REVIEW ARTICLE

# Efficacy of cosmetic products in cellulite reduction: systematic review and meta-analysis

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## Abstract

**Background** The number of original articles investigating the efficacy of cosmetic products in cellulite reduction increased rapidly in the last decade; however, to our knowledge, no systematic review and meta-analysis has been performed so far.

**Objective** We conducted a systematic review of *in vivo* studies on humans adopting the PRISMA guidelines. Moreover, we used a meta-analytic approach to estimate the overall effect of cosmetic creams in cellulite treatment from controlled trials with more than 10 patients per arm, using thigh circumference reduction as the outcome measure.

**Methods** Medline and Embase were searched up to August 2012 to identify eligible studies.

**Results** Twenty-one original studies were included in the present systematic review. All studies were clinical trials, most of them recruited women only and 67% had an intra-patient study design. About half of the active cosmetic creams tested only contained one active ingredient among xanthenes, herbals or retinoids. The other studies tested cosmetic creams with more complex formulations and most of them included xanthenes. A total of seven controlled trials satisfied the inclusion criteria for the meta-analysis. The pooled mean difference of thigh circumference reduction between the treated and the controlled group was −0.46 cm (95% confidence intervals, CI: −0.85, −0.08), with significant heterogeneity between studies ($P < 0.001$).

**Conclusion** This article provides a systematic evaluation of the scientific evidence of the efficacy of cosmetic products in cellulite reduction and supports a moderate efficacy in thigh circumference reduction.

Received: 10 January 2013; Accepted: 7 May 2013

## Conflict of interest

The authors have no conflict of interest to declare.

## Funding sources

None.

## Introduction

Cellulite is defined as a localized metabolic disorder of subcutaneous tissue that alters the local body shape leading to an orange peel or cottage cheese-like appearance of the skin.[1,2] It mainly affects women and the predominant localization is on thighs and buttocks.[2,3] Although cellulite may be found in any area where excess adipose tissue is deposited, obesity is not necessary for its presence.[1]

The range of products and professional (surgical or not) approaches to treat cellulite is extremely large: varying from non-invasive techniques, such as cosmetic products, oral regimens with or without nutritional supplements, manual or mechanical massages and garments, to invasive ones, such as liposuction and subcision.[2–5]

The efficacy testing of cosmetic products is a key point to support efficacy claims.[6] The number of original published articles reporting the efficacy of cellulite treatment increased rapidly in the last decade and several reviews or overviews were published on this issue.[1–5,7–16] However, to our knowledge, no systematic review and meta-analysis has been performed so far.

Cosmetic and/or cosmeceutical treatments in cellulite reduction are probably the most commonly used non-invasive techniques. Topical agents used for the improvement of cellulite reduction include xanthenes, retinoids and several types of

botanical extracts.[1] Although there are numerous types of treatments on the market (in pharmacies, supermarkets, beautyspas, etc.) there has been no large-scale study demonstrating their efficacy. Also, most published studies are based on a limited number of subjects with a low power to detect a difference, if any.

The aim of this article is to evaluate and summarize the efficacy of cosmetic products in cellulite reduction from published data in human studies, using a systematic approach and adopting the PRISMA Statement to improve accuracy, reliability and transparency of the research.[17] Furthermore, to provide a quantitative overall estimate of the efficacy of cosmetic products, we combined all published data that measured thigh circumference reduction (i.e. the most frequently reported and probably the most important parameter for the evaluation of cosmetic effect), using a meta-analytic approach.

## Materials and methods

### Systematic review

This systematic review followed the PRISMA guidelines for reporting systematic reviews and meta-analyses.[17] In August 2012, we performed a literature search in the Medline database and Embase using the string "cellulite OR gynoid lipodystrophy OR adiposis edematous OR (dermopanniculosis AND deformans) OR (status AND protrusus AND cutis)" in Pubmed, or similar combination of terms in Embase. We found 222 references in Medline and 548 in Embase, as reported in Fig. 1. We considered only original articles in English reporting data on the efficacy of cosmetic treatments of cellulite from *in vivo* studies on humans. Two review team members (C.G. and F.T.) retrieved and independently assessed the potentially relevant articles, and checked the reference list of all papers of interest and that of several reviews[1–5,7–16] for other pertinent publications. We considered conference papers whenever available, but we excluded conference abstracts, since the information was not sufficiently accurate to evaluate the quality measurement, as suggested by PRISMA guidelines. Discrepancies in results between the two review team members were discussed and resolved. One study on a slimming product that did not assess cellulite reduction as an efficacy outcome was not included.[18]

We finally collected 21 articles from which the two review team members abstracted the following information: country and period, number of subjects and trial type, main baseline characteristics of the subjects [age, Body Mass Index (BMI)/weight and grade of cellulite], type(s) of cosmetic cream tested, dose and duration of the intervention, application procedures and outcome measures (Table 1).[19–39] No studies were excluded *a priori* because of weakness of design or data quality.

The evaluation of potential risk of bias in individual studies was performed independently by the same review team members, as part of the data extraction process. The following data were collected: presence of a control group, use of a placebo cream control, randomization and/or intra-patient design, blinding, sample size justification, whether the groups were at least equal to 20 subjects,[6] description of statistical methods used, computer validation, information on the safety of the treatment and dropout rate (Table 2). Disagreements of judgment were resolved by discussion.

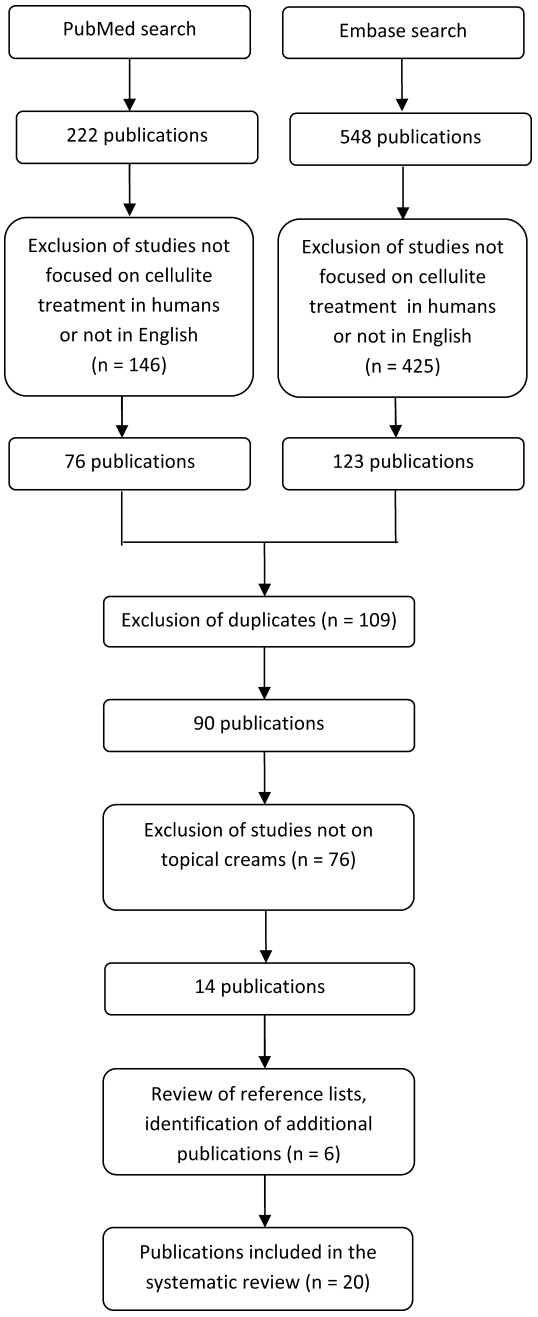


**Figure 1** Flowchart for search and selection of publications for the systematic review and meta-analysis.

**Table 1** Characteristics of *in vivo* studies on humans included in the systematic review

| Reference | First author, year | Country, period | Study design; No. of subjects in the trial | Baseline characteristics: Age; BMI (kg/m$^2$)/ weight; grade of cellulite | Active cream(s) tested | Frequency of application | Duration of the intervention | Description of the application | Outcome measures |
|---|---|---|---|---|---|---|---|---|---|
| 27 | Greenway and Bray, 1987 | NR,NR | Trial CT (P-C) I-P 23 W* | Obese women that wished to lose weight | Product I: Cream with colforsin (forskolin), aminophylline and yohimbine ($n$ = 5) Product II: Yohimbine cream ($n$ = 4) Product III: Colforsin cream ($n$ = 4) Product IV: Aminophylline cream ($n$ = 5) | Once/day five times-week | 4 weeks | All women were placed on diet and encouraged to engage in a walking programme and application of one of the tested cream. At each visit, warm wraps were applied to each thigh for 30 min, followed by the application of an active cream or a placebo cream (xipamide-based only) | Circumference (thigh) |
| 20 | Artz and Dinner, 1995 | NR, NR | Trial 12 (M + W) | 35–48 year | 2% aminophylline/ theopillyne gel | Twice/day | 3 months | On the lateral thighs and buttocks | Circumference (thighs, waist and hips) Ultrasounds of the skin in the lateral thighs area Aminophylline serum levels, lipid profiles and blood glucose level |
| 23 | Buscaglia *et al.*, 1996 | NR, NR | Trial 89 W (Group I, monotherapy: Product I; Group II, triple therapy: Product II) | >18 year; clinical diagnosis of cellulite | Product I: Cream with active ingredients including botanical extracts Product II: Triple therapy with alternate application according to a specific schedule of: (i) cream with caffeine and the same botanical extracts contained in Product I, (ii) a mud with the same botanical extracts contained in Product I and (iii) a serum with the same botanical extracts contained in Product I | Once/day | 1 month | On the thighs | Circumference (thigh) Ultrasounds for fat tissue evaluation Clinical assessment Self-evaluation survey |
| 25 | Epstein *et al.*, 1997 | NR, NR | Trial CT I-P (Group I: Active vs. no treatment; Group II: Placebo vs. no treatment) 17 W | mean age 35.9 year; normal bodyweight | Skinny Dip$^{TM}$ -Aminophylline | Twice/day | 8 weeks | One thigh, and half abdomen with a 5 min massage, unilaterally C-G: no treatment | Circumference (thigh, abdomen) Caliper (inner and outer thigh, abdomen) |
| 24 | Collis *et al.*, 1999 | NR, NR | Trial CT (P-C) I-P 23 W† | >18; thighs and buttocks cellulite | 2% aminophylline with 10% glycolic acid | Twice/day | 12 weeks | On thighs and buttocks, unilaterally, with massage | Circumference (thigh) Ultrasound measurements of thigh subcutaneous fat depth Clinical evaluation of cellulite Self-evaluation survey |
| 29 | Kligman *et al.*, 1999 | NR, NR | Trial CT (P-C) I-P 20 W | 28–45 year; slightly to moderately overweight; moderate degrees of cellulite | 0.3% retinol formulation | Twice/day (~3 mg/cm$^2$ per application) | 6 months | On one thigh, with a 15-second massage, unilaterally | Laser doppler velocimetry Ultrasound measurements of thickness among 5 subjects only Clinical evaluation of the improvement with a global scale (none, fair, good, excellent) Self-evaluation survey |
| 30 | Lesser *et al.*, 1999 | NR, NR | Trial CT (P-C) I-P (Group I: Formulation I vs. placebo; Group II: Formulation II vs. placebo) 49 W + M | 18–65 year; slight to moderate amounts of subcutaneous adipose tissue in the hips, thighs, abdomen or upper posterior arm area | Liposome-encapsulated caffeine-based formulations Formulation I: 2% caffeine ($n$ = 23) Formulation II: 1% caffeine ($n$ = 18) | Twice/day | 2 months | On the thigh, arm, hip, lateral abdomen, unilaterally, with massage | Circumference (triceps, thighs, abdomen and hips) Caliper (triceps, lateral thighs, posterior thighs, abdomen and hips) Dermatological evaluation (cellulite appearance, skin tone and skin tension) |
| 34 | Perin *et al.*, 2000 | NR, NR | Trial CT (P-C) I-P 30 W | >18 year (mean 30.8 year); 18–25 Kg/m$^2$ (mean 21.2 Kg/m$^2$) | Slimming product | Twice/day | 2 months | On the thigh, unilaterally | Ultrasound measurements of the subcutaneous adipose tissue thickness Photograding assessment of cellulite intensity Self-evaluation survey |

**Table 1** *(Continued)*

| Reference | First author, year | Country, period | Study design; No. of subjects in the trial | Baseline characteristics: Age; BMI (kg/m$^2$)/ weight; grade of cellulite | Active cream(s) tested | Frequency of application | Duration of the intervention | Description of the application | Outcome measures |
|---|---|---|---|---|---|---|---|---|---|
| 35 | Piérard-Franchimont *et al.*, 2000 | NR, NR | Trial CT (P-C) I-P 15 W | 26–44 year; mild cellulite | Retinol Actif Pur® | Once/day | 6 months | On the thigh, unilaterally | Ultrasound measurements of dermo-epidermal thickness<br>Tensile proprieties of the skin (i.e. biological elasticity, differential distension, elastic function, maximum distension, relative elastic recovery, viscoelastic ratio) |
| 22 | Bertin *et al.*, 2001 | NR; March to May 1999 | Trial CT (P-C) I-P 46 W | ≥18 year; 20–25 Kg/m$^2$; moderate cellulite in the thighs | Product containing retinol, caffeine, ruscogenine extract and alcohol | Twice/day | 3 months | On the thigh with a circular massage, unilaterally | Macro-relief of the skin of the external face of the thighs (evaluation of orange peel effect)<br>3D ultrasound imaging for the evaluation of dermis and hypodermis structure<br>Mechanical characteristics of the skin (maximum extensibility of the skin, instant vertical extensibility, viscoelasticity, immediate retraction, total retraction, biological elasticity, viscoelasticity rate, recovery rate, residual deformation)<br>Laser Doppler flowmetry to evaluate skin perfusion |
| 28 | Jouandeau *et al.*, 2004 | NR, NR | Study I: Trial CT (P-C) 24 W<br>Study II: Trial CT (P-C) 26 W | Study I: mean age 34 ± 2 year; 21–26 Kg/m$^2$; fat percentage with respect to bodyweight between 26 and 35%<br>Study II: mean age 38 ± 2 year | 4% slenderizing emulsion with complex formulation (*Prunella vulgaris* and *Celosia cristata)* | Study I: Twice/ day<br>Study II: Twice/day | Study I: 28 days<br>Study II: 56 days | NR | Study I: Biomechanical proprieties of thigh skin (i.e. skin elasticity, skin tone)<br>Study II: Abdomen circumference |
| 36 | Rao *et al.*, 2005 | NR, NR | Trial CT (P-C) I-P 40 W | 26–74 year (mean 49 year); cellulite score of at least II out of IV | Spa MD Anti-Cellulite Cream™<br>Active ingredients: piper nigrum, citrus aurantiu dulcis, zingiber officinale, camellia sinesis, cinnamomum cassia, capsicum annum resin, caffeine | Once/day | 4 weeks | Posterior and lateral aspect of the thigh; bioceramic-coated neoprene shorts were worn immediately afterwards, for at least 6 hours. | Circumference (lower and upper thigh)<br>Clinical evaluation (visual improvement of cellulite)<br>Self-evaluation survey |
| 31 | Lupi *et al.*, 2007 | NR, NR | Trial CT I-P 134 W | 20–39 year; 20–24 Kg/m$^2$; clinically apparent cellulite | 7% caffeine solution | Twice/day | 1 month | On one leg (thigh and hip), unilaterally<br>C-G: no treatment | % of patients with reduction/rise of thigh and hip circumferences<br>% of changes in perivascular dermic oedema (functional capillary density, dermal capillaries diameter)<br>Self-evaluation survey |
| 21 | Bazela *et al.*, 2011 | NR, NR | Trial 25 W | 25–55 year; grade 2/3 cellulite on thighs | Cream gel with Hydrolysed *Cucurbita Pepo*, L-ergothioneine, *Vaccinium Macrocarpon*, *Citrus Aurantium Dulcis* | Once/day | 4 weeks | Both thighs | Ultrasound measurements of the subcutaneous tissue thickness<br>Skin moisturization evaluated using corneometry<br>Skin roughness evaluated with a camera<br>Self-evaluation survey |
| 26 | Escudier *et al.*, 2011 | NR; April to June | Trial CT I-P 50 W | 18–45 year (mean 32 year); 20–27 Kg/m$^2$; cellulite score of at least 2 on the L'Oréal Cellulite Chart® (scoring from 0 to 4) | 5% caffeine and a flavonoid-rich *Nelumbo nucifera* extract | Twice/day | 4 weeks | On one leg (thigh and hip), unilaterally<br>Well-balanced food regimen<br>C-G: no treatment | Circumference (upper part of the thighs)<br>Cellulite clinical score without pinching and after pinching<br>Skin tonicity, using a dermal torque metre<br>Volume reconstruction of the thigh, hip and buttock |

**Table 1** *(Continued)*

| Reference | First author, year | Country, period | Study design; No. of subjects in the trial | Baseline characteristics: Age; BMI (kg/m$^2$)/ weight; grade of cellulite | Active cream(s) tested | Frequency of application | Duration of the intervention | Description of the application | Outcome measures |
|---|---|---|---|---|---|---|---|---|---|
| 32 | Mlosek *et al.*, 2011 | NR, 2008–2010 | Trial CT 61 W | 22–61 year (mean 43.9 year); cellulite diagnosis (mean stage of cellulite 2.3 in T-G and 2.7 in C-G) | Cosmetic preparation containing: Hydrolysed *Cucurbita Pepo*, *Vaccinium macrocarpon*, *Citrus Aurantium Dulcis*, L-ergothioneine | Twice/day | 30 days | T-G: cream ($n$ = 45) C-G: pills ($n$ = 16) | Circumference (thigh) Classic ultrasound measurements of subcutaneous tissue and dermis thickness High-frequency ultrasound measurements of epidermis and dermis thickness, subcutaneous tissue fascicle length, surface area, echogenicity, presence/absence of oedemas Clinical evaluation of cellulite |
| 37 | Roure *et al.*, 2011 | NR, NR | Trial CT (P-C) 78 W | 18–60 year (mean age in T-G 41; mean age in C-G 38); 20–26 kg/m$^2$; grade 2 or 3 (Curri's classification) orange peel on thighs, hips, buttocks and stomach | Cream containing tetrahydroxypropyl ethylenediamine, caffeine, carnitine, forskolin, retinol | Twice/day | 12 weeks | Slight massage on the buttocks, hips, stomach, waist, one thigh and one arm | Circumference (abdomen, thighs, hips, buttocks, waist) Hydration evaluation Clinical evaluation using analogical scale (tonicity, orange peel, stubborn cellulite and contracted buttocks) |
| 38 | Sparavigna *et al.*, 2011 | NR, NR | Trial CT (P-C) I-P 25 W | 30–55 year; fat accumulation and/or slight-to-moderate oedematous-fibrosclerotic panniculopathy in the lower limbs | Active cream (Visnadine 0.25% + Ginko biloba 0.5%, Escin 1%) | Twice/day | 4 weeks | On the thigh, unilaterally | Thigh circumference (upper, median and lower third) Skin plastoelasticity (inner thigh) Contact thermography (assessment of the cellulite stage) Ultrasound measurements (outer thigh) Spectrophotometric analysis (evaluation of surface microcirculation) Clinical evaluation of cellulite |
| 39 | Vogelgesang *et al.*, 2011 | | Trial CT (P-C) I-P 50 W (Group I: Product I vs. placebo; Group II: Product II vs. Product III) | 21–49 year | Product I: 3% sulfo-carrabiose Product II: 3% sulfo-carrabiose + 3% caffeine Product III: 3% caffeine | Twice/day | 8 weeks | On the thigh with small circular movements fully absorbed into the skin, unilaterally | Circumference (thigh) Clinician's evaluation of cellulite appearance with a scoring 10-grade scale Thighs volume (using fringe projection techniques) |
| 19 | Al-Bader *et al.*, 2012 | NR; NR | Trial CT (P-C) I-P 35 W | 36–65 year; grade 3.5–5 of cellulite severity on pinched thighs on a dermatological scoring scale (from 0 to 9) | Complex formulation with *Furcellaria lumbricalis*, *Fucus vesiculosus*, retinol, conjugated linoleic acid, glaucine plus a set of vehicle ingredients | Once/day | 12 weeks | On the thigh with a circular massage until fully absorbed into the skin, unilaterally | Clinical evaluation of cellulite appearance (9-grade scale) Ultrasound imaging for fat tissue thickness evaluation |
| 33 | Perez Machado *et al.*, 2012 | NR, NR | Trial CT 36 W | 18–29 year; 18.5–29.9 kg/m$^2$ (mean BMI 22.9 in T-G and 20.6 in C-G); localized android and/or gynecoid adiposities | Cryotherapy with camphor and menthol gel | Three- or four times-week, with a 1- or 2-day interval between applications | Average of 8.45 applications | T-G: Thin layer of gel on the body perimeter; remain supine for 30 min. Remove the gel and apply a body hydration lotion ($n$ = 20) C-G: no treatment ($n$ = 16) | Circumference (body perimeter: arm, waist, hip, abdomen and thigh) Cutaneous folds (tricipital, subscapular, medial axillary, pectoral, suprailiac, abdominal, femoral) Body fat percentage (Tetrapolar bioelectric impedance) Body self-image scale |

*The study enrolled 28 patients. Five patients were treated with isoproterenol injections vs. placebo and 18 with different formulations of creams vs. placebo. In this article, we considered only the latter non-invasive treatment.

†The study enrolled 69 patients and divided them in three groups: aminophylline cream vs. placebo, endermologie vs. placebo and both treatments. Since the trial was intra-patient, in this article we considered only the first group of aminophylline cream vs. placebo among 23 women.

W, women; M, men; CT, controlled trial; P-C, placebo-controlled; I-P, intra-patient; NR, not reported; T-G, treated group; C-G, controlled group; BMI, body mass index; WHR, waist-to-hip ratio.

**Table 2** Quality measures of studies included in the meta-analysis

| First author, year | Control group* (No/Yes) | Placebo-controlled (No/Yes) | Randomization and/or intra-patient (No/Yes) | Blinding (No/Single/ Double) | Sample size calculation (No/Yes/NA†) | If there is no sample size justification, the groups are more or equal to 20 excluding the dropout (No/Yes)‡ | Description of statistical methods (No/Yes) | Computer validation (No/Yes) | Information on safety (No/Yes) | % who did not complete the study |
|---|---|---|---|---|---|---|---|---|---|---|
| Greenway and Bray 1987 | Yes | Yes | Yes | Double | No | No | Yes | No | Yes | 5/23 = 22% |
| Artz and Dinner 1995 | No | No | NA | No | No | No | No | No | Yes | 0 |
| Buscaglia *et al.*, 1996 | No | No | No | No | No | Yes | Yes | No | Yes | 21/110 = 19% |
| Epstein *et al.*, 1997 | Yes | No | Yes | Single (patients) | No | No | Yes | Yes | Yes | 6/17 = 35% |
| Collis *et al.*, 1999 | Yes | Yes | Yes | Double | No | No | No | No | Yes | 6/23 = 26% |
| Kligman *et al.*, 1999 | Yes | Yes | Yes | Double | NA (Pilot Study) | No | No | No | Yes | 1/20 = 5% |
| Lesser *et al.*, 1999 | Yes | Yes | Yes | Double | No | Yes/No§ | Yes | No | No | 8/49 = 16% |
| Perin *et al.*, 2000 | Yes | Yes | Yes | Double | NA | Yes | Yes | No | No | 0 |
| Piérard-Franchimont *et al.*, 2000 | Yes | Yes | Yes | Single (assessor) | No | No | Yes | No | No | 5/15 = 33% |
| Bertin *et al.*, 2001 | Yes | Yes | Yes | Double | No | Yes | Yes | No | No | NR |
| Jouandeau *et al.*, 2004 | Yes | Yes | No | No | No | No | Yes | No | No | NR |
| Rao *et al.*, 2005 | Yes | Yes | Yes | Double | No | Yes | No | No | Yes | 6/40 = 15% |
| Lupi *et al.*, 2007 | Yes | No | Yes | No | No | Yes | Yes | No | Yes | 35/134 = 26% |
| Bazela *et al.*, 2011 | No | No | NA | No | No | Yes | Yes | No | Yes | 0 |
| Escudier *et al.*, 2011 | Yes | No | Yes | Single (assessor) | No | Yes | No | No | No | 0 |
| Mlosek *et al.*, 2011 | Yes | No | No | No | NA | No | Yes | Yes | No | 0 |
| Roure *et al.*, 2011 | Yes | Yes | Yes | Double | No | Yes | Yes | No | No | NR |
| Sparavigna *et al.*, 2011 | Yes | Yes | Yes | Single (patients) | No | Yes | No | No | Yes | 2/25 = 8% |
| Vogelgesang *et al.*, 2011 | Yes | Yes | Yes | Double | No | Yes | Yes | No | NR | NR |
| Al-Bader *et al.*, 2012 | Yes | Yes | Yes | Double | No | Yes | Yes | Yes | Yes | 11/35 = 31% |
| Perez Machado *et al.*, 2012 | Yes | No | Yes | Single (assessor) | No | No | Yes | No | No | 0 |

*Including placebo, non-intervention or other intervention.

†NA, not applicable; if the primary aim of the study is not efficacy.

‡The criteria follow the indication reported in Serup 2001.[6]

§"Yes" for the evaluation of efficacy of formulation I vs. placebo and "No" for that of formulation II vs. placebo.

### Meta-analysis

We used a meta-analytic approach to estimate the overall effect of cosmetic creams in cellulite treatment, using thigh circumference reduction (i.e. the most frequently reported measure) as the outcome measure in trials with more than 10 patients per arm. For this reason, we excluded eight articles without information on the outcome of interest,[19,21,22,28,29,31,34,35] as well as a study with not enough patients.[27] Three studies without any control group were not considered for the meta-analysis.[20,21,23] If different measurements of thigh circumference were reported, we considered the wider one. However, in one study, we considered the medial thigh instead of proximal thigh circumference for an inconsistency between quantitative data on the control group reported in Tables 1 and 2 and Results of the original paper.[33]

We finally included seven controlled trials, reporting the mean thigh circumference reduction in both arms and their standard deviations (SD), or the information needed to calculate them (e.g. *P*-values from parametric tests).[24,26,30,32,33,36,37] In one study, the mean reduction in thigh circumference was calculated excluding subjects with no circumference reduction.[33] Since the authors reported all original data in the text, we recalculated the mean values without excluding these subjects. When SDs from thigh circumference reduction were not reported or not directly calculable from data (e.g. *P*-values from non-parametric tests only),[33,40] they were imputed in the cosmetic cream group[40] and in the control group,[33] and calculated as the mean of the available SDs of the studies included in this meta-analysis by arms.[17] Sensitivity analyses were later conducted to assess the effect of these assumptions by varying the inputed SD from minimum to maximum values among the available SDs by arms.

### Statistical analysis

We used the mean difference (MD) in thigh circumference as the measure of treatment effect. We calculated summary estimates of the weighted MD using both fixed-effects models, using the inverse variance method, based on a mathematical assumption that every study is evaluating a common treatment effect, and random-effects models, which consider both within- and between-study variations, using the DerSimonian and Laird method.[41–43]

We presented MDs from random-effects models, that assume that the exposure effects observed in the studies are a random sample from a distribution of exposure effects, thus yielding a more global and conservative estimate.[43] Further, random-effects models have the advantage of increasing the accuracy of the exposure estimates, since the information from the study error stratum is used in addition to that from the residual stratum.

We presented combined estimates using forest plots. Results from each study are displayed as a square and a horizontal line, representing the intervention effect estimate together with its confidence interval (CI). The area of the square reflects the weight that the study contributes to the meta-analysis. The combined-effect estimate and its CI are represented by a diamond.[43] Statistical heterogeneity among studies was assessed using the chi-squared test (results were defined as heterogeneous for a *P*-value $< 0.10$),[42] and the potential inconsistency was quantified through the $I^2$ statistic, which describes the percentage of total variation across studies that is due to heterogeneity rather than chance.[44] Usually, values of the $I^2$ statistic <25% are indicative of low heterogeneity, those ranging between 25% and 75% of moderate heterogeneity, and those >75% of high heterogeneity.

For each trial, we plotted the effect by the inverse of its standard error. The symmetry of such funnel plot was assessed both visually and formally with Egger's and Begg's tests, to analyse if the effect decreased with increasing sample size.[45,46]

We conducted sensitivity analyses by excluding each study at a time from the meta-analysis. Sub-group analyses were performed to examine the treatment effect according to quality measurements. The original placebo-controlled, double-blind studies with randomization or intra-patient design were classified as studies with "High quality trial design," otherwise as "Low quality trial design."

All the statistical analyses were performed using STATA software (version 11; StataCorp, College Station, TX, USA).

## Results

### Systematic review

The main findings from the 21 selected *in vivo* studies on humans that investigated the efficacy of cosmetic products in cellulite reduction are described in Appendix 1.

For an overview of the most relevant characteristics of these studies, we reported in Table 1 the following information: first author and year, country and period, study design and number of subjects enrolled; baseline characteristics, including age, BMI and grade of cellulite, active cream tested, frequency of application, duration of intervention, description of the application and outcome measures. A brief description of each characteristic is also reported below.

The first study was published in 1987 and half of the articles were published after 2005. None of them reported the country and the period of the study setting. All studies were clinical trials, most of them recruited women only and 66% had an intra-patient study design. The smallest trial enrolled a total of 12 volunteers[20] and the biggest one 134 subjects.[31] Most of the controlled trials included a placebo group of subjects treated with an inactive cream. Four studies used a non-intervention control group[25,26,31,33] and another one used a control group of subjects treated with pills.[32]

Most of the studies that reported information on age at baseline included women below 45 years old, and the mean age was generally between 30 and 38 years. With reference to BMI, two

studies focused exclusively on obese[27] and overweight women[29] and seven studies on normal weight or slightly overweight women.[22,25,26,28,31,34,37]

About half of the active cosmetic creams tested only contained one active ingredient among xanthenes (six studies), herbals (five studies) or retinoids (two studies). The other studies tested cosmetic creams with more complex formulations, and most of them included xanthenes. In 67% of the studies, the frequency of cream application was twice/day. The duration of the studies varied between 1 month (in nine studies) and 6 months (in two studies). The specific instruction regarding the duration of the massage while applying creams was reported in two studies: 15 s in Kligman *et al.*[29] and 5 min in Epstein *et al.*[25] The efficacy of the treatment was mainly assessed using instrumental evaluations (such as thigh circumference, ultrasound analysis and plicometry), clinical observations and self-evaluation.

In Table 2, we considered potential risk of bias in individual studies, following the PRISMA Statement, including the presence of control group, placebo, randomization, blinding, sample size calculation, description of statistical methods, computer validation, information on safety and dropout.

Among all the studies considered, 18 had a control group and 13 of these used an inactive cream as placebo. Two thirds of the studies were randomized and/or had an intra-patient study design. Fifteen studies were at least single-blind. Finally, 10 studies were considered of a high quality level, that is, placebo-controlled double-blind trials with randomization and/or an intra-patient design. None of the studies reported details on sample size calculation or study power, and nine studies included less than 20 subjects. As reported by Serup in the proposal to the European Community on efficacy testing of cosmetic products,[6] groups smaller than 20 subjects are usually not considered convincing in substantiating cosmetic products that normally induce minor changes, in contrast to medical products used for skin diseases. All included papers presented results of data analysis but almost one third of these did not mention which statistical methods were used. Only three articles reported details on the statistical software used. Information on safety was described in about half of the papers and information on dropout was reported in most of the studies. The dropout rate was greater than 20% in seven studies.

### Meta-analysis

Figure 2 shows the study specific and the pooled efficacy of cosmetic creams used in cellulite treatment vs. control, using thigh circumference reduction as the outcome measure, overall and

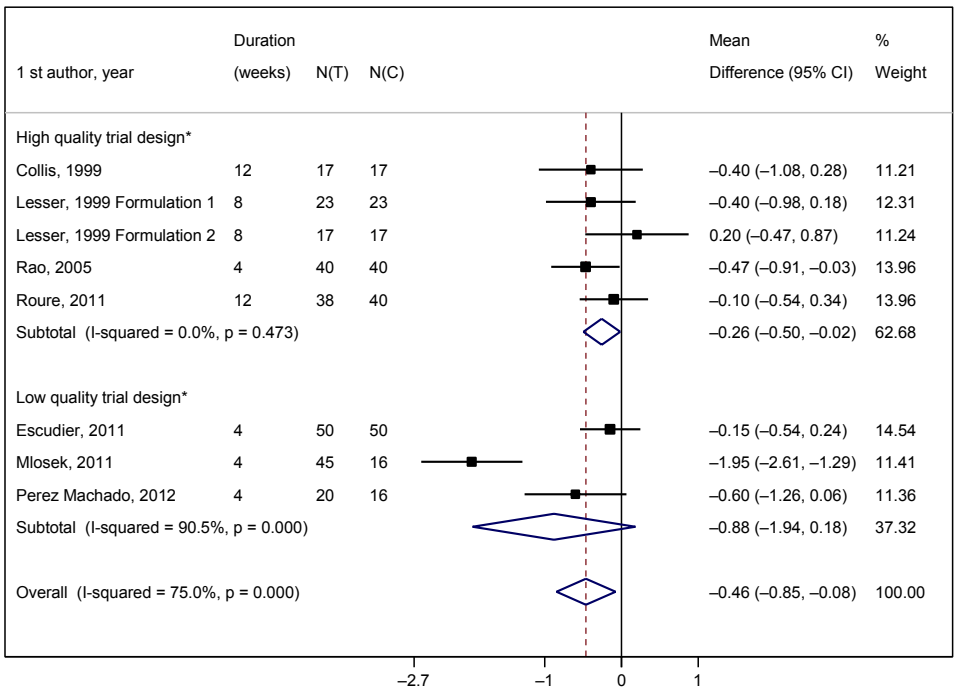


**Figure 2** Overall efficacy of cream in cellulite treatment vs. control, using the thigh circumference reduction as outcome measure, according to quality trial design. CI, confidence interval ; N(T), number of patients in the treatment group; N(C), number of patients in the control group. *The original placebo-controlled double-blind studies with randomization or an intra-patient design were classified as studies with "High quality trial design," otherwise as "Low quality trial design."

according to quality trial design. The pooled MD was −0.46 cm (95% CI: −0.85, −0.08), with significant heterogeneity between studies ($P < 0.001$). The corresponding estimates for high and low quality trial design studies were −0.26 cm (95% CI:−0.50,−0.02; $P$ for heterogeneity = 0.47) and −0.88 cm (95% CI: −1.94, 0.18; $P$ for heterogeneity < 0.001) respectively. When we considered only the three high quality trial design studies with at least 20 patients per arm, the pooled MD was −0.31 cm (95% CI: −0.59, −0.03) with no significant heterogeneity (data not shown).

The funnel plot did not show meaningful asymmetry of the studies (Fig. 3). However, one trial seemed to differ from the others due to the greater thigh circumference reduction.[40] The exclusion of this trial did not affect the overall efficacy estimate, with a corresponding pooled weighted MD equal to −0.26 cm (95% CI: −0.46, −0.07). The Egger ($P = 0.33$) and Begg ($P = 0.99$) tests confirmed that there is no evidence of publication bias, although the statistical power was modest.

## Discussion

Despite the high number of treatments for cellulite reduction available on the market, only a few scientific investigations on the efficacy of these treatments have been published. Several congress abstracts on the efficacy of anti-cellulite treatment are available in scientific databases, but data given in such short reports are scanty; thus, for most of them it is not possible to evaluate the quality of the study.

Most of the studies reviewed had important methodological flaws or lacks in reporting the methods used. There is a need for studies on this issue to improve the reporting of sample size calculations, statistical methods and details on numbers and characteristics of participants. Missing data and losses to follow-up are important sources of information and attrition bias, and for these reasons it is important to describe them. The safety profile of the tested treatment should be reported in all studies with a description of all adverse events. The use of the CONSORT (Consolidated Standards of Reporting Trials) statement would lead to better quality reporting[47] also in cosmetic science, as found with the adoption of this statement in medicine,[48] including dermatology,[49] and it is therefore highly recommended.

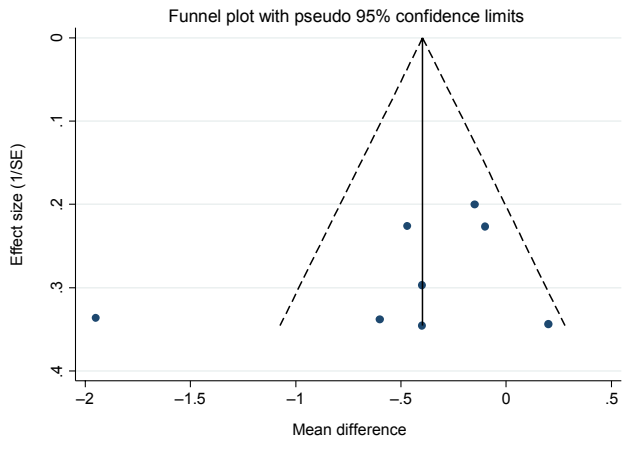


**Figure 3** Funnel plot of trials on efficacy of cosmetic products in cellulite reduction.

Randomized controlled trial is considered the gold standard for a clinical trial in proving the efficacy of a treatment, because the use of randomization and comparison to a control group is the most effective strategy to avoid potential bias in the efficacy assessment. The use of blind (or, even better, double-blind) experiments and placebo are other strategies that improve the quality of the trials. If applicable, the use of intra-patient design is an efficient strategy to reduce the number of volunteers in a trial, since it is reasonable to assume that the intra-subject variation is limited. For these reasons, the adoption of high quality trial design studies, that is, placebo-controlled double-blind studies with randomization or intra-patient design, is strictly encouraged for testing the efficacy of cosmetic products in cellulite reduction.

There are no standard technique to evaluate cellulite. Circumference measurements recorded on thighs, hips and ankles are most often used. Circumference reduction is due to both the reduction in oedema and the effect on the fatty layer, and it is utilized as an indirect measurement of the thickness of the panniculus. However, this measurement is appropriate to evaluate obesity and localized fat, but it is not accurate for cellulite, as there may be weight loss, with a consequent circumference reduction, without any improvement in the condition.[12] The other most used non-invasive techniques for the evaluation of cellulite were as follows[10,12]: the ultrasound, used to study the thickness and the quality of the connective tissue and the oedematous component of cellulite; the laser Doppler flowmetry, used to evaluate skin microcirculation; the thermography used to evaluate the local skin temperature; the plicometry, which allows to evaluate the thickness of cutaneous plicae or folds; the computerized tomography and magnetic resonance imaging, used to measure the thickness of the fatty tissue.

Among the 21 studies included in the systematic review, only seven provided sufficient information to be considered in the meta-analysis for the overall quantification of thigh circumference reduction. This points out the need for the studies to upgrade the quality of results reporting, to improve the synthesis of existing evidence.

The meta-analysis estimated a pooled MD of thigh circumference reduction between the treated and the controlled group equal to −0.46 cm (95% CI: −0.85, −0.08), with significant heterogeneity between studies. However, findings from high quality trial design studies were substantially homogeneous and when pooled together the MD decreased to 0.26 cm, being still significant.

The most relevant efficacy of a cosmetic product was reported in a trial by Mlosek *et al.*[32] This might be due to the use of pills in the control group, instead of a placebo cream, without any thigh massage. In fact, the massage itself can have a beneficial action on cellulite since it has been shown to accelerate blood flow and prevent fibrosclerosis.[50] However, the exclusion of this study, or any other study, from the meta-analysis did not materially change the summary estimate, showing that results were not driven by any single study. We tried to perform subgroup analyses by bodyweight and grade of cellulite at baseline, but the information from the original studies was scant and/or not comparable.

We were not able to identify the efficacy of a specific active agent, including caffeine, retinols or herbal extracts since most of active creams contain caffeine, alone or in a more complex formulation, and therefore we were not able to distinguish the role of each component.

In conclusion, this article provides, for the first time, a systematic evaluation of the scientific evidence of the efficacy of cosmetic products in cellulite reduction, following a rigorous methodological approach proposed by the PRISMA Statement. Using a meta-analytic approach, we found a moderate efficacy of cosmetic products in thigh circumference reduction.

## Acknowledgement

We thank Dr. Raffaella Zanzottera for the bibliographic research.

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## Appendix 1

The first study on efficacy of cosmetic product in cellulite reduction was published in 1987 and reported the efficacy of a calorie-restricted diet in combination with various treatments, including isoproterenol injections and different cream formulations, in 28 obese women who wished to lose weight.[27] With reference to cream applications only, 18 women were seen 5 days a week for 4 weeks. The study design was intra-patient, double-blind and placebo-controlled. At each visit, warm wraps with a magnesium sulphate solution were applied to each thigh for 30 min, followed by the application of one of the following formulations: (i) cream-containing colforsin (forskolin), aminophylline and yohimbine; (ii) yohimbine cream; (iii) colforsin cream; (iv) aminophylline cream. The legs treated with cream (i) reported a circumference reduction of 2.03 cm more than the control legs, treated with placebo. The corresponding values were 0.75, 1.0 and 1.5 cm for creams (ii), (iii); and (iv) respectively. Results were statistically significant for all creams except for the second one. One adverse reaction was reported for the first cream.

In a trial, 12 healthy volunteers were enrolled and treated twice a day for 3 months with Opticell-U-Lite™ Gel (i.e. an aminophylline/theopillyne gel in a 2% solution) on thighs and buttocks.[20] Photographs, ultrasounds of the lateral thighs skin and measurements of the thighs, waist and hips were collected at baseline and after 3 months of treatment. Aminophylline serum levels, lipid profiles and blood glucose levels were collected at baseline, after 1 h, 3 weeks, 6 weeks and at the end of the study. The only anthropometric measurement that decreased during the study period was thigh circumference, with an average decrease of 0.5 cm, with no weight reduction. A decrease in the thinning of the lateral thigh subcutaneous layer was observed in eight patients out of 12. Photographic analysis showed an improvement in the appearance of cellulite in all patients. During the study period, the lipid levels did not show any significant change and aminophylline blood levels tended to increase after 6 weeks of treatment.

In another investigation, 110 female patients were enrolled and 89 completed the study.[23] All patients were treated and divided into two groups using different products and methods of application. The cosmetic cream was applied to the affected areas of the thighs once a day for 1 month. The first group (mono-therapy) used a cosmetic cream with active ingredients of botanical extracts (horsechestnut, ivy, algae, bladder-wrack, thermal plankton, butcherbroom and soy protein). The second group applied three active products (triple therapy) with alternate application according to a specific schedule. Ultrasound, thigh circumference measurements, and clinical assessment (including photography) were collected at baseline, at 30 (end of the efficacy study) and 60 days (maintenance study). Circumference measurements were not presented because they did not correlate with ultrasonographic or subjective response, even though they were standardized and performed by the same individual at all visits. After 30 days of treatment, patients treated with mono-therapy or triple therapy reported a significant average subcutaneous loss of 1.9 and 2.8 mm respectively. Most patients perceived improvement in their cellulite reduction. Two patients reported minor adverse events.

In another study, 17 healthy women with normal bodyweight were recruited and randomly assigned to two groups: the first group tested the active agent Skinny Dip™ and the second one the placebo cream. Both trials had an intra-patient design with a duration of 8 weeks.[25] The active or placebo cream was applied only twice a day on the treated thigh, with a 5 min massage. At baseline and at each weekly visit, subjects were weighted, photographed and visually examined. Also, anthropometric circumferences (thigh and abdomen) and thickness of skin folds at fixed points were recorded. Data analyses revealed no differences in either circumference or skin fold thickness when comparing areas treated with active or placebo cream to untreated ones. No adverse events and significant weight change were reported during the study period.

Collis *et al.* reported results of a 12-week, randomized, intra-patient, controlled trial where the efficacy of two different treatments for cellulite was assessed.[24] The treatments investigated were twice-daily application of aminophylline cream (2% aminophylline with 10% glycolic acid) and twice-weekly treatment

 

with Endermologie. Sixty-nine women with cellulite on thighs and buttocks were enrolled and randomized into one of three groups (23 patients in each) to receive one or both treatments. Since the aim of this systematic review is focused on cream cellulite treatment only, we describe here the results of the group receiving aminophylline to one thigh/buttock and a placebo cream to the other, in a double-blind setting. Morphological measurements (i.e. BMI, thigh circumference and ultrasound-determined subcutaneous fat thickness) and photographs were undertaken at baseline and after 12 weeks. Of the 23 patients initially enrolled in the aminophylline cream vs. placebo group, 17 completed the study. Two women developed a dermatological reaction to the aminophylline cream. There was no significant difference in the thickness depth and thigh girth between legs treated with the aminophylline cream and those treated with placebo. A subjective assessment of the cellulite appearance by both the patient and the investigator (based on photograph and clinical examination) revealed poor results from the aminophylline treatment: 3 of 17 patients reported an improvement in cellulite appearance in the leg treated with the aminophylline cream, and the investigator did not detect any clear difference between them.

In a double-blind randomized preliminary trial, a group of 20 women with moderate cellulite on thighs was treated twice a day on one side for 6 months with a 0.3% stabilized retinol cream. The opposite side was treated with placebo (i.e. vehicle ingredients only).[29] Each application consisted in a 15-seconds gentle massage. The efficacy of the tested active formulation was assessed through a clinical evaluation by a dermatologist, a self-evaluation survey, ultrasounds analysis (on five women only) and local blood flow measured by laser Doppler. These measurements were undertaken at baseline and the end of the study. Out of 19 subjects completing the study, 13 rated the retinol-treated side as the most improved, five subjects noted no difference between the sides and one chose the placebo-treated side. The dermatologist estimated the retinol-treated side as the most improved in 12 of 19 subjects. In seven patients a difference could not be discerned. Both by self-assessment and by dermatologist's rating, the differences in favour of the retinol-treated sides were statistically significant. Laser Doppler showed that the blood flow value increased significantly from 30.8 at baseline to 35.2 after the treatment on the retinol side; on the placebo-treated side instead, blood perfusion remained unchanged at the end of the treatment period. On five women, thickness increased from 1.44 to 1.60 mm on the retinol-treated sides, while on the placebo-treated sides, the values were similar before and after treatment. There was no adverse event.

Two formulations with different percentages of caffeine were tested in a double-blind placebo-controlled study with intra-patient design including 41 patients.[30] Anthropometric measurements (abdomen, hips, triceps and thighs) and dermatological evaluation were collected at baseline and after one and 2 months of treatment. The differences between measurements at baseline and at the end of the study were reported. Both 2% and 1% cream showed a significant improvement in thickness of the adipose tissue in all the measured areas. The more concentrated cream was significantly more effective than the less concentrate one in the hips and triceps areas. Anthropometric measures did not show a significant change for any area of the body for either cream. Clinical evaluation reported an improvement in orange peel skin appearance, skin tone and skin tension with non-considerable change in the appearance of skin lesions or stretch marks.

A study focused on the validity of a new photographic technique in the evaluation of the skin treatments efficacy presented results from the first 2 months of a double-blind intra-patient clinical trial comparing the effect of a slimming product to a placebo formulation, with a left-right side randomization.[34] The trial enrolled 30 healthy women, with a BMI of 18–25 kg/m$^2$, smoking less than 10 cigarettes a day and drinking less than two alcoholic drinks a day. For 2 months, volunteers applied each of the two formulations either on the right or the left thigh twice a day. Photographic and echographic examinations were carried out at the beginning of the trial and after 2 months. At the end of the study, the average scores of cellulite intensity obtained by the photographic technique (ranging from one, i.e., no sign of cellulite, to seven, i.e., severe local lipodystrophy) decreased on average from 3.64 to 2.1 in thighs treated by active cream, whereas placebo-treated thighs did not show significant recovery. An improvement in the orange-peel look of the skin of the treated thighs was observed in 21/30 subjects, while eight volunteers experienced an apparent aggravation. An 8.5% decrease in the thickness of subcutaneous adipose tissue was noted on average on thighs treated with the slimming product, while a 2.9% increase was recorder on the placebo-treated thighs. The 11.4% differential slimming was significant. On the basis of a self-evaluation questionnaire, distributed to each volunteer after the study completion, the difference in the satisfaction towards the two products was significantly in favour of the active cream.

Fifteen women aged between 26 and 44 years, who requested liposuction to improve mild to moderate cellulite were included in a clinical trial comparing the effect of retinol to a placebo hydrating formulation, using a left-right randomization.[35] The active cream was applied on one thigh on a daily basis for 6 months; a placebo was applied on the other thigh. Investigators were not informed about the randomized left-right side allocation of the products. Ultrasounds measurements and measurements of skin elasticity were performed at study entry and after 3 and 6 months. Three and 6 months after the study entry, the mean dermal thickness remained almost unchanged both in retinol-treated and placebo-treated areas. Tensile properties of the skin showing the mattress phenomenon progressively improved on the retinol-treated thighs, with a 17% increase in elasticity and a 15.8% decrease in viscosity, while no changes were observed in the placebo-treated thighs. In five women with

 

lumpy-bumpy skin, the appearance of the skin showed either little response or no response to the retinol treatment.

The efficacy of an anti-cellulite product containing retinol, caffeine and ruscogenine compared to a placebo was assessed in a double-blind, randomized clinical trial enrolling 46 healthy women with a moderate level of cellulite on the thighs and a BMI between 20 and 25 kg/m$^2$.[22] The products were applied regularly and uniformly over the entire thigh by circular massage, twice a day for 3 months, with one thigh treated with the active product and the other one with the placebo. Treatment efficacy was evaluated using profilometric analyses of the skin macrorelief of the external thigh face, 3D ultrasound imaging, cutometry and laser Doppler flowmetry. Measurements were carried out before the first application and after 28, 56 and 84 days of application. With the active product, the skin macrorelief decreased by 53.1% after 84 days, compared to 14% in the placebo group. The improvement of the macrorelief was significant at each measurement for the active product and after 56 or 84 days for the placebo. 3D ultrasounds found that both the active product and the placebo significantly improved the texture of the dermis and the structure of the hypodermis (echogenicity and texture). The active and the placebo products had a similar significant firming effect. Although the increases in mean blood flow and in homogeneity were greater with the active product than with placebo, no significant differences were observed between the two formulations.

A French study was focused on the mechanism of adipocyte differentiation. This study tested a slenderizing complex formulated at 4% in an emulsion rich in flavonols, obtained from the combination of two plants: *Prunella vulgaris* and *Celosia cristata*.[28] Tests were carried out both *in vitro* and *in vivo*. The *in vivo* study consisted in two clinical trials. A placebo-controlled clinical trial enrolled 24 healthy volunteers with a BMI between 21 and 26 kg/m$^2$ and a bodyweight fat percentage between 26% and 35%. After 28 days of twice-daily application, the slenderizing complex significantly improved the skin elasticity (+7.5%) and tone (+15.6%) if compared to placebo group. The slenderizing effect of the new complex was tested in another trial involving 26 healthy volunteers as compared to a group treated with placebo cream. After 56 days of twice-daily application, the reduction in abdominal circumference was 0.9 cm in the placebo group and 2.2 cm in the active group, without significant weight loss. The comparison between the groups was significant.

A two-centre, double-blinded, randomized placebo-controlled trial with intra-patient design was performed on 34 women to evaluate the efficacy and safety of Spa MD Anti-Cellulite Cream™.[36] The active ingredients of the anti-cellulite cream tested were as follows: piper nigrum, citrus aurantiu dulcis, zingiber officinale, camellia sinesis, cinnamomum cassia, capsicum annum resin and caffeine. After the application of the active and placebo cream, the volunteers worn a bioceramic neoprene shorts for at least 6 h (ideally while the subject was sleeping) to enhance the penetration of the agents by occlusion. Circumference of the lower and upper thigh and digital photographs were collected at baseline and after 4 weeks of treatment. The average decrease in the lower thigh circumference was 2.08 cm for the leg treated with the active cream and 1.04 cm for the one treated with the placebo cream. The corresponding average circumference reductions of upper thigh were 1.78 and 1.50 cm. Pre- and post- study photographic evaluations were performed by five blinded, independent board-certified dermatologists. Overall, the improvement in cellulite reduction was observed in legs treated with active cream in 68% of women. From the self-evaluation survey, it emerged that 62% of women noticed an overall improvement in their cellulite, 62% of whom reporting greater improvement in the thigh treated with the active cream. No adverse events were reported.

A Brazilian clinical trial published in 2007 enrolled 134 women, the highest number of volunteers recorded in the published anti-cellulite trials.[31] The aim of the study was to determine the efficacy of a 7% caffeine solution to treat cellulite, based on microcirculatory parameters and centimetric measurements. The study design was intra-patient, with a leg treated with active cream and a leg without any treatment. The evaluated parameters were the changes of perivascular dermic oedema and the circumference of thighs and hips in treated and non-treated legs. After 28 days of twice-daily application, 99 volunteers completed the study. A significant reduction in thigh and hip circumference was recorded in more than 80% and 67.7% of the women, respectively, for the treated legs. Microcirculatory parameters did not change significantly after treatment. Smoking habits, alcohol drinking and regular physical activity were not significantly related to circumference reduction. No adverse events were reported.

The efficacy of an anti-cellulite cream gel with a defined protein fraction of pumpkin, cranberry fruit and orange extracts was tested in an uncontrolled trial including 25 women, aged 25–55 and with a two to three cellulite grade on thighs.[21] During the 4-week study, skin moisturization, roughness and ultrasonography analyses were conducted at baseline, after 2 and 4 weeks of treatment. At the end of the study, the skin moisturization significantly increased by 23% from baseline. The corresponding value for skin roughness was a significant decrement of 21%. At baseline, the thickness of the hypodermis was 3.4–23 mm (mean value: 12.6 mm). After 4 weeks of treatment the thickness was reduced to 2.2–16.6 mm (mean value: 10.07 mm). The difference between mean values was statistically significant. The volunteer's self-evaluations showed improvements in the skin appearance after treatment. No skin reaction was observed.

In a recent study, the efficacy in improving skin cellulite appearance of a newly developed slimming product in conjunction with a balanced but not low-calories diet was evaluated.[26] Fifty non-obese women with a cellulite severity score of at least two on the L'Oréal Cellulite Chart® and a BMI between 20

 

and 27 kg/m$^2$ were enrolled in a monocentric, randomized, intra-patient trial. The test product, containing 5% caffeine and a flavonoid-rich *Nelumbo nucifera* extract, was applied on one side (left or right) of the thigh and the hip twice a day for 4 weeks, according to the randomization list. The untreated sides were used as controls. Efficacy was assessed by blind assessors through clinical evaluation (Cellulite Clinical Score according to the L'Oréal Cellulite Chart® without tissue mobilization and after pinching), skin tonicity measurements, circumference measurements of the upper part of each thigh, and reconstructed volume of the thigh, hip and buttock. The mean BMI among all subjects was 24 kg/m$^2$ at baseline and 23.8 kg/m$^2$ at the final visit. With regard to the cellulite clinical score without pinching, there was a reduction in the score on both treated and untreated sides vs. baseline values at 4 weeks, but this reduction was statistically greater on the treated side than on the untreated side. The difference in the evolution of the clinical score after pinching between baseline and after 4 weeks was significantly in favour of the treated side. Skin tonicity increased significantly on the treated side only, with a notable difference vs. the untreated side after 2 ($P = 0.006$) and 4 ($P = 0.039$) weeks. After 2 weeks, the circumference measurement showed a significant reduction in the upper part of the thighs, with no considerable difference in the treated (−0.27 cm) and the untreated ones (−0.21 cm). After 4 weeks of treatment, the reduction in the upper thigh circumference was significant for the treated side only (−0.33 cm vs. −0.18 cm), with a notable difference between the treated and untreated side ($P = 0.037$).

A study aimed at investigating the possibilities of imaging of subcutaneous tissue and skin using classical and high-frequency ultrasonographies in aesthetic dermatology, showed results from a clinical trial that tested the efficacy of an anti-cellulite cream from dermocosmetic line Pharmaceries, containing hydrolysed Cucurbita Pepo, Vaccinium macrocarpon, Citrus Aurantium Dulcis and L-ergothioneine, as compared to a control group.[32] Sixty one women aged 22–62 years with a cellulite diagnosis based on a palpation examination were involved in the trial. A first group of 45 women applied the anti-cellulite cream twice a day for 30 days on the cellulite-affected area. The second group of 16 women took a placebo in the form of pills. Classic and high-frequency ultrasound examinations on the posterior part of the thigh, clinical evaluation of the cellulite stage according to Nürnberger-Müller scale, and measurements of thigh circumference were performed before the therapy and after its completion. Classical ultrasound examination revealed significant changes in the subcutaneous tissue thickness and total thickness of subcutaneous tissue and dermis after therapy in the active cream group, but no significant changes in the control group. The analysis of the high-frequency ultrasound examination showed improvements in most of the evaluated parameters, including epidermal and dermal thickness, only in the group of patients using the anti-cellulite cream. Average thigh circumference decreased from 56.74 to 54.58 mm in the group using the active cream and from 58.09 to 57.88 in the control group. A reduction in the cellulite stage according to the Nürnberger-Müller scale was detected in about 84% of the women using the active cream, while no significant differences emerged in the control group.

A French study presented results from three studies investigating the mechanism of action (*in vivo* and *ex vivo* studies) and the efficacy (clinical study) of an anti-cellulite product combining tetrahydroxypropyl ethylenediamine, caffeine, carnitine, forskolin and retinol.[37] The clinical study was a double-blind, randomized, comparative trial and included two parallel groups of women presenting a modest amount of orange peel on thighs, hips, buttocks and stomach. Forty of the 78 recruited women tested a placebo (a basic gel with the same texture of the active product containing mainly water, gelifying and preservative system), whereas the remaining subjects tested the active cream. Each subject applied the active product or the placebo through as light massage on buttocks, hips, stomach, waist and one arm according to a randomization table. The applications were performed twice daily (morning and evening) for 12 weeks. Clinical evaluation, skin hydration, and circumference measurements of one arm, waist, abdomen, hips/buttocks and one thigh were performed by the same blinded technician before the first application and after 2, 4, 8 and 12 weeks of application. After 4 weeks of twice-daily application of the product, significant reductions in circumference of abdomen, hips–buttocks and waist were observed. Improvements concerned all the measured body parts after 12 weeks; the average measured reduction ranged from −1.1 cm for the abdomen to −0.3 cm for the arm or middle thigh. In the placebo group, after 12 weeks, the circumference of three areas (arm, abdomen and upper thigh) was significantly decreased; the average measured reduction ranged from −0.8 cm for the abdomen to −0.1 cm for the middle thigh. At the end of the study, no significant difference between the anti-cellulite product and placebo was found. After 12 weeks, the percentage of improvement in skin hydration was 67% in the active and 37% in the placebo group, with a significant difference. Clinical evaluation of the tonicity, orange peel, stubborn cellulite and contracted buttocks showed a general improvement of the tested areas at any points in both groups. After 12 weeks of application, the active product had a higher effect than the placebo on 9 parameters of 13 tested.

The anti-cellulite efficacy of an Italian multifunctional formulation containing visnadine, Ginko Biloba Dimeric Flavonoids Phytosome® and escin was tested on 25 female volunteers affected by fat accumulations, as well as by slight-to-moderate cellulite in the lower limbs.[38] The clinical study was a single-blind, randomized, intra-patient, placebo-controlled trial. The following measurements were performed at baseline and at the end of the 4-week study: clinical evaluation of cellulite, morphometric measures of thigh circumferences (upper, median and lower third), contact thermography for the assessment of the

 

thermographic stage of cellulite, skin elasticity measured on the inner thigh for the evaluation of elasticizing/firming efficacy, ultrasonography performed on the outer thigh to measure the thickness of the panniculus adiposus and spectrophotometric analysis for the assessment of the activity on surface microcirculation There were two dropouts due to personal reasons independent from the trial itself and there were no remarkable bodyweight variations during the study period. A statistically significant reduction in thigh circumference was observed in the active group as compared to placebo group. In particular, the mean reductions in the active group were as follows: −0.9 cm in the upper third, −1.2 cm in the median third and −0.6 in the lower third. A significant 17% reduction in the mean score of the thermographic stage of cellulite was reported in the active group, as compared to baseline. The comparison to placebo was borderline significant ($P = 0.06$). As compared to placebo, significant improvements in skin tone (20%) and in the general vascular condition (3%) were observed; a non-significant reduction in the panniculus adiposus (9.4%) was found. Clinical evaluation showed a general improvement of the areas treated with the active product. During the study period, one adverse event was reported, classified as "aspecific skin reaction."

Another study tested the *in vitro* and *in vivo* efficacy of sulfo-carrabiose, a sugar-based cosmetic ingredient with anti-cellulite properties.[39] In particular, the clinical study included 50 female volunteers followed up for 8 weeks, divided into two different randomized, double-blind, intra-patient controlled trial. In the first trial, a cosmetic formula containing 3% of sulfo-carrabiose solution was tested against a placebo formula. In the second trial, a cosmetic formula containing only 3% of caffeine was tested against a formulation with a combination of caffeine 3% + 3% of sulfo-carrabiose solution. The volunteers applied twice daily the assigned cream for 8 weeks, with small circular movements until it was fully absorbed into the skin. As compared to placebo, the appearance of cellulite was significantly reduced by 9% after 4 weeks of treatment and by 11% after 8 weeks among the volunteers who used the formula containing 3% sulfo-carrabiose solution. After 4 weeks, the volume of volunteers' thighs treated with 3% sulfo-carrabiose solution was significantly reduced by 16 $cm^3$, as compared to placebo group. The reduction in thigh circumference in the arm treated with 3% sulfo-carrabiose solution was 0.6 cm after 4 weeks and 0.7 cm after 8 weeks of treatment, statistically significant as compared to placebo group. The results obtained with the sulfo-carrabiose solution were even better than those reported in the group treated with caffeine only: after 8 weeks, the circumference reduction reported in the group treated with combination of sulfo-carrabiose solution and caffeine was 0.7 cm as compared to 0.3 cm in the group treated with caffeine only.

A recent study evaluated the *in vitro* and *in vivo* efficacy of selected cosmetic ingredients as anti-cellulite agents.[19] The clinical *in vivo* study was a randomized, double-blind, intra-patient trial on 35 healthy women with a modest amount of orange peel visible on unpinched thighs, where the efficacy of a complex formulation containing *Furcellaria lumbricalis, Fucus vesiculosus*, retinol, conjugated linoleic acid and a glaucine mixture was compared to a placebo formulation containing vehicle ingredients only. Subjects were asked to apply the products on the thigh unilaterally once a day with a circular massage. Ultrasound imaging and clinical evaluation of cellulite appearance by a single dermatologist through a nine-grade scale were collected at baseline and after 4, 8 weeks, and at the end of the study, that is, 12 weeks. In the thighs treated with the active cream, from baseline, tissue thickness decreased in average of 0.2 mm at 4 weeks, 0.15 mm at 8 weeks and 0.55 mm at 12 weeks. In the placebo-treated thighs, the corresponding average reductions from baseline were 0.17, 0.05 and 0.004 mm respectively. The difference in thickness reduction between the active cream and the placebo cream was significant at 12 weeks. A decrease in cellulite on both thighs treated with active and placebo creams was noted every time a scheduled measurement was taken (vs. baseline). On average, the active complex formulation significantly improved cellulite grading at 8 weeks, with a 1.3 grade reduction vs. a 0.7 grade reduction for placebo. At 12 weeks, the active product improved cellulite by 1.7 grade and the placebo product by 0.9. No adverse event was reported in any of the subjects tested with either formulation.

In a Brazilian study, 36 women aged between 18 and 29 years and with BMI ranging between 18.5 and 29.9 $kg/m^2$ were enrolled to test the effects of cryotherapy with a camphor and menthol gel, used alone, on the body composition, fat percentage and body self-image.[33] Volunteers were randomly divided into two groups: 20 in the treatment group and 16 in the control group (i.e. no treatment). The treatment consisted in the application of a thin gel layer (carbomer, glycerine, triethanolamine, phenoxyethanol/methyldibromoglutaronitrile, alcohol, camphor, menthol, menthe piperita extract, zingiber officinale extract, cinnamomum zeylanicum extract, CI 42090 1%, water) on the body perimeter. Volunteers wore two-piece bathing suit. Afterwards, they could choose to remain in supine position or in a sitting or orthostatic position for 30 min. The gel was removed by the volunteers with a dry towel or absorbent paper. After that, a body hydration lotion was applied; all volunteers were asked not to take a shower for the two hours following the gel removal, to avoid possible unpleasant sensations. On average, 8.45 applications were performed by the volunteers in the treatment group. The applications were three or four times a week with a 1- or 2-day interval between the applications. As compared to baseline, at the end of the follow-up, a significant decrease in body perimeter measure (arm, waist, hip abdomen and thigh) and in medial axillary, pectoral and abdominal skin fold, were reported in the treatment group.