

Efficacy evaluation of a herbal anti-cellulite lotion: a phase 2, randomized, double-blind, right-left comparison clinical trial

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Background: Cellulite is a cosmetic problem, especially in women. We compared the safety and efficacy of a herbal anti-cellulite lotion with a placebo in a randomized, double-blind, right-left comparison clinical trial.

Methods: Ten healthy women (22-58 years) with cellulite (grades 2-4) participated in this study. The anti-cellulite lotion and placebo were applied twice daily on the thighs and buttocks for two months. Treated areas were photographed, and the thigh circumference, subcutaneous fat thickness, and dermal echo density were assessed and compared before and after the treatment. The satisfaction of the participants was also assessed.

Results: A comparable improvement in cellulite grade was detected by a blinded dermatologist on both treatment sides. Cellulite improved much in one participant, improved in six, and did not change in three participants. The dermis thickness increased compared with placebo after two months ($P = 0.046$). A significant reduction was observed in subcutaneous fat thickness on the treated side ($P = 0.03$). However, the decrease was not significant on the placebo site. There was an increase in the echo density of the dermis in the treatment site, though it was not statistically significant. Both products were well tolerated, and none of the participants experienced skin burning or itching.

Conclusion: The studied anti-cellulite lotion reduced the thickness of subcutaneous fat and increased the dermis thickness without serious adverse effects.

Keywords: anti-cellulite, cellulite, woman, efficacy, dermis, thickness

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INTRODUCTION

Cellulite is a common cosmetic problem for females. It is defined as the orange peel appearance of the skin that usually affects the outer and posterior thighs, buttocks, and breasts of post-pubertal women¹. The exact pathogenesis of cellulite remains elusive, though

non-inflammatory cellular atrophy of mesenchyme tissue with a reduction in vascular and lymphatic microcirculation, abnormal increase in water absorbency and edema, collagen breakdown in the dermis, and fat accumulation are observed, usually after conditions like pregnancy, menstrual cycle, and use of

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contraceptives and hormonal replacement ^{2,3}. Genetic predisposition to cellulite is related to a particular polymorphism in the angiotensin-converting enzyme and hypoxia-inducible factor 1A genes; however, several other factors are also involved in cellulite formation, such as metabolic imbalances, alterations in connective tissue structure, inflammatory conditions, reduced microcirculation, and hormonal factors.

The prevalence of cellulite is high in women; approximately 85–90% of women over 20 have some degree of cellulite, whether they are obese or not ³. Four clinical grades are defined for cellulite based on skin appearance. There is smooth skin at rest in grade I; in grade II, orange peel skin appears; in grade III, nodules are seen (panniculitis); and in grade IV, cottage cheese appearance of the skin is evident ^{2,3}.

Treatment for cellulite has not been adequately established; however, numerous approaches like weight loss, massage-suction techniques, liposuction, subcision, pharmaceutical, and cosmeceutical preparations are employed ^{1,5}. Caffeine, peptides, and some herbal extracts are administered topically to decrease adipogenesis and increase lipolysis by inducing thermogenesis and microcirculation. Retinoids and ascorbic acid induce signaling pathways of dermal collagen production and could increase the hypodermis layer's strength and collagen fibers' thickness ^{6,7}.

There is limited research on the effects of combining active ingredients to target cellulite's manifestations. The present pilot study aimed to assess the clinical efficacy and safety of a topical botanical lotion containing Lipocare[®], Intenslim[®], Phytosonic[®], Lanachrys[®], Regestril[®], Keratoline[®], and ginger extract compared with a vehicle placebo in the treatment of cellulite.

METHODS

Study design

This was a phase 2, randomized, double-blind, right-left comparison clinical trial conducted at the Pharmaceutical, Cosmeceutical, and Hygienic Evaluation Lab (DermaLab) of the Center for Research & Training in Skin Diseases & Leprosy (CRTSDL), Tehran University of Medical Sciences (TUMS) from April 2015 to October 2015.

Participants

Ten healthy women aged 22 to 58 with cellulite

grades 2 to 4 participated in the study. Other inclusion criteria were symmetrical cellulite lesions on both thighs, no significant changes in diet, lifestyle, and exercise program during the study, and completing the informed consent form. The exclusion criteria were acute medical diseases, history of allergy reactions to ingredients of test lotion, using any products for cellulite or diet pills in the past two months, presence of scar in the test area, and any history of venous thrombosis or related surgery in the past two years.

Intervention

The test product was Prime[®] anti-cellulite lotion (Dr. Akhavi Co., Tehran, Iran), which contains Lipocare[®], Intenslim[®], Phytosonic[®], Lanachrys[®], Regestril[®], Keratoline[®], and ginger extract. The placebo was a simple lotion with similar texture, odor, and viscosity, without any active ingredients. Both formulas were filled and packed in identical laminate 30g tubes. The anti-cellulite lotion and placebo were randomly applied twice daily with rotational movements on the right or left thighs and buttocks for two months.

Assessments

The following assessments were performed before the beginning of the treatment and two months later:

- Weight and height
- Digital photography from the anterior and posterior aspects of the thighs using a digital camera (DSC/F707; Sony Corporation, Tokyo, Japan) at a distance of 60 cm with constant light conditions in the upright position.
- Thigh circumferences, measured using a measuring tape.
- The thickness of the subcutaneous fat in the supine position and on the anterior surface of both thighs using a caliper.
- The thickness and echo density of the thigh's dermis, measured by 22 MHz high-frequency ultrasonography (DUB-USB Skin Scanner, TPM Co. Luneburg, Germany).
- Patient satisfaction for each product, evaluated on a 0 to 10 visual analog scale (VAS).
- The improvement in cellulite on both sides was recorded from "much worsened" to "much improved" by an independent blinded dermatologist, comparing before and after pictures. The incidence of adverse effects

(itching, irritation, swelling, redness, and scaling) was asked and recorded on a 0 to 3 scale (0: none, 1: slight, 2: moderate, 3: severe).

Ethics approval

The present study was conducted in compliance with the ethical principles of the Declaration of Helsinki and compliance with the guidelines of Good Clinical Practice (GCP). All subjects provided signed informed consent. The Research Committee of CRTSDL approved the study protocol in March 2015, and an Iranian Registry of Clinical Trials (IRCT) code was not required at the time of the study.

Statistical analysis

After the study was completed, data were analyzed using IBM SPSS Statistics 20. The changes in measured variables on both treated sides were calculated and compared using the following equation:

Change = (value after two months – value before treatment) / value before treatment × 100.

Due to the normal distribution of data, the paired t-test was performed, and p-values less than 0.05 were considered significant.

RESULTS

Ten female participants aged 22–58 years (mean ± standard deviation, 45.1 ± 6.70 years) were enrolled in this study. All participants completed the trial. Before and after treatment, the mean BMI of subjects was 29.9 ± 3.41 and 29.63 ± 2.91 kg/m², respectively ($P = 0.39$). This outcome confirmed that all the participants observed made no significant changes in their lifestyles.

A significant reduction was observed in subcutaneous fat thickness on the side of the application of anti-cellulite lotion, but not placebo after two months (Table 1). Also, the thickness of

Table 1. Thigh circumference, subcutaneous fat thickness, thickness of dermis layer, and skin density before and after two months of treatment with Prime® anti-cellulite lotion and placebo

Variable	Treatment	Before	After 2 months	P-value
Thigh circumference (cm)	Anti-cellulite lotion	58.50 ± 7.58	56.30 ± 7.58	0.01
	Placebo	57.9 ± 7.37	56.05 ± 6.94	0.00
Thickness of subcutaneous fat (mm)	Anti-cellulite lotion	4.41 ± 1.62	3.82 ± 1.04	0.03
	Placebo	4.4 ± 1.44	3.75 ± 0.95	0.06
Dermal thickness (µm)	Anti-cellulite lotion	1773.4 ± 620.33	2506.9 ± 540.56	0.05
	Placebo	2025.29 ± 637.22	2342.4 ± 384.44	0.17
Dermal density	Anti-cellulite lotion	25.193 ± 12.19	28.23 ± 16.26	0.60
	Placebo	24.871 ± 9.84	31.043 ± 14.94	0.28

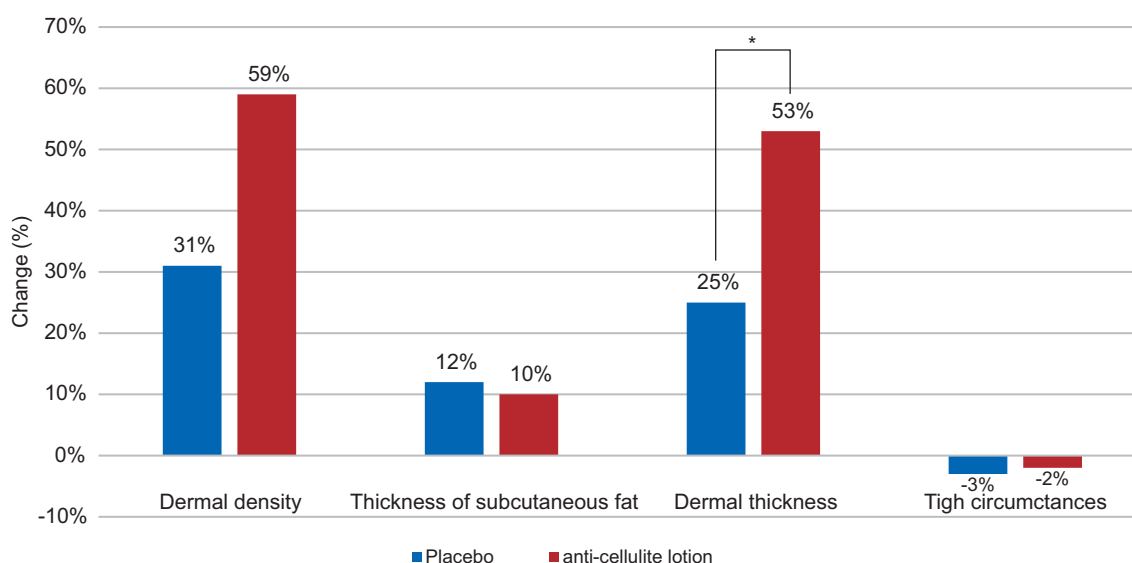


Figure 1. The changes of skin biometric parameters of Prime® anti-cellulite lotion, placebo, and their comparison after two months of treatment.

the dermis increased significantly after applying the anti-cellulite lotion (Table 1 and Figure 1). There was a noticeable increase in echo density of the dermis on the treatment side (Figure 2); however, this was not significant compared to the baseline assessment and the placebo-treated side (Table 1 and Figure 1). There was no significant difference in thigh circumference between the two groups.

The assessment of before and after pictures by a

blinded dermatologist showed no significant difference between the two sides; cellulite improved much in one participant, improved in six, and did not change in three participants (Figure 3).

Seven participants reported smoother and firmer skin and better improvement in the orange peel appearance of the skin on the side treated with the anti-cellulite lotion compared with the placebo-treated side. The mean VAS scores for the sides treated with

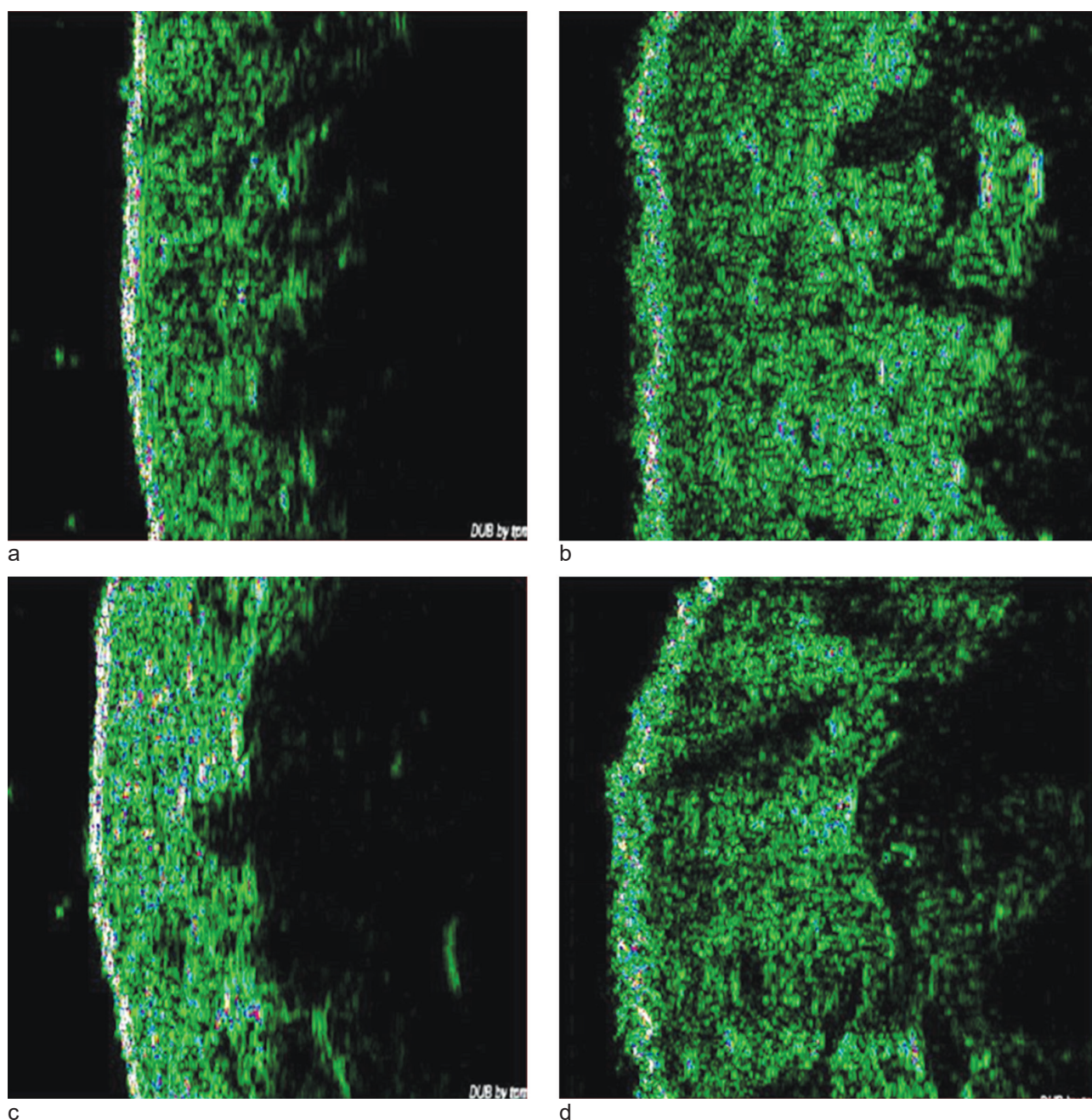


Figure 2. Ultrasound images before (a and b) and two months after treatment with Prime® anti-cellulite lotion (c) and placebo (d).

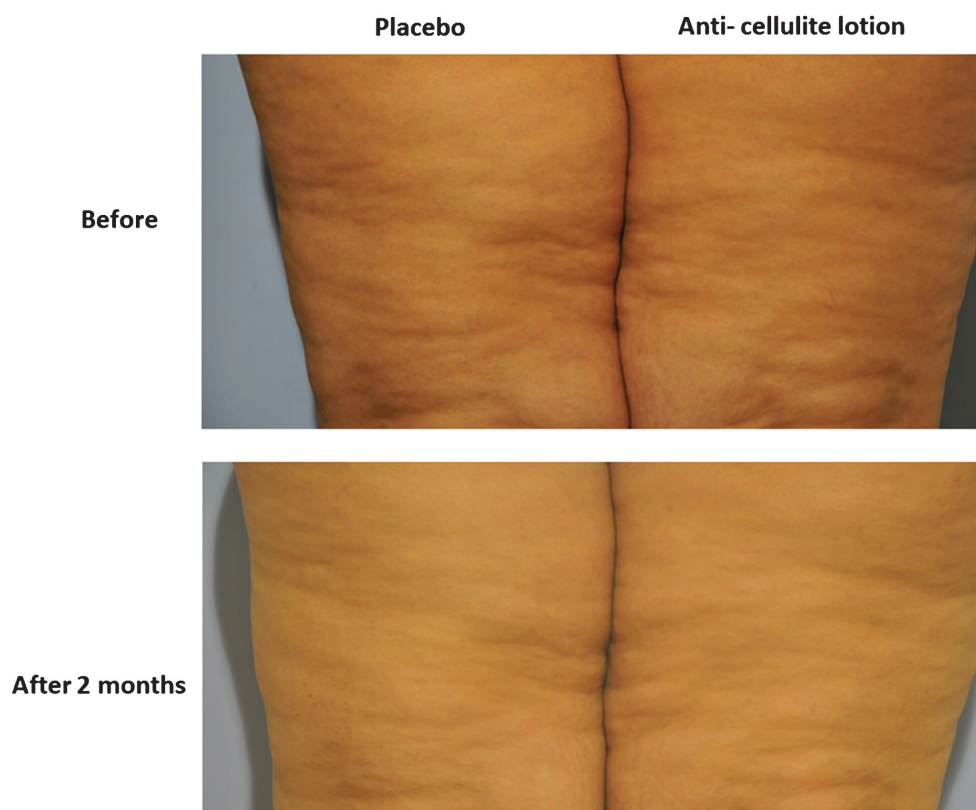


Figure 3. The appearance of the skin before and two months after treatment with Prime® anti-cellulite lotion and placebo.

anti-cellulite lotion and placebo were 6.5 and 5.3 out of 10, respectively ($P > 0.05$).

Both products (anti-cellulite lotion and placebo) were well tolerated during the two months of the study. None of the participants experienced skin burning, itching, erythema, swelling, or scaling.

DISCUSSION

We trialed an anti-cellulite lotion that contained a number of products. Lipocare (a combination of caffeine, coenzyme A, and Bupleurum Chinese extract) stimulates lipid catabolism and empties fat stores in adipocytes; caffeine can also stimulate lymphatic and microvascular flow⁹. Intenlim (butylene glycol, *Globularia cordifolia* callus culture extract, *Zingiber zerumbet* extract, and caffeine) soothes the inflammation reaction caused by trans fatty acids and acts against the accumulated fat by promoting the synthesis of desnutrin, a critical enzyme in triglyceride hydrolysis¹⁰. Phytosonic (a combination of caffeine, algae, and Poppy) selectively detaches hypertrophied adipocytes without destroying them and reduces subcutaneous fat through an ultrasound-like effect⁵.

Lanachrys (a mixture of butylene glycol, water, and *Chrysantellum indicum* extract) stimulates lipolysis, Regestril (*Phaseolus lunatus* extract, rutin, and two matrikines) inhibits skin degradation, Keratoline (an alternative of alfa-hydroxy acid) makes skin smoother, promotes epidermal cell renewal, and potentially improves the absorption of the other active ingredients, and ginger extract prevents fat storage by increasing fat burning and adjusting the skin's moisture due to its amino acids and polysaccharides^{10,11}.

Ingredients such as Lipocare, Intenlim, Phytosonic, Lanachrys, and ginger can reduce or eliminate subcutaneous adipocytes. Our findings confirmed this, where the thickness of subcutaneous fat was significantly reduced after the topical application of the anti-cellulite lotion (Table 1). We also detected decreased dermal thickness via ultrasound evaluation after two months of applying the tested lotion (Figure 2). Caffeine is one of the main active ingredients in anti-cellulite formulations^{12,13}. Caffeine activates lipase in the lipolysis process by blocking α -adrenergic receptors and secreting catecholamines, which affect β -2 adrenergic receptors and, in

turn, inhibit the breakdown of cyclic adenosine monophosphate (cAMP) in fat cells ¹⁴. Caffeine's effectiveness is magnified when combined with other anti-cellulite ingredients ¹⁵. Our outcomes align with the literature in this regard.

Two months after the application of Prime[®] anti-cellulite lotion, we observed a significant increase in the thickness of the dermis layer. This improvement might be related to Regestril, which inhibits the degradation of dermal proteins. The long-term effect of Keratoline in the activation of fibroblast cells could also induce the neogenesis of collagen fibers and increase the thickness of the dermis layer. Increasing the dermis's main proteins and thickness improves skin tonicity and extensibility ^{12,16}. For instance, Melosek *et al.* (2011) ran a clinical trial on 61 women with a cosmetic preparation containing hydrolyzed *Cucurbita pepo*, *Vaccinium macrocarpon*, *Citrus Aurantium Dulcis*, and L-ergothioneine, which demonstrated twice daily application of this cream increased dermal thickness, decreased edema, and improved the cellulite grade ¹⁷. In another study, the daily application of retinol to treat cellulite influenced dermo-epidermal thickness and natural elasticity ¹⁸.

Detaching and reducing the size of fat deposits by Phytosonic, Lipocare, and other active ingredients enable the release of water in the deep dermis. Water released from the space between the adipocytes results in the thickening of the dermis layer. The lymphatic system may discharge this infiltrated water. The final mechanism that may increase dermis thickness is tissue proliferation due to mechanical stretching ¹⁹.

In this study, a comparable improvement in cellulite grade was detected by a blinded dermatologist on both treatment sides. This could be due to the massage protocol, as manual massage therapy is a partially effective independent treatment method for cellulite ²⁰.

A relative improvement trend was also observed in the thickness of subcutaneous fat and thigh circumference, though it was not statistically significant. Future studies with a larger sample size and longer duration of treatment may prove these effects.

Both volunteers and physicians reported an improvement in the orange peel appearance of the skin after applying the lotion. This can be explained by the role of active ingredients such as Intenslim, Lanachrys, and ginger extract. The lotion also

contained Keratoline, which could increase stratum corneum hydration and result in a smoother, more hydrated skin appearance.

Previous research on herbal anti-cellulite formulations indicated the unsuccessful effects of products derived from *Centella asiatica*, *Ruscus aculeatus*, and *Carica papaya* in treating cellulite. At the same time, other herbal ingredients like *Rosmarinus officinalis*, *Annona squamosa*, *Zanthoxylum americanum*, *Ginkgo biloba*, and red grapes (*Vitis vinifera*) are helpful in the reduction of cellulite symptoms ²⁰. Unfortunately, most clinical studies of herbal anti-cellulite cosmetics are based on a limited number of subjects and products containing caffeine or its derivatives, making it difficult to distinguish each herbal ingredient's role ²¹. Our results confirm that the Prime[®] anti-cellulite lotion with the mixture of mentioned botanical ingredients could be a suitable formula for patients with a constant diet and lifestyle.

Due to the complex pathogenesis of cellulite, its treatment using topical formulations may require more extended treatment periods, added physical activity, and additional massage therapy on the affected area. Previous studies reported that fat absorbance in the upper extremities and the trunk occurred rapidly, but regional fat loss in the legs did not occur effortlessly, which could be explained by variations in local adipose tissue metabolism ^{22,23}.

The main limitation of the current study is the small number of subjects, where increased efficacy might be seen in larger studies. In addition, the long-term efficacy was not evaluated.

CONCLUSION

The present study indicated that Prime[®] anti-cellulite lotion is a safe treatment after two months of topical application. Moreover, the increased dermis thickness indicated the relative efficacy of the herbal ingredients in reducing adipocytes, diminishing the orange peel appearance, and improving the skin. Our results depicted that using the combination of actives in anti-cellulite products could be beneficial for improving the sign of this cosmetic disorder with different mechanisms of action.

Authors' contributions

Saman Ahmad Nasrollahi and Alireza Firooz conceptualized the study. Zeynab Variji and Aniseh

Samadi developed the methodology. Somayeh Yadangi, Zeynab Varij, and Zahra Ghasemi performed the data analysis and conducted the investigation. Zahra Ghasemi and Aniseh Samadi prepared the original draft. Saman Ahmad Nasrollahi and Alireza Firooz did the final writing, review, and editing.

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