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Clinical Effect of *Nigella Sativa* Oil Gel on Oral Traumatic Ulcer Healing in Albino Rats

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Abstract
Context: Oral ulcers extensively occur and need to be treated. Medicinal plants and their derivations have been applied for the treatment of ulcers. This study was conducted evaluate the effects of *Nigella sativa* gel on oral traumatic ulcer healing in albino rats.
Methods: An oral ulcer with diameter of 3 mm was induced in left buccal mucosa with help of a punch in 30 rats. A group was considered as control and any intervention did not conduct on them (n=15). Other rats were treated with *N. sativa* gel (n=15) and placebo gel (sham group). The rats were treated once daily for 14 days with help of an applicator. On days 3, 7 and 14, ulcer region was evaluated for clinical signs, including wound area, wound contraction, minimum and maximum diameters, pseudo-membrane color, secretory exudate, ulcer wound, granulation tissue and scar tissue.
Findings: The administration of *N. sativa* gel significantly decreased wound area (P=0.001), maximum wound diameter (P=0.014),minimum wound diameter (P=0.009), granulation tissue and pseudo-membrane color, secretory exudate and redness of ulcer and increased wound contraction (P<0.005) and pink color in wound site (P<0.05), but it did not have significant effects on scar tissue (P>0.05).
Conclusion: In conclusion, *N. sativa*oil gel could exhibit significant role in the wound healing process for oral ulcers. Future mechanistic studies are required to confirm the effects of *N. sativa* oil gel in the treatment of oral ulcers.

Key words: Medicinal plants, Oral ulcers, Scar tissue, Wound color, Wound contraction

Introduction

An oral traumatic ulcer is damage to the mucous membrane which causes to loss of surface tissue, disintegration and epithelial tissue necrosis, which causes inflammation, pain and burning sensation(1).The oral mucosa is a resultof physical, chemical and thermal trauma (2). Oral traumatic ulcers are mostlyseen in clinical dentistry and do not treatwith the usual treatments (3).Ulcers occur in lips, tongue, the floor of the mouth, soft palate, uvula, etc and pharyngeal mucosa and its prevalence rate is 5% to 20% in the general population(4). Studies have reported a prevalence rate of 47% in traumatic oral ulcers in adults and 29% in adolescents(5). Oral ulcers negatively influence the daily life of patients(6). The oral cavity provides a complex and dynamic environment in thatulcer healing occurs in a warm fluid containing a broad range of microorganisms and it is easily colonized by various species. Colonization does not cause to wound infection, but an increase in microbial load correlates with exacerbation of ulcers and retards the healing process (7). Different treatments have been utilized for the management of oral ulcers. However, medicinal plants and their derivations have been utilized for the treatment of wounds (8-10). Medicinal plants and their derivatives are known as safe substances and have received much attention in the treatment of wounds(11).Using natural antimicrobial compoundscould beconsidered as appropriate strategy for inhibiting the bacterialgrowth and expediting the wound healing process(12). *Nigella sativa* L. or black cumin is a medicinal plant traditionally used as a remedy for fatigue improvement, chronic headache, fever, infection, inflammation,

rheumatism, cough, bronchitis, asthma, cardiovascular, gastrointestinal, and metabolic disorders (13). It is known to have antibacterial, anti-inflammatory and antioxidant properties(14). Thymoquinone is a majorin black cuminand is responsible for the pharmaceutical properties of plants (15). Several studies have reported the wound healing activity of *N. sativa*(16-18). Since medicinal plants cannot be directly applied to the oral cavity.Topical drug delivery systems areutilized to deliver a variety of drugs to the body by diffusion across the skin layers, such as gels(19). Gels are transparent to opaque semisolids, containing gelling agent that merges or entangles to form a three-dimensional colloidal network structure. They are utilized as a vehicle to deliver drugs(20). We could not find any study evaluating the effects of *N. sativa* on oral traumatic ulcer healing. This study was conducted to evaluate the effects of *N. sativa* gel on oral traumatic ulcer healing in albino rats.

Materials and Methods

Animals

This experimental study was conducted on 45 adult male albino ratswith weight of 250-300 g in 8-10 weeks of age. All the efforts were performed to minimize pain in animals. The Ethical Committee of Semnan University of Medical Sciencesapproved all the procedures used for the care and the treatment of the rats (IR.SEMUMS.REC.1400.118). The rats were purchased from ShahidBeheshtiUniversity of Medical Sciencesand acclimated with new environment for one week. The rats were kept in polycarbonate cages and had free access water and feed. Animals were kept at 22 ± 2 ºC and a lighting diet of 12 h lightness/ 12 h darkness.

The induction of ulcer

To induce anesthesia, 3 mg/kg Xylazine hydrochloride (Alfasan Company-Netherland) and 90 mg/g ketamine hydrochloride (RotexmedicaCompany-Germany) were intramuscularly administrated. An oral ulcer with diameter of 3 mm was induced in left buccal mucosa with help of a punch in 30 rats. A group was considered as control andintervention did not perform them (n=15). Other rats were treated with *N. sativa* gel (n=15) and placebo gel (sham group). The rats were treated once dailyfor 14 days with help of an applicator.

The preparation of N. sativa gel

To prepare *N. sativa gel*, 2 g chitosan and 50 mL deionized water were mixed and stirred at 500 rpm in 50 ºC.To dissolve chitosan, 500 mL acetic acid was added into it. Following the preparation of chitosan solution, 5 g sodium alginate was dissolved in 45 mL of water and added chitosan solution, dropwise. Also, 5 mL ethanol was dissolved in*N. sativa gel* oil. Chitosan solution and oil solution were mixed and solution was obtained.

Clinical evaluations

On days 3, 7 and 14, ulcer region was evaluated for clinical signs. Wound area and wound contraction were evaluated as reported by others (21).

Wound contraction = [(original wound area-unhealed area)/original wound area] × 100%

Other properties included minimum and maximum diameters, pseudo-membrane color (0=lack, 1=white and 2=yellow), secretory exudate (0=lack, 1=low, 2=medium and 3=high),ulcer wound (1=pink and 2=red), granulation tissue (0=lack and 1=presence) and scar tissue (0=lack and 1=presence).

Data analysis

The data were investigated for normality using Shaipro-Wilk test. Since the data were not normal, they were analyzed using Kruskal-Wallis and bonferronitests. The data were reported as mean ± SD. The data were analyzed using SPSS software (version 26) and figures were illustrated with help of Graph Pad Prism software.

Findings

Wound area

Figure 1 depicts the effects of the administration of *N. sativa* on wound area. The results showed that wound area were significantly lower compared with control group on days 3 (P=0.001), 7 (P=0.001) and 14 (P=0.012). There were also significant differences between the placebo group with the gel group on days 3 (P=0.001), 7 (P=0.002) and 14 (P=0.014). The administration of the *N. sativa* gel also increased wound contraction compared with other groups on day 14. The results showed that wound contraction was 98.56 ± 1.69%, 87.19 ± 15.03% and 87.43 ± 9.20% in the *N. sativa*gel, placebo and control groups, respectively.

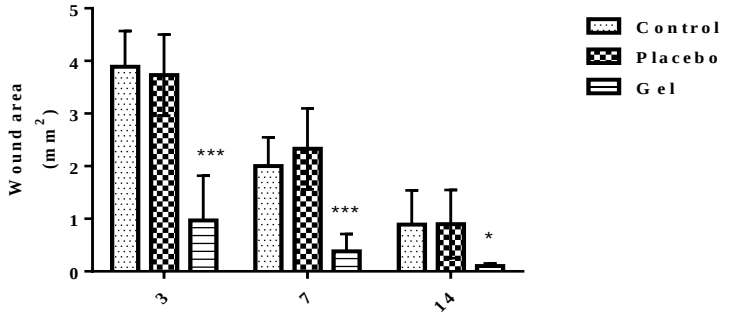

Figure 1 Wound area (mm^2) in the rats treated with gel on days 3, 7 and 14. Superscripts *** and * show significant differences between gel group with other group in the same day at $P<0.001$ and $P<0.05$, respectively.

Minimum and maximum diameter

Figure 2 depicts the results for the effects of *N. sativa*gel on maximum (A) and minimum (B) diameter. The results showed that the administration of the gels significantly decreased minimum and maximum diameter compared with control and placebo groups on days 3 ($P=0.001$), 7 ($P=0.001$) and 14 ($P=0.001$). There was no significant differences between placebo and control groups for minimum and maximum diameter in all the days ($P>0.05$).

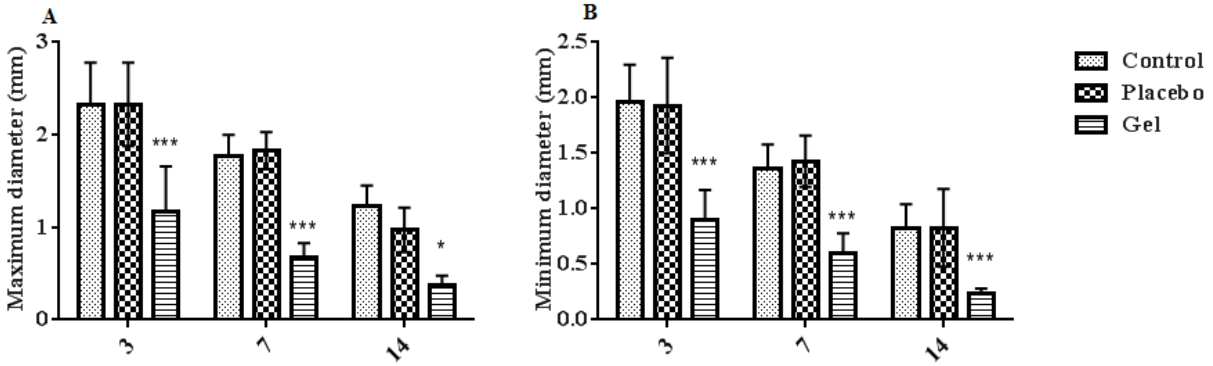

Figure 2 Maximum (A) and minimum (B) diameter (m) in the rats treated with gel on days 3, 7 and 14. Superscript *** shows significant differences between gel group with other group in the same day at $P<0.001$.

Pseudo-membrane color

Table 1 illustrates the results for the effects of *N. sativa*gel on pseudo-membrane color in days 3, 7 and 14. The results showed that number of pseudo-membrane was significantly lower in N. sativa group compared with other groups.There was no significant differences between placebo and control groups in all the days ($P>0.05$).

Table 1 The effects of *N. sativa* gel on pseudo-membrane color

Days		**3**			**7**			**14**	
	Control	Placebo	N. sativa	Control	Placebo	N. sativa	Control	Placebo	N. sativa
Yellow	13 (86.70%)	11 (73.30%)	2 (13.30%)	6 (40.00%)	8 (53.30)	1 (6.70%)	2 (13.30%)	4 (26.70%)	2 (13.30%)
White	2 (13.30)	3 (20.00%)	1 (6.70%)	9 (60.00%)	7 (46.70)	1 (6.70%)	0 (0.00%)	3 (20.00%)	0 (00.00%)
None	0 (0.00%)	1 (6.70%)	12 (80.00%)	0 (0.00%)	0 (0.00%)	13 (86.70%)	13 (86.70%)	8 (53.30%)	13 (86.70%)
P-value		0.001			0.001			0.001	

Exudate rate

Table 2 depicts the results for the effects of *N. sativa*gel on exudate rateon days 3, 7 and 14. The results showed that number of exudate rate was significantly lower in *N. sativa* group compared with other groups on days 7 and 14. The results did not show significant between groups on day 3 (*P*=0.064). There was no significant differences between placebo and control groups in all the days (*P*>0.05).

Table 2 The effects of *N. sativa* gel on exudate rate

Days		**3**			**7**			**14**	
	Control	Placebo	N. sativa	Control	Placebo	N. sativa	Control	Placebo	N. sativa
High	3 (20.00%)	2 (13.30%)	0 (0.00%)	1 (6.70%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Medium	5 (33.30)	7 (46.70%)	3 (20.00%)	7 (46.70%)	4 (26.70%)	0 (0.00%)	1 (6.70%)	0 (0.00%)	1 (6.70%)
Low	6 (40.00%)	4 (26.70%)	9 (60.00%)	7 (46.70%)	6 (40.00%)	3 (20.00%)	8 (53.30%)	9 (60.00%)	8 (53.30%)
None	1 (6.70%)	2 (13.30%)	3 (20.00%)	0 (0.00%)	5 (33.30%)	12 (80.00%)	6 (40.00%)	6 (40.00%)	6 (40.00%)
P-value		0.064			0.000			0.003	

Ulcer color

Table 3illustrates the results for the effects of *N. sativa*gel on exudate rate on days 3, 7 and 14. The results showed that pink-colored ulcers were significantly more in *N. sativa* group compared with other groups on days 3(*P*=0.006) and 7 (*P*=0.022) compared with other groups. The results did not show significant between groups on day 14 (*P*=0.220). There was no significant differences between placebo and control groups in all the days (*P*>0.05).

Table 3 The effects of *N. sativa* gel on ulcer color

Days		**3**			**7**			**14**	
	Control	Placebo	N. sativa	Control	Placebo	N. sativa	Control	Placebo	N. sativa
Red	13 (86.70%)	13 (86.70%)	14 (93.30%)	8 (53.30%)	12 (80.00%)	3 (20.00%)	4 (26.70%)	5 (33.30%)	2 (13.30%)
Pink	2 (13.30%)	2 (13.30%)	1 (6.70%)	7 (46.70%)	3 (20.00%)	12 (80.00%)	11 (73.30%)	10 (66.70%)	13 (86.70%)
P-value		0.651			0.000			0.003	

Granulation tissue

Table 4 depicts the results for the effects of *N. sativa*gel on granulation tissue on days 3, 7 and 14. The results showed a significant difference on day 7 (*P*=0.004). The results did not show significant between groups on day 3 (*P*=0.651) and 14 (*P*=0.220). There was no significant differences between placebo and control groups in all the days (*P*>0.05).

Table 4 The effects of *N. sativa* gel on granulation tissue

Days		**3**			**7**			**14**	
	Control	Placebo	N. sativa	Control	Placebo	N. sativa	Control	Placebo	N. sativa
Lack	13 (86.70%)	13 (86.70%)	14 (93.30%)	8 (53.30%)	12 (80.00%)	3 (20.00%)	4 (26.70%)	5 (33.30%)	4 (26.70%)
Presence	2 (13.30%)	2 (13.30%)	1 (6.70%)	7 (46.70%)	3 (20.00%)	12 (80.00%)	11 (73.30%)	10 (66.70%)	11 (73.30%)
P-value		0.651			0.004			0.220	

Scar tissue

Table 5 depicts the results for the effects of *N. sativa*gel on scar tissue on days 3, 7 and 14. The results did not show significant differences between groups on day 3 (*P*=0.757), day 3 (*P*=0.507) and 14 (*P*=0.879). There was no significant differences between placebo and control groups in all the days (*P*>0.05).

Table 5 The effects of *N. sativa* gel on scar tissue

Days	**3**			**7**			**14**		
	Control	Placebo	N. sativa	Control	Placebo	N. sativa	Control	Placebo	N. sativa
Lack	7 (46.70%)	5 (33.30%)	6 (40.00%)	10 (66.70%)	8 (53.30%)	11 (73.30%)	11 (73.30%)	12 (80.00%)	12 (80.00%)
Presence	8 (53.30%)	10 (66.70%)	9 (60.00%)	5 (33.30%)	7 (46.70%)	4 (26.70%)	4 (26.70%)	3 (20.00%)	3 (20.00%)
P-value		0.757			0.507			0.879	

Discussion

This study aimed to evaluate clinical effect of *N. sativa* oil gel on oral traumatic ulcer healing in albino rats. The results showed that administration of gels significantly increased wound contraction and decreased wound area. The results are in agreement with those reported by Al-Douri et al. who evaluated the effects of *N. sativa* oil on wounds and showed that *N. sativa* oil expedites the wound healing process via a decrease in the inflammation(22). Parallel to our findings, Sari et al. assessed the effects of *N. sativa*oil gel in the treatment of diabetic wounds and reported that *N. sativa* oil gel accelerated the wound healing process via a decrease in the inflammation (23). In the current study, we investigated oral ulcers and Sari et al. investigated diabetic wounds, however, both studies showed positive effects of *N. sativa* oil gel in the treatment of wounds. It means that *N. sativa* oil gel works as a healer in different wounds. Sari et al. wound healing activity of*N. sativa* oil gel attributed to the anti-inflammatory effects of active compounds in *N. sativa* oil gel(23). In this study, we did not evaluate the anti-inflammatory effects of *N. sativa* oil gel and this gel may work in the same way in oral ulcers. Another study evaluated the effects of *N. sativa* on wound healing process and reported the positive effects of*N. sativa*in accelerating wounds due to antioxidant properties of active compounds of *N. sativa*gel(24). Several studies have reported the positive role of antioxidant compounds in expediting the wound healing process in type of wounds (9, 10, 21, 25).Free radicals are increased on days after injury and an increase in free radicals negatively affects the wound healing process via damages on cellularnucleotide, protein, and lipid backbones (25). In addition, antibacterial and anti-inflammatory properties of medicinal plants accelerate wound healing process (9, 10, 21, 25).Several studies have reported antibacterial and antioxidant properties of *N. sativa*(26, 27). The decrease in bacterial count and inflammation moves the wound healing process toward proliferation phase and complete healing of wounds (9, 10, 21, 25). It can be stated that the administration of *N. sativa* oil expedites the ulcer healing process due to antibacterial, antioxidant and anti-inflammatory properties. The results also showed that pseudo-membrane was lower and did not observe on day 14. The results concur with those reported by Nambiar et al. (2021) who showed that administration of coconut oil decreased number of pseudo-membrane in the patients withminor recurrent aphthous ulcers(28). Decrease in pseudo-membrane is considered as a sign for the wound healing process. The results also showed that exudate rate was significantly lower on the first days and then disappeared. It highlightson the positive effects of*N. sativa*oil in improving the wound healing process via decrease in exudate. The results are in agreement with previous studies that showed plant essential oils decrease exudate in the wound region (29). Exudate has a closed relation with inflammation. As mentioned previously, *N. sativa*oil works as an anti-inflammatory compound and accelerates the wound healing process. Thus, decrease in exudate confirms the efficiency of *N. sativa*oil as anti-inflammatory compounds in accelerating the oral ulcer wounds. Change in color also confirms the effects of *N. sativa*oil in acceleration of wounds. The results did not confirm the effects of *N. sativa*oil in the wound healing process by modulation in granulation and scar tissues are in contrast with other studies for the effects of other medicinal plants. Shedoeva et al. evaluated the effects of medicinal plants in the wound healing process and showed that herbal medicines accelerate the wound healing process by modulation in granulation tissue(30). Previous studies have shown that medicinal plants accelerate wound healing process via an increase in granulation tissue in infected skin wounds (9, 10, 21, 25). The difference in the current study and other studies could be attributed to the differences in type of wounds. The mechanisms for improving different wounds are different.

Conclusions

This study evaluated clinical effect of *N. sativa* oilgel on oral traumatic ulcer healing in a rodent model. The administration of the oil gel accelerated the oral ulcer healing. In sum, *N. sativa* oilgel is a promising structure for expediting the wound healing process in rat model. However, future mechanistic studies are required to evaluate the effects of*N. sativa* oilgel on oral traumatic ulcer healing. However, the results are promising and can be utilized for the treatment of oral ulcers after more clinical studies. The current study was conducted on rodent model and the results cannot be used for humans which is a major limitation in this study.

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