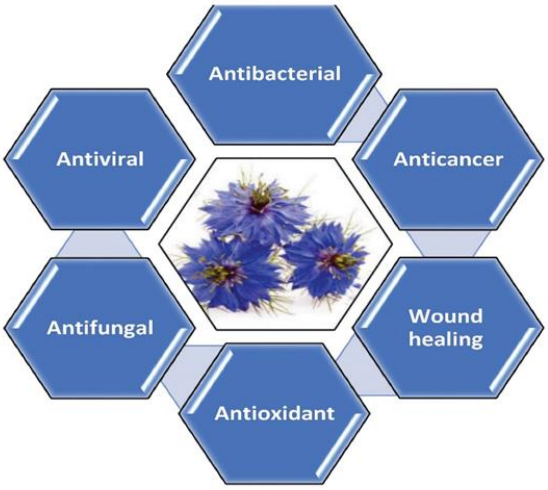

Figure 1. Main characteristics of thymoquinone

Materials and Methods

This narrative review was conducted to explore the role of thymoquinone-loaded scaffolds in wound healing applications. A comprehensive literature search was performed using electronic databases including Google scholar, PubMed, Science Direct and Medline Plus databases. Relevant articles published up to between 2001 and 2024 were identified using combinations of keywords such as *thymoquinone*, *wound healing*, *scaffolds*, *biomaterials*, and *drug delivery systems*. Eligible studies included are original research articles and reviews published in English that investigated the application of thymoquinone in scaffold-based wound healing strategies . Studies unrelated to wound healing, lacking full-text availability, or not involving scaffold-based systems were excluded. The selection of articles was based on relevance determined through title and abstract screening, followed by full-text evaluation. Key information regarding scaffold type, fabrication methods, biological outcomes, and therapeutic efficacy was extracted and qualitatively analyzed to provide an integrative overview of current advancements in the field.

Results

Nigella sativa

Nigella sativa (family Ranunculaceae) is a widely used medicinal plant with a long history in traditional systems such as Unani, Ayurveda, and Siddha. Its seeds and oil hold significant cultural and therapeutic importance. In Islamic literature, particularly "*Tibb-e-Nabwi*" (Prophetic Medicine), it is regarded as a highly effective remedy. Numerous studies highlight its potential due to bioactive compounds with broad pharmacological applications. Thus, *N. sativa* remains a promising natural source for disease treatment (Begum and Mannan 2020). Key active chemicals in *N. sativa* comprise thymoquinone (30-48%), thymohydroquinone, dithymoquinone, p-cymene (7-15%), carvacrol (6-12%), 4-terpineol (2-7%), t-anethol (1-4%), longifolene (1-8%), α-pinene, and thymol. Moreover, black seeds contain trace quantities of additional chemicals including oligocondensation products. The seeds of *N. sativa* comprise 26.7% protein, 28.5% fat, 24.9% carbs, 8.4% crude fiber, and 4.8% total ash. They also encompass an array of vitamins and minerals, including copper, phosphorus, zinc, and iron, along with carotene, which may be metabolized into vitamin A in the liver. Vanillic acid has been found in the roots and shoots of *N. sativa* (Al-Jassir 1992; Malik et al. 1995; Nickavar et al. 2003). Preclinical and clinical studies demonstrate various effects of this seed on multiple body systems including antibacterial, antiviral, antifungal, anti-hair loss, antioxidant, preservative, sun protection, wound healing, antimelanogenic, anti-inflammatory, anti-aging, anticancer (notably skin cancer), vitiligo, antidiabetic, cosmetic applications, hypotensive, hypoglycemic, gastroprotective, nephroprotective, cardiovascular activity, pulmonary-protective activity, anti-asthmatic, and hepatoprotective effects (Begum and Mannan 2020; Hosseinzadeh et al. 2016). In rat models, thymoquinone (TQ) exhibited protective benefits against olanzapine-induced hepatic and renal damage by diminishing oxidative stress indicators and enhancing antioxidant state. TQ shown the capacity to alleviate metabolic adverse effects, such as weight gain and changes in lipid profiles (Bilgiç et al. 2017; Parvardeh et al. 2018). Moreover, this seed can have beneficial benefits in the management of hypercholesterolemia, obesity, Hashimoto's thyroiditis, allergic rhinitis, seizures, rheumatoid arthritis, memory, attention, and cognitive impairments, as well as nonalcoholic fatty liver disease (Ustun-Argon et al. 2022).

Effect of thymoquinone on wound healing

Despite its medicinal promise, TQ restricted bioavailability and susceptibility to light and heat provide obstacles for pharmaceutical development. Recent initiatives have concentrated on enhancing its bioavailability for clinical use (Goyal et al. 2017). Although multiple preclinical studies substantiate TQ effectiveness, human clinical trials are still required to comprehensively assess its therapeutic potential (Darakhshan et al. 2015; Goyal et al. 2017). TQ beneficial effects are largely attributed to its modulation of the Nrf2 signaling pathway (Talebi et al. 2021). The beneficial benefits of TQ on wound healing occur through many routes. Induction of angiogenesis, anti-inflammatory effects, collagen production, fibroblast proliferation, and antibacterial properties (Ti et al. 2022; Vitale et al. 2022). TQ has shown significant efficacy in mitigating tissue damage resulting from ischemia-reperfusion, a condition defined by transient blood flow restriction followed by restoration to an organ or tissue

(Hosseinzadeh et al. 2007). Moreover, TQ has antibacterial effects and can alter resistance to several illnesses (Canpolat et al. 2021). Moreover, research has shown that it can augment anti-inflammatory effects, reduce oxidative stress, stimulate fibroblast proliferation and development, expedite wound contraction, and boost re-epithelization (Negi et al. 2020; Selçuk et al. 2013). According to the principal findings of a pre-clinical study on rats, TQ treatment—encompassing topical, systemic, or combined modalities—expedited wound healing by diminishing necrotic regions, augmenting antioxidant levels, alleviating oxidative stress, and leading to reduced bacterial counts, thereby potentially facilitating improved healing (Selçuk et al. 2013). *Nigella sativa* essential oil, TQ, and carvacrol exhibit antibacterial activity against both methicillin-susceptible and methicillin-resistant *Staphylococcus aureus* by inhibiting efflux pumps and disrupting bacterial membrane integrity (Mouwakeh et al. 2019). Moreover, notable antimicrobial efficacy against *Listeria monocytogenes* has been reported for TQ, reducing antibiotic minimum inhibitory concentrations (MICs) and inhibiting efflux pump activity. These effects are presumably attributable to the ability of TQ to block bacterial efflux pumps and compromise bacterial membrane integrity (Mouwakeh et al. 2018). Thymoquinone, an efficient topical agent for wound therapy, provides direct delivery to targeted regions; nevertheless, its therapeutic efficacy is constrained by poor solubility, inadequate skin penetration, and limited systemic bioavailability. Notwithstanding these constraints, it has potential in medicinal applications (Al-Qubaisi et al. 2019; Rani et al. 2018). Alloxan-induced diabetic rats were used as a chronic delayed wound model, and TQ was administered at a concentration of 10% w/v. The results showed that TQ accelerated wound healing during the inflammatory phase, likely due to its antioxidant, anti-inflammatory, and antibacterial activities. However, in the proliferative phase, TQ slowed the healing process, which appears to be related to its antiangiogenic activity. This differential effect suggests that the therapeutic application of TQ in clinical settings requires careful consideration of the wound healing stage, as well as optimization of dose and delivery method. Further studies, particularly in human models, are necessary to clarify these effects and support safe and effective clinical translation (Yusmin and Ahmad 2017). A further research demonstrated that TQ, delivered systemically and/or topically, enhances wound healing in a rat burn model by decreasing inflammation and oxidative stress (Selçuk et al. 2013). TQ enhanced cell survival, promoted wound healing, and elevated the protein levels of β-catenin *in vitro*, indicating its potential as an effective wound-healing agent (Pekmez and Mılat 2020). Certain herbal extracts may be efficacious in the healing of mucosal wounds. A pre-clinical investigation on rats demonstrated enhanced healing of colon anastomosis by increased bursting pressure, hydroxyproline levels, and fibrous tissue synthesis (Kızıltan et al. 2016).

Thymoquinone-loaded scaffolds in wound healing

Various scaffold technologies, including hydrogels, nanofibers, films, and 3D-printed matrices, have been explored as delivery systems for TQ in wound healing applications. Each type offers distinct advantages and limitations depending on wound characteristics such as exudate level, infection risk, and tissue ischemia. A critical understanding of these scaffold types is essential to guide the selection of an appropriate delivery system. Research shows that while over 200 synthetic and natural polymers are used in biomedical applications, only a small number are appropriate for electrospinning (Ferahtia 2021; Khazaei et al. 2024a). While polyvinyl alcohol is a synthetic, non-ionic, hydrophilic polymer, it is not commonly used in technical applications despite its high potential for electrospun nanofiber fabrication. However, in biomedical applications, particularly skin tissue engineering, it is frequently employed as a researched scaffold for wound dressing (Baykara and Taylan 2021). Research has indicated that a 5 to 10% Polyvinyl alcohol (PVA)solution has good fiber content. PVA is a green polymer that is also non-toxic, biodegradable, and has excellent film forming characteristics (Shahid et al. 2022). In a study, Ali et al. created PVA-based nanofiber mats containing *N. sativa* extract to examine the antibacterial qualities and wound healing. The structure, bonding behavior, and moisture management capabilities of the created electrospun nanofibers have all been examined in the study. Additionally, the wound-healing properties of the mats as well as their antibacterial activity against the microorganisms *Escherichia coli* and *Staphylococcus aureus* were investigated. By forming inhibition zones of 10.27 mm and 7.8 mm against both bacterial cells,*(Escherichia coli and Staphylococcus aureus)* the inclusion of *N. sativa* extract into PVA mats demonstrated good antibacterial efficacy. It was found that by creating a network structure on the skin, the generated mats quickly healed the wound. The scanning electron microscopy (SEM) analysis showed the formation of nanofiber having diameter of 178.8 ± 16.9 nm and the presence of TQ in the electrospun fibers was confirmed by fourier transform infrared spectroscopy (FTIR). Besides, the developed mat was classified as water penetrated according to American Association of Textile Chemists and Colorists (AATCC) test characteristics. Thus, the newly developed nanofibrous mat could turn out to be a suitable material for the wound dressing purpose (Ali et al. 2021a).

Researchers are interested in using nanotechnology in conjunction with biological materials to produce different kinds of nanocomposites with various morphologies for rapid skin regeneration, which is a recent focus of tissue engineering. For the reasons stated above, Alam et al. used the electrospinning process to create a hybrid nano-biological scaffold for skin tissue creation that included collagen, *N. sativa*, and chitosan in varied ratios. The mentioned scaffolds performed FESEM, FTIR analysis, tensile property studies, antibacterial activity examinations, and wound healing evaluations. The analysis of the data suggested that the scaffolds loaded with 50% collagen, 25% *N. sativa* extract, and 25% chitosan create an excellent fiber diameter of around 381 ± 22 nm and a porosity of approximately 78 ± 6.9%. Additionally, the resultant scaffolds demonstrated excellent antibacterial activity against *E. coli* and *S. aureus*, suggesting that they are appropriate for suppressing bacterial activity. Data analysis revealed that wound closure in the mentioned scaffolds takes approximately 10 days, which is 1.5 times faster than the time it takes for a commercial bandage (standard gauze dressing) used as control. While these results are promising, it is important to critically evaluate the study: the sample size was limited, and the exact characteristics of the commercial bandage were not fully detailed, which may affect the comparability of results. Moreover, the study was conducted in animal models, and clinical translation in humans remains to be confirmed. These limitations highlight the need for further investigations to validate the effectiveness of N. *sativa*-loaded scaffolds in diverse wound types. Overall, these results indicate that skin tissue engineering may benefit from the constructed scaffold, but careful consideration of study design, control selection, and translational relevance is essential (Alam et al. 2023) (Figure 2).

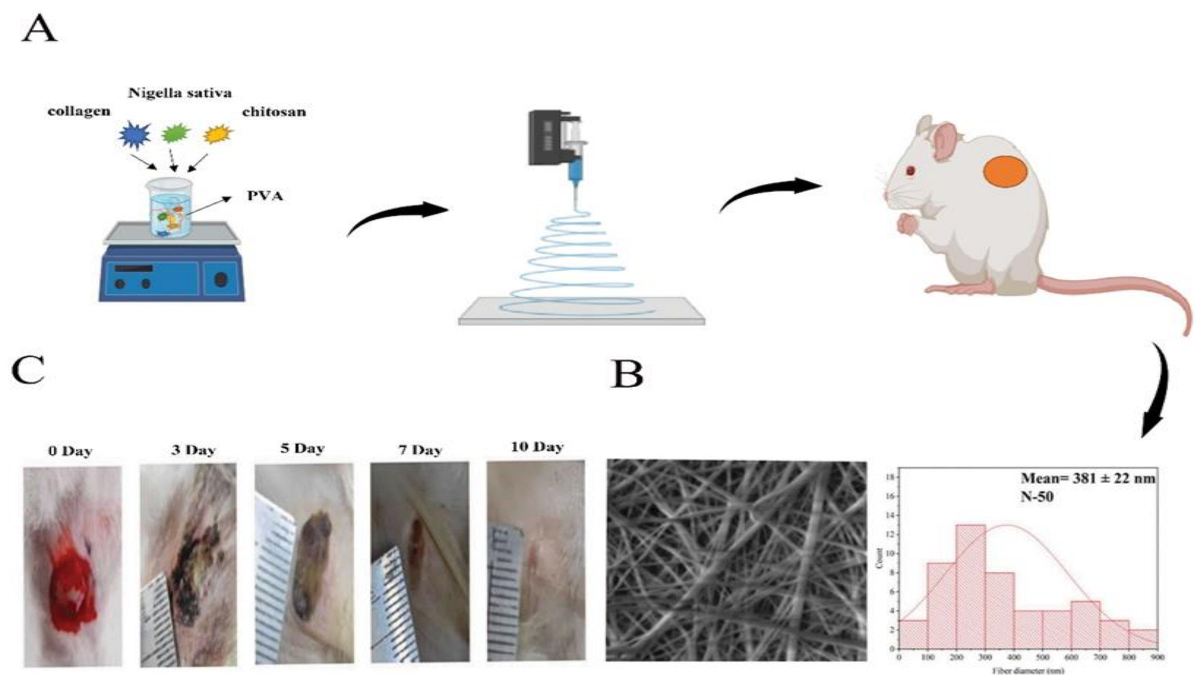

Figure 2. (A) Design of hybrid nanobiological scaffold based on collagen, chitosan, black seed and PVA polymer. (B) The analysis of the images indicated the optimal diameter of the fibers and the appropriate size of the pores of the resulting scaffold (Ferahtia 2021). (C) Application of the resulting scaffold resulted in wound closure within 10 days (Ferahtia 2021).

Haq et al. developed polyvinylpyrrolidone (PVP) films and hydrogels loaded with TQ using solvent casting. *In vitro* skin studies showed a release rate of 2.3 µg/cm²/h and 85% wound closure in keratinocyte models by day 6. Antibacterial assays demonstrated complete inhibition of *S. aureus in vitro, ex vivo* (human cadaver skin), and *in vivo* (mouse wound infection model). These findings suggest that TQ-loaded PVP films and hydrogels are promising for treating and controlling wound infections (Haq et al. 2020) (Figure 3). In a different study, Khan et al. examined the effects of a salve including ostrich oil, honey, beeswax, and extracts of *N. sativa*, propolis, and *Cassia angustifolia* on the diabetic rats' ability to heal wounds. The findings were positive. As demonstrated by the results, the ointment exhibited exceptional antibacterial action against common pathogens including P. aeruginosa, *E. coli*, *S. aureus*, and *Acinetobacter baumannii*. *In vivo* collagen deposition was increased, and wound healing was significantly accelerated up by the ointment in comparison to the control group. In addition, a histological analysis of the group receiving the ointment showed the presence of arteries, sebaceous glands, and hair follicles. The results demonstrate that the ointment performed well to speed up the healing of diabetic wounds and may be a good option for wound healing (Khan et al. 2003). The physicochemical effects, antioxidant capacity, and antibacterial qualities of *N. sativa* honey from Turkey's Burdur region were investigated in a recent study. High levels of antibacterial activity were demonstrated by the honey samples against a variety of bacteria, including *S. aureus*, *E. coli*, *Chromobacterium violaceum*, *Bacillus cereus*, *Klebsiella pneumoniae*, and *Acinetobacter haemolyticus* (Khodabakhshi et al. 2023). Sedik et al. evaluated the effect of TQ treated with cold plasma (TQcp) on wound healing in rats, using a full-thickness wound model. Treatments were applied twice daily for seven days and compared with TQ alone. The findings showed that TQcp significantly enhanced skin regeneration by increasing hyaluronic acid and collagen type I synthesis, reducing Tumor Necrosis Factor-alpha (TNF-α) levels, and preventing hypertrophic scarring through upregulation of Transforming Growth Factor-beta (TGF-β). Moreover, TQcp elevated Vascular Endothelial Growth Factor (VEGF) expression, which promoted angiogenesis, fibroblast proliferation, endothelial migration, and collagen production. Fibroblast activation and differentiation into myofibroblasts were also enhanced, as indicated by higher α-SMA levels. In addition, TQcp increased Interleukin-10 (IL-10), an anti-inflammatory cytokine, contributing to a balanced immune response. Overall, these results demonstrated that TQcp exerts superior wound-healing effects compared to TQ alone by modulating key growth factors, cytokines, and extracellular matrix remodeling (Sedik et al. 2023). In a study, Javadi and associates combined black seed extract with honey in a 1:1 ratio to promote wound healing. Analysis of the information at 5, 10, 15, and 20 days showed a significant reduction in the size of the wounds' surface and spaces between them. As a result, Javadi and colleagues suggested that applying a mixture of topical honey and black seed solutions can quicken the healing of wounds (Javadi et al. 2018a) (Figure 4). Sari et al. conducted a study to compare the effects of aloe vera gel and *N. sativa* oil gel on diabetic rats' ability to heal wounds. They showed that on day 5, the amount of tissue necrosis and inflammation in the group treated with aloe vera gel was noticeably lower than that of the gel containing black seed oil on the diabetic patients' wound healing process. According to their claims, *N. sativa* oil gel is inferior to aloe vera gel (Sari et al. 2018). Ahmadi et al. created an alloxan-induced diabetic wound model before using topical administration of TQ 10% W/V in their investigation. They showed that using TQ topically sped up the inflammatory phase—the third day following wounding—of wound healing. Additionally, on day 7, following the wound, there is an important decrease in wound healing (proliferative stage). Furthermore, a histological study performed on day 14 following the injury revealed a postponement in the wound's development in rats with diabetes. They stated that TQ antioxidant, anti-inflammatory, and antimicrobial qualities speed up wound healing during the inflammatory stage, while its anti-angiogenic effect fully documents the slowdown of wound healing during the proliferative phase (Yusmin and Ahmad 2017).

Nourbar et al. performed a study to examine the hydroethanolic effect of *N. sativa* extract on the healing of skin lesions in male rats that were induced to become diabetic using streptozosin. Analyzing the information revealed that the groups treated with *N. sativa* extract (40%) up until day 15 and 20% up until day 18 had the smallest average wound level over the duration of the trial. They suggested that *N. sativa* aids in accelerating wound healing because of their anti-inflammatory and antibacterial qualities (Nourbar et al. 2019b). In a study, Yaman and colleagues examined the medicinal effects of silver sulfadiazine and *N. sativa* cream on days 4, 9, and 14 of wound healing in mice. The analysis of histopathological results on days 4, 9, and 14 revealed that the *N. sativa* and silver sulfadiazine (SDD) groups' burn healing fared better than that of the control group, and there were significant variations in the wound healing processes on these days. Furthermore, they asserted that the cream in a mouse model, NS is superior to SSD in healing skin wounds produced on by burns (Yaman et al. 2010). Turhan and et al. performed a study to examine the potential benefits of *N. sativa* oil and silver nanoparticles in enhancing the process of wound healing. On the back of twenty rats, they made a 1 cm^2 skin defect. The wounds treated with NS and silver nanoparticles together healed considerably faster and had less scarring than those treated with NS oil or silver nanoparticles alone, according to an analysis of the histology data on day 15 (Turhan et al. 2019a) (Figure 5).

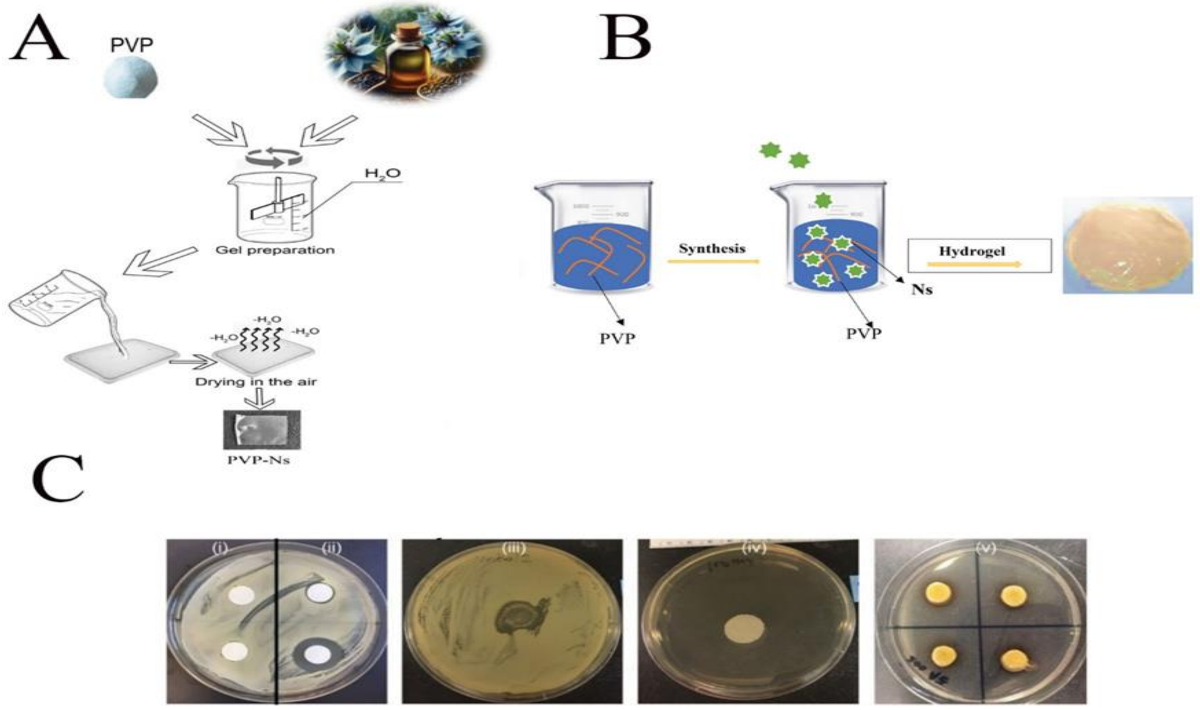

Figure 3. (A). Film design based on polypyrrolidone polymer containing thymoquinone (Forysenkova et al. 2023). (B). Hydrogel design based on polypyrrolidone polymer containing thymoquinone (C). Bacterial inhibition study. Inhibition of bacterial growth on agar plate by Control negative (i); Gentamicin positive control 50 µg/ml (ii) right upper and 500 µg/ml (ii) right lower; Control film (iii); Thymoquinone (TQ) hydrogel (iv) and TQ film (v) against *S. aureus* (Haq et al. 2020).

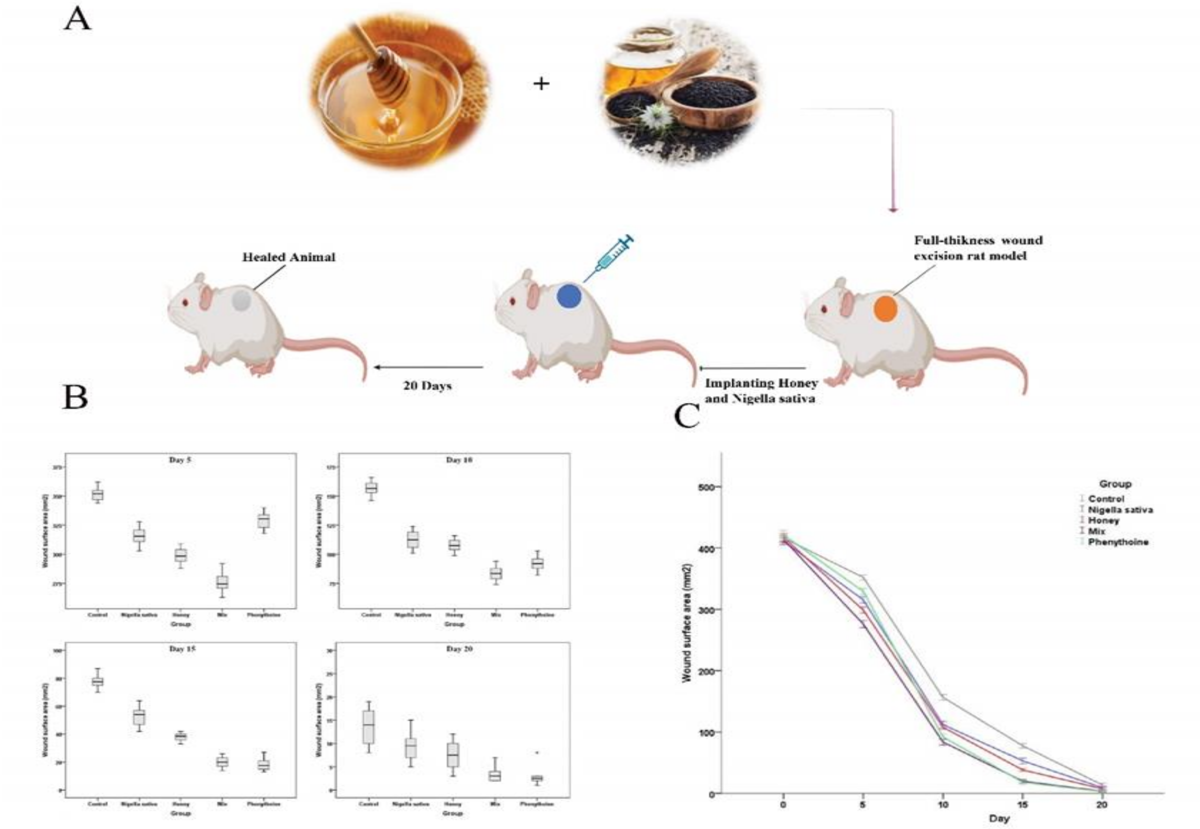

Figure 4. (A): Evaluation of the effect of honey and *N. sativa* on full-thickness skin wound. (B): The wound surface area in day 5,10,15 and 20 (Javadi et al. 2018b). (C): The trend of reduction of wound surface area through the post excision days in each group (Javadi et al. 2018b).

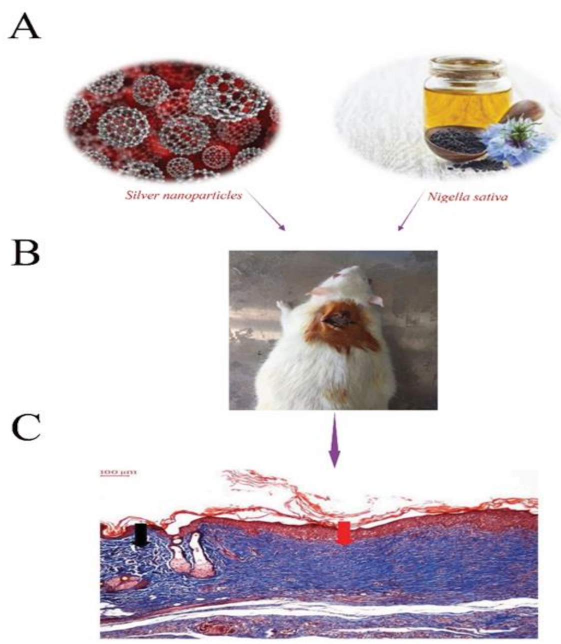

Figure 5. (A, B) investigating the synergistic effect of silver nanoparticles and honey on full-thickness wound. C: Increased collagen density and loss of skin appendage in the scar area (red arrow) compared with the normal skin (black arrow) (Masson’s trichrome stain, X100) (Turhan et al. 2019a).

Discussion

Safety and adverse effects

Thymoquinone, the principal bioactive component of *N. sativa*, has been documented to possess a wide range of beneficial properties. Its range of uses has been emphasized in numerous research, and an abundance of information has been published regarding its antibacterial, anti-inflammatory, anti-allergic, antioxidant, anti-neoplastic, and anti-diabetic properties. It is noteworthy that TQ has greatly enhanced the development of granulation tissue, contraction, and re-epithelialization in addition to improving the formation of fibroblasts as a wound healing agent. Thymoquinone is a good treatment for wounds because it allows for direct penetration into the damaged areas (Negi et al. 2020). Additionally, it has been reported that the active ingredients in *N. sativa* oil and seeds have antimicrobial qualities, such as anthelminthic, antiviral, antifungal, and antibacterial activities. It has been suggested that the immunomodulatory properties of *N. sativa* seeds constituent parts account for part of their antibacterial activities. Numerous bacterial species, including *E. coli*, Bacillus subtilis (B. subtilis), *Streptococcus faecalis*, *S. aureus*, and *P. aeruginosa*, have been reported to be susceptible to the antibacterial activity of *N. sativa*. It has also been demonstrated to have antifungal properties and to be effective against several fungi as well as the pathogenic yeast *Candida albicans* (Mohamad et al. 2019).

Further research is necessary for determining the most effective concentration of TQ, as well as the optimal dosage for treatment and the clinical trial performance of these natural compounds. The identification of isolated bioactive compounds, particularly TQ, and maintaining their high purity present numerous challenges as well (Al-Qubaisi et al. 2019). Additionally, because of its low water solubility, minimal skin penetration, and limited systemic availability, TQ therapeutic efficacy is constricted. Because of its multifunctional action, TQ has demonstrated promise for usage in medical applications despite these disadvantages (Li et al. 2023). Thus, based on the previously mentioned information, it can be concluded that further research is urgently needed to investigate the cellular and molecular mechanisms of TQ in wound healing. This research should involve both animal models and clinical trials (Sallehuddin et al. 2020a).

It should be noted that despite promising results from preclinical trials, there are several important hurdles to translating TQ into clinical use.

1. Scalability of scaffold production: Industrial production must be uniform and reproducible to maintain scaffold properties.

2. Sterilization methods: Scaffolds must be rendered free of contamination without reducing TQ activity.

3. Regulatory and legal pathways: These compound products may be

considered as drugs, medical devices, or combination products, which have complex regulatory pathways.

4. Affordability: The cost of production and clinical use must be practical and economical.

5. Standardization of TQ extract: Due to natural variability between batches, it is necessary to maintain the quality, efficacy, and safety of the extract.

Addressing these challenges is essential for the clinical use of TQ-loaded scaffolds. Accordingly, further research in both animal models and clinical trials is needed to better understand the cellular and molecular mechanisms of TQ in wound healing.

Clinical trial and commercial product

Numerous pre-clinical and clinical investigations demonstrate the benefits of TQ on inflammation, fibrosis in multiple organs, and wound healing (Nordin et al. 2019). Different wounds have been investigated (Table 1). Table 2 and 3 also mentions the use of TQ without scaffolds in wound healing. Furthermore, there are different brands and forms of *N. sativa* products for various usages in some countries (Table 4).

Research has shown its effectiveness in healing burn wounds, excisional wounds, corneal wounds, and diabetic ulcers (Sallehuddin et al. 2020a; Selçuk et al. 2013). TQ has demonstrated efficacy in the management of chronic wounds, which are frequently challenging to cure. These encompass diabetic ulcers and pressure sores, whereby TQ facilitates the healing process by augmenting cellular activity and diminishing inflammation (Kmail et al. 2023a; Pekmez and Mılat 2020). Its characteristics render it appropriate for post-surgical wound management, since its antibacterial capabilities may inhibit infections and its anti-inflammatory effects might expedite the healing process (Sallehuddin et al. 2020b; Sedik et al. 2023). It has shown beneficial effects in wounds impacted by ischemia-reperfusion injury, characterized by temporary blood flow restriction followed by restoration, resulting in tissue damage. TQ aids in alleviating harm and facilitating recovery in these circumstances (Kmail et al. 2023a). The chemical has demonstrated efficacy in the treatment of severe wounds by mitigating oxidative stress and facilitating expedited healing (Kmail et al. 2023a; Sallehuddin et al. 2020a).

Limitation and challenge

The application of *N. sativa* (black seed) and its active ingredient, TQ, encounters various limitations and challenges, despite their potential therapeutic benefits.

1-The TQ content in *N. sativa* oil is rather low, necessitating the use of significant quantities of oil (from 3 to 10 ml) to achieve effective therapeutic dosages. This method may be unfeasible and might lead to increased adverse effects from excessive oil intake (Derosa et al. 2024). Poor Oral Bioavailability: Thymoquinone exhibits low oral bioavailability, hence restricting its efficacy when taken orally. This requires the investigation of alternate delivery mechanisms, such as nanoformulations, to improve absorption and therapeutic efficacy (Ali et al. 2021b; Derosa et al. 2024). Optimal Dosage Uncertainty: No consensus exists about the appropriate dose and delivery method for TQ. Diverse investigations indicate varying effective concentrations, complicating the establishment of consistent treatment methods (Kmail et al. 2023b). 2-Safety and Toxicity Concerns: Potential Toxicity: Although *N. sativa* is often regarded as harmless, several studies have indicated potential adverse effects, including allergic responses, gastrointestinal problems, and minor elevations in liver and kidney enzymes. These consequences underscore the necessity for vigilant oversight throughout therapy (Table 5)(Li et al. 2023; Mashayekhi-Sardoo et al. 2020).

Table 1. Some studies of thymoquinone-loaded scaffolds for wound healing

Treatment	Experimental Model	Mechanism of Action	Conclusion	Reference
TQ-PMs-hydrogel, pure TQ, *Nigella sativa* oil, silver sulfadiazine ointment	Mice excision wound model	Anti-inflammatory effects; Enhanced collagen synthesis and angiogenesis; Improved epithelialization.	TQ-loaded chitosan-lecithin micelles incorporated into a carbopol hydrogel (TQ-PMs-hydrogel) exhibited superior wound healing efficacy compared to pure TQ, *Nigella sativa* oil, and silver sulfadiazine ointment.	(Negi et al. 2020)
TQ-loaded PLA/CA nanofibrous mats (TQ-F1), TQ-loaded PLA scaffolds (TQ-F3), gauze	Mice dorsal wound model	Antimicrobial activity; Enhanced cell proliferation and migration; Improved extracellular matrix deposition.	TQ-loaded PLA/CA nanofibrous mats (TQ-F1) promoted wound healing by increasing re-epithelialization, controlling the formation of granulation tissue, and exhibiting faster wound contraction compared to gauze and TQ-loaded PLA scaffolds (TQ-F3).	(Gomaa et al. 2017)
TQ-containing polyvinyl pyrrolidone (PVP) films	Mice full-thickness wound	Antimicrobial activity against *S. aureus*; No significant effect on wound healing parameters.	TQ-containing polyvinyl pyrrolidone (PVP) films significantly controlled *Staphylococcus aureus* infection. However, there was no significant effect of TQ on wound healing.	(Haq et al. 2020)
Uncoated polypropylene mesh, Polypropylene mesh coated with PLA, Polypropylene mesh coated with PLA and TQ	Female Wistar rats in an experimental incisional hernia model	Anti-inflammatory and antioxidant properties; Reduction in inflammatory cell infiltration and collagen deposition.	TQ-coated mesh is shown to reduce adhesion formation and TQ is a promising coating material for mesh surface modification.	(Aydin et al. 2017)

TQ, thymoquinone; PMs, polymeric micelles; PLA, poly(lactic acid); CA, cellulose acetate; F1, formulation 1; F3, formulation 3; PVP, polyvinylpyrrolidone; S. aureus, Staphylococcus aureus.

Table 2. Overview of thymoquinone-loaded scaffold studies: scaffold characteristics, wound challenges, and therapeutic outcomes

Scaffold/Carrier	Polymer properties (diameter/porosity)	Model	TQ release	Study Challenge	Results	Reference
Nanofiber PVA +NS	Diameter 178.8 ± 16.9 nm	in vitro / in vivo	Slow	Bacterial infection	Accelerate wound healing	(Ali et al. 2021a)
Collagen-NS-chitosan hybrid scaffold	Diameter ~381 ± 22 nm, porosity ~78%	Mouse	Controlled	Excessive discharge, infection	Accelerates wound healing, exhibits antibacterial properties	(Alam et al. 2023)
film/hydrogel PVP + TQ	Uniform	in vitro / mice	2.3 µg/cm²/h	S. aureus infection	85% wound closure on the 6th day	(Haq et al. 2020)
TQ + Cold Plasma	---	Rat	---	Inflammation	↑ Collagen I and hyaluronic acid, ↑ TGF-β and VEGF	(Sedik et al. 2023)
NS extract + honey (1:1)	---	Rat	---	Inflammation and infection	Reducing the wound surface	(Javadi et al. 2018b)
NS Gel / Aloe Vera Gel	---	Rat	---	Inflammation, tissue necrosis, and biofilm secretions	The wound area was significantly smaller in the aloe vera gel group on days 6 and 7, and epidermal regeneration was better in this group than in the other groups. In fact, aloe vera gel performed better than NS gel.	(Sari et al. 2018)
TQ 10% W/V	---	Rat	---	Infection	Acceleration of the inflammatory phase, slowing of the proliferative phase	(Yusmin and Ahmad 2017)
NS hydroethanolic extract	20%-40%	Rat	---	The exact mechanism of wound healing by the extract has not been determined, and only a general anti-inflammatory and antibacterial effect has been proposed.	Rapid reduction of wound surface, anti-inflammatory effect	(Nourbar et al. 2019a)
Cream NS	----	Mouse	---	Limitations of this study include the lack of investigation into the precise molecular mechanisms of N. sativa's therapeutic effects and the need for clinical studies to confirm the results in humans.	Reducing inflammation and improving the tissue characteristics of wounds	(Gamarra et al. 2010)

Table 2 continued

NS + Silver Nanoparticles	-------	Rat	---	Limitations of this study include the lack of investigation of the precise molecular mechanisms of the therapeutic effects of the combination of *N. sativa* oil and silver nanoparticles and the need for clinical studies to confirm the results in humans.	The results showed that treatment with the combination of N. sativa oil and silver nanoparticles reduced wound healing time and reduced scarring compared to the other treatment groups. The combination also increased collagen density and improved the tissue characteristics of the wounds.	(Turhan et al. 2019b)
TQ-loaded topical nanoemulsion gel	----	Rat	Controlled	Infection	↑ Epidermis, ↑ Collagen I	(Algahtani et al. 2021)
PVA nanofiber / collagen-chitosan-NS scaffold / PVP-TQ hydrogel	Controlled diameter and porosity	in vitro / in vivo	Controlled	Excessive secretions, biofilm infection, diabetic ischemia	Antibacterial, ↑ collagen, ↑ fibroblasts, ↓ inflammation	(Zhang et al. 2020)

TQ, thymoquinone; NS, *Nigella sativa*; PVA, polyvinyl alcohol; PVP, polyvinylpyrrolidone; S. aureus, Staphylococcus aureus; TGF-β, transforming growth factor-beta; VEGF, vascular endothelial growth factor; W/V, weight per volume.

Table 3. Some clinical and preclinical studies of thymoquinone wound healing in different types of wounds

Experimental model	**Treatment**	**Outcome measures**	**Results**	**Conclusion**	**Ref.**
Cutaneous Incisional Wound					
Full thickness wound in Wistar rats	50% topical *Nigella sativa* (NS) cream	1. Wound contraction. 2. Biochemical analysis. 3. Histological evaluation.	Treatment with NS cream increases wound contraction rate and antioxidant activity but have no effect in tissue granulation.	NS heals via its antioxidant effect in full thickness wound.	(Han et al. 2017)
Cutaneous Burn Wound					
Burn wound model in albino rats	Topical micro-emulsion of 5% NS honey and 5% of its propolis	Wound contraction.	Treatment of NS honey and its propolis increases wound contraction rate.	Microemulsion of NS honey and propolis contribute to faster burn wound healing.	(Sulaiman et al. 2014)
Burn wound model in Sprague-Dawley rats	2 mg/kg/day oral TQ or 0.5% topical TQ	1. Histological assessment. 2. Total antioxidant state. 3. Total oxidative stress. 4. Bacterial assessment	Topical treatment of TQ was superior compared to oral TQ in improving wound histology, enhancing antioxidant activity, and reducing bacterial growth.	Topical TQ is superior to oral TQ in improving wound healing.	(Selçuk et al. 2013)
Burn wound model in male, Wistaralbino rats	50% topical NS oil (NSO)	1. Gross morphology of the wound. 2. Histological evaluation.	Treatment with NSO reduces inflammation and demonstrated better tissue granulation in wound.	NSO has been shown to promote faster burn wound healing.	(Yaman et al. 2010)
Cutaneous Diabetic Wound					
Chronic delayed wound in alloxan-induced diabetic rats	10% topical TQ	1. Wound contraction. 2. Histological evaluation.	Treatment with TQ increased healing and reduced inflammatory cells and fibroblast at day 3. However, wound improvement declines on day 7 and day 14.	TQ heals faster in inflammatory phase but slower during the proliferative phase due to its antiangiogenic properties	(Yusmin and Ahmad 2017)
Corneal Wound					
Formaldehyde-induced corneal toxicity in albino rats	40 mg/kg/day oral NSO	Histological evaluation.	Treatment with NSO reverses formaldehyde-induced pathological changes.	NSO shown to resolved corneal injury induced by formaldehyde toxicity	(Salem et al. 2016)

TQ, thymoquinone; NS, *Nigella sativa*; NSO, *Nigella sativa oil*

Table 4. A list of commercial products containing *Nigella sativa* (black seed) specifically for wound healing, including their brand, usage, and form

Product Name	**Brand**	**Usage**	**Form**
Nubian Heritage Black Seed & Tea Tree Oil Balm	Nubian Heritage	Moisturizes and soothes minor wounds	Balm
Biotique Bio Kalonji	Biotique	Skin rejuvenation and healing; effective on cuts	Cream
Black Seed Healing Cream	Various Brands	Applied to cuts, burns, and dry skin	Cream
Moksha Black Seed Cream	Moksha	Healing properties for skin conditions	Cream
Herbal Secrets Black Seed Oil Cream	Herbal Secrets	Moisturizing and healing skin	Cream
Black Seed Oil Skin Cream by Pure Oil	Pure Oil	Promotes healing and hydration	Cream
Black Seed Ointment by Nature's Way	Nature's Way	Soothing and healing minor cuts	Ointment
Black Seed Cream by Pome	Pome	Applied to wounds and skin irritations	Cream
Kalonji Cream by Al Haramain	Al Haramain	Skin healing and nourishment	Cream
Black Seed Foam by Herbalife	Herbalife	Moisturizing and promoting skin healing	Foam
Black Seed Healing Ointment by Z Natural Foods	Z Natural Foods	Applied to wounds and skin irritations	Ointment
Black Seed Repair Cream by Kiva	Kiva	Repairing and soothing damaged skin	Cream
Black Seed Skin Therapy Cream by Garden of Life	Garden of Life	Supports skin healing and overall health	Cream
Black Seed Anti-Aging Cream	Various Brands	Skin rejuvenation and healing; effective for aging skin	Cream
Black Seed Moisturizing Cream by Organic India	Organic India	Hydrates and promotes healing for dry skin	Cream
Amazing Herbs Black Seed Oil	Amazing Herbs	Applied topically for skin health	Oil
Heritage Store Black Seed Oil	Heritage Store	For minor wounds and skin conditions	Oil
HealthAid Black Seed Oil Capsules	HealthAid	Taken orally to support immune function	Capsules
Patanjali Black Seed Oil	Patanjali	Applied to the skin for healing	Oil
Kalonji Oil by Nature's Way	Nature's Way	Used topically for wound care	Oil
Al Haramain Black Seed Oil	Al Haramain	Topical applications on wounds	Oil
Çörek Otu Yağı (Black Seed Oil)	Various brands	For various skin conditions	Oil
Yunnan Baiyao	Yunnan Baiyao	Traditional remedy for wound healing	Powder/Capsules
Moksha Black Seed Oil	Moksha	Applied to skin for its healing properties	Oil
NutraBlast Black Seed Oil Capsules	NutraBlast	Taken orally for skin health	Capsules
Black Seed Soap	Nubian Heritage	Cleansing and promoting healthy skin	Soap
Black Seed Herbal Tea	Alvita	Consumed for internal health benefits	Tea Bags
Black Seed Oil by Z Natural Foods	Z Natural Foods	Applied directly to skin for healing	Oil
Kalonji Oil by Pure Oil	Pure Oil	Topically for skin conditions	Oil
Black Seed Oil by Kiva	Kiva	Taken orally or applied topically	Oil
Black Seed Oil by Herbal Secrets	Herbal Secrets	For skin health and wound healing	Oil
Black Seed Oil by Solgar	Solgar	Taken as a dietary supplement	Capsules
Black Seed Oil by Starwest Botanicals	Starwest Botanicals	For skin applications and health benefits	Oil
Black Seed Oil by Now Foods	Now Foods	Topically or taken as a supplement	Oil/Capsules
Black Seed Oil by Garden of Life	Garden of Life	Taken as a supplement; supports skin health	Capsules
Black Seed Cream by Pome	Pome	Applied to wounds and skin irritations	Cream
Black Seed Oil by Organic India	Organic India	For skin health and healing	Oil/Capsules

Table 5. Various toxicities were reported for *N. sativa*

Type of Study		**Findings**
In Vivo Studies	Acute Toxicity	Behavioral disorders
	Subacute Toxicity	Increased gamma-glutamyl transferase Prothrombin time increase
		Decreased activated partial thromboplastin time
		Decreased thrombin time
	Subchronic Toxicity	Increased alanine transaminase
		Increased aspartate aminotransferase
		Increased mean corpuscular volume
		Decreased RBCs
		Decreased Hemoglobin
		Decreased mean corpuscular hemoglobin concentration (MCHC)
		Decreased packed cell volume
	Chronic Toxicity	Decreased platelet number
		Decreased hematocrit
		Decreased mean globular volume
		Decreased MCHC
		Decreased MCH
In Vitro Toxicity	Genotoxicity	Chromosomal aberrations
	Cytotoxicity	Decreased cell viability
		Decreased proliferation
		Increased apoptosis
		Activation of caspase 9/3 pathway
		Cleavage of PARP
In Humans		Allergic dermatitis contact,
		Severe bullous target-like lesions, compatible with erythema multiforme

GGT, gamma-glutamyl transferase; RBCs, red blood cells; MCHC, mean corpuscular hemoglobin concentration; MCH, mean corpuscular hemoglobin; PARP, poly(ADP-ribose) polymerase

Lack of Comprehensive Toxicological Studies: numerous investigations fail to sufficiently describe the plant material or its extracts, resulting in deficiencies in comprehending the complete toxicological profile of *N. sativa* and TQ. Further comprehensive studies are necessary to evaluate long-term safety and any adverse effects (Mashayekhi-Sardoo et al. 2020).

Although these data underscore TQ promise in wound healing, more study is required to ascertain appropriate doses, delivery methods, and possible adverse effects in therapeutic contexts (Kmail et al. 2023a).

Thymoquinone (TQ), the principal bioactive component of *N. sativa*, has demonstrated strong anti-inflammatory, antioxidant, and antimicrobial activities, making it a promising candidate for wound healing. Beyond these pharmacological benefits, recent research highlights the potential of scaffold-based delivery systems—such as electrospun nanofibers, hydrogels, films, and 3D-printed matrices—as innovative platforms for controlled and sustained release of TQ at wound sites. These scaffolds not only enhance local bioavailability but also provide structural support for tissue regeneration. Despite this progress, several knowledge gaps remain. Current studies are largely preclinical, with limited clinical translation. Standardization of TQ dosage, release kinetics, and scaffold composition remains unresolved. Furthermore, challenges such as large-scale manufacturing, sterilization without loss of bioactivity, and regulatory classification (drug, device, or combination product) must be addressed before widespread application. Future research should move beyond proof-of-concept to advanced strategies. Smart, stimuli-responsive scaffolds capable of responding to wound microenvironmental cues (e.g. pH, oxidative stress, and bacterial enzymes) represent a compelling direction. Additionally, integration with in vivo imaging techniques could allow real-time monitoring of TQ release and scaffold performance. Combining TQ with other natural or synthetic bioactives, and employing advanced fabrication approaches such as 3D bioprinting, could further enhance therapeutic outcomes. In conclusion, TQ-loaded scaffolds stand at the intersection of natural product pharmacology and biomaterial innovation. With careful optimization and rigorous translational studies, they hold strong potential as next-generation wound healing therapies.

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Conflicts of interest

The authors declare there is no conflict of interest

Author Contributions

Tayebeh Sadat Tabatabai: Writing – review & editing, Writing – original draft, Visualization, Methodology, Investigation, Conceptualization. Mohammad Mehdi Monazah: Writing – review & editing, Writing – original draft, Validation, Methodology, Investigation, Conceptualization. Neshat Ahmadi: Writing – review & editing, Writing – original draft, Visualization, Investigation, Conceptualization. Alireza Masoudi: Writing – review & editing, Writing – original draft, Investigation. Leila Rezakhani: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Project administration, Methodology, Investigation, Conceptualization. All authors have read and agreed to the published version of the manuscript.

Abbreviations

TQ – Thymoquinone. NS – *Nigella sativa*. PVA – Polyvinyl Alcohol. PVP – Polyvinylpyrrolidone. CS – Chitosan. COL – Collagen. HA – Hyaluronic Acid. VEGF – Vascular Endothelial Growth Factor. TNF-α – Tumor Necrosis Factor-alpha. TGF-β – Transforming Growth Factor-beta. ROS – Reactive Oxygen Species. RCTs – Randomized Controlled Trials. FESEM – Field Emission Scanning Electron Microscopy. FTIR – Fourier Transform Infrared Spectroscopy

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