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Tasmannia lanceolata leaf extract alleviates stretch mark appearance in a randomized, placebo-controlled clinical trial in women and stimulates extracellular matrix synthesis in ex vivo human skin explants

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Abstract

Background: The leaves of *Tasmannia lanceolata* mainly contain polygodial that is known to exhibit a range of biological functions including anti-inflammatory effects.

Aims: These studies aimed to assess the effects of *Tasmannia lanceolata* extract (TLE) on skin and more particularly on stretch marks in women.

Patients/Methods: A double-blind, randomized, placebo-controlled clinical study was carried out on 29 women, aged from 25 to 60 years, to investigate the effects of TLE on stabilized stretch marks. TLE and placebo products were topically applied daily for 8 weeks. Skin roughness and firmness of stretch marks were assessed by 2D and 3D photograph processing and analyses. Dermal density and thickness were evaluated using ultrasound, while stretch mark conditions (length, color, and depth) were determined by clinical scoring. Matricial proteins (pro-collagen I and elastin) and pro-matricial factors, like TGF-β concentrations, were quantified from cultures of human skin explants presenting stretch marks, treated with TLE or vehicle control.

Results: Skin roughness of stretch marks was significantly reduced in the TLE group after 8 weeks of treatment. Skin firmness of stretch marks was significantly increased in the TLE group after 4 weeks of treatment, and this improved effect was maintained until the end of the study. Dermal density and thickness were significantly increased in the TLE group compared to the placebo group. Furthermore, TLE restored the dermal condition of the stretch mark skin, up to normal skin levels. In addition, pro-collagen I and elastin concentrations were found to be higher in the TLE-treated stretch mark skin explants compared to the untreated ones, associated with higher quantities of TGF-β production.

Conclusion: These results revealed that TLE could help improve the aspect of stabilized stretch marks in women by restoring the matricial environment.

KEYWORDS

extracellular matrix, human skin explants, in vivo study, skin physiology/structure, stretch marks, *Tasmannia lanceolata*

Emmanuelle Gaillard and Sylvie Boisnic equally contributed to this study.

1 | INTRODUCTION

Stretch marks, also known as striae distensae (SD), are common, permanent, and visible cutaneous lesions, which appear mainly on the abdomen and the lower back, as well as, on the breasts, the buttocks, and the thighs.[1] Although SD do not cause any significant medical problems, they can affect self-esteem and cause distress for people affected by them, primarily due to their unaesthetic aspect. SD are characterized by linear bands of different lengths, with certain roughness and different pigmentations. There are two clinically and histopathologically distinct forms of SD: the initial erythematous striae rubrae (SR) which appear during the acute stage, and then the wrinkled and hypopigmented striae albae (SA) which become manifest during the chronic stage,[2,3] the latter being considered as the stabilized form.

The apparition of SD is known to be multifactorial and includes pregnancy, puberty/adolescence, any sudden weight gain and tissue expansion, genetic predisposition, and skin types.[4] Stretch marks result from the mechanical stress of the skin and of hormonal variations which are highly prevalent in pregnant women, where between 55% and 90% of women have reportedly developed them.[5] Usually, stretch marks are thought to occur when the skin stretches faster than its capacity to repair and to produce extracellular matrix components, leading to reduced strength and elasticity of the skin. At the cellular level, it has been suggested that initially, there is a local development of inflammation with a recruitment of immune cells, mainly mast cells and macrophages, followed by a disruption of the dermal connective tissue framework. The latter would mainly be due to excessive elastolysis of the elastic fibers[6,7] along with decreased expression of collagen and fibronectin in dermal fibroblasts under the influence of the matrix metalloproteinases. Indeed, numerous studies confirm that fibroblasts play a key role in the pathogenesis of stretch marks because they progressively become functionally dormant and present altered contractile forces in SD areas.[8,9] Furthermore, the transforming growth factor-β (TGF-ß), an activator of fibroblasts and type 1 collagen synthesis, is reported to be downregulated in stretch marks.[10] A study comparing human dermal fibroblasts isolated from an SD lesion to those from the adjacent normal skin revealed a generalized altered composition of the extracellular matrix and notably a huge decrease in collagen type I and TGF-β1 protein levels, in parallel to overexpression of certain inflammatory markers such as TNF-α.[10] Because of their high prevalence and their psychosocial impact, there is a growing demand for an effective treatment for SD. So far, a large and diversified panel of topical treatments is offered to prevent or correct SD.[11] However, only a few have been able to demonstrate sufficient clinical evidence associated with mechanistic explanations.[12]

Tasmannia lanceolata (*T. lanceolata*) is endemic to southeastern Australia and Tasmania where it grows wildly.[13] Commonly known as Tasmanian pepper, it is traditionally used as a flavoring agent: The leaves are used as a herb and the berries as spice. *T. lanceolata* has also been used for its medicinal properties to treat stomach disorders and as an emetic, as well as general usage as a tonic.[14] Additionally, curative effects on skin disorders have also been reported.[14] Moreover, the leaves of *T lanceolata* contain polygodial, a sesquiterpene dialdehyde, present in levels varying from 0.1% to 3% w/w[14,15] and exhibiting a range of biological functions, including antifungal,[16,17] antibacterial,[18] and anti-inflammatory actions.[19] In addition, Indigenous Australians have been using the extract for the therapy of skin conditions. Consequently, we decided that TLE is an ideal candidate for studying the amelioration of skin disorders, such as stretch marks.

Thus, the aim of these studies was to assess the clinical efficacy of a topical application of*T. lanceolata* leaf extract (TLE) on the skin and more specifically on stabilized stretch marks of women, in a randomized and double-blind placebo-controlled study and to define its mode of action on an ex vivo model of human stretch-marked skin.

2 | MATERIALS AND METHODS

2.1 | In vivo study

2.1.1 | Study design

A monocentric double-blind, randomized, placebo-controlled trial was performed on 30 healthy women for 8 weeks (W). This study was carried out according to Good Clinical Practices (CPMP, July 1996), the law of December 20, 1988 (n° 2004-806 of August 9, 2004), and the Declaration of Helsinki (1964).

2.1.2 | Population studied

Thirty healthy women aged 20 to 65 years (y) were recruited between September and December 2018 and randomly assigned to two groups of 15; one group received the *Tasmannia lanceolata* leaf Extract (TLE) product, and the other group received the placebo, for 8 weeks of topical application. One subject in the placebo group dropped out of the study by missing her last study visit and thus did not complete her participation. Hence, the analyses were performed on 29 subjects with a mean age of 47.0 ± 10.2 years and a mean body mass index (BMI) of 26.9 ± 7.0 kg/m^2 (Table 1). Subjects included in the study presented with non-inflammatory and non-pigmented stretch marks of more than 6 months after their appearance, with hollow lesions measuring <1 cm wide. Exclusion criteria were unhealthy subjects, and dermatological or connective tissue pathologies. Additional exclusion criteria were pregnant and breastfeeding women and those with recent weight alterations. Subjects were asked to maintain their dietary and cosmetic habits throughout the study.

2.1.3 | Products tested

TLE was obtained according to a patented manufacturing process (Patent WO2019/197173). Briefly, the leaves of *T. lanceolata* were

collected and dried in northern Tasmania. The dried leaves were ground, and the extract was obtained through a process of extraction using supercritical CO_2 at a pressure of between 150 and 285 bars and a temperature of between 40 and 50°C. TLE was then obtained after standardization of polygodial levels (0.3%-0.8% of total extract) with Miglyol®, a mixture of medium-chain triglycerides and in compliance with the regulatory limit content (below 100 ppm) of methyl eugenol.

Randomly assigned subjects were instructed, in a double-blind procedure, to apply the oil topically, containing either 2% of TLE or the placebo (0% TLE), twice daily for 8 weeks. The compositions of the tested products are detailed in Table 2.

2.1.4 | Skin roughness assessment by photography and analysis

At the beginning of the study, a single stretch mark was identified and selected for each subject and this same stretch mark was followed up and evaluated throughout the study.

For each subject, two- and three- dimensional photographs of the selected stretch mark area were taken with 3D imaging systems for skin macro- and microstructure analyses (LifeViz Mini® and LifeViz Micro®—QuantifiCare), before and after treatment to observe the evolution of the stretch mark.

To evaluate the smoothing effect, the difference of the measurements of roughness between W0 and W4 or W8 was calculated. The reduction between these two measurements reflected the smoothing effect of the product.

TABLE 1 Demographic and clinical data of study groups at W0

	TLE group (n = 15)	Placebo group (n = 14)
Age (years)	48.1 ± 11.1	45.9 ± 9.6
BMI (kg/m^2)	25.1 ± 3.8	28.6 ± 8.8
SD in belly	46.6%	42.8%
SD in hips	46.6%	28.6%
SD in thighs	33.3%	35.7%
Pregnancy originated	60.0%	78.5%
Weight variation originated	40.0%	21.5%

Note: For the TLE and the placebo groups, age and body mass index (BMI) are shown at W0 before treatment and expressed as means ± SD (standard deviation). The distribution of SD in the body was expressed as percentage (%) of total bodily SD areas in each group.

2.1.5 | Skin elasticity and skin firmness determination

The cutometer evaluation of skin elasticity and other biomechanical parameters of the skin were carried out as described previously. The measurement was based on the resistance of skin to suction, using a Cutometer (Dual MPA 580, Courage + Khazaka Electronics GmbH). The resistance of the skin to negative pressure (firmness) and its ability to return to its original position (elasticity) were displayed as curves in real time during the measurement. R0 corresponds to passive behavior of the skin to force, that is, its firmness. When skin firmness increases, the R0 score decreases. R5 reflects net elasticity, and the closer the value is to 1 the more elastic the skin is.

2.1.6 | Measurement of dermal density and thickness by ultrasound

Striae distensae were characterized by a lower dermal density than normal skin.[3] Echography or ultrasound scanning is a well-established technique for measuring skin thickness based on the reflection of ultrasounds on tissues and the emission of an "echo" signal that is then translated into an anatomical image of the area being explored. The instrument used here was an ultrasound equipment (DermaScan® C USB High Frequency Skin Ultrasound, Cortex Technology), with a 20-Mhz frequency 2D probe that provided images that were 12.1 mm wide and 13 mm deep. A single representative image was analyzed with Advanced Control software. The difference in density and thickness was measured between W4-W0 and W8-W0. The normal skin thickness of each subject was also measured and compared to the thickness of their stretch mark area.

2.1.7 | Assessment of product efficiency and tolerance by a dermatologist

The dermatologist scored the global effectiveness of the product.

Dermatological scores ranged from 0 to 3:

- stretch mark depth (0 for a smooth skin to 3 for deep stretch marks);
- stretch mark coloration (0 for identical to skin color to 3 for a pearly white color).

TABLE 2 Composition of TLE and placebo oil topic products

Ingredients	*Tasmannia lanceolata* (Tasmanian pepper) leaf extract (%)	Caprylic/capric triglyceride (%)	Tocopherol and *Helianthus annuus* seed oil (%)	*Corylus avellana* seed oil (%)
TLE product	2.0	20.0	0.3	77.7
Placebo	0.0	20.0	0.3	79.7

Note: The ingredients used for making *Tasmannia lanceolata leaf* extract and for placebo are indicated in percentage.

Moreover, self-assessment using a questionnaire was also carried out by each subject.

Product acceptance and tolerance were evaluated by the dermatologist, *via* the collection and documentation of the nature and frequency of adverse events if any.

2.2 | Ex vivo study

2.2.1 | Biological sample preparation

Five human skin fragments presenting stretch marks were obtained from healthy Caucasian women undergoing abdominoplasty (28, 34, 38, 40, and 57 years; mean age: 39.4 ± 10.8 years). Informed consent was obtained from each donor prior to study initiation. Skin sample preparations and cultures were performed according to the procedure previously described.[20] Briefly, skin samples were cut into 1-cm^2 full-thickness pieces and washed three times with an antibiotic solution. Subcutaneous fat and lower dermis were mechanically removed using a surgical scalpel. Skin samples were then put with the epithelium uppermost at an air/liquid interface on culture inserts (Costar, Poly Labo Paul Block) placed in a 12-well plate. A culture medium especially adapted for survival conditions (Dulbecco's minimal essential medium [Gibco BRL]) containing antibiotics and fetal calf serum was added to the wells. There was a slow diffusion of medium between the two compartments through a porous membrane (12 μm). The skin fragments were maintained in survival conditions for 12 days at 37°C in air/CO_2 atmosphere. The medium was renewed three times per week. At D12, the skin fragments were frozen, and the culture media were stored for biochemical assays.

2.2.2 | Topical application of TLE

TLE diluted at 2% in PBS (phosphate-buffered saline) or PBS alone was applied topically on skin explants in duplicate, every day at 15 μL per cm^2 for 12 days.

Two conditions were compared:

- Control skin treated with PBS only.
- TLE skin treated with 2% TLE in PBS.

2.2.3 | Measurement of TGF-ß1 concentration

TGF-ß1 concentration (in pg/mL) in the culture media of the skin explants was determined by immunoassay (Quantikine ELISA Kit, BioTechne) according to the manufacturer's recommendations.

2.2.4 | Measurement of pro-collagen I concentration

Skin fragments were first homogenized in a buffer solution containing Tris-HCl 100 mmol/L, NaCl 100 mmol/L, and Triton X-100 0.1%, at pH 7.4. The concentration of pro-collagen type I (in ng/mL) was evaluated using an ELISA assay kit (Human Pro-Collagen I alpha 1, DuoSet ELISA Kit, BioTechne) of the lysates according to the manufacturer's recommendations. The final results were normalized in ng/mg of skin tissue.

2.2.5 | Measurement of elastin concentration

Insoluble elastin was extracted from skin fragments with oxalic acid at 0.25 mol/L at 100°C. Soluble alpha-elastin polypeptides fragments were obtained. After centrifugation to remove undigested tissue, the soluble elastin was detected and quantified using the specific binding of the dye reagent (5,10,15,20-tetraphenyl-21 H, 23 H-porphine tetrasulfonate, TPPS). The elastin-dye complex was measured by a spectrocolorimetric assay and detected at 513 nm (Fastin Elastin Assay Kit, Interchim). The results were expressed in μg elastin per mg of skin.

2.3 | Statistical analysis

All statistical analyses were performed with the StatView software.

In the clinical study, in each group, sample results were analyzed with the Shapiro-Wilk normality test. If a normal distribution was verified, a paired *t* test was performed; otherwise, a Wilcoxon test was used. Comparisons between the groups were performed on the differences of values at Wx and W0 and used the paired *t* test when a normal distribution was verified; otherwise, a Mann-Whitney test was used. For *ex vivo* studies, results obtained in duplicates for each condition were analyzed with a bilateral Wilcoxon test, comparing treatment versus control conditions. Differences were considered statistically significant when the *P*-value was $< .05$.

3 | RESULTS

3.1 | In vivo study

The main stretch mark areas were the belly for 46.6% and 42.8% of the subjects in the TLE group and the placebo group, respectively, followed by the hips and thighs (Table 1). Stretch mark causes were pregnancy, for 60% and 78.5% of the subjects in the TLE group and the placebo group, respectively, and weight variations for the rest (Table 1).

The demographic and anthropometric data, as well as the characteristics of the stretch mark areas at baseline, were comparable between the two groups (Table 1).

3.2 | Clinical assessment

3.2.1 | Skin roughness in stretch mark

Skin roughness tended to decrease in both groups after 4 weeks of both topical treatments.

After 8 weeks, only the TLE treatment significantly reduced the skin roughness of the stretch marks by 0.021 mm (−13.8%) compared to W0 ($P = .0099$) whereas no significant modulation in the placebo group (Figure 1A) occurred. However, the variations from baseline (W4-W0 and W8-W0) were not significant between the two groups (Figure 1B).

3.2.2 | Skin firmness and elasticity of stretch marks

Skin firmness (R0) and skin elasticity (R5) on stretch marks were evaluated with a Cutometer. With this apparatus, when skin firmness increases, the R0 score decreases and measurements of R5 reflect the net skin elasticity, and the closer the value is to 1 (100%), the more elastic the skin is.

R0 score decreased only in the TLE group (Figure 2A), revealing that skin firmness was significantly improved at W4 and at W8 ($P < .05$) but the differences between the two groups were not significant (Figure 2B). Skin elasticity (R5) was neither significantly modulated with the TLE nor with the placebo (data not shown).

3.2.3 | Dermal density of stretch marks

After 4 and 8 weeks of treatment with TLE, there was a significant increase of dermal density in the stretch marks, with +8.2% ($P = .0016$) and +10.5% ($P = .0005$), respectively, whereas there was no modification with the placebo (Figures 3A and 5A). The differences in density between the two groups were significant only with the TLE treatment (Figure 3B) at W4 ($P = .0325$) and at W8 ($P = .0028$). Interestingly, the comparison of the evolution of dermal density in stretch mark skin with that of normal skin showed that from week 4 of the treatment, TLE improved dermal density to reach normal skin levels (Figure 3C).

3.2.4 | Dermal thickness of stretch marks

Both TLE and the placebo treatments significantly increased dermal thickness (Figures 4A and 5A). In comparison with W0, the placebo increased dermal thickness by 0.15 μm at W4 ($P = 0{,}001$) and by 0.18 μm at W8 ($P = .0001$), while TLE enhanced it by 0.22 μm at W4 ($P = .0031$) and 0.42 μm at W8 ($P = .0012$). After 8 weeks of treatment with TLE, there was a significant increase in the dermal thickness of stretch marks versus the placebo ($P = .026$) (Figure 4B). However, comparison of the evolution of dermal thickness of stretch marks with that of normal skin revealed that after 8 weeks of treatment, TLE increased dermal thickness at a slightly higher level than normal skin (Figure 4C).

3.2.5 | Global assessment by the dermatologist

After 4 and 8 weeks of treatment with the TLE, the dermatological score of stretch mark depth was reduced while it was also reduced with the placebo without any significant differences versus placebo.

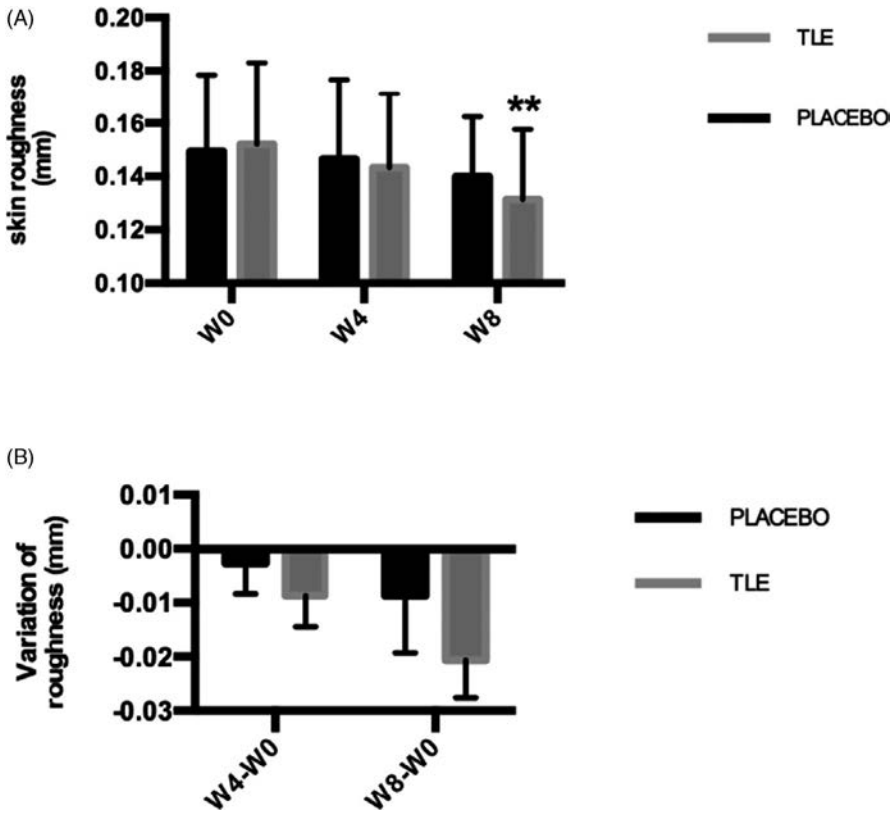

FIGURE 1 Skin roughness evaluation with LifeViz Micro®. A, Evolution of skin roughness on stretch marks in each group of subjects throughout the 8-wk study: Results are expressed as means ± SEM of skin roughness in mm. B, Comparative analysis of skin roughness variation during the treatment period, with 2% TLE or the placebo, compared to W0 (W4-W0; W8-W0): Results are expressed as means ± SEM of variation in skin roughness for each group. $^{**}P < .01$

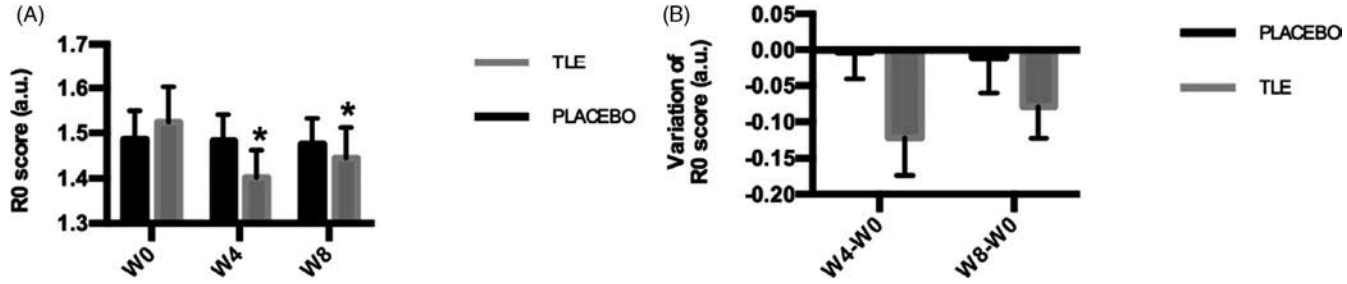

FIGURE 2 Skin firmness evaluation by Monaderm cutometer. When the R0 score decreases, skin firmness increases. A, Evolution of R0 scores from a cutometer in each group, throughout the 8 wk of the study: Results are expressed as means ± SEM (arbitrary unit, a.u.). B, Comparative analysis of the variation in R0 score during the treatment period, with 2% TLE or the placebo, compared to W0 (W4-W0; W8-W0): Results are expressed as means ± SEM of change in R0 score for each group. *$P < .05$

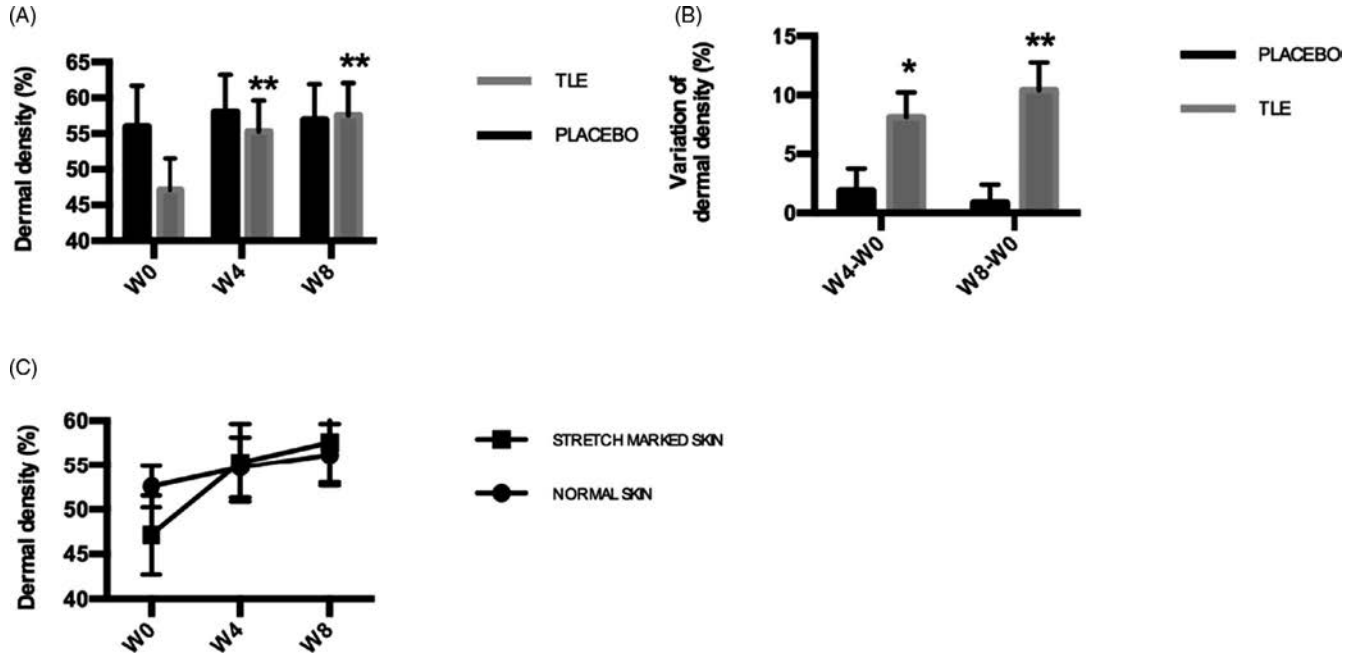

FIGURE 3 Dermal density evaluation by echography. A, Evolution of dermal density in each group of subjects, throughout the 8 wk of study: Results are expressed as means ± SEM of dermal density (% of echogenicity). B, Comparative analysis of dermal density variation during the treatment period, with 2% TLE or the placebo, compared to W0 (W4-W0; W8-W0): Results are expressed as means ± SEM of change in dermal density for each group. C, Evolution of dermal density in TLE group when comparing stretch-marked skin to normal skin throughout the 8-wk study: Results are expressed as means ± SEM of dermal density (% of echogenicity). *$P < .05$; **$P < .01$

After 8 weeks, the dermatological score of stretch mark coloration was significantly reduced in TLE compared to W0 (Table 3). Tolerance was considered as excellent. No adverse events linked to the product or placebo were reported during the clinical study.

3.2.6 | Self-assessment of stretch marks

A significant reduction of the appearance of stretch marks was observed in the TLE group after only 4 weeks of topical application, whereas no visible effects were reported in the placebo group (data not shown). Furthermore, after 8 weeks of treatment, 80% of the subjects in the TLE group and 64.3% of the placebo group demonstrated apparent reductions in their stretch marks. Moreover, stretch marks were less deep for 80% of the subjects in the TLE group versus 57.1% in the placebo group (Figure 5B).

3.3 | Ex vivo assessment

3.3.1 | Measurement of TGF-β1 concentration

The treatment of human stretch mark skin fragments with TLE significantly stimulated the concentration of TGF-ß1 in the medium from 29.3 to 59.7 pg/mL compared to the control treatment ($P = .0059$) (Figure 6A).

3.3.2 | Measurement of pro-collagen I concentration

Treatment with TLE induced a significant increase in the concentrations of pro-collagen I to 17.35 ng/mg, as opposed to the control explant at 13.29 ng/mg ($P = .0059$) (Figure 6B).

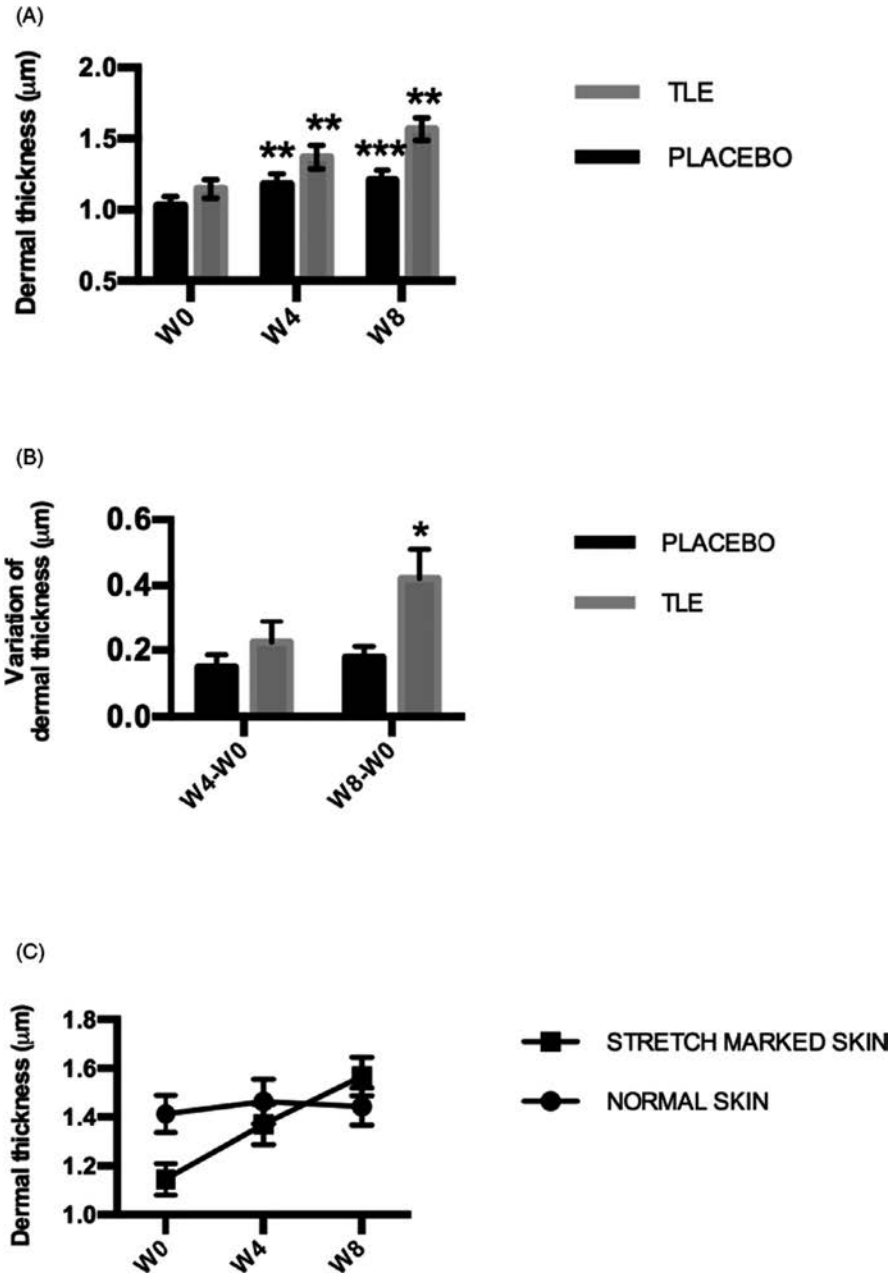

FIGURE 4 Dermal thickness evaluation by echography. A, Evolution of dermal thickness in each group of subjects throughout the 8-wk study: Results are expressed as means ± SEM of dermal thickness in µm. B, Comparative analysis of dermal thickness variation during the treatment period, with 2% TLE or the placebo, compared to W0 (W4-W0; W8-W0): Results are expressed as means ± SEM of change in dermal thickness for each group. C, Evolution of dermal thickness in the TLE group, comparing stretch-marked skin to normal skin throughout the 8 wk of the study: Results are expressed as means ± SEM of dermal density (% of echogenicity). *$P < .05$; **$P < .01$; ***$P < .001$

3.3.3 | Measurement of elastin concentration

The concentration of elastin in the tissue explants rose from 14.6 µg/mg in the controls to 16.2 µg/mg for the TLE-treated skin. ($P = .0039$) (Figure 6C).

4 | DISCUSSION

Nowadays, there is a marked contrast between the high prevalence of *stria distensae* (SD), commonly known as stretch marks, and the lack of truly effective products for the prevention or treatment of this skin defect. The studies reviewed by Brennan et al[21] and Ud-Din et al[12] concluded the lack of high-quality data supporting the use of topical products in the prevention or treatment of stretch marks. In fact, very few clinical studies present a robust and rigorous methodology and demonstrate clear benefits of topical preparations in eradicating or improving the appearance of SD. More recently, a study on a plant cosmetic oil, consisting mainly of linoleic and oleic acids from Safflower and olive oils, revealed its potential benefits of improving the aspect of SD, in a panel of 80 volunteers presenting nonhypertrophic scars or stretch marks after 8 weeks of treatment.[22] Similarly, daily applications for 6 weeks of a plant cream containing *P. granatum* seed oil and *C. lechleri* resin extracts showed an increase in dermal thickness, hydration, and elasticity on both healthy skin and stretch mark areas in 20 volunteers.[23] Even though clinical benefits of the reduction of stretch marks were observed in these studies, the mechanisms by which these topical preparations can improve their appearance were not completely described. Further studies, using better, more up-to-date methodologies are

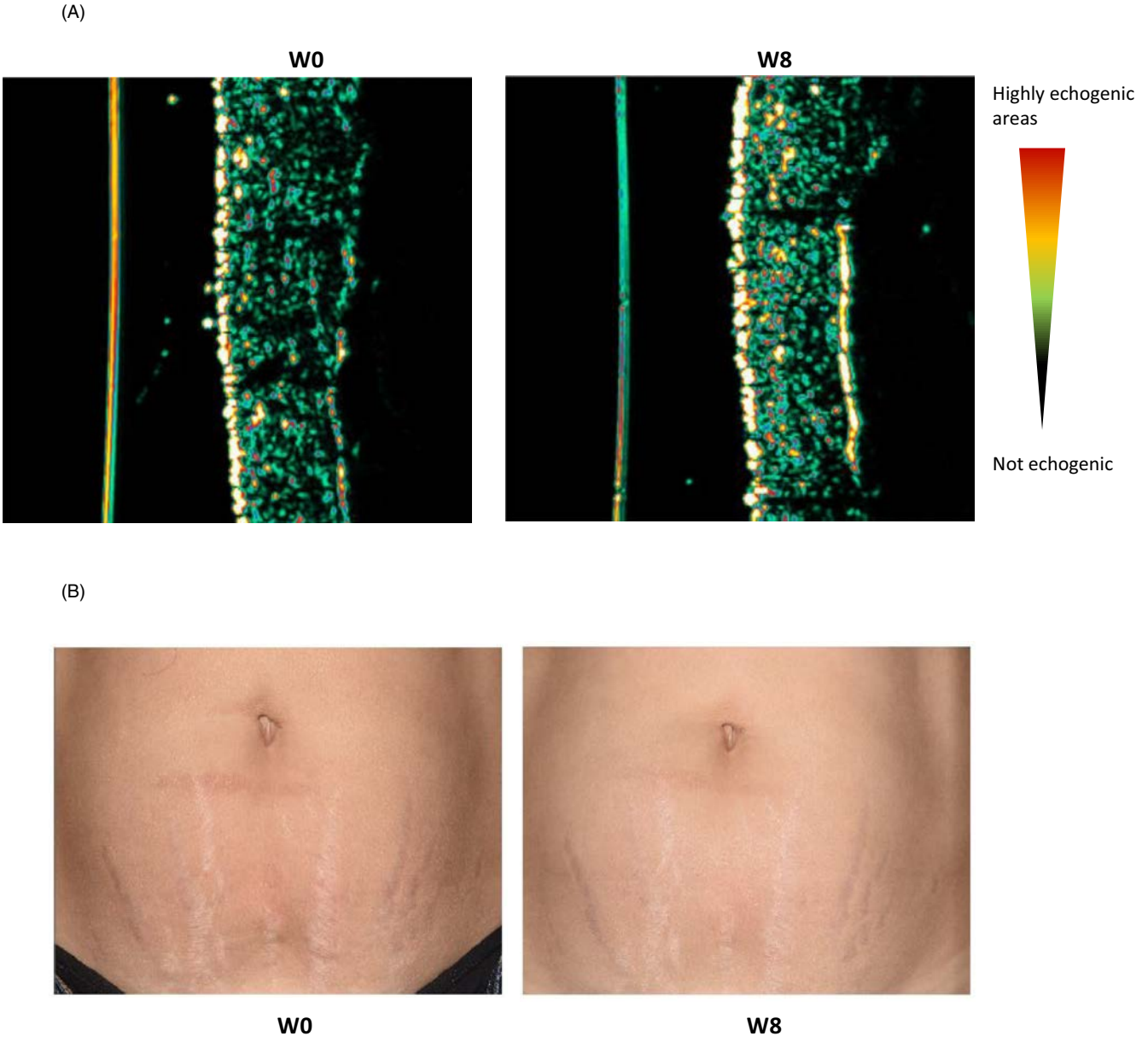

FIGURE 5 Ultrasound and superficial images of stretch marks. Representative dermal ultrasound images (A) and stretch mark photographs (B) from one woman (subject no. 3; 55 y old) in the *Tasmannia lanceolata* leaf extract (TLE) group during the topical application period (W0 and W8)

thus required to better characterize the clinical effects and clearly define their mechanisms of action.

Consequently, we carried out research work integrating both a double-blind, randomized, and placebo-controlled clinical investigation in women presenting wide and deep stretch marks and a mechanistic study in an ex vivo human skin model, to assess and explain the effects of a topically administered oil product, containing *Tasmannia lanceolata* leaf extract (TLE), on SD.

We first demonstrated that TLE treatment decreased skin roughness in stretch marks areas as well as improved its firmness. These effects were observed as early as W4 of usage and were maintained until the end of the study. However, significant differences between TLE and placebo treatments were not demonstrated, probably because of the low subject number, the interindividual biological variability, and the duration of the treatment. Nevertheless, the TLE product restored dermal density and thickness to normal levels seen in the placebo at W4 and W8, respectively, and in a significant way. More importantly, these results obtained from widely used quantitative methods supported the clinical and appreciations scores performed by the dermatologist.

The human skin explants study showed that the clinical effectiveness of TLE on stretch marks was due to increased synthesis of two major matricial proteins, collagen I and elastin, in parallel with an increased secretion of TGF-β1. Thus, suggesting that TLE has a direct as well as an indirect effect on the dermal fibroblast activity through TGF-β1 excretion, which is a growth factor known to

TABLE 3 Global assessment by the dermatologist

Dermatological scores	Week of treatment	TLE group (n = 15)	Placebo group (n = 14)
Stretch mark depth	W0	2.07 ± 0.88	2.11 ± 0.66
	W4	1.92 ± 0.90*	1.86 ± 0.69*
	W8	1.50 ± 0.65**	1.71 ± 0.78**
Stretch mark coloration	W0	2.07 ± 0.70	2.05 ± 0.65
	W4	1.77 ± 0.62**	1.84 ± 0.66*
	W8	1.43 ± 0.62**	1.75 ± 0.70**

Note: The dermatological scores of stretch mark depth (arbitrary units) and coloration were evaluated at W0 and after 4 and 8 wk of treatment in the TLE and placebo groups, mean scores ± standard deviation.

*$P < .05$.

**$P < .01$ in comparison with W0.

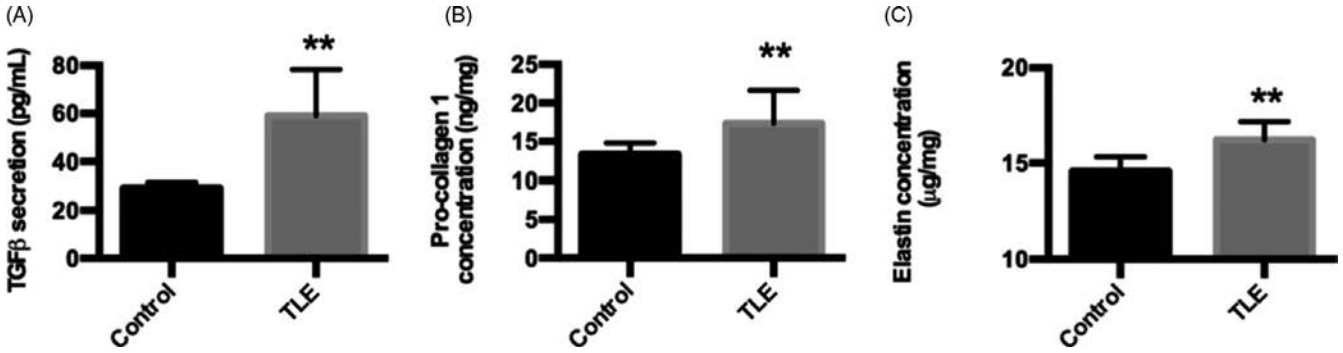

FIGURE 6 Measurement of growth factor and matricial proteins in human skin explants presenting stretch marks. Two skin explants, exhibiting stretch marks, from each of five donors were treated with either TLE or PBS (control) for 12 d. A, Concentrations of TGF-β secreted by the skin samples were measured in the media. B, C, Pro-collagen 1 and elastin concentrations were determined from skin explant lysates. Results are expressed as means ± SEM in pg/mL for TGF-β and in ng/mg or µg/mg of skin tissue for pro-collagen 1 and elastin, respectively. **$P < .01$

promote differentiation of fibroblasts into myofibroblasts. The latter exhibit higher migration capacities and express higher levels of extracellular matrix and fibrogenic cytokines than fibroblasts. Consequently, the evidence of collagen production observed after TGF-β stimulation is a consequence of myofibroblast differentiation.[24] This mechanistic speculation is supported by preliminary experiments we performed on human dermal fibroblasts. After 7 days of exposure to 1, 5, and 10 ppm of TLE, an increase in collagen I synthesis was observed in these fibroblasts when compared to the control conditions (Figure S1A). Moreover, we demonstrated that moderate doses of TLE (1 and 2.5 ppm) were also able to induce the migration of fibroblasts after a mechanical scratch mimicking wound healing (Figures S1B,C). However, these preliminary data obtained from a single donor of fibroblasts need to be confirmed in cells from other donors.

Nevertheless, although improved cutaneous elasticity of the stretch-marked areas of women enrolled in this study could not be demonstrated, there were increased concentrations of elastin in the stretch mark skin explants after treatment with TLE. This is probably due to the 8 weeks of TLE application not being sufficient to clinically improve or show skin elasticity in the SD areas.

Thus, it would be interesting to conduct a larger clinical trial with a longer period of treatment in order to confirm these results and the restorative properties of TLE on skin quality and appearance. Moreover, skin biopsies and histological experiments could be undertaken to confirm the restorative properties of TLE on skin matricial structure. Additional mechanistic studies focused on its main compound polygodial alone should also be carried out.

In conclusion, to our knowledge, this is the first study reported in the literature which reveals the beneficial effects of *Tasmannia lanceolata* on stabilized stretch marks. In our double-blind, randomized, and placebo-controlled clinical study, we have demonstrated a significant improvement of dermal density and thickness leading to visible ameliorations of stretch marks. In addition, the *ex vivo* experiments on human skin explants illustrated the mechanistic actions of TLE by potentiating the activity of matrix synthesis by dermal fibroblasts.

Considering the data presented here, highlighting the anti-inflammatory and the skin restructuring properties of TLE, numerous possibilities of this extract to treat other skin conditions, such as acne or surgical scars, among others, can be envisaged in future studies.

DATA AVAILABILITY STATEMENT

All patients gave their written informed consent to take part in the study.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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