Research Article

The effect of geraniol dressing obtained from rose oil wound healing in diabetic rats

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ABSTRACT

Introduction: Diabetic foot is one of the most important chronic complications of diabetes mellitus. In this study, the aim was to investigate the healing effect of dressing with geraniol material obtained from rose oil. **Materials and Methods:** The experimental period of the study was carried out between June 2, 2016, and 27, 2016. Sprague-Dawley rats were used and three experimental, two control groups were formed. In the study conducted with a total of 40 rats, each group consisted of eight rats. Geraniol dressing, isotonic wet dressing, and hydrocolloid wound dressing were applied topically once a day to the first, second, and third groups, respectively. No dressing was applied to the positive and negative control groups. Index of oxidative stress of wound healing was assessed by total antioxidant status/total oxidant status measurements. **Results:** Due to the macroscopic results, it was determined that wound score was significantly decreased on day 3 in the first group and non-diabetic groups compared with other groups. When the microscopic findings were compared with day 0, in the first group, significant decrease of the level of collagen density and epithelization was observed on day 10. In the first group, increase in fat cells had become significant than other groups. In the CD34, SMA and vimentin staining, the first group showed superiority to other dressings. In the last measurements, the highest drop was seen in geraniol dressed and negative control groups. **Conclusion:** According to the study, geraniol dressed group provided similar wound healing with negative control group and showed superiority to the other products used as a standard in wound care.

Key words: *Diabetic foot, Geraniol, Hydrocolloid cover, Rat, Rose oil*

Diabetes mellitus (DM) is a chronic disease with serious complications [1,2]. Diabetic foot is one of the most important chronic complications of DM. In diabetic foot complications, deterioration in the patient's state of health, increase in mortality, morbidity, the frequency, and duration of hospitalization can be seen. Diabetic foot complication also causes high health expenditures for the patient and the society. The conducted studies reported that infected diabetic foot ulcers result in 5% major and 20–30% minor amputations [3-5].

Experts have turned to herbs for wound care because of their antioxidant, antiseptic, and antimicrobial properties [6-8]. Among the plants, rose and rose products' use are widespread. In recent years, studies showing antibacterial, anti-HIV, anxiolytic, anti-inflammatory, analgesic, hypnotic, anti-spasmodic, and antitussive effects of rose are common [9-12]. Geraniol, among the extracts that make up the rose oil, has anti-inflammatory, anticancer, antioxidant, and immunosuppressive effects and it was reported that it can be used for the prevention and treatment of diabetic neuropathy. In addition, there are data on the anti-atherogenic, anti-cholesterol, antibacterial, and anti-*Candida* properties of geraniol [13-19].

This study was planned in the light of the available data. We conducted a pre-clinical, *in vivo*, experimentally designed study to compare three wound care products (GD, hydrocolloid dressing, and IWD) in wound healing among diabetic rats [20].

MATERIALS AND METHODS

A diabetic wound model was created in 40 adult, male and female Sprague-Dawley rats with an average weight of 200–350 g. The groups consisted of eight rats provided that they include male and female. After the wound was opened from the HD group, a rat died on the 12th day and after the wound was opened from the PC group, a rat died on the 6th day and the study ended with 38 rats. Diabetic model was created with 60 mg/kg streptozotocin dissolved in cold citrate buffer (0.1 M, pH: 4.5) intraperitoneally. Only citrate buffer IP was applied to the rats in the negative control group. Rats with blood glucose levels above 250 mg/dl at 72 h were considered diabetic. On the 3rd, 5th, 7th, 10th, 13th, and 15th days, blood glucose measurements, mean food and water consumption, and urine volume monitoring were repeated. Under general anesthesia (90 mg/kg ketamine and 10 mg/kg xylazine), three ischemic wounds were opened with a tissue loss of 1 cm apart, starting 3–4 cm behind the head and that day was accepted as day 0. After washing the wounds with distilled water before

each dressing; in the first group, one drop of geraniol was used, in the second group, it was moistened with 0.9% NaCl solution and the squeezed hydrophilic gauze was used, and in the third group, hydrocolloid wound dressing was used and the wound was covered with a thin gauze bandage. In the positive control group, DM was developed, wound was opened but no dressing was applied. On the 15th day of the wound formation, the subjects were sacrificed with high-dose anesthesia. Macro-monitoring of wound healing was done using head-tail alignment on the 3rd, 5th, 7th, 10th, 13th, and 15th days using paper ruler measurements, wound diameter shapes, and photographing and it was evaluated by wound scoring (Walker formula).

Immunohistochemical and histopathological examinations of wound healing were performed by a pathologist who did not know about the experiment (blind study). Blood samples were taken from the rats on the beginning and the last day of the study. Total antioxidant status (TAS)/total oxidant status (TOS) was measured, oxidative stress index was used.

In our study, geraniol was obtained by water vapor method (steam distillation-traction distillation) from rose oil. This rose oil was obtained from roses collected during the last rose oil distillation season.

Statistical Evaluation

In this study, variance analysis technique was applied in the features measured in a single time, in factorial order. Levene's test was used to test the homogeneity of the group variances and the Tukey's test was used for the difference between the groups. In all results, $p<0.05$ was considered statistically significant.

RESULTS

Rat's weight, food, water consumption, and urine amounts were evaluated in 5 different times. As a result of the analyses, Time × Group binary interaction showed statistically significant difference, respectively; (F=5.02/p=0.000) (F=2.865/p=0.001), (F=53.090/p=0.000). In diabetic rats, diabetes markers were observed during modeling (weight loss, polyphagia, polydipsia, and polyuria).

The greatest improvement was observed in the non-diabetic control group, while the closest improvement was observed in the geraniol dressing group. Then, it was listed as isotonic wet dressing group, hydrocolloid dressing group, and positive control group (Fig. 1). Average differences between the wound areas among the groups were examined (Table 1).

In group × gender two interaction (F=3.683/p=0.016); in the NC group, the male and female rats had a statistically significantly lower wound score than all other groups, and the geraniol group was the closest to this group. When the group × time two interaction (F=12.205/p=0.000) was evaluated in terms of the relationship between the groups at each time; the wound score in the GD group and NC group decreased more significantly from the 3rd day compared to the other groups.

When the samples of the wounds taken on days 0, 5, 10, and 15 were compared in terms of collagen density, fibroblast count, inflammatory cell infiltration, and angiogenesis, it was observed that collagen density increased in all groups from the beginning and a significant difference was found ($p<0.001$) (Table 2). When the measurements made from time to time in each group were examined, it was seen that the median was not equal ($p<0.001$) in all groups. When the groups were compared at each time, the difference between the collagen density level among median showed statistical significance only on the 10th day ($\chi^2=13.186/p=0.010$). The highest number of fibroblasts was observed in the GD group than the NC group. Inflammatory cell infiltration increased significantly on the 10th day in other groups, while it increased on the 15th day in the PC group. On the 15th day, significantly higher angiogenesis level was determined in the IWD group and in the NC group than in the other groups ($\chi^2=24.719/p<0.001$).

When the rat groups in the model were compared in terms of epithelialization amount and fat cell, a significant difference was found. In the analysis, in the IWD group, epithelialization decreased on the 5th day compared to the baseline in the HD group, and the 10th and 15th days were similar to the 5th day. On the 15th day, the amount of epithelialization tended to decrease in groups other than GD and IWD groups ($\chi^2=18.610/p=0.001$). Fat cell increased significantly on the 10th day compared to baseline in the PC group and NC group. On the 15+ day, it decreased to a similar level to the beginning.

Histoscore of samples taken from the groups was evaluated after staining with anti-CD34, anti-SMA, and anti-vimentin. In the variance analysis, group × time interaction (F=11.192/p=0.000), (F=9.298/p=0.000), (F=3.037/p=0.006) was statistically significant (Table 3) (Fig. 2).

On the 5th day, tissue endothelial development and vascularization were observed best in the GD group. With the onset and increase of fibrosis, angiogenesis was replaced by increased connective tissue and decrease in CD34 activity was observed. While vimentin stains mesenchymal cells in general, SMA also stains vascular smooth muscle and myofibroblasts. An increase in SMA intensity indicates an increase in fibroblastic activity. When the tissues were examined in terms of SMA and vimentin, the closest group to the NC group was the GD group. The reason for the fluctuations in the staining with vimentin was thought to be close to complete closure of wounds in the NC group and GD group on the 15th day.

In the initial and termination stages, TAS and TOS were measured and a significant difference was found (F=563.606, p=0.000) (Table 4).

TAS measurements also differed between groups (F=34.720, p=0.000) and genders (F=7.299, p=0.011). Group × time (F=26.138, p=0.000) and gender × time (F=4.212, p=0.049) interactions were found to be statistically significant. Initial TAS values were similar in all groups. Last TAS values increased more in GD and NC groups than in other groups. There was a significant difference in TOS measurements between beginning and ending times (F=60.692, p=0.000), and between groups (F=7.087,

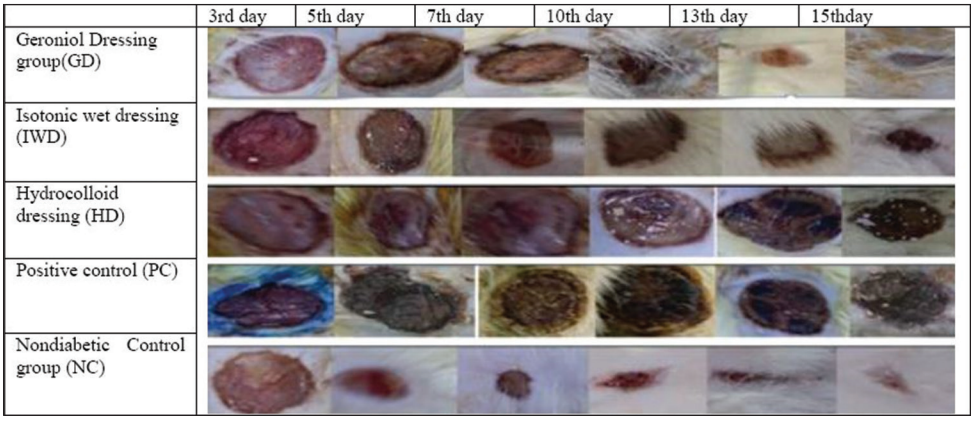

Figure 1: Monitoring of wound healing in rat groups in modeling

Table 1: Evaluation of wound score in terms of gender and time in all groups

	Group					Statistical analysis/p
	GD	IWD	HD	PC	NC	
	Avg±SS.	Avg±SS.	Avg±SS.	Avg±SS.	Avg±SS.	
Gender						
Male	45.71Bb±2.80	73.48Aa±2.80	71.53Aa±2.80	82.60Aa±2.80	43.54Ba±2.80	F=3.683/p=0.016
Female	57.77Ba±2.80	65.49Ba±2.80	79.54Aa±3.23	83.53Aa±3.23	44.93Ca±2.80	
Wound opening time						
Day 0	100.00Aa±0.00	100.00Aa±0.00	100.00Aa±0.00	100.00Aa±0.00	100.00Aa±0.00	F=12.205/p=0.000
3rd day	85.90Bb±2.74	100.00Aa±2.74	100.00Aa±2.96	100.00Aa±2.96	80.52Bb±0.00	
5th day	63.52Cc±3.08	80.45Bb±3.08	88.01Bab±3.32	94.11ABa±3.32	59.59Cc±3.08	
7th day	44.11Dc±3.00	71.80Bb±3.00	78.49Bab±3.24	86.48BCa±3.24	37.50Dc±3.00	
10th day	32.24Ec±3.56	56.83Cb±3.56	65.51Cab±3.84	77.47Ca±3.84	22.06Ec±3.56	
13th day	22.21EFc±3.38	45.28Db±3.38	51.58Db±3.65	66.14Da±3.65	8.74Fd±3.38	
15th day	14.17Fc±3.96	32.05Eb±3.96	45.18Db±4.27	57.24Da±4.27	1.24Fd±3.96	

Gender column: Upper case letters show the difference between groups in each gender and lower case letters show the difference between genders in each group separately. Wound opening time column interpretation: Upper case letters show the difference between groups at each time, and lower case letters show the difference between times in each group separately

p=0.000). The difference between the times in the IWD, HD, and PC groups showed statistical significance (F=6.550/p=0.001).

While there is no significance between the beginning and ending times (F=0.464, p=0.501) among the OSI values in our model groups, there was a significant difference between groups (F=13.118, p=0.000) and genders (F=7.261, p=0.110) and group × time (F=7.429, p=0.000) interaction. The oxidative stress index (OSI) (374.987b±25.051) value in male rats was found to be statistically lower than the OSI (470.450a±25.051) value in female rats.

DISCUSSION

In our study, diabetes developed within 48 h, in line with other literatures and after the rats became diabetic, weight loss started as expected with osmotic diuresis and hypovolemia due to an increase in blood sugar level and catabolic process [21]. Weight loss in HD and PC groups started on the 5th day, while it occurred late in geraniol and IWD groups. Klein *et al*. reported that low weight adversely affects general glycemic controls and diabetes may progress more severely [22]. The recovery in weight in the GD group may have slowed the transition to the severe stage of diabetes.

The amount of water consumption increased significantly with diabetes. Prevention of reabsorption from the kidneys with increased blood glucose concentration and the increase in urinary osmotic pressure causes polyuria [23]. The absence of polydipsia in rats can be explained by the osmotic diuresis process.

In the GD group, the increase in sugar level in female rats was more obvious than male rats. In the studies done with geraniol [24,25], generally, only male rats were used. However, there is no single gender concept known or concentrated in chronic diseases; in other words, the disease rate changes and it is seen in both sexes. Similarly, Van der Worp *et al*., in their compilation, emphasized this issue [26]. Our study differs due to the use of rats of both sexes. It will contribute to the literature as it is the only study that allows us to obtain data about the effects of geraniol in female rats. Ibrahim *et al*. showed that orally administered geraniol improves hyperglycemia and improves insulin sensitivity [27]. In our study, glucose levels rose later and remained lower than other groups during the study. This can be explained by the positive effects of geraniol on glucose hemostasis.

In the 3rd, 5th, and 7th days evaluations of the groups, wound healing in the GD and NC group was statistically significantly than the other groups. The earliest drop in the wound score started

Table 2: Comparison of time difference of microscopic follow-up criteria in each group

Group	N	Wound opening time	Collagen density		Fibroblasts number		Inflammatory cell infiltration		Epithelization		Angiogenesis		Fat cell	
			Rank Number Average.	χ^2/p	Rank Number Average	χ^2/p	Rank Number Average.	χ^2/p	Rank Number Average	χ^2/p	Rank Number Average	χ^2/p	Rank Number Average	χ^2/p
GD	8	0 day	1.00b	21.247/0.000	1.00b	21.863/0.000	1.00b	20.130/0.000	3.56a	19.279/0.000	1.00b	21.203/0.000	1.19b	12.930/0.005
		5th day	2.19ab		2.13ab		2.56ab		1.25b		2.38ab		2.81ab	
		10th day	3.25a		3.38a		3.63a		2.00ab		2.81ab		3.19a	
		15th day	3.56a		3.50a		2.81ab		3.19a		3.81a		2.81ab	
IWD	8	0 day	1.00b	21.369/0.000	1.00b	20.956/0.000	1.00b	19.091/0.000	3.56a	18.662/0.000	1.00b	20.597/0.000	1.50b	8.550/0.036
		5th day	2.38ab		2.31ab		2.63ab		1.13b		2.75ab		2.88a	
		10th day	3.19a		3.31a		3.38a		2.31ab		2.63ab		2.81ab	
		15th day	3.44a		3.38a		3.00a		3.00a		3.63a		2.81ab	
HD	7	0 day	1.00b	19.210/0.000	1.00b	18.619/0.000	1.00b	18.409/0.000	4.00a	18.789/0.000	1.00b	18.900/0.000	1.79b	13.500/0.004
		5th day	2.21ab		2.21ab		2.29ab		1.57b		2.43ab		3.57ab	
		10th day	3.14a		3.21a		2.93a		1.79b		2.86ab		2.64ab	
		15th day	3.64a		3.57a		3.79a		2.64ab		3.71a		2.00ab	
PC	7	0 day	1.00b	19.138/0.000	1.00b	19.230/0.000	1.00b	16.922/0.001	3.93a	18.350/0.000	1.00b	20.463/0.000	1.29b	11.411/0.010
		5th day	2.57ab		2.43ab		2.50ab		1.29b		2.21ab		2.57ab	
		10th day	2.71ab		2.79ab		2.86ab		2.07ab		2.79ab		3.21a	
		15th day	3.71a		3.79a		3.64a		2.71ab		4.00a		2.93ab	
NC	8	0 day	1.06b	17.261/0.000	1.00b	17.870/0.000	1.06b	17.074/0.000	3.19a	12.191/0.000	1.00b	21.092/0.000	1.31b	11.507/0.009
		5th day	2.50ab		2.63ab		2.56ab		1.63b		2.44ab		2.75ab	
		10th day	3.25a		3.19a		3.25a		2.25ab		3.06a		3.19a	
		15th day	3.19a		3.19a		3.13a		2.94ab		3.50a		2.75ab	

*Lower case letters show the time difference between each group in meaningful results

Table 3: Histoscores assessment after immunohistochemical staining of groups

Paint	Group time	GD	IWD	HD	PC	NC	F/p
		Avg±SS	Avg±SS	Avg±SS	Avg±SS	Avg±SS	
Anti-CD34	5th day	1.688Ac±0.169	0.500EFab±0.169	0.400EFa±0.169	0.638DEb±0.169	1.362Bc±0.169	F=11.192/p=0.000
	10th day	0.950CDb±0.075	0.913CDb±0.075	0.988Cb±0.075	0.650Db±0.075	0.525Eab±0.075	
	15th day	0.318Fa±0.113	0.469EFa±0.113	0.750CDb±0.113	0.425EFa±0.113	0.144Fa±0.113	
Anti-SMA	5th day	0.025CDb±0.013	0.006Db±0.013	0.006Db±0.013	0.012Db±0.013	0.044CDb±0.013	F=9.298/p=0.000
	10th day	1.038ABa±0.124	0.138CDab±0.124	0.106CDb±0.124	0.031CDb±0.124	1.188Aba±0.124	
	15th day	1.350Aa±0.126	0.469BCab±0.126	0.750Bab±0.126	0.287Cab±0.126	1.500Aa±0.126	
Anti-vimentin	5th day	0.875BCb±0.047	0.231Dc±0.047	0.425CDcb±0.047	0.300Dc±0.047	0.987BCb±0.047	F=3.037/p=0.006
	10th day	1.237Bab±0.116	0.712Ccb±0.116	0.650Ccb±0.116	0.350CDc±0.116	1.538ABab±0.116	
	15th day	1.762ABa±0.119	1.112Bb±0.119	0.862BCb±0.119	0.612Ccb±0.119	2.025Aa±0.119	

Uppercase letters show the difference between groups at each time, lower letters show the difference between times in each group

in the GD group. Kruse *et al*. showed that high glucose delays fibroblast migration and wound healing [28]. In our study, the effectiveness of GD in wound area and in wound healing can also be associated with a low blood glucose level. While antimicrobial effect [29] is mentioned in plants containing geraniol; polymicrobial flora was reported to be dominant in diabetic foot wound samples [30,31]. The studies showing the effectiveness of geraniol against possible bacteria, explain better wound healing and wound score regardless of glucose level.

The increase in collagen density in the PC group occurred later than in the other groups. Collagen density level difference was determined only on the 10th day. With damage to the skin, collagen synthesis increases. Loss of collagen in DM is related to the decrease in production and increase in catabolism [32]. Consistent with the literature, there was an increase in collagen synthesis in all groups. The highest collagen density after than NC group belongs to GD group. Based on these data, we think that the absorption of geraniol from the wound surface has positive effects on the collagen level. Studies reported that fibroblast proliferation decreases and wound tensile strength decreases in DM [33,34]. In the 5th and 10th days analysis, the highest number of fibroblasts after NC group belongs to the GD group. Despite DM, the increase in the number of fibroblasts increased wound tension resistance in rats in the GD group and positively affected the cutaneous wound healing process. Abnormalities related to wound healing in diabetes include microvascular and macrovascular abnormalities, impaired epithelization, and decreased angiogenesis [35]. Wang *et al*. applied IP geraniol treatment to rats and they stated that epithelialization began earlier and it was higher than other groups by providing endothelium-induced vasorelaxation, decreased NOX-2-related ROS production, and decreased VCAM-1 and ICAM-1 expression in these rats [36]. In inflammation, macrophages produce mediators such as nitric oxide (NO) to prevent infections. Excessive NO production damages normal tissue [37,38]. In studies, it was stated that decreased oxidative stress may lead to acceleration of wound healing [37,39]. In the results we found in our study, the positive effects of geraniol on epithelialization and angiogenesis may be associated with reducing oxidative stress and preventing NO formation.

Kim *et al*. showed that increased macrophage migration inhibitory factor (MIF) expression and rapid activation of the MIF gene in fat tissue can play a role in wound healing [40]. In our modeling, early increase of fat cells in the experimental groups may be related to the increase in MIF originating from fat cells in the inflammation region.

CD34 score increases in the GD group in our model in the early period. As stated by Kim *et al*., it can be explained by the increased proliferation and differentiation capabilities of stem cells originating from fat tissues [40,41] and as Suga *et al*. showed that this can be explained by increased angiogenesis gene expression [42]. Based on the results obtained in the studies, it was thought that the increase of CD34 score in the GD group in the early period in our modeling accelerated wound healing.

In studies of vimentin, they reported that it increases *in vitro* cell mobility, accelerates wound healing by inducing

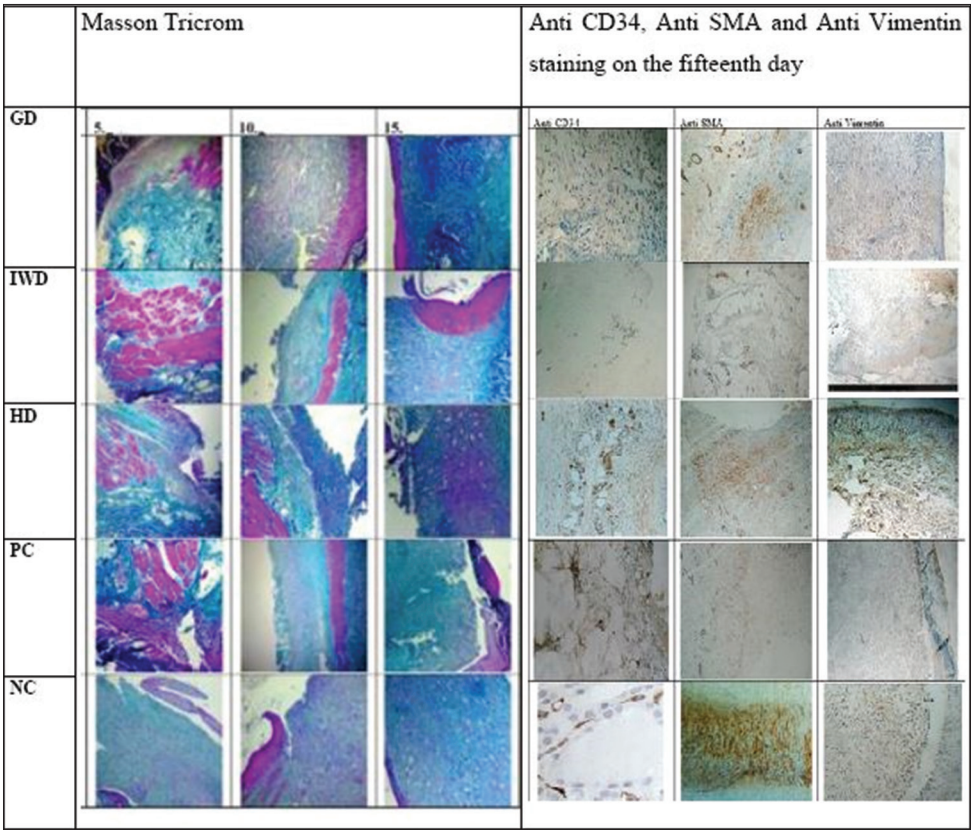

Figure 2: Masson trichrome staining, anti-CD34, anti-SMA, and anti-vimentin staining on the 15th day

Table 4: The change of TAS, TOS, and OSI levels according to time and groups and genders

	Time	TAS		TOS		OSI	
		Avg±SS	F/p	Avg±SS	F/p	Avg±SS	F/p
Group							
GD	Beginning	1.315Ab±0.034	F=26.138/p=0.000	6.324Aa±0.496	F=6.550/p=0.001	484.111Aa±36.169	F=7.429/p=0.000
	End	4.701Aa±0.214		8.261Ba±1.740		178.849Cb±70.845	
WD	Beginning	1.355Ab±0.034		6.100Ab±0.496		447.381Aa±36.169	
	End	2.780Ba±0.214		10.698Ba±1.740		408.921Ba±70.845	
HD	Beginning	1.321Ab±0.034		6.040Ab±0.496		455.692Ab±36.169	
	End	2.758Ba±0.214		17.339Aa±1.740		665.579Aa±70.845	
PC	Beginning	1.265Ab±0.034		6.002Ab±0.496		475.374Ab±36.169	
	End	2.724Ba±0.214		17.126Aa±1.740		645.333Aa±70.845	
NC	Beginning	1.714Ab±0.034		5.261Aa±0.496		311.884Aa±36.169	
	End	5.113Aa±0.214		7.699Ba±1.740		154.060Ca±70.845	
Gender							
Male	Beginning	1.434Ab±0.021	F=4.212/p=0.049	5.669±0.313	F=1.367/p=0.251	406.520±22.875	F=1.176/p=0.287
	End	3.847Aa±0.135		11.006±1.101		343.454±44.806	
Female	Beginning	1.355Ab±0.021		6.222±0.313		463.256±22.875	
	End	3.384Ba±0.135		13.444±1.101		477.643±44.806	

***In the main column of the group, uppercase letters show the differences of the groups at each time, while the lower case letters show the differences between times in each group.**
****In the main column of gender, uppercase letters show the difference of genders at each time, while lower case letters show the difference between times in each gender**

proliferation of fibroblasts, collagen accumulation, keratinocyte transdifferentiation, and reepithelialization [43].

In our modeling, in GD, NC groups had higher vimentin histoscores than other groups; faster, stronger and almost complete wound healing was achieved. In our modeling, higher vimentin histoscores were obtained on the 10th and 15th days in the GD and NC groups than in the other groups; 5 days after the increase in the vimentin level, the increase of SMA histoscore became significant. Li *et al*. showed that the peak of vimentin expression after the operation is 10–14 days, whereas the peak of SMA is around the 21st day [44]. These findings are consistent with our modeling; SMA increase in all groups occurred later

than the vimentin increase. Myofibroblasts are reactive cells that occur after acute or chronic injury, and SMA is a marker of the myofibroblastic phenotype. In our study, the SMA histoscore was found significantly higher in the GD and NC groups than the other groups on the 10th and 15th days.

Oxidative stress facilitates the development of insulin resistance and diabetes complications and plays a role in its pathogenesis [45,46]. In our study; it was determined that initially, TAS score was higher and TOS score was lower in NC group than other groups. Since, diabetes is associated with decrease in total antioxidant capacity [47], after rats become diabetic, the increase in TAS values in the NC group and the low TOS score in rats without diabetes are consistent with the literature. Anti-inflammatory [48], antimicrobial [29], and antioxidant [49,50] effects of geraniol have already been proven. NOX2 is widely expressed in many cell types that are important in vascular pathophysiology, such as endothelial cells and vascular smooth muscle cells [51]. Wang *et al*. showed that geraniol provides protection against endothelial dysfunction in rats fed on a high-fat diet by reducing NOX-2-associated ROS production [36,47]. In our study, when the results were evaluated, it can be said that geraniol contributes to antioxidant activity by decreasing ROS production. It is also effective in increasing TAS score and decreasing TOS.

CONCLUSION

In this study, the negative effects of diabetes on wound healing were emphasized and the effects of classical dressings and geraniol dressing on diabetic wound healing were compared. GD was superior in terms of macroscopic, microscopic, immunohistochemical, and biochemical aspects. Superior wound healing was observed in the geraniol group.

Despite its topical application, it positively affected OSI and showed antihyperglycemic properties. It has been shown that geraniol can be applied as an alternative treatment method in diabetic wound care and DM treatment. We believe that this study will guide the future studies on diabetic foot and diabetic treatments.

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