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EVIDENCE-BASED REVIEW

Cellulite: An Evidence-Based Review

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Abstract

Background Cellulite is a multifactorial condition that is present in 80–90 % of post-pubertal women. Despite its high prevalence, it remains a major cosmetic concern for women. A wide range of products and treatments for cellulite reduction is available; however, no systematic review has been performed so far to evaluate the efficacy of the available treatment options for cellulite.

Objective The objective of this review is to provide a systematic evaluation of the scientific evidence of the efficacy of treatments for cellulite reduction.

Methods This systematic review followed the PRISMA guidelines for reporting systematic reviews and meta-analyses. Only original articles in English or German reporting data on the efficacy of cellulite treatments from in vivo human studies were considered. In total, 67 articles were analyzed for the following information: therapy, presence of a control group, randomization, blinding, sample size, description of statistical methods, results, and level of evidence.

Results Most of the evaluated studies, including laser- and light-based modalities, radiofrequency, and others had important methodological flaws; some did not use cellulite severity as an endpoint or did not provide sufficient statistical analyses. Of the 67 studies analyzed in this review, only 19 were placebo-controlled studies with randomization. Some evidence for potential benefit was only seen for acoustic wave therapy (AWT) and the 1440 nm Nd:YAG minimally invasive laser.

Conclusion This article provides a systematic evaluation of the scientific evidence of the efficacy of treatment for cellulite reduction. No clear evidence of good efficacy could be identified in any of the evaluated cellulite treatments.

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Key Points

- No biophysical measurement exists with which to evaluate cellulite.
- Most of the studies reviewed had important methodological flaws.
- No clear evidence of good efficacy could be identified in any of the evaluated cellulite treatments.
- Some evidence indicates acoustic wave therapy (AWT) and the 1440 nm minimally invasive laser treatment could have a potential benefit on cellulite.

1 Introduction

Cellulite is a topographic and localized skin condition that is most commonly found on the posterolateral thighs, buttocks, and abdomen. It is often identified by a dimpled or orange-peel appearance of the skin's surface. In 1978, Nürnberger and Muller [1] first described cellulite as a result of sex-related differences in the structure of skin and subcutaneous tissue. It is widely accepted that the perpendicular orientation of the fibrous septa in women allows the underlying fat to protrude, creating a rippled appearance.

The oblique nature of these fibers in men appears to prevent this phenomenon. More recent studies confirm these sex-related structural differences [2] and further explain the appearance of cellulite as a result of several overlapping physiological alterations, such as focally enlarged fibrosclerotic septa that tether the skin in areas of cellulite and/or an uneven dermal–hypodermal interface [3, 4].

Although exact epidemiological data are still lacking, most studies claim that cellulite is present in 80–90 % of post-pubertal women [3]. Given the ubiquitous nature of cellulite, it is more appropriately thought of as a secondary sex characteristic rather than a disease. However, digitally altered photos in the media continue to not only alter the perception of beauty, but also to deceive the public about the true frequency of this condition that remains a major cosmetic concern for women.

One of the main problems in the evaluation of anti-cellulite products and procedures is the lack of a precise and reproducible method for quantifying cellulite. Available methods that objectify skin topography are either not precise enough (e.g., stereoscopic systems) or use a measurement field that is too small to capture the whole cellulite pattern (e.g., fringe projection systems). Therefore, a myriad of techniques measure cellulite indirectly with a surrogate marker instead of measuring the cellulite itself.

The most common approach taken to assess the improvement of cellulite is to compare thigh circumference measurements before and after treatment [5, 6]. However, this technique has low reliability, and it is not yet proven that a reduction in circumference and/or subcutaneous fat corresponds with a decrease in cellulite severity. The same applies to the use of calipers [7], magnetic resonance imaging (MRI) [8], or X-ray imaging [9], although MRI assessments can be used to identify the presence of underlying septa associated with the presence of depressed cellulite lesions [4]. Another approach taken to assess the efficacy of cellulite treatment is the measurement of skin elasticity [10] or through dermal parameters like dermal thickness or density measurements [11]. While it is accepted that these are important in skin aging, whether they have a significant influence on cellulite is unclear. This also applies to other methods that assess blood flow or vascularization, like laser Doppler [12] or thermography [13]. As long as there is no clear proof for a correlation between these parameters and cellulite, the suitability of these methods remains speculative.

The clinical assessment of cellulite remains a subjective one despite clear qualitative and quantitative measures taken to make evaluation more effective and reliable. While the 4-point Nürnberger–Muller (NM) scale has been used for decades [1], the Cellulite Severity Scale (CSS) by Hexsel et al. [14] has become the new standard classification system for clinical evaluation and treatment response. This scale adds four additional clinical morphologic features to the NM scale: the number of evident depressions, the depth of the depressions, the morphological appearance of skin surface alterations, and the grade of laxity and flaccidity (sagging skin). The severity of each item is graded from 0 to 3, allowing for a final sum between 1 and 15. The sum could also be 0, in case of complete cellulite absence. Even though the scale is validated and comes with a set of pictures illustrating each morphological feature, the clinical rating of cellulite is still not entirely objective and is subject to variation. This is complicated by the fact that the process of taking standardized photos of cellulite is difficult and might require special equipment with specific room conditions for optimal performance [15].

The objective of this review is to provide a systematic evaluation of the scientific evidence of the efficacy of treatments for cellulite reduction. Providing physicians and practitioners with an overview of available treatment options, including their capabilities and limits, will increase understanding in the treatment of this challenging skin condition.

2 Materials and Methods

This systematic review followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines [16]. In September 2014, we performed a literature search in the PubMed and ScienceDirect databases using the string: cellulite OR 'edematous fibrosclerotic panniculopathy' OR 'gynoid lipodystrophy' OR 'adiposis edematosa', resulting in 1000 references. Only original articles in English or German reporting data on the efficacy of cellulite treatments from in vivo human studies were considered. Two review team members (SL and NK) retrieved and independently assessed the potentially relevant articles as well as their references [3, 17–28]. One relevant study that has not yet been published was also added because study information is publicly available [29]. Conference papers and abstracts were excluded, as suggested by PRISMA guidelines. In total, 67 articles were analyzed for the following information: therapy, presence of a control group (placebo, untreated, or active), randomization, blinding, sample size, description of statistical methods, results, and level of evidence (Fig. 1).

3 Results

Although cellulite is not a disease in the proper sense and there is no current cure for it, a multitude of treatments have been developed to improve its appearance. Along with the application of laser, light, sound or radiofrequency (RF) energy, more conventional treatment modalities have been evaluated, including cosmeceuticals, supplements,

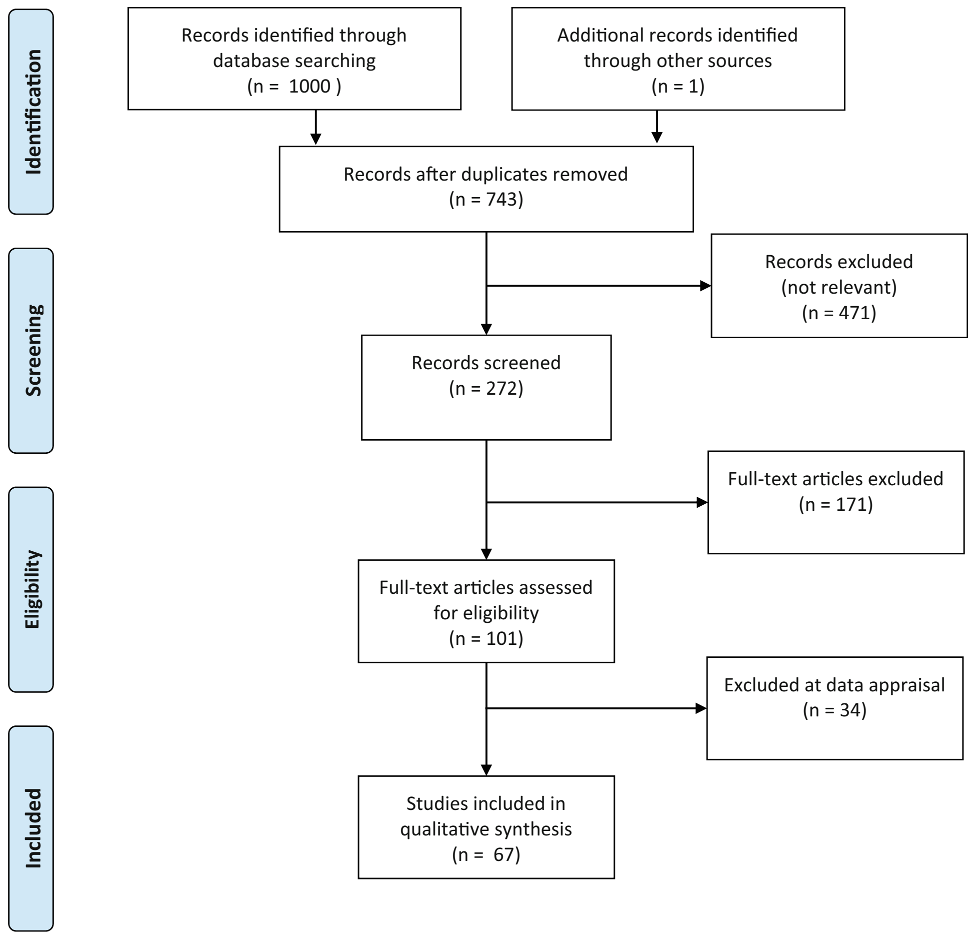

Fig. 1 Flow chart showing identification and selection of studies

and mechanical stimulation. Minimally invasive techniques, like subcision and collagenase injections, are intended to break the septa that cause dimpling. Although the treatments widely differ, they are all designed to minimize the cellulite appearance and to achieve a smoother skin surface.

3.1 Mechanical Stimulation

One of the oldest methods of cellulite treatment is mechanical tissue stimulation. This involves lymphatic drainage of the skin, which is either performed manually or with an assisted device. A device-based modality delivers positive pressure to the skin and subcutaneous tissue via rhythmic folding and unfolding as well as negative pressure through aspiration [30]. It is assumed that this mechanical stimulation causes damage to the subcutaneous fat cells. As these damaged fat cells heal, they are purported to rebuild with an improved distribution that evens skin contour [31]. Manual mechanical stimulation of the skin is further supposed to stimulate microcirculation as well as lymphatic drainage to improve lymphedema, which may further improve the appearance of cellulite [32, 33].

Six studies evaluated the effect of mechanical stimulation on the appearance of cellulite (Table 1). Among the studies, only one was a randomized controlled study (RCT) [7], whereas five were observational studies [30, 32, 34–36]. The efficacy of the treatments was mainly assessed by clinical assessment and circumference measuring. One study used a digital caliper to determine fat thickness [7].

The device-based deep tissue massage was evaluated in two uncontrolled studies [30, 34]. In total, 151 subjects were treated with 15 treatments each. Both studies found a significant improvement in cellulite severity and circumference reduction when compared with baseline. Three studies [32, 35, 36], with a total of 39 subjects, evaluated manual tissue stimulation and found a significant reduction of thigh circumference after 10–14 treatments. However, clinical improvement in cellulite appearance was not seen. The only RCT, conducted by Bayrakci Tunay et al. [7], compared the effectiveness of several massage techniques: manual massage, manual lymphatic drainage, and connective tissue manipulation. The results of 60 treated patients reported a significant decrease in thigh circumference and fat thickness assessed by skin fold caliper in each of the treatment methods.

Table 1 Overview of studies evaluating the efficacy of mechanical stimulation therapies in the treatment of cellulite

Therapy	References	Year	Design	Control	Number	Statistical analysis	Results[a]	Evidence[b]
Device based	Güleç [30]	2009	OS	UC	33	Yes	++	4
Combination	Bayrakci Tunay et al. [7]	2010	RCT	A	60	Yes	NA	2b
Manual	De Godoy and De Godoy [32]	2011	OS	UC	14	Yes	+	4
Manual	De Godoy et al. [35]	2012	OS	UC	10	Yes	NA	4
Device based	Kutlubay et al. [34]	2013	OS	UC	118	Yes	++	4
Manual	Schonvvetter et al. [36]	2014	OS	UC	15	Yes	−	4

A active, *MA* meta-analysis, *NA* not evaluated, *OS* observational study, *P* placebo, *RCT* randomized controlled study, *SR* systematic review, *U* untreated, *UC* uncontrolled, + indicates non-significant improvement, ++ indicates significant improvement, +++ indicates significant improvement and superiority over control, − indicates no improvement to baseline, −− indicates worsening to baseline

[a] With regard to the endpoint improvement of cellulite appearance

[b] Levels of evidence: 1a = MA or SR (with homogeneity[a]) of RCTs; 1b = Individual RCT (with narrow confidence interval); 2a = SR (with homogeneity) of cohort studies; 2b = Individual cohort study (including low-quality RCT); 3 = SR (with homogeneity) of case-control studies or individual case–control Study; 4 = case-series (and poor-quality cohort and case–control studies); 5 = Expert opinion without explicit critical appraisal, or based on physiology or bench research

The efficacy of mechanical tissue stimulation in the treatment of cellulite is not clear. Though an improvement in cellulite grading and a reduction in thigh circumference was observed after device-based deep tissue massage in most of the studies, none of these studies compared mechanical tissue stimulation with a placebo or an untreated control.

3.2 Topicals

Cosmetics and cosmeceuticals are among the most commonly used methods to reduce the unwanted appearance of cellulite. Most anti-cellulite products contain caffeine, and/or retinol formulations, and/or botanical derivatives as the main active ingredients. The presumed therapeutic effect of these ingredients is through the lipolysis of the adipose tissue, the stimulation of the peripheral microcirculation to facilitate lymphatic drainage, and the reduction of edema [37]. Alkaloids, like caffeine, are used because of their suggested effect on adipocyte lipolysis where phosphodiesterase activity is inhibited and cyclic adenosine monophosphate (cAMP) levels are increased [23, 38]. Caffeine should further activate the triglyceride lipase enzyme that converts triglycerides into free fatty acids and glycerol [37]. Retinol serves as an anti-adipogenic by inhibiting the differentiation of human adipocyte precursor cells [39, 40] to improve skin thickness and tensile properties of cellulite skin in vivo [41]. The potential aim of potent botanicals, such as *Gingko biloba*, C*entella asiatica*, and horse chestnut are not only to slow lipogenesis and to activate lipolysis, but also to act as antioxidants with anti-inflammatory effects [37].

A total of 14 RCTs [12, 13, 41–52] plus one meta-analysis with a systematic review [53] and two observational studies [54, 55] that are missing inductive statistics have been published on the treatment of cellulite with topical formulations (Table 2). In total, over 600 patients participated in these clinical trials. Five of these studies enrolled fewer than 20 subjects [42, 44, 45, 52, 55], six studies enrolled 21–50 subjects [12, 41, 43, 46, 49, 54], and four studies enrolled 51–100 subjects [47, 48, 50, 51]. About half of the published studies evaluated complex topical formulations combining caffeine and/or retinol with other, mainly plant-derived, ingredients. Only two studies [46, 48] evaluated the effects of caffeine alone on cellulite treatment, and two studies [45, 55] evaluated retinol exclusively. Of the four studies that tested a single active ingredient, only one study [45] found the results of the treatment group to be more promising than the results from placebo treatment, whereas two studies [46, 55] found only a non-significant improvement of cellulite appearance after the treatment. The efficacy of the treatments was mainly determined by clinical assessment, comparison of circumference measurements or additional biophysical measurements, and/or by subject's self-evaluation.

Of the 14 RCTs evaluating topical formulations, 11 were placebo-controlled RCTs [12, 13, 41–47, 51, 52]. Of those 11, one [51] used oral placebo pills instead of a topical placebo cream as a control. Nine studies [12, 41, 43, 45–47, 49, 52, 54] were double-blind, three [13, 42, 50] were single-blind, and four [44, 48, 51, 55] were open-label. Of the 14 controlled RCTs, only five [13, 41, 45, 49, 51] found a significant improvement in cellulite grade and circumference when compared with the control. Three studies [12, 43, 47] found no difference between the treatment and the control groups, and about three studies [44, 50, 52] found no significant improvement post-treatment in either the treated group or the non-active control group.

Table 2 Overview of studies evaluating the efficacy of topical therapies in the treatment of cellulite

Therapy	References	Year	Design	Control	Number	Statistical analysis	Results[a]	Evidence[b]
Combination	Epstein et al. [44]	1997	RCT	P	11	Yes	–	2b
Retinol	Kligman et al. [45]	1999	RCT	P	19	Yes	+++	2b
Caffeine	Lesser et al. [46]	1999	RCT	P	41	Yes	+	2b
Combination	Collis et al. [50]	1999	RCT	P/U/A	52	Yes	–	2b
Combination	Piérard-Franchimont et al. [42]	2000	RCT	P	15	Yes	NA	2b
Combination	Bertin et al. [12]	2001	RCT	P	46	Yes	++	2b
Combination	Rao et al. [54]	2005	OS	P	34	No	+	4
Retinol	Fink et al. [55]	2006	OS	U	15	No	+	2b
Combination	Sasaki et al. [52]	2007	RCT	P	9	Yes	–	2b
Caffeine	Lupi et al. [48]	2007	RCT	U	99	Yes	NA	2b
Combination	Vogelgesang et al. [49]	2011	RCT	P/A	50	Yes	+++	2b
Combination	Mlosek et al. [51]	2011	RCT	P	61	Yes	+++	2b
Combination	Sparavigna et al. [13]	2011	RCT	P	23	Yes	+++	2b
Combination	Roure et al. [47]	2011	RCT	P	78	Yes	++	2b
Combination	Al-Bader et al. [43]	2012	RCT	P	35	Yes	++	2b
Various	Turati et al. [53]	2014	MA/SR	UC	NA	NA	–	1a
Combination	Dupont et al. [41]	2014	RCT	P	40	Yes	+++	2b

A active, *MA* meta-analysis, *NA* not evaluated, *OS* observational study, *P* placebo, *RCT* randomized controlled study, *SR* systematic review, *U* untreated, *UC* uncontrolled, + indicates non-significant improvement, ++ indicates significant improvement, +++ indicates significant improvement and superiority over control, – indicates no improvement to baseline, –– indicates worsening to baseline

[a] With regard to the endpoint improvement of cellulite appearance

[b] For categories of levels of evidence, see Table 1

Despite the fact that primarily RCTs have been published on this topic, there is little evidence that topical treatments have a potential positive effect on the appearance of cellulite. Most of the studies suggest that the treatment has either no [44, 50, 52] or non-significant efficacy compared with baseline [46, 54, 55] or compared with a non-active topical treatment [12, 43, 47]. The meta-analysis by Turati et al. [53] corroborates this assumption.

3.3 Acoustic Wave Therapy

Shock waves are high-amplitude acoustic longitudinal waves that transmit energy from the point of origin to the therapy regions. Due to the high compressibility of gases, even small pressure variations induce large changes in the density and temperature of the treated medium [56, 57]. In the 1980s, high-energy focused extracorporeal generated shock waves were first used for the lithotripsy fragmentation of kidney stones [58]. Today, less powerful acoustic shock wave therapies (AWT) use focused or radial waves to treat various diseases of the musculoskeletal system, muscle aches, and pain syndromes. AWT has since been introduced as a treatment option for cellulite [59]. It is supposed that AWT may improve local blood circulation via neovascularization [58]. Shock waves should further increase cell proliferation of collagen and elastin fibers to improve skin elasticity and to revitalize the dermis [56, 58, 60]. AWT may also have a positive effect on lymphedema by promoting lymph transport, which is a pathway often associated with cellulite [61]. In vitro tests have further shown that AWT may increase cell permeability, which may stimulate the exchange of fat cells and activate phospholipases through the beta-receptors on the fat cells' membrane [60].

Seven publications [56, 58, 60, 62–65] that evaluate the effects of AWT on the appearance of cellulite are currently available (Table 3). In total, 189 treated subjects received approximately seven treatments in a period of 3–7 weeks (averaging approximately 4.5 weeks). Only two of these studies [63, 64] are double-blind and placebo-controlled RCTs. The other articles are open-label, of which four are observational studies [56, 58, 60, 65] and one is an RCT using an untreated control [62]. Five studies [56, 58, 62, 63, 65] treated one to 25 patients each, and two studies [60, 64] treated up to 59 patients. Biophysical measurements and photographs were mainly used in the clinical assessment of cellulite improvement. Overall, the study results are inconsistent. Three [62–64] of the seven studies published found AWT to be effective in the treatment of cellulite when compared with the untreated control or compared

Table 3 Overview of studies evaluating the efficacy of acoustic wave therapy in the treatment of cellulite

References	Year	Design	Control	Number	Statistical analysis	Results[a]	Evidence[b]
Angehrn et al. [58]	2007	OS	UC	21	No	+	4
Christ et al. [60]	2008	OS	UC	59	No	NA	4
Kuhn et al. [56]	2008	OS	UC	1	No	NA	4
Adatto et al. [62]	2010	RCT	U	25	Yes	+++	2b
Russe-Wilflingseder et al. [63]	2013	RCT	P	16	Yes	+++	2b
Knobloch et al. [64]	2013	RCT	P	53	Yes	+++	2b
Schlaudraff et al. [65]	2014	OS	UC	14	Yes	+	4

NA not evaluated, *OS* observational study, *P* placebo, *RCT* randomized controlled study, *U* untreated, *UC* uncontrolled, + indicates non-significant improvement, ++ indicates significant improvement, +++ indicates significant improvement and superiority over control, − indicates no improvement to baseline, − indicates worsening to baseline

[a] With regard to the endpoint improvement of cellulite appearance

[b] For categories of levels of evidence, see Table 1

with those treated with the sham device. However, the results of two studies [58, 65] were not able to determine a significant effect of AWT on cellulite improvement compared with baseline.

Numerous meta-analyses and systematic reviews of AWT in other medical applications have reported good efficacy regarding the treatment of chronic plantar fasciitis and tendinopathies [66–69]. Although more studies are needed to further evaluate the ability of AWT to treat cellulite, there might be some evidence that suggests AWT has good efficacy.

3.4 Laser- and Light-Based Devices

Although the proposed mechanism of action is not yet fully understood, non-invasive long-pulsed 1064 nm Nd:YAG lasers have been used in the treatment of cellulite. This wavelength has been used successfully for non-ablative facial rejuvenation [70, 71]. It is known to deliver thermal energy into the deep dermis and the hypodermis to generate a wound-healing response that promotes the formation of new collagen [72, 73]. Previous studies postulated that a thicker layer of collagen may compress fat herniation, thereby improving the appearance of cellulite [2, 74].

So far, only two open-labeled randomized studies [74, 75] have been published evaluating the effect of non-invasive 1064 nm Nd:YAG laser light on cellulite (Table 4). In both studies, an untreated area served as a control. A total of 31 subjects received three treatments at 3- to 4-week intervals. Bousquet-Rouaud et al. [75] found a significant improvement of dermis density and a reduction of dermis thickness assessed by ultrasound; however, a significant improvement of cellulite severity was not observed. This outcome is consistent with the results of Truitt et al. [74], who reported a non-significant improvement in cellulite grading only in 5 of 16 subjects. Heretofore, there is little evidence that the non-invasive use of a 1064 nm Nd:YAG laser is effective for the treatment of cellulite.

A different approach to treating cellulite is with the minimally invasive pulsed 1440 nm Nd:YAG laser, formerly 1064 nm. The apparatus has a side-firing fiber and temperature-sensing cannula that is placed subdermally. This technology is supposed to have three different effects on the structural features that cause the clinical appearance of cellulite. First, this technique should smooth the uneven dermal-hypodermal interface by selectively melting the hypodermal adipocytes that protrude into the dermis. Second, it should sever the hypodermal septa that connect the dermal and muscle layers by thermal subcision. Lastly, the 1440 nm Nd:YAG laser should heat the dermis from the inside out to increase dermal thickness and skin elasticity by stimulating neocollagenesis and collagen remodeling [76].

Five observational studies [10, 76–79] evaluated the minimally invasive Nd:YAG laser for the treatment of cellulite (Table 4). In total, 154 subjects participated in the clinical trials, but only two studies included more than 50 patients [77, 79]. All subjects received one treatment along the upper thigh and buttock and were followed-up for between 6 and 30 months. The efficacy of the treatments was mainly assessed through biophysical measurements, photographic documentation, and subject's self-evaluation. Three of these studies [10, 77, 78] utilized a blinded investigator to evaluate the results. Overall, the study results confirmed positive efficacy of minimally invasive 1440 nm Nd:YAG laser treatment on cellulite. In fact, two studies showed a significant improvement of the clinical appearance of cellulite, especially a reduction in dimple depth and count, as well as a smoother contour [77, 78]. In addition, two studies [10, 76] found a significant increase in skin elasticity and dermal thickness post-treatment. However, Goldman et al. [79] did not perform statistical analyses of the collected data to corroborate previous trends.

Table 4 Overview of studies evaluating the efficacy of laser- and light-based therapies in the treatment of cellulite

Therapy	References	Year	Design	Control	Number	Statistical analysis	Results[a]	Evidence[b]
LLLT	Nootheti et al. [83]	2006	RCT	A	20	Yes	+	2b
Combination	Lach [8]	2008	RCT	A	74	Yes	NA	2b
1440 nm Nd:YAG minimally invasive	Goldman et al. [79]	2008	OS	UC	52	No	+	4
1064 nm Nd:YAG	Bousquet-Rouaud et al. [75]	2009	RCT	U	12	Yes	–	2b
Combination	Kulick [91]	2010	OS	UC	17	No	+	4
Combination	Gold et al. [90]	2011	RCT	U	83	Yes	NA	2b
1440 nm Nd:YAG minimally invasive	DiBernado [76]	2011	OS	UC	10	Yes	+	4
IR	Paolillo et al. [87]	2011	RCT	U	20	Yes	NA	2b
1064 nm Nd:YAG	Truitt et al. [74]	2012	RCT	U	19	Yes	+	2b
1440 nm ND:YAG minimally invasive	DiBernado et al. [77]	2013	OS	UC	57	Yes	++	4
1440 nm ND:YAG minimally invasive	Katz [78]	2013	OS	UC	15	Yes	++	4
1440 nm ND:YAG minimally invasive	Sasaki [10]	2013	OS	UC	20	Yes	+	4
LLLT	Jackson et al. [84]	2013	RCT	P	68	Yes	++	2b
LLLT	Savoia et al. [85]	2013	OS	UC	33	Yes	NA	4
IR	Bagatin et al. [11]	2013	RCT	U	25	Yes	–	2b
Combination	Hexsel et al. [92]	2013	OS	UC	15	Yes	+	4

A active, *IR* infrared, *LLLT* low-level laser therapy, *NA* not evaluated, *Nd:YAG* neodymium-doped yttrium aluminium garnet laser, *OS* observational study, *P* placebo, *RCT* randomized controlled study, *U* untreated, *UC* uncontrolled, + indicates non-significant improvement, ++ indicates significant improvement, +++ indicates significant improvement and superiority over control, – indicates no improvement to baseline, – – indicates worsening to baseline

[a] With regard to the endpoint improvement of cellulite appearance

[b] For categories of levels of evidence, see Table 1

In addition to high-energy lasers, low-level lasers that operate in the milliwatt power range are also used in the treatment of cellulite. Unlike common high-energy lasers, low-level laser therapy (LLLT) does not cause significant heating in the tissue structure. The proposed increase of cAMP production via cytochrome C oxidase should result in the breakdown of the cell's lipids in adipocytes, the formation of transitory pores in their cell membrane, and subsequent cell collapse [80]. Therefore, LLLT should stimulate collagen synthesis by inducing a biological cascade at the cellular level [81, 82].

Three studies [83–85], which enrolled between 20 and 68 subjects each, have been published evaluating the efficacy of LLLT on cellulite (Table 4). One study [84] used a low-level laser light device employing a 532 nm wavelength. This study is randomized, single-blind, and sham controlled. Results indicate significant cellulite improvement and circumference reduction within the treated group. Nootheti et al. [83] published a second RCT on this topic comparing the ability of a low-energy diode laser in the 808 nm infrared (IR) light spectrum to treat cellulite with an RF device. The study does not show any significant changes in cellulite severity after the treatment. An observational study [85] was recently published evaluating the efficacy of 635 nm low-level laser light on localized adiposity and cellulite. Though the results from the ultrasound assessment showed a significant reduction of fat thickness, there was no visible improvement in the clinical appearance of cellulite verifiable.

In summary, whether LLLT is able to effectively treat cellulite is unclear because of inconsistent results. Therefore, more studies with larger sample sizes are necessary to evaluate the true efficacy of these devices.

IR light, produced from light-emitting diode (LED) light sources, is also used in the treatment of cellulite. The heating of the skin is supposed to promote microcirculation, lymphatic drainage, and collagen synthesis [86]. Paolillo et al. [87] conducted an RCT with 20 subjects who were treated with 850 nm IR radiation (Table 4). The results indicate that tissue heating may significantly reduce thigh circumference. In a double-blind RCT conducted by Bagatin et al. [11], IR radiation has a significant positive impact on the subjects' quality of life, but not on the improvement of cellulite appearance.

Devices that combine laser- and light-based radiation with mechanical stimulation are frequently used to treat cellulite in practice today. A common approach combines a lower-level 915 nm continuous wave diode laser and 650 nm LED energy with mechanical manipulation. The IR 915 nm laser light is supposed to be absorbed by adipocytes to elicit thermal effects [88], while the low-level 650 nm light should create temporary pores on the cellular membrane to increase permeability. These actions allow the fat to escape into the extracellular space [89]. Mechanical massage is not only supposed to facilitate the transport of the fat into the lymphatic system, but also to promote lymphatic drainage, subcutaneous blood flow, new collagen deposition, and to firm and tone the skin [50, 89].

Four studies have been published evaluating the efficacy of treatment: two larger RCTs ($n_{total} = 157$) [8, 90] and two small, open-label observational studies ($n_{total} = 32$) [91, 92] (Table 4). The RCTs used either massage alone or an untreated area as a control. Overall, the subjects received 3–14 (average: 8.25) treatment sessions on the thighs, ranging from 3 days to 6 weeks. All available studies used circumference measurements and photographic documentation for clinical assessment. Only Gold et al. [90] assessed the efficacy with a blinded evaluation of the photographs, while Lach [8] used an MRI to evaluate fat thickness. The reduction of thigh circumference in the studies conducted by Gold et al. [90] and Hexsel et al. [92] was significant, suggesting that combination therapy may have relatively good efficacy. In a comparable study, Lach [8] reported a reduction in fat thickness. However, none of the published studies indicated a significant improvement in cellulite appearance. Moreover, the observational study by Kulick [91] only provides descriptive results.

In summary, it cannot be stated that all laser- and light-based approaches are efficient. While there is very little evidence that the non-invasive use of 1064 nm Nd:YAG lasers is effective, the minimally invasive 1440 nm lasers seem to significantly improve the clinical appearance of cellulite, decrease dimple depth, the number of dimples, and smoothen the contour of the skin. However, consistent reproducibility of these results is still pending. The efficacy of LLLT for the treatment of cellulite is also unclear, as study results are conflicting. Because a significant improvement in cellulite appearance has not yet been found in any of the clinical studies, devices that combine light energy and mechanical stimulation are not recommended treatments at this point.

3.5 Radiofrequency

RF techniques are frequently used to treat cellulite. It is commonly proposed that heating skin with RF energy leads to a thermally mediated reaction in the dermis associated with collagen denaturation and followed by tissue tightening. The extent of the thermal effect in the skin is dependent on the level of the tissue's resistance to the electricity flowing through it [93]. The heat that is delivered to the subcutaneous layer is presumed to be absorbed by adipocytes to supposedly induce the breaking down of fat cells through the membrane's lysis [94, 95]. Subsequently, a wound-healing process such as collagen neosynthesis would therefore improve various tissue characteristics [95, 96].

An array of RF devices is used to treat cellulite that vary on the basis of power (high- and low-RF devices) and whether they combine IR radiation and/or massage. So far, three studies have been published investigating low-level RF energy up to 50 W: one observational study [97] and two RCTs [95, 98] (Table 5). The RCTs used either a sham device or an untreated area as a control. In total, 106 patients were treated, receiving 8–36 treatments each. The subject-blinded RCT conducted by Mlosek et al. [98] found the low-level RF device to be superior to the sham device in improving cellulite. A significant improvement was observed in epidermis/dermis thickness, cellulite appearance, and reduction of circumference. Though the findings of Boisnic et al. [95] and Manuskiatti et al. [97] are consistent, there was no significant clinical improvement in the appearance of the cellulite.

Four studies have been published evaluating uni- [93, 99, 100] or bipolar [94] high-energy RF (150–200 W) devices (Table 5). Subjects of these studies ($n_{total} = 116$) received 2–12 treatments each. One RCT [99] and three observational open-label studies [93, 94, 100] used the untreated thigh as the control area. Though the studies report an improvement in cellulite after high-energy RF treatment, the results were either not significant or do not provide proper statistical analysis.

A combination therapy of RF (1 MHz, 20 W), IR light (700–1500 nm, 12.5 W), and suction (750 mmHg negative pressure) is also used to treat cellulite. Among the RF devices, combination therapy is the most investigated technique, with nine published scientific papers. Two RCTs [83, 101] and seven observational studies [5, 6, 102–106] are currently available. The studies enrolled between 2 and 35 subjects each ($n_{total} = 142$). Of the observational studies, five [5, 6, 103–105] only provided a descriptive statistic, including a simple summary of observations without supporting statistical evidence (Table 5). However, no significant improvements were found in the RCTs that used an untreated area or those that used another treatment device as a control [83, 101]. Only the observational study conducted by Hexsel et al. [102] reported a significant reduction in hip circumference and a significant improvement of buttock cellulite severity; however, there was no significant reduction of thigh circumference.

In summary, the evidence provided for the efficacy of high-energy RF and RF combination therapy for treating cellulite is low; either no valid statistical analyses were provided or the results did not show significant treatment success. One exception could be the use of low-level RF because one RCT showed significant improvement in cellulite appearance after the treatment. However, more double-blind RCTs with larger sample sizes are necessary to confirm these results.

Table 5 Overview of studies evaluating the efficacy of radiofrequency in the treatment of cellulite

Therapy	References	Year	Design	Control	Number	Statistical analysis	Results[a]	Evidence[b]
Combination	Sadick and Mulholland [104]	2004	OS	UC	35	No	+	4
Combination	Alster and Tanzi [5]	2005	OS	U	20	No	+	4
Combination	Kulik [103]	2006	OS	UC	16	No	+	4
Combination	Alster and Tehrani [106]	2006	OS	UC	2	No	+	4
Combination	Nootheti et al. [83]	2006	RCT	A	20	Yes	+	2b
Combination	Wanitphakdeedecha and Manuskiatti [105]	2006	OS	UC	12	No	+	4
Unipolar RF	Emilia del Pino et al. [93]	2006	OS	UC	26	No	NA	4
Unipolar RF	Goldberg et al. [100]	2008	OS	UC	30	No	+	4
Combination	Sadick and Magro [6]	2007	OS	U	16	No	+	4
Combination	Romero et al. [101]	2008	RCT	U	10	Yes	+	2b
Unipolar RF	Alexiades-Armenakas et al. [99]	2008	RCT	U	10	Yes	+	2b
Bipolar RF	van der Lugt et al. [94]	2009	OS	UC	50	No	+	4
Low-level RF	Manuskiatti et al. [97]	2009	OS	UC	37	Yes	+	4
Low-level RF	Boisnic et al. [95]	2010	RCT	U	24	Yes	+	2b
Low-level RF	Mlosek et al. [98]	2012	RCT	P	45	Yes	+++	2b
Combination	Hexsel et al. [102]	2011	OS	UC	11	Yes	++	4

A active, *NA* not evaluated, *OS* observational study, *P* placebo, *RCT* randomized controlled study, *RF* radiofrequency, *U* untreated, *UC* uncontrolled, + indicates non-significant improvement, ++ indicates significant improvement, +++ indicates significant improvement and superiority over control, − indicates no improvement to baseline, −− indicates worsening to baseline

[a] With regard to the endpoint improvement of cellulite appearance

[b] For categories of levels of evidence, see Table 1

3.6 Other Modalities

Additional cellulite treatments have been evaluated and published in scientific journals on the topics of weight loss, nutritional supplements, minimally invasive subcision, carbon dioxide (CO_2) therapy, occlusive compression stockings, phonophoresis with hyaluronidase, as well as collagenase injections.

The correlation of weight loss and appearance of cellulite was evaluated by Smalls et al. [9] (Table 6). Ultrasound, X-ray, skin biomechanical properties, anthropomorphic measurements, as well as 3D laser surface scanning were used to assess cellulite improvement in a cohort of 51 women with visible cellulite. Female subjects who participated in a medically supervised weight loss program were compared with those in a stable weight control group. On average, cellulite severity decreased following weight loss. However, for some subjects, the severity increased with weight reduction. As a study shows that there is no irregular deposition of fat [33], this effect may be caused by septa acting as a tethering system, thus producing the typical dimpling pattern [4, 107]. Another possible explanation is that skin laxity might worsen with major weight loss, which makes the appearance of cellulite more prominent [9].

Several nutritional supplements are marketed with the claim of improving the signs of cellulite. In two [108, 109] of the three published studies, the tested formulation contained a plant complex based on *Vitis vinifera*, G*inkgo biloba*, C*entella asiatica*, *Mellilotus officinalis*, *Fucus vesiculosus*, fish oil, and borage oil (Table 6). Savikin et al. [110] evaluated the ability of organic chokeberry juice (OCJ) to treat cellulite. The proposed mechanism of all these plant extracts is an enhancement of cell metabolism by increasing collagen and elastin synthesis, the reduction of edema and intestinal inflammation, and the improvement of microcirculation. The plant extracts should further act as potent antioxidants that inhibit the oxidation of tissue molecules [108, 110]. A total of 239 subjects received dietary supplements in two RCTs [108, 109] and in one observational study [110]. Distante et al. [108] found the active treatment to be superior to the control treatment and reported a significant reduction in weight and circumference. There is also a significant improvement in edema and cellulite appearance. However, Lis-Balchin [109] did not find any significant improvement in cellulite appearance when investigating the effect of the same plant-derived supplements, but a statistically significant increase in body weight. The observational study of Savikin et al. [110] found a significant improvement in thickness of all skin layers after the consumption of 100 mL OCJ for 90 days. However, changes in cellulite severity were not statistically analyzed.

Lee [111] evaluated the efficacy of transcutaneous administration of CO_2 for the treatment of cellulite (Table 6).

Table 6 Overview of studies evaluating the efficacy of different modalities in the treatment of cellulite

Therapy	References	Year	Design	Control	Number	Statistical analysis	Results[a]	Evidence[b]
Nutrition	Lis-Balchin [109]	1999	RCT	P	20	Yes	−−	2b
Subcision	Hexsel, Mazzuco [116]	2000	OS	UC	232	No	+	4
Stockings	Rao J et al [113]	2004	OS	U	17	No	+	4
Nutrition	Distante [108]	2006	RCT	A	190	Yes	+++	2b
Weight loss	Smalls et al. [9]	2006	RCT	U	51	Yes	+++	2b
CO_2 therapy	Lee [111]	2010	OS	UC	101	Yes	NA	4
Hyaluronidase	da Silva et al. [114]	2013	RCT	A	42	Yes	+	4
Nutrition	Savikin et al. [110]	2014	OS	UC	29	Yes	−	4

A active, *NA* not evaluated, *OS* observational study, *P* placebo, *RCT* randomized controlled study, *U* untreated, *UC* uncontrolled,, + indicates non-significant improvement, ++ indicates significant improvement, +++ indicates significant improvement and superiority over control, − indicates no improvement to baseline, −− indicates worsening to baseline

[a] With regard to the endpoint improvement of cellulite appearance

[b] For categories of levels of evidence, see Table 1

CO_2 therapy is supposed to disrupt adipocyte tissue and alter microcirculation [112]. In this observational study, 101 female subjects underwent treatment of the abdomen and the thigh. Though cellulite severity was not evaluated over time, a significant weight loss and circumference reduction in the treated group was reported.

The influence of occlusive compression stockings on cellulite was assessed in a randomized observational study conducted by Rao et al. [113] (Table 6). The female subjects used an anti-cellulite cream on both legs and were assigned an occlusive neoprene garment to wear on either the left or right leg. Of the 17 subjects who completed the study, 13 noticed an overall improvement of cellulite on both legs, but only six noted a greater improvement on the leg that was occluded. Independent evaluators found a slightly better improvement on the leg treated with occlusion.

Da Silva et al. [114] evaluated the effect of ultrasound in combination with topical hyaluronidase on patients with cellulite (Table 6). The RCT included 42 subjects who received ten ultrasound treatments of the gluteal region over the course of 3 weeks. Either standard ultrasound alone or ultrasound therapy with additional hyaluronidase gel was applied. The drug was added with the intention of promoting the depolymerization of fibrous edema in the interstitial tissue to facilitate local metabolic changes. The results show that combination therapy may significantly decrease skin thickness better than exclusive ultrasound. Changes in cellulite severity were neither specified nor statistically analyzed.

The treatment efficacy of subcision, a technique in which connective tissue septa is cut through to elevate depressed and dimpled skin [115], was also reviewed as a cellulite treatment option. In a retrospective observational study, Hexsel and Mazzuco [116] evaluated the cases of 232 female patients. They found the surgical procedure to be effective in the improvement of cellulite and to yield a high patient satisfaction rating (Table 6). However, a reliable and inductive statistical analysis was not performed.

A new approach to treating cellulite is the injection of collagenase (*Clostridium histolyticum*) into the septa that supposedly cause cellulite dimpling. The results of a first randomized controlled phase IIa study of 150 females indicated that this approach seems to be safe and efficient for the treatment of cellulite [29]. In this study, those who received mid or high doses had a significant improvement in the cellulite appearance, according to investigators and patients.

Scientific evidence for other cellulite therapies is presently weak. While weight loss seems to improve cellulite in most patients, it worsened in some. Additionally, the use of nutritional supplements produced inconsistent results. Only single studies have been published on CO_2 therapy, compression stockings, surgical subcision, or combination of ultrasound and topically applied hyaluronidase treatment. None of the studies met the criteria to be considered a viable efficacious option to treat cellulite. The efficacy, safety, and result sustainability of collagenase injections in the treatment of cellulite needs to be proven in larger phase III studies.

4 Conclusion

This review provides for the first time a systematic evaluation of previous scientific evidence (67 studies) regarding the efficacy of various cellulite treatments. Most of these studies have important methodological flaws; some do not use cellulite severity as an endpoint or do not provide sufficient statistical analyses. We strongly recommend that more authors use the CONSORT (Consolidated Standards of Reporting Trials) statement to improve the quality of study reporting in aesthetic medicine. The use of blinding, randomization, and comparison with a placebo is the most effective strategy to avoid potential bias in the efficacy assessment. In many cases, the use of an intrapatient design is an efficient strategy to reduce the number of study subjects while increasing the quality of the trial. The use of high-quality trial design is strongly encouraged for testing the efficacy of cellulite treatments. A validated cellulite scale should be used until an objective biophysical method for the assessment of cellulite becomes available. Of the 67 studies analyzed in this review, only 19 were placebo-controlled studies with randomization.

Following a rigorous methodological approach proposed by the PRISMA Statement, we were not able to identify clear evidence of good efficacy in any of the evaluated cellulite treatments, even with the most researched topics. The only device with at least three RCTs that show clear superiority over control is AWT. Another device that showed congruent improvements in five studies was the 1440 nm minimally invasive laser. However, none of these studies were controlled.

While there are precise techniques that assess many dermatological conditions, there is still no biophysical measurement technique to evaluate cellulite. Therefore, most of the studies analyzed in this review used surrogate markers to measure efficacy, including circumference measurements, ultrasound, laser Doppler flowmetry, thermography, plicometry, computerized tomography, and MRI. Although a validated and widely accepted clinical rating scale is available [14], a surprisingly high number of studies did not use a clinical assessor's rating. In conclusion, the treatment of cellulite remains challenging. More RCTs with high-quality trial design, a sufficient number of subjects, and profound statistical analysis are needed for an evidence-based recommendation.

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