Acta Scientific Pharmaceutical Sciences (ISSN: 2581-5423)

Volume 9 Issue 2 February 2025

Review Article

Nigella sativa and its Role in Diabetic Wound Management: A Review of Therapeutic Applications

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Received: January 09, 2025

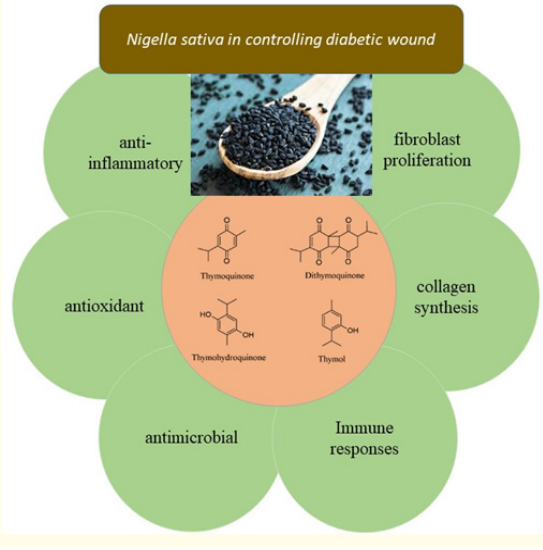
Published: January 30, 2025

Abstract

Nigella sativa, commonly known as Black Cumin seed, has been traditionally used for its medicinal properties and used in various healthcare application. Diabetic wounds represent a significant challenge in medical care due to their tendency for slow healing and high risk of complications. *Nigella sativa* attributed to its active compounds such as thymoquinone, thymohydroquinone, and dithymoquinone. Recent studies have explored its potential in promoting wound healing, especially in the context of diabetes. This review aims to consolidate current knowledge on the efficacy of *Nigella sativa* in management of diabetic wound care, The Key active compounds, including thymoquinone, exhibit notable anti-inflammatory, antioxidant, and antimicrobial activities, which are crucial for effective wound healing. Studies demonstrate that *Nigella sativa* extracts can accelerate wound closure, reduce inflammation, and combat microbial infections, thereby enhancing the overall wound healing process in diabetic patients. Additionally, Nigella sativa ability to modulate immune responses and promote collagen synthesis further supports its application in diabetic wound care, thus facilitating better wound management in diabetic patients. Wounds Despite encouraging preclinical results, comprehensive clinical trials are necessary to establish its efficacy and safety in human subjects. Integrating *Nigella sativa* into diabetic wound management protocols could offer a promising, natural adjunct to existing therapeutic options, improving outcomes for patients with diabetic wounds.

Keywords: *Nigella sativa*; Thymoquinone; Thymohydroquinone; Dithymoquinone; Diabetic Wound; Wound Healing

Graphical Abstract



Citation: Nagadharshini R and SP Suriyaraj. "*Nigella sativa* and its Role in Diabetic Wound Management: A Review of Therapeutic Applications". *Acta Scientific Pharmaceutical Sciences* 9.2 (2025): 12-23.

Introduction

Diabetic wounds, particularly diabetic foot ulcers (DFUs), are a significant complication of diabetes mellitus, affecting approximately 25% of diabetic patients. These wounds are challenging to heal due to prolonged hyperglycemia, which leads to impaired angiogenesis, neuropathy, a sub-optimal chronic inflammatory response, barrier disruption, and polymicrobial infections. The complexity of DFUs, combined with their high recurrence rates and potential for lower limb amputation, underscores the need for advanced treatment strategies that address the multiple factors contributing to impair healing. As the prevalence of diabetes continues to rise, developing effective therapies for diabetic wounds becomes increasingly critical [14]. Medicinal plants have been integral to human healthcare since ancient times, with their therapeutic applications documented in ancient papyrus writings from various civilizations. Even today, indigenous cultures rely on herbs in their healing rituals, recognizing the rich phytochemical composition of these plants as vital for developing new drugs. One such remarkable plant is *Nigella sativa*, commonly known as black seed or kalonji, often referred to as the miracle herb (Shown in the figure 1). Black cumin, scientifically known as *Nigella sativa*, belongs to the family Ranunculaceae. Native to regions of Asia and the Middle East, it has a rich history of use in both traditional medicine and culinary practices [37].

Figure 1: Nigella sativa, commonly known as black cumin seed or kalonji, often referred to as the miracle herb.

It is also known by various other names, including black seed, black caraway, kalonji, and Habbatussauda, earning nicknames like "the herb from heaven," "Haba-al-Barakh" (blessed seeds), or "miracle seeds" due to its extensive medicinal applications. The name "Nigella" comes from the Latin word "niger," meaning black, referring to the color of the seeds, while "sativa" comes from the Latin verb "serere" (to sow) or "sativum" (cultivated). The plant features erect, branched stems that become hollow with age, ranging in color from green to dark green. It has green leaves and flowers that turn from red to blue as they mature. The plant's fruits consist of three to six carpels, each containing seeds that turn black after maturation and exposure to air. Historically, black cumin seeds have been used for medicinal purposes for centuries, known for their distinct flavor and aroma, often used as spices in cooking. Widely studied for its numerous medicinal benefits, *Nigella sativa* is used not only as a spice but also in various traditional medicine systems, including Ayurveda, for its healing properties in treating diverse diseases. The seeds and oil of *Nigella sativa* have been used for centuries globally to treat various ailments and hold a significant place in Indian traditional medicine systems like Unani and Ayurveda. The nutritional composition of black cumin seeds includes Protein (20-85%), Fat (38.20%), Fiber (7-94%), Total carbohydrates (31.94%), Crude fiber (8.4%), Total ash (4.8%), Vitamins and minerals such as Copper, phosphorus, zinc, iron, etc. Carotene Converted to vitamin A by the liver [37]. Extensive research has shown that *Nigella sativa* exhibits a wide spectrum of biological activities and therapeutic potential. These include diuretic, antihypertensive, antidiabetic, anticancer, immunomodulatory, analgesic, antimicrobial, anthelmintic, anti-inflammatory, spasmolytic, bronchodilator, gastroprotective, hepatoprotective, renal protective, and antioxidant properties [1]. Much of its therapeutic efficacy is attributed to thymoquinone (TQ), the major active component of its essential oil. Research highlights the plant's potential as an antioxidant, in glycemic control, anticancer, antimicrobial, and various other health benefits. Experimental studies have reported *Nigella sativa* oil and extracts possess significant antimicrobial activity against a broad range of microbes, notably multiple-antibiotic-resistant bacteria. This review aims to provide a comprehensive yet concise overview of the medicinal applications of *Nigella sativa*, in the context of emerging Diabetic Wound Care [16].

Black cumin seed for diabetic wound

Diabetes is a complex metabolic disorder affecting over 340 million people worldwide, with approximately 20% of these individuals developing diabetic wounds. Among these, leg or foot ulcers are the most common. Diabetic patients struggle to metabolize glucose effectively, leading to hyperglycemic conditions that complicate the wound healing process. This often results in stalled chronic wounds. A comparative view of wound healing and skin regeneration reveals significant differences between healthy and diabetic individuals is (shown in figure 2) The global incidence of delayed wound healing in diabetic patients is rising, exacerbated by a lack of effective preventive and control measures. Traditionally, natural sources derived

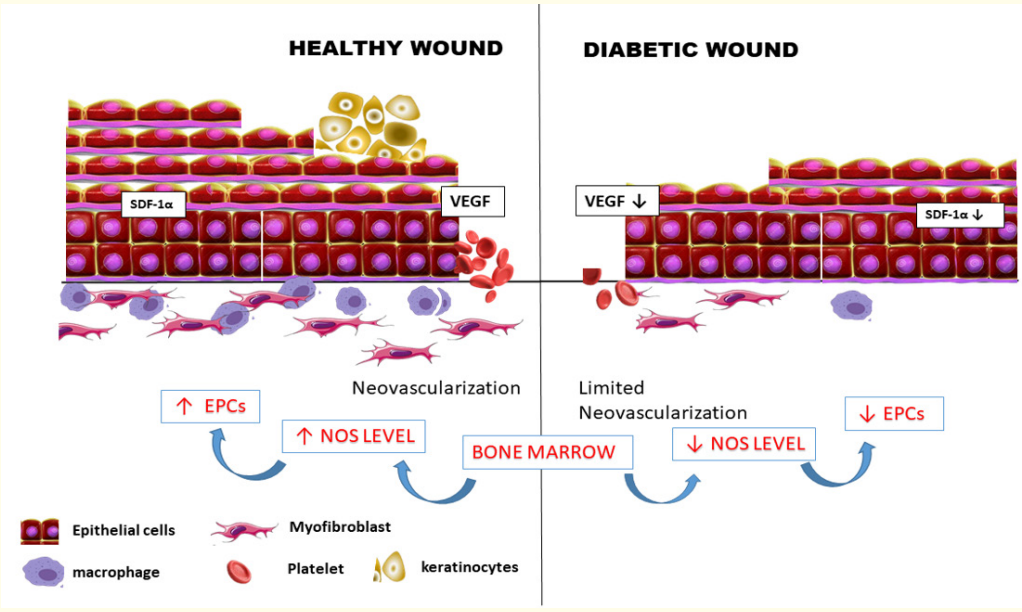


Figure 2: The image compares wound healing in healthy and diabetic individuals, highlighting key differences in cellular and molecular factors. In healthy wounds, there is an increase in endothelial progenitor cells (EPCs), nitric oxide synthase (NOS) levels, stromal cell-derived factor 1-alpha (SDF-1α), and vascular endothelial growth factor (VEGF), all promoting effective neovascularization and faster healing. In contrast, diabetic wounds show reduced levels of EPCs, NOS, SDF-1α, and VEGF, leading to limited neovascularization and impaired wound healing. These differences emphasize the challenges in wound healing for diabetic patients.

from various plants have played a crucial role in wound healing. Plants have been used for their therapeutic properties. It's noteworthy that approximately 70% of commercialized wound healing products contain active ingredients sourced from plants, while 20% are mineral-based and 10% are derived from animal sources. Over 13,000 plant-derived compounds have been identified for their potential to accelerate the wound healing process [34].

Diabetic wound healing significantly differs from the routine wound healing process due to intrinsic pathophysiological abnormalities and extrinsic factors that result in delayed and abnormal healing. Diabetic wound healing is compromised due to a combination of intrinsic abnormalities, such as poor angiogenesis and impaired tissue regeneration, and extrinsic factors like infections. Chronic oxidative stress, hyperglycemia, and its related factors also play a significant role in impeding the healing process. This complex interplay of factors makes managing diabetic wounds challenging and highlights the need for comprehensive and targeted therapeutic strategies [4]. Chronic non-healing ulcers in diabetes mellitus affect 2-4% of patients, often resulting from impaired healing due to macrovascular and microvascular changes (show in figure 3). These systemic complications can delay wound healing, potentially leading to limb amputation. The condition is challenging to treat due to the presence of polymicrobial infections with multidrug resistance and biofilm formation [3].

Nigella sativa (NS), commonly known as black cumin or black seed, is a plant that has been traditionally used in various cultures for its medicinal properties (shown in figure 4). Research has shown that *Nigella sativa* has several therapeutic effects, particularly in the context of skin wound healing. The main mechanisms through which it aids in wound healing include its anti-inflammatory, tissue growth stimulation, and antioxidative properties. Anti-inflammatory Properties, Inflammation is a natural part of the wound healing process, but excessive inflammation can delay healing and cause further tissue damage. *Nigella sativa* contains compounds such as thymoquinone, which have been found to reduce inflammation by inhibiting pro-inflammatory mediators. This helps in creating a more favorable environment for wound healing. Tissue Growth Stimulation, *Nigella sativa* promotes the growth and proliferation

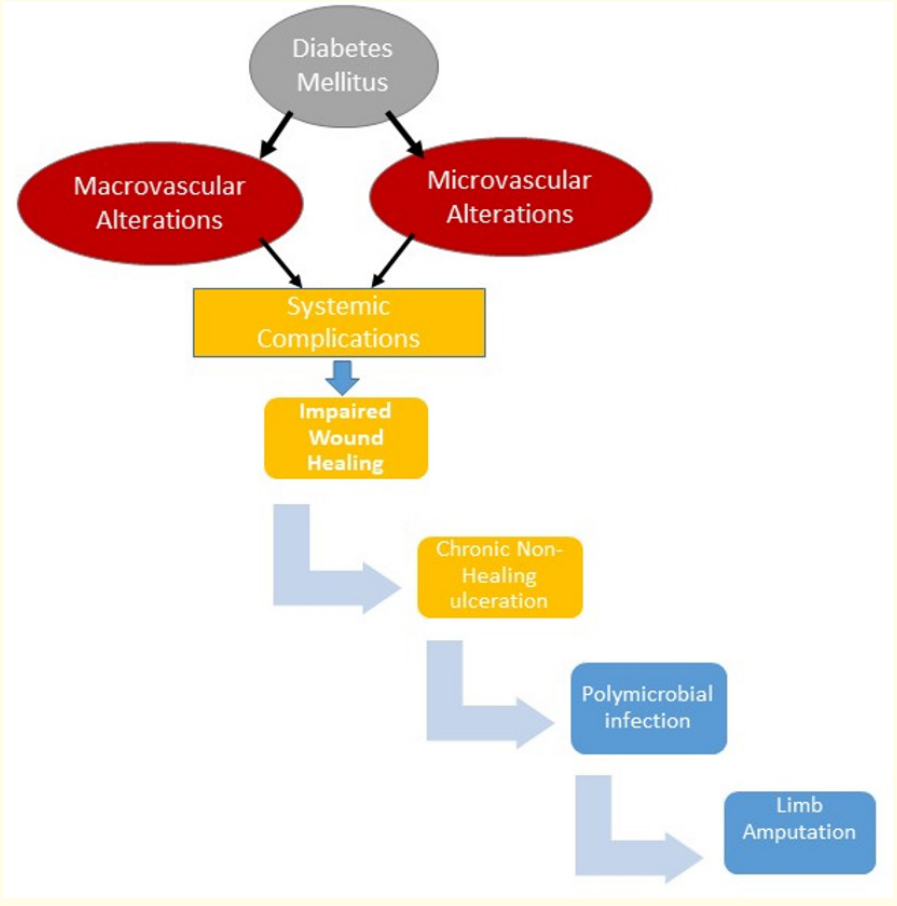


Figure 3: This diagram illustrates the progression from Diabetes Mellitus to Chronic Non-Healing Ulceration and its severe outcomes. Diabetes Mellitus, which causes Macrovascular and Microvascular Alterations. These vascular changes lead to Systemic Complications, including Impaired Wound Healing. This impairment can result in Chronic Non-Healing Ulceration, such as foot ulcers. These ulcers often become infected with multiple microorganisms, leading to complications like biofilm formation and multidrug resistance, and can ultimately result in severe outcomes like limb amputation.

of various cell types that are essential for wound healing, such as fibroblasts and keratinocytes. These cells play a crucial role in the formation of new tissue and the re-epithelialization process, which is the restoration of the skin's surface layer. Antioxidative Properties, The antioxidative properties of *Nigella sativa* help in neutralizing free radicals and reducing oxidative stress at the wound site. Oxidative stress can damage cells and delay the healing process. By protecting cells from oxidative damage, *Nigella sativa* supports faster and more efficient wound healing. These combined effects make *Nigella sativa* a potent natural remedy for enhancing the wound healing process and improving skin health. Black seed (*Nigella sativa*) contains over 100 medicinal components that work together to produce a synergistic effect, with 69 of these components characterized and identified so far. Research highlights that *N. sativa* products, such as oil, extracts, and active ingredients like thymoquinone, have antinociceptive, anti-inflammatory, and analgesic effects. Studies using mammalian wound models have demonstrated that *N. sativa* oil is a potent wound healing booster due to its anti-inflammatory and immunomodulatory effects. Black seeds exhibit anti-inflammatory properties for various skin inflammations and help reduce skin pigmentation. Notably, a mixture of propolis, black seed, and honey has been shown to be particularly effective in healing and recovering diabetic wounds.

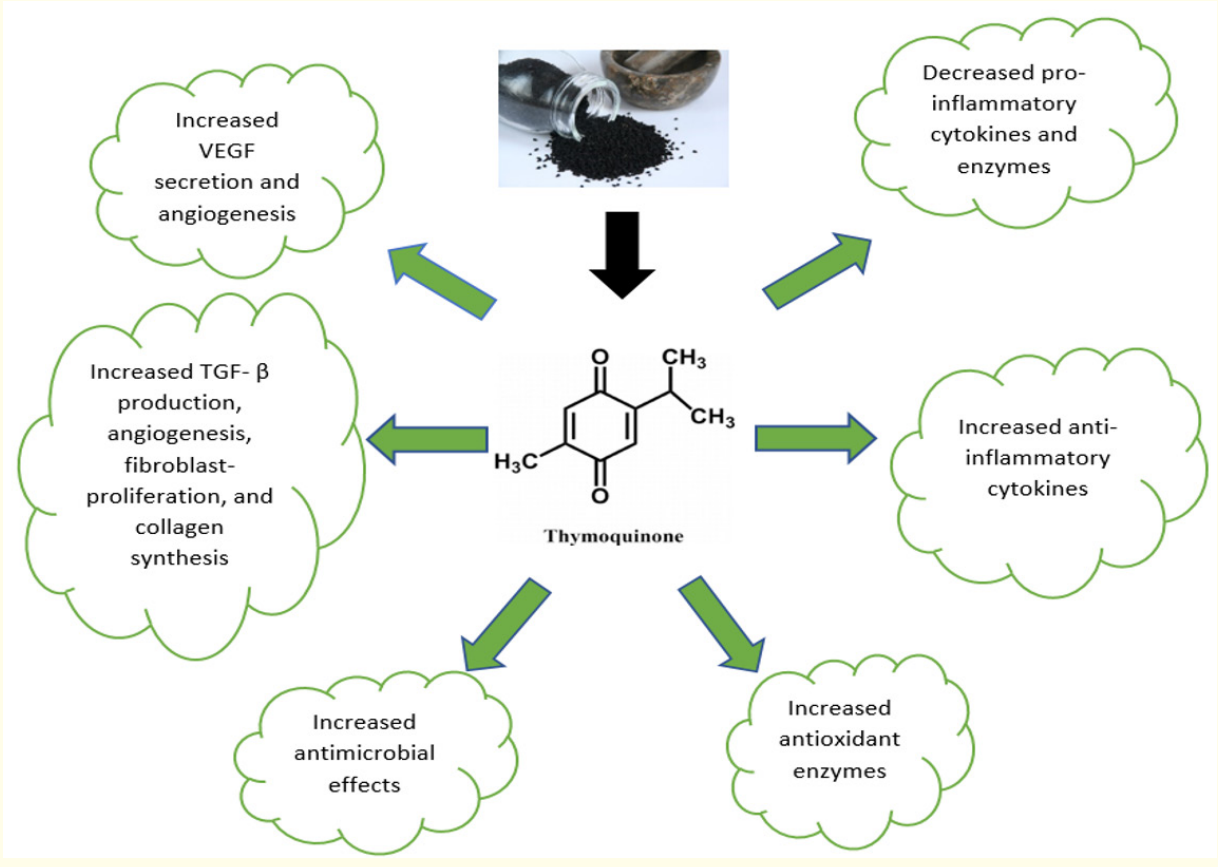


Figure 4: Various applications of Nigella sativa, commonly known as black cumin, contains active compounds thymoquinone, which have been utilized in different forms including oils, extracts.

A study investigating the effects of thymoquinone (TQ) and rosmarinic acid (RA) on retinal pigment epithelial cells (ARPE-19) using a wound healing model. The materials used were TQ and RA, known for their antioxidant and anti-inflammatory properties. The application involved determining the IC50 doses of these compounds using the MTT assay, followed by their administration at various doses (IC50, IC50/2, and IC50/4) to evaluate wound closure percentages. The most effective wound healing was observed at the IC50/4 dose. The results indicated that RA significantly enhanced wound healing, potentially through elevated levels of MMP-9 and TLR-3, without affecting VEGF mRNA expression. TQ improved wound healing by increasing TGF-β1 and MMP-9 protein levels while reducing TLR3 and IFN-γ mRNA expression levels. Since the thymoquinone(TQ) offer protective healing against retinal pigment epithelial cells damage it can be used in the wound healing application [35].

Eliza Arman., *et al*. conducted a study evaluating the combined effect of Virgin Coconut Oil (VCO) and Black Cumin Oil (*Nigella sativa*) on wound healing in diabetic ulcerated rats. The materials used were VCO, containing fatty acids, and Black Cumin Oil, rich in thymoquinone, both known for their antioxidant and anti-inflammatory properties. The application involved treating diabetic rats with ulcerated wounds using various combinations of these oils. The results demonstrated that the combination significantly upregulated VEGF gene expression, a key factor in angiogenesis and wound healing. Additionally, the treatment reduced inflammation, increased fibroblast numbers, and enhanced collagen synthesis, leading to more efficient wound healing compared to control groups. This study help to evaluate the wound healing application [11].

Retno Susilowati., *et al*. conducted a study on the wound healing effects of a combination of *Nigella sativa* and *Trigonella foenum-graecum* seed extracts in diabetic mice. The materials used were extracts of *Nigella sativa* and *Trigonella foenum-graecum*, known for their bioactive properties. The application involved treating diabetic mice with different combinations of these extracts. The results demonstrated that this combination significantly accelerated the wound healing process by reducing inflammation, increasing fibroblast proliferation, and enhancing collagen synthesis. Notably, the treatment group with *Nigella sativa* at 10% and *Trigonella foenum-graecum* at 5% showed the most pronounced improvement in wound healing, particularly by the 7th day of treatment. The study tells that the synergistic effects of these extracts offer a potent therapeutic approach for promoting wound healing in diabetic patients [32].

Cansu Aras., *et al*. conducted a study on the use of *Nigella sativa* oil (NSO) loaded onto electrospun polyurethane (PU) with the oil incorporated into nanofibrous mats produced via electrospinning for the application involved evaluating the antibacterial activity, biocompatibility, and wound healing efficacy of these NSO-loaded PU nanofibers. Which show the results that the NSO-loaded mats produced beadless, continuous fibers with significant antibacterial activity against E. coli and S. aureus. They were non-toxic and enhanced cell viability *in vitro*, while *in vivo* studies demonstrated accelerated wound closure and the mechanism included the antibacterial properties of NSO and the biocompatibility of the PU nanofibers, which together promoted faster healing. This effectiveness in enhancing wound healing, safety, and antibacterial properties aids to promising wound dressing materials for skin tissue applications [7].

Junfang Liang., *et al*. investigated the effects of thymoquinone (TQ), an active compound extracted from *Nigella sativa* seeds, on UVA-induced skin injury using HaCaT cells, a human keratinocyte cell line for its protective effects which in the results showed that TQ significantly improved cell viability and reduced cytotoxicity in UVA-irradiated cells thought the mechanism which involved inhibiting oxidative stress and inflammation, preventing mitochondrial dysregulation, and reducing apoptosis in keratinocytes. These protective effects were mediated through the activation of the NrF2/ARE pathway and the suppression of COX-2 expression. The study concluded that TQ effectively mitigates the damaging effects of UVA radiation on the skin, highlighting its potential as a protective agent in skin care [16].

Bibliography

Mohammad Reza Mahmoodi., *et al*. reviewed the potential benefits of various extracts and compounds from *Nigella sativa* (*N. sativa*) in diabetic wound healing. The materials studied included hydroalcoholic and aqueous extracts, as well as oils of *N. sativa*, with thymoquinone identified as a key bioactive component. The application of these extracts spanned different durations, ranging from 3 weeks to 1 year, and involved various animal models, including diabetic rats and mice. The results demonstrated multiple benefits, such as improved antioxidant enzyme activities, reduced fasting blood glucose levels, enhanced insulin sensitivity, better glucose tolerance, and reduced oxidative stress. Mechanistic insights revealed increased eNOS expression, improved endothelial function, reduced inflammatory markers, and enhanced insulin signaling pathways. The study concluded that *N. sativa* extracts and thymoquinone possess significant antidiabetic, antihyperlipidemic, and antioxidant properties, which contribute to the effective management of diabetic complications and enhanced wound healing [25].

Maha I. Alkhalaf., *et al*. conducted a study on the green synthesis of silver nanoparticles using *Nigella sativa* extract for investigated their antidiabetic effects, with a focus on diabetic neuropathy, a serious complication of diabetes which involves the application assessing their effects on hyperglycemia, oxidative stress, inflammation, and apoptosis. The results demonstrated that these nanoparticles effectively mitigated hyperglycemia, reduced oxidative stress and inflammation, and decreased apoptosis, leading to improved wound healing in diabetic conditions included the nanoparticles ability to reduce oxidative stress and inflammation, thereby promoting faster and more effective wound healing. From this study we concluded that *Nigella sativa*-derived silver nanoparticles can be used in therapeutic approach for treating diabetic complications, particularly in enhancing wound healing [19].

Nusaibah Sallehuddin., *et al*., used *Nigella sativa* extract for evaluated its effects on chronic delayed wound healing in streptozotocin-induced diabetic rats; with the experimental groups included Nondiabetic untreated (NU), Nondiabetic treated with 1% phenytoin (NP), Eucerin-treated sham (NE), Diabetic untreated (DU), Diabetic treated with 1% phenytoin (DP), Diabetic treated with 20% *Nigella sativa* extract (DNS20), and Diabetic treated with 40% *Nigella sativa* extract (DNS40). The application of *Nigella sativa* extract, especially at a higher concentration of 40%, was found to significantly accelerate the wound healing process, with the healing time ranked from fastest to slowest as DNS40, DNS20, NP, NU, DP, NE,

and DU. Additionally, the DNS40 group exhibited the highest levels of epidermal thickness, collagen fibers, and fibroblast infiltration, indicating enhanced wound repair mechanisms likely involves the bioactive compounds in *Nigella sativa* that promote cellular proliferation, collagen synthesis, and inflammation modulation, all of which are critical for effective wound healing. From this we concludes that *Nigella sativa* extract, particularly at a concentration of 40%, shows significant promise in enhancing wound healing in diabetic conditions, suggesting its potential as a therapeutic agent for managing chronic wounds in diabetic patients [29].

Abid Nordin., *et al*. conducted a systematic review to examine the effects of *Nigella sativa* (black seed) and its bioactive compound, thymoquinone (TQ), on type 2 epithelial to mesenchymal transition (EMT), a process pivotal to the balance between wound healing and tissue fibrosis, and influenced by the state of inflammation.this study indicates that *Nigella sativa* and thymoquinone significantly improved wound healing rates, reduced tissue inflammation, and prevented organ fibrosis. These effects were attributed to the promotion of EMT-related pathological changes during wound healing and the reversal of such changes in cases of fibrosis and inflammation following treatment with *Nigella sativa* or thymoquinone. The mode of action is suggested to involve the modulation of the EMT process, which plays a crucial role in both wound healing and the prevention of pathological fibrosis. From this review we concludes that *Nigella sativa* and thymoquinone are vital in regulating the EMT process, enhancing wound healing, mitigating tissue inflammation, and preventing organ fibrosis, making them promising agents in managing related conditions [2].

Majed Alwadei., *et al*. successfully developed and optimized a Self-Nanoemulsifying Drug Delivery System (SNEDDS) formulation incorporating curcumin (CUR) and black seed oil. The formulation included 12% black seed oil, 12% Imwitor 988, 6% Transcutol P, and 70% Cremophor RH40 as the surfactant. This innovative system achieved nanometer-range droplet sizes with favorable polydispersity and significantly enhanced solubility, which led to an increased dissolution rate. The liquid SNEDDS was subsequently solidified and encapsulated in hard gelatin capsules without compromising the formulation's physical parameters. The optimized liquid and solid CUR-loaded SNEDDS formulations demonstrated a significantly higher cumulative CUR release compared to pure drug powder. The findings confirmed that this SNEDDS formulation, which also included thymoquinone (THQ), outperformed marketed CUR products in terms of *in vitro* dissolution profiles. The mechanism of this attributed to the enhanced solubility and dissolution properties provided by the nanoemulsifying system, which improves the bioavailability of CUR and THQ. This shows that SNEDDS formulation represents a promising nanocarrier system for delivering high amounts of CUR and THQ to systemic circulation, thereby enhancing their bioavailability and therapeutic efficacy [22].

Apaydin Yildirim Betul., *et al*. investigated the effects of *Nigella sativa* L. essential oil on oxidative stress and its associated complications in streptozotocin-induced diabetic rats. The essential oil demonstrated potent antioxidant, antimicrobial, and anti-inflammatory properties, which contributed to a reduction in oxidative stress and its related complications in diabetic conditions. The study suggests the essential oil's ability to neutralize free radicals, reduce inflammation, and inhibit microbial growth, thereby protecting against oxidative damage and improving overall health in diabetic rats. This shows that *Nigella sativa* L. essential oil holds significant potential as an alternative treatment for managing diabetes-related complications, offering a natural therapeutic option with multiple beneficial effects [6].

Anum Javed., *et al*., conducted research that demonstrated the significant anti-inflammatory properties of crude oil from *Nigella sativa* and its active component, thymoquinone, in *in-vitro* studies involving peritoneal leukocytes (comprising 80% polymorphonuclear leukocytes and 20% mononuclear cells, with 95% viability) and found that *Nigella sativa* effectively inhibited eicosanoid generation and membrane lipid peroxidation. Additionally, it was shown to inhibit both the cyclooxygenase and 5-lipoxygenase pathways of arachidonate metabolism, which are critical to its anti-inflammatory activity. This attributed to the suppression of these key inflammatory pathways, thereby reducing inflammation at the cellular level. The study concludes that *Nigella sativa* crude oil and thymoquinone exhibit potent anti-inflammatory effects, which make them promising candidates for therapeutic applications in conditions characterized by inflammation [4].

Elham Nourbar., *et al*. evaluated the effects of *Nigella sativa* extract on diabetic rats, focusing on its anti-inflammatory and antimicrobial properties and significantly of the extract reduced inflammation and exhibited strong antimicrobial activity, suggesting its potential as a therapeutic agent for managing diabetes-related complications and infections and the bioactive compounds in *Nigella sativa* modulate inflammatory responses and inhibit micro-

bial growth, thereby protecting against infections and reducing complications associated with diabetes. It tells that *Nigella sativa* extract offering both anti-inflammatory and antimicrobial benefits give a promising natural treatment option for managing diabetes and its related complications [10].

Heba M. A. Abdelrazek., *et al*. conducted an experimental study investigating the protective effects of *Nigella sativa* (black seed oil, NSO) in streptozotocin (STZ)-induced diabetic male Wistar rats by utilized seeds from which the oil, rich in the active compound thymoquinone, was extracted. Known for its antioxidant and hypoglycemic properties, thymoquinone was applied to improve insulin secretion and reduce oxidative stress in diabetic rats and it demonstrated that NSO significantly improved pancreatic function by enhancing insulin secretion and reducing blood glucose levels. The underlying mechanism is attributed to thymoquinone's ability to counteract oxidative stress and boost antioxidant defenses, which aids in normalizing blood glucose levels and improving overall pancreatic health. *Nigella sativa* oil, particularly due to the presence of thymoquinone, holds potential as a therapeutic agent for managing diabetes by improving insulin function and protecting against oxidative stress-induced damage can used for wound healing application [13].

Yunita Sari., *et al*. study on *Nigella sativa* Oil (NSO) which investigated for its therapeutic effects on diabetic ulcers. The NSO significantly reduces inflammation, enhances reepithelialization, and promotes granulation tissue formation in diabetic rats. These findings indicate that NSO effectively addresses key aspects of wound healing, particularly in diabetic conditions where these processes are often compromised. The therapeutic benefits of NSO are attributed to its anti-inflammatory properties and its ability to support tissue regeneration. By modulating the inflammatory response and facilitating new tissue formation, NSO shows promise as a natural remedy for diabetic ulcers. The study underscores its potential for further investigation and clinical application in managing diabetic wounds, where efficient wound healing and inflammation control are crucial [39].

Mahmoud Balbaa., *et al*. discussed a review on the primary active compound found in *Nigella sativa* oil, thymoquinone, was explored for its therapeutic effects, particularly in the context of diabetes and neurodegenerative diseases. The study, tells the cold-pressed *Nigella sativa* oil was administered to streptozotocin (STZ)-induced diabetic rats, demonstrating that thymoquinone significantly enhanced insulin secretion, reduced oxidative stress, and helped restore the normal architecture of pancreatic tissues. These findings highlight the potential of *Nigella sativa* oil as an anti-diabetic treatment. Another study included in the review focused on high-fat diet (HFD) and STZ-induced diabetic rats to investigate the neuroprotective and anti-Alzheimer's potential of *Nigella sativa* oil. The study found that thymoquinone improved insulin signaling in the brain, normalized brain glucose levels, reduced acetylcholinesterase (AChE) activity, and significantly decreased the levels of amyloid-beta 42 (Aβ-42), a key marker associated with Alzheimer's disease. The mechanisms identified in these studies suggest that *Nigella sativa* oil may help preserve cognitive function and prevent neurodegenerative diseases, underscoring its potential as a multifaceted therapeutic agent. These study helps to develop a wound healing material from the active compound found in *Nigella sativa* oil for their application [21].

R.M. Shrivastava., *et al*. discussed that *Nigella sativa* seed oil, extract, and its active compound, thymoquinone, along with other constituents, exhibit significant anti-inflammatory, antioxidant, and antimicrobial properties crucial for wound healing. The study indicates that *Nigella sativa* aids in accelerating the wound healing process by modulating inflammatory responses and enhancing collagen synthesis, which are essential for tissue repair. Additionally, its antioxidant properties help in reducing oxidative stress in wounds, which can otherwise delay healing. From this, we conclude that *Nigella sativa* seed oil, extract, and its active compound have significant potential as adjunct therapies for managing diabetic wounds, promoting faster recovery, and reducing complications associated with diabetes [33].

Nigella sativa seed, has been historically used as a medicinal remedy across various cultures for centuries. It gained fame through Prophetic Medicine, which advocates its use as a remedy for numerous ailments, excluding death. The seed contains several active compounds such as thymoquinone, thymohydroquinone, dithymoquinone, thymol, carvacrol, nigellimine, nigellicine, nigellidine, and alpha-hederin. These compounds contribute to its medicinal properties, including anti-inflammatory and antioxidant effects. Studies have shown that *N. sativa* seed and its oil can promote wound healing in animals. For instance, topical application of ether extract from *N. sativa* seeds on staphylococcal-infected skin in mice accelerated healing processes. It reduced inflammatory markers, facilitated wound closure by promoting gingival fibroblast growth, and demonstrated low-level free radical scavenging activity. Ad-

ditionally, research highlights the anti-inflammatory effects of *N. sativa* fixed oil and thymoquinone, corroborating their potential therapeutic benefits in wound healing and other inflammatory conditions [31].

Traditionally, applying black seed oil topically has been highly effective in treating skin eruptions, hemiplegia (paralysis on one side of the body), back pain, rheumatism, and other inflammatory conditions. Likewise, crude oil from *Nigella sativa*, when combined with thymoquinone, acts as an inhibitor of eicosanoid production and membrane lipid oxidation. This is achieved by blocking the cyclooxygenase and 5-lipoxygenase pathways involved in arachidonate metabolism, thereby contributing to its anti-inflammatory effects [30].

The aqueous extract of *Nigella sativa* (*N. sativa*) exhibits significant anti-inflammatory and analgesic activities in animal models, as evidenced by its inhibitory effects on carrageenan-induced paw edema and increased hot plate reaction time in mice. However, the extract does not affect yeast-induced pyrexia, indicating no antipyretic activity. These findings support the traditional use of *N. sativa* in folk medicine for its analgesic and anti-inflammatory properties and highlight the need for further research to understand its mechanisms of action [27].

The study aimed to assess the protective effects of *Nigella sativa* L. (NS) on β- with streptozotocin (STZ)-induced diabetes rat. Diabetes was induced by administering a single intraperitoneal dose of STZ (50 mg/kg). NS was given at 0.2 ml/kg/day intraperitoneally for 3 days before STZ administration and continued for the 4-week duration of the study. Since oxidative stress plays a role in the development of diabetes mellitus (DM), the study measured the activities of antioxidant enzymes (glutathione peroxidase (GSHPx), superoxide dismutase (SOD), and catalase (CAT)) in pancreatic tissues. Serum nitric oxide (NO) levels and malondialdehyde (MDA) levels in erythrocyte and pancreatic tissues were also measured to evaluate the balance between oxidants and antioxidants. Immunohistochemical methods were used to examine pancreatic β-cells. The results indicated that STZ caused a significant increase in lipid peroxidation and serum NO levels, along with a decrease in antioxidant enzyme activity. However, NS treatment reduced lipid peroxidation and serum NO levels while enhancing antioxidant enzyme activity. In STZ-induced diabetic rats, islet cell degeneration and weak insulin staining were observed, whereas NS-treated diabetic rats showed stronger insulin staining and better preservation of β-cell numbers. These findings suggest that NS treatment provides a protective effect in diabetes by reducing oxidative stress and preserving pancreatic β-cell integrity, indicating its potential clinical use for protecting β-cells against oxidative damage [23].

This study assesses the susceptibility of multidrug-resistant *Staphylococcus aureus* to *Nigella sativa* oil [18]. *Staphylococcus aureus* was isolated from the wounds of 34 diabetic patients attending the Renaissance hospital in Nsukka, Southeast Nigeria. The isolates were identified using standard microbiological techniques and cultured for a comparative *in vitro* antibiotic susceptibility test using the disk diffusion method. Of the 34 samples, 19 (56%) showed multidrug resistance to commonly used antibiotics. The antibacterial activity of *Nigella sativa* oil against these multidrug-resistant isolates was then tested at varying concentrations using the well diffusion method. The oil exhibited a dose-dependent antibacterial effect on the isolates. Out of 19 isolates, 8 (42%) were sensitive to the undiluted oil sample; 4 (21%) of these showed sensitivity at concentrations of 200 mg/ml, 400 mg/ml, and 800 mg/ml, respectively. However, 11 (58%) of the isolates were completely resistant to all tested oil concentrations.

The study on *Nigella sativa*, has shown promising potential in diabetic wound healing due to its various pharmacological effects. The plant's active compound, thymoquinone (TQ), plays a significant role in these effects. Several studies, both on animal models and human trials, have demonstrated the benefits of using black seed extracts and oils. In diabetic wound healing, black seed exerts its effects through multiple mechanisms. It has strong anti-inflammatory and antioxidant properties that help reduce inflammation and oxidative stress, which are common issues in diabetic wounds. Additionally, it enhances insulin secretion and modulates glucose absorption and lipid profiles, further contributing to better wound healing outcomes [15].

The study reports that the plant's bioactive compound, thymoquinone (TQ), exhibits anti-inflammatory, anti-microbial, and antioxidant effects, which are crucial for promoting wound healing in diabetic patients. Research indicates that these properties help reduce inflammation, prevent infection, and enhance the body's natural healing processes. Moreover, *N. sativa* anti-diabetic effects contribute to better glycemic control, which is essential for effective wound healing. The plant's ability to modulate the immune system and support tissue regeneration further underscores its therapeutic potential in managing diabetic wounds [38].

The study on HFD/STZ-induced diabetic rats highlighted the

neuroprotective and anti-Alzheimer's potential of NSO. Thymoquinone improved insulin signaling in the brain, normalized brain glucose levels, reduced acetylcholinesterase (AChE) activity, and significantly decreased amyloid-beta 42 (Aβ-42) levels, indicating its role in preserving cognitive function and preventing neurodegenerative diseases. Additionally, in a study aiming to develop an ideal animal model for type II diabetes, NSO was investigated for its effects alone and in combination with standard anti-diabetic drugs like metformin (MET) or glibenclamide (GLI). The study showed that NSO improves insulin sensitivity, reduces blood glucose levels, enhances antioxidant activity, and modulates lipid profiles in diabetic rats. The combination of NSO with MET or GLI resulted in significant reductions in blood glucose, insulin resistance markers (HOMA-IR), total cholesterol (TC), triglycerides (TG), and inflammatory markers such as TNF-α. The synergistic interaction between NSO and these drugs suggests a potential for combined therapeutic strategies in diabetes management. These findings collectively underscore the multifaceted mechanisms of NSO, including the enhancement of insulin signaling, reduction of oxidative stress, and modulation of lipid metabolism, making it a promising candidate for diabetes treatment.

The study investigates the effect of thymoquinone, an active compound derived from *Nigella sativa*, on wound healing in alloxan-induced diabetic rats. Conducted as an *in vivo* study, it demonstrates that thymoquinone significantly enhances the wound healing process. The mechanism behind this involves thymoquinone's antioxidant and anti-inflammatory properties, which reduce oxidative stress, promote fibroblast proliferation, and increase collagen synthesis. These actions collectively contribute to improved wound healing, suggesting thymoquinone's potential therapeutic application for enhancing wound repair in diabetic conditions [3]. The Summarizing diagram for the wound healing mechanisms of *Nigella sativa* and its compounds, particularly in diabetic conditions (Shown in Figure 5) and Comprehensive summary of the different parts or extracts of *Nigella sativa* used in wound healing, especially in the context of diabetic conditions. It outlines the active compounds present, the types of studies conducted (*in vitro*, *in vivo*, or clinical), and the specific wound healing applications observed. (Shown in Table 1) this overview highlights the extensive research on *Nigella sativa* and underscores its potential as a valuable therapeutic agent for wound management, particularly in the management of diabetic wounds.

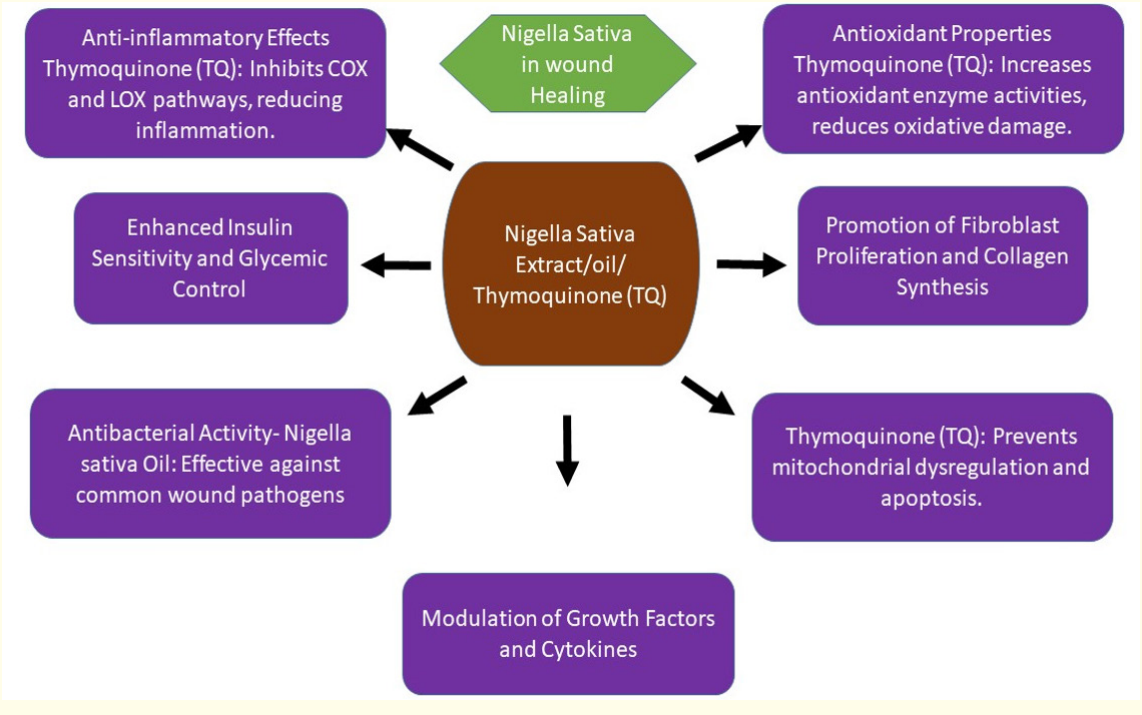


Figure 5: The textual diagram provides a clear, hierarchical breakdown of the mechanisms by which *Nigella sativa* and its compounds support wound healing, particularly under diabetic conditions. Each section focuses on a specific biological action or effect, making it easier to understand how these compounds contribute to the overall healing process.

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