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Determination the effect of Lavender ethanolic extract derived ointment on wound healing in Alloxan-induced diabetic Wistar rats

Fatemeh Salimi[1]*, Abbas Nazemi[2] , Mehrdad Yadegari[3]

Abstract: The current study aimed to determine the effect of using different levels of lavender diethyl ether extract-derived ointment on wound healing in alloxan-induced diabetic Wistar rats. For a reason the twenty experimental rats at the age of three month were divided randomly in five groups whereas normal rats were treated with simple ointment base; diabetic rats were treated with simple ointment base as control, diabetic rats were treated with simple ointment base containing extracts (2.5% and 5%) and the diabetic rats received the nitrofurazone drug at 250 mg/kg dose per day for all treatments. The efficacy of wound healing treatment was evaluated based on wound area relative and histopathological characteristics. Data from the current study showed that the extract-treated diabetic animals showed a significant reduction in the wound area when compared with the control. In addition, histological studies of the tissue obtained on days 10^{th} and 20^{th} from the extract treated with the extract of lavender showed increased well-organized bands of collagen, more fibroblasts, and fewer inflammatory cells. In conclusion, we may demonstrate that the extract of lavender effectively stimulates wound contraction as compared to the control group and others, and it has accelerated wound healing in Alloxan-induced diabetic male Wistar rats.

Keywords: Lavender, Ethanol extract, Wound healing, Diabetic Wistar rats.

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Corresponding author email: Fatemehsalimivetmed@gmail.com
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[1].Department of Vet Med, Shk.C., Islamic Azad University,Shahrekord, Iran.
[2].Department of Vet Med, Shk.C., Islamic Azad University,Shahrekord, Iran.
[3].Department of Clinical Science, ShK.C., Islamic Azad University,Shahrekord, Iran.

Introduction

Nowadays, the use of complementary and alternative medicines for the treatment variety of conditions is increasing, and interest in their potential has been growing all over the world. Aromatherapy, which employs essential oils extracted from herbs, is widely used and is becoming a major complementary and alternative medicine (NASCIMENTO al., 2022).

Wound healing is a natural physiological process that develops in response to tissue damage to restore the function and integrity of damaged skin tissues (WILKINSON AND HARDMAN, 2020). It is a fundamental response to tissue injury that occurs by a process of connective tissue repair (REDDY et al., 2013).

A fibrous scar is the product of this process, the predominant constituent of which is collagen. Collagen and other components of the ground substance are synthesized by the highly vascular granulation tissue that is formed within the wound space. It provides strength and integrity to the dermis (MORADI et al., 2020, and AFSHARI et al., 2018).

Diabetes mellitus is a condition that is known to be associated with a variety of connective tissue abnormalities (AKBARZADEH et al., 2007).

The collagen content of the skin is decreased because of reduced biosynthesis and accelerated degradation of newly synthesized collagen. These abnormalities contribute to the impaired wound healing observed in diabetes. Lavender extract can promote wound healing through several mechanisms, including accelerating wound contraction, increasing collagen production, and enhancing tissue remodeling (CAVANAGH AND WILKINSON, 2002).

Many studies showed it could help with various wounds like burns, cuts, and scrapes by promoting tissue growth and potentially preventing scarring (SAMUELSON et al., 2020).

In addition, (Vakilian et al., 2008 and Cardia et al., 2018) assessed the effect of lavender on postpartum episiotomy wound healing, pain intensity, and reported that edema decreased significantly in the group using lavender essential oil.

Hosseini Abroush et al. (2015) have indicated that the anti-nociceptive effects of lavender on controlling acute and chronic pain considerably varied among different studies due to the nature of pain and method of drug administration.

Mori et al (2016) suggested that lavender oil might accelerate wound closure through a rapid decrease in granulation tissue

induced by platelet-derived growth factors and progression of re-epithelialization induced by epidermal growth factors. Results of many researchers' studies strongly suggest that the wound healing potential of lavender oil and its extract (MUH et al., 2022; VAKILIAN et al., 2008).

However, there are not enough yet, and it is still unclear how essential oils and herbal extracts act on various parts of the wound healing process. Thus, the current study aimed to determine the effect of lavender essential extract wound healing activities of Alloxan-induced diabetic male Wistar rats.

Material and methods

Lavender extract preparation

The Lavender flowers were purchased from the herbal plant market and approved by a botanist. Identity was confirmed, and voucher specimens were deposited at the Spice, Aromatic and Medicinal Plant Research Center, Islamic Azad University, Iran. About 100 g of powdered flowers of lavender were extracted with absolute diethyl ether (Merck, Germany) using a Soxhlet apparatus for 12^{h}. The concentrated extracts were filtered using Whatman No.1 filter paper and lyophilized and used as an ointment.

Diabetic rats

The total of twenty and three month aged of male Wistar rats with an average weight of 190-210 g were housed in standard environmental conditions of temperature and humidity and under a 12^{h} light-dark cycle condition.

During the experimental period, experimental rats were given a standard pellet diet and water ad libitum. All the procedures were approved by the Medical Ethics Committee of Islamic Azad University, Shahrekord Branch, Shahrekord, Iran.

During the study period, after $15^{h,}$ fasting, experimental rats were intraperitoneally injected daily with 150 mg per kg of alloxan monohydrate freshly dissolved in distilled water for two or three consecutive days.

Blood was drawn from the orbital plexus 24^{h} after the injection, and the glucose level was estimated. Wounds were made on the rats showing elevated blood glucose. Rats were divided randomly into five groups as follows A: normal rats were treated with a simple ointment base. B: Diabetic rats were treated with a simple ointment base as a control. C and D diabetic rats were treated with a simple ointment base containing

extracts (2.5% and 5%), and E: the diabetic rats received the nitrofurazone drug at a 250 mg/kg/day dose.

Evaluation of wound healing activity

The dorsal skin of the Wistar rats was shaved, and they were anesthetized with 1.5 mg per kg of ketamine and xylazine. The full thickness of the excision wound, such as a circular area about 150_{mm} 2 and 2_{mm} depth, was created along the markings using toothed forceps, a surgical blade, and pointed scissors. The wound area was calculated. At days 6, 8, 10, 12, 14, 16, and 18 of the experiment periods was terminated, and the wound area was removed from the surviving animals for histological examination.

The excision skin biopsies were fixed in 10 percentage of formaldehyde solution after two days during the experimentation period.

Data statically analysis

After obtaining the data results of wound relative area was statistically analyzed by (SAS 6.18) software as the (mean±S.D), and statistical significance between the treated and control groups was analyzed. Data are significant at ($p \leq 0.05$)

Result and Discussion

The results of the effects of treatments of the wound area relative (cm^2) in experimental Wistar rats are presented in Table 1. The wound healing potential in diabetic animals for lavender ointment was evident on day 18, and this potential was further confirmed in the histological evaluation. According to the observation, no healing effect was shown with a simple ointment in diabetic rats. On days 6, 8, 10, 16, and 18, animals treated with lavender ointment application showed results with improved wound healing process in experimental diabetic rats.

On day 18, normal rats were treated with a simple ointment base, and diabetic rats were treated with a simple ointment base containing the lavender extracts, healed totally, while the standard drug showed half healing. It was also observed that epithelialization periods of the extract groups were shorter in comparison to the simple ointment base-treated group. The obtained results of the current study are in support that wound healing and repair are accelerated by applying lavender extract, which was highlighted by the full thickness coverage of the wound area by an organized epidermis in the presence of mature scar tissue in the dermis. The enhanced capacity of wound healing with the lavender extract may be due because of the anti-inflammatory effects of the lavender active compounds that are mentioned in the other literature.

Table1. Effects of treatments of wound area relative (cm^2) in experimental wistar rats

Treatments / Days	6	8	10	12	14	16	18
Simple ointment on nondiabetic rats	1.41±3.29	1.32±3.08	1.25±2.85	1.18±2.63	1.09±2.02	0.451±.820	0.0± 0.0
Simple ointment on diabetic rats	1.52±3.42	1.48±3.16	1.42±2.98	1.38±2.79	1.32±2.50	1.28±1.69	1.16 ±1.2 5
Nitrofurazone on diabetic rats	1.42±3.31	1.35±3.21	1.28±2.94	1.02±2.01	0.991±1.05	0.880±0.95	0.72 0±0. 68
Lavender (2.5%) on diabetic rats	1.28±3.19	1.16±2.65	1.08±2.01	0.995±1.52	0.849±1.16	0.472±.450	0.0± 0.0
Lavender (5%) on diabetic rats	1.18±3.01	1.12±2.24	1.06±2.03	0.952±1.23	0.821±0.82	0.342±.951	0.0± 0.0

In each column, each value represents the mean ± S.D

The results of the evaluation of wound inflammation cells, collagen fibers, re-epithelization, collagen organization, and necrosis of experimental rats after 10 and 18 days of ointment application are shown in Table 2. On day 10, the study of the histological structure showed that tissue regeneration was greater in the skin wound treated with a simple ointment base containing extract of lavender.

Results showed that on the day 18, incision and dead space type of wounds in groups of lavender extracts shown complete healing as in collagenation, fibroblasts cells and angiogenesis, whereas the skin wound treated with simple ointment base on diabetic rats presented edema, monocyte cells and area with cellular necrosis that were not observed in the treated with lavender ointments and standard drug such as nitrofurazone. Wound healing is a process by which damaged tissue is restored as closely as possible to its normal state, and wound contraction is the process of shrinkage of the area of the wound and mainly depends upon the type and extent of damage, the general state of health, and the ability of the tissue to repair. In addition, the final target of these processes is to regenerate and reconstruct the disrupted anatomical continuity and functional status of the skin.

The granulation tissue formed in the final part of the proliferative phase is primarily composed of fibroblasts, collagen, edema, and new small blood vessels.

Samuelson et al (2020) showed use of lavender extract could help with various wounds like burns, cuts, and scrapes by

promoting tissue growth and potentially preventing scarring. Muh et al (2022) showed that topical treatment with lavender oil promoted the differentiation of fibroblasts into myofibroblasts in the wound granulation during the early stages of wound healing.

In the Mori et al (2016) study, the area of wounds topically treated with lavender oil was significantly decreased as compared to that of wounds of control rats at 4, 6, 8, and 10 days after wounding.

Table 2- The evaluation of wounds after 10 and 18 days of ointments application in experimental wistar rats

Treatments / Wound characteristics in days	Inflammation cells		Collagen fibers		Re-epithelization		Collagen organization		Necrosis	
	10	18	10	18	10	18	10	18	10	18
Simple ointment on nondiabetic rats	**	*	*	**	-	**	*	-	*	*
Simple ointment on diabetic rats	***	***	-	**	-	*	-	*	***	**
Nitrofurazone on diabetic rats	*	*	**	**	*	**	-	*	**	*
Lavender (2.5%) on diabetic rats	*	-	**	**	*	**	-	*	*	-
Lavender (5%) on diabetic rats	*	-	**	***	**	**	*	*	-	-

*: slight, **: moderate, ***: extensive, -: absent

They also showed that an increased number of myofibroblasts was observed in wounds treated with lavender oil at 4 days after wounding, suggesting promotion of differentiation of fibroblasts and wounds accelerate wound healing through formation of granulation tissue by collagen synthesis. Lavender extract shows promise in promoting wound healing in diabetic mice due to its anti-inflammatory, antioxidant, and angiogenic properties. In line with our study results, other studies indicate that lavender extract can accelerate wound closure, increase collagen synthesis, and enhance angiogenesis in diabetic rats. Collagen is an important component that strengthens and supports extracellular tissue, and it is composed of the amino acid hydroxyproline, which has been used as a biochemical marker for tissue collagen.

Muh et al (2022) also showed that the mechanisms of action of lavender essential

oil include cell wall disruption, cytoplasmic membrane damage, cytoplasmic coagulation, membrane protein damage, increased permeability leading to leakage of cell contents, decreased proton motive force, decreased ATP synthesis, and hydration. In the (Mori et al., 2018) study, the results also showed that topical treatment with lavender oil significantly increased collagen synthesis by fibroblasts. Polyphenol compounds in lavender may be responsible for antimicrobial activity (Cardia et al., 2018). This may be due either to the individual or the additive effect of the phyto-constituents involved in the process of wound healing.

Conclusion

According to the result, we may demonstrated that the extract ointments of lavender has effectively stimulate wound contraction and effectively stimulates wound contraction as compared to others. Therefore, the lavender-derived extract in 2.5 and 5 % levels of ointment has accelerated wound healing in Alloxan-induced diabetic male Wistar rats.

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Data availability

The data presented will be available free of charge to any researcher

Declarations

Authors are involved equally in the research process

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Conflict of interest

The authors have declared that there are no conflicts of interest.

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