



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

Anum Javed^{1*}, Muhammad Usman², Nimra Akram³, Sonaina Kanwal⁴, Ibtasam Riaz⁵ & Syed Muneeb Haider⁶

¹Department of Zoology, University of Sargodha (RCS, Sub campus), Narowal, 51750, Pakistan

^{2, 3, 4, 5, 6}Department of Zoology, University of Gujrat (Sub campus), 1-KM Daska road, Sialkot, 51310, Pakistan

Keywords:

Herbal medication, *Nigella sativa*, Wound healing, Diabetic wounds, Diabetic foot ulcers, Thymoquinone.

Correspondence:

Anum Javed. Department of Zoology, University of Sargodha (RCS, Sub campus), Narowal, 51750, Pakistan.

Funding Information:

No funding information provided.

Manuscript History:

Received: May 2019

Accepted: June 2019

International Journal of Scientific Footprints 2019; 7(1): 35 - 43

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.

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 (Al-Douri and Al-Kazaz, 2010). Taxonomic position of *N. sativa* is as follows:

Table 1: Taxonomic Position of *N. sativa*

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)

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 (Javed and Qazi, 2016). 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 (Icli *et al.*, 2016). For the recovery and regeneration of diabetic wounds biochemical boosters without any toxic effects are required (Santos *et al.*, 2008). 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 (Yaman *et al.*, 2010).

Diabetes mellitus is a common and serious metabolic disorder has association with various functional and

structural complications (Mariano *et al.*, 2010) and its sufferers are more than 422 million people worldwide (WHO, 2016). 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 (Javed, 2017).

1. 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 (Dunnill *et al.*, 2017). In diabetes mellitus, retarded wound sites regeneration is one of chief complications and can have a long-term adverse impact on life like morbidity and mortality (Siersma *et al.*, 2013; Karri *et al.*, 2016).

Currently, diabetic wound treatment begins primarily with diagnosis, prevention and disease handling awareness of patient (Allen *et al.*, 2014; Karri *et al.*, 2015). Although, the pathogenesis of diabetic wound remedial is multi-factorial, prolonged dermal redness accompanied by important oxidative stress are the principal factors that impair wound healing (Kant *et al.*, 2014). 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 (Icli *et al.*, 2016).

2. Reasons of Diabetic Wounds Retarded Healing

Diabetic wound healing varies from routines 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 (Falanga, 2005; Arya *et al.*, 2014). Furthermore, various studies have highlighted that chronic oxidative stress associates with the progression of diabetic complications and impaired wound cure (Kant *et al.*, 2014).

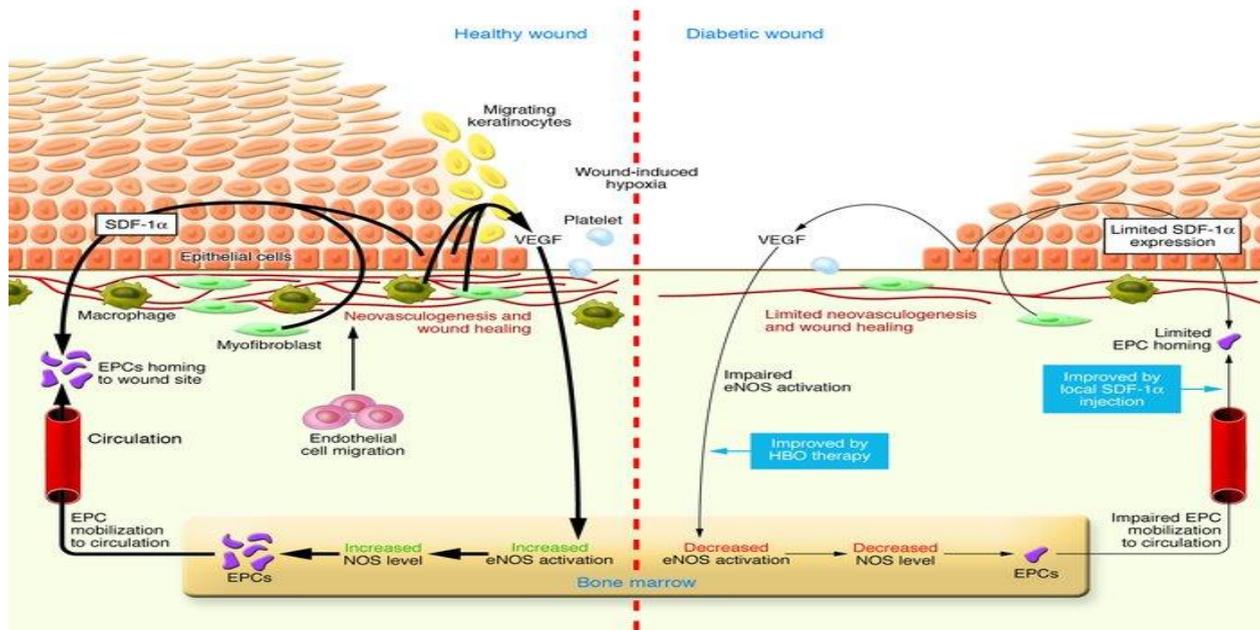


Figure 1: Comparative View of Wound Healing and Skin Regeneration in Healthy and Diabetic Persons (Berm and Tomic-Canic, 2007)

Decreased dermal healing and recovery is a major diabetic complication which is directly concerned with extensive mortality rate (Jeffcoate & Harding, 2003). 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 (Boulton *et al.*, 2004; Armstrong *et al.*, 2005; Katz *et al.*, 2005). In addition, hyperglycemia & an integer of hyperglycemia-related factors have been connected to lessened diabetic wound

recovery, as well as advanced glycation end products (AGE) (Goova *et al.*, 2001). Interleukin (IL)-8 by keratinocyte is key stimulator for neutrophils transport towards wounded sites & results in delayed recovery accompanied by intense irritation (Lan *et al.*, 2013). Other contributing factors that could also delay wound healing include impaired re-epithelialization & angiogenesis, formation of pericapillary fibrin cuffs, neuropathy and bacterial infiltration (Pradhan *et al.*, 2009).

3. 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 (Ahmad *et al.*, 2014; Hussain and Hussain, 2016). 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 (Toma *et al.*, 2010; Randhawa and Alghamdi 2011; Kaskoos, 2011; Yuan, 2014; Amin and Hossein, 2015; Hussain and Hussain, 2016). 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 (Tubasha *et al.*, 2011; Al-Okaily *et al.*, 2012; Elshiekh and Abdelmageed, 2015; Gharby *et al.*, 2015; Hussain and Hussain, 2016).

4. 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, Mukhtaṣar

Tareekh Dimashq, 3:393). Prophet Muhammad (PBUH), moreover, prepared limited statements on 65 different healing floral species (Hussain & Hussain, 2016). 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).

5. 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 (Goreja, 2003; Sharma *et al.*, 2005). *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 (Khaled, 2009; Assayed, 2010; Boskabady, 2010; Abdel-Zaher *et al.*, 2011; Abel-Salam, 2012).

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 (Osama and Zinadah, 2009; Nezhad *et al.*, 2013). In this regard, black seeds have been indulged for centuries for the care of several dermatological conditions and disorder, and in cosmeceutical formulations (Ramadan, 2013). For example, it is used for bad skin vulgaris, burn, wounds, and injury treatment (Yaman *et al.*, 2010). It also serves as anti-inflammatory for diverse kinds of skin inflammation (Silveira *et al.*, 2013), and is employed to tone down the skin pigmentation effect (Ali and Meitei, 2011; Ghorbanibirgani *et al.*, 2014). 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 (Hussain and Hussain, 2016). 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 (Rahman *et al.*, 2014; Amin and Hossein, 2015). 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 (Yaman *et al.*, 2010).

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 (Sarkhail *et al.*, 2011). 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 (Abu-Al-Basal, 2011; Ghonime *et al.*, 2011).

6. Pharamcognosal applications of Black seeds in Pakistan

6.1. 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 (Ghaznavi, 1996).

6.2. 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 (Houghton *et al.*, 1995).

6.3 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* (Akhtar and Riffat, 1991; Sokmen *et al.*, 1999).

6.4. Hypoglycemic Effects

During a mammalian model based investigation, the mixture of *Nigella sativa*, Myrrh, gum olibanum and gum asafetida has been reported quite effective to lower down blood glucose level (Al-Awadi and Gumaa, 1987).

6.5 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 (Zaoui *et al.*, 2000).

6.6. 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 (Swamy and Tan, 2000). In another study, the aqueous and alcoholic extracts of *N. sativa* individually or in mixture form in combination with H₂O₂ serves as an oxidative stressor, were noted as effectual for inactivating MCF-7 breast malignant cells in vitro (Farah and Begum, 2003).

6.7. 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 (Al-Naggar *et al.*, 2003).

6.8. 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 (Akhtar *et al.*, 1996).

6.9. 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 (Badary *et al.*, 2000; Kabir *et al.*, 2001; Abdul-Nasr *et al.*, 2001).

6.10 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 (Chakravarty, 1993).

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 pharamcognosol pursuits. It may serve as local cost effective alternative drug in replacement of expensive synthetic drugs for third world countries like Pakistan.

References

- [1] Abdel-Zaher, A. O. 2011. Protective effect of *Nigella sativa* oil against tramadol-induced tolerance and dependence in mice: role of nitric oxide and oxidative stress. *Neurotoxicology*, 32(6): 725-733
- [2] Abdul-Nasr, S. M., M. D. M. El-Shfey and M. M. H. Osfor. 2001. Amelioration by *Nigella sativa* of methotrexate-induced toxicity in male albino rats: a biochemical, haematological and histological study. *Scieintia Agriculture Bohemica*, 32: 123-160
- [3] Abel-Salam, B. K. 2012 Immunomodulatory effects of black seeds and garlic on alloxan-induced diabetes in albino rat. *Allergol Immunopathol (Madr)*, 40(6): 336-340
- [4] Abu-Al-Basal, M. A. 2011. "Influence of *nigella sativa* fixed oil on some blood parameters and histopathology of skin in staphylococcal-infected BalB/C mice," *Pakistan Journal of Biological Sciences*, 14(23): 1038-1046
- [5] Ahmad, I., J. Tripathi, M. Sharma. 2014. *Nigella sativa*—a medicinal herb with immense therapeutic potential (a systematic review). *Int J Biol Pharm Res*, 5: 755-762
- [6] Akhtar, A. H., K. D. Ahmad, S. N. Gilani and A. Nazir. 1996. Antiulcer effect of aqueous extracts of *Nigella sativa* and *Pongamia pinnata* in rats. *Fitoterapia*, 67: 195-199
- [7] Akhtar, M. S. and S. Riffat. 1991. Field trial of *Saussurea lappa* roots against nematocides and *Nigella sativa* seeds against cestodes in children. *J. Pak. Med. Association*, 41: 185-187
- [8] Al-Awadi, F. M. and K. A. Gumaa. 1987. Studies on the activity of individual plants of an antidiabetic plant mixture. *Acta. Diabetol. Let*, 24: 37-41
- [9] Al-Douri, A. S. and S. Al-Kazaz. 2010. The Effect of *Nigella sativa* Oil (Black Seed) on the Healing of Chemically Induced Oral Ulcer in Rabbit (Experimental Study). *Al- Rafidain Dent J*, 10(1): 151-157
- [10] Ali, S. A., and K. V. Meitei. 2011. *Nigella sativa* seed extract and its bioactive compound thymoquinone: the new melanogens causing hyperpigmentation in the wall lizard melanophores. *Journal of Pharmacy and Pharmacology*, 63(5): 741-746
- [11] Allen, J., M. A. Soares, I. D. Haberman, C. Szpalski, J. Schachar, C. D. Lin, S. M. Warren. 2014. Combination Therapy Accelerates Diabetic Wound Closure. *PLoS ONE*, 9(3): e92667
- [12] Al-Naggar, T. B., M. P. Gomez-Serranillos, M. E. Carretero and A. M. Villar. 2003. Neuropharmacological activity of *Nigella sativa* extracts. *J. Ethnopharmacol*, 88: 63-68
- [13] Al-Okaily, B. N., K. A. Al-Mzain, K. K. Khudair, and R. S. Mohammed. 2012. "Effect of flavonoids extracted from Black Cumin (*Nigella sativa*) and vitamin E in ameliorating hepatic damage induced by sodium nitrate in adult male rats," in *Proceedings of the 11th Veterinary Scientific Conference*, 172-181
- [14] Amin, B., and H. Hosseinzadeh. 2015. Black Cumin (*Nigella sativa*) and Its Active Constituent, Thymoquinone: An Overview on the Analgesic and Anti-inflammatory Effects. *Planta Medica*, 82: 8-16
- [15] Aqeel, M. and R. Shaheen. 1996. Effects of the volatile oil of *Nigella sativa* seeds on the uterine smooth muscle of rat and guinea pig. *J. Ethnopharmacol*, 52: 23-26
- [16] Armstrong, D. G., L. A. Lavery, S. Wu and A. J. M. Boulton. 2005. Evaluation of Removable and Irremovable Cast Walkers in the Healing of Diabetic Foot Wounds: A randomized controlled trial. *Diabetes Care*, 28(3): 551-554
- [17] Arya, A. K., R. Tripathi, S. Kumar and K. Tripathi. 2014. Recent advances on the association of apoptosis in chronic non healing diabetic wound. *World J Diabetes*, 5: 756-762
- [18] Assayed, M. E. 2010. Radioprotective effects of black seed (*Nigella sativa*) oil against hemopoietic damage and immunosuppression in gamma-irradiated rats. *Immunopharmacol Immunotoxicol*, 32(2): 284-296
- [19] Badary, O. A., A. B. Abdel-Naim, M. H. Abdel-Wahab and F. M. Hamada. 2000. The influence of Thymoquinone on doxorubicin-induced hyperlipidemic nephropathy in rats. *Toxicol*, 143: 219-226
- [20] Boskabady, M. H., N. Mohsenpoor and L. Takaloo. 2010. Antiasthmatic effect of *Nigella sativa* in airways of asthmatic patients. *Phytomedicine*, 17(10): 707-713
- [21] Boulton, A. J. M., R. S. Kirsner and L. Vileikyte. 2004. Neuropathic Diabetic Foot Ulcers. *New England Journal of Medicine*, 351(1): 48-55
- [22] Brem, H. and Tomic-Canic. M. 2007. Cellular and molecular basis of wound healing in diabetes. *J Clin Invest.*, 117(5):1219-1222.

- [23] Chakravarty, N. 1993. Inhibition of histamine release from mast cells by nigellone. *Ann-Allergy*, 70: 237-242
- [24] Dunnill, C., T. Patton, J. Brennan, J. Barrett, M. Dryden, J. Cooke and N. T. Georgopoulos. 2015. Reactive oxygen species (ROS) and wound healing: the functional role of ROS and emerging ROS-modulating technologies for augmentation of the healing process. *International Wound Journal*, 14(1): 89-96
- [25] Durmus, A. S., S. Ceribasi and M. Yaman. 2010. Effects of *Nigella sativa* and silver sulfadiazine on burn wound healing in rats. *Vet Med*, 55(12): 619-624
- [26] Elshiekh, Y. H. and M. A. M. Abdelmageed. 2015. "Phytochemical screening and antimicrobial activity of *Striga hermonthica* and *Nigella sativa* seeds," *American Journal of Research Communication*, 3(3): 24-33
- [27] Falanga, V. 2005. Wound healing and its impairment in the diabetic foot. *Lancet*, 366: 1736-1743
- [28] Farah, I. O. and R. A. Begum. 2003. Effect of *Nigella sativa* and oxidative stress on the survival pattern of MCF-7 breast cancer cells. *Biomed. Sci. Instrum*, 39: 359-364
- [29] Gharby, S., H. Harhar and D. Guillaume. 2015. Chemical investigation of *Nigella sativa* L. seed oil produced in Morocco. *J Saudi Soc Agric Sci*, 14(2): 172-177
- [30] Ghaznavi, K. 1996. *Tibbe Nabvi aur Jadeed Science*. Al-Faisal Publishers, Lahore, Pakistan, 246-254
- [31] Ghonime, M., R. Eldomany and A. Abdelaziz. 2011. Evaluation of immunomodulatory effect of three herbal plants growing in Egypt. *Immunopharmacol Immunotoxicol*, 33(1): 141-145
- [32] Ghorbanibirgani, A., A. Khalili and D. Rokhafrooz. 2014. Comparing *Nigella sativa* Oil and Fish Oil in Treatment of Vitiligo, *Iran Red Crescent Med J*, 16(6): e4515
- [33] Goova, M. T., J. Li, T. Kislinger, W. Qu, Y. Lu, L. G. Bucciarelli and A. M. Schmidt. 2001. Blockade of Receptor for Advanced Glycation End-Products Restores Effective Wound Healing in Diabetic Mice. *The American Journal of Pathology*, 159(2): 513-525
- [34] Goreja, W. G., 2003. *Black seed: nature's miracle remedy*. New York, NY 7 Amazing Herbs Press
- [35] Houghton, P.J., R. Zarka, B. De-las-Heras and J. R. Hoult, 1995. Fixed oil of *Nigella sativa* and derived Thymoquinone inhibit eicosanoid generation in leukocytes and membrane lipid peroxidation. *Planta Medica*, 61: 33-36
- [36] Hussain, D. A. S. and M. M. Hussain. 2016. *Nigella sativa* (black seed) is an effective herbal remedy for every disease except death – a Prophetic statement which modern scientists confirm unanimously: A review. *Adv Med Plant Res*, 4(2): 27-57
- [37] Icli, B., C. S. Nabzdyk, J. Lujan-Hernandez, M. Cahill, M. E. Auster, A. K. M. Wara and M. W. Feinberg. 2016. Regulation of impaired angiogenesis in diabetic dermal wound healing by microRNA-26a. *Journal of Molecular and Cellular Cardiology*, 91: 151-159
- [38] Javed, A. 2017. Evaluation of ethanolic crude extracts of *Azadirachta indica* and *Solanum nigrum* efficacy for dermal wounds healing. *JIARM*, 5(8): 01-11.
- [39] Javed, A. and Qazi, J.I. 2016. Efficacy of *Azadirachta indica* and *Solanum nigrum* for skin regeneration in mice. *Pak. J. life Soc. Sci.*, 14(3): 158-166.
- [40] Jeffcoate, W. J. and K. G. Harding. 2003. Diabetic foot ulcers. *Lancet*, 361: 1545-1551
- [41] Kabir, K. K., J. P. Varshney, C. V. S. Rawal, R. S. Srivastava and M. R. Ansari. 2001. Comparative efficacy of herbal preparations in the management of anoestrus in non-descript rural buffaloes. *Indian J. Animal Reproduction*, 22: 143-145
- [42] Kant, V., A. Gopal, N. N. Pathak, P. Kumar, S. K. Tandan and D. Kumar. 2014. Antioxidant and anti-inflammatory potential of curcumin accelerated the cutaneous wound healing in streptozotocin-induced diabetic rats. *International Immunopharmacology*, 20(2): 322-330
- [43] Karri, V. V. S. R., G. Kuppasamy, S. V. Talluri, K. Yamjala, S. S. Mannemala and R. Malayandi. 2016. Current and emerging therapies in the management of diabetic foot ulcers. *Current Medical Research and Opinion*, 32(3): 519-542
- [44] Karri, V. V. S., Narayana and Reddy. 2015. Understanding the implications of pharmaceutical excipients and additives in the treatment of diabetic foot ulcers. *Journal of Excipients and Food Chemicals*, 6(1): 7-22
- [45] Kaskoos, R. 2011. Fatty acid composition of black cumin oil from Iraq. *Res J Med Plant*, 5(1): 85-89
- [46] Katz, I. A., A. Harlan, B. Miranda-Palma, L. Prieto-Sanchez, D. G. Armstrong, J. H. Bowker and A. J. M. Boulton. 2005. A Randomized Trial of Two Irremovable Off-Loading Devices in the Management of Plantar Neuropathic Diabetic Foot Ulcers. *Diabetes Care*, 28(3): 555-559

- [47] Keshri, G., V. Lakshmi and M. M. Singhe. 1998. Postcoital contraceptive activity of some indigenous plants in rats. *Contraception*, 57: 357-360
- [48] Khaled, A. A. S. 2009. Gastroprotective effects of *Nigella sativa* oil on the formation of stress gastritis in hypothyroidal rats. *Int J Physiol Pathophysiol Pharmacol*, 1: 143-149
- [49] Khare, C. P. 2004. *Encyclopedia of Indian medicinal plants*. New York Springer-Verlag Berlin Heidelberg
- [50] Lan, C. C. E., C. S. Wu, S. M. Huang, I. H. Wu and G. S. Chen. 2013. High-Glucose Environment Enhanced Oxidative Stress and Increased Interleukin-8 Secretion From Keratinocytes: New Insights Into Impaired Diabetic Wound Healing. *Diabetes*, 62(7): 2530–2538
- [51] Mariano, R., M. Messori, A. Morais, M. Nagata, F. Furlaneto, C. Avelino, F. Paula, S. Ferreira, M. Pinheiro and J. P. Sene. 2010. Bone healing in critical size defects treated with platelet rich plasma: a histologic and histometric study in the calvaria of diabetic rat. *Oral. Surg. Oral. Med. Oral. Pathol. Oral. Radiol. Endod.*, 109:72-78
- [52] Nezhad, H. R., N. M. Shahri and Rakhshandeh. 2013. The importance of turmeric extract on wound repair biological research. 4(12): 123-128
- [53] Organization WH. *Global report on diabetes: World Health Organization*, 2016
- [54] Osama, A. and Abu-Zinadah. 2009. Using *Nigella sativa* oil to treat and heal chemical induced wound of rabbit skin. *JKAU: Sci*, 21(2): 335-346
- [55] Pradhan, L., C. Nabzdyk, N. D. Andersen, F. W. LoGerfo and Veves. 2009. Inflammation and neuropeptides: the connection in diabetic wound healing. *Expert reviews in molecular medicine*, 11
- [56] Rahman, A. B., F. Abdul Razak and M. Mohd Bakri. 2014. Evaluation of Wound Closure Activity of *Nigella sativa*, *Melastoma malabathricum*, *Pluchea indica*, and *Piper sarmentosum* Extracts on Scratched Monolayer of Human Gingival Fibroblasts. *Evidence-Based Complementary and Alternative Medicine*, 1–9
- [57] Ramadan, M. F. 2013. Healthy blends of high linoleic sunflower oil with selected cold pressed oils: Functionality, stability and antioxidative characteristics. *Industrial Crops and Products*, 43: 65–72
- [58] Randhawa, M. A. and M. S. Alghamdi. 2011. Anticancer activity of *Nigella sativa* (black seed)—A review. *Am J Chin Med*, 39(6): 1075-1091
- [59] Santos, V., R. Gomes, R. Mesquita, Mariela, D. Moura, E. Franca, E. Aguiar, M. Naves, J. Abreu and R. Abreu. 2008. Efficacy of Brazilian propolis gel for the management of denture stomatitis: a pilot study. *Phytotherapy Res*, 11(22): 1544–1547
- [60] Sarkhail, P., H. Esmaily, A. Baghaei. 2011. “Burnhealing potential of *Nigella sativa* seed oil in rats,” *International Journal of Pharmaceutical Sciences and Research*, 2(1): 34–40
- [61] Sharma, P. C., M. B. Yelne and T. J. Dennis. 2005. *Database on medicinal plants used in Ayurveda*. New Delhi, 420-440
- [62] Siersma, V., H. Thorsen, P. E. Holstein, M. Kars, J. Apelqvist, E. B. Jude and N. C. Schaper. 2013. Health-Related Quality of Life Predicts Major Amputation and Death, but Not Healing, in People With Diabetes Presenting With Foot Ulcers: The Eurodiale Study. *Diabetes Care*, 37(3): 694–700
- [63] Silveira, R., L. Andrade and D. Sousa. 2013. A Review on Anti-Inflammatory Activity of Monoterpenes. *Molecules*, 18(1): 1227–1254
- [64] Sokmen, A., B. M. Jones and M. Erturk. 1999. The in vitro antibacterial activity of Turkish medicinal plants. *J. Ethnopharmacol*, 67: 79-86
- [65] Toma, C. C., G. M. Simu and D. Hanganu. 2010. Chemical composition of the Tunisian *Nigella sativa*. Note I. Profile on essential oil. *Farmacia*, 58: 458-464
- [66] Tubesha, Z., S. Iqbal, and M. Ismail. 2011. “Effects of hydrolysis conditions on recovery of antioxidants from methanolic extracts of *Nigella sativa* seeds,” *Journal of Medicinal Plant Research*, 5(22): 5393–5399
- [67] Yaman, I., A. S. Durmus, S. Ceribasi, and M. Yaman. 2010. “Effects of *Nigella sativa* and silver sulfadiazine on burn wound healing in rats,” *Veterinari Medicina*, 55(12): 619–624
- [68] Yuan, T., P. Nahar and M. Sharma. 2014. Indazole-type alkaloids from *Nigella sativa* seeds exhibit antihyperglycemic effects via AMPK activation in vitro. *J Nat Prod*, 77(10): 2316-2320
- [69] Zaoui, A., Y. Cherrah, M. A. Lacaille-Dubois, A. Settaf, H. Amarouch and M. Hassar. 2000. Diuretic and hypotensive effects of *Nigella sativa* in the spontaneously hypertensive rat. *Therapie*, 55: 379-382