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Review

Dermatological effects of *Nigella sativa*

Salih H.M. Aljabre [a,*], Omar M. Alakloby [a], Mohammad A. Randhawa [b]

[a] *Department of Dermatology, College of Medicine, King Fahd Hospital of the University, University of Dammam, Dammam, Saudi Arabia*
[b] *Department of Pharmacology, College of Medicine, Northern Border University, P.O. Box 1321, Arar 91431, Saudi Arabia*

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Abstract

Nigella sativa seed, commonly known as black seed, has been employed as a natural remedy for many ailments for centuries in many cultures. It contains many active components including thymoquinone, thymohydroquinone, dithymoquinone, thymol, carvacrol, nigellimine, nigellicine, nigellidine and alphahederin. It was reported to possess numerous pharmacological effects related to several organs of the body. In this article, the literature pertaining to dermatological effects of *N. sativa* is reviewed. To the best of our knowledge this is the first review in this subject and we expect it stimulates further studies on the dermatological effects and application of *N. sativa*.

Keywords: *Nigella sativa* seed; Black seed oil; Active components; Dermatological effects; *Nigella sativa* and the skin

Contents

* Corresponding author at: Department of Dermatology, King Fahd Hospital of the University, University of Dammam, P.O. Box 2208, Alkhobar 31952, Saudi Arabia.
E-mail addresses: Saljabre@yahoo.com, sjabre@uod.edu.sa (S.H.M. Aljabre).
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1. Introduction

Nigella sativa (*N. sativa*) belongs to the botanical family of *Ranunculaceae* and commonly grows in the Eastern Europe, Middle East, and Western Asia. It is a small shrub with tapering green leaves and rosaceous white and purplish flowers. Its ripe fruit contains tiny seeds, dark black in color, known as "Habba Al-Sauda" or "Habba Al-Barakah" in Arabic and black seed in English. The seed and oil of *N. sativa* were frequently used in ancient remedies (Unani, Ayurveda, Chinese and Arabic) in Asian countries and in the middle east. Several uses of the *N. sativa* seed had been mentioned by Ibne-Sina (980–1037) in his famous book Al-Qanoon fi el-Tibb (El-Kadi and Kandil, 1986; Al-Jishi, 2000).

Numerous active components have been isolated from *N. sativa* seed and its oil including thymoquinone, thymohydroquinone, dithymoquinone, thymol, carvacrol, nigellimine-N-oxide, nigellicine, nigellidine and alpha-hederin. The pharmacological properties of *N. sativa* and its ingredients had been investigated by *in vitro* and *in vivo* studies conducted on human and laboratory animals. These studies showed that *N. sativa* and its ingredients have a wide range of pharmacological effects; immune-stimulatory, anti-inflammatory, hypoglycemic, antihypertensive, antiasthmatic, antimicrobial, antiparasitic, antioxidant and anticancer effects (reviewed in Randhawa and Alghamdi, 2002, 2011; Ali and Blunden, 2003; Salem, 2005; Padhye et al., 2008; Randhawa, 2008). Acute and chronic toxicity studies on laboratory animals have reported that *N. sativa* seed, its oil and thymoquinone, the most abundant and widely studied active principle, are safe, particularly when given orally (Badary et al., 1998; Mansour et al., 2001; Al-Ali et al., 2008). The objective of this article is to review the reported dermatological effects of *N. sativa*. An online and PubMed search of published articles related to the dermatological effects of *N. sativa* seed, its oil and active ingredients was conducted. Only articles substantiated by appropriate scientific methodology were reviewed and included. The following are categories of the studies: antimicrobial, antiviral, antifungal, antiparasitic, wound healing, psoriasis, acne vulgaris, vitiligo, skin cancer, percutaneous absorption, cosmetic application and cutaneous side effects.

2. Antimicrobial effects

2.1. Antibacterial

Topozada et al. (1965) were first to report the antibacterial effect of the phenolic fraction of *N. sativa* oil. El-Fatatry (1975) isolated thymohydroquinone from the volatile oil of *N. sativa*, which was found to have high activity against gram-positive microorganisms, including *Staphylococcus aureus*. Diethyl-ether extract of *N. sativa* was reported to possess concentration dependent inhibitory effect on gram-positive bacteria (represented by *S. aureus*) and gram-negative bacteria (represented by *Pseudomonas aeruginosa* and *Escherichia coli*) (Hanafi and Hatem, 1991). It also showed synergistic effect with streptomycin and gentamycin and additive effect with spectinomycin, erythromycin, tobramycin, doxycycline, chloramphenicol, nalidixic acid, ampicillin, lincomycin and co-trimoxazole and successfully eradicated a non-fatal subcutaneous staphylococcal infection induced experimentally in mice when injected at the site of infection (Hanafi and Hatem, 1991). *N. sativa* extract showed almost similar results to topical mupirocin in the treatment of neonates with staphylococcal pustular skin infections with no side effects (Rafati et al., 2014). Microbial resistance to drugs is a common and important issue. Studies of the effects of *N. sativa* extracts *in vitro* against resistant microorganisms, including resistant *S. aureus* and *P. aeruginosa*, showed promising and good results against many multi-drug-resistant gram positive and gram negative bacteria (Morsi, 2000; Mashhadian and Rakhshandeh, 2005; Salman et al., 2005).

2.2. Antiviral

N. sativa was found to enhance helper T cell (T4) and suppressor T cell (T8) ratio and increased natural killer (NK) cell activity in healthy volunteers (El-Kadi and Kandil, 1986). Besides improvement in immunity, *N. sativa* extract had some inhibitory effect on the human immune deficiency virus protease but the active principle(s) responsible for this activity was not identified (Ma et al., 1994). Moreover, *N. sativa* oil when given intraperitoneally to mice infected with murine cytomegalovirus for 10 days, the virus was undetectable in the liver and spleen, while it was still detectable in the control mice. This action was

considered to be related to increase in the number and function of M-phi and CD4 +ve T cells and increased production of INF-gamma (Salem and Hossain, 2000).

2.3. Antifungal

Hanafi and Hatem (1991) were the first to demonstrate the inhibitory effect of the diethyl-ether extract of *N. sativa* extract against *Candida albicans*. The ether extract of *N. sativa* was reported to inhibit the growth of *Candida* yeasts in several organs in experimental animal infections (Khan et al., 2003). Thymoquinone was also shown to inhibit *in vitro Aspergillus niger* and *Fusarium solani* and the activity was comparable to amphotericin-B (Al-Jabre et al., 2003; Alqorashi et al., 2007; Randhawa et al., 2005). It was reported to be more effective than amphotericin-B and griseofulvin against *Scopulariopsis brevicaulis* growth *in vitro*. There was 100% inhibition of the growth of *S. brevicaulis* with thymoquinone 1 mg/ml, while amphotericin-B 1 mg/ml inhibited only 70% growth. However, clotrimazole was much more effective than the above mentioned drugs, with an MIC of 0.03 mg/ml (Aljabre, 2005).

The ether extract of *N. sativa* was found to inhibit dermatophytes isolated from sheep skin infection (Kader et al., 1995). Thymoquinone was shown to possess moderate activity against clinical isolates of the three main groups of dermatophytes: *Trichophyton*, *Epidermophyton* and *Microsporum* and the ether extract of *N. sativa* were also found to be effective but in relatively higher concentrations (Aljabre et al., 2005). The MIC of thymoquinone against various dermatophytes ranged from 0.125 to 0.25 mg/ml, while the ether extract inhibited 80–100% of the growth of most dermatophytes at 40 mg/ml. Proportionately, greater effect of thymoquinone than *N. sativa* extract points out to that, the antifungal activity of *N. sativa* is primarily due to thymoquinone (Aljabre et al., 2005). In another study also thymoquinone, thymohydroquinone and thymol demonstrated antifungal effect against many clinical isolates, including dermatophytes, molds and yeasts at a concentration of 1 mg/ml (Taha et al., 2010). Using broth microdilution assay, extract of *N. sativa* inhibited the growth of *Madurella mycetomatis*, an important causative fungus of mycetoma, at a concentration as low as 1 μg/ml (Elfadil et al., 2015).

2.4. Antiparasitic

An ointment prepared from the alcoholic extract of *N. sativa* seeds was applied daily for 15 weeks to cutaneous leishmaniasis produced experimentally in mice by a subcutaneous inoculation of *Leishmania major* at the dorsal base of the tail. The morphology of the lesion and the body weight of mice were monitored daily. There was no significant difference between the average weight of mice receiving *N. sativa* extract ointment and controls but the lesion diameter and symptoms of inflammation were significantly lesser in the test group as compared to the controls (Bafghi et al., 2011).

N. sativa seed was tested against miracidia, cercariae and adult worms of Schistosoma mansoni and showed strong biocidal activity against all stages of the parasite, as well as an inhibitory effect on egg-laying of adult female worms, indicating an antischistosomal potential of the *N. sativa* (Mohamed et al., 2005). In *S. mansoni* experimentally infected mice, the antischistosomal activity of *N. sativa* oil was found to be comparable to praziquantel and when given in combination with praziquantel there was potentiation of its effect (Mahmoud et al., 2002).

3. Wound healing

N. sativa seed and its oil were found to promote wound healing in farm animals (Ahmed et al., 1995). Moreover, ether extract of *N. sativa* seed applied topically onto staphylococcal-infected skin in mice enhanced healing by reducing total and absolute differential WBC counts, local infection and inflammation, bacterial expansion and tissue impairment (Abu-Al-Basal, 2011). Using human gingival fibroblast as a monolayer, aqueous extract of *N. sativa* exhibited low free radical scavenging activity and induced gingival fibroblast proliferation with accelerated wound closure activity despite its non-significant effect on collagen synthesis (Ab Rahman et al., 2014). It also resulted in elevation of basic fibroblast growth factor and transforming growth factor beta (Ab Rahman et al., 2014).

4. Anti-inflammatory

4.1. Psoriasis

The ethanolic extract of *N. sativa* seed was evaluated for antipsoriatic activity *in vivo* by using mouse tail model for psoriasis and *in vitro* by using sulforhodamine B assay employing HaCaT human keratinocyte cell lines (Dwarampudi et al., 2012).

Significant epidermal differentiation was produced by the ethanolic extract of *N. sativa*, 71.36 ± 2.64%. In the negative control the epidermal differentiation was 17.30 ± 4.09% and in the positive control (tazarotene 0.1%) was 90.03 ± 2.00%. The antiproliferant activity of the ethanolic extract of *N. sativa* was good, IC_{50} value of 239 μg/ml, as compared to that of the positive control, asiaticoside, which showed potent activity with IC_{50} value of 20.13 μg/ml.

4.2. Acne vulgaris

In a clinical study (Abdul-Ameer and Al-Harchan, 2010), *N. sativa* oil lotion 10% significantly reduced mean lesion count of papules and pustules after 2 months of therapy. In the test group, the response to treatment was graded as good in 58%, moderate in 35% and no response in 7%. The satisfaction of patients with treatment was found to be full in 67%, partial in 28%, and no satisfaction in 5%. While in the control

group, the lesions showed no significant reduction after 2 months and the response to treatment was good in 8%, moderate in 34%, and no response in 58%. The satisfaction of patients with treatment in this group was full in 8%, partial in 24%, and no satisfaction in 68%. There were no side effects in the group treated with *N. sativa* oil lotion 10%. The authors attributed the results to the antimicrobial, immunomodulatory and anti-inflammatory effects of *N. sativa* oil. The molecular mechanisms of anti-inflammatory and antioxidative activities of thymoquinone, the most abundant active principle of *N. sativa* had been studied. Pretreatment of female HR-1 hairless mouse skin with thymoquinone attenuated 12-*O*-tetradecanoylphorbol-13-acetate (TPA)-induced expression of cyclooxygenase-2 (COX-2). Thymoquinone diminished nuclear translocation and the DNA binding of nuclear factor-kappa-B (NF-κB) via the blockade of phosphorylation and subsequent degradation of IκBα in TPA-treated mouse skin. Thymoquinone also attenuated the phosphorylation of Akt, c-Jun-N-terminal kinase and p38 mitogen-activated protein kinase, but not that of extracellular signal-regulated kinase-1/2. Moreover, topical application of thymoquinone induced the expression of hemeoxygenase-1, NAD(P)H-quinoneoxidoreductase-1, glutathione-S-transferase and glutamate cysteine ligase in mouse skin (Kundu et al., 2013).

Similar anti-inflammatory effect of *N. sativa* fixed oil and thymoquinone has also been reported earlier by Houghton et al. (1995). The effect was demonstrated via the dose-dependent decrease in the formation of thromboxane B2 and leukotriene B4 showing the inhibition of cyclooxygenase and 5-lipooxygenase pathways of arachidonate metabolism in rat peritoneal leukocytes.

5. Skin pigmentation

5.1. Vitiligo

Lyophilized seed extract of *N. sativa* and its active ingredient, thymoquinone, showed significant skin darkening on the isolated melanophores of the wall lizard (Ali and Meitei, 2011). The pigment cells when exposed to the extract or thymoquinone responded by distinct dispersion of melanin leading to skin darkening. The melanin dispersal effect was antagonized by anticholinergic drugs, atropine and hyoscine, and potentiated by an anticholinesterase agent, neostigmine. The authors suggested that cholinergic mechanisms of muscarinic nature are involved in the melanin dispersion (Ali and Meitei, 2011). In a randomized double blind clinical study, patients applied *N. sativa* oil to lesions of vitiligo twice daily for 6 months had a significant decrease in the vitiligo area scoring index with no significant side effects (Ghorbanibirgani et al., 2014).

6. Hypersensitivity reactions

Earlier, carbonyl fraction of *N. sativa* and its active components, thymoquinone and nigellone were shown to counter the manifestations of allergic reactions; inhibition of histamine release from mast cells (Chakravorty, 1993), protection from histamine-induced bronchospasm in guinea pigs (El-Dakhakhany, 1982) and decreases in the lung eosinophilia, elevated Th2 cytokines and raised IgE and IgG1 antibodies in a mouse model of allergic asthma induced by ovalbumin (El Gazzar et al., 2006).

Recently, a clinical study was conducted to compare the efficacy of *Nigella*, Betamethasone and Eucerin ointments applied topically twice daily for 4 weeks in new cases of hand eczema. Changes in the severity of eczema and life quality were assessed by hand eczema severity index (HECSI) and dermatology life quality index (DLQI), respectively. *Nigella* and Betamethasone showed rapid improvement in the hand eczema and the quality of life as compared to Eucerin. No significant difference was detected in the mean HECSI and DLQI scores of the *N. sativa* and Betamethasone groups, indicating to the possibility that, *N. sativa* had same efficacy as Betamethasone in the improvement of hand eczema and life quality (Yousefi et al., 2013).

7. Skin cancers

The anticancer activity of *N. sativa* was revealed, for the first time, when an enhancement of the natural killer (NK) cell activity was observed in advanced cancer patients receiving multimodality immunotherapy program in which *N. sativa* seed was one of the components (El-Kadi and Kandil, 1986). Regarding dermatology, Salomi et al. (1991) were first to investigate the antineoplastic effect of *N. sativa.* They reported that the topical application of *N. sativa* and *Crocus sativus* extracts inhibited two-stage initiation/promotion of [dimethylbenz [a] anthracene (DMBA)/croton oil] induced skin carcinogenesis in mice, delayed the onset of papilloma formation and reduced the number of papillomas per mouse. Later, the protective effect of bee honey and *Nigella* was studied on the oxidative stress and carcinogenesis induced by methylnitrosourea (MNU) in Sprague Dawely rats. It was observed that MNU produced oxidative stresses ranging from severe inflammatory reaction in lung and skin to colon adenocarcinoma in four out of six animals. The serum malondialdehyde (MDA) and nitric oxide (NO) were also raised. Treatment with *N. sativa* seed given orally protected against MNU-induced oxidative stress and carcinogenesis by 80% (12/15), whereas honey and *N. sativa* seed together protected 100% (12/12); and serum MDA and NO also significantly decreased in both cases compared to active controls (Mabrouk et al., 2004).

In another study, antineoplastic activity of thymoquinone was investigated using mouse keratinocytes, papilloma (SP-1) and spindle-17 carcinoma cells. In SP-1 cells thymoquinone induced G0/G1 cell-cycle arrest, which correlated with sharp increases in the expression of the cyclin-dependent kinase inhibitor p16 and a decrease in cyclin D1 protein expression. While in spindle 17 cells,

G2/M cell-cycle arrest was noticed, this was associated with an increase in the expression of the tumor suppressor protein p53 and a decrease in cyclin B1 protein. At longer times of incubation, thymoquinone induced apoptosis in both cell lines by remarkably increasing the ratio of Bax/Bcl-2 protein expression and decreasing Bcl-xL protein. These findings support a potential role for thymoquinone as a chemopreventive agent, particularly at the early stages of skin tumorigenesis (Gali-Muhtasib et al., 2004). Antitumor activity of thymoquinone and thymohydroquinone was also demonstrated using tumor cell lines (squamous cell carcinoma, SCC VII) and fibrosarcoma, FsaR) and murine tumor models of fibrosarcoma and squamous cell carcinoma (Ivankovic et al., 2006).

Thymoquinone and diosgenin, the active ingredients obtained from *N. sativa* and fenugreek (*Trigonella foenum-graecum*), respectively, were shown to exert potent bioactivity against squamous cell carcinoma *in vitro*. They inhibited cell proliferation and induced cytotoxicity in A431 and Hep2 cells. These agents induced apoptosis by increasing the sub-G1 population, LIVE/DEAD cytotoxicity, chromatin condensation, DNA laddering and TUNEL-positive cells. There was also an increase in Bax/Bcl-2 ratio, activation of cell proliferation of caspases and cleavage of poly ADP ribose polymerase in the treated cells. In combination, thymoquinone and diosgenin had synergistic effects, resulting in cell viability as low as 10%. In a mouse xeno-graft model, a combination of thymoquinone and diosgenin significantly reduced tumor volume, mass and increased apoptosis (Das et al., 2012).

Using an *in vitro* cell migration assay, Ahmad et al. (2013) found that, thymoquinone inhibited the migration of both human and mouse melanoma cells. The inhibition of metastasis by thymoquinone was also observed *in vivo* in B16F10 mouse melanoma model and was accompanied by a decrease in expression of NLRP3 (NACHT, LRR, and pyrin domain-containing protein 3) inflammasome which resulted in decreased proteolytic cleavage of caspase-1. Inactivation of caspase-1 by thymoquinone resulted in the inhibition of IL-1β and IL-18. Thymoquinone also inhibited NF-κB activity in mouse melanoma cells and reactive oxygen species and the later in turn resulted in the partial inactivation of NLRP3 inflammasome. The authors suggested that, thymoquinone can be a potential immunotherapeutic agent not only as an adjuvant therapy for melanoma, but also, in the control and prevention of metastatic melanoma (Ahmad et al., 2013).

8. Percutaneous absorption

The effect of *N. sativa* oil on the percutaneous absorption of model lipophilic drug-carvedilol was investigated using excised rat abdominal skin (Amin et al., 2008). *N. sativa* oil in 5% v/v had high degree of enhancing permeation as indicated by transdermal flux, permeability coefficient and enhancement factor. Employing differential scanning calorimetry, Fourier transform infrared and histopathology, *N. sativa* oil in 5% v/v, was found to work by extracting lipids from stratum corneum and by loosening the hydrogen bonds between ceramides with subsequent fluidization of the lipid bilayer. The increased permeability of the lipophilic drug-carvedilol was considered to be due to increased diffusivity through the stratum corneum under the influence of *N. sativa* oil. It was postulated that, the higher content of linoleic acid and other unsaturated fatty acids in *N. sativa* oil was responsible for the enhancement of *in vitro* percutaneous absorption of the drug (Amin et al., 2010).

9. Cosmetic application

Using pH meter, corneometer, tewameter, methyl nicotinate model of micro-inflammation in human skin, and tape stripping of the stratum corneum, the *in vivo* and *ex vivo* properties of emulsions with the seedcake extracts of *N. sativa* have been evaluated (Amin et al., 2010). Emulsions with Borago officinalis, and *N. sativa* seedcakes significantly reduced skin irritation and improved the skin hydration and epidermal barrier function as compared with placebo. The authors suggested the potential use of seedcakes in anti-aging, moisturizing, mitigating, and protective cosmetics due to their antioxidant and anti-inflammatory activities.

10. Cutaneous side effects

Contact dermatitis developed after the application of ointment made from the *N. sativa* seed oil but it could have been due to some impurity in the commercial black seed oil (Zedlitz et al., 2002). Bullous drug eruption with sub-epidermal detachment and necrosis of the epidermal surface has been reported in a 53-year-old woman after 2 weeks of applying *N. sativa* oil to her skin and ingesting it as well (Gelot et al., 2012).

11. Conclusion

The published original research articles on the effects of *N. sativa* and its ingredients strongly indicate its pharmacological potential in dermatology. Standard methods of drug development are needed to formulate topical therapy for use in dermatology.

Conflict of interest

None.

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