

Nigella sativa a Potent Healer for Diabetic Wounds and Its Other Pharamcognosal attributes

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Abstract

Implementation of herbal medication is traditionally employed for treating broad spectrum diseases. Among this remedial flora, *Nigella sativa* is emerging as potent pharmaceutically significant plant with supportive religious background. Produce formulated from *N. sativa* have been found effective as anti-inflammatory, analgesic, antipyretic, antimicrobial, antineoplastic drugs for various disorders and also as an ideal healer for variety of wounds. As in daily routine, minor injuries, abrasions and burns are common and inevitable. In consequence, wound healing which is a physiological and systematic process in response to injury may be impaired due to several external and internal factors like in case of several infections and in diabetic patients, and it may lead to diabetic foot ulcers with significant morbidity and mortality risks. Retarded diabetic wounds' healing is mainly due to interleukin-8, hyperglycemia and other contributing factors are like poor epithelialization, angiogenesis and skin regeneration. Biochemically, black seeds contain 35% fatty acids, 21% proteins and 38% carbohydrates and vast variety of other vitamins and minerals. Among them, thymoquinone frequently reported constituent as potent wound healer either of diabetic origin or due to other reasons. So far explored broad spectrum efficacy of this plant is also directly a proof of hadith of Prophet Muhammad (HPBU): "Use black seeds regularly; because, it cures every disease excluding death". So its biochemical screening and dose optimization to cure and heal not only the diabetic wounds in better way but also for other pharamcognosal pursuits should be explored in future to provide general public of third world countries like Pakistan, as local cost effective alternative drug in replacement of expensive synthetic drugs for better medical treatment.

Keywords: herbal medication, *Nigella sativa*, wound healing, diabetic wounds, diabetic foot ulcers, thymoquinone.

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INTRODUCTION

Herbal pharamcognosy is in practice for curing vast range of diseases for centuries. Such herbal produce are still in use in several regions of the world because they are considered comparatively safer than modern allopathic remedies. This wing needs more attention yet as only few botanical species have been systematically investigated for their curative properties, mode of action, immune response evaluation and toxicological effects estimation so far. Among many curative plants, *Nigella sativa* (family: Ranunculaceae)

is emerging as potent remedial floral species with strong pharmaceutical and religious background. It is an annually grown plant with southwest Asian origin. Commonly known as black seed or black cumin which is employed in herbal pharmacy around the globe to treat and prevent diverse ailments. *N. sativa* based products have been found effective as anti-inflammatory, analgesic, antipyretic, antimicrobial and antineoplastic drugs [1]. Taxonomic position of *N. sativa* is as follows:

Kingdom	Plantae
Sub kingdom	Tracheobionta
Super division	Spermatophyta
Division	Magnoliophyta
Class	Magnoliopsida
Order	Ranunculales
Family	Ranunculaceae
Genus	<i>Nigella</i>
Species	<i>N. sativa</i> (Khare, 2004) [2]

Wound healing is a physiological process in response to injury and a systematic route that involves hemostasis, cellular migration, proliferation, re-epithelialization, angiogenesis, extracellular matrix deposition, wound reduction and scar formation, respectively. Its rate of healing basically highlights efficiency of internal homeostasis [3]. However, patients with diabetes mellitus suffer with impaired wound recovery which may lead to diabetic wounds or ulcers formation, and may result in several complications even sometimes limb amputation [4]. For the recovery and regeneration of diabetic wounds biochemical boosters without any toxic effects are required [5]. Thymoquinone is a reported dermal healer due to its anti-inflammatory, antioxidant nature and it also prevents membrane lipid peroxidation in tissues; these effects suggest that topical application of *N. sativa* accelerates injury cure [6].

Diabetes mellitus is a common and serious metabolic disorder has association with various functional and structural complications [7] and its sufferers are more than 422 million people worldwide [8]. Wound healing is impaired in diabetes, and usually diabetic foot ulcers (DFU) cause significant morbidity and mortality risks. In daily routine, minor injuries, abrasions and burns are common and unavoidable. But even small cuts and insect bites can cause wound healing difficulties in diabetic patients. The sufferers of diabetes may develop dermal wounds that either recover slowly or do not heal at all. Sometimes, infections may occur and may lead to serious health issues. Thus, current review was done to evaluate effects of *N. sativa* for wound healing in diabetic patients and significantly to find out cost effective remedy of this serious global issue for persons of third

world countries like Pakistan who have considerable economic constraints [9].

Diabetic Wounds

Diabetic wounds are multifactorial in origin, with enhanced inflammation, onset of reactive oxygen species (ROS), but reduced angiogenesis, and impaired keratinocyte migration along with other pathophysiological mechanisms [10]. In diabetes mellitus, retarded wounded sites regeneration is one of chief complications and can have a long-term adverse impact on life like morbidity and mortality [11, 12].

Currently, diabetic wound treatment begins primarily with diagnosis, prevention and disease handling awareness of patient [13, 14]. Although, the pathogenesis of diabetic wound remedial is multifactorial, prolonged dermal redness accompanied by important oxidative stress are the principal factors that impair wound healing [15]. However, diabetic patients mainly suffer with retarded healing and regeneration of typical diabetic wounds or ulcers, and may result in severe complications including limb exclusion [4].

Reasons of Diabetic Wounds Retarded Healing

Diabetic wound healing varies from routine wound healing mechanism; in it, intrinsic pathophysiological abnormalities are expected like poor angiogenesis, impaired wounded site healing and matrix regeneration, moreover, extrinsic factors e.g., infections that lead to delayed and abnormal wound curing course [16, 17]. Furthermore, various studies have highlighted that chronic oxidative stress associates with the progression of diabetic complications and impaired wound cure [15].

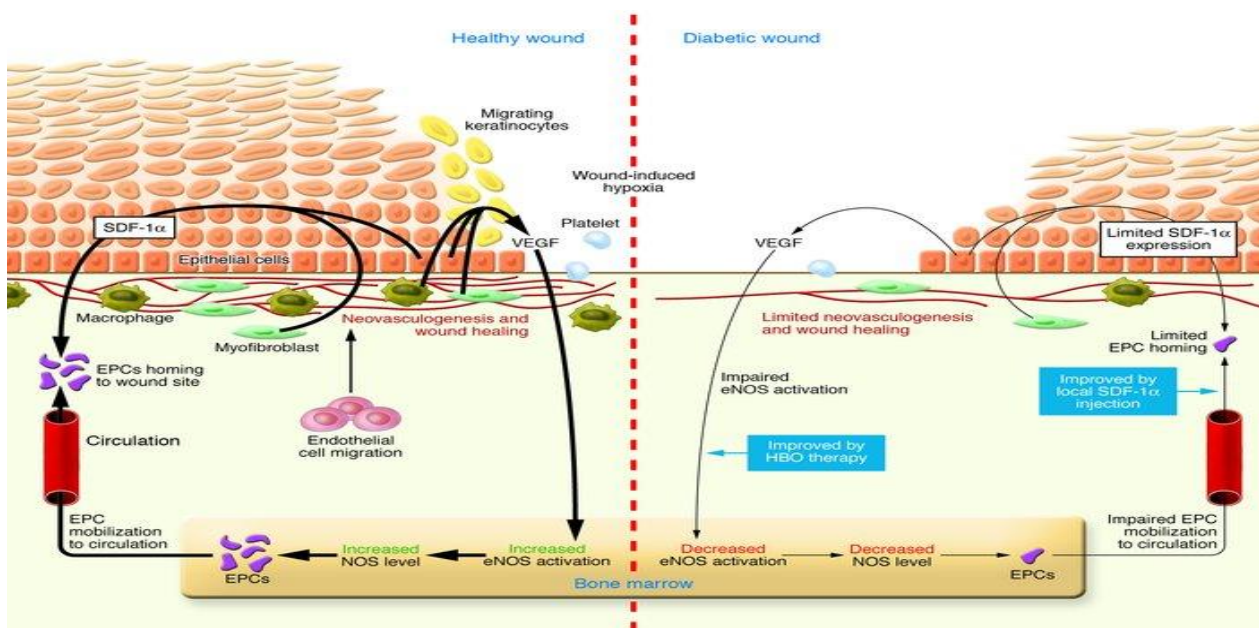


Fig-1: Comparative view of wound healing and skin regeneration in healthy and diabetic persons [18]

Decreased dermal healing and recovery is a major diabetic complication which is directly concerned with extensive mortality rate [19]. Often it also results in micro- or macrovascular disorders. Similarly, diabetic neuropathy and may cause loss of protective sensation (LOPS) has been reported as one of the chief causes for delayed healing in diabetic foot ulcer patients [20-22]. In addition, hyperglycemia and an integer of hyperglycemia-related factors have been connected to lessened diabetic wound recovery, as well as advanced glycation end products (AGE) [23]. Interleukin (IL)-8 by keratinocyte is key stimulator for neutrophils transport towards wounded sites and results in delayed recovery accompanied by intense irritation [24]. Other contributing factors that could also delay wound healing are: impaired re-epithelialization and angiogenesis, formation of pericapillary fibrin cuffs, neuropathy and bacterial infiltration [25].

Biochemical Composition of Black Seeds

Black seed is a notable aromatic plant that has been used for over 3000 years for various pursuits. Biochemically, it is composed of approximately 100 different constituents, among which essential 35% fatty acids, 21% proteins and 38% carbohydrates and other vitamins and minerals. Additionally, sterols are also present; major content is of beta-sitosterol which is anti-carcinogenic [26, 27]. It has been reported that *N. sativa* also contains 15 amino acids including 9 essential ones, carbohydrates, essential fatty acid (EFA) including myristic acid, palmitic acid, stearic acid, folic acid, palmitoleic acid, arachidonic acid, oleic acids and linolenic acid as (omega-3) and (omega-6).

Similarly, vitamins: A, B1, B2, B3, B6, C, folacin and niacin as well as calcium, sodium, potassium, iron, copper, magnesium, zinc, phosphorous and selenium are present [28-32, 27]. The three leading phytochemical compounds in black seed oil are thymoquinone (TQ), thymohydroquinone (THQ) and thymol (THY). Other bioactive compounds in the seed contain α -hederin, alkaloids, flavonoids and antioxidants [33-36, 27].

Islamic & Pharmaceutical Importance of Black Seeds

Herbal medication is employed in human civilization for centuries. According to a hadith narrated by Ibn' Abbas (R.A), Prophet Muhammad (PBUH) said that Prophet Sulayman (A.S) recorded the names and uses of numerous herbal remedies after finishing the construction of his temple (Ibn' Asakir, Mukhtasar Tareekh Dimashq, 3:393). Prophet Muhammad (PBUH), moreover, prepared limited statements on 65 different healing floral species [27]. Amongst the plants, prescribed by Him (PBUH), black seeds (*Nigella sativa*) are potent healers. About this plant, Abu Hurayrah (R.A) narrated that Prophet Muhammad (HPBU) said: Use black seeds regularly; because, it

cures every disease excluding death (Reference: Sahih Al-Bukhari 71:591, 592; Sahih Muslim 26: 5489).

Black Seeds as Potent Wound Healer

Globally, the implementation of *N. sativa* based products is in practice for wounds treatment and for other cures for ancient times like in traditional remediation of Indian medicine like Unani and Ayurveda. Likewise, in Muslim cultures, it is also considered as one of the best forms of curative medicine [37, 38]. *N. sativa* has been extensively employed for its broad spectrum biological actions like healing action and diuretic, antihypertensive, antidiabetic, anticancer, immunomodulatory, analgesic, antimicrobial, anthelmintics, anti-inflammatory, spasmolytic, bronchodilator, gastroprotective, hepatoprotective, renal protective and antioxidant properties. Commonly bronchitis, asthma, diarrhea, rheumatism and dermal ailments are treated by seeds of *N. sativa*. It also serves as liver tonic, gastrointestinal booster, antidiarrheal agent, appetizer, menstrual cycle regulator, lactation improver, prevents from bloodsucking infections and improves immune system [39-43].

Although wound healing and regeneration involves inflammation, granulation and tissue remodeling along with interactions of atypical cells, extracellular matrix proteins and their receptors which are drawn towards wounded site, and are mediated by cytokines and progression factors [44, 45]. In this regard, black seeds have been indulged for centuries for the care of several dermatological conditions and disorder, and in cosmeceutical formulations [46]. For example, it is used for bad skin vulgaris, burn, wounds, and injury treatment [6]. It also serves as anti-inflammatory for diverse kinds of skin inflammation [47], and is employed to tone down the skin pigmentation effect [48, 49]. Moreover, according to the reported data, the appliance of a mixture of propolis, black seed and honey is quite effective for healing and recovery of diabetic wounds.

In addition to this, black seed contains over 100 medicinal components which work simultaneously to produce a synergetic effect. Out of these, simply 69 have been characterized and identified [27]. So far published data highlights that *N. sativa* products like oil, extracts, and their active ingredients, in particular, thymoquinone, which possess antinociceptive, anti-inflammatory and analgesic effects [50, 32]. Another mammalian wound model was evaluated the curing effect of *N. sativa* oil and it was concluded that it serves as potent wound healing booster due to its anti-inflammatory and immunomodulatory effects [6].

N. sativa oil has been found effective to enhance collagen formation and it rapidly increases the proportion of epithelialization at wounded site. That is why; it is considered as potent wound healer and

moisturizing agent [51]. Similar, results were obtained in another investigation in which ether extract of *N. sativa* seed was applied on injured dermis and enhanced the healing was observed along with decrease in the total and absolute white blood cells count, reduced tissue damage and declined bacterial expansion [52, 53].

Pharmacognosial applications of Black seeds in Pakistan

Pharmacological Preference Due To Religious Background

In an Islamic civilization, *N. sativa* has its own worth in wounds healing and skin regeneration domain. These wounds may be due to diabetes or some other reasons. It can also be noted from sayings of the Holy Prophet Mohammad (PBUH) that the black seeds have a great medicinal value [54].

Effective for Inflammation

Traditionally, the topical application of oil of black seeds is quite effective to cure skin eruption, paralysis hemiplegia, back pain, rheumatism and related inflammatory diseases. Similarly, the crude oil of *N. sativa* in combination with thymoquinone serves as inhibitor eicosanoid generation and membrane lipid peroxidation, through the inhibition of cyclooxygenase and 5-lipoxygenase pathways of arachidonate metabolism, consequently liable for anti-inflammatory activity [55].

Antimicrobial Activity

According to the reported data, the methanolic extract of *N. sativa* seeds has been found effective to exhibit antimicrobial action against *Streptococcus mutans* that is why; serve as protector from dental caries. Moreover, alcoholic extract of the black seeds has been noted as anticestodal in nature and serves as potent antibacterial agent against *Micrococcus pyogenes* var. *aureus*. In addition to that, its ether extract has presented in vitro antimicrobial activity against gram-positive bacteria; e.g., *Streptococcus aureus*, gram-negative bacteria; e.g., *Pseudomonas aeruginosa* and *Escherichia coli* [56, 57].

Hypoglycemic Effects

During a mammalian model based investigation, the mixture of *Nigella sativa*, Myrrh, gum olybanum and gum asafetida has been reported quite effective to lower down blood glucose level [58].

Effects on Cardiovascular System

N. sativa seeds oil has been reported as depressant in action on the frog heart to regulate it whereas in another study, it has been found as relaxant effect producer on cardiac muscles of rat. In another experimental effort, the crude extract *N. sativa* was found as quick stimulator to lower down the blood pressure in hypertensive rats [59].

Effects on Immune System and Cancer

It has been reported that ethanolic extract of black seeds serves as inhibitor against malignant cells and endothelial cells progression in vitro and also exhibit cytotoxic activity to cure oral cancers [60]. In another study, the aqueous and alcoholic extracts of *N. sativa* individually or in mixture form in combination with H_2O_2 serves as an oxidative stressor, were noted as effectual for inactivating MCF-7 breast malignant cells in vitro [61].

Effects on the Nervous System

Published data highlights that the appliance of *N. sativa* seeds induces pain relieving effect due to improved functioning of mediated opioid receptors. In another investigation, the aqueous and methanolic extracts of *N. sativa* seeds have been found as an effective remedy to lower down high fever and as significant pain reliever along with the CNS depressant action [62].

Effects on the Gastrointestinal System

Traditionally, the seed of *N. sativa* have been employed to cure in a wide range of gastrointestinal disorders. The aqueous extract of its seeds has been reported to exhibit anti-ulcer mode of action by reducing the amount of acid found in gastric juice during an animal model based study [63].

Effect on Genitourinary System

The ethanolic extract of *N. sativa* seeds showed infertility reducing effects by boosting estrogen level in an animal model based investigation. In another study, the hexane extract of black seeds exhibited significant contraceptive action in rats. Similarly, in another mammalian model based investigation, the paste of *N. sativa* was found as potent anti-oxytocin agent [64-66].

Effects on the Respiratory System

Powder of black seeds is implied traditionally to relieve respiratory disorders e.g., asthma, bronchospasm and chest congestion. Nigellone, significant ingredient of *N. sativa*, has been found as potent healer for asthma and bronchitis [67].

CONCLUSION

It can be concluded that healing potential of Black seeds is remarkable and its significance can be judged from religious aspect too. So it should be further employed after its biochemical constituents screening and dose optimization to cure and heal not only the diabetic wounds in better way but also for other pharmacognosial pursuits. It may serve as local cost effective alternative drug in replacement of expensive synthetic drugs for third world countries like Pakistan.

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