

IFSCC 2025 full paper (IFSCC2025-1238)

"Upcycled apple flower extract demonstrate clinical efficacy in cellulite reduction through activation of caloric restriction"

Angela Roca ¹, Miguel Pérez-Aso ¹, Jordi Bosch ¹, David Manzano ¹

¹ Provital S.A.

1. Introduction

Cellulite refers to the fat accumulation in thighs and buttocks mostly in women conveying a visible orange peel appearance on the skin. Underlying causes of cellulite lie in the number, size and conformational arrangement of adipocytes localized beneath the dermis. This subcutaneous fat is organized as vertical lobules in women and small protrusions of fat (papillae adipose) into the dermis causes cellulite [1]. This structural alteration of subcutaneous fat protruding into the dermis gives the skin the bumpy appearance in cellulite. There are different treatments for cellulite from topical creams or gels to energy-based devices or injectable biological agents. One of the topical standard treatments is caffeine and retinol since the first promotes lipolysis and retinol can prevent *in vitro* preadipocyte differentiation [2].

Apple is one of the most consumed fruits all over the world, and its chemical composition consists in polyphenols, carbohydrates, and carotenoids that have been reported with health benefits [3]. Phloridzin and phloretin are flavonoids found mostly in apples which have anti-inflammatory and antioxidant properties. Moreover, it has been described that both phloridzin and phloretin promote lipolysis in mouse 3T3-L1 cells [4] and inhibit adipogenesis [5].

In this respect, we previously reported [6] the identification of an ingredient, *Pyrus malus* flower extract (PME) that exerts a lipolytic and anti-adipogenic effect on human adipocytes. To investigate the mechanism of action of PME, we performed a multi-omics study where it was revealed that PME, via PI3K-Akt-mTOR pathway, downregulates the formation of mTORC1, the master regulator of lipid metabolism. This impairment will induce autophagy of lipid vesicles, resulting in an increase in lipolysis rate. Moreover, PME also modulates other pathways such as TNF signaling, IL18, NFKB and other cytokines showing an anti-inflammatory and antioxidant activity. Taken all together, PME exhibits a similar effect to caloric restriction in mature adipocytes and it can be employed not only to reduce cellulite, but also to improve certain metabolic disorders, protect cells from stress damage and increase lifespan.

The objective of the present study was to investigate whether the mechanism of action of upcycled apple flowers activating lipolysis in a caloric restriction-like mechanism, could elicit an anti-cellulite effect in volunteers by means of instrumental analysis.

2. Materials and Methods

2.1. Evaluated formulations and study protocol

The anti-cellulite efficacy of the active *Pyrus malus* flower extract (PME) was tested in a randomized double-blind placebo-controlled study at 2%. The evaluations were performed on 56 subjects and both products were applied on the same volunteer, on each side of the thighs and buttocks chosen randomly.

The volunteers had the following characteristics:

- Sex: female
- Age: 18-55 years old
- Skin: all types of skin
- Subjects presenting cellulite on the measurement area (buttocks and thighs) with clinical grade 2 and 3 following the Nurnberger & Müller scale.

Study parameters were evaluated at the beginning (D0), after 28 days (D28) of the treatment, and at the end (D56) of the study. All the evaluations were carried out under temperature and humidity-controlled conditions (temperature 18-26°C and humidity 50 ± 10%).

To avoid circadian changes, 2 evaluation periods were defined (Morning: 9h-13.30h; Afternoon: 13.30h-18.30h). All the evaluations of each subject were performed on the same period of the day.

2.2. Instrumental analysis

Centimetric measurement

The perimeter of the thighs was obtained with a flexible meter (SECA 201) with a precision of 1 mm. All the measurements were obtained in mm.

Skin topography assessment

Skin topography was measured using an *in vivo* system (AEVA-HE, Eotech, France) where the 3D images of the skin topography are obtained by a stereo camera combined with a fringe projection system. A fringe standard is projected on the skin and detected by the dual cameras of the optical system. The 3D effect is calculated by the deflection in the fringes which represent qualitative and quantitative the skin profile and by the stereo-combination of the image projected by both cameras.

The measuring area was on the cellulite area and the standard roughness and depression volumes are calculated in the full aligned image. The parameter for roughness is Rz (average of the 5 highest peaks and the 5 lowest valleys in the image area).

Ultrasonography assessment

Ultrasound images are generated using a Dermascan C ultrasound system (Cortex technology, Denmark) with a special modified 20 Mhz probe. The echo dense tissue is detected, and a B-ultrasound image is generated.

The measuring area was in the cellulite area, where the dermis-hypodermis junction (DHJ) and the hypodermis thickness were analyzed.

Photographies: VECTRA-XT

Standardized 3D images were obtained before, during and after the treatment with the system VECTRA - XT (Canfield, USA). This imaging system consists of six high-resolution cameras strategically aligned to capture various angles of the targeted area. The photograph is then processed by imaging software and generated to a computer as a 3D digital image.

Images were captured on each experimental day. Each of the 3D surfaces is registered to the 0-coordinate point in space, where x, y, and z planes intersect. A selection area is painted on the surface used as baseline surface, on the areas that have not been affected by the treatment.

On the 3D images, a segmentation of cellulite-affected areas (in orange) was performed using Ilastik, a machine learning-based tool for pixel classification, enabling the transformation of the original image into a corresponding segmentation mask accurately highlighting the regions of interest.

Skin biomechanical properties evaluation

To evaluate the effectiveness of PME in certain biomechanical parameters of the skin, we used two different methods: cutometer and a kinematic evaluation.

Kinematic evaluation – dynamic firmness

Using a high-speed rate camera, it is possible to analyze and monitor the elastic deformation of body skin during specific movements. To analyze this deformation, we asked the volunteers to perform a step in a step device and the subjects were filmed at 4300 frames per second with a High-Speed Camera (IX-230, Sony Corporation). When they perform this movement, there are a series of movements in the cellulite area. Firmer skin will produce less bumps and reduced motion time; therefore, this value should decrease.

The measuring area was in the body and the measurements were performed at D0 and D56.

Assessment of skin firmness and elasticity

Skin biomechanical evaluation was performed by a Cutometer® dual MPA 580 using an 8mm probe. This system is used to measure elasticity of the upper skin layers using negative pressure which deforms the skin mechanically. Parameters R0 and R2 were measured on the cellulite area in each subject.

Skin hydration assessment

The measurements were performed with a Corneometer® CM 825 probe connected to a Cutometer® dual MPA 580 or Multi Probe Adapter MPA 6 (Courage+Khazaka Electronic GmbH, Köln, Germany).

Statistical data analysis

The instrumental efficacy data are expressed in numbered data and are submitted to a suitable statistical treatment (Student-t Test, Wilcoxon Signed-Ranks Test or Mann-Whitney Test) for all the comparisons within the measurement times and within the treatments.

All the calculations were performed using GraphPad Prism® v10 software. A 95% level of significance was adopted.

3. Results

3.1. Thighs perimeter measurements

Both treatments reduced the perimeter of the thighs, however this decrease was consistently more pronounced in the PME group. A statistically significant reduction of approximately 0.5 cm in thigh perimeter was observed in the volunteers treated with PME after 28 days, as compared to the placebo group (Figure 1). This reduction increased to approximately 0.7 cm after 56 days of treatment.

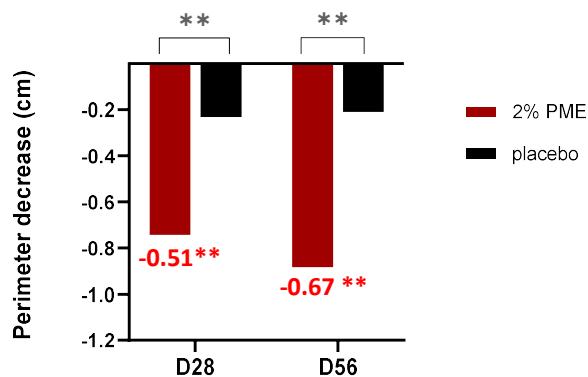


Figure 1. Thighs perimeter measurement in centimeters. Results are expressed in centimeters as the difference between days 28 and 56 of treatment versus day 0 for each product. **p<0.01.

These findings suggest that PME exerts a slimming effect in this area, which can be attributed to its lipolytic activity.

3.2. Skin topography assessment

One of the visible manifestations of cellulite is the orange peel or bumps in the superior part of the thighs and buttocks. To evaluate the effect of PME on the skin surface, we measured roughness and the volume of the depressions with the AEVA equipment.

An initial decrease in skin roughness of 3.4% within the cellulite area after 28 days of treatment with PME was observed. This reduction significantly increased, reaching a value of approximately 8% at D56 of treatment compared to the placebo in all the volunteers (Figure 2). The difference between both treatments was statistically different at D56.

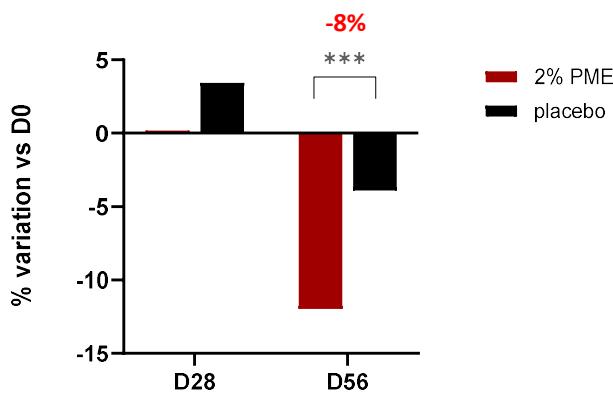


Figure 2. Skin roughness evaluated with AEVA (Rz parameter). Results are expressed as a percentage of the mean variation of each group vs D0 at different times considering all the volunteers. ***p<0.0001.

Another parameter was the volume of the depressions or bumps in the cellulite area (Figure 3). We observed a 2.4% decrease in the volume of the area treated with PME as compared to placebo after 56 days of treatment.

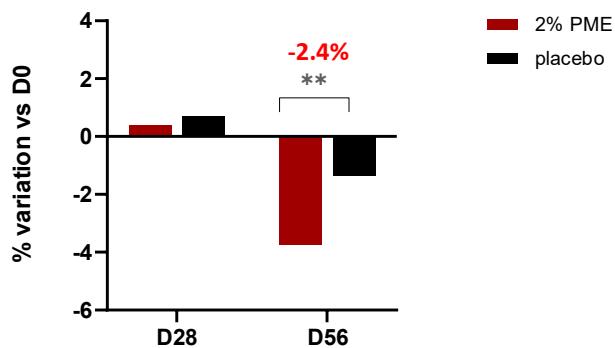


Figure 3. Volume depression in the cellulite area. Results are expressed as a percentage of the mean variation of each group vs D0 at different times in all the volunteers. * $p<0.05$.

Therefore, PME increases the skin smoothness making cellulite bumps less noticeable and less hollow in the participants.

As can be seen in the images (Figure 4), the skin in the red-framed area is smoother and there are fewer bumps and depressions at the end of the treatment (D56). This is also reflected by the automatic detection of cellulite-associated pixels in orange (right images).

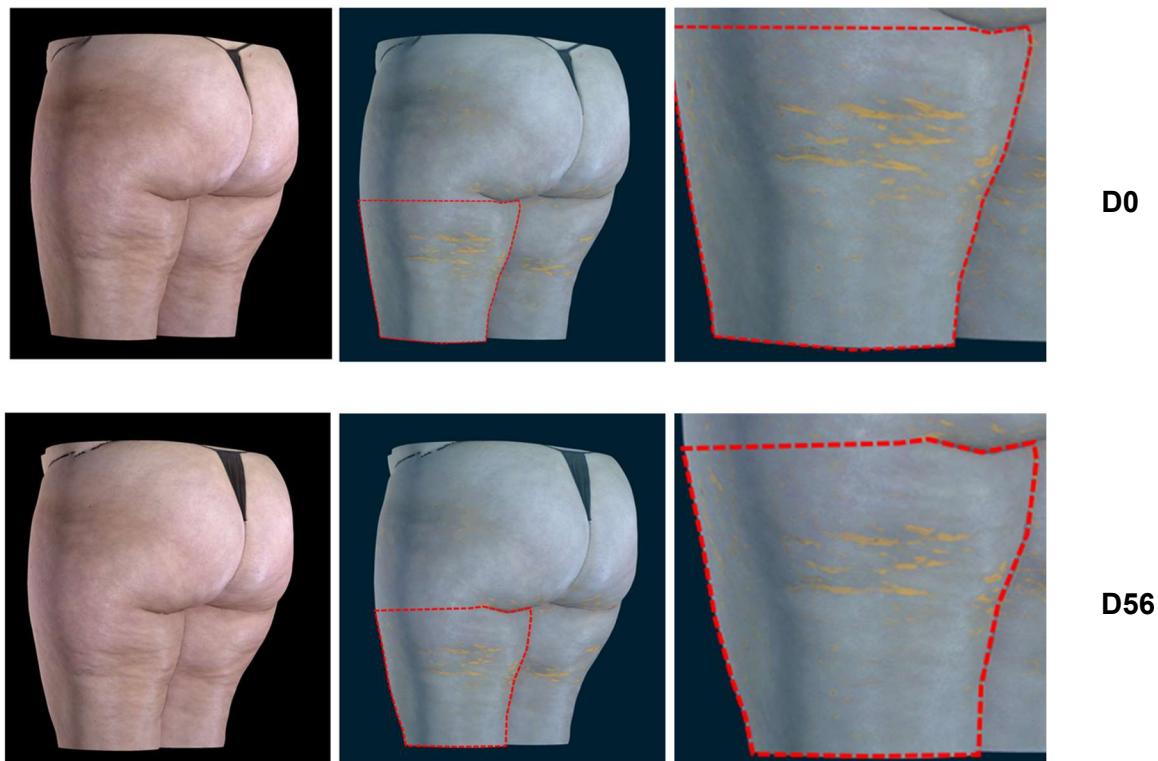


Figure 4, Representative cellulite evolution in volunteer number 3 after 56 days of treatment with 2% PME. Images were taken with VECTRA equipment (left image) and an automatic detection reflected a smaller surface area of cellulite-associated pixels in orange (right image).

3.3. Ultrasonography assessment

As commented in the introduction, women with cellulite have a different arrangement of the adipocytes that cause fat infiltration into the dermis. These changes are observed in the dermis hypodermis (DH) junction as a more irregular conformation with a wavy appearance, and by measuring its length, we can test the effectiveness of PME.

The treatment with PME resulted in a reduction of the length in the DH junction of 5% and 6% after 28 and 56 days of treatment respectively, whereas the reduction with placebo was inferior. Once subtracted the effect of placebo, PME confirmed a decrease in DH junction length, with a reduction of 1.7% after 28 days and a significant reduction of nearly 7% after 56 days of treatment (Figure 5).

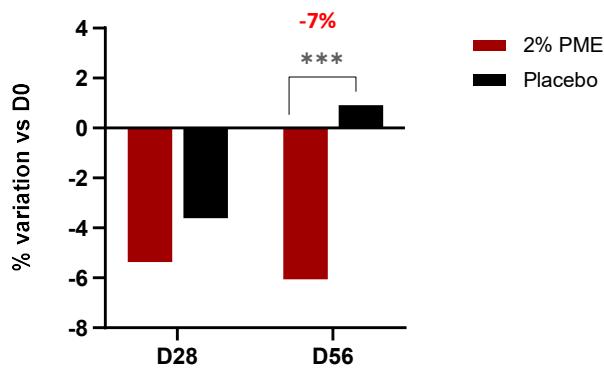


Figure 5. Dermo-hypodermal junction length. Results are expressed as a percentage of the mean variation of each group vs D0 at different times. ***p<0.01

These results indicate that the use of PME reduces the length of the DH junction, being more homogeneous and straight. This reflects the disappearance of fat infiltration into the dermis, therefore reducing the hypodermis size.

To corroborate this hypothesis, the hypodermal thickness was measured. As observed in Figure 6, the treatment with PME diminished the subcutaneous tissue by 4% after 28 days and by 12% after 56 days after subtracting the effect made by placebo.

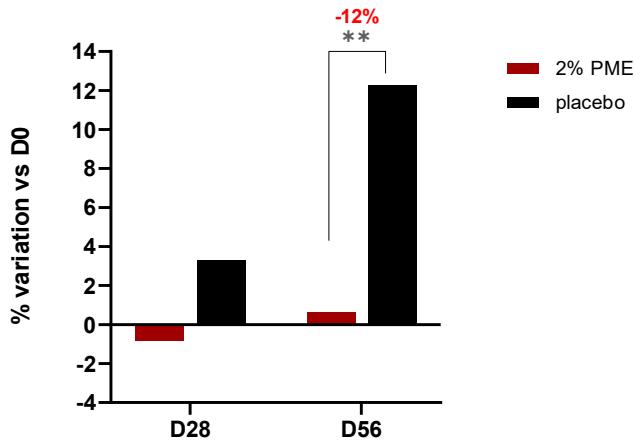


Figure 6. Hypodermis thickness reduction due to PME. Results are expressed as a percentage of the mean variation of each group vs D0 at different times. **p<0.01

3.4. Biomechanical properties assessment

Dynamic firmness

This is a new method to evaluate skin firmness while performing some skin movements. It is based on previous research done by imaging facial movements where a delay between the upper parts of the skin and the lower parts during motion can be monitored [7]. This delay becomes more perceptible as the lack of firmness appears, but it is something difficult to perceive with the naked eye. For this reason, it is necessary to film this motion with a high-speed camera to be able to perform the precise measurement and obtain this parameter.

Volunteers were requested to step onto a step device at D0 and D56 while they were filmed until the cessation of skin movement. The times to rest were 824.5 msec and 819.9 msec for PME and placebo at D0 respectively. After 56 days of treatment, these times decreased to 660.4 and 702.1 msec for PME and placebo respectively. When we analyzed the time variation (Figure 7) in comparison to D0 group, the PME group exhibited a significant decrease in time with a mean difference of 164.12 msec, whereas the placebo group exhibited a decrease in time with a mean difference of 117.76 msec. Therefore, a more substantial reduction in motion time is observed with PME compared to placebo, thereby demonstrating the efficacy of the treatment in enhancing skin firmness.

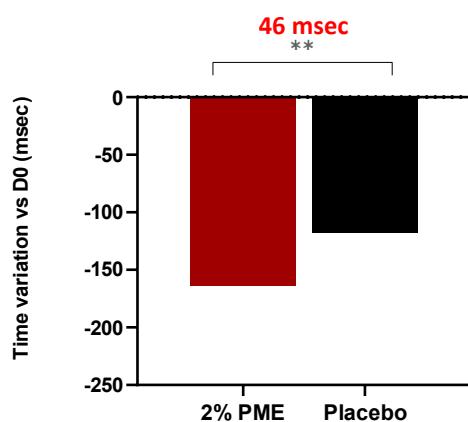


Figure 7. Dynamic firmness evaluation measured as msec to stop motion. Results are expressed as a percentage of the mean variation of each group vs D0 at D56 in all the volunteers. **p<0.01.

Assessment of firmness and elasticity

Furthermore, PME improved both parameters, firmness and elasticity in the cellulite area, as compared to placebo. PME significantly increased skin firmness by 14% and 18% after 28 and 56 days of treatment respectively, once subtracting the placebo effect. (Figure 8). In the same way, skin elasticity improved around 0.5% and 4.5% after 28 and 56 days of PME treatment at 2%.

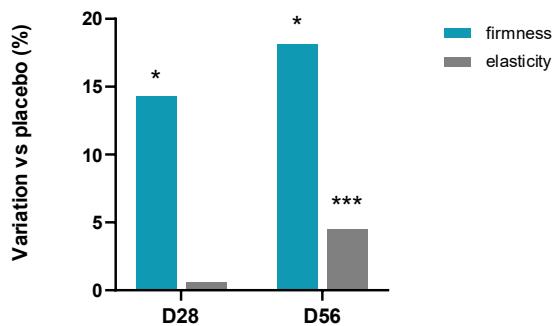


Figure 8. Skin firmness and elasticity improvement due to PME treatment. Results are expressed after subtracting the placebo variation vs D0 after 28 and 56 days of treatment. * $p<0.05$, *** $p<0.001$.

3.5. Hydration evaluation

The results showed increased skin hydration in both treatments, although the improvement achieved by PME was always higher during all the study (Figure 9). PME increased hydration by 28% after 28 days and by 37% after 56 days, whereas the treatment with placebo was about 21% and 28% after 28 and 56 respectively.

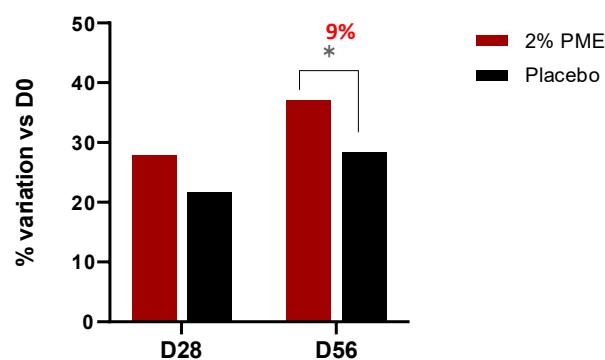


Figure 9. Hydration evaluation in the cellulite area. Results are expressed as a percentage of the mean variation of each group vs D0 at different times in all the volunteers. * $p<0.05$.

These results displayed a 9% significant increase in skin hydration of PME as compared to placebo after 56 days of treatment.

4. Discussion

Cellulite is characterized by the appearance of dimpling, which gives the skin an orange peel appearance. This clinical manifestation is widely considered the hallmark of cellulite. The results of this study substantiate the initial hypothesis that *Pyrus malus* flower extract (PME), through an emerging mechanism of action that mimics caloric restriction effects, can exert clinically anti-cellulite benefits by modulating lipid metabolism and skin structure. The molecular mechanism via PI3K/Akt/mTOR pathway inducing adipocytes lipolysis [6] was effectively translated into *in vivo* clinical outcomes, notably reduction of thigh circumference, diminished dermal-hypodermal junction irregularities, and improvement of skin biomechanical properties.

These observations are consistent with previous reports on flavonoids such as phloridzin and phloretin—key components of PME—known to inhibit adipogenesis and promote lipolysis in 3T3-L1 cells [4], [5]. Moreover, phloretin has been shown to inhibit matrix metalloproteinases

and elastase activity [8], thereby preserving structural extracellular matrix (ECM) proteins like collagen and elastin. These actions have been demonstrated to contribute to the maintenance of dermal integrity and elasticity, two critical factors that have been observed to play a significant role in the visible manifestations of cellulite. Additionally, it has been described that both flavonoids possess antioxidant and anti-inflammatory properties, which contribute to cellular resilience against oxidative stress [9], [10]. Therefore, our findings in reducing skin roughness and depression volume serve to reinforce the hypothesis that PME contributes to dermal remodeling by reducing fat protrusion and enhancing extracellular matrix organization.

Notably, the study introduces novel assessments such as dynamic firmness by using high-speed motion capture, providing support for PME's capacity to improve skin elasticity and tone in motion.

These biomechanical capacities, alongside ultrasonographic evidence of decreased hypodermal thickness, confirm that PME exerts structural effects at multiple skin levels. In addition, this multifaceted mechanism is reflected in the study's findings, which showed significant improvements, not only in subcutaneous fat reduction and skin topography, but also in skin firmness, elasticity, and hydration.

In a broader context, PME represents a promising cosmetic innovation derived from sustainable sources, aligning with current trends favoring upcycled, multifunctional natural ingredients. Given its dermal remodeling capacity and systemic metabolic implications, PME may also hold cosmetic potential beyond cellulite treatment.

5. Conclusion

The clinical data presented confirms the efficacy of *Pyrus malus* flower extract (PME) as a potent anti-cellulite agent, supporting the working hypothesis of its caloric restriction-like activity in the skin. PME significantly reduced thigh circumference, improved skin topography, and enhanced dermal structure and biomechanical properties within 56 days. These effects are positively mediated through modulation of lipid metabolism, ECM organization, and anti-inflammatory and antioxidant mechanisms associated with phloretin and phloridzin. PME ability to improve body skin hydration, firmness, and elasticity further supports its multifunctional cosmetic potential. Ultimately, as a sustainable and upcycled ingredient, PME represents an innovative and eco-conscious approach in cosmetic formulations.

6. References

- [1] M. Wanner and M. Avram, "An evidence-based assessment of treatments for cellulite.,," *J Drugs Dermatol*, vol. 7, no. 4, pp. 341–345, 2008.
- [2] L. S. Bass and M. S. Kaminer, "Insights Into the Pathophysiology of Cellulite: A Review," Oct. 01, 2020, *NLM (Medline)*. doi: 10.1097/DSS.0000000000002388.
- [3] J. Boyer and R. H. Liu, "Nutrition Journal Apple phytochemicals and their health benefits," 2004. [Online]. Available: <http://www.nutritionj.com/content/3/1/5>
- [4] W. C. Huang, W. T. Chang, S. J. Wu, P. Y. Xu, N. C. Ting, and C. J. Liou, "Phloretin and phloridzin promote lipolysis and inhibit inflammation in mouse 3T3-L1 cells and in macrophage-adipocyte co-cultures," *Mol Nutr Food Res*, vol. 57, no. 10, pp. 1803–1813, Oct. 2013, doi: 10.1002/mnfr.201300001.

- [5] A. Casado-Díaz, Á. Rodríguez-Ramos, B. Torrecillas-Baena, G. Dorado, J. M. Quesada-Gómez, and M. Á. Gálvez-Moreno, "Flavonoid phloretin inhibits adipogenesis and increases opg expression in adipocytes derived from human bone-marrow mesenchymal stromal-cells," *Nutrients*, vol. 13, no. 11, Nov. 2021, doi: 10.3390/nu13114185.
- [6] A. Roca *et al.*, "A multi-omics study reveals that apple flower extract reduces cellulite by mimicking caloric restriction.," IFSCC Congress 2024.
- [7] P. Pinto,; Almeida, Joana,; Fitas, and Manuel, "Skin dynamic firmness: a new evaluation method using High Speed Cameras and kinematic analysis," IFSCC Congress 2023.
- [8] H. S. Tuli *et al.*, "Phloretin, as a Potent Anticancer Compound: From Chemistry to Cellular Interactions," Dec. 01, 2022, *MDPI*. doi: 10.3390/molecules27248819.
- [9] S. Habtemariam, "The Molecular Pharmacology of Phloretin: Anti-Inflammatory Mechanisms of Action," Jan. 01, 2023, *MDPI*. doi: 10.3390/biomedicines11010143.
- [10] S. Khanam, D. A. Mishra, A. Shahid, and N. M. Pujari, "Therapeutic indication of Phloridzin: A new Gleam for metabolic disorders," Feb. 01, 2022, *Elsevier B.V.* doi: 10.1016/j.phyplu.2021.100200.