Systematic Reviews

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Effects of photobiomodulation on multiple health outcomes: an umbrella review of randomized clinical trials

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Abstract

Background Photobiomodulation (PBM) is a non-invasive therapy increasingly used for pain, inflammation, and tissue repair, yet a comprehensive synthesis of its effectiveness across multiple health outcomes remains lacking. Herein, we aimed to systematically assess the clinical effects and strength of evidence for PBM across a wide range of health outcomes using data from existing meta-analyses of randomized controlled trials (RCTs).

Methods We conducted an umbrella review of meta-analyses of RCTs, searching five databases up to December 8, 2023. Two reviewers independently assessed methodological quality using AMSTAR 2 and evaluated certainty of evidence using a modified GRADE framework. Pooled effect sizes were recalculated as equivalent standardized mean differences (eSMD) with 95% confidence intervals (CI). The study was registered with PROSPERO (CRD42023495502).

Results A total of 15 meta-analyses encompassing 204 RCTs and over 9000 participants were included, covering 35 health endpoints across 15 disease conditions. PBM showed significant effects for 12 outcomes, with moderate certainty of evidence supporting improvements in burning mouth syndrome (pain reduction, eSMD − 0.92 [95% CI − 1.38 to − 0.46]), knee osteoarthritis (disability, 0.65 [0.14 to 1.15]), fibromyalgia (fatigue, 1.25 [0.63 to 1.87]), androgenetic alopecia (hair density, 1.32 [1.00 to 1.63]), and cognitive function (0.49 [0.14 to 0.84]). Most other outcomes exhibited low or very low certainty due to heterogeneity or small-study effects. P-curve and funnel plot analyses indicated evidential value for several outcomes, though potential publication bias was identified in some.

Conclusions PBM appeared beneficial for some health conditions, such as the strongest support for fibromyalgia, osteoarthritis-related disability, and cognitive impairment. However, given the overall low-to-moderate certainty of evidence for most endpoints, further high-quality trials and standardization of PBM protocols are warranted before widespread clinical adoption.

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Keywords Health outcomes, Low-level light therapy, Photobiomodulation, Randomized controlled trials, Umbrella review

Introduction

Photobiomodulation (PBM), utilizing non-thermal red or near-infrared light within the 600–1100 nm wavelength range, has emerged as a non-invasive treatment modality for various diseases [1]. PBM was also referred to as low-level light therapy, and its wavelength spectrum is pertinent to mitochondrial light absorption, resulting in activating the mitochondrial respiratory electron transport chain and increased adenosine triphosphate (ATP) production [2]. PBM has a role in pain reduction, wound healing, tissue regeneration, and reducing inflammatory responses [1]. Recently, PBM has been included in treatment guidelines for oral mucositis in cancer therapies and approved by the National Institute for Health and Care Excellence and the Multinational Association of Supportive Cancer Care [3].

The mechanism of action of PBM therapy includes the activation of antioxidant enzymes and the inhibition of inflammatory mediators [4]. The therapy regulates the production of free radicals such as reactive oxygen species (ROS) and nitric oxide (NO), thereby reducing oxidative stress and improving the cellular environment [5]. These biochemical changes promote cytoprotective effects and are particularly important in the treatment of neurological, skin, and musculoskeletal disorders [1]. PBM also has a positive impact on overall tissue repair and regeneration by enhancing mitochondrial function and increasing the energy efficiency of cells [3]. Through these various mechanisms, PBMs are considered a comprehensive therapeutic approach that can improve a variety of pathological conditions.

Clinical trials have suggested the beneficial effect of PBM for various health outcomes, especially oral and musculoskeletal diseases [6–12]. Although several meta-analyses have evaluated the effects of PBM on specific conditions, they vary in methodological quality, effect size estimation, and certainty assessment criteria. Furthermore, no previous umbrella review has provided a comprehensive synthesis across multiple disease areas using a unified framework to evaluate the strength, consistency, and credibility of evidence. To address this gap, we conducted an umbrella review of meta-analyses of randomized controlled trials (RCTs), re-analyzing pooled estimates and assessing the certainty of evidence using a standardized Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach. This study aims to offer an overarching evaluation of the therapeutic potential of PBM across diverse health outcomes, while also identifying research gaps and informing clinical decision-making.

Methods

Literature search strategy

We performed an umbrella review of meta-analyses of RCTs to synthesize evidence from meta-analyses of RCTs and explore the effects of PBM on various health outcomes. Our study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines 2020 [13, 14], and a priori protocol (PROSPERO database; CRD42023495502).

We included only peer-reviewed meta-analyses of RCTs that investigated the clinical effects of PBM or low-level laser therapy in human participants. Eligible studies had to report pooled effect estimates along with heterogeneity statistics (I^2). We excluded network meta-analyses, non-RCT designs, narrative reviews, and preclinical (animal or in vitro) studies.

Two authors, J.K. and Y.S., independently and systematically screened literature by searching PubMed/MEDLINE, Embase, CINAHL, Web of Science, and Google Scholar systematic reviews databases from database inception to December 8, 2023, and extracted data into a spreadsheet. This study aimed to identify meta-analyses of RCTs investigating the effect of PBM on various health outcomes. The key search strategy was "meta-analysis" AND ("PBM" OR "Photobiomodulation" OR "low-level laser" OR "low-intensity laser light") and related variants. The search strategies for each database are provided in Supplementary Table 1. All articles identified through database searches were systematically and manually screened at the title/abstract and full-text levels by two independent reviewers (J.K. and Y.S.). No automation tools or machine-assisted screening software were used at any stage of the review process.

Selection criteria

Two researchers (J.K. and Y.S.) independently and manually screened the references of the eligible articles and rigorously reviewed the titles, abstracts, and full texts. When two or more original meta-analyses examined the same outcome, we prioritized the study that included (1) the largest number of participants, (2) higher methodological quality based on AMSTAR 2, and (3) broader outcome coverage. If these factors were equivalent, we selected the most recently published study [15]. The primary outcomes were the effects of PBM on several health

conditions (e.g., burning mouth syndrome and temporomandibular disorders) in meta-analyses of RCTs.

For each effect from RCTs, we extracted the effect sizes, including mean difference (MD), risk ratio (RR), or standardized mean difference (SMD), of individual studies reported in each meta-analysis, recalculating the pooled effect sizes and 95% confidence intervals (CI) using random or fixed effects model [16]. RR was converted to SMD in re-analysis to consolidate all data metrics as continuous data. To harmonize effect sizes across studies, RRs were converted to SMDs using the following formula $SMD \approx \log(RR) * \frac{\sqrt{3}}{\pi}$, as described in previous methodological literature [17, 18].

Data extraction and analysis

Each study provided the following information: year of publication, quantity of primary studies encompassed, categories of investigated outcomes, geographical location of the study, counts of cases and participants, research design, the method employed for effect estimation (random or fixed effects), indicators of heterogeneity, and the extensively adjusted effect size accompanied by a 95% confidence interval [19–21]. To re-analyze the initial meta-analyses, we utilized the DerSimonian and Laird method for outcomes including ten or more studies, and the Hartung-Knapp-Sidik-Jonkman method for those including fewer than ten studies, under a random-effects model. This strategy was chosen to ensure appropriate estimation precision and minimize type I error rates depending on the number of included studies, following established meta-analytical recommendations [22]. Network or dose-dependent meta-analyses were not reconsidered due to insufficient estimations and evidence [23]. Additionally, various subsequent analyses were undertaken to investigate specific aspects: (1) Heterogeneity was evaluated, with a substantial heterogeneity indicated by an I^2 value exceeding 75%; (2) The P-curve was employed to detect potential p-hacking, a statistical manipulation for achieving significant results; (3) The 95% prediction interval was utilized to gauge the uncertainty of the observed estimates and offer guidance for future research employing Bayesian statistics; (4) The Knapp-Sidik-Jonkman random effects model was implemented to minimize inappropriate type I errors; (5) Examination of publication bias was conducted, with an Egger's *P*-value below 0.1 suggesting potential publication bias [24]. Following recent guidelines, we estimated comparable SMDs across various metrics, including MD or RR [14]. All analyses were conducted using R software version 4.2.2 (R Foundation for Statistical Computing, Vienna, Austria). For outcomes including ten or more studies, the DerSimonian and Laird random-effects model was applied. For outcomes with fewer than ten studies, the Hartung-Knapp-Sidik-Jonkman method was applied in R using the rma.uni() function from the metafor package, with the argument knha = TRUE. Statistical significance was determined based on a two-sided *P*-value threshold of < 0.05 [25].

Assessment of quality of study and evidence

The methodological quality of the included systematic reviews and meta-analyses was assessed using the A Measurement Tool to Assess Systematic Reviews 2 (AMSTAR 2) checklist, which consists of 16 items, including 7 critical domains [26]. Two reviewers (J.K. and Y.S.) independently evaluated each study. Discrepancies in item-level assessments were resolved through discussion, and a third reviewer (D.K.Y.) was consulted when necessary to reach consensus. Item-level results and overall confidence ratings (high, moderate, low, critically low) are presented in Supplementary Table 2, following the AMSTAR 2 guidance [27].

The certainty of evidence for each outcome was assessed using a modified version of the GRADE approach. Certainty was categorized as high, moderate, low, or very low based on five domains: risk of bias, inconsistency, indirectness, imprecision, and publication bias. The operational rules used to grade each domain, along with the resulting assessments, are provided in Supplementary Table 3.

Publication bias was assessed using funnel plots, Egger's test (*P* values), and/or P-curve analysis. In addition, we evaluated whether the effect size was large (e.g., SMD > 0.8), whether there was a dose–response relationship, and whether credible residual confounding existed, each of which was considered as a factor potentially upgrading the certainty of evidence.

Patient and public involvement

No patients or members of the public were involved in the development of this umbrella review. However, the scope and methods of this review were informed by the literature and discussions with experts in the field.

Results

Of 1489 studies screened, 684 full-text studies were assessed after duplicate removal, with 15 meta-analyses of RCTs included (Fig. 1). Excluded study characteristics are shown in Supplementary Table 4. Although no publication year restrictions were applied, all included studies were published between 2019 and 2023. A total of 204 original articles across 32 countries (Australia, Austria, Brazil, Canada, China, Colombia, Croatia, Denmark, Egypt, England, France, Greece, Hong Kong, Hungary, India, Indonesia, Iran, Israel, Italy, Japan, Korea, New Zealand, Norway, Saudi Arabia, Scotland, Spain, Sweden,

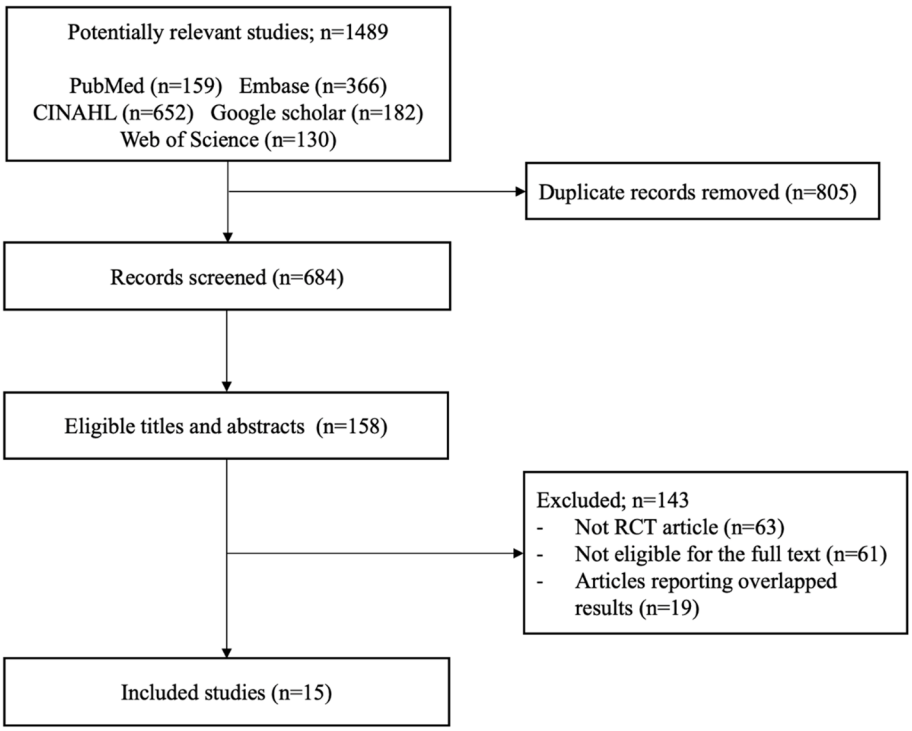

Fig. 1 PRISMA 2020 flow diagram. Abbreviations: RCT, randomized controlled trials

Taiwan, Thailand, Turkey, the UK, and the United States) and six continents were included (Table 1) [6–12, 28–35].

The quality of the original meta-analysis based on AMSTAR 2 was high in one meta-analysis, moderate in two, and low in twelve (Supplementary Table 2). Fifteen meta-analyses of RCTs covered over 9000 patients with 35 unique health endpoints and 15 unique health outcomes, including burning mouth syndrome, temporomandibular disorders, rheumatoid arthritis, plantar fasciitis, tendinopathy, knee osteoarthritis, fibromyalgia, cognitive function, myofascial neck pain, Achilles tendinopathy, fractures, carpal tunnel syndrome, diabetic foot ulcers, tinnitus, and androgenetic alopecia. The protocol of PBM widely varies in aspects of the wavelengths of laser, duration of treatment, and number of treatment sessions, and particularly, there is no existing standard protocol (Table 2).

Based on the GRADE, 17.1% (6/35) meta-analytical effects met the moderate certainty criteria, 57.1% (20/35) effects met low certainty, and 25.7% (9/35) met very low certainty (Supplementary Table 3). Except for nine outcomes (quality of life in patients with burning mouth syndrome, pain levels in patients with temporomandibular disorders, pain reduction in patients with knee osteoarthritis, changes in fibromyalgia impact questionnaire [FIQ] score in patients with fibromyalgia, changes in pain severity in patients with fibromyalgia, changes in number of tender points in patients with fibromyalgia, changes in severity of fatigue in patients with fibromyalgia, changes in severity of anxiety in patients with fibromyalgia, and pain reduction in patients with fractures), the shape of the P-curve exhibited a pronounced rightward skewness in the case of continuous metrics ($P < 0.05$). This skewness suggests the absence of any indications of P-hacking. By re-evaluating the 19 results through random and fixed effects analyses, it was identified that 42.9% (15 out of 35) exhibited significant heterogeneity ($I^2 > 75$). We found statistical indications of publication bias in 20.0% (6 out of 30) of the studies using Egger's regression test. To explore potential sources of heterogeneity, we performed a sensitivity analysis for outcomes with substantial heterogeneity ($I^2 \geq 75\%$) by excluding studies in the lowest 25th percentile of sample size. As a result, heterogeneity was substantially reduced in two outcomes, including pain levels in patients with rheumatoid arthritis ($I^2 = 44.61\%$) and handgrip strength in patients with rheumatoid arthritis ($I^2 = 0\%$). In contrast, heterogeneity in remaining outcomes either persisted or increased, suggesting that small study effects were not the primary contributors of inconsistency in most cases. The forest plot, Funnel plot, and P-curve for each health outcome are presented in Supplementary Materials (Supplementary Fig. 1–35).

Table 1 Characteristics of meta-analyses of randomized clinical trials studying PBM

Outcome	First author	Published year	Included countries	AMSTAR2
1. Burning mouth syndrome				
Pain intensity in patients with burning mouth syndrome	C Lu	2023	China, Croatia, Iran, Spain	Low
Quality of life in patients with burning mouth syndrome	C Lu	2023	Croatia, Iran, Italy, Spain	Low
2. Temporomandibular disorders				
Pain levels (VAS score) in patients with temporomandibular disorders	R Hanna	2021	Austria, Brazil, India, Iran, Italy, Turkey	High
3. Rheumatoid arthritis				
Pain levels in patients with rheumatoid arthritis	I Lourinho	2023	Brazil, England, Scotland, Turkey	Low
Morning stiffness in patients with rheumatoid arthritis	I Lourinho	2023	Brazil, England, Japan, Scotland	Low
Handgrip strength in patients with rheumatoid arthritis	I Lourinho	2023	Brazil, Japan, Turkey	Low
Functional capacity in patients with rheumatoid arthritis	I Lourinho	2023	Brazil, Scotland, Turkey	Low
Inflammation in patients with rheumatoid arthritis	I Lourinho	2023	Brazil, England, Scotland, Turkey	Low
Activity score in patients with rheumatoid arthritis	I Lourinho	2023	England, Japan	Low
4. Plantar fasciitis				
Pain intensity in patients with plantar fasciitis	JV Ferlito	2023	Greece, United States	Low
5. Tendinopathy				
Pain reduction (VAS score) in patients with tendinopathy	N Tripodi	2021	Greece, Hong Kong, Iran, Turkey	Low
Muscle strength in patients with tendinopathy	N Tripodi	2021	Greece, Hong Kong, Turkey	Low
6. Knee osteoarthritis				
Pain reduction in patients with knee osteoarthritis	MB Stausholm	2019	Brazil, Denmark, Greece, Hungary, Indonesia, Iran, Saudi Arabia, Sweden, Turkey, United Kingdom	Moderate
Reduction in disability in patients with knee osteoarthritis	MB Stausholm	2019	Brazil, Indonesia, Iran, Sweden, Turkey, United Kingdom	Moderate
7. Fibromyalgia				
Changes in FIQ score in patients with fibromyalgia	SW Yeh	2019	Brazil, Spain, Turkey	Low
Changes in pain severity in patients with fibromyalgia	SW Yeh	2019	Brazil, Spain, Turkey	Low
Changes in number of tender points in patients with fibromyalgia	SW Yeh	2019	Brazil, Turkey	Low
Changes in severity of fatigue in patients with fibromyalgia	SW Yeh	2019	Brazil, Spain, Turkey	Low
Changes in severity of stiffness difference in patients with fibromyalgia	SW Yeh	2019	Brazil, Turkey	Low
Changes in severity of depression in patients with fibromyalgia	SW Yeh	2019	Brazil, Turkey	Low
Changes in severity of anxiety in patients with fibromyalgia	SW Yeh	2019	Brazil, Turkey	Low
8. Myofascial neck pain				
Neck pain level in patients with myofascial neck pain syndrome	MR Tehrani	2022	Denmark, Egypt, Iran, Italy, Turkey	Low
Pressure pain threshold in patients with myofascial neck pain syndrome	MR Tehrani	2022	Egypt, Italy, Korea, Turkey	Low
9. Achilles tendinopathy				
Pain intensity in patients with Achilles tendinopathy	ALC Martimbianco	2020	New Zealand, Norway	Low
Function in patients with Achilles tendinopathy	ALC Martimbianco	2020	New Zealand	Low

Table 1 (continued)

Outcome	First author	Published year	Included countries	AMSTAR2
10. Fractures				
Pain reduction (VAS score) in patients with fractures	FCJ Neto	2020	Canada, Iran, Taiwan	Low
11. Carpal tunnel syndrome				
Pain levels (VAS score) in patients with carpal tunnel syndrome	AH Bekhet	2017	Iran, Thailand, Turkey	Low
Symptom severity scale in patients with carpal tunnel syndrome	AH Bekhet	2017	Iran, Taiwan, Thailand, Turkey	Low
Functional severity scale in patients with carpal tunnel syndrome	AH Bekhet	2017	Iran, Taiwan, Thailand, Turkey	Low
12. Diabetic foot ulcers				
Complete healing rate in diabetic foot ulcers	J Huang	2021	Brazil, China, Colombia, Iran, Israel	Moderate
Ulcer area reduction percentage in diabetic foot ulcers	J Huang	2021	Brazil, India, Iran	Moderate
Mean healing time in diabetic foot ulcers	J Huang	2021	China	Moderate
13. Tinnitus				
Overall symptoms (THI score) in patients with tinnitus	CH Chen	2020	Denmark, Italy, Korea	Low
14. Androgenetic alopecia				
Hair density in patients with androgenetic alopecia	KH Liu	2019	Iran, Korea, Taiwan, United States	Low
15. Cognitive function				
The effects on age-related cognitive impairment	Y Gao	2023	Australia, China, Egypt, France, Iran, and United States	Low

Abbreviations: *FIQ* Fibromyalgia impact questionnaire, *PBM* Photobiomodulation, *THI* Tinnitus Handicap Inventory, *VAS* Visual analogue scale

We identified 35 health endpoints and grouped them into 15 unique disease conditions: burning mouth syndrome, temporomandibular disorders, rheumatoid arthritis, plantar fasciitis, tendinopathy, knee osteoarthritis, fibromyalgia, cognitive function, myofascial neck pain, Achilles tendinopathy, fractures, carpal tunnel syndrome, diabetic foot ulcers, tinnitus, and androgenetic alopecia (Table 3 and Supplementary Table 5). Among 35 health endpoints, 34.3% (12/35) of unique significant effects between PBM and health endpoints relating to 9 unique disease conditions were reported. The results are summarized by showing evidence maps of each health endpoint among participants with PBM interventions (Fig. 2 and Table 3).

Burning mouth syndrome

PBM significantly reduced pain intensity (eSMD, − 0.92 [95% CI − 1.38 to − 0.46]) with moderate certainty of evidence. Although the funnel plot showed slight asymmetry, Egger's test was non-significant ($P = 0.13$). P-curve results confirmed evidential value ($P < 0.0001$). No significant effect on quality of life was found (low certainty).

Temporomandibular disorders

PBM reduced pain levels (eSMD − 0.56 [95% CI − 0.83 to − 0.29]) with low certainty of evidence. Despite consistent forest plot trends, publication bias was suggested by funnel plot asymmetry and Egger's test ($P < 0.001$). P-curve results supported evidential value ($P < 0.0001$).

Tendinopathy

PBM led to reduced pain (eSMD, 0.16 [95% CI, 0.07 to 0.24]) with low certainty. Forest plot trends were consistent; funnel plot showed mild asymmetry, but P-curve confirmed evidential value ($P < 0.0001$). No significant effect on muscle strength (very low certainty).

Knee osteoarthritis

PBM significantly improved pain (eSMD, 0.02 [95% CI, 0.01 to 0.03]) and disability (eSMD, 0.65 [95% CI, 0.14 to 1.15]) in patients with knee osteoarthritis, with low and moderate certainty of evidence, respectively. Despite funnel plot asymmetry for pain and possible small-study effects, P-curve analyses for both outcomes indicated

Table 2 Summary of the design and main findings of included meta-analyses of RCTs

Study ID	Number of included studies	Population	Laser type	Duration of treatment	Number of sessions/ weeks	Summary of results	AMSTAR2
C Lu et al., 2023 [9]	14	Patients with BMS	630–1064 nm 1–176 J/cm^2 4–300 s/point	2 weeks to 4 months	Once per two weeks–5	LLLT was more effective for reducing burning pain than placebo LLLT or clonazepam	Low
R Hanna et al., 2021 [7]	32	Patients with TMD	630–1064 nm 0.1–400 J/cm^2 0.33–300 s/point	1 day to 8 weeks	1–7	Improvement in pain reduction, functionality, anxiety reduction, and quality of life	High
I Lourinho et al., 2023 [8]	18	Patients with RA	632.5–1060 nm 0.0075–25 J/cm^2 30 nsec–600 s/point	4 weeks to 4 months	2–6	No difference between using infrared laser and sham in terms of pain, morning stiffness, grip strength, functional capacity, inflammation, ROM, disease activity, and adverse events	Low
JV Ferlito et al., 2023 [29]	19	Patients with PF	635–904 nm 3–216 J/cm^2 33–720 s/point	2–6 weeks	2–7	PBMT alone or with exercise improved pain intensity in short-term treatment	Low
N Tripodi et al., 2021 [34]	17	Patients with tendinopathy or -related disorders	810–905 nm 0.5–5 J/cm^2 40–300 s/point	2–8 weeks	2–6	When PBM plus exercise was compared to sham treatment plus exercise, PBM demonstrated greater decrease in pain	Low
MB Stausholm et al., 2019 [12]	22	Patients with KOA	785–904 nm 0.054–8 J/point 20–180 s/point	2–8 weeks	Twice per three weeks–6	LLLT reduces pain and disability in KOA	Moderate
SW Yeh et al., 2019 [35]	9	Patients with fibromyalgia	640–905 nm 2–143 J/cm^2 40–300 s/point	2–10 weeks	1–5	LLLT demonstrated significantly greater improvement in their FIQ score, pain sensitivity, number of tender points, fatigue, stiffness, depression, and anxiety	Low
Y Gao et al., 2023 [30]	11	Patients with SCD, MCI, or dementia	630–1080 nm 20 mW/cm^2–56.5 J/cm^2 33 s–30 min	1 day to 12 weeks	Twice per day–Twice per week	PBM had a significant moderated effect on global cognition function	Low
MR Tehrani et al., 2022 [33]	13	Patients with MNP	632.5–904 nm 0.5–135 J/point	1 day to 6 weeks	1–7	LLLT was significantly effective in pain reduction, PPT and right bending ROM were improved	Low

Table 2 (continued)

Study ID	Number of included studies	Population	Laser type	Duration of treatment	Number of sessions/ weeks	Summary of results	AMSTAR2
ALC Martimbianco et al., 2020 [10]	4	Patients with Achilles tendinopathy	810–904 nm 20mW/cm^2–2.375W/cm^2 30–180 s/point	1 day to 8 weeks	1–3	Laser therapy associated to eccentric exercises when compared to eccentric exercise and sham had very low to low certainty of evidence in pain and function assessment	Low
FCJ Neto et al., 2020 [11]	2	Patients with fractures	808–830 nm 6–9.7 J/cm^2 20–600 s/point	1 day to 2 weeks	5 days per week	Significantly difference in favor of PBM for pain reduction, but this difference was not clinically significant	Low
AH Bekhet et al., 2017 [6]	8	Patients with CTS	780–880 nm 9–11 J/cm^2 90–600 s/point	2–5 weeks	1–5	The overall effect estimates did not favor LLLT therapy group over placebo in all primary outcomes: VAS, SS, FSS	Low
J Huang et al., 2021 [31]	13	Patients with DFUs	400–904 nm 1.5–10 J/cm^2 30–240 s/point	10 days to 20 weeks	2–7	LLLT significantly increased the complete healing rate, reduced the ulcer area, and shortened the mean healing time	Moderate
CH Chen et al., 2020 [28]	11	Patients with complaints of tinnitus	650–830 nm 6–20 min	1 day to 3 months	1–7	No significant difference in the overall effect according to the THI score and the rating scale score improvement rate	Low
KH Liu et al., 2019 [32]	11	Patients with AGA	630–808 nm 8–30 min	16–26 weeks	3–7	Significant increase in hair density for those treated by LLLT versus sham group	Low

BMS Burning mouth syndrome, *LLLT* Low-level laser therapy, *TMD* Temporomandibular disorder, *RA* Rheumatoid arthritis, *ROM* Range of motion, *PF* Plantar fasciitis, *PBMT* Photobiomodulation therapy, *PBM* Photobiomodulation, *KOA* Knee osteoarthritis, *FIQ* Fibromyalgia impact questionnaire, *SCD* Subjective cognitive decline, *MCI* Mild cognitive impairment, *MNP* Myofascial neck pain, *PPT* Pain pressure threshold, *CTS* Carpal tunnel syndrome, *VAS* Visual analogue scale, *SS* Symptom severity scale score, *FSS* Functional status score, *DFUS* Diabetic foot ulcers, *THI* Tinnitus Handicap Inventory, *AGA* Adult androgenetic alopecia

Table 3 Evidence maps of umbrella review of associations between PBM and health outcomes

	eSMD (95% CI)	Direction	GRADE
1. Burning mouth syndrome			
Pain intensity in patients with burning mouth syndrome	**-0.92 (-1.38 to -0.46)**	Association	Moderate
Quality of life in patients with burning mouth syndrome	0.03 (-0.73 to 0.78)	No association	Low
2. Temporomandibular disorders			
Pain levels (VAS score) in patients with temporomandibular disorders	**-0.56 (-0.83 to -0.29)**	Association	Low
3. Rheumatoid arthritis			
Pain levels in patients with rheumatoid arthritis	-0.03 (-0.16 to 0.10)	No association	Very low
Morning stiffness in patients with rheumatoid arthritis	-0.02 (-0.15 to 0.10)	No association	Low
Handgrip strength in patients with rheumatoid arthritis	-0.03 (-2.15 to 2.09)	No association	Very low
Functional capacity in patients with rheumatoid arthritis	-0.19 (-1.45 to 1.07)	No association	Very low
Inflammation in patients with rheumatoid arthritis	-0.01 (-0.77 to 0.75)	No association	Low
Activity score in patients with rheumatoid arthritis	0.35 (-0.28 to 0.98)	No association	Very low
4. Plantar fasciitis			
Pain intensity in patients with plantar fasciitis	-0.10 (-0.24 to 0.05)	No association	Low
5. Tendinopathy			
Pain reduction (VAS score) in patients with tendinopathy	**0.16 (0.07 to 0.24)**	Association	Low
Muscle strength in patients with tendinopathy	0.68 (-0.06 to 1.43)	No association	Very low
6. Knee osteoarthritis			
Pain reduction in patients with knee osteoarthritis	**0.02 (0.01 to 0.03)**	Association	Low
Reduction in disability in patients with knee osteoarthritis	**0.65 (0.14 to 1.15)**	Association	Moderate
7. Fibromyalgia			
Changes in FIQ score in patients with fibromyalgia	**1.15 (0.61 to 1.69)**	Association	Low
Changes in pain severity in patients with fibromyalgia	2.49 (-1.19 to 6.18)	No association	Very low
Changes in number of tender points in patients with fibromyalgia	2.00 (-0.61 to 4.61)	No association	Very low
Changes in severity of fatigue in patients with fibromyalgia	**1.25 (0.63 to 1.87)**	Association	Moderate
Changes in severity of stiffness difference in patients with fibromyalgia	**1.06 (0.36 to 1.77)**	Association	Low
Changes in severity of depression in patients with fibromyalgia	1.15 (-0.20 to 2.50)	No association	Low
Changes in severity of anxiety in patients with fibromyalgia	1.64 (-0.13 to 3.42)	No association	Low
8. Myofascial neck pain			
Neck pain level in patients with myofascial neck pain syndrome	**-0.02 (-0.03 to -0.01)**	Association	Low
Pressure pain threshold in patients with myofascial neck pain syndrome	2.75 (-0.11 to 5.61)	No association	Very low
9. Achilles tendinopathy			
Pain intensity in patients with achilles tendinopathy	-0.02 (-0.16 to 0.13)	No association	Low
Function in patients with achilles tendinopathy	-0.02 (-0.20 to 0.16)	No association	Low
10. Fractures			
Pain reduction (VAS score) in patients with fractures	0.18 (0.00 to 0.36)	No association	Low
11. Carpal tunnel syndrome			
Pain levels (VAS score) in patients with carpal tunnel syndrome	-0.07 (-0.20 to 0.06)	No association	Low
Symptom severity scale in patients with carpal tunnel syndrome	-0.01 (-0.13 to 0.10)	No association	Low
Functional severity scale in patients with carpal tunnel syndrome	-0.07 (-0.19 to 0.04)	No association	Low
12. Diabetic foot ulcers			
Complete healing rate in diabetic foot ulcers	-0.22 (-0.62 to 0.01)	No association	Low
Ulcer area reduction percentage in diabetic foot ulcers	**3.65 (0.54 to 6.76)**	Association	Very low
Mean healing time in diabetic foot ulcers	-1.41 (-3.19 to 0.37)	No association	Low
13. Tinnitus			
Overall symptoms (THI score) in patients with tinnitus	-0.05 (-0.17 to 0.06)	No association	Moderate
14. Androgenetic alopecia			
Hair density in patients with androgenetic alopecia	**1.32 (1.00 to 1.63)**	Association	Moderate
15. Cognitive function			
The effects on age-related cognitive impairment	**0.49 (0.14 to 0.84)**	Association	Moderate

The numbers in bold indicate a significant difference ($P < 0.05$)

Color represents the levels of SMD in data with statistically significance ($P < 0.05$)

BI Barthel Index, *CI* Confidence interval, *CRS-R* Coma Recovery Scale-Revised, *eSMD* Equivalent standard mean difference, *FMA-LE* Fugl-Meyer Assessment Lower Extremity, *FMA-UE* Fugl-Meyer Assessment Upper Extremity, *HADS* Hospital Anxiety and Depression Scale, *ICARS* International Cooperative Ataxia and Rating Scale, *MADRS* Montgomery-Asberg Depression Rating Scale, *MAS* Modified Ashworth Scale, *MCCB* Matrics Consensus Cognitive Battery, *MD* Mean difference, *NPS* Numeric pain scale, *PANSS-G12* Positive and Negative Syndrome Scale G12, *SARA* Scale for Assessment and Rating of Ataxia, *VAS* Visual analogue scale, *Y-BOCS* Yale-Brown Obsessive–Compulsive Scale

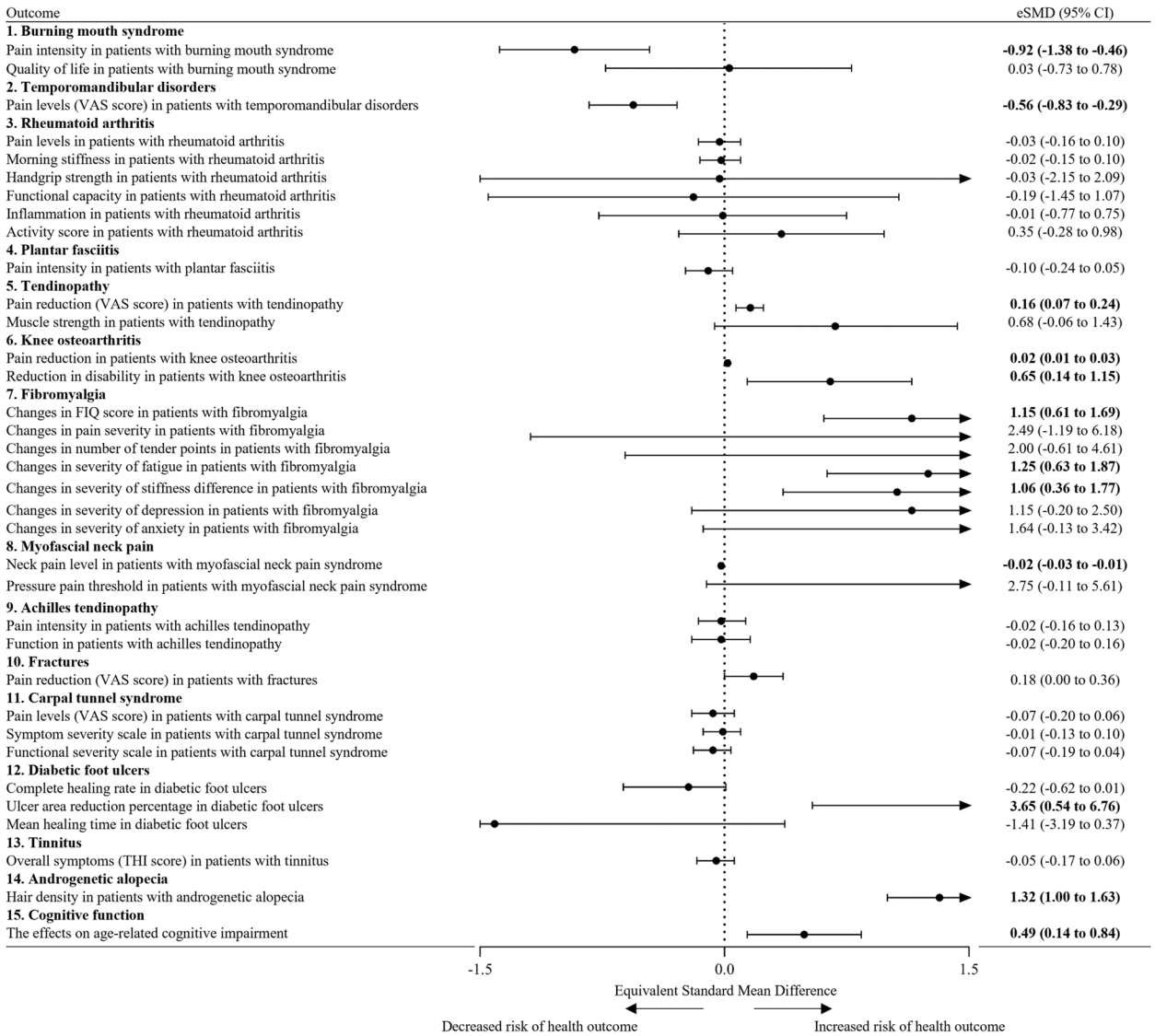

Fig. 2 Point estimates of health outcomes following PBM intervention. Abbreviations: CI, confidence interval; eSMD, equivalent standard mean difference; FIQ, fibromyalgia impact questionnaire; PBM, photobiomodulation; THI, Tinnitus Handicap Inventory; VAS, visual analogue scale

strong right-skew ($P < 0.0001$) and high power (> 90%), supporting evidential value.

Fibromyalgia

Among the seven health endpoints related to fibromyalgia, 42.9% (3/7) showed significant effects of PBM with low certainty of evidence. Improvements were observed in FIQ score (eSMD, 1.15 [95% CI, 0.61 to 1.69]), fatigue severity (eSMD, 1.25 [95% CI, 0.63 to 1.87]), and stiffness severity difference (eSMD, 1.06 [95% CI, 0.36 to 1.77]). Forest plots showed consistently positive effects across studies. Funnel plots were largely symmetric with non-significant Egger's tests, and all three outcomes exhibited right-skewed P-curves ($P < 0.01$), supporting the evidential value of the findings.

Diabetic foot ulcers

PBM reduced ulcer area (eSMD, 3.65 [95% CI, 0.54 to 6.76]) with very low certainty. Funnel plot asymmetry and low P-curve power (59%) suggest possible small-study effects and limited evidential value.

Androgenetic alopecia

PBM significantly increased hair density (eSMD, 1.32 [95% CI, 1.00 to 1.63]) with moderate certainty. The funnel plot was symmetric, and the right-skewed P-curve

(100% $P < 0.025$) indicated strong evidential value (power 98%).

Cognitive function

PBM has beneficial effects on age-related cognitive impairment (eSMD, 0.49 [95% CI, 0.14 to 0.84]) with moderate certainty of evidence. The forest plot showed consistent positive effects, and although the funnel plot suggested mild asymmetry, Egger's test was not significant. The right-skewed P-curve ($P < 0.0001$) with 94% estimated power supported the presence of evidential value.

No significant effects of PBM on several disease conditions

Previous studies reported beneficial effects of PBM on several diseases (Supplementary Table 5); however, our re-analyses showed that 65.7% (23/35) of no significant effects were observed, reporting on no effects of PBM on several health outcomes, including rheumatoid arthritis, plantar fasciitis, Achilles tendinopathy, fractures, carpal tunnel syndrome, and tinnitus (Table 3).

Discussion

Key findings

We aimed to suggest evidence-based recommendations and insights into PBM for clinicians and patients. To our knowledge, this umbrella review represents the first comprehensive evaluation of PBM effects on several health outcomes, analyzing data from 15 meta-analyses of RCTs with over 9000 patients and assessing the evidence using GRADE criteria. Our findings indicated that PBM had beneficial effects on nine unique diseases, including burning mouth syndrome, temporomandibular disorders, tendinopathy, knee osteoarthritis, fibromyalgia, myofascial neck pain, diabetic foot ulcers, androgenetic alopecia, and cognitive impairment.

Among the 35 health endpoints assessed, no outcome was supported by high certainty of evidence. However, moderate certainty of evidence supported significant associations between PBM and improved outcomes in five domains: reduced pain intensity in burning mouth syndrome, reduced disability in knee osteoarthritis, decreased severity of fatigue in patients with fibromyalgia, increased hair density in androgenetic alopecia, and improved cognitive function. Several other outcomes, reduction pain levels in temporomandibular disorders, tendinopathy, and knee osteoarthritis, decreased FIQ score, diminished severity of stiffness in fibromyalgia, and reduced neck pain level, were supported by low certainty of evidence, while the effects of PBM on temporomandibular disorders and diabetic foot ulcers were rated as very low, indicating limited confidence in these findings.

Plausible underlying mechanisms

PBM, involving low-level lasers or LEDs, is a safe and feasible treatment method for various health conditions based on its cellular and molecular effects [36]. It primarily affects mitochondrial function, specifically targeting the cytochrome C oxidase, a large transmembrane protein complex and part of the electron transport chain in mitochondria [36]. Therefore, PBM activated the electron transport chain in mitochondria, resulting in increased production of ATP, essential for cell proliferation, cell survival, and tissue regeneration [37]. The therapeutic effects of PBM extend to pain reduction, improved circulation, and reduced inflammatory responses [1]. It reduces pro-inflammatory cytokines and induces anti-inflammatory ones, which is crucial in conditions like osteoarthritis and fibromyalgia as a critical change in the pathological process [38]. In addition, the role of PBM in decreasing oxidative stress through increased activity of antioxidant enzymes further supports its anti-inflammatory and tissue-protective properties [38].

In pain management, the effects of PBM are attributed to its modulation of pain and neural circuits. It decreases the expression of pain-inducing substances like substance P and bradykinin and triggers the release of serotonin, enkephalins, and endorphin for analgesic effects [39]. This mechanism is particularly significant in health outcomes such as tendinopathy and temporomandibular disorders. In addition, PBM can improve cell viability, proliferation, and microcirculation pathways for conditions like androgenetic alopecia, enhancing blood flow and oxygenation to stimulate hair follicles [40].

While research on PBM in dental and musculoskeletal diseases, particularly in burning mouth syndrome and knee osteoarthritis, is well supported by moderate certainty of evidence, studies in neurological or neurodegenerative disorders are less extensive. However, recent RCTs show promising results of transcranial PBM in traumatic brain injury and Parkinson's disease [1, 2], with our study affirming its beneficial effects in age-related cognitive impairment. Furthermore, PBM has a therapeutic role in neural regeneration and enhanced neuronal function via increasing the expression of nerve growth factor, neuronal tissue regeneration, and cell death inhibition in neurons [41]. These findings suggest the potential of PBM as a non-invasive treatment for neurological and neurodegenerative disorders, warranting further research to solidify its role in these areas.

Policy implication

In the context of clinical implications, it is essential to differentiate between statistically significant findings and those that are clinically meaningful. According to widely accepted benchmarks for SMDs, namely,

approximately 0.2 as small, 0.5 as moderate, and 0.8 or greater as large effect, only a limited number of outcomes exhibited effect sizes that are likely to translate into perceptible clinical benefits [42]. For instance, the observed improvements in fatigue and FIQ scores among patients with fibromyalgia exceeded the threshold for a large effect, suggesting a potentially meaningful impact in real-world settings. In contrast, certain outcomes such as pain reduction in tendinopathy (SMD = 0.16) and knee osteoarthritis (SMD = 0.02), although statistically significant, may have limited clinical utility unless combined with adjunctive therapies. These distinctions underscore the importance of contextualizing statistical outcomes within clinical frameworks and support the need for further translational research to inform evidence-based decision-making.

The observed effects of PBM across a range of health conditions suggest potential integration into clinical care pathways, particularly for outcomes supported by moderate certainty of evidence, such as burning mouth syndrome, knee osteoarthritis, fibromyalgia-related fatigue, androgenetic alopecia, and age-related cognitive impairment. Implementing PBM into standard treatment protocols would require additional high-quality investigations, refinement of clinical guidelines, and health policy adaptations to support its application. When applied in appropriate clinical contexts, PBM may offer a viable, non-invasive, and safe therapeutic option for select patient populations [43].

Comparison with previous studies

Our findings align with prior meta-analyses that have explored the efficacy of PBM in managing musculoskeletal conditions, particularly knee osteoarthritis and fibromyalgia. In the context of knee osteoarthritis, Oliveira et al. conducted a systematic review and meta-analysis [44], concluding that PBM can reduce pain intensity and may improve disability. However, they noted that the certainty of evidence was very low, cautioning against recommending PBM as a standalone treatment and suggesting its use as a complementary therapy. Similarly, in fibromyalgia management, a systematic review by Yeh et al. reported significant improvements in FIQ scores [35], pain severity, and fatigue levels among patients receiving low-level laser therapy. Furthermore, Fitzmaurice et al. highlighted that whole-body PBM led to significant reductions in pain and enhancements in quality of life for patients with fibromyalgia [45]. While these studies support the therapeutic potential of PBM, our updated GRADE reassessment, applying stricter criteria for heterogeneity and imprecision, resulted in more conservative certainty ratings. This distinction underscores the importance of re-evaluating evidence using unified grading rules and highlights the need for standardized protocols in future trials.

Strengths and limitations

To the best of our knowledge, this is the first umbrella review of meta-analyses of RCTs to investigate the effects of PBM on various health outcomes, suggesting its potential as a feasible and effective treatment for various diseases. However, several limitations warrant consideration. First, our reliance on previous original meta-analyses, which did not explore the adverse outcomes of PBM, limits our ability to investigate its side effects or safety. Second, the variability in PBM protocols across the original studies introduces heterogeneity, potentially influencing our findings. Third, the lack of direct quality assessment of individual studies within each original meta-analysis may impact the precision and reliability of our findings [46]. Fourth, the methodology of umbrella reviews, including factors like sample size, heterogeneity, and statistical significance, can vary and affect the categorization and interpretation of evidence [47, 48].

Conclusions

In this umbrella review of meta-analyses of randomized controlled trials, we found that PBM exhibited statistically significant therapeutic effects across nine unique health conditions, including burning mouth syndrome, temporomandibular disorders, tendinopathy, knee osteoarthritis, fibromyalgia, myofascial neck pain, diabetic foot ulcers, androgenetic alopecia, and age-related cognitive impairment. However, the certainty of evidence, as assessed using a modified GRADE framework, ranged from very low to moderate, with no outcomes supported by high-certainty evidence. PBM yielded moderate-certainty evidence for selected outcomes such as pain reduction in burning mouth syndrome, disability improvement in knee osteoarthritis, fatigue reduction in fibromyalgia, hair density increase in androgenetic alopecia, and cognitive improvement in older adults. These findings suggest that PBM may serve as a promising non-invasive adjunctive therapy, particularly for outcomes supported by moderate-certainty evidence. Nevertheless, further large-scale, high-quality trials with standardized protocols are warranted to validate its clinical efficacy, particularly for conditions where the current evidence remains limited or uncertain.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13643-025-02902-3.

Supplementary Material 1.

Supplementary Material 2.

Acknowledgements
None.

Authors' contributions
Dr DKY had full access to all of the data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis. All authors approved the final version before submission. Study concept and design: JK, YS, Hyeri Lee, TK, and DKY; acquisition, analysis, or interpretation of data: JK, YS, Hyeri Lee, TK, and DKY; drafting of the manuscript: JK, YS, Hyeri Lee, TK, and DKY; critical revision of the manuscript for important intellectual content: all authors; statistical analysis: JK, YS, Hyeri Lee, TK, and DKY; study supervision: JK, TK, and DKY. DKY supervised the study and is the guarantor for this study. YS, Hyeri Lee, and SY contributed as co-first authors. JK, TK, and DKY contributed as co-corresponding authors. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Funding
This research was supported by the MSIT (Ministry of Science and ICT), South Korea, under the ITRC (Information Technology Research Center) support program (IITP-2024-RS-2024–00438239) supervised by the IITP (Institute for Information & Communications Technology Planning & Evaluation), and Ministry of Science & ICT (RS-2022-NR070607). The funders had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Data availability
Not applicable.

Declarations

Ethics approval and consent to participate
An ethics statement is not applicable because this study is based exclusively on published literature. In its reporting, this manuscript follows PRISMA 2020 Guideline.

Consent for publication
This article does not contain any studies with human participants or animals performed by any of the authors. This paper is a systematic review of published literature, so ethical approval and consent were not required.

Competing interests
The authors declare no competing interests.

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Received: 16 January 2025 Accepted: 22 June 2025
Published online: 06 August 2025

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