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Original article

Histological evaluation of the effect of *Nigella sativa* on the healing of created bony defect in the animal jaw

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ABSTRACT

Background: *The bone healing process is a complicated and highly specific action that includes deposition, resorption, and remodeling phases occurring in a tidy and overlapping schedule. Herbal medicine has improved substantially in the last decade, and herbal products have spread widely to prevent or treat various problems and diseases. Nowadays, different herbs are employed to heal soft or hard tissue in humans.* ***Purpose:*** *This study aims to evaluate the effect of topically applying Nigella sativa oil in healing bony defects.* ***Methods:*** *Fifteen rabbits were used in this study. Two round holes were created on the buccal side of the mandible: the anterior hole was filled with black seed oil, while the other was left unfilled as the control group. Animals were sacrificed after 1 week, 2 weeks, and 4 weeks, respectively, and sent for histopathological examination.* ***Results:*** *During the first week of bone healing, the experimental group showed substantially fewer inflammatory reactions than the control group. Granulation tissue formation increased considerably in the experimental group compared with the control group. The experimental group also showed higher bone tissue formation, with more mature woven bone compared with the control group.* ***Conclusion:*** *Nigella sativa has an anti-inflammatory effect and can positively influence bone healing by increasing bone cell production and bone tissue development in the bone defect.*

Keywords: *black seed; bone defect; bone healing; herbal products; Nigella sativa; thymoquinone*
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INTRODUCTION

Bone is a unique active biological connective tissue consisting of active cells combined into a structure. Bones not only support the body but also have various other roles. The renovation of bone defects arising from congenital deformities, trauma, or pathology is a fundamental issue in restoring the usual activities of the bone and associated structures and has drawn the attention of researchers in various domains of healthcare.[1–3]

The treatment and repair of these defaults may need bone grafts. Many techniques such as local or systemic application of growth factors[4] or mesenchymal stem cells[5,6] can provide valuable support to the bone graft. Furthermore, the use of natural substances as substitutes for imitative treatments in managing different illnesses, including bone defects, has increased in the last few decades.[7,8]

Herbal medicinal plants have been and still are a very interesting subject, and they are employed to treat and avoid numerous disorders, particularly deteriorating diseases such as diabetes and hypertension, in various systems of traditional and local medicine. Furthermore, they earn notable acknowledgment due to their therapeutic properties. The World Health Organization (WHO) reported that 70%–80% of people in primary health care completely trust folk medicine.[9,10]

Nigella sativa, known as black cumin or *habitus sauda*, is a yearly blooming herb from the Ranunculaceae family. It has a historical and religious background and is commonly planted in the Mediterranean area, Western Asia, Eastern Europe, and the Middle East.[11–13] *Nigella sativa* seeds are black triangular grains measuring 2–3 mm in size. They comprise water, cinder, protein, phenolic compounds, fibers, steroidal materials, carbohydrates, and volatile oil, along with substantial amounts of several vitamins and minerals such as Cu, P, Zn, and Fe.[14–16]

Black cumin seeds and oils have been widely used for many years to heal various disorders worldwide,

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including antioxidant, antimicrobial, antihypertensive, hypoglycemic, anticancer, anti-inflammatory, diuretic, anti-diarrheal, appetite stimulant, analgesic, antiallergic, hepatoprotective, antinociceptive, neuroprotective, antibacterial, anticonvulsant, antifungal, antihyperlipidemic, antitussive, immunopotentiating, and skin disease-curing properties.[17–21]

Thymoquinone (TQ; 2-isopropyl-5-methyl-1,4-benzoquinone), an active constituent of *Nigella sativa* oil, has the ability to intensify bone creation and shows a substantial effect in diabetic osteopenia. It exhibits strong anti-inflammatory action in many inflammatory conditions, including encephalomyelitis, colitis, peritonitis, edema, and arthritis, as it inhibits pro-inflammatory mediators such as prostaglandins and leukotrienes.[12,22–26]

TQ inhibits the osteoclastic process, which causes bone resorption, as it decreases the levels of IL-1α, IL-6, and TNF (pro-inflammatory cytokines). Additionally, it increases bone formation due to its antioxidant properties.[4]

We hypothesized that the use of *Nigella sativa* for bone defect healing, as a substitute for natural or synthetic bone grafts, could be more effective, easily prepared and applied, avoid local complications associated with bone graft taking or application, and be less harmful and cost-effective. This study aims to estimate the influence of *Nigella sativa* in decreasing the inflammation period and cells, with its ability to incentivize granulation tissue formation and hasten the normal healing process of the bone by increasing woven and lamellar bone formation through the stimulation of new osteoblast and osteocyte production. We believe that *Nigella sativa* has both anti-inflammatory and healing properties.

MATERIALS AND METHODS

This randomized study includes 15 New Zealand albino rabbits. The justification for using rabbits is that they are considered the animals most resembling the human skeleton anatomically and histologically, with a faster healing period that saves time, making them more suitable for academic research. Their weights ranged between 1.5–2.2 kg. They were independently kept and nourished with natural food (vegetables, grains, and corn) and water in a chamber with a natural light cycle and a constant temperature (24 ± 2°C) in the animal house of our institution. The College of Dentistry of Mosul University Animal Care and Scientific Committee approved this protocol with reference number UoM/A.L.49/21 on 1/3/2022. Before the procedure, the male rabbits were adapted for 1 week to examine their general health and ensure no contagious diseases were present.

The animals were anesthetized by intramuscular injection into the thigh muscle with 40 mg/kg ketamine and 4 mg/kg xylazine.[27–29] An incision was created along the inferior border of the mandible of the rabbit, and the periosteum was elevated. Using a sterile handpiece with a round bur and normal saline irrigation, two round holes of 4 mm diameter and 2 mm depth were created on the buccal side of the mandible, with a distance of 1.5 cm between them. The two holes were irrigated with normal saline; the anterior one was filled with about two drops of 100% concentration black seed oil (from the local market), produced by Al-Emad, a local factory in Mosul City, Iraq, by squeezing the seeds under sterile conditions. The oil was applied using a sterile dropper (experimental group), while the second hole was left unfilled (control group). The wound was then sutured with a black silk suture.

Five animals were sacrificed after 1 week, 2 weeks, and 4 weeks, respectively. It was decided to evaluate bone regeneration after these periods due to the rapid bone turnover in rabbits, with bone maturation occurring eight weeks later.[30] The mandibular piece containing the defects was cut, placed in 10% formalin for 48 hours, and then washed with water. It was decalcified in 5% formic acid for 1 month. After that, the specimen was dried in ascending concentrations of ethanol, followed by xylene, and embedded in paraffin wax. The specimen was then cut by microtome into slices of 5-µm width and stained with hematoxylin and eosin for inspection under a light microscope for histological examination. The histological features were included in the results.

The histological scoring system followed the criteria of Lucaciu et al.,[31] with some modifications. The scoring system includes inflammation: 0 (absent), 1 (low), 2 (moderate), 3 (high); granulation tissue: 0 (absent), 1 (few), 2 (moderate), 3 (profound); and new bone: 0 (absent), 1 (peripheral), 2 (central), 3 (peripheral and central). The data for the parameters were presented as mean rank with standard deviation. IBM SPSS Statistics version 25.0 was used for all data analyses. For non-parametric data comparisons between groups, the Mann–Whitney U test was applied. A p-value ≤ 0.05 was considered significant.

RESULTS

At the euthanization stage, the animals were clinically well. The samples were evaluated by two histopathologists and displayed no contamination, dehiscence, or defects. Histopathological results showed variances between the groups in variable means, with significant results based on p-values.

The inflammation score depended on the presence of macrophage cells stained with hematoxylin and eosin. After 1 week, the control group revealed a high inflammatory cell infiltrate with a mean rank of 7.3, while the experimental group slides showed a substantial decrease in acute inflammation with a mean rank of 3.7, as seen in Figures 1 and 2. This trend continued throughout the study period. At 2 weeks, the mean score for the experimental group was 5.8, while for the control group, it was 6. After 4 weeks, the mean score for the control group was 5.8, whereas for the experimental group, it was 5.2.

The development of granulation tissue was greater in the experimental group, especially after 2 weeks, with a

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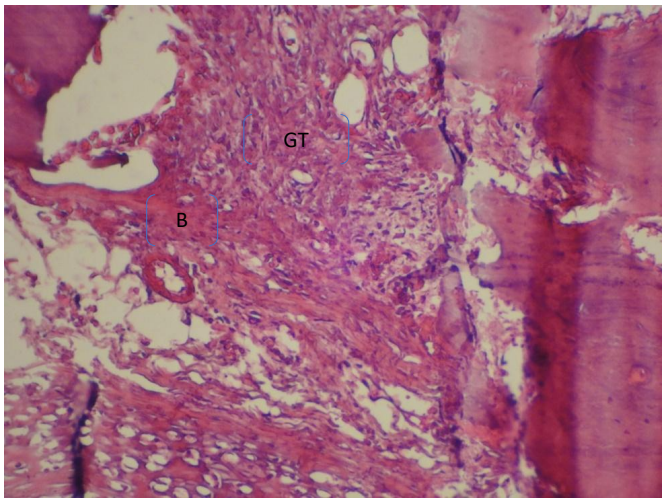

Figure 1. Biopsy of the control group (7 days) shows a high number of inflammatory cells and profound granulation tissue (GT) with few new bones (B) at the peripheries, x100 magnification.

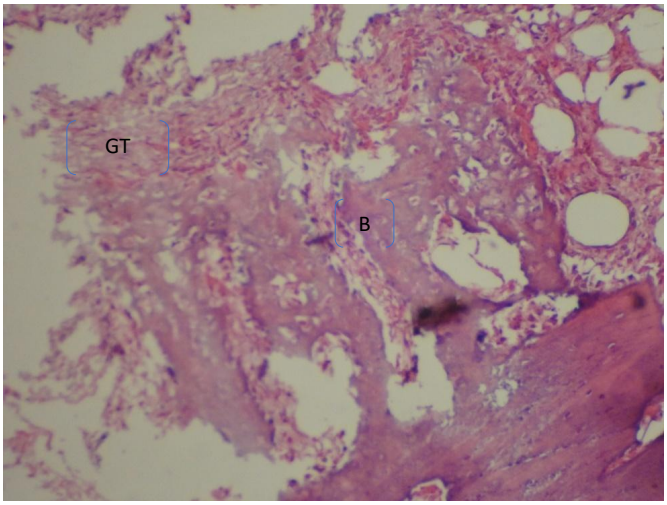

Figure 2. Biopsy of the experimental group (7 days) shows low inflammatory reaction with few granulation tissue (GT) and many new bones (B) and osteoblasts at the peripheries, x100 magnification microscope.

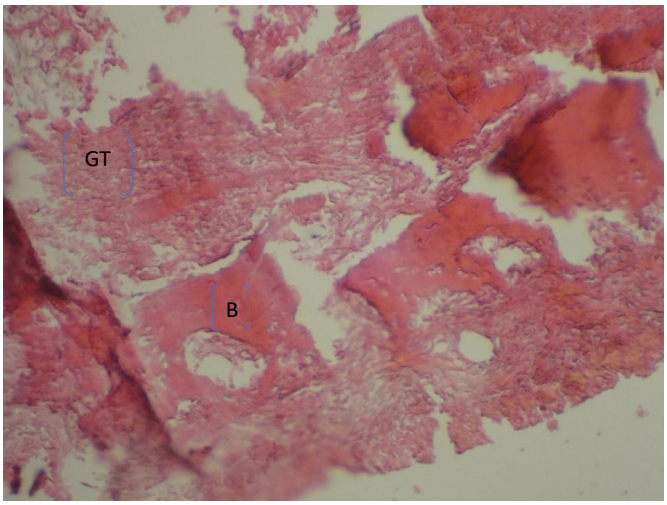

Figure 3. Biopsy of the experimental group (14 days) shows few to moderate inflammatory cells and profound granulation tissue (GT) formation with high newly formed bone trabeculae (B) at the center, x100 magnification microscope.

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mean rank of 7.4, while the control group appeared at 3.6, as shown in Figure 3. After 4 weeks, the experimental group showed a decreased granulation tissue score compared with the control, with mean values of 4.5 and 6.5, respectively.

New bone creation was detected after 1 week as woven bone, with a mean rank of 6.0 in most study samples, while the control group's mean rank was 5.0. After 2 weeks, bone formation increased substantially in the experimental group, with a mean rank of 7.5, appearing as woven and lamellar bone, as shown in Figure 3. In contrast, the control group showed absent or very little bone at the peripheries, with a mean rank of 3.5, as shown in Figure 4. At 4 weeks, in the experimental group, the lamellar bone became more prevalent than woven bone, with a mean score of 6.1, as shown in Figure 5. Histopathological results and variations between groups are presented in Tables 1, 2, and 3.

DISCUSSION

Hastening bone healing following surgery is one of the most challenging actions in oral surgery. Raw *Nigella sativa* seeds have been broadly employed as a cure for numerous illnesses in prophetic medicine; they have multiple crucial properties, such as anti-inflammatory, antioxidant, and immunological effects. *Nigella sativa* oil does not prompt adverse impacts on liver function and has a very low grade of toxicity.[4,32,33]

In this study, a mandibular defect in the rabbit model was utilized to detect bone rejuvenation due to the simplicity of surgical operations. Observations could be concentrated on the action of bone reformation, as the defects are located in the maxillofacial area, and tissue section formulation is straightforward.[2]

Nigella sativa and its original products have been employed as a cure for liver illness, rheumatism, and severe

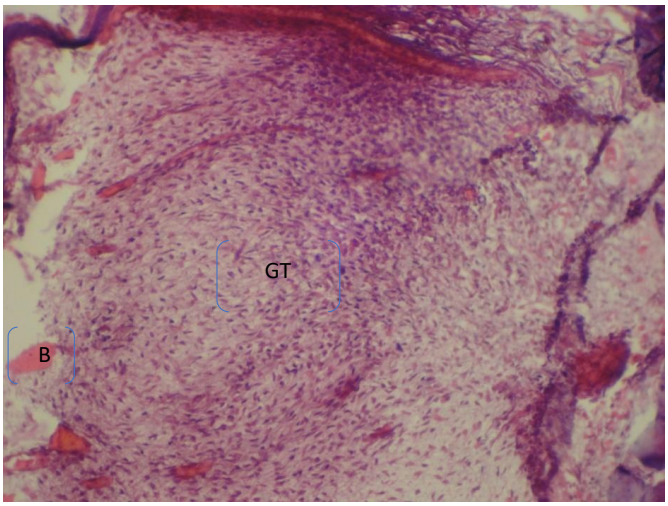

Figure 4. Biopsy of the control group (14 days) shows moderate inflammation with a large amount of granulation tissue (GT) in a profound stage and absent or very little bone at the peripheries, x100 magnification microscope.

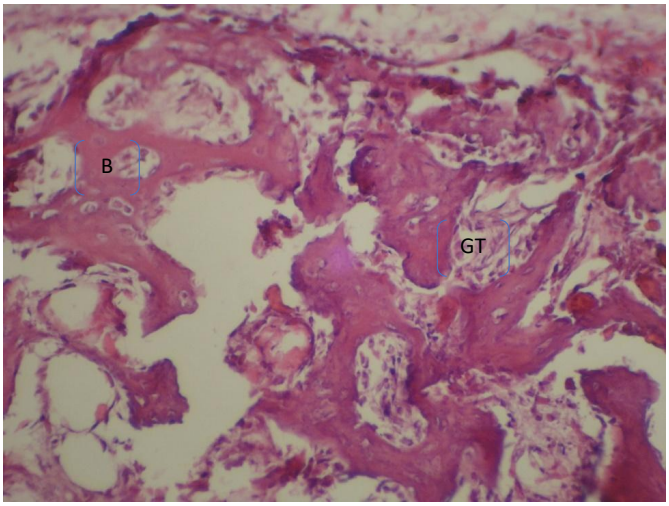

Figure 5. Biopsy of the experimental group (30 days) shows a few granulation tissue (GT) and many bone trabeculae (B) formation at the center and peripheries, x100 magnification microscope.

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Table 1. Descriptive and comparison between control and experimental groups in 1, 2, and 4 weeks in inflammatory reaction

Inflammatory Reaction		Standard Deviation	Mean Rank	Mann–Whitney U Test	P-value
1 Week	Control	0.396	7.300	3.500	0.050*
	Experimental	0.579	3.700		
2 Week	Control	0.559	6.000	10.000	0.589
	Experimental	0.498	5.000		
4 Week	Control	0.652	5.800	11.000	0.723
	Experimental	0.224	5.200		

* Significant at $P \leq 0.05$

Table 2. Descriptive and comparison between control and experimental groups in 1, 2, and 4 weeks in granulation tissue reaction

Granulation Tissue		Standard Deviation	Mean Rank	Mann–Whitney U Test	P-value
1 Week	Control	0.527	5.800	11.000	0.750
	Experimental	0.555	5.200		
2 Week	Control	0.719	3.600	3.000	0.046*
	Experimental	0.454	7.400		
4 Week	Control	0.575	6.500	7.500	0.280
	Experimental	0.570	4.500		

* Significant at $P \leq 0.05$

Table 3. Descriptive and comparison between control and experimental groups in 1, 2, and 4 weeks in new bone formation

New Bone		Standard Deviation	Mean Rank	Mann–Whitney U Test	P-value
1 Week	Control	0. 274	5.000	10.000	0.575
	Experimental	0.454	6.000		
2 Week	Control	0.379	3.500	2.500	0.035*
	Experimental	0.454	7.500		
4 Week	Control	0.285	4.900	9.500	0.527
	Experimental	0.810	6.100		

* Significant at $P \leq 0.05$

inflammatory diseases. Numerous studies have revealed and established that TQ, present in the seeds, is responsible for the anti-inflammatory action of *Nigella sativa*.[24]

Amin and Hosseinzadeh,[34] in their study, stated that various ingredients of *Nigella sativa* play a role in its antioxidant and anti-inflammatory features. The quinolones obstruct Cyclooxygenase (COX)-1 and COX-2, while thymol inhibits COX-1. TQ acts specifically on COX-2 and prevents free radical nitric oxide (NO) creation in the supernatants of LPS-stimulated macrophages via the NO synthase (iNOS) enzyme.[34]

Inflammation is a fundamental, broad reaction of the innate immune system, which not only cooperates with the adaptive immune system but also directs and initiates it to create active immune reactions. The innate system produces many immune mediators, such as interferons, antibacterial elements, and acute-phase proteins, which manage interactions between various elements such as neutrophils, macrophages, and T and B cells, thereby affecting inflammation.[35]

In this study, the experimental group shows less inflammatory reaction than the control group, which was significant, especially in the first week, with a p-value of 0.059. This result is considered the most prominent and important to demonstrate the effect of *Nigella sativa*, as inflammation continues for the first 2 to 3 days in the wound healing process. In the second and fourth weeks, the inflammation, although not significant, was still less in the experimental group than in the control group, aiding in speedier healing.

From our point of view, an increase in the time for inflammation with inflammatory exudate and cells such as macrophages, which activate and attract fibroblasts for a prolonged period, leads to more fibrous tissue formation, prolongs the proliferative phase and reduces bone turnover. Thus, decreased inflammation time equals faster healing.

This may be related to the anti-inflammatory and antioxidant effects of *Nigella sativa* and its effective component, TQ. It has been reported that TQ reduces tissue destruction caused by ischemia-reperfusion and enhances resistance against pathogens with antimicrobial activity. Besides, TQ enhances fibroblast creation, amplifies granulation tissue formation, boosts wound contraction, and facilitates re-epithelization.[36–38]

In addition, TQ has immunomodulatory effects. Numerous animal and in vitro studies have shown that TQ can regulate the growth and functions of various immune cells, such as T-cells, B-cells, macrophages, neutrophils, natural killer cells, and dendritic cells.[35] This agrees with Islam et al.,[39] who found that *Nigella sativa* extracts, seed oil, and TQ have anti-inflammatory effects by inhibiting NO formation and other inflammatory mediators such as interleukin-1 (IL-1), IL-1β, IL-6, TNF-α, IFN-γ, and PGE2. Srinivasan,[40] in his study, found that *Nigella sativa* oil has an anti-inflammatory effect by constraining NF-κB and mitogen-activated protein kinases in LPS-stimulated RAW cells.

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In our study, granulation tissue was present in small amounts from the first week in both groups, with no significant differences between them. However, at 14 days, the amount of granulation tissue in the experimental group appeared more obvious and increased significantly compared with the control group in the second week, with a p-value of 0.046. This increase occurred as a result of increased blood flow and vascularization to the area, which may be related to the high angiogenic activity of *Nigella sativa* and its components, improving fibroblast proliferation and subsequent collagen production.

The same conclusion was made by Han et al.,[41] who observed that the *Nigella sativa* group showed greater wound closure macroscopically, reinforced microscopically by greater granulation tissue creation and collagen formation compared with HP and the control. Similarly, Abd Elrahman et al.[15] revealed in their study that the histological outcomes of dental sockets treated with *Nigella sativa* showed dilated blood vessels during new bone development, unlike control sockets, which showed restricted blood supply in the marrow space. New bone creation in the socket takes place when the granulation tissue decreases in amount and transitions to fibrous tissue, which new blood vessels and osteoblasts penetrate, initiating woven bone production.[42]

Histologically, Day 10 is part of the healing process, identified by slight fibrous tissue presentation and the creation of a soft callus formed from hyaline and fibrous tissues. During this stage, intramembranous and endochondral calcification occur.[43]

Our results revealed that *Nigella sativa* has highly positive effects on bone by enhancing bone formation due to the initiation of bone formation in the defect, which started from the first week in both groups but was greater in amount in the experimental group. After 14 days, the study group showed a substantial increase in soft callus (woven bone) compared with the control group, with dilated Haversian canals and more prominent osteoblasts. This makes sense as the granulation tissue in the study group also increased substantially in the same period, serving as the base for osteoblast differentiation and woven bone creation.

This result agrees with Ezirganli et al.,[2] who reported in their study that fresh bone and connective tissue filled nearly all surgical defect areas after 2 weeks of the study, with a substantial presence of thick, solid, ossified tissue, fibroblast connective tissue, osteoblasts, and osteoclasts. Similarly, Al-Mutheffer[3] applied topical *Nigella sativa* oil extract to bone defects in rabbits and detected its effects both histologically and radiographically. He found that *Nigella sativa* has a valuable role in increasing blood flow to the defect site, which in turn enhances angiogenesis, a fundamental phase of bone healing. He also stated that histopathologically, the *Nigella sativa* group showed an enhancement in bone healing as early as the first week, continuing to the 5th week, compared with the control group. Additionally, Abd Elrahman et al.[15] studied the influence of *Nigella sativa* on socket healing in rabbits after extraction of bilateral lower first premolars and found that the experimental group sockets treated with *Nigella sativa* oil showed increased bone formation activity with denser bony trabeculae and highly vascular bone marrow.

In this study, after 4 weeks, the bone became more mature, with calcification of the soft callus converting to a thicker lamellar type, containing a high number of osteoblast and osteocyte cells and numerous narrow Haversian canals in both groups. Although not substantial, the study group showed a greater amount of calcified tissue than the control group. This aligns with a previous study, which showed that at 4 weeks, lamellar bone comprising bone marrow occupied these defects.[2]

The limitation of this study was the small sample size, which needs to be increased as it may influence the histological results. Increasing the number of slides could provide more precise histological investigation results. In conclusion, *Nigella sativa* has an anti-inflammatory effect and can positively impact bone healing by increasing bone cell creation and bone tissue development in the bone defect.

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