

# Crossing the boundaries of traditional therapy: a study of the potential of laserobarria in wound healing — basis of this therapy — a systematic review

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## Abstract

**Introduction:** Faced with the challenges of treating diabetic foot complications and other hard-to-heal wounds, this systematic review sheds light on a new technology — the Laserobarria treatment method. Focusing on therapeutic modalities such as Topical Oxygen, Topical Ozone Therapy, Extremely Low-Frequency Pulsed Electromagnetic Fields, and Low-Level Red and UV Light Therapy, we analyze their efficacy and safety.

**Material and methods:** Conducted in accordance with PRISMA guidelines, our review includes an in-depth literature search across PubMed, Wiley Online Library, and Google Scholar, covering publications from 2017 to 2021. The study used PICO strategies to compare the results of studies where we considered meta-analyses, systematic reviews and RCTs examining the effect of individual therapeutic agents and their combinations. We identified 31 studies conducted on a total of  $n = 3821$  patients including  $n = 354$  patients treated with Laserobarria.

**Results:** Our analysis reveals promising results: accelerated wound healing, improved blood circulation, and enhanced quality of life for patients, highlighting the benefits of combined therapies using the Laserobarria treatment method. Findings indicate the safety and cost-effectiveness of this approach, without reporting any adverse events.

**Conclusions:** This review not only confirms the potential of the Laserobarria treatment method in regenerative medicine but also underscores the need for further research to optimize therapeutic parameters. The evidence provided by our study adds to the state of the art in the field of physical therapy and demonstrates its contribution to improving wound healing outcomes.

**Keywords:** diabetic foot ulcers; chronic wounds; topical physical agents; light therapy; pulsed electromagnetic field (PEMF) therapy; topical ozone therapy; topical oxygen therapy

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## Introduction

With the increasing prevalence of chronic diseases, hard-to-heal wounds, particularly the diabetic foot (DFU), represent a significant clinical and social challenge. They dramatically reduce patients' quality of life, leading to long-term disability and even amputation, which are both costly for health systems and debilitating for patients and their families. In the context of these challenges, innovative therapeutic approaches such as Laserobaria are gaining prominence as methods to promote healing. This article focuses on the role and potential of Laserobaria in the treatment of hard-to-heal wounds, with a focus on its impact on reducing amputations and improving outcomes in the DFU patient population. It also examines the challenges and opportunities of applying this method in clinical practice, highlighting its importance as part of a comprehensive treatment plan.

Laserobaria treatment technology implemented and promoted by INVENTMED Ltd. allows local treatment in the upper or lower extremities with the use of physical therapies using Topical Oxygen (TOT), Topical Ozone, Extremely Low-Frequency Pulsed Electromagnetic Field (PEMF), as well as Low-Level Red and UV Light Therapy (LLLT).

## Material and methods

### Decision problem

Evaluation of the current state of knowledge regarding therapeutic methods utilized in the Laserobaria 2.0\_S device, with particular emphasis on clinical experiences gained and studies conducted using products with similar technical parameters.

### Search strategies

The systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement, especially focusing on clinical data encompassing information regarding population, intervention, comparison, and outcomes (PICO). The protocol for this review was developed a priori and was not subject to modification once the search began.

The databases of literature were searched: PubMed, Wiley Online Library, Google Scholar. English-language literature was sought using the following phrases: 'topical oxygen therapy', 'topical oxygen', 'topical hyperbaric oxygen', 'limb', 'topical ozone', 'wound', 'topical ozone wound', 'pemf', 'lllt', 'LED', 'wound', and their combinations using Boolean operators 'AND' and 'OR' applying filters: Clinical Trial, Meta-Analysis, Randomized Controlled Trial, Systematic Review. Full-text artic-

les in English were considered for clinical assessment updates, including articles published from 2017 to 2021. The last search was conducted on October 24, 2022. Figure 1 illustrates the full search strategy.

### Study selection

The primary intervention health condition is diabetes-related complications: Diabetic foot, Diabetic microangiopathy, Leg ulcers, Chronic wounds, Skin Infections, Limb burns, Chronic lymphedema, Delayed bone fusion, Pseudarthrosis, Sudeck's, Osteoporosis, Inflammatory joint conditions, Post-operative conditions, Neuralgia and neuropathic pain, Phantom limb pain.

The subject of this assessment are therapies conducted using physical therapy modalities with local application of ozone, oxygen, low-frequency electromagnetic field, and red and UV light.

In the study population, the comparator may be standard treatment or other forms of physical therapy or baseline data.

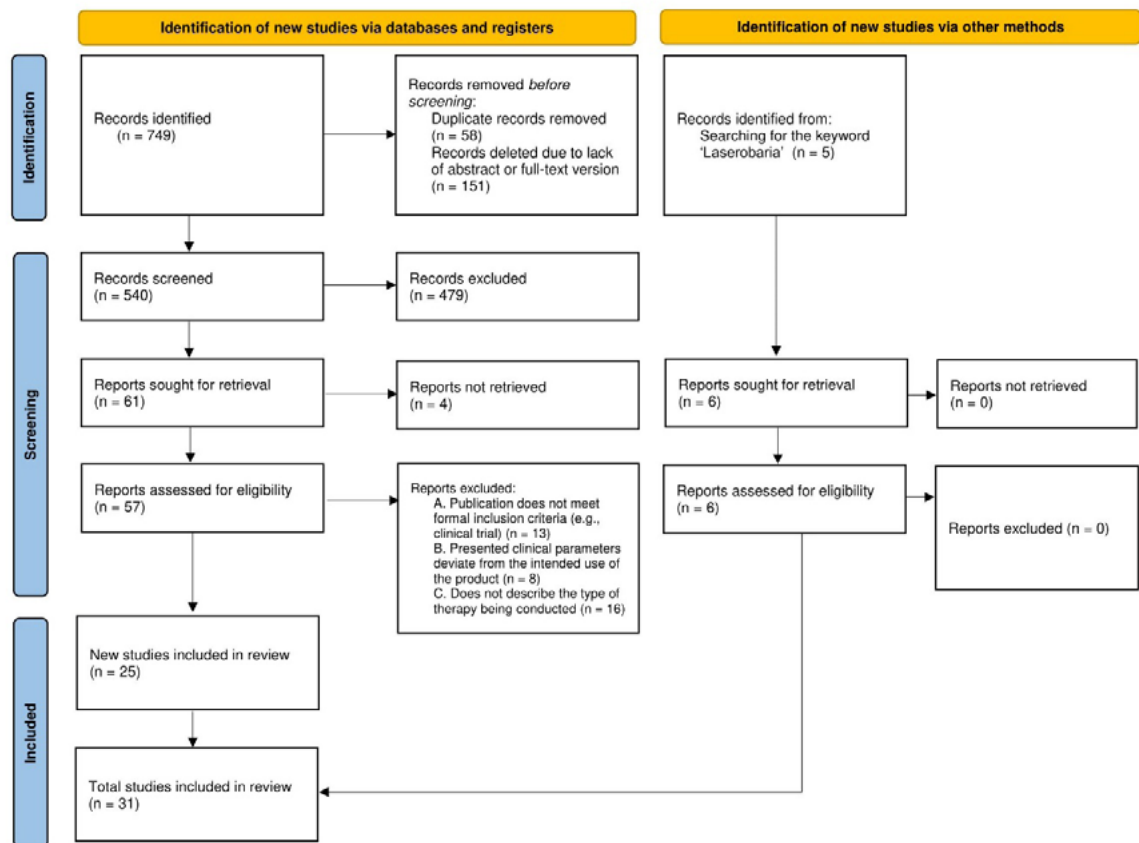
Clinical endpoints under evaluation:

- Side effects: Does the use of selected physical modalities individually, sequentially, or simultaneously result in clinical effects other than expected?
- Adverse events: Does the use of selected physical modalities individually, sequentially, or simultaneously lead to adverse health effects?
- Quality of life: Does the quality of life of patients undergoing individual, sequential, or simultaneous physical therapy change compared to comparators?

All data obtained during the literature search process were collected using the Zotero 6.0.15 reference management software. The data were categorized according to their nature, highlighting the thematic groups of individual therapies such as oxygen therapy, ozone therapy, PEMF, LLLT, and data related to the Laserobaria 2.0\_S device or technically similar ones. Using Zotero's built-in automated tools, all duplicate materials were removed. Subsequently, records for which the abstract was unavailable were discarded.

The cataloged publications underwent manual screening by two independent authors, and in cases of discrepancies, the publication remained in the catalog.

From the selected publications, relevant information corresponding to the main research objectives was obtained. Information was primarily collected on authors, title, publisher, study type, study population, intervention, comparators, and results/conclusions. The collected data were discussed by at least two authors and consensually placed in a table containing the following information: title of the work, authors, study type, population, intervention, comparators, outcomes.



**Figure 1.** Search strategy

Publications rejected at this stage were registered along with the reason for exclusion from further analysis.

During the collection of clinical evidence, systematic literature searches were conducted, including both favorable and unfavorable studies.

The screening, study selection and data extraction was conducted by two independent experts. In case of discrepancies in the assessment of publication qualification, the deciding vote was held by the third member of the research team.

To assess the risk of bias in individual studies included in the review, tools were used depending on the study type. The NICE scale for single-arm studies, the JADAD scale and ROB2 tool for RCT studies, and AMSTAR 2 for systematic reviews were employed.

To minimize the risk of systemic error in individual studies, a principle of publication hierarchy has been adopted, starting from the least burdened by the risk of error: meta-analyses, systematic reviews, randomized controlled clinical trials. In particularly justified cases, including clinical data regarding the Laserobarbia 2.0\_S device or equivalents, the analysis of lower-category

data is allowed. All publications have been evaluated by the team for quality, validity, and timeliness. Attention is paid to potential inconsistencies if they could arise in the analyzed publications. Also, the use of publications that are repetitions by the same author is avoided.

The systematic review protocol was designed to minimize the risk of bias or selective data collection. To minimize the risk of bias, experts in the field of medicine and medical devices were appointed to the research team, who conducted studies. Literature analysis is conducted with a critical approach, hence publications whose arguments are contrary to the assumed analysis goals are taken into account.

### Results

Due to the high heterogeneity of the obtained data, various objectives were set in the conducted observations, and the evaluation of results was performed using different rating scales and assessment methods. Therefore, the results obtained were not directly comparable. It was not possible to apply „summing up” to obtain a single synthetic result. At the same time, this contributed positively to the evaluation of the Laseroba-

**Table 1.** Literature excluded from analysis

No.	Title	Exclusion reason
<b>Oxygen therapy</b>		
1.	Andersen, 2021 [1]	A
2.	Bomfim et al., 2021 [2]	C
3.	Howell et al. [3]	C
4.	Henshaw et al. [4]	C
5.	Golledge and Singh, 2019 [5]	C
6.	Chen et al., 2017 [6]	C
7.	Joshi et al., 2017 [7]	C
8.	Lipsky et al., 2020 [8]	C
9.	Löndahl and Boulton, 2020 [9]	A
10.	Oropallo et al., 2021 [10]	A
11.	Vas et al., 2020 [11]	C
12.	Tentolouris and Tentolouris, 2020 [12]	C
<b>Ozone therapy</b>		
1.	Braidy et al., 2018 [13]	C
2.	Grande et al., 2020 [14]	C
3.	Isler et al., 2018 [15]	B
<b>PEMF</b>		
1.	Morberg et al., 2018 [16]	B
2.	Mohajerani et al., 2019 [17]	B
3.	Miller et al., 2020 [18]	B
4.	McLaughlin et al., 2020 [19]	C
5.	Khooshideh et al., 2017 [20]	C
6.	Galli et al., 2019 [21]	A
7.	„Bone Healing Stimulator: External,” 2019 [22]	A
8.	Zhu et al., 2017 [23]	B
9.	VADALÀ et al., 2018 [24]	B
10.	Troy et al., 2021 [25]	C
11.	Tenuta et al., 2020 [26]	B
12.	Pesqueira et al., 2018 [27]	A
13.	Peng et al., 2021 [28]	A
14.	Lv et al., 2021 [29]	A
<b>Light therapy</b>		
1.	Bensadoun et al., 2020 [30]	A
2.	Brunke, 2018 [31]	A
3.	Fekrazad et al., 2018 [32]	A
4.	Silva et al., 2018 [33]	B
5.	“Lasers and Wound Healing,” 2021 [34]	C
6.	Vitoriano et al., 2019 [35]	C
7.	Oyebode et al., 2021 [36]	A
8.	Fallah et al., 2017 [37]	A

ria treatment method; examining issues using different research methods achieved a comparable therapeutic effect (Table 1).

Exclusion criteria from the analysis:

- A. Publication does not meet formal inclusion criteria (e.g., clinical trial).
- B. Presented clinical parameters deviate from the intended use of the product.
- C. Does not describe the type of therapy being conducted.

### Risk of bias

The studies included in the analysis were selected in a manner that limits the risk of bias. Tools for assessing the credibility of studies were applied depending on the type of studies included. For RCT studies, four out of five included studies are of high quality according to the Jadad scale. Figure 2 presents a summary of the risk of bias for RCT studies. The risk of bias assessment is summarized in Figure 2. The confidence of the secondary research included in the study was measured using the AMSTAR 2 tool, and the verification results were presented in the Table 3. The single-arm studies were assessed using the NICE scale, and the results were included in the Table 4. In light of the limited availability of comprehensive literature, all studies lacking features of the exclusion criteria were included in the analysis.

### Discussion

The majority of studies confirm the effectiveness of using the physical therapies available in the Lase-robaria 2.0\_S device for the purposes outlined by the manufacturer. Despite a clear increase in the number of studies, many researchers consistently refrain from drawing conclusions while awaiting confirmation of their own results. However, none of the studies indicate the occurrence of adverse side effects, deterioration in patient health, or other incidents related to the safety of therapy. Due to the high heterogeneity of the analyzed studies, conclusions drawn from the literature data have been cataloged and cumulated in descriptive form (Table 2).

### Oxygen therapy

Local oxygen therapy is characterized by a wide variety of methods for delivering oxygen to the wound. Collectively, these methods are often referred to as TWO2 (Topical Wound Oxygen). However, regardless of the form of oxygen delivery and the duration of exposure to oxygen, the analyzed studies indicate the effectiveness of therapy primarily by significantly accelerating wound closure time [38, 39]. Clinical studies conducted using local oxygen delivered from an oxygen concentrator, the form most closely aligned

	Random sequence generation (selection bias)	Blinding of participants and personnel (performance bias)	Incomplete outcome data (attrition bias)	Blinding of outcome assessment (detection bias)	Selective reporting (reporting bias)	Summary
Frangėž et al., 2018	+	-	+	+	+	-
Frangėž et al., 2017	+	?	+	+	+	?
Kurtti et al., 2021	+	?	+	+	+	?
Perper et al., 2020	+	+	+	+	+	+
Multanen et al., 2018	+	+	+	-	+	-
Liu et al., 2021	+	+	+	+	+	+
Gomes Gobbi et al., 2019	+	+	+	+	+	?
Pasek et al., 2020	?	+	+	+	?	?
Pietrzak et al., 2022	?	+	+	+	?	?

**Figure 2.** Summary of risk of bias for RCT studies

with the technology used in the Laserobaria 2.0\_S, confirm improvements in microcirculation within the wound area and shorten the time required for complete healing [40, 41]. Researchers emphasize the need for further research to be conducted in a standardized manner, enabling the identification of optimal therapy parameters.

**Ozone therapy**

The analyzed systematic reviews indicate that currently there is no conclusive evidence that ozone therapy is a better treatment for chronic wounds compared to standard treatment. However, research results consistently favor the use of ozone in the treatment of chronic wounds, suggesting potential for mainstream clinical practice. These studies encompass a wide range of ages and demographics of participants, chronic wounds, and methods of ozone application. Ozone therapy protocols have shown therapeutic effects in all included studies, with none reporting adverse effects [42, 43]. A study focused solely on the treatment of diabetic foot ulcers using ozone (in gaseous form or dissolved in water or oil) indicated that compared to standard control therapy for diabetic foot ulcers, ozone therapy,

regardless of monotherapy or combination therapy, significantly accelerated wound healing (standardized mean difference (SMD) = 66.54%, 95% confidence interval (CI) = [46.18, 86.90], P < 0.00001) and reduced the amputation rate (risk ratio (RR) = 0.36, 95% CI = [0.24, 0.54], P < 0.00001). However, there was no improvement in the percentage of participants with completely healed wounds and length of hospital stay. No adverse events related to ozone treatment were reported [44].

**PEMF**

Low-frequency pulsed electromagnetic fields (PEMF) are widely used as adjunctive therapies in the treatment of musculoskeletal disorders, especially in stimulating bone regeneration. Studies consistently demonstrate high efficacy. Aggregate research findings showed that the healing rate in the PEMF group was 79.7% (443/556), compared to 64.3% (370/575) in the control group. PEMF increased the healing rate (RR = 1.22; 95% confidence interval [CI] = 1.10–1.35; I2 = 48%) using Mantel-Haenszel analysis, alleviated pain (standardized mean difference (SMD) = -0.49; 95% CI = -0.88 to -0.10; I2 = 60%), and accelerated healing time (SMD = -1.01; 95% CI = -2.01 to -0.00; I2 = 90%) [45]. Wan Fang, VIP, EMBase, PubMed, CENTRAL, Web of Science, Physiotherapy Evidence Database, and Open Grey websites for randomized controlled trials (published before July 2019 in English or Chinese). The study on the therapeutic properties of low-frequency magnetic fields in the treatment of fibromyalgia did not show improvement in the treatment group compared to the control group [46]. Based on studies conducted over 3 months, pulsed electromagnetic field therapy has shown significant improvement in postoperative pain, quality of life, and function. Additionally, it has been found to improve bone microstructure [47]. However, another study demonstrated strong analgesic properties in patellofemoral pain syndrome with chondropathy. It was effective compared to placebo in the third month, showing a significant improvement in the Kujala score. The improvement was progressive and persisted for up to 12 months [48].

**Phototherapy**

Low-level light therapy is described across a wide spectrum of wavelengths from UV radiation to near-infrared. This radiation is most commonly produced by lasers and light-emitting diodes (LEDs). In most analyzed studies, no significant differences were found between treatment using LED diodes or lasers. The difference in the operation of LED diodes and laser diodes lies solely in the different principles of operation. LED diodes utilize the phenomenon of electroluminescence.

**Table 2.** Literature included in the analysis

Study	Type	Population	Comparison	Outcomes	Source of funding
<b>Intervention: Oxygen Therapy</b>					
de Smet et al., 2017 [38]	SR	N/A	N/A	TWO2 provided significant acceleration in wound closure in most studies	No financial support was received in support of this manuscript
Rayman et al., 2020 [39]	Guidelines	n/a	n/a	Local oxygen therapy can be defined as a therapy that delivers continuous or cyclic diffusion of pure oxygen to the wound surface	n/a
Kasprzyk-Kuciewicz et al., 2021 [40]	Pilot Study	n = 12 (M: 8, F: 4), age: 52–85, chronic venous ulcers	Baseline values	THBOT indirectly lead to a statistically significant decrease in the temperature of the areas around the wound	This research was funded by a grant from the Medical University of Silesia, number PCN-I-003/K/O/K
Tang et al., 2021 [41]	Clinical Trial	n = 20 (M: 13, F: 7), DFU	Baseline values	Closure of the wound > 75% was observed in 14/20 (70.0%) patients	Inotec AMD Ltd, Somnotec Ltd
<b>Intervention: Ozone therapy</b>					
Bomfim et al., 2021 [42]	SR	n = 506 adults with chronic wounds	n/a	Protocols of ozone therapy demonstrated therapeutic effects in all included studies, with none indicating any adverse effects	Conselho Nacional de Desenvolvimento Científico e Tecnológico/CNPq/Brazil and Fundação de Amparo à Pesquisa do Estado de Sergipe/FAPITECSE
Fitzpatrick et al., 2018 [43]	SR	n = 453, chronic wounds	Standard treatment/ /baseline values	Research results consistently favor the use of ozone in the treatment of chronic wounds, suggesting potential for mainstream clinical practice	No information
Wen et al., 2022 [44]	SR	All ages, chronic wounds of various etiology	Standard treatment	SMD = 66.54%, 95% CI = [46.18, 86.90], P < 0.00001 and reduced the amputation rate (RR = 0.36, 95% CI = [0.24, 0.54], P < 0.00001	the Sichuan Science and Technology Program, Grant/Award Number: 2019YFS0085
<b>Intervention: PEMF</b>					
Peng et al., 2020 [45]	SR	n = 1131, no age, gender, or race restrictions	Sham group	PEMF increased the healing rate and alleviated fracture pain, while very low-quality evidence indicated that PEMF accelerated healing time	National Natural Science Foundation of China; grant number: 81572231
Multanen et al., 2018 [46]	RCT	Female aged 18-60 years with fibromyalgia	Placebo	This study demonstrated that treatment with low-energy pulsating electromagnetic field was not more effective than treatment with a sham device in reducing pain and stiffness or improving function in women with fibromyalgia	The Medical Research Foundation of Jyväskylä Central Hospital; grant number: KSSHBP1601
Liu et al., 2021 [47]	RCT	n = 82	Standard treatment	It was found that pulsed electromagnetic field therapy showed significant improvement in postoperative pain, quality of life, and function. The study further demonstrates that pulsed electromagnetic field treatment may also improve bone mass and bone microstructure	the Qinghai Province Health System Guiding Plan Project (Grant no. 2019-wjzdx-08)

Study	Type	Population	Comparison	Outcomes	Source of funding
Gomes Gobbi et al., 2019 [48]	RCT	n = 24, aged 20–50 with patellofemoral pain Syndrome, patellar chondropathy	Sham PST	PST in patellofemoral pain syndrome with chondropathy was effective compared to placebo at 3 months, showing significant improvement in the Kujala score. Improvement was progressive and sustained up to 12 months. PST is safe and should be considered as a non-invasive option in the treatment of this condition	Sao Paulo Research Foundation (Fundac~ao de Amparo a Pesquisa do Estado de S~ao Paulo FAPESP grant number: 2012/5067-6
<b>Intervention: LLLT</b>					
Dos Santos Mendes-Costa et al., 2021 [49]	SR	n/a	n/a	No significant differences between treatment with LED or laser	L.S.M is fellowship in Fundacao Cearense de Apoio a Pesquisa-FUNCAP (grant PIBIC 2019/2020–no.7/2019)
Zhou et al., 2021 [50]	SR	n = 480 from eight countries, adults with diabetic foot ulcers	Routine treatment with or without placebo	30.90% of the ulcer area was significantly reduced in the treatment group compared to the control group (Z = 3.95, P < 0.001) with a very large effect size (g = 2.81). A 4.2 cm <sup>2</sup> reduction in ulcer area was observed in the treatment group compared to the control group (Z = 2.17, P = 0.03) with a very large effect size (g = 1.37). Additionally, the treatment group was 4.65 times more likely to have a diabetic foot ulcer heal completely than the control group (Z = 3.02, P = 0.003). Low-level light therapy speeds wound healing and reduces the size of diabetic foot ulcers	No information
Huang et al., 2021 [51]	SR	n = 413, DFU	Standard treatment/ /placebo	LLLT significantly increased the rate of complete healing (risk ratio [RR] = 2.10, 95% confidence interval [CI] 1.56–2.83, P < 0.00001), reduced ulcer area (standardized mean difference [SMD] = 3.52, 95% CI 1.65–5.38, P = 0.0002) and reduced mean healing time (SMD = –1.40, 95% CI –1.90 to –0.91, P < 0.00001) in patients with DFUs	Nursing Science Research Fund of Chongqing Medical University, Grant/Award Number: 2019hlxk07
Petz et al., 2020 [52]	SR	n = 160, ulcers of various etiologies and places	Standard care	Red-wave PBMT (658 nm) was effective in promoting healing compared with standard care	No information
Frangež et al., 2018 [53]	RCT	n = 60 diabetic patients With chronic wounds	Placebo	The Falanga scale assessment showed significantly faster healing of the wound bed in the LED group compared to the Co group (p < 0.05)	No competing financial interests exist
Frangez et al., 2017 [54]	RCT	n = 82, chronic wound, with or without diabetes	Placebo	Significant increase in blood flow in patients with and without diabetes (p = 0.040 and p = 0.033), while there was no difference in the control groups. Falanga wound bed score showed significant improvement in both treatment groups compared to the control group	There is no funding source
Kurtti et al., 2021 [55]	RCT	n = 30 adult women non-Hispanic Caucasian	Sham therapy	There were no significant differences in scar flexibility between treated and control scars. LED-RL phototherapy can be safely used in the early postoperative period on facial skin and can reduce postoperative scarring	National Institute of General Medical Sciences of the National Institutes of Health, Grant/Award Number: K23GM117309

Study	Type	Population	Comparison	Outcomes	Source of funding
Perper et al., 2020 [56]	RCT	n = 14 (M: 8, F: 6), age: 61–86, with surgical defects	Virtual light	Photomodulation with a red LED at a wavelength of 633 nm did not result in clinical improvement in the healing of postoperative wounds in the lower limbs	No information
<b>Intervention: Combination therapies (LLLT, PEMF, TOT, Ozone Therapy)</b>					
Pasek et al., 2020 [57]	Clinical trial	n = 65 (F: 29 M:36), Age: 41–86, venous leg ulcer, average BMI: 30.6 kg/m <sup>2</sup>	Topical Oxygen Therapy	Mean percentage reduction in the ulcer area (36.44% ± 11.04%) statistically significantly greater (P = 0.00001) compared with the Co group (13.65% ± 8.32%). Average increase in the EuroQoL score (61.03 ± 7.14) was statistically significantly (P = 0.00001) higher compared to Co group (25.27 ± 8.16)	Funding information Medical University of Silesia, Grant/Award Number: KNW-I-003/K/8/K
Pietrzak et al., 2022 [58]	Preliminary research	n = 36 (F: 14, M: 22) aged 18–80, chronic venous leg ulcers	Topical Oxygen Therapy	Statistically significant reduction in the ulcer area was achieved (25.11 ± 17.8 cm <sup>2</sup> to 16.93 ± 13.89 cm <sup>2</sup> , p = 0.000196) vs. (34.17 ± 14.82 cm <sup>2</sup> to 23.99 ± 15.15 cm <sup>2</sup> , p = 0.004337). Statistically significant decrease in fibrinogen level in patients who received combined physical therapy (p = 0.01). Statistically significant reduction in the fibrinogen level (p = 0.01 and p < 0.001) and total protein level (p = 0.01) was achieved. Decrease in the concentration of the inflammatory marker — C-reactive protein (CRP) was observed	Authors' Contribution
Pasek et al., 2021a [59]	Clinical trial	n = 147 (F: 67, M: 80), aged: 41–79, venous ulcers	Baseline data	Statistically significant reduction in the area of the treated ulcer, on average by 5.4 cm <sup>2</sup> (16.3 cm <sup>2</sup> vs 10.5 cm <sup>2</sup> ) (p < 0.05). Reduction in the intensity of pain experienced by patients was achieved, assessed using the VAS scale (2.55 points vs. 0.48 points) (p < 0.05)	The author(s) received no financial support for the research, authorship, and/or publication of this article
Pasek et al., 2021b [60]	Clinical trial	n = 54, (F: 25, M: 29), aged 38–89	Baseline data	Statistically significant increase in the partial pressure of oxygen in the tissues surrounding the ulcer, from an average value of 68.63 ± 17.04 mm Hg before the start of the therapeutic cycle, to an average value of 74.20 ± 18.92 mm Hg after the first treatment (P < 0.001) and to a mean value of 83.79 ± 20.74 mm Hg (P < 0.001) after the end of the therapeutic cycle	The author(s) received no financial support for the research, authorship, and/or publication of this article
Sieroń, 2022 [61]	Series of cases	n = 52 (F: 23 M: 29), All patients had chronic wounds	n/a	Wound disinfection using UV light and ozone should be performed with greater intensity in situations where there is strong wound colonization. However, UV light should not be used during the granulation process, and more attention should be paid to therapies that stimulate tissue growth, such as oxygen therapy, magnetotherapy and red light therapy	No information



**Table 3.** Assessment of secondary research according to the AMSTAR 2 scale

de Smet et al., 2017 [38]	Bomfim et al., 2021 [42]	Fitzpatrick et al., 2018 [43]	Wen et al., 2022 [44]	Peng et al., 2020 [45]	Zhou et al., 2021 [50]	Huang et al., 2021 [51]		Petz et al., 2020 [52]	Dos Santos Mendes-Co-sta et al., 2021 [49]
<b>I. Inclusion of PICO components in the question or exclusion criteria</b>									
YES	YES	YES	YES	YES	YES	YES		YES	YES
<b>2. Protocol registration prior to conducting the PICO Study</b>									
P. YES	YES	P. YES	P. YES	YES	YES	P. YES		P. YES	NO
<b>3. Rationale for the selection of the types of studies included in the Systematic Review</b>									
YES	YES	YES	YES	YES	YES	YES		YES	YES
<b>4. Thorough conduct of systematic search for primary research studies</b>									
P. YES	P. YES	P. YES	P. YES	P. YES	P. YES	P. YES		P. YES	P. YES
<b>5. Execution of publication selection by at least 2 analysts</b>									
YES	YES	NO	YES	YES	YES	YES		YES	YES
<b>6. Data extraction performed by at least 2 analysts</b>									
YES	YES	YES	YES	YES	YES	YES		NO	YES
<b>7. Justification for the exclusion of individual studies evaluated in full text</b>									
NO	NO	NO	YES	P. YES	NO	NO		P. YES	NO
<b>8. Comprehensive characterization of primary research studies included in the systematic review</b>									
P. YES	YES	P. YES	NO	P. YES	P. YES	P. YES		P. YES	–
<b>9. Assessment of Risk of Bias in each of the primary research studies included in the systematic review, particularly related to: For RCT studies: blinding of the patient randomization process and double-blinding, For non-randomized studies: factors confounding the assessment of intervention effectiveness and sample selection</b>									
NO	YES	YES	P. YES	P. YES	P. YES	P. YES		P. YES	–
<b>10. Information on the funding sources of primary research studies</b>									
NO	NO	NO	YES	YES	NO	YES		NO	–
<b>II. Proper methodology for conducting meta-analysis</b>									
N/A	N/A	YES	YES	YES	YES	YES		YES	–
<b>12. Conducting an analysis of potential impact of Risk of Bias (RoB) in primary studies or differences in outcomes between individual primary studies</b>									
N/A	N/A	YES	YES	YES	YES	YES		YES	–
<b>13. Incorporating the potential impact of Risk of Bias (RoB) in primary studies when interpreting the results of the Systematic Review or differences in outcomes between individual primary studies</b>									
NO	YES	YES	YES	YES	NO	YES		YES	–
<b>14. Presentation and discussion of each observed heterogeneity in the results of the Systematic Review</b>									
YES	YES	NO	YES	YES	YES	YES		YES	–
<b>15. Assessment of Publication Bias and its impact on the results of the review, which included meta-analysis</b>									
N/A	YES	YES	YES	YES	NO	YES		YES	–
<b>16. Presentation of each source of conflict of interest, including the funding received by the authors for conducting the systematic review</b>									
YES	NO	NO	YES	YES	YES	YES		YES	–
CRITICALLY LOW	LOW	LOW	HIGH	HIGH	CRITICALLY LOW	LOW		MODE-RATE	CRITICALLY LOW

**Table 4.** Assessment of primary studies according to the NICE scale for single-arm trials

Study	Study type	NICE scale	Interpretation
Kasprzyk-Kucewicz et al., 2021 [40]	One-arm pilot study	6/8	High quality study
Tang et al., 2021 [41]	One-arm observational clinical trial	5/8	Moderate quality study
Pasek et al., 2021a [59]	One-arm clinical trial	7/8	High quality study
Pasek et al., 2021b [60]	One-arm clinical trial	6/8	High quality study
Sieroń, 2022 [61]	One-arm case series	2/8	Low quality study

science, while laser diodes involve the phenomenon of stimulated emission of radiation. Laser diodes can also achieve higher output powers. However, there is no difference in wavelengths. In a broader sense, it has been observed that both treatment categories provide clinical improvement in terms of wound size and tissue repair processes, significant acceleration of wound healing, reduction in signals and symptoms, faster granulation in the wound healing process, and reduction in fibrin levels [49]. Another study indicates that 30.90% of the ulcer area was significantly reduced in the therapeutic group compared to the control group ( $Z = 3.95$ ,  $P < 0.001$ ) with a very large effect ( $g = 2.81$ ). A reduction of 4.2 cm<sup>2</sup> in ulcer area was observed in the therapeutic group compared to the control group ( $Z = 2.17$ ,  $P = 0.03$ ) with a very large effect ( $g = 1.37$ ). Furthermore, the likelihood of complete healing of diabetic foot ulcers in the therapeutic group was 4.65 times greater than in the control group ( $Z = 3.02$ ,  $P = 0.003$ ). Low-level light therapy accelerates wound healing and reduces the size of diabetic foot ulcers [50]. Compared to the control group, LLLT significantly increased the proportion of complete healing (risk ratio [RR] = 2.10, 95% confidence interval [CI] 1.56–2.83,  $P < 0.00001$ ), reduced the ulcer area (standardized mean difference [SMD] = 3.52, 95% CI 1.65–5.38,  $P = 0.0002$ ), and shortened the mean healing time (SMD = -1.40, 95% CI -1.90 to -0.91,  $P < 0.00001$ ) in patients with DFUs [51]. Red wave photobiomodulation therapy (658 nm) in stage 2 and 3 pressure ulcers was effective in promoting healing compared with standard care. No strong evidence has been found to disprove its clinical use [52]. LED treatment significantly accelerates the healing of chronic diabetic wounds and prepares the wound bed for further coverage options. After 8 weeks of treatment, the wound area treated with LED was 56% of the initial area, while in the Co group it was 65% of the initial area ( $p > 0.05$ ). The Falanga scale assessment showed significantly faster healing of the wound bed in the LED group [53]. In both diabetic and non-diabetic patient groups, there was a significant increase in blood flow following treatment ( $p = 0.040$  and  $p = 0.033$ , respectively), whereas no notable difference was observed in the control groups. Further-

more, an additional improvement was observed in the Falanga wound bed score for both treatment groups compared to the control group. Our results indicate that LED phototherapy serves as an effective adjunctive treatment for chronic wounds in patients, regardless of diabetic status [54]. In the case of postoperative scars, in one study, no significant differences in scar flexibility were found between treated and control scars. At certain light intensity values, treated scars showed greater improvement in observer-rated scar appearance and scar flexibility, reflected by greater reduction in stiffness, from baseline to 6 months, compared to control scars. Adverse events at the treatment site included blisters ( $n = 2$ ) and swelling ( $n = 1$ ), which were mild and resolved without consequences. LED-RL phototherapy is safe in the early postoperative period and may reduce scars [55]. However, other studies indicate that red LED photobiomodulation with a wavelength of 633 nm did not result in clinical improvement in the healing of postoperative wounds on the lower limbs [56].

### Combination therapies

Combined therapies using the therapeutic agents available in the Laserobarbia 2.0\_S device are currently an evolving direction of application. The use of multiple therapeutic agents yields a positive clinical effect. Users of Laserobarbia 2.0\_S device have reported improvements in patients' health status, indicating the high effectiveness of the device compared to other medical treatment methods used in their medical practice in the context of manufacturer's clinical indications.

In a comparative study comparing the use of local hyperbaric oxygen therapy to combined, simultaneous therapies (local hyperbaric oxygen, pulsed electromagnetic field therapy, red light, and UV light), both local hyperbaric oxygen therapy alone and the combination of physical methods resulted in a significant reduction in ulcer area, decreased pain intensity, and improved quality of life. In both groups, a statistically significant reduction in ulcer area was achieved ( $P < 0.05$ ). However, patients treated with combined physical therapy exhibited a significantly greater average percentage reduction in ulcer area ( $36.44\% \pm 11.04\%$ ) compared to the second group ( $13.65\% \pm 8.32\%$ ) ( $P = 0.00001$ ).

In both patient groups, there was a significant reduction in pain frequency and intensity, decreased use of painkillers, and improved physical activity limitations, as well as a statistically significant enhancement in quality of life ( $P < 0.05$ ). Nonetheless, patients receiving combined physical therapy demonstrated a significantly higher average increase in EuroQoL score ( $61.03 \pm 7.14$ ) compared to the second group ( $25.27 \pm 8.16$ ) ( $P = 0.00001$ ). The combination of physical methods proved to be the most effective comparing TOT and combination therapy [57].

In another study comparing to topical oxygen therapy statistically significant reductions in ulcer size were observed in both groups, but in patients treated with combined physiotherapy, the average percentage reduction in ulcer size ( $36.44\% \pm 11.04\%$ ) was statistically significantly greater ( $P = 0.00001$ ) compared to the second group ( $13.65\% \pm 8.32\%$ ). In both groups of patients, statistically significant reductions in pain frequency and intensity, decreased use of analgesic drugs, decreased physical activity limitations, and statistically significant improvement in quality of life were observed, but in patients treated with combined physiotherapy, the average increase in EuroQoL score ( $61.03 \pm 7.14$ ) was statistically significantly greater ( $P = 0.00001$ ) compared to the second group ( $25.27 \pm 8.16$ ). It was found that both local hyperbaric oxygen therapy alone and the combination of physical methods led to significant reductions in ulcer size, decreased pain intensity, and improvement in quality of life, but the combination of physical methods was more effective. These data were confirmed in another similar study. In both groups, statistically significant reductions in ulcer size were achieved ( $25.11 \pm 17.8 \text{ cm}^2$  to  $16.93 \pm 13.89 \text{ cm}^2$ ,  $p = 0.000196$ ) vs ( $34.17 \pm 14.82 \text{ cm}^2$  to  $23.99 \pm 15.15 \text{ cm}^2$ ,  $p = 0.004337$ ). In blood morphology, statistically significant reductions in fibrinogen levels were observed in patients in group II who received combined physiotherapy ( $p = 0.01$ ). Statistically significant reductions in fibrinogen levels ( $p = 0.01$  and  $p < 0.001$ ) and total protein levels ( $p = 0.01$ ) were achieved in both groups. In group II, a decrease in the concentration of the inflammatory marker — C-reactive protein (CRP) — was noted. Local hyperbaric oxygen therapy and combined physical therapy had a statistically significant effect on reducing the surface area of treated venous leg ulcers. Changes in morphological and biochemical parameters may indicate the anti-inflammatory and anticoagulant effects of combined physical therapy [58].

Studies on the effectiveness of combined therapeutic methods indicate a statistically significant reduction in the surface area of the treated ulcer, on average by  $5.4 \text{ cm}^2$  ( $16.3 \text{ cm}^2$  vs.  $10.5 \text{ cm}^2$ ) ( $p < 0.05$ ). Furthermore, as a result of the performed combined therapy pro-

cedures, there was a statistically significant reduction in pain intensity perceived by patients, assessed using the VAS scale (2.55 points vs. 0.48 points) ( $p < 0.05$ ). The achieved improvement did not depend statistically significantly on any of the analyzed selected factors potentially influencing the regenerative and analgesic effects of the applied therapy. The use of combined physiotherapy with the LASEROBARIA-S device results in a significant reduction in the surface area of venous ulcers, as well as a decrease in the intensity of accompanying pain, and this therapeutic effect was independent of the gender and age of the patients, as well as the initial size of the ulcer and the duration of its presence [59].

Confirmed in another study; combined physiotherapy shows a statistically significant increase in tissue oxygen partial pressure values surrounding the ulcer, from an average value of  $68.63 \pm 17.04 \text{ mm Hg}$  before the start of the therapeutic cycle, to an average value of  $74.20 \pm 18.92 \text{ mm Hg}$  after the first treatment ( $P < 0.001$ ) and to an average value of  $83.79 \pm 20.74 \text{ mm Hg}$  ( $P < 0.001$ ) after the completion of the therapeutic cycle. Combined physiotherapy treatments lead to a statistically significant increase in tissue oxygen partial pressure values surrounding the ulcer, assessed by objective transcutaneous oximetry, both in women and men [60].

Based on the clinical experience with the use of combined physical therapeutic forms in the treatment of difficult-to-heal wounds regarding dosing and sequencing of therapy, it is important to remember about an individual approach to the patient and the selection of therapeutic agents in such a way as to maximize the therapeutic effect. This primarily means adjusting the intensity of individual therapeutic agents in the context of the current condition of the wound. Wound disinfection using UV light and ozone should be performed with greater intensity in situations where there is strong wound colonization. However, UV light should not be used during the granulation process, and more attention should be paid to therapies that stimulate tissue growth, such as oxygen therapy, magnetotherapy and red light therapy [61].

## Conclusions

The analyzed evidence does not show any negative aspects of using any of the available therapeutic forms, whether used individually, sequentially, or in combination. In the majority of the discussed publications, a clear positive therapeutic effect was also noted. Furthermore, combined physical therapies show increased efficacy compared to single therapies used alone.

The systematic literature review presented above, serving as an update to the clinical evaluation of the Laserobaria method of treatment, expands the knowledge base with valuable evidence regarding dosing and effectiveness of individual therapies. Through literature analysis, no evidence was found to challenge previous assumptions, and notably, no evidence of patient health deterioration was found.

Simultaneous exposure to therapeutic agents allows for longer exposure time to each of them while shortening the overall treatment time. From the user's perspective, this allows for more treatments with one device while maintaining similar operating costs. The increased economic efficiency on the healthcare facility's side creates an opportunity to reduce final costs for the patient, thus increasing access to modern treatment methods. This is particularly significant for patients dealing with non-healing limb wounds.

### Conclusions regarding effectiveness

The conclusions described in the clinical evaluation document remain current. Further observation is warranted regarding the conclusions arising from combined therapies, which is a developmental goal of the assessed therapy.

### Conclusions regarding safety

No adverse events, incidents, or serious medical incidents were recorded.

### Conclusions regarding risk-benefit ratio

This analysis demonstrates that the level of threats is low, while the benefits for patients are high, advocating for the dissemination of the technology.

The use of combined, simultaneous methods of physical therapy can be a safe and cost-effective way to support the treatment of non-healing wounds.

## Article information and declarations

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**Conflict of interest:** Dominik Dziadek and Kinga Kostera are employees of INVENTMED, the manufacturer of the Laserobaria 2.0\_S device, Prof. Aleksander Sieron is not associated with the operational activities of the company and as an author remained independent. The publication is the result of one's own scientific work without financial participation of the company. The authors declare that they made every effort to conduct a fair study despite potential conflicts of interest. The study followed recognized guidelines for the design of systematic reviews and the evaluation of study results. Favorable and unfavorable papers were included in the review, a full list of rejected articles was provided, along with the reason, and a table for assessing the reliability of individual studies. Extensive description of the methodology allows for replication of the study.

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