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Effect of the liquid solution of *Nigella sativa* seed on prolactin levels in rabbits females after parturition

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Abstract
The study include 30 rabbit females in latest period of pregnancy with measurement of prolactin hormone level after parturition directly, and then divided the rabbits into three groups: the first group (10 rabbits) given liquid solution of *Nigella sativa* seed, in dose (2.5 ml liquid solution of 0.25 gm of *Nigella sativa* seed) daily for one month. Second group (10 rabbits) given liquid solution of Bromocriptine in dose (0.1 mg) daily for one month. Third group (10 rabbits) as control. Prolactin hormone measured in these three groups at 7,14,21,28 days from parturition and within administration period.
The results revealed obvious decrease in prolactin hormone level (less than 0.5 nanogm) in newly parturition rabbits after third week from administration in first group which administrated with Melissa in a nearly result to second group which treated with Bromocriptine which decrease prolactin hormone level after second week from treated compared with control group which persist prolactin hormone in high level for first month from parturition.

Keywords: *Nigella sativa* seed, Black seed oil, Hormon, parturition, rabbit

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. The scientific classification of *Nigella sativa* is:
Kindom: Plantae
Clade: Angiosperms
Clade: Eudicots
Order: Ranunculales
Family: Ranunculaceae
Genus: *Nigella*
Speieces: N. sativa
Binomial name: Nigella sativa

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) [56, 7]. 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) [76, 77, 2, 79, 80, 73, 1]. 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) [11, 69, 1]. 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) [89] were first to report the antibacterial effect of the phenolic fraction of *N. sativa* oil. El-Fatatry (1975) [54] 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) [59]. 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) [59]. *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) [73]. 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) [72, 70, 83].

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) [55]. 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) [65]. 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 S.H.M. Aljabre *et al*. Journal of Dermatology & Dermatologic Surgery 19 (2015) 92–98 93 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) [81, 82].

2.3. Antifungal Hanafi and Hatem (1991) [59] 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) [63]. 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) [7, 8, 4]. 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) [4]. 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) [4]. 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) [4]. 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) [87, 88]. 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 lg/ml (Elfadil *et al*., 2015) [53].

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) [12]. *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) [70]. 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) [67].

Materials and Methods

1- Prepare liquid solution of Melissa

Nigella sativa seeds were obtained from commercial sources (from Baghdad) and the vouchers specimen of the plant were deposited to be identified and authenticated at the National Herbarium of Iraq Botany Directorate in Abu-Ghraib, under scientific name *Nigella sativa* belongs to the family *Ranunculaceae*. After cleaning and milling, crushed seed were kept in dark glass bottles and taking 5 gm from brayed *Nigella sativa* seeds and boiled with (50 ml) of distilled water and after cooling drench every animal with (2.5 ml) from liquid solution which equalizes (0.25 gm) from *Nigella sativa* seeds.

2 Prepare liquid solution of Bromocriptine

We taking Bromocriptine drug at pills form in concentration (5mg) and soluble in (50 ml) of distilled water and then drench every animal with (1 ml) of liquid solution which equalizes (0.1 mg) from Bromocriptine.

3 Experimental animals

Thirty rabbit females in the last period of pregnancy were used in this investigation. Animals in all stages of the experiment housed in plastic cages in conditioned room (22-25˚C) in the animal house of Department of animals Production, at College of agriculture- Universityof Sumer for the period from December 2017 to March 2018 with providing daily light of twelve hours (7.00 to 19.00) and twelve hours night cycle. They were left for ten days for adaptation with the experimental conditions. Animals had free access to water and standard pellet di*et al*ong the experiment.

The animal divided into three groups each group contain 10 rabbits and after parturition directly we measured prolactin hormone level and then drench the first group with liquid solution of *Nigella sativa* seeds in dose (2.5 ml) liquid solution of (0.25 gm) from *Nigella sativa* seeds daily for month. While the second group drench liquid solution of Bromocriptine in dose (0.1 mg) daily for month. The third group considered as control. During the experiment prolactin hormone measured in three groups of animals in day 7,14,21,28 from drench after taking (3-5 ml) blood, was drawn by cardiac puncture technique from anesthetized rabbits {intramuscular injection of Ketamine (60mg/Kg B.W.) and xylazine (40mg/kg B.W.) administering 1 mL/kg of body weight by intramuscular injection.}. and after separated the serum, measured the prolactin hormone level.

4 Measuring prolactin hormone level

After blood collection directly from the heart, the serum separated from blood by centrifugation, then serum taking for measure prolactin hormone level by Minividus System through used necessary kit for prolactin hormone which produced from French Immunotech Company.

After obtaining the results of prolactin hormone level of all groups its compared with results of first group and second compared with control group.

Results and Discussion

The results revealed no decrease in prolactin hormone level in the first group which drench liquid solution of *Nigella sativa* seed in first and second week from drench after parturition compared with second group which drench with liquid solution of Bromocriptine drug which appear obvious decrease in second week from drench compared with control group which persist prolactin hormone in high level (table 1 and plane 1).

		Prolactin hormone level rate (ng/ml)				
Experimental						
animals		After parturition	After one week from drenching	After 2 weeks from drenching	After 3 weeks from drenching	After 4weeks from drenching
firsat group drenching with *Nigella sativa* seeds	10	1.73	2.11	1.44	<0.5	<0.5
Second group dreniching with Bromocriptine	10	2.31	3.21	<0.5	<0.5	<0.5
Control group	10	2.10	3.51	3.86	3.10	3.48

Whereas results showed that occurrence extremely obvious decrease in prolactin hormone level in first group after third week from drench which persist in decrease for fourth week compared with control group which appear high level of prolactin hormone for fourth week in experiment (table 1).

The results showed as results of (clanton, 2005) [13] which refer to *Nigella sativa* seeds have the ability to regulate sexual hormones after long period of treatment, most common herbs treatment take time to give the positive results which come conformity with most researchers in medical herb treatments that late in occurrence of positive results compared with chemical drugs and results as coming to results of (Grosignani *et al*.,1982) which refer to Bromocriptine drug competency in decrease prolactin hormone level in short period from beginning treatment. Persistence of high prolactin hormone level in control group come conformity with all studies, as prolactin hormone is responsible hormone for milk production in most animals specially after parturition (Hafez *et al*. 2000) [18].

Conclusions

1. Efficiency of *Nigella sativa* seeds in decrease prolactin hormone level in rabbit females after parturition.
2. *Nigella sativa* seeds can be used in cases of infertility and esterus cycle disturbances which result from abnormal secretion of prolactin hormone during and after lactation period.

3. Despite of positive effect of *Nigella sativa* seed herb in decrease prolactin hormone level but its need long period to give its positive effect.
4. It decreases the side effects on animal compared with drugs due to slowly effect in decrease level of prolactin.
5. It is used in regulation and synchronization estrous cycles in some lactating animals (in lactation period).
6. Plantation of *Nigella sativa* seeds herb periodically play a good role in regulation of estrous cycles, in addition to multiple advantages (antiviral, antibacterial, antifungal, antiprotozoal, etc.).

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