

## ORIGINAL ARTICLE

# The efficacy and safety of non-pharmacological therapies for the treatment of acne vulgaris: A systematic review and best-evidence synthesis

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## Abstract

**Background** Acne vulgaris is a multifaceted skin disorder, affecting more than 85% of young individuals worldwide. Pharmacological therapy is not always desirable because of the development of antibiotic resistance or the potential risk of adverse effects. Non-pharmacological therapies can be viable alternatives for conventional therapies. However, sufficient evidence-based support in the efficacy and safety of non-pharmacological therapies is lacking.

**Objective** To assess the efficacy and safety of several non-pharmacological therapies in the treatment of acne vulgaris.

**Methods** A systematic literature review, including a best-evidence synthesis, was performed to identify literature. Three electronic databases were accessed and searched for studies published between January 2000 and May 2017.

**Results** Thirty-three eligible studies were included in our systematic review. Three main types of non-pharmacological therapies were identified laser- and light-based therapies, chemical peels and fractional microneedling radiofrequency. The majority of the included studies demonstrated a significant reduction in acne lesions. However, only seven studies had a high methodologic quality. Based on these seven trials, a best-evidence synthesis was conducted. Strong evidence was found for glycolic acid (10–40%). Moderate evidence was found for amino fruit acid (20–60%), intense pulsed light (400–700 and 870–1200 nm) and the diode laser (1450 nm). Initially, conflicting evidence was found for pulsed dye laser (585–595 nm). The most frequently reported side-effects for non-pharmacological therapies included erythema, tolerable pain, purpura, oedema and a few cases of hyperpigmentation, which were in most cases mild and transient.

**Conclusion** Circumstantial evidence was found for non-pharmacological therapies in the treatment of acne vulgaris. However, the lack of high methodological quality among included studies prevented us to draw clear conclusions, regarding a stepwise approach. Nevertheless, our systematic review including a best-evidence synthesis did create order and structure in resulting outcomes in which a first step towards future research is generated.

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## Conflicts of interest

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## Introduction

Acne vulgaris is one of the most common skin diseases affecting more than 85% of individuals worldwide. While acne is most prevalent among adolescents between 15 to 24 years old, it is

not uncommon in adults either.<sup>1–5</sup> The pathogenesis of acne vulgaris is not fully understood yet, although various underlying mechanisms that occur before the onset of the disease have been identified, including androgenic stimulation of sebaceous glands,

abnormal follicular hyperkeratinization, obstruction of the pilosebaceous follicle and inflammation. Different types of acne can be distinguished based on the occurrence of clinical features of inflammatory lesions (papules, pustules, nodules, cysts) and non-inflammatory lesions (comedones).<sup>6,7</sup>

Although acne is often considered a cosmetic problem, the disease can have a large impact on patients' psychosocial and physical well-being. Also, acne may have a lifelong effect by disfiguring scars. The presence of acne correlates with various psychological factors such as depression, anxiety, anger, frustration, shame, low self-esteem, social isolation and body dissatisfaction.<sup>7,8</sup>

According to recent dermatologic guidelines, the current first-line treatments for acne are conventional pharmacological therapies such as antibiotics, retinoids, hormonal agents and benzoyl peroxide.<sup>6,9</sup> However, conventional therapy is not always desirable because of the development of antibiotic resistance of the *Propionibacterium acnes* and other bacteria<sup>10</sup> and the potential risk of adverse effects associated with topical and systemic treatments.<sup>5,6</sup>

Besides conventional therapies available to treat acne vulgaris, non-pharmacological therapies are applied more often by care professionals. The most commonly applied non-pharmacological therapies are laser and light-based therapies, chemical peels, microneedling, (micro)dermabrasion and (mechanical) lesion removal. Non-pharmacological therapies are applied as independent therapies, in combination with conventional therapies or as maintenance therapy, especially in more persistent or chronic types of acne where long-term therapy is required.<sup>10</sup> However, sufficient evidence-based support in the efficacy and safety of non-pharmacological therapies is scarce. This systematic review assesses the efficacy and safety of several non-pharmacological therapies in the treatment of acne vulgaris.

## Materials and methods

### Search strategy

A systematic review of the literature was performed according to the guidelines of preferred reporting items for systematic reviews and meta-analyses (PRISMA).<sup>11</sup> Three electronic databases (MEDLINE, Cochrane library, CINAHL) were accessed and searched for studies on non-pharmacological therapies for acne vulgaris, published between January 2000 and May 2017. We designed a search strategy which combined the term 'Acne' (MESH and Title/Abstract) using the Boolean operator 'AND' with the following key MESH subject headings and text words, separated by 'OR': *Keratolytic agents, Desquamating agent, Peel, Jessner, Phenol, Hydroxy acids, Glycolic acid, Alpha hydroxy acid, Lactic acid, Fruit acid, Salicylic acid, Trichloroacetic Acid, Trichloroacetic Acid, TCA, Lesion removal, Lesion incision, Comedo removal, Dermabrasion, Microdermabrasion, Epidermabrasion, Lasers, Intense pulsed light, IPL, ND-yag, Blue light, Red light, Microneedling, Radio frequency*. In all databases, truncation

symbols were used to define variations in spelling. The complete search strategy is demonstrated in Appendix S1.

We further delineated the search by adding a set of predefined inclusion and exclusion criteria. Inclusion criteria were as follows: studies on participants with acne vulgaris, non-pharmacological therapies, randomized controlled trials (RCTs) and controlled clinical trials (CCTs), control group designs, split-face designs and parallel group designs, all stages and phases of acne severity, all acne outcome tools, studies that were exclusively performed in humans and studies that were published in English, Dutch or German. Exclusion criteria were as follows: studies reported on acneiform dermatoses other than acne vulgaris, acne scars, studies combining several therapies (e.g. photodynamic therapy), pharmacological therapies (except when served as a control intervention), surgical procedures, experimental therapies, studies with home use devices, studies without a control group and studies that were unavailable in full text.

### Selection of studies and data extraction

The reference management software program RefWorks® (ProQuest LLC, Ann Arbor, MI, USA) was used to manage all data retrieved from the three electronic databases. Two reviewers (de Vries and Meulendijks) independently screened all studies that were retrieved from the databases and selected potentially relevant studies that met the predefined inclusion and exclusion criteria. To determine eligibility, titles were screened first, then the abstracts of the remaining studies and finally the full text of those remaining. Both reviewers resolved any differences of opinion on whether or not to include a particular study by consulting a third reviewer (Driessen). Relevant characteristics extracted from the remaining full-text studies were as follows: study design, patient characteristics, disease characteristics, interventions, dose and parameters, outcome tools, previous and concomitant treatments and study outcome measures.

### Quality assessment

Eligible studies meeting the predefined criteria were independently assessed on methodological quality by both reviewers, using the Cochrane risk of bias tool.<sup>12</sup> This tool includes seven specific domains to critically judge a study's risk of bias (low, high or unclear), namely sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting and other issues that may lead to bias.

### Outcomes and data analysis

The primary outcome of interest was changes in the clinical signs of inflammatory lesions (papules, pustules, nodules, cysts) and non-inflammatory lesions (comedones), reported through absolute values (the number of acne lesions or sebum level), relative

values (percentage improvement of acne compared to baseline) or by an ordinal level (based on acne grading scales). We included all types of primary outcome tools measuring the primary outcome of interest. The secondary outcome of interest was safety of non-pharmacological therapies, reported as (adverse) side-effects and tolerability. Where available, *P*-values were reported. *P* < 0.05 was considered statistically significant. Both significant differences between the intervention group and a control group (between-group results) and significant differences between baseline measurement and a predefined number of clinical assessment visits (within-group results) had our focus of interest.

### Best-evidence synthesis

If non-pharmacological therapy characteristics were sufficiently homogeneous, a meta-analysis was performed. If combining study results in a meta-analysis was inappropriate, a best-evidence synthesis was conducted with the following classification of level of evidence:<sup>13,14</sup>

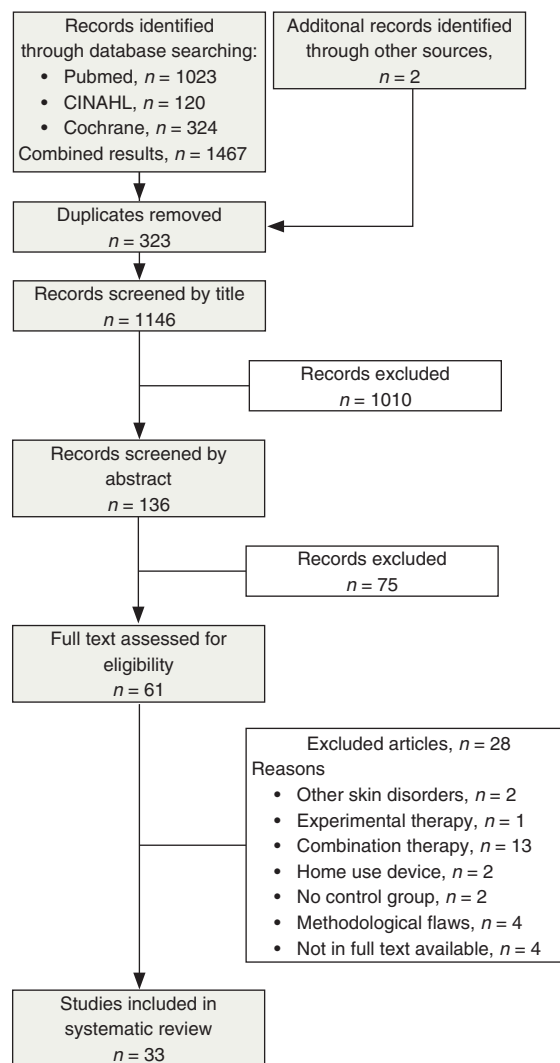
- Strong: consistent findings among multiple high-quality RCTs
- Moderate: consistent findings among multiple low-quality RCTs and/or CCTs and/or one high-quality RCT
- Limited: one low-quality RCT and/or CCT
- Conflicting: inconsistent findings among multiple RCTs and/or CCTs
- No evidence from trials: no RCTs or CCTs

A threshold for high methodological quality was set on studies with five or more bias-free domains, according to the Cochrane risk of bias tool.<sup>12</sup>

## Results

### Study characteristics

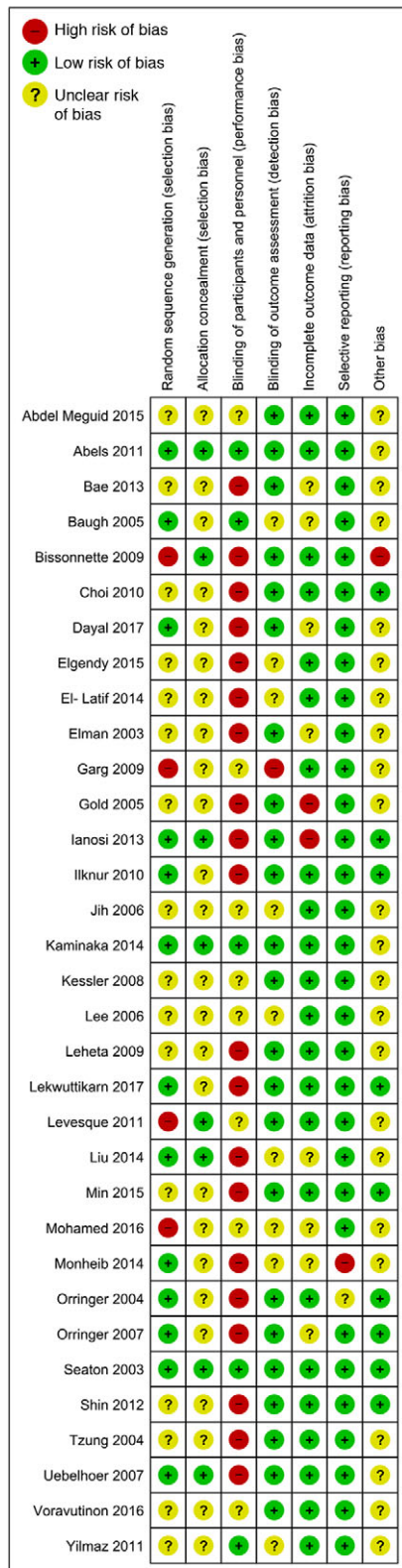
Our search strategy identified 1467 studies. Thirty-three eligible studies (1404 participants) met the inclusion criteria and were included in our systematic review. The complete search strategy and reasons for exclusion are presented in a flow chart (Fig. 1). All included studies were RCTs or CCTs, 10 of which used a control group, placebo or sham treatment, 20 a split-face design and three a parallel group design. The majority of the studies were executed on participants having mild-to-moderate acne or inflammatory acne. The included studies used several primary outcome tools to measure the changes in acne severity. Of the 33 eligible studies, the main non-pharmacological therapies identified were as follows: (i) laser and light-based therapies (*N* = 20), (ii) chemical peels (*N* = 11), (iii) fractional microneedling radiofrequency (*N* = 2). Performing a meta-analysis was not appropriate, due to the diversity in study characteristics and outcome measurements. Therefore, a best-evidence synthesis was conducted (Fig. 2 and Tables 1–3). Tables S1–S3 show the extensive results and study characteristics.



**Figure 1** Flowchart: study flowchart of the literature search and selection process.

### Laser- and light-based therapies

Twenty (*N* = 20/33) studies investigated the efficacy of laser- and light-based therapies. Photothermal therapies: fractional erbium glass laser 1550 nm,<sup>30</sup> Nd:YAG laser 1064 nm<sup>32</sup> and 1320 nm<sup>31</sup> and diode laser 1450 nm.<sup>33,34</sup> Photochemical therapies: blue light 405–420 nm.<sup>17–20</sup> Photochemical/photothermal therapies (multifactorial effects): potassium titanyl phosphate laser (KTP) 532 nm,<sup>15,16</sup> intense pulsed light (IPL) 530–1200 nm,<sup>21–23,27,32</sup> Pulsed Dye Laser (PDL) 585–595 nm.<sup>24–29</sup> The majority of the studies reported a significant reduction in acne lesions, of which eight studies found significant results in comparison with a control group (between-group



**Figure 2** Risk of bias evaluation for each included study.

results)<sup>17,18,21,22,26,27,30,31</sup> and 10 studies showed significant results as measured from baseline to a predefined number of clinical assessment visits (within-group results).<sup>16,23,27–29,32–34</sup> Despite the high amount of statistically significant results, sub-optimal methodologic quality of the majority of these studies resulted in limited evidence of efficacy (Table 1 and Fig. 2), except Ianosi *et al.*<sup>21</sup> who conducted a high-quality RCT on IPL (40–700 and 870–1200 nm, 100 ms, 20 J/cm<sup>2</sup>, 20 ms, 18 J/cm<sup>2</sup>), finding a significant reduction in the number of papules, pustules and comedones in IPL group compared with the control group. In addition, Uebelhoer *et al.*<sup>34</sup> conducted a high-quality RCT with a Diode laser (1450 nm 9.5–11.0 J/cm<sup>2</sup>, 29–30 ms) and demonstrated a statistically significant reduction in inflammatory acne on both single-pass and double-pass laser treatments. The high quality of both studies resulted in a moderate evidence of the intervention efficacy. Initially, a conflicting evidence was found on behalf of PDL (significant results vs. no significant results). Seaton *et al.*<sup>26</sup> found a significant improvement on inflammatory acne 12 weeks after one treatment (585 nm, 1.5–3 J/cm<sup>2</sup>, 0.350 ms, 5 mm). Letwuttikarn *et al.*<sup>24</sup> found no statistically significant difference between PDL and control side except on papule count (595 nm, 8 J/cm<sup>2</sup>, 10 ms, 7 mm). Although these results initially seem contradictory, this can be explained by the different nature of the treatments in terms of devices and settings (0.350 ms shows more pronounced effect on capillaries than 10 ms). Furthermore, four studies compared laser- and light-based therapy to pharmacological therapy (isotretinoin,<sup>19</sup> clindamycin,<sup>20</sup> benzoyl peroxide<sup>23</sup> and a combination of benzoyl peroxide and tretinoin<sup>28</sup>). None of these studies found convincing differences between study groups, indicating that no treatment group was more superior to the other. The methodological quality of these studies was, however, suboptimal. Most commonly reported side-effects were transient erythema, tolerable pain, purpura and oedema, which in most cases resolved within a few hours. In five studies, postinflammatory hyperpigmentation was observed within a few patients, which resolved within 3 months.<sup>24,25,29,31,34</sup>

**Chemical peel**

Eleven studies (N = 11/33) investigated the efficacy of chemical peels (Table 2 and Fig. 2). The chemical peeling agents were as follows: salicylic acid 20–30%,<sup>35–39,45</sup> glycolic acid 10–70%,<sup>38–43</sup> Jessner solution,<sup>35,36,42</sup> trichloroacetic acid (TCA) 25%,<sup>37</sup> mandelic acid 10%,<sup>39</sup> amino fruit acid 20–60%<sup>43</sup> and lipo-hydroxy acids 0.3–10%.<sup>44,45</sup> The majority of the studies (N = 8/11) compared two peeling agents to each other.<sup>35–39,42,43,45</sup> Most of these studies reported a significant decrease in the number of acne lesions after a predefined number of clinical assessment visits (within-group results)<sup>35–39,43,45</sup> and found no evident superiority between one type of chemical peel compared to another. Except for the studies of Bae *et al.*<sup>35</sup> and Dayal *et al.*<sup>36</sup> who reported significant improvements on non-inflammatory lesions with

**Table 1** Best evidence synthesis laser and light-based therapies

Intervention	Control group	Statistical significance Between groups	Statistical significance Within groups		Bias-free	References domains
			Intervention group	Control group		
<b>Photothermal therapies</b>						
Diode ++	Diode double pass	No	Yes	Yes	5	Uebelhoe <sup>34</sup>
	Diode 16 J	No	Yes	Yes	2	Jih <sup>33</sup>
Fractional erbium glass laser +	Untreated	Yes	NR	–	1	Monheib <sup>30</sup>
Nd:YAG +	Untreated	Yes	NR	–	4	Orringer <sup>31</sup>
	IPL	No	Yes	Yes	1	Mohammed <sup>32</sup>
<b>Photochemical therapies</b>						
Blue light +	Untreated	Yes	NR	–	3	Tzung <sup>18</sup>
	Untreated	Yes	NR	–	2	Elman <sup>17</sup>
	Isotretinoin	No	NR	NR	2	Elgendy <sup>19</sup>
	Clindamycin	No	NR	NR	2	Gold <sup>20</sup>
<b>Photochemical and photothermal therapies (multifactorial effects)</b>						
IPL ++	Untreated	Yes	NR	–	5	Ianos <sup>21</sup>
	PDL	No	Yes	Yes	4	Choi <sup>27</sup>
	Untreated	Yes	NR	–	3	Lui <sup>22</sup>
	Benzoyl peroxide	No	Yes	Yes	2	El-latif <sup>23</sup>
	Nd:YAG	No	Yes	Yes	1	Mohammed <sup>32</sup>
KTP +	Untreated	No	NR	–	3	Baugh <sup>15</sup>
	Untreated	No	Yes	–	3	Yilmaz <sup>16</sup>
PDL ±	Untreated	Yes	NR	–	7	Seaton <sup>26</sup>
	Untreated	No	NR	–	5	Lekwuttikarn <sup>24</sup>
	Untreated	No	NR	–	4	Orringer <sup>25</sup>
	IPL	Yes	Yes	Yes	4	Choi <sup>27</sup>
	BPO/Tretinoin/TCA	No	Yes	Yes	3	Leheta <sup>28</sup>
	PDL 6–7.5 J	No	Yes	Yes	3	Voravutinon <sup>29</sup>

+++; strong evidence; ++, moderate evidence; +, limited evidence; ±, conflicting evidence; –, Not applicable; Yes, Statistical significance ( $P < 0.05$ ); No, No Statistical significance; NR, Statistical significance not reported; Untreated, The control group included a placebo or sham treatment or remained untreated; Between groups, Statistical significant results between the intervention group and a control group; Within groups, Statistical significant results within the intervention group or control group measured from baseline to a predefined number of clinical assessment visits; IPL, intense pulsed light; PDL, Pulsed Dye Laser; TCA, trichloroacetic acid.

salicylic acid (30%) compared to Jessner solution. However, sub-optimal methodological quality of these studies suggested a limited evidence. Strong evidence of efficacy was found on behalf of glycolic acid (10% and 40%). This was due to two randomized, double-blinded, placebo-controlled studies with high methodological quality.<sup>40,41</sup> One study investigated the efficacy of lipohydroxy acid (0.3%) compared to benzoyl peroxide,<sup>44</sup> demonstrating no statistically significant results between the lipohydroxy acid-group and the benzoyl peroxide-group. In general, chemical peels were well tolerated. Frequently reported side-effects were transient erythema, oedema, dryness, desquamation, burning, itching and frosting. Two studies reported cases of temporary postinflammatory hyperpigmentation, which was due to the use of salicylic acid,<sup>36</sup> Jessner solution<sup>36</sup> and TCA.<sup>37</sup>

### Fractional microneedling radio frequency

The efficacy of fractional microneedling radio frequency (FMRF) on acne was demonstrated in two split-face RCTs ( $N = 2/33$ ).

One study demonstrated a significant reduction of 80% and 65% on both inflammatory and non-inflammatory acne, in favour of the FMRF treatment side.<sup>46</sup> In another study, a substantial reduction in the number of papules and pustules on the FMRF-treated side was observed compared with a baseline measurement.<sup>47</sup> Despite the statistically significant results of the intervention, both trials were of a suboptimal methodological quality, which led to limited evidence of efficacy (Table 3 and Fig. 2). No severe side-effects other than mild pain, transient oedema and erythema were reported after treatment.<sup>46,47</sup>

### Discussion

This systematic review, based on 33 studies, assesses the efficacy and safety of three main non-pharmacological therapies in the treatment of acne vulgaris: laser- and light-based therapies, chemical peels and FMRF. Although a high rate of statistically significant results was found in most of the studies, indicating efficacy of non-pharmacological therapies, the low

**Table 2** Best evidence synthesis chemical peels

Intervention	Control group	Statistical significance Between groups	Statistical significance Within groups		Bias-free domains	References
			Intervention group	Control group		
Glycolic acid +++	Untreated	Yes	Yes	–	6	Abels <sup>40</sup>
	Untreated	Yes	Yes	–	6	Kaminaka <sup>41</sup>
	Amino fruit acid	No	Yes	Yes	5	Ilknur <sup>43</sup>
	Salicylic acid	No	Yes	Yes	3	Kessler <sup>38</sup>
	Salicylic–Mandelic	No	Yes	Yes	2	Garg <sup>39</sup>
	Jessner's solution	No	No	No	2	Lee <sup>42</sup>
Amino fruit acid ++	Glycolic acid	No	Yes	Yes	5	Ilknur <sup>43</sup>
Lipo hydroxyacids +	Benzoyl peroxide	No	Yes	Yes	4	Bissonnette <sup>44</sup>
	Salicylic acid	No	Yes <sup>a</sup>	Yes	4	Levesque <sup>45</sup>
Salicylic acid +	Lipo-hydroxy acids	No	Yes <sup>a</sup>	Yes	4	Levesque <sup>45</sup>
	Jessner's solution	Yes <sup>b</sup>	Yes	Yes	3	Dayal <sup>36</sup>
	Trichloroacetic acid	No	Yes	Yes	3	Abdel <sup>37</sup>
	Glycolic acid	No	Yes	Yes	3	Kessler <sup>38</sup>
	Jessner's solution	Yes	Yes	Yes	2	Bae <sup>35</sup>
Jessner's solution +	Salicylic acid	No <sup>b</sup>	Yes	Yes	3	Dayal <sup>36</sup>
	Salicylic acid	No	Yes	Yes	2	Bae <sup>35</sup>
	Glycolic acid	No	No	No	2	Lee <sup>42</sup>
Trichloroacetic acid +	Salicylic acid	No	Yes	Yes	3	Abdel <sup>37</sup>
Salicylic–Mandelic acid +	Glycolic acid	Yes	Yes	Yes	2	Garg <sup>39</sup>

+++ , strong evidence; ++ , moderate evidence; + , limited evidence; Yes, Statistical significance ( $P < 0.05$ ); No, No Statistical significance; –, Not applicable; Untreated, The control group included a placebo or sham treatment or remained untreated; Between groups, Statistical significant results between the intervention group and a control group; Within groups, Statistical significant results within the intervention group or control group measured from baseline to a predefined number of clinical assessment visits.

<sup>a</sup>Significant improvement of non-inflammatory lesions.

<sup>b</sup>Significant improvement of comedones with salicylic acid compared to Jessner solution.

**Table 3** Best evidence synthesis fractional microneedling radio frequency (FMRF)

Intervention	Control group	Statistical significance Between groups	Statistical significance Within groups		Bias-free domains	References
			Intervention group	Control group		
FMRF +	Bipolar RF	Yes	Yes	No	4	Min <sup>45</sup>
	CO <sub>2</sub> fractional	No	Yes	Yes	4	Shin <sup>46</sup>

+ , limited evidence; Yes, Statistical significance ( $P < 0.05$ ); No, No Statistical significance; Between groups, Statistical significant results between the intervention group and a control group; Within groups, Statistical significant results within the intervention group or control group measured from baseline to a predefined number of clinical assessment visits.

methodological quality of the included studies made it difficult to draw clear conclusions. By conducting a best-evidence synthesis, strong evidence of the treatment efficacy for glycolic acid (10–40%) was demonstrated,<sup>40,41</sup> whereas moderate evidence was found for amino fruit acid (20–60%),<sup>43</sup> IPL (400–700 and 870–1200 nm)<sup>21</sup> and the diode laser (1450 nm).<sup>33</sup> Initially, a conflicting evidence was found for PDL therapy (585–595 nm).<sup>24,26</sup> The most frequently reported side-effects for non-pharmacological therapies included erythema, tolerable pain, oedema and a few cases of hyperpigmentation, which were in most cases mild and transient. In general, non-pharmacological therapies are relatively safe to use, in particular, compared to the risk of developing antibiotic resistance or adverse effects such as with oral isotretinoin.

Our findings are in line with previous reviews. Haedersdal *et al.*<sup>48</sup> conducted an evidence-based review of lasers, light sources and photodynamic therapy in the treatment of acne vulgaris ( $N = 19$ ). This review indicates that optical treatments possess the potential to improve inflammatory acne on a short-term basis. Hamilton *et al.*<sup>49</sup> conducted a systematic review on laser- and light-based therapies ( $N = 25$ ) and found a beneficial effect of therapies with blue light, blue-red light and infrared radiation compared with yellow, red or green light. Barbaric *et al.*<sup>50</sup> reported similar results in a large Cochrane review on laser- and light-based therapies ( $N = 71$ ). In case of chemical peels, Dreno *et al.*<sup>51</sup> reported a small scientific evidence to support the use of chemical peels in acne, despite methodological flaws in some studies ( $N = 13$ ). Although circumstantial

evidence for the use of non-pharmacological therapies was found in almost all studies, most researchers stipulated that they were unable to draw firm conclusions due to the low methodological quality of the included studies.

Our systematic review resulted in a complete and up to date overview of available evidence on several non-pharmacological therapies, using three electronic databases. The strict application of inclusion and exclusion criteria led to the exclusion of several studies on other frequently applied non-pharmacological therapies, such as (micro)dermabrasion and mechanical lesion removal (mostly due to the absence of a control group). However, this strict selection process did lead to better evidence for the remaining studies.

An important limitation of our review is the high level of heterogeneity among included studies. Point of attention is the non-uniform approach of the studies, concerning the variability in outcome measurement tools, different study characteristics (e.g. parameters, concentrations, number of treatments, follow-up periods) and differences in reporting results (e.g. absolute values, percentages, graphs and figures). These variabilities have probably contributed to the contradictory findings concerning the PDL therapy.<sup>24,26</sup>

We also experienced limitations in the inclusion of studies, in particular studies in which results were measured from baseline to a predefined number of clinical assessment visits (i.e. within groups). Although such within-group results provided substantial insights into two separate interventions in which no statistically significant results between groups were found, it remained difficult to interpret these results due to a lack of a control group/side measurement. For instance, active acne within an individual can be variable and may change over time by the interference of hormones. By not comparing the effect of an intervention with a control group, no clear conclusion can be drawn because the observed effect (reduction in acne), could be both due to the non-pharmacological physical therapy and to hormonal changes. This emphasizes the need for inclusion of a control group/side in the study design aiming to determine the efficacy of an intervention.

Another limitation of our study is the scarce data on the treatment with fractional microneedling radiofrequency. Only two studies met the inclusion criteria and were taken into account in our review. Although both studies demonstrated significant results, an overall conclusion based on two studies must be interpreted with caution.

The majority of the included studies demonstrated low methodological quality. First, the small numbers of participants (only two studies enrolled more than 100 participants<sup>21,40</sup>) made the majority of the studies probably underpowered, which may have resulted in non-statistically significant results. Secondly, most studies used short follow-up periods, which made that our conclusions may not be applicable for the effects on long-term treatments. Furthermore, the high risk of bias among the

majority of the studies (Fig. 2) possibly affected the study results. The most common risk of bias noted was performance bias. In 28 of the 33 included studies, participants and/or performing clinicians were not blinded, or it was unclear whether they were blinded properly, indicating that participants and/or performing clinicians were most likely aware of the treatment side. Five studies (five of 33) ensured blinding integrity by exposing the control group/side to a sham laser treatment or identically labelled bottles.<sup>15,16,26,40,41</sup> However, it remained unclear to what extent complete blinding of the participant and/or clinicians on non-pharmacological therapies is viable. For that reason, the best-evidence synthesis has a threshold of  $\geq 5$  bias-free domains for high methodological quality, instead of a total of seven domains. Furthermore, in most studies, the research integrity was unclear, such as possible conflict of interest, a commercial sponsorship by the intervention supplier (especially for laser devices, FMRF devices or chemical peels), which might have introduced some bias in the results too. Finally, studies did not always properly describe the use of concomitant home use products, such as sunscreen products which made it difficult to solely evaluate the efficacy of the investigated non-pharmacological therapy.

In conclusion, our systematic review found circumstantial evidence for non-pharmacological therapies in the treatment of acne vulgaris. Also, this review has created order and structure in resulting outcomes in which a first step towards future research is generated. The large amount of studies performed in the area of acne treatment and the frequent application of these therapies in daily practice indicates a great interest in this topic and the urgent demand for effective non-pharmacological treatment options for acne in addition to the use of conventional therapies. This emphasizes the need for further research, using double-blinded placebo-controlled study designs with a homogeneous data collection and processing, in order to assess the added value of non-pharmacological therapies as an alternative, next to or in combination with conventional therapy.

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### Supporting information

Additional Supporting Information may be found in the online version of this article:

**Table S1.** Extensive results tables and study characteristics Laser and light based therapies.

**Table S2.** Extensive results tables and study characteristics Chemical peel.

**Table S3.** Extensive results tables and study characteristics Fractional Microneedling Radiofrequency.

**Appendix S1.** Search strategy.