Journal of Taibah University Medical Sciences (2018) 13(5), 438–443

Taibah University

Journal of Taibah University Medical Sciences

www.sciencedirect.com

Original Article

Effect of ultrasound-enhanced *Nigella sativa* seeds oil on wound healing: An animal model

Hany M. Elgohary, PhD [a,*], Soad KH. Al Jaouni, PhD [b] and Samy A. Selim, PhD [c]

[a] *Department of Physical Therapy for Surgery, Faculty of Physical Therapy, Cairo University, Giza, Egypt*
[b] *Department of Hematology and Youssef Abdulatif Jameel Chair of Prophetic Medicine Application (YAJCPMA), Faculty of Medicine, King Abdulaziz University, Jeddah, KSA*
[c] *Department of Clinical Laboratory Sciences, College of Applied Medical Sciences, Jouf University, Sakaka, KSA*

Received 26 September 2017; revised 8 February 2018; accepted 11 February 2018; Available online 27 June 2018

الملخص

أهداف البحث: يعد استخدام زيت الحبة السوداء، والموجات فوق الصوتية ومرهم "ميبو" كعلاج تحفظي للحروق قد انتشر في المجال الطبي نظرا لأهميته في التغلب على الالتهابات، وكذلك في حث التئام الجروح دون وجود آثار جانبية، ولذا فإن هدف هذه الدراسة هو تقييم دور الموجات فوق الصوتية وحدها أو عن طريق الإدخال الصوتي للجزيئات، وزيت الحبة السوداء وكذلك مرهم ميبو في علاج الحروق الكيميائية.

طرق البحث: تم اختيار ٣٥ من الأرانب المحلية في الدراسة وتقسيمهم إلى سبع مجموعات متساوية في العدد، مجموعة الموجات فوق الصوتية المتقطعة، ومجموعة الموجات فوق الصوتية المستمرة، ومجموعة التطبيق الظاهري لزيت الحبة السوداء، ومجموعة الإدخال المتقطع للجزيئات، ومجموعة الإدخال المستمر للجزيئات، ومجموعة مرهم ميبو وكذلك المجموعة الضابطة. تم حساب مساحة الحروق عن طريق ورق الرسم البياني وباستخدام التصوير الفوتوغرافي في بداية الدراسة، وبعد سبعة أيام، وبعد أربعة عشرة يوما وبعد واحد وعشرين يوما.

النتائج: دلت النتائج على أن هناك فروق ذات دلالة إحصائية بين جميع المجموعات قبل وبعد العلاج ما عدا المجموعة الضابطة، وكانت أقل النتائج لصالح مجموعة الموجات فوق الصوتية المستمرة.

الاستنتاجات: إن استخدام الموجات فوق الصوتية، والاستخدام الظاهري لزيت الحبة السوداء، والإدخال الصوتي للجزيئات وكذلك مرهم ميبو له تأثير فعال في حث التئام الحروق الكيميائية ومن الممكن إضافة هذه الوسائل لخطة علاج الجروح.

الكلمات المفتاحية: الموجات فوق الصوتية المتقطعة؛ زيت الحبة السوداء؛ الموجات فوق الصوتية؛ الحروق؛ الجروح

Abstract

Objectives: *Nigella sativa* oil, ultrasound, and moist-exposed burn ointment (MEBO) have been suggested as noninvasive treatments for a number of inflammatory conditions and to accelerate wound healing. The aim of this study was to evaluate the efficiency of pulsed and continuous modes of ultrasound either alone or through phonophoresis, with *N. sativa* oil, or MEBO ointment in the treatment of chemical burns.

Methods: Thirty-five local rabbits were randomly divided into seven equal groups: pulsed ultrasound, continuous ultrasound, topical *N. sativa* oil, pulsed phonophoresis, continuous phonophoresis, topical MEBO ointment, and control group. Wound surface area was measured on days 0, 7, 14, and 21 using metric graph paper and photographs.

Results: Significant differences were found between pre- and post-treatment wounds in all groups, except for the control group, in favor of the pulsed phonophoresis. In contrast, low results were found in favor of continuous ultrasound.

Conclusion: Ultrasound, topical application of N. *sativa* oil, phonophoresis, and MEBO ointment have the potential to accelerate wound healing induced by chemical burns. Such treatment modalities may be used to treat wounds.

Keywords: Burn; *Nigella sativa* oil; Pulsed phonophoresis; Ultrasound; Wound

* Corresponding address: Department of Physical Therapy for Surgery, Faculty of Physical Therapy, Cairo University, El-Tahrir st. Dokki, Giza, P.O. 11432, Egypt.
E-mail: gohary75pt@hotmail.com (H.M. Elgohary)

Peer review under responsibility of Taibah University.

ELSEVIER Production and hosting by Elsevier

 https://doi.org/10.1016/j.jtumed.2018.02.008

Introduction

Wound healing represents a clinical dilemma whenever exact and suitable wound management is necessary.[1] Many studies have investigated wound supervision, with more attention paid to distinct therapeutic procedures and the improvement of strategies for all types of wound management.[2] Wound healing involves differential cell proliferation, extracellular components, and the effects of soluble chemical mediators, including growth factors and cytokines.[3] Although the healing process is ongoing, it can be classified into four major steps: coagulation, the inflammatory phase, the reproductive phase, and the wound reconstructive phase, including scar tissue production. A suitable strategy to treat wounds can affect clinical outcomes.[4]

Because of the dynamic structure of wounds and the high number of possible treatment modalities, it is not feasible to state which product is preferred for a specific wound,[5] despite recommendations being made for various wound dressings. *Nigella sativa* (NS) has been used as a natural source of medicinal treatment for thousands of years by different societies and cultures throughout the world,[6] as well as a food supplement to promote good health.[7] It is very popular for the principle of respecting the holy prophet Muhammad P.B.U.H; "Hold on to use the Black seed, for it has a remedy for every illness except death." Here, the term "hold on to" indicates the prolonged use.[8]

NS seeds have been regularly and broadly used in herbal medicine to treat and prevent various skin injuries and diseases.[9] NS oil (NSO) contains many types of proteins, saponins, and alkaloids.[10] Most of the physiological effects of NS seeds are due to the presence of thymoquinone, which produces both essential and volatile oils, These have been reported to protect the body, especially the skin, against neurological disorders and hepatotoxicity caused by chemicals or a disease.[11,12] The beneficial effects associated with the use of NS seeds and thymoquinone may be due to their cell protection activities and antioxidant responses, and their influence on inflammatory mediators.[13] Studies into major types of burns have gained the attention of inspectors, in terms of the value of the skin's biological role. Despite this, few studies have reported results of traditional low-intensity ultrasound on the healing of full-thickness burns. Accordingly, further studies investigating the value of ultrasound in the management of burn wounds are needed. Hence, the present study determined the effectiveness of different modes of ultrasound, phonophoresis, NSO, and MEBO on wound healing and tissue regeneration of full-thickness chemical burns. Phonophoresis is the transdermal administration of a medication with the aid of ultrasound. The transmission force of ultrasound emission pushes the medication distant from the transducer approaching the target area[14]; the heat generated by the ultrasound intensifies the possibility of dissipation to the tissue leading to dilatation of the blood vessels, and the streaming induced by the ultrasound modifies cell permeability and improves tissue dispersion.[15] Furthermore, sonic waves enhance the active potential of the drug, leading to more efficient distribution within the target tissue. MEBO is a local ointment produced to manage burns. It has a slight yellow-brown appearance, comprising wax originating from bees, sesame seed oil, proteins, fats, and carbohydrates. The principal constituent is beta-sitosterol.[16] Additionally, MEBO comprises Chinese herbal constituents, such as *Radix Scutellaria*, *Cortex Phellodendri*, and *Rhizoma Coptidis*, which are thought to alleviate pain and improve tissue regeneration.[17] Application of MEBO is an accessible approach to maintain moistened background for proper restoration, and for the formation of new epithelial tissue with no need of further spreading dressing.[18] It was supposed to administer pain-free treatment and diminish the number of solutions needed for resuscitation.[19]

Materials and Methods

Material and instruments

NSO was extracted by staff members from the College of Pharmacy, Aljouf University. MEBO ointment (0.25% beta-sitosterol) was from Gulf Pharmaceutical Industries, UAE. The ultrasonic device (model Sonopuls 490u) was from ENRAF NONIUS B.V (Netherlands). The measuring instrument included a transparent plastic film, metric graph paper (1 mm^2), and a digital camera (NIKON D7500; Malaysia).

Animals

Thirty-five albino rabbits, approximately 20-weeks-old at the beginning of the study, and weighing 1000−1250 g, were obtained from the animal house, College of Pharmacy, Aljouf University. The rabbits were housed individually under hygienic conditions with determined environmental parameters that provided sufficient air passage, food complements, and lighting. Rabbits had unrestricted access to water and food (standard food as a grain). The enclosures containing each group were cleaned regularly. Anesthesia was provided by chloroform (bioethics agreement according to the Ethical Committee, Aljouf University, KSA).

Procedures

The dorsal surface of each rabbit was stripped mechanically and left to rest for day. On the following day, each rabbit was anesthetized with chloroform, as described by Divekar and Naik[20] before induction of the burn wound. Concentrated HCl (38%) was applied topically to the bare skin (three drops) to provoke burn. The area of the burn was bathed with normal saline and then debrided to eliminate the residual dead tissue.

Experimental design: this was a double blind randomized comparative study conducted in an animal model.

After burn induction, rabbits were randomly divided into seven equal groups; A, B, C, D, E, F, and G. (Five rabbits in each group):

Group (A): Five rats received pulsed ultrasound.
Group (B): Five rats received continuous ultrasound.
Group (C): Five rats received topical application of NSO.
Group (D): Five rats received pulsed phonophoresis using NSO.
Group (E): Five rats received continuous phonophoresis through the use of NSO.
Group (F): Five rats received topical application of MEBO ointment.
Group (G): Five rats received local wound care.

Interventions

Treatment protocol

Treatment was initiated in each group the day following burn induction. Group A (PUS) received pulsed ultrasound, in which a sterile plastic bag filled with aquasonic gel was applied to all wounds and surrounding tissues to prevent any cross-contamination of the device. Pulsed ultrasonic (applicator 1.9 cm^2) was applied over the gel pad while the ultrasound head was moved in a circular motion over the wound cavity. Holding the rabbits securely was essential to ensure the wound area was covered by the ultrasound applicator with the following parameters; pulsed duty cycle 20% (2 ms on, 8 ms off) and power density of 0.8 W/cm^2, for 6 min, five times a week, over 3 consecutive weeks.

Group B (CUS) received continuous ultrasound with the following parameters: pulsed duty cycle 100% and power density 0.5 W/cm^2, 6 min, five times a week, for 3 consecutive weeks.

Group C (NS) received topical application of extracted NSO, daily, with a 3 mL volume that dogged by a disinfected syringe then emptied to the burn area and set aside by non-adherent sterile gauze for three consecutive weeks.

Group D (PPH) received pulsed phonophoresis of NSO, in which a 3 mL volume of oil were dogged by a disinfected syringe then emptied onto the burn area. A sterile plastic drape was applied to all wounds and surrounding tissues to prevent any cross-contamination of the device. The plastic drape should overlap the wound margins by at least 3 cm and its surrounding ends fixed on to rabbit skin by adhesive tape. A pulsed ultrasound (applicator 1.9 cm^2) was applied over a plastic drape and movement was initiated over the wound cavity or wound scab, then over the wound margins in all groups. Ultrasound therapy was in the 'on' mode only in group (A) with the following parameters; pulsed duty cycle 40% (4 ms on, 6 ms off) and power density 0.5 W/cm^2, 5 min each session, five times a week, for 3 consecutive weeks.

Group E (CPH) received continuous phonophoresis of NSO through the aforementioned technique.

Group F (MEBO) received topical application of MEBO ointment to the wound bed twice daily for 3 consecutive weeks.

Group G (Control) received daily local wound care with normal saline.

Measurement protocols

All measurements were made 24-h post-burn, and at the end of each successive week over a 3-week period. Wound surface area was measured by the tracing method as described by Bohannon and Pfaller.[21] A clean transparent sheet was placed on the wound. The wound margins were determined with a fine-tipped marker. The area of each wound was outlined three times to ascertain the reliability of the procedure. After outlining, the transparent sheet surface facing the burn was cleaned with sterilized cotton and ethanol. Carbon paper was placed over the metric graph paper (1 mm^2). The transparent sheet was fixed over the carbon paper with white paper in between, and the outline was copied by tracing on the graph paper. The wound surface area was determined in millimeters-squared using metric graph paper. The surface area was transformed into centimeters-squared. The average of the three examinations was determined and used to denote the total burn surface area.

Photographs, used to determine changes in the healing process at the beginning of the study, and after 7, 14, and 21 days, were obtained with a digital camera with a span of 1.5 ft between the wound bed and the camera. at 90°.

Data analysis

Data were examined by SPSS v.20 using two-way ANOVA and Tukey's tests, and the results are presented as the mean ± standard deviation (mean ± SD) with a confidence interval of 95%. A p-value less than 0.05 was recognized as significant.

Results

One-way ANOVA revealed significant differences in the WSA values of all groups (A, B, C, D, E, and F) after 21 days of treatment, except for the control group (Group G), with p-values of <0.001, <0.001, <0.001, <0.001, <0.001, <0.001, and 0.214, respectively (Table 1).

When comparing the results of WSA before treatment, there was a significant difference after 7, 14, and 21 days with p values of 0.029, <0.001, and <0.001, respectively; the p-value at the beginning of the treatment was 0.882, as displayed in Table 1.

Two-way ANOVA showed that there was a significant effect of treatment type, time, and the interaction of treatment type and time, with p-values of <0.001, <0.001, and <0.001, respectively, as presented in Table 2.

In terms of the efficacy of each treatment, the results favored the pulsed phonophoresis group (Group D) with high percentage, while the least effect was in the control group (Group G) with very low percentage as revealed in Table 3.

Discussion

Wound healing is the process through which broken tissue is repaired as similarly as it reaches to its healthy status, while wound contraction is way of diminishing the surface area of the wound. This principle depends on the capability of the tissue to adjust, the nature and degree of impairment, and the overall status and vitality of the tissue.[22] The repair of skin injury is characterized by an established and definite array of physiological issues that are associated with wound

Table 1: Mean and standard deviation (confidence interval 95%) for WSA before and after treatment in all groups.

Mean, standard deviation, and p-value for WSA before and after the treatment (cm^2)				
	0 days	7 days	14 days	21 days
Group A	14.26 ± 0.24	13.72 ± 0.28[a]	12.84 ± 0.57[a]	11.7 ± 0.54[a]
Group B	14.14 ± 0.34	13.64 ± 0.46[a]	13.04 ± 0.59[a]	11.96 ± 0.74[a]
Group C	14.4 ± 0.26	13.2 ± 0.11[a]	11.68 ± 0.19[a]	10.52 ± 0.28[a]
Group D	14.08 ± 0.53	13.36 ± 0.26[a]	11.36 ± 0.48[a]	9.52 ± 0.38[a]
Group E	14.14 ± 0.28	13.14 ± 0.94[a]	12.2 ± 0.91[a]	11.1 ± 1.13[a]
Group F	14.28 ± 0.54	13.88 ± 0.61[a]	13.42 ± 0.93[a]	10.18 ± 0.26[a]
Group G	14.18 ± 0.28	14.1 ± 0.20	14 ± 0.16	13.9 ± 0.19

WSA: wound surface area.
[a] Statistically significant.

Table 2: Mean difference (confidence interval 95%) between all groups in the study after 7, 14, and 21 days.

Groups and time			Mean difference (confidence interval 95%)
Group A	0 days	7 days	0.54000
		14 days	1.42000[a]
		21 days	2.56000[a]
	7 days	14 days	0.88000[a]
		21 days	2.02000[a]
	14 days	21 days	1.14000[a]
Group B	0 days	7 days	0.50000
		14 days	1.10000[a]
		21 days	2.18000[a]
	7 days	14 days	0.60000
		21 days	1.68000[a]
	14 days	21 days	1.08000[a]
Group C	0 days	7 days	1.22000[a]
		14 days	2.70000[a]
		21 days	3.86000[a]
	7 days	14 days	1.48000[a]
		21 days	2.64000[a]
	14 days	21 days	1.16000[a]
Group D	0 days	7 days	0.72000
		14 days	2.72000[a]
		21 days	4.56000[a]
	7 days	14 days	2.00000[a]
		21 days	3.84000[a]
	14 days	21 days	1.84000[a]
Group E	0 days	7 days	1.00000
		14 days	1.94000[a]
		21 days	3.04000[a]
	7 days	14 days	0.94000
		21 days	2.04000[a]
	14 days	21 days	1.10000
Group F	0 days	7 days	0.40000
		14 days	0.86000
		21 days	4.10000[a]
	7 days	14 days	0.46000
		21 days	3.70000[a]
	14 days	21 days	3.24000[a]
Group G	0 days	7 days	0.08000
		14 days	0.18000
		21 days	0.28000
	7 days	14 days	0.10000
		21 days	0.20000
	14 days	21 days	0.10000

[a] Statistically significant.

contraction and advancing the regeneration and reconstruction of the spoiled tissue.[23] Recent studies have found that wound healing sequelae might be hastened and improved with the aid of herbal or synthetic composites. Plant ingredients could enhance the property of wound restoration.[24]

In the current study, a chemical wound was induced with concentrated HCL in rabbits to investigate the wound healing capacity as well as the antimicrobial load of pulsed ultrasound, continuous ultrasound, topical application of NSO, transdermal delivery of NSO through both pulsed and continuous modes of ultrasound, and the topical application of MEBO ointment. The outcomes of our study provide strong evidence for the ability of these treatment modalities to accelerate wound closure and healing of burns in an animal model after 21 days of treatment; the pulsed phonophoresis group was favored. The better results of group D and the superiority to other groups (pulsed phonophoresis) may be attributed to the use of NSO, which was augmented by pulsed ultrasound; NSO enhanced wound healing in farm animals.[25] Furthermore, ether extracts of NSO applied topically to infected skin wounds in mice promote healing by diminishing both total and absolute differential white blood cells, cutaneous germs, inflammation, bacterial augmentation, and tissue damage.[26] Aqueous extracts of NS presented weak free radical scavenging activity, induced gingival fibroblast reproduction, and enhanced wound contraction properties, although it had a non-significant impact on collagen construction.[27] It also resulted in increased levels of growth factors.[28] NSO exerts a range of treatment effects, which reduce inflammation, decrease blood glucose level, bactericidal action, remove

Table 3: Percentage improvement in wound surface area in all groups.

Percentage improvement in all groups (%)			
	7 days	14 days	21 days
Group A	3.8	6.4	8.9
Group B	3.5	4.4	8.3
Group C	8.5	11.3	9.9
Group D	5.1	14.9	16.2
Group E	7.1	7.2	9
Group F	2.8	3.3	14.2
Group G	0.6	0.7	0.7

free radicals, potentiate the immune system,[29] are antiallergic, and lower blood pressure.[30] The anti-inflammatory and antioxidant activities of NSO may be due to the presence of fixed and essential oils. The anti-inflammatory and analgesic effects of NSO may be due to the high amount of thymoquinone, which is an effective component of oil.[31]

Fatty acids are essential compounds of the cell membrane, and are required to assure epidermal well-being and to maintain the water barrier of the skin. Fatty acids, such as oleic and linoleic acid, might promote wound healing through improvement of the entire quantity of cells transferring over the wound track during the compensation process.[32] Furthermore, fatty acids also activate neutrophils, which play an important role in wound healing through the release of cytokines and growth factors, enhancement of antibacterial activity, and the removal of destroyed tissue.[33] Ultrasound at lower intensities, similar to those utilized in the current study to enhance the transdermal delivery of oils, diminish cellular destruction through the use of pulsed acoustic power, which accelerates fibroblast reproduction and improves tissue restoration in different kinds of wounds. In contrast, Cambier and Vanderstraeten[34] assessed the impact of pulsed LITUS with a duty cycle of 20%. They used LITUS on 20 female rats with full-thickness burns for 5 min over 6 weeks, and found non-significant histological data.

The results of the current study showed that the pulsed ultrasound led to better results than continuous ultrasound when applied alone or through the phonophoresis technique. This is because low-intensity ultrasound and the pulsed mode initiate the mechanical effects of ultrasound, which allow drugs to be transferred and to be deposited in target tissues the power which thermal influence does not admit and this harmonious with Loyd et al.,[35] who declared that phonophoresis promotes the transdermal penetration of a drug by mechanical impacts such as cavitation property and acoustic power. The drugs are incorporated within the intracellular space, between cells and in the appendages. While appropriating ultrasound for delivering drugs through the skin, blood flow increases in target tissues and the drug crosses the skin stratum corneum, transferring immediately to the blood circulation before reaching the target tissues where it induces a rapid effect.[36] Numerous laboratory studies have attempted to clarify the impacts of ultrasound on the wound healing process. To date, ultrasound has been shown to induce cellular enhancements, the formation of new collagen, improved tensile strength of collagen fibers, formation of new blood vessels, wound approximation, stimulation of both fibroblasts and macrophages, breakdown of fibrin, modification of inflammation, and advancement of the proliferative process of wound.[37]

MEBO treats wounds with moisture, which originates from the oil, and berberine. Additionally, it inhibits microbial growth and encourages the rapid formation of epithelial tissue. This is thought to be supported by beta-sitosterol, a corticosteroid located in different plants, mainly soya. MEBO diminishes the vulnerability of the burn, which, as noted by Smahel et al.,[38] restricts tissue destruction and promotes restorative effects. Although the in vitro antibacterial effects of MEBO have not been explained, studies have shown that it limits wound infection, probably by hindering invasion of eschar formation via injurious microbes. Maintenance of organic serum on the wound surface inhibits the desiccation of cells and improves the movement of keratinocytes over the wound.[39] It also enhances the capacity of common cytokines and growth agents to heal wounds in ways that are yet to be described.[40] This study was limited to a small sample size, with the hope that future studies using large sample sizes will gain more evidence-based results through the use of different plant sources that can be delivered to the body via phonophoresis.

Conclusion

Wound healing can be accelerated by various mechanisms that promote wound contraction and inhibit inflammation by means of pulsed phonophoresis using NSO as an adjunct treatment with limited side effects.

Conflict of interest

The authors have no conflict of interest to declare.

Ethical approval

All the animals which had been included in this study were evaluated and treated according to the principles of the guide for the care and use of laboratory animals (DHHS Publ. No. (NIH) 85-23, Revised 1985) and conformed to the approval of the ethical committee of Aljouf University, KSA.

Authors' contribution

HE designed the study, conducted phonophoresis studies, wrote the article, and carried out careful revision of this article. SS conducted the statistical analysis interpretation. SA supervised the work. All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

Acknowledgments

This work was funded by Y.A. Jameel Scientific Chair of Prophetic Medical Applications, King Abdulaziz University, KSA, under grant no. [PM 0002 (2.1) - 1438]. The authors acknowledge, with thanks, the Y.A. Jameel Scientific Chair of Prophetic Medical Applications technical and financial support.

References

1. Jayasutha J, Monic J, Nithila S. Evaluation of wound healing activity of ethanolic extract of Aristolochia bracteata and Cassia tora on wistar albino rats. **Int J Pharm Tech Res 2011**; 3: 1547–1550.
2. Bjarnsholt T, Kirketerp-Møller K, Jensen PØ, Madsen KG, Phipps R, Krogfelt K, et al. Why chronic wounds won't heal: a novel hypothesis. **Wound Repair Regen 2008**; 1: 2–10.
3. Bishop A. Role of oxygen in wound healing. **J Wound Care 2008**; 17: 399–402.

4. Brem H, Tomic-Canic M. Cellular and molecular basis of wound healing in diabetes. **J Clin Invest 2007**; 117: 1219–1222.
5. Campos A, Groth A, Branco A. Assessment and nutritional aspects of wound healing. **Curr Opin Clin Nutr Metab Care 2008**; 11: 281–288.
6. Khan MA, Chen H, Tania M, Zhang D. Anticancer activities of *Nigella sativa* (black cumin). **Afr J Tradit, Complementary Altern Med 2011**; 8: 226–232.
7. Chah K, Eze C, Emuelosi C, Esimone C. Antibacterial and wound healing properties of methanolic extracts of some Nigerian medicinal plants. **J Ethnopharmacol 2006**; 104: 164–167.
8. Atta M. Some characteristics of nigella (*Nigella sativa L.*) seed cultivated in Egypt and its lipid profile. **Food Chem 2003**; 83: 63–68.
9. Abu-Al-Basal M. Influence of *Nigella sativa* fixed oil on some blood parameters and histopathology of skin in staphylococcal-infected BALB/c mice. **Pak J Biol Sci 2011**; 14: 1038–1046.
10. Babayan V, Koottungal G, Halaby G. Proximate analysis, fatty acid and amino acid composition of *Nigella sativa* L. seeds. **J Food Sci 1978**; 43: 1315–1319.
11. Bamosa A, Basil A, Zubaida A. The effect of thymoquinone on blood lipids in rats. **Indian J Pharmacol 2002**; 46: 195–201.
12. El-Saleh S, Al-Saqair O, Al-Khalaf M. Thymoquinone and *Nigella sativa* oil protection against methionine-induced hyperhomocysteinemia in rats. **Int J Cardiol 2004**; 93: 19–23.
13. Gilani A, Jabeen Q, Khan M. A review of medicinal uses and pharmacological activities of *Nigella sativa*. **Pak J Biol Sci 2004**; 7: 441–451.
14. Watson T. Ultrasound in contemporary physiotherapy practice. **Ultrasonics 2008**; 48: 321–329.
15. Zhou S, Schmelz A, Seufferlein T, Li Y, Zhao J, Bachem MG. Molecular mechanisms of low intensity pulsed ultrasound in human skin fibroblasts. **J Biol Chem 2004**; 52: 54463–54469.
16. Ang ES, Lee ST, Gan CS, See PI, Chan YH. The role of alternative therapy in the management of partial-thickness burns of the face; experience with use of moist exposed burn ointment (MEBO) compared with silver sulphadiazine. **Ann Acad Med 2000**; 29: 7–10.
17. Xu R. The medical science of burns and ulcers: a general introduction. **Chin J Burns Wounds Surf Ulcers 1989**; 1: 11–21.
18. Ioannovich J, Tsati E, Tsoutsos D, Frangia K, Papalois A. Moist exposed burn therapy: evaluation of the epithelial repair process (an experimental model). **Ann Burns Fire Disasters 2000**; 13: 3–9.
19. Dham R, Fathi A, Al Numairy A, Kadhim M, Wasielisky C, Shazly M, et al. MEBO ointment in the treatment of burn wounds: a multicenter study. **Mod Med 1999**; 16: 3–7.
20. Divekar V, Naik L. Evolution of anaesthesia in India. **JPGM 2001**; 47(2): 149–152.
21. Bohannon R, Pfaller B. Documentation of wound surface area from tracings of wound perimeters. Clinical report on three techniques. **Phys Ther 1983**; 63: 1622–1624.
22. Shivananda N, Poorna N, Steve S, Vidyasagar B, Andrew A. Evaluation of wound healing activity of Allamandacathartica. L. and Laurusnobilis. L. extracts on rats. **BMC Compl Alternative Med 2006**; 6: 12.
23. Phillips G, Whitehead R, Knighton D. Initiation and pattern of angiogenesis in wound-healing in the rat. **Am J Anat 1991**; 192: 257–262.
24. Al-Bayaty FH, Abdulla MA, Abu Hassan MI, Ali HM. Effect of Andrographis paniculata leaf extract on wound healing in rats. **Nat Prod Res 2012**; 26: 423–429.
25. Ahmed IH, Awad MA, El-Mahdy M, Gohar HM, Ghane AM. The effect of some medicinal plant extracts on wound healing in farm animals. **Assiut Vet Med J 1995**; 32: 236–244.
26. Ab Rahman M, Abdul Razak F, Bakri M. Evaluation of wound closure activity of *Nigella sativa*, Melastoma malabathricum, Pluchea indica, and Piper sarmentosum extracts on scratched monolayer of human gingival fibroblasts. **Evid Based Complement Altern Med 2014**: 190342–190351.
27. Ali B, Blunden G. Pharmacological and toxicological properties of *nigella sativa*. **Phytother Res 2003**; 17: 299–305.
28. Houghton PJ, Zarka R, Heras B, Hoult JR. Fixed oil of *Nigella sativa* and derived thymoquinone inhibit eicosanoid generation in leuko cytes and membrane lipid peroxidation. **Planta Med 1995**; 61: 33–46.
29. Sharma NK, Ahirwar D, Jhade D, Gupta S. Medicinal and pharmacological potential of *Nigella sativa*: a review. **Ethnobot Rev 2009**; 13: 946–955.
30. Boskabady MH, Shirmohammadi B, Jandaghi P, Kiani S. Possible mechanism (s) for relaxant effect of aqueous and macerated extracts from *Nigella sativa* on tracheal chains of Guinea pig. **BMC Pharmacol 2004**; 4: 3–8.
31. Hosseinzadeh H, Parvardeh S, Asl MN, Sadeghnia HR, Ziaee T. Effect of thymoquinone and *Nigella sativa* seeds oil on lipid peroxidation level during global cerebral ischemia-reperfusion injury in rat hippocampus. **Phytomedicine 2007**; 14: 621–627.
32. Suboh S, Bilto Y, Aburjai T. Protective effects of selected medicinal plants against protein degradation, lipid peroxidation and deformability loss of oxidatively stressed human erythrocytes. **Phytother Res 2004**; 18: 280–284.
33. Ruthig D, Meckling-Gill K. Both (n-3) and (n-6) fatty acids stimulate wound in the rat intestinal epithelial cell line, IEC-6. **J Nutr 1999**; 129: 1791–1798.
34. Cambier D, Vanderstraeten G. Failure of therapeutic ultrasound in healing burn injuries. **Burns 1997**; 23: 248–249.
35. Loyd V, Nicholas G, Howard C. *Ansel's pharmaceutical dosage forms and drug delivery system*. 9th ed. 2011. pp. 300–303.
36. Mitragotri S. Healing sound: the use of ultrasound in drug delivery and other therapeutic applications. **Drug Discov 2005**; 4: 255–260.
37. Ter R, Kessels A, Knipschild P. Randomized clinical trial of ultrasound in the treatment of pressure ulcers. **Phys Ther 1996**; 76: 1301–1311.
38. Smahel J. The problem of dehydration and healing of burn wounds. **Burns 1993**; 19: 511–512.
39. Atiyeh BS, Al-Am CA, El-Musa KA, Dham R. The effect of moist exposed dressing: healing, barrier function and restoration of partial-thickness burn wounds. **Eur J Plast Surg 2003**; 26: 5–11.
40. Yeh G, Eisenberg D, Kaptchuk T. Systematic review of herbs and dietary supplements used in glycemic control in diabetes. **Diabetes Care 2003**; 26: 1277–1294.

How to cite this article: Elgohary HM, Al Jaouni SKH, Selim SA. Effect of ultrasound-enhanced *Nigella sativa* seeds oil on wound healing: An animal model. J Taibah Univ Med Sc 2018;13(5):438–443.