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A pilot study on the efficacy of a seaweed mud application in the treatment of cellulite

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Abstract

Background: Cellulite represents a common multi-factorial condition that affects nearly all women and is now recognized as a clinical condition associated with systemic factors and negative psychological effects. Several noninvasive and minimally invasive treatments were developed during the last few years, but limited evidence supports many of them due to lack of evidence, insufficient participants, and potential adverse effects.

Methods: This study aimed to evaluate the efficacy of a seaweed mud application in improving both the structure and function of tissues affected by cellulite. Sixty women with cellulite underwent 4-week applications of seaweed mud on the buttocks and thighs. The following assessments were performed at baseline and after the last treatment: photographic, clinical, and anthropometric evaluation; tests for elasticity and hydration; ultrasonography of cellulite nodules; and cellulite biopsies in the trochanteric region. Patient satisfaction was assessed using a 5-point Likert-scale questionnaire.

Results: The treatment resulted in a significant improvement in the severity of cellulite severity between the initial assessment and the 4-week follow-up, with enhanced structure, elasticity, and hydration of the affected tissues. Microscopic analysis of the cellulite biopsies revealed a significant restoration of dermal organization with induced collagen synthesis and reduced inflammation, edema, and lipid deposition following the 4-week seaweed mud applications. Additionally, the treatment led to a remarkable improvement in comfort and satisfaction as well as a reduction in body circumferences.

Conclusions: The cosmetic application of seaweed mud has proven to be a safe, non-invasive treatment for improving the tissue alterations characteristic of cellulite.

KEYWORDS
cellulite, cosmeceutical, non-invasive therapy, seaweed mud

1 | INTRODUCTION

Cellulite is a widely spread condition that affects between 80% and 90% of post-pubertal women and is also present in males.[1] Although previously regarded as a harmless skin condition primarily affecting aesthetics, cellulite is now recognized as a clinical condition associated with systemic factors and has been shown to cause negative psychological effects in patients.[2] The thighs, hips, and buttocks are the most common areas affected by cellulite, which is characterized by the presence of skin dimpling. The complete understanding of cellulite's physiology is yet to be fully clarified. However, several experimental evidence suggest that cellulite is a complex process involving multiple factors that may have an impact, to varying degrees, on cellular and non-cellular components of the skin and subcutaneous tissues in an asynchronous, chronic, and unpredictable manner, like a chronic progressive degenerative condition.[3,4] Indeed, the etiology and exacerbation of cellulite have been associated with chronic inflammation, suggesting its significance as a risk factor. Notably, it has been shown that cellulite can be accompanied by chronic inflammation that alters local tissue, causing skin atrophy and adipolysis.[5,6] In the pathogenesis of cellulite, mesenchymal stem cells (MSCs), characterized by their abundance of estrogen receptors, may play a pivotal role. These cells are mobilized in response to various stressors, including oxidative stress, extracellular matrix remodeling, and the generation of reactive oxygen species (ROS). The interplay between chronic inflammation and oxidative stress is further substantiated by the observation that the absence of antioxidant defense mechanisms is associated with an enhanced inflammatory phenotype. Conversely, the upregulation of ROS-producing enzymes also contributes to the inflammatory state.[7]

There have been studies on various noninvasive techniques, including massage, cosmeceuticals, and laser therapy, as well as minimally invasive techniques such as subcision and collagenase injection, to improve cellulite.[2,8] However, limited evidence supports many of these treatments due to the lack of a validated and convenient tool for evaluating cellulite severity or an insufficient number of study participants. Additionally, some of these procedures may lead to adverse effects including scars and keloid formation.

Among non-invasive techniques, cosmetic and/or cosmeceutical treatments are commonly employed for cellulite reduction. Cosmeceuticals are topical products that occupy a niche between cosmetics and pharmaceuticals, aiming to improve both the health and aesthetics of the skin.[9,10] Their primary challenge is to transport the active ingredients to their target in sufficient concentration to have a therapeutic effect.[11] Over-the-counter gels or creams, frequently utilized to mitigate cellulite, typically comprise caffeine, methylxanthines, retinol, ascorbic acid, alpha-bisabolol, papaya extract, other plant extracts, vegetable oils, urea, and squalene. Seaweed, in particular, is recognized as a valuable source of functional foods and innovative cosmeceutical compounds. Consequently, research over the past two decades has extensively explored the bioactive effects of seaweeds on skin health. Seaweeds, especially brown seaweeds, produce both primary and secondary metabolites, including polysaccharides, proteins, polyphenols, carotenoids, and phytosterols, that demonstrate different beneficial activities on biological systems. Therefore, these bioactive constituents have primarily shown anti-inflammatory and antioxidant properties that may impact cellulite pathogenesis, such as the suppression of ROS, which are critical mediators of inflammatory processes; the regulation, predominantly inhibition, of the proinflammatory nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) signaling pathway and proinflammatory molecules, including tumor necrosis factor (TNF)-α, interleukin (IL)-1β, and IL-6; the stimulation of the expression of anti-inflammatory molecules such as IL-10; modulation of adaptive immune responses; and reduction of edema.[12–18]

However, very few studies have explored the effect of seaweeds on cellulite.[19] Accordingly, the present study aimed to assess the effectiveness and tolerability of a cosmetic mud containing seaweed in improving tissue alterations characteristic of cellulite, using both clinical and instrumental measurements over a 4-week treatment period.

2 | MATERIALS AND METHODS

2.1 | Patients' population

A group of 60 female patients, ranging in age from 32 to 71 years, participated in this clinical study. The participants were selected from 92 female patients. The inclusion criteria included being at least 18 years of age, female, and providing consent to participate in the study. All enrolled patients had clinically detected cellulite on their gluteal and posterior thighs. Patients who had received any aesthetic treatments within the 6 months before the study, those with a history or current diagnosis of heart, thyroid, or metabolic disorders, tumors, or immunosuppression, those with a body mass index (BMI) greater than 30, and pregnant or lactating patients were excluded from the study. All patients successfully attended all scheduled visits.

2.2 | Patient written informed consent and ethical approval

Each patient provided written informed consent before the study, which adhered to the principles outlined in the Declaration of Helsinki.

2.3 | Study protocol

Participants underwent application for 4 weeks (three applications of 45 minutes in the first week, two in the second and third weeks, and one in the fourth week) of a commercially available cosmetic seaweed mud (Fanghi d'alga GUAM® F.I.R., Lacote s.r.l., San Prospero, Modena, Italy) on the buttocks and posterior thighs. The seaweed mud is composed of over 15% dried brown seaweed (*Laminaria digitata*), 6% phyto-extracts of brown seaweed (*Laminaria digitata* and *Fucus vesiculosus*), clay, and black tourmaline for the remaining percentage. A minimal percentage of other extracts are included for their fragrance. One kilogram of seaweed mud was used per application. The product was stirred prior to use and applied with a gentle massage onto the designated treatment areas that were wrapped with transparent film, as reported in Figure 1. After 45 min, the seaweed mud was rinsed with fresh water. Before the initial application (baseline) and after the 4-week treatment period, morphometrics, dermatology, instrumentation analyses, and histological evaluations were conducted. Patient satisfaction was assessed using a 5-point Likert-scale questionnaire.

2.4 | Physical examination

The initial physical examination was carried out on each patient before the treatment with seaweed mud, as previously described.[20] The examination included measurements of weight, height, BMI, and various circumferences such as waist, belly, hips, upper thigh, and median thigh.

2.5 | Clinical and dermatological evaluation

The patients underwent a total body skin examination in a standing position with relaxed muscles. The examination assessed the following parameters: the presence of paresthesia, telangiectasias, varices, skin stretch marks, scars, positive ulnar fovea sign test, pain at the tissue pinch test, malleolar edema, and heaviness in the lower limbs. The color of the trochanteric region, which is commonly affected by cellulite, was also evaluated. The color could be unchanged, exhibit a yellowish-gray tone, or display skin pallor. Following the dermatological examination, the patient's skin hydration and elasticity levels were measured (SoftPlus, Callegari, Parma, Italy). Additionally, ultrasonography of the trochanteric region of the thighs was performed using the MyLab™ Gamma linear probe (Esaote Touch, Genova, Italy) with a frequency of 12 MHz. Each patient was evaluated at both the beginning and conclusion of the last treatment (4 weeks).

2.6 | Histological analysis

Local anesthesia was administered prior to performing a biopsy on the skin affected by cellulite. The biopsies were obtained from the trochanteric region using a specific biopsy punch (Kai Medical, Oyama, Japan), with a diameter of 4.0 mm and a length of 13.0 mm. Sample preparation and histological analysis with hematoxylin and eosin (H&E) staining were performed as previously described.[21] Furthermore, two distinct H&E-stained fields at 40× magnification (1 mm^2) were selected for the inflammatory cell count for each patient.

2.7 | Statistical analysis

GraphPad Prism software (version 8.0; GraphPad Software, San Diego, CA, USA) was utilized for statistical analyses. The normality of the data distribution was evaluated using the Shapiro–Wilk normality test. For normally distributed data, comparisons were made using the paired parametric Student's *t*-test. In cases where data did not follow a normal distribution, the Wilcoxon matched-pairs signed rank test (two-tailed) was used. Results are presented as the arithmetic mean ± standard deviation (SD). A significance level of $p < 0.05$ was considered to indicate statistical significance.

3 | RESULTS

3.1 | Physical and anthropometric examination

A total of 60 female patients (mean age of 50.20 ± 11.15 years) were included in the study (Table 1). In detail, the age distribution of the patients was as follows: 15 patients between 30 and 39 years, 18

FIGURE 1 (A) Frontal and (B) posterior view of a patient during the treatment with seaweed mud.

patients between 40 and 49 years, 16 patients between 50 and 59 years, and 11 patients over 60 years. Among these, 22 women were in menopause (36.7%) and 39 had a history of at least a pregnancy to term (65.0%). The average height was 162.9 ± 5.4 cm, the mean weight was 67.7 ± 6.8 kg, and the average BMI was 25,1 ± 2.1 kg/m^2. As part of the physical examination, the circumferences of the waist, belly, hips, and upper and median thighs of all patients were evaluated at baseline and after 4 weeks of treatment. A significant reduction of all circumferences analyzed was observed (Figure 2). No adverse events were reported during or following the treatment period, including interference with normal thyroid activity. No reddening, swelling, or irritation was observed around treatment areas at the time of testing. Overall, patients reported experiencing only a slight, non-painful tingling sensation during the treatment. A 5-point Likert scale questionnaire assessed subjective satisfaction. With a score of 3.68 ± 0.6, patients expressed satisfaction with the results of the treatment. Details and statistics of all anthropometric evaluations are reported in Table 2.

TABLE 1 Characteristics of female patients analyzed in this study.

N° of female patients	60
Smoking habits *n* (%)	9 (15.0)
Pregnancy to term history *n* (%)	39 (65.0)
Menopause *n* (%)	22 (36.7)
Regular physical activity (%)	43 (71.7)
Height (cm)	162.9 ± 5.4
Weight (kg)	67.7 ± 6.8
BMI (kg/m^2)	25.1 ± 2.1

3.2 | Clinical and dermatological evaluation

In the skin evaluation, it was discovered that 54 patients (90%) exhibited noticeable orange peel skin, while six patients (10%) showed visible alterations following the pinch test. Among the participants, 15 patients (25%) experienced pain during the pinch sensation. Upon examining the affected anatomical sites for cellulite, three patients presented with pale skin, and four patients exhibited a yellowish-gray tone. Additionally, one of these patients also suffered from severe venous insufficiency. Furthermore, skin hydration and elasticity levels were significantly higher after the 4-week treatment with seaweed mud, indicating an overall improvement in tissue properties (Table 3).

Ultrasound observations confirmed that cellulite lesions exhibited a rich echo pattern in the epidermis and dermis, while the adipose protrusions in the subcutis displayed a low echo pattern and were scattered with hyperechoic connective shoots.[21] Before the treatment, the common pattern was characterized by an increased thickness of the skin and subcutaneous layers with a low-echo signal, the presence of inflammation, and a reduction in vascularization. Additionally, low-echo nodules and fascial bands were observed in most patients. The predominant feature in all patients was the obliquely oriented fascial band, which was observed in great detail. Concurrently, a difference in band orientation was detected in most patients (Figure 3A). Results demonstrated that, compared with baseline, the 4-week treatment with seaweed mud resulted in a significant decrease in adipose tissue thickness, improvement of vascularization, and re-organization of the cutaneous and sub-cutaneous architecture due to the induction of collagen synthesis (Figure 3B). Moreover, a clear correlation was found between the severity of cellulite and the increased presence of adipose protrusions in the

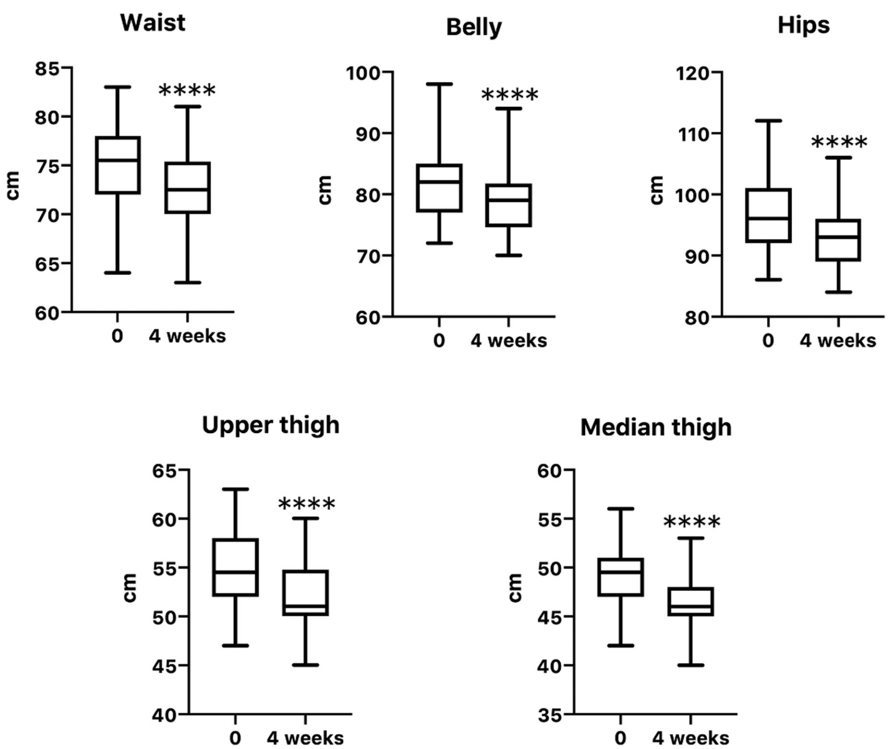


FIGURE 2 Differences of circumferences of waist, belly, hips, and upper and median thigh at baseline and after 4 weeks of treatment with seaweed mud; **** = $p < 0,0001$ (GraphPad Prism software v.8).

TABLE 2 Detailed statistics (GraphPad Prism software v.8) about differences of circumferences of waist, belly, hips, and upper and median thigh at baseline and after 4 weeks of treatment with seaweed mud.

Circumferences	Baseline (cm)	After 4 weeks treatments (cm)	Difference between means (cm)	95% confidence interval	*p* Value
Waist	74.87 ± 4.36	72.76 ± 4.06	−2.11 ± 0.98	−2.361 to −1.855	<0.0001
Belly	81.82 ± 5.23	78.75 ± 4.65	−3.07 ± 1.08	−3.344 to −2.789	<0.0001
Hips	96.75 ± 5.67	92.95 ± 4.75	−3.80 ± 1.50	−4.187 to −3.413	<0.0001
Upper thigh	55.13 ± 3.72	52.20 ± 3.39	−2.93 ± 1.04	−3.202 to −2.665	<0.0001
Median thigh	49.17 ± 3.03	46.43 ± 2.73	−2.74 ± 1.33	−3.086 to −2.397	<0.0001

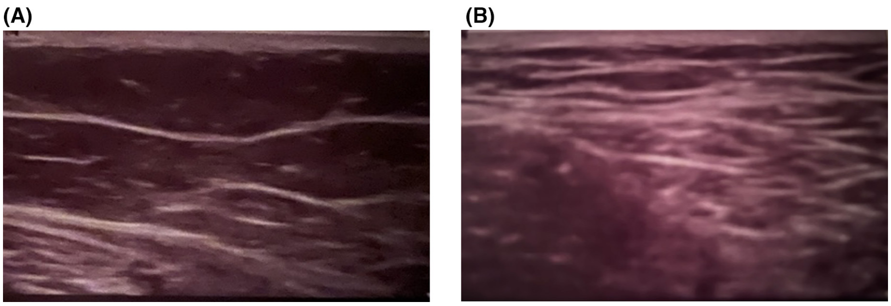
Note: Data are represented as the arithmetic mean ± SD.

TABLE 3 Skin hydration and elasticity parameters of the trochanteric region of the thigh at baseline and after 4-week treatment with seaweed mud (GraphPad Prism software v.8).

Parameters	Baseline	After 4 weeks treatments	Difference between means	95% confidence interval	*p* Value
Hydration (c.u.)	29.07 ± 7.26	45.97 ± 12.16	16.91 ± 5.64	15.451 to 18.362	<0.0001
Elasticity (c.u.)	33.74 ± 9.57	47.28 ± 13.26	13.54 ± 4.40	12.406 to 14.677	<0.0001

Note: Data are represented as the arithmetic mean ± SD.
Abbreviation: c.u., conventional unit.

FIGURE 3 Representative images of ultrasonography at baseline and after 4 weeks of treatment with seaweed mud.



ultrasound images. The significant reduction of low-echo subcutaneous micronodules after a 4-week treatment with seaweed mud suggests a reduction in the severity of cellulite (Figure 4).

3.3 | Histological analysis

Before treatment, histological analysis of stained slides at 10×, 20×, and 40× magnification revealed the presence of various histological features associated with cellulite in most patients. In the epidermis, peculiar changes in cell replication at the baseline and islands of keratinocyte hypertrophy at the stratum corneum were observed. The dermis exhibited alterations in the quality of hyaluronic acid and a disruption in the structural architecture of collagen and elastic fibers. Other characteristics of the dermis included chronic inflammation with reactive fibrosis, changes in microcirculation, the presence of edema in the reticular dermis, thickening of connective fibers, and adipocytes that appeared distinct in shape from subcutaneous adipocytes. The hypodermis displayed anisopoikilocytosis, fibrotic thickening of collagen surrounding the lobules, a concentric arrangement of adipose cells contributing to the formation of micronodules, and alterations in the microcirculation of arterioles and venules (Figure 5A–G).

After the 4-week treatment with seaweed mud, many of the peculiar histological features of cellulite disappeared, with an overall restoration of normal tissue architecture (Figure 5H–K). Histological analysis of cellulite biopsies showed a significant improvement in dermal organization with the induction of collagen synthesis, the structural architecture of the extracellular matrix, and microcirculation. In parallel, reduction in chronic inflammatory infiltrate, lipid deposition, reactive fibrosis, and edema were also observed.

In detail, pre-treatment tissues were characterized by a rich concentration of chronic inflammatory lymphocytes (35.89 ± 7.18 cells per mm^2) mainly localized around the vascular structures and the collagen fibers. These cells were significantly reduced and sometimes absent (6.55 ± 3.05 cells per mm^2, $p < 0.0001$) in the post-treatment histological samples, suggesting an inflammation-inhibiting effect. Rare histiocytes (<5 cells per mm^2) were identified with no significant differences between pre- and post-treatment samples. No accumulation of neutrophilic or eosinophilic granulocytes in pre- and post-treatment samples was detected, excluding tissue necrosis and allergic phenomena, respectively (Figure 5).

4 | DISCUSSION AND CONCLUSIONS

Seaweeds are recognized sources of important bioactive components such as polysaccharides (e.g., alginate, fucoidan), proteins (e.g., phycobiliproteins), polyphenols (e.g., phlorotannins), carotenoids

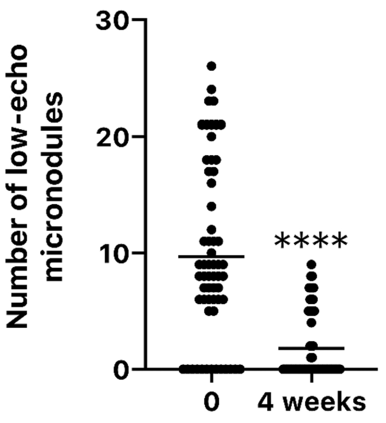


FIGURE 4 Differences in the number of low-echo nodules at the trochanteric region of the thigh at baseline (9.68 ± 7.54) and after 4 weeks of treatment with seaweed mud (1.80 ± 2.83); **** = $p < 0{,}0001$ (GraphPad Prism software (v.8).

(e.g., astaxanthin and fucoxanthin), phytosterols (fucosterol) and *n*-3 long-chain polyunsaturated fatty acids (e.g., eicosapentaenoic acid).[22] Numerous experimental systems have tested different seaweed species and their compounds for their impact on human health, and despite the wide range of systems used, a consistent picture emerges regarding their positive effects on various pathological processes. Most of them have the potential to counteract many pathological processes involved in cellulite, including chronic inflammatory state, ROS production, and release, alteration of extracellular matrix composition, and lipid deposition.[23–25]

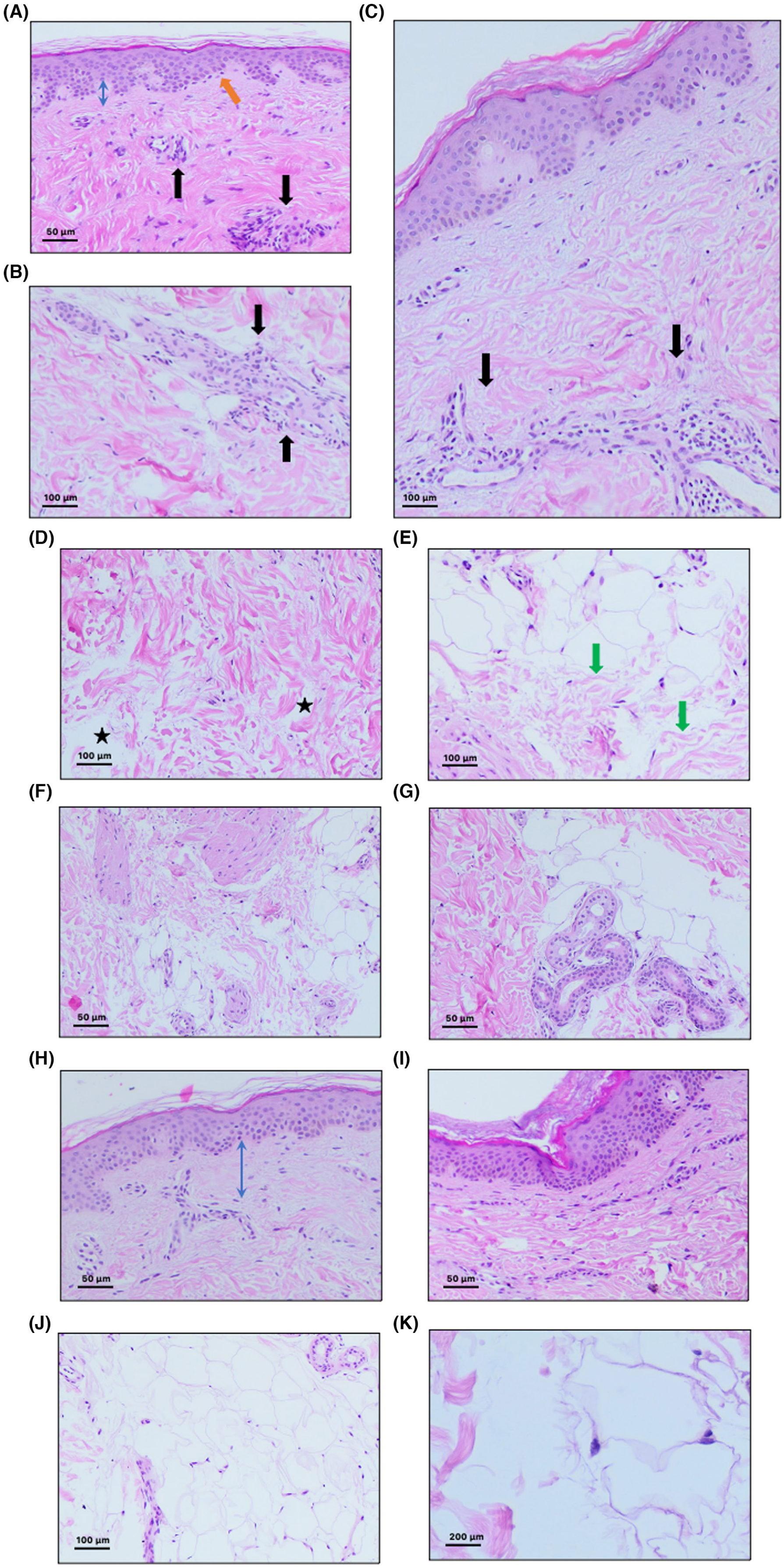
However, very few clinical trials have investigated the potential positive effects of seaweed on cellulite lesions. A recent study conducted by Al-Bader et al. examined the clinical effects of a cosmeceutical formulation containing red seaweed (*Furcellaria lumbricalis*) and brown seaweed (*Fucus vesiculosus*) on cellulite. The study followed a randomized, double-blind, placebo-controlled design and found that after 8 and 12 weeks, there was a significant improvement in cellulite as assessed by dermatologist grading compared to the placebo group. Additionally, ultrasound imaging revealed a significant reduction in fat thickness. The authors suggest that the combination of seaweed extracts, along with other ingredients, can effectively enhance changes in the skin affected by cellulite.[26]

The primary aim of this study was to evaluate the efficacy of a seaweed mud cosmetic application over 4 weeks in improving the structure and, consequently, the function of tissues affected by cellulite in 60 female patients. To our knowledge, this is the first study where seaweed mud efficacy against cellulite was not limited to slimming and aesthetic effects but was assessed with the comprehensive support of ultrasonography, histological, and instrumental analyses.[21] Overall, this study's results highlighted that this 4-week seaweed mud application may restore the structure and ameliorate the function of the skin affected by cellulite.

Indeed, several dysfunctions in tissues affected by cellulite are described in the literature, ranging from structural alterations to functional deficits.[4] As shown in the results, during cellulite, the general architecture of the subcutaneous tissue is impaired by several events, such as chronic inflammation, reactive fibrosis, edema, and alteration of the canonical extracellular matrix structure. The ultrasonography and the histological analysis of cellulite biopsies showed a significant improvement in the organization of the cutaneous and subcutaneous tissue after a 4-week treatment with seaweed mud. This improvement is characterized by increased collagen synthesis, restoration of the structural architecture of the extracellular matrix, improved microcirculation, reduced adipose tissue thickness, chronic inflammation, low-eco nodules, lipid deposition, reactive fibrosis, and edema. In addition, the elasticity and hydration of tissues affected by cellulite as well as body circumferences were significantly improved after the 4-week treatment with seaweed mud. Overall, these data support that this seaweed mud has anti-inflammatory properties, disrupts lipid accumulation, and promotes structural and functional tissue restoration against cellulite. Therefore, several anti-inflammatory effects of seaweed have been described so far. For example, brown seaweeds and their metabolites showed beneficial effects on different phases of acute and chronic inflammation, counteracting reactive oxygen radical production, the release of mediators, such as interleukin (IL)-1, IL-10, tumor necrosis factor (TNF), chemokines and arachidonic acid metabolites, and infiltration of leukocytes in tissue.[18] Moreover, other effects of seaweeds are described against lipid accumulation and extracellular matrix degeneration, two typical conditions of cellulite. For example, the seaweeds *F. lumbricalis* and *F. vesiculosus* can act in vitro improving lipolysis mechanisms and promoting pro-collagen I production, with effects on the surrounding extracellular matrix.[26] Fucoidan, a compound extracted from brown seaweed *F. vesiculosus*, has been found to have several effects on human adipocytes. It stimulates the secretion of lipoprotein lipase, which helps regulate triglyceride clearance.[27] It also inhibits the differentiation of adipocytes and reduces the expression of a gene involved in their function.[28]

Previous proteomic studies have shown that cellulite-affected adipose tissue experiences high levels of oxidative stress, which is linked to changes in its structure and function. Hence, when cellulite occurs, both the structure and function of the microcirculation are

FIGURE 5 Representative histological sections of regions affected by cellulite (A–G) before (A: H&E staining, 10×; B: H&E staining, 20×; C: H&E staining, 20×; D: H&E staining, 20×; E: H&E staining, 20×; F: H&E staining, 10×; G: H&E staining, 10×) and (H–K) after 4-week treatment with seaweed mud (H: H&E staining, 10×; I: H&E staining, 10×; J: H&E staining, 20×; K: H&E staining, 40×). (A) Orange arrows indicate islands of keratinocyte hypertrophy. (A–C) Black arrows show the lymphocytes aggregated around the vessels. (A, H) Blue arrows evidence superficial dermis below the epidermis. (D) Black stars indicate the large space of edema. (E) In the pre-treated dermis lobules of adipocytes separated by dense collagenous bands are detected (green arrows). Adipocytes exhibit an irregular shape. (H–K) In post-treated tissue, there are no evidence of inflammation or edema and thinner linear collagen fibers run parallel to each other intertwining in a thinner texture. The lobules are not visible and adipocytes exhibit slight pleomorphism.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altered simultaneously. This leads to a decrease in oxygen levels and an increase in oxidative stress. Mesenchymal stem cells may play a significant role in the development of cellulite, as they are recruited in response to stress triggers such as oxidative stress, matrix remodeling, and ROS production. This recruitment leads to a deep remodeling of the dermis and the activation of pro-inflammatory pathways.[29] Furthermore, there is a known connection between oxidative stress and fibrotic processes in the skin, where ROS can stimulate the growth of fibroblasts.[30] The significantly reduced reactive fibrosis in the cellulite lesions after treatments propose that this seaweed mud may counteract the increasing pro-oxidant condition during cellulite.[31] Similarly, it is reported in the literature that oral supplementation with *Fucus* spp., the same genus of brown seaweed present in this mud formulation, showed a distinctive antioxidant protective action.[32]

However, beyond the limited number of patients analyzed, the principal limitation of this study is the absence of a placebo-controlled trial. While this does not undermine the validity and significance of these results, it precludes a definitive conclusion that the observed positive effects on cellulite lesions can be solely attributed to the seaweed mud. It is conceivable that other components of the cosmetic formulation may contribute to these effects or that a synergistic action may occur when combined with seaweed mud.

In conclusion, the cosmetic seaweed mud tested in this pilot trial has proven to have potentially beneficial effects, resulting in a safe and non-invasive treatment for improving the biochemical and structural alterations typical of cellulite. Further studies are required to understand the molecular mechanisms promoted by this seaweed mud.

AUTHOR CONTRIBUTIONS

D.A., A.M., G.S., and A.S. designed the research study; D.A., A.G., E.L.I., L.R.B., and A.S. performed the research; D.A., A.M., and S.D. analyzed the data; A.M. and G.S. wrote the original draft; S.D., E.L.I., and G.S. reviewed and edited the final manuscript. All authors have read and agreed to the published version of the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

INFORMED CONSENT STATEMENT

Informed consent was obtained from all subjects involved in the study. Written informed consent has been obtained from the patients to publish this paper.

ETHICS STATEMENT

The study was performed in compliance with the Declaration of Helsinki and subsequent amendments. The study was approved by the institutional ethics committee, Comitato di Approvazione per la Ricerca sull'Uomo (C.A.R.U.), at the University of Verona, Italy (n. 2019-UNVRCLE-0175710).

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