
Dimpless®
Shape your body
- New scientific evidences -
ROBERTET
HEALTH & BEAUTY

CELLULITE, A UNIVERSAL BEAUTY CONCERN

Gynoid lipodystrophy, more commonly referred to as cellulite, is a structural and biochemical disorder of the subcutaneous tissue, visually characterized by an uneven dimpled skin surface, especially on the buttocks and thighs.

With 85 to 95% of women concerned, dermatologists describe cellulite as a normal physiologic state in post-adolescent females [1]. For women, however, it appears as a major concern responsible for ill-tolerated lack of aesthetics, discomfort and a significant decrease in quality of life [1].

Within the last 3 decades our globalized society has portrayed a new version of the ideal female body: youthful, almost pre-pubertal, with well-defined muscles and very little body fat. This redefined model of beauty has led to the development of a new "medical disease": cellulite [1].

A neglected disease and unconvincing solutions

With 200 million women affected in Europe and almost 2 billion worldwide, with no distinction of race, cellulite can undeniably be called a universal issue [2].

And yet, in spite of this high prevalence, there have been only few scientific articles devoted to cellulite in the medical literature of the past 30 years. Its etiology and physiology being complex and far from fully comprehended, this greatly complicates the development of effective treatment strategies.

If a wide and varied range of solutions is today available, topical and mechanical for the main part, they appear to be only partially or temporarily effective.

Cosmetics, although abundant on the market, only show a relative effect on cellulite. Most of the evidences today available are subjective, based upon patient self-assessment or satisfaction. According to some researchers, it even is unlikely that topically applied active agents can alter the fundamental cutaneous architecture existing in cellulite-prone areas [3].

Physical and mechanical treatments on the other side (liposuction or endermologie for instance), besides being invasive and expensive, benefit for some of them of only little evidence to support their beneficial effects.

Finally, in spite of a rising credibility and attraction of nutricosmetics, oral treatments are still largely under-represented. It is interesting to note that according to some researchers, the synergies between both oral and topical routes could be the best intervention to ameliorate the signs and symptoms of cellulite [4].

A growing, innovation-friendly, market

Despite the relative efficacy of the solutions currently made available to consumers, cellulite is a significant and rapidly growing industry. In particular, cellulite treatment is extremely popular in Europe, in the US where "*not a day goes by in clinical practice without a patient asking about cellulite treatments*" [1] as well as in some sunny areas, where exposing

the body is more common, such as Latin America [5].

In these countries, sales of various topical therapies is a multimillion dollar business. In the meantime, minimally invasive and non-surgical aesthetic procedures experienced a significant rise among the last years, especially in Brazil, where more than 1.4 million were performed in 2016 [5].

First reason behind that, if cellulite is not a serious condition from a medical point of view, it does represent the most widespread and undesirable aesthetic concern among women. In today's globalized culture, where physical well-being is highly valued, women are willing to try everything to get rid of it.

Secondly, even though cellulite is not a direct consequence of being overweight, a correlation between weight gain and exacerbation of cellulite does exist. Non-balanced diet, smoking or sedentary lifestyle, typical of modern western culture, are identified aggravating factors of cellulite [6].

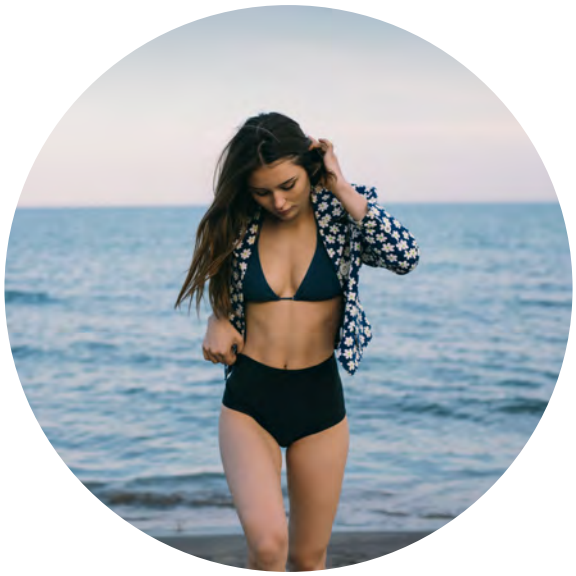
An innovation designed for consumers

Today, there is a real consumer's expectation for novel and effective solutions against cellulite. With the current soaring of beauty-positioned supplements (+61% of sales in the US between 2017 and 2018 [7]), the time seems right for the extension of oral solutions.

Introduced to the market in 2012, Dimpless® is the first oral ingredient benefiting from a clinically demonstrated efficacy on cellulite. Today, Dimpless® comes back with a greater understanding of its mechanism of action and a second clinical trial.

Natural, low-dose, safe and environment friendly, Dimpless® is able to meet the needs and habits of today's consumers. On a market looking for holistic and plant-based solution, Dimpless® offers a promising alternative to traditional solutions.

DIMPLESS®, A CLINICALLY PROVEN EFFICACY ON SUBCUTANEOUS FAT DEPOSIT



100% natural melon juice concentrate, Dimpless® is obtained from our unique variety of Cantaloupe melon, exclusively grown in the south of France. Original composition and high source of natural and protected SOD, Dimpless® benefits from a proven efficacy now demonstrated through 2 clinical trials.

Dimpless® efficacy was initially evidenced in a randomized, double blind and placebo-controlled clinical trial. Conducted on 41 healthy women, the study was able to highlight a reduction of visible cellulite on tights reaching 10% after 28 days and amplified to 12% after 56 days [8].

To go further, a second clinical trial was recently conducted (and not published yet). The impact of Dimpless® on subcutaneous fat deposit, and visible cellulite in particular, has been investigated in a new randomized, double blind and placebo-controlled clinical study. The study was assessed on a total of 35 overweight women (25<IMC<31) between 25 and 50 years old, with visible cellulite. The

population was divided into 2 groups and orally supplemented for 90 consecutive days with 2 capsules of Dimpless® per day, corresponding to 40mg or 480IU of SOD, or Placebo. The supplementation was associated with a balanced nutritional intake and a moderate caloric restriction, consistent with current dietary recommendations, and consisting in a 20% decrease of their habitual food intake.

Cellulite was assessed through the measure of several skin folds, in areas specifically concerned by subcutaneous fat storage and cellulite: the buttocks (Gluteal fold) and the thighs (Femoral fold) (cf Figure 1). This method was chosen preferentially to visual scoring (used in our previous trial) as it is less operator-dependent and thus less subjective. In order to confirm the correlation between skin fold and "orange-peel" aspect, before-and-after photographs of those specific areas were taken.

Additional measures were assessed in 2 locations specifically concerned by subcutaneous fat storage but not cellulite, namely the waist and the hips (cf Figure 1).

Figure 1. *Location of the different folds and circumferences assessed*

Dimpless® reduces skin folds and visibly impacts cellulite

Reported in Figure 2 and Figure 3, the results highlight that Dimpless® was able to decrease gluteal and femoral fold compared to Placebo, with respectively -23% and -28%. Those results were observed after 3 months of supplementation and for an average weight loss of 4kg (observed in both groups).

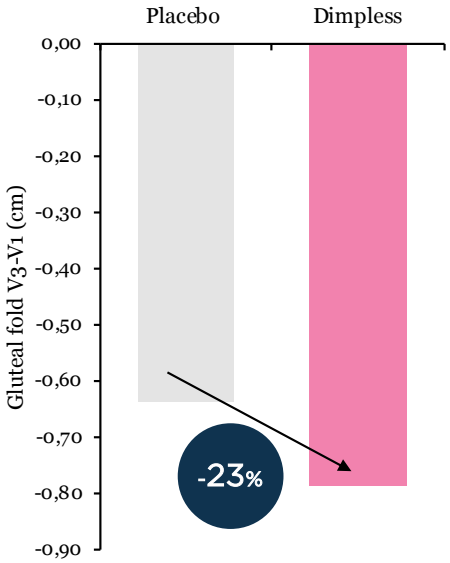


Figure 2. *Gluteal fold progression for an average weight loss of 4kg*

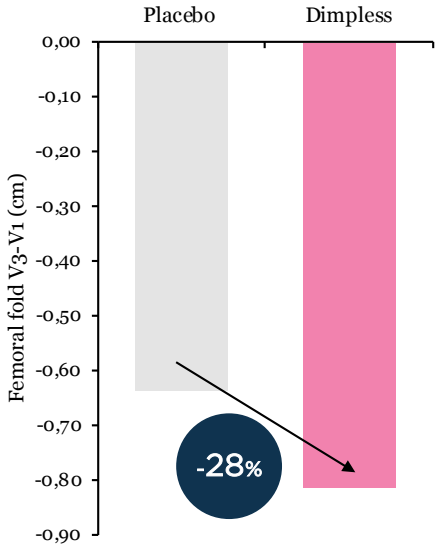


Figure 3. *Femoral fold progression for an average weight loss of 4kg.*

Additionally to this loss of centimeters, the pictures taken before and after the supplementation highlight very clearly the impact of Dimpless® on visible cellulite: after

only 3 months the skin looks smoother and the "orange-peel" effect substantially attenuated.

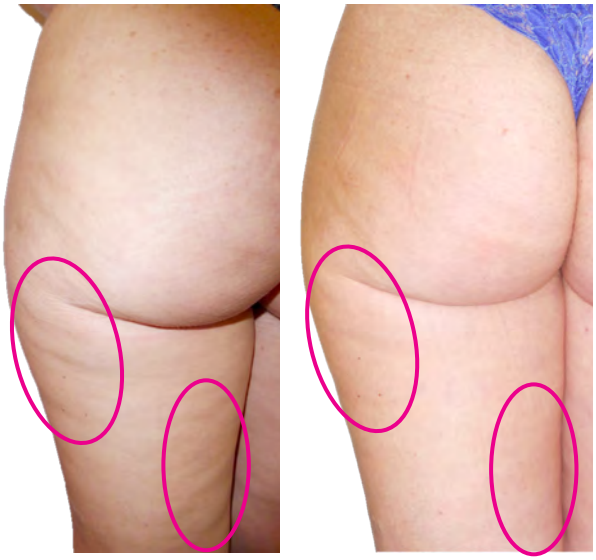


Figure 4. *Before-and-after pictures of a subject's buttocks and thighs after 3 months of oral supplementation with Dimpless®*

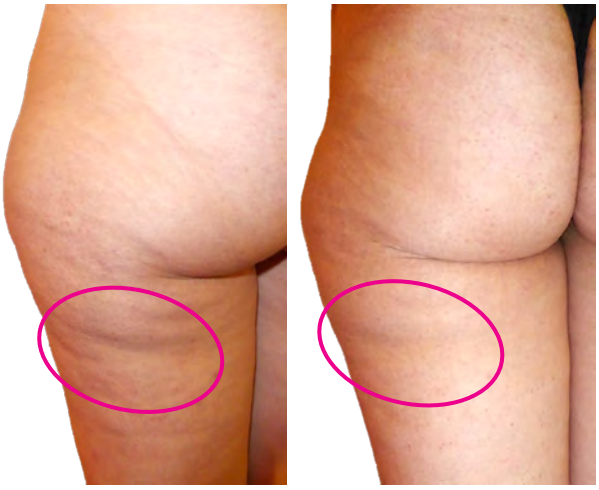


Figure 5. *Before-and-after pictures of a subject's buttocks and thighs after 3 months of oral supplementation with Dimpless®*

Dimpless® accelerates reduction in hips and waist size

Finally, reported in Figure 6 and Figure 7, our results highlight that Dimpless® was additionally able to decrease hips and waist size compared to Placebo, with respectively -40% and -46%, after 3 months of supplementation. Obtained for a similar weight loss in both groups, those results support the fact that Dimpless® is not only acting on visible cellulite, but more generally on subcutaneous fat deposits, thus accelerating the loss of centimeters at the waist and hips.

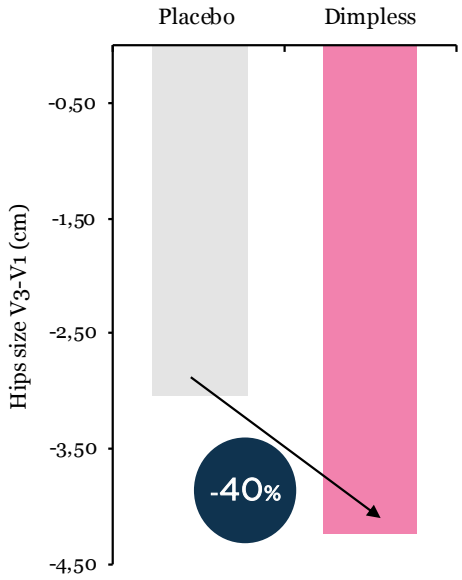


Figure 6. *Hips circumference progression for an average weight loss of 4kg*

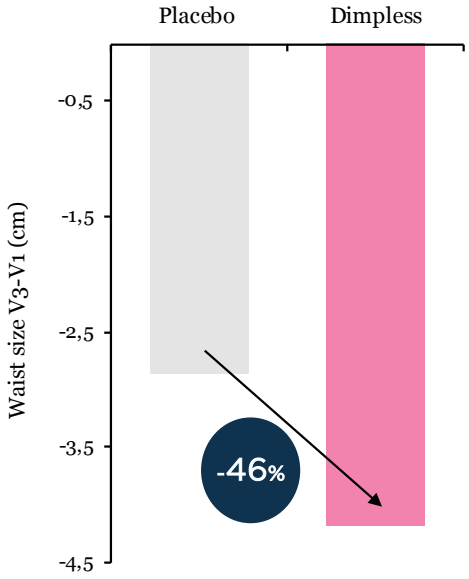


Figure 7. *Waist circumference progression for an average weight loss of 4kg*

This new study was not only able to confirm Dimpless® efficacy on visible cellulite, but also to demonstrate its capacity to act on subcutaneous fat deposit, thus accelerating hips and waist size lost. This efficacy is directly associated to Dimpless® specific mechanisn of action.

DIMPLESS®, A TARGETED ACTION ON FAT TISSUE DISORDERS

Pathophysiology of cellulite

From a physiological point of view, cellulite refers to a localized complex skin disorder caused by the protrusion of subcutaneous fat into the dermis. This phenomenon results in structural, inflammatory, morphologic, and biochemical alterations in the tissue, visually characterized by a modification of the topography of the skin [1].

Even though its pathogenesis and physiology are complex and not fully elucidated yet, cellulite is known to be linked to two main phenomena: the fat accumulation in adipose tissue, conducing to adipocytes hypertrophy; and the fibrotic state of the conjunctive tissue located in the hypodermis (see Figure 8).

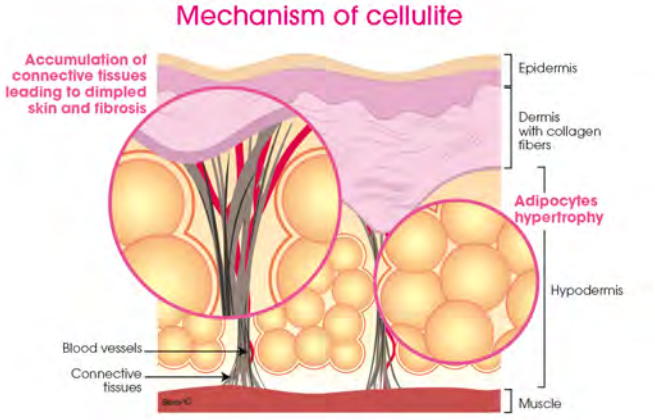


Figure 8. *Mechanism of action of cellulite*

In some regions of the body, such as women's hips and abdomen, the number of adipocytes is higher. Because they are included in a connective tissue of lamellar structure, which hinders lipolysis [1], these adipose cells are more sensitive to sugar and less to blood flow variations. This disturbance in lipid metabolism promotes lipid storage, leading to an increase in fat volume as well as in tension forces within the fat lobules. When subjected to pressure changes, these adipocytes and fat-cell chambers must adapt their shape without changing their volume. Cellulite morphology results from an increase of fat herniation into the dermis [9]: the skin compartment bulges and lead to the noticeable "orange-peel" aspect of the skin.

The second main cause associated to cellulite appearance is the development of fibrosis of the connective tissue, as a result of the evagination of fat lobules in the dermis [10][11]. The gradual accumulation of fats leads to the destruction of collagen fibers and the development of thickened and stiffened fibrous strands. This accumulation of connective tissue, which is characteristic of a localized fibrosis, limits the evagination of fat lobules, and is responsible for herniation of subcutaneous fat[6][11].

Cellulite, an oxidative disorder

If the pathway behind the initiation and functioning of cellulite is still under study, it appears evident that it is linked not only to hormonal issues, but also to a dysregulation of oxidative status.

First of all, changes in adipocytes metabolism, associated with the expansion of adipose tissue, play a major role. Studies indeed showed that fat accumulation itself was directly correlated to Reactive Oxygen Species (ROS) overproduction. Through the activation of NADPH oxidase, an elevated level of fatty acids is indeed able to increase ROS levels, leading to oxidative stress [12].

In the meantime, there is a close relationship between disruption in oxidative status and fibrosis [13]. One of the main mechanisms responsible for fibrosis is the release of ROS by inflammatory cells [14]: due to their high instability, ROS bind to adjacent structures and cause damages to the connective tissue and vascular network [15]. The generation of oxidative damages has been reported in many cases of fibrosis in both animal and humans models [16] and the use of antioxidants is a well-established treatment. In the 1990s, SOD was even used as a drug in injectable form (Orgotein®, Pegorgotein®, and Ormentein®) to prevent and treat radiotherapy-induced fibrosis.

This multi-parametric implication of oxidative stress in cellulite physiology explains Dimpless® efficacy on fat tissue disorders.

Dimpless®, a demonstrated mechanism of action

Dimpless® effect on adipocytes metabolism disorders was evidenced in a model of obese hamsters [17][18].

For that, seventeen 3-weeks-old hamsters, divided into 3 groups, were used. In a first place, obesity was induced in 2 groups (n=5) using a high-calorie "cafeteria" diet. After 15 weeks, one of the 2 groups of obese animals was given Dimpless® orally for 4 additional weeks, while the other one was maintained on the cafeteria diet alone. The last group (n=7) was fed a standard pellet diet the whole time and served as controls.

After 1 month of supplementation, several parameters were assessed in order to evaluate adipose tissue dysfunctions associated with induced obesity, as well as Dimpless® ability to prevent them. The following observations were made:

- While obesity induced an hypertrophy of abdominal adipocytes, Dimpless® was able to significantly reduce their area, with a 54% decrease compared to untreated obese hamsters.

- Whereas fibrosis was twofold increased in abdominal adipose tissue of obese group, Dimpless® was able to completely correct its level, with a reduction of more than 50%.

- Whereas lipolytic activity was altered in obese subjects (-43% compared to control group), Dimpless® was able to restore lipolysis to a normal level.

- Finally, Dimpless® was able to correct several markers of obesity and metabolic syndrome, with a significant improvement of insulin sensitivity, LDL-cholesterol and glucose levels.

This efficacy on fat tissue disorders is directly related to Dimpless® antioxidant capacity. Indeed, whereas antioxidant enzymes expression was significantly impaired in obese group (-28% in total SOD level, -54% in Glutathione Peroxidase and -42% in Catalase when compared to control), Dimpless® was able to restore the expression of those 3 enzymes to a healthy level. This boost in endogenous antioxidants was directly correlated to a decrease in oxidative stress, clearly evidenced in the adipose tissue of hamsters by the reduction of Superoxide anion production.

Through an increase in endogenous antioxidant enzymes, thus restoring a healthy oxidative status, Dimpless® is able to positively impact lipolysis, adipocytes hypertrophy, and fibrosis. This multi-parametric effect on fat tissue disorders explains Dimpless® efficacy on subcutaneous fat deposit and visible cellulite.

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