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Photobiomodulation therapy on chemo- and radiotherapy induced oral conditions: an umbrella review

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Abstract

Objectives Photobiomodulation (PBM) is a laser-based therapy used to promote tissue repair, reduce inflammation and pain, and has been extensively studied in chemo- and radiotherapy-induced oral mucositis (OM). This review examines the level of evidence of systematic reviews (SRs) that have investigated PBM in such cases of OM.

Materials and methods SRs evaluating PBM for both the treatment and prevention of OM in patients undergoing chemotherapy and/or radiotherapy and published before November 30, 2023, on PubMed, Cochrane, Embase, Web of Science, LILACS, TRIP and Open Grey databases were eligible for inclusion. We assessed the level of methodological and meta-analytic procedures.

Results Of the 1201 SRs, 21 that met the inclusion criteria were included. The quality of evidence was assessed using the Assessing the Measurement Tool to Assess Systematic Reviews (AMSTAR2), and the majority was of critically low quality ($n=15$, 71.4%) with only 28.5% of low quality. A total of 40 meta-analytic estimates were obtained and analyzed. Approximately 87.5% of the meta-analysis were significant ($n=33$), but only one meta-analyses had a strength of "highly suggestive", while the rest were classified as "weak". When analyzing the overlap values, the covered area was 12.14% and the corrected covered area was 7.75%, indicating a moderate overlap. Only 4 SRs had a very high overlap and one had a high overlap.

Conclusion The efficacy of PBM in the treatment of chemotherapy-induced OM is supported by low to critically low quality SRs and meta-analysis of low strength. This review highlights important areas that need to be addressed in future research on this topic.

Registration CRD42023484013 (PROSPERO).

Keywords Photobiomodulation, Oral mucositis, Chemotherapy, Radiotherapy

Introduction

Characterized as a debilitating condition of the oral epithelium, oral mucositis (OM) is one of the most common toxic side effects of chemo- and radiotherapy, affecting up to 90% of patients undergoing these treatments [1, 2]. OM results in extremely painful erythematous/ulcerative lesions on non-keratinised mucosa, such as the tongue, buccal mucosa, oropharynx, and lips, which can prevent oral intake. Not only does it have a negative impact on

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the patient's quality of life, but in cases of severe OM there is an increased risk of local and systemic infection and, a reduction or delay in antineoplastic treatment, which may have a worrying impact on prognosis, and an increase in the cost of patient management. [3–5].

Furthermore, OM is associated with increased mortality in patients undergoing haematopoietic cell transplantation (HCT) (also known as haematopoietic stem cell transplantation). Despite its potentially devastating consequences, OM remains a significant challenge for patients undergoing cancer therapy, and therefore the management of OM is critical to the well-being of oncology patients. [4, 6].

Several interventions are currently available to prevent, relieve or alleviate the symptoms of OM, but their effectiveness remains uncertain. Basic oral care, anti-inflammatory agents, analgesics, photobiomodulation (PBM) and cryotherapy are the most common options [7]. PBM, also known as Low Level Laser Therapy (LLLT), is a non-invasive and non-thermal treatment that involves the application of low-level light sources of a specific wavelength to injured areas over a period of time to promote tissue repair and reduce inflammation and pain [8, 9]. The mechanism remains unclear, but evidence suggests that PBM acts on mitochondrial cytochrome C oxidase (CCO), which activates secondary signalling pathways leading to increased levels of ATP, cAMP and reactive oxygen species (ROS), promoting tissue regeneration [8, 9].

PBM has extensive applications in the prevention and treatment of OM in cancer patients undergoing various treatments. PBM is effective in preventing and treating OM in patients undergoing cancer treatment, such as high-dose chemotherapy for haematopoietic stem cell transplantation (HSCT) and radiotherapy for head and neck (H&N) cancer without concurrent chemotherapy (CT) [7]. In a recent guideline update, prevention of OM with intraoral PBM therapy was recommended in patients undergoing HSCT or in patients receiving H&N radiotherapy with or without CT [10].

Although many studies have evaluated the efficacy of PBM in the prevention and treatment of OM in cancer patients, the quality of these studies is variable and there is no consensus on laser parameters such as wavelength, power, amount and rate of energy delivered to the tissue, and time [7, 11]. Another explanation for ambiguous recommendations is the wide variety of protocols that can be applied, which exacerbates the lack of agreement on laser parameters and leads to different outcomes [12].

Therefore, we conducted an umbrella review to assess the level of evidence from systematic reviews (SRs) and meta-analysis that have examined PBMs the effect on the prevention and treatment of OM in patients undergoing CT and/or radiotherapy. Our objective was to offer an extensive overview of the current evidence and to pinpoint crucial elements that warrant enhancement in future investigations.

Materials and methods

We report this umbrella review upon the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guideline updated in 2020 [13]. The review protocol was approved a priori by all authors. The protocol was defined and discussed a priori with all authors and registered in the International Prospective Register of Systematic Reviews (PROSPERO) with the following reference: CRD42023484013.

The review question was: "What is the level of evidence for the efficacy of PBM for chemo- and or/radiotherapy induced OM?"

The following PICO(S) statements were specified: Population (P) - cancer patients undergoing chemo- and/or radiotherapy with OM; Intervention (I) - PBM; Comparison (C) - placebo or related therapy; Outcome (O) - level of methodological and meta-analytic evidence of SRs; Setting (S) - SRs with or without meta-analysis.

2.1. Eligibility criteria

The following eligibility criteria were considered in the selection process: (1) the study must be a systematic review or a meta-analysis, (2) the data must be sourced from human studies, and (3) the study must examine the effectiveness of PBM in addressing chemo- and/or radiotherapy oral conditions. No restrictions on publication year or language were imposed.

2.2. Information sources search

Seven electronic databases were searched: Medline (via PubMed), Web of Science, EMBASE (The Excerpta Medica Database), LILACS (Latin-American scientific literature in health sciences), Cochrane Database of Systematic Reviews, CINAHL, and TRIP (Turning Research Into Practise). Grey literature was searched on https://opengrey.eu/. We merged keywords and subject headings in accordance with the thesaurus of each database and applied exploded subject headings, with the following syntax: (chemotherapy-induced OR chemotherapy) AND laser.

2.3. Study selection

IR and JB independently screened the titles and abstracts of the research papers. The level of agreement between the reviewers was assessed using kappa statistics. Any paper identified as potentially eligible by either reviewer was ordered for full-text review, which was also independently screened by the reviewers. Any disagreements that arose were resolved by discussion with a third reviewer, CZ.

2.4. Data extraction process and data items

Two researchers, IR and JB independently extracted authors and year of publication, objective/focal question, databases searched, number of studies included, type of studies included, main outcomes and main conclusions. Disagreements were resolved by discussion with a third reviewer, CZ.

2.5. Methodological quality appraisal

Two researchers (IR and JB) used the Assessing the Measurement Tool to Assess Systematic Reviews (AMSTAR 2) to evaluate the methodological quality of the reviews included in the present study. The AMSTAR 2 tool is a 16-item assessment that determines the overall confidence in the results of the review [14]. The quality of the SRs was rated based on the AMSTAR guidelines as follows: High quality meant "Zero or one non-critical weakness," Moderate quality meant "More than one non-critical weakness," Low quality meant "One critical flaw with or without non-critical weaknesses," and Critically Low quality meant "More than one critical flaw with or without non-critical weaknesses." The AMSTAR 2 online tool (https://amstar.ca/Amstar_Checklist.php, accessed in November 2023) was used to calculate the AMSTAR quality rate for each study.

2.6. Strength and validity of meta-analytic estimates

Data were processed and managed using Excel from MS Office 365. To assess the strength of meta-analytic estimates, according to Papadimitrou et al. [15], four levels of evidence have been defined: strong, very suggestive, suggestive and weak. [15, 16] (Table 1):

The fail-safe number (FSN) for statistically significant meta-analysis was then determined using Rosenberg's FSN method [20]. Subsequently, the median and range were calculated for each evidence grade (strong, highly suggestive, suggestive, and weak). If the FSN is small in comparison to the actual number of studies, it suggests that the results derived from the observed studies are not reliable due to publication bias, specifically the type of bias assumed by the method (i.e., a set of studies with null results is missing).

Table 1 Categorization of meta-analytical estimates

Evidence	Conditions
Strong	● > 1000 cases included in the meta-analysis * ● p-value ≤ 10^{-6} [17–19]; ● I^2 < 50%; ● Null value was excluded by the 95% prediction interval; ● No evidence of small study effects or excess significance bias.
Highly Suggestive	● > 1000 cases included in the meta-analysis * ● p-value ≤ 10^{-6} [17–19] ● Largest study in the meta-analysis was statistically significant
Suggestive	● > 1000 cases included in the meta-analysis * ● p-value ≤ 10^{-6} [17–19]
Weak	● None of the above conditions were verified

* Based on a threshold that ensured 80% power for hazard ratios ≥ 1.20 (α = 0.05) [15]

2.7. Overlap

Overlaps are identified as fundamental in well-done surveys, and this can be done comprehensively using the Corrected Covered Area (CCA) method. [21]. For this reason, we estimated CCA as percentages and categorised as per Pieper et al. [21]: 0–5 indicates low overlap, 6–10 moderate overlap, 11–15 high overlap, and >15 very high overlap. A pairwise CCA grid was built in Microsoft Excel to identify which combinations of paired reviews had the highest overlap [21].

Results

3.1. Study selection

After a search of databases, a total of 1201 articles were retrieved for our search. Following removal of duplicates (n = 141), a total of 1060 records were screened for eligibility criteria using titles and abstracts, and 984 were excluded after title and/or abstract screening. Of the 76 articles assessed for eligibility for full paper review, 55 were excluded, with reasons for exclusion detailed in Supplementary Data 1. A final number of 21 SRs [12, 22–42] were therefore included in the qualitative synthesis. The PRISMA diagram is shown in Fig. 1.

3.2. Studies characteristics

Overall, these SRs were mainly produced in Brazil (n = 8) [12, 23, 25, 27, 31, 36, 42], China (n = 2) [26, 34] and the United Kingdom (n = 2) [33, 37], with contributions from groups in Canada [24], Iran [28], Israel [29], Indonesia [39], Malaysia [35], Norway [22], Singapore [40], Spain [38] and Syria [41] (Table 2). The populations included in the SRs were adults and children, with five reviews evaluating both. The type of cancer was heterogeneous, some studies didn't specify the type of cancer, while others included more than one, such as head and neck and haematological cancers. The majority followed the PRISMA (n = 14) [24–27, 30, 31, 33, 35–41].

In terms of risk of bias (RoB), the Cochrane ROB tool (n = 9) [24, 26, 27, 30, 33, 37, 39, 40, 42], the Jadad scale (n = 4) [22, 23, 28, 34], the Cochrane ROB2 tool (n = 4) [31, 35, 36, 41], the PEDro scale (n = 1) [25] and the Critical Appraisal Skills Program Español (CASPe) checklist (n = 1) [38] were used, although one was not reported [12] and another was not assessed [29].

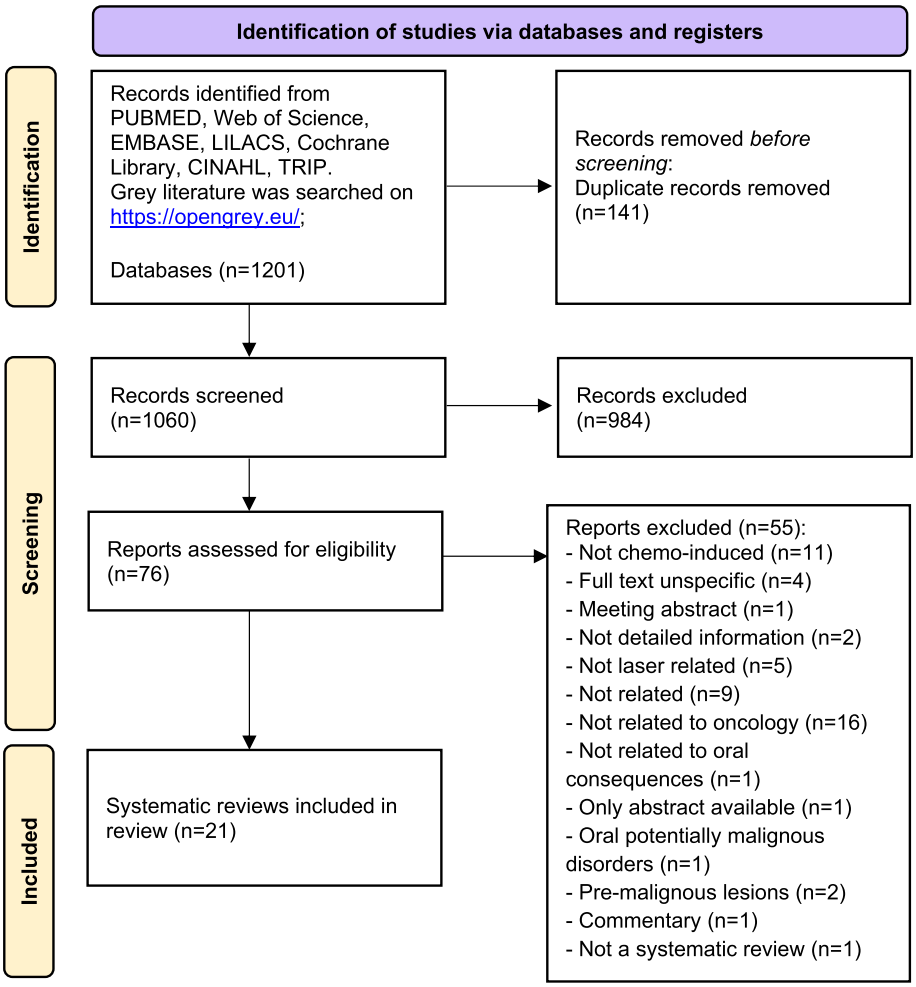

Fig. 1 PRISMA flowchart. Flow diagram visually summarising the screening and selection processes, and the numbers of articles recorded at each different stage

3.3. Methodological quality

When analysing the inter-rater reliability of the AMSTAR 2, good agreement was found (Cohen kappa score = 0.82; 95% confidence interval (CI): 0.78–0.86). None of the SRs were of high or moderate methodological quality. The majority were of critically low quality ($n = 15$, 71.4%) and only 28.5% were of low quality (Table 3). The included meta-analyses predominantly failed to report the sources of funding for the studies included in the review ($n = 21$, 95.5%), to explain the selection of study designs for inclusion in the review ($n = 20$, 90.9%), to provide a list of excluded studies and the reasons for the exclusions ($n = 19$, 86. 4%), to consider RoB in individual studies when interpreting and discussing the results of the review ($n = 14$, 63.6%), to use a comprehensive literature search strategy ($n = 13$, 59.1%), and to assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis ($n = 13$, 86.7%, considering that 7 SRs did not perform meta-analysis).

3.4 Meta-analytic estimates of strength, validity and overlap

Of the 21 SRs, 15 conducted meta-analysis (71.4.1%) [22–28, 30, 31, 34–37, 40, 42]. A total of 40 meta-analytic estimates were obtained and analysed. Overall, 27 meta-analyses used ratio measures (16 risk ratio and 11 odds ratio) and 13 difference measures (7 standardised mean difference [22, 26, 40] and 6 mean difference [22, 26–28, 36]). About 87.5% of the meta-analyses were significant ($n = 33$), but only one meta-analysis had a strength of "highly suggestive" [34], while the rest were classified as "weak". The highly suggestive meta-analysis included 1190 participants, while the median number of participants in the meta-analysis classified as weak was 258 (ranging from 55 to 1035).

Table 2 Characteristics of the included systematic reviews

Authors, Year and Country	Population	Cancer type(s)	Studies (*n*)	Guideline / Guidance	Risk of Bias tool	Search period	Main conclusions	Funding
Bjordal et al. (2011) [22] (Norway)	Children and adults	NR	11	Quorum	Jadad scale	1997–2009	Doses of 1–6 J per point of LLLT prevents OM occurrences and reduces severity, pain, and duration of OM ulcers.	NR
Migliorati et al. (2013) [12] (Brazil)	NR	Head and neck cancer patients undergoing HSCT	24	NR	NR	before 31 Dec 2010	Protocols vary greatly. LLLT has the potential in the prevention and treatment of OM and associated pain. Conclusions cannot be applied separately for each of the individual laser devices.	NR
He et al. (2018) [26] (China)	< 23 years old	Any childhood cancer or going through HSCT	8	PRISMA	Cochrane ROB tool	2007–2017	Prophylactic LLLT reduces OM, severe OM and the average severity of OM.	Shanghai Municipal Education Commission Gaoyuan Nursing Grant Support and the Shanghai Supporting and Training Funds for Young Teachers in University
Carneiro-Neto et al. (2016) [25] (Brazil)	22–94 years old	Head and Neck	6	PRISMA	PEDro Scale	Jan 2010 - May 2015	Diode Laser LLLT is safe.	NR
Redman et al. (2022) [37] (United Kingdom)	< 18 years old	Different childhood cancer types	14	PRISMA	Cochrane ROB tool	From inception until 28 Jun 2020	LLLT is a safe therapy in adults and children and may reduce OM and associated pain. Protocols vary greatly.	None
Al-Rudayni et al. (2021) [35] (Malaysia)	NR	NR	6	PRISMA and Cochrane Handbook	Cochrane ROB2 tool	From inception until 07 Jun 2020	PBM is effective in chemotherapy-induced OM.	International Medical University

Table 2 (continued)

Authors, Year and Country	Population	Cancer type(s)	Studies (*n*)	Guideline / Guidance	Risk of Bias tool	Search period	Main conclusions	Funding
Sánchez-Martos et al. (2023) [38] (Spain)	Adults	Head and neck cancer	10	PRISMA	CASPe	Nov 2021 - Feb 2022	PBM therapy is effective in preventing the incidence of OM since our findings show that the prophylactic use of PBM decreases the risk of severe OM grades.	None
Anschau et al. (2019) [27] (Brazil)	Adults and children	NR	5	PRISMA	Cochrane ROB tool	1992–2017	Moderate evidence that LLLT is effective in resolving OM lesions in adult patients undergoing cancer therapy. Not enough evidence to point out effectiveness in the curative treatment of OM in children.	Hospitalar Conceição Group
de Oliveira et al. (2021) [36] (Brazil)	< 18 years old to 81 years old	Lymphatic and breast cancer	5	PRISMA and EQUATOR	Cochrane ROB2 tool	Feb1990 - May 2020	Photodynamic therapy alone and combined with low-level light therapy show promising results for the treatment of OM. More randomized clinical trials need to be carried out.	CAPES & FAPESP (grants 2021/01191-0, 2020/07110-0, 2018/18440-0, 2018/23015-7 and 2019/08375-0) and by CNPq (grant number 313473/2019-6)
Mazhari et al. (2019) [28] (Iran)	< 18 years old	NR	4	NR	Jadad scale	Jan 2006 – Dec 2017	Laser treatment can be used as a supportive treatment for OM caused by chemotherapy. However, it is expensive and requires technology and special training.	Mashhad University of Medical Sciences (Iran)

Table 2 (continued)

Authors, Year and Country	Population	Cancer type(s)	Studies (*n*)	Guideline / Guidance	Risk of Bias tool	Search period	Main conclusions	Funding
de Lima et al. (2020) [30] (Brazil)	Adults	Head and neck cancer	4	PRISMA	Cochrane ROB tool	1945–2018	LLLT was effective in preventing the incidence of OM, but was not effective in preventing pain incidence.	None
Campos et al. (2020) [31] (Brazil)	NR	Head and neck cancer	13	PRISMA	Cochrane ROB2 tool	2007–2018	Laser therapy is efficient and cost-effective in comparison with the placebo group.	NR
Cronshaw et al. (2020) [33] (United Kingdom)	NR	NR	29	PRISMA	Cochrane ROB tool	Jan 1995 - Dec 2019	PBM is safe and effective to mitigate OM. There is a lack of optimised clinical protocols.	None
Zadik et al. (2019) [43] (Israel)	NR	hematological and head and neck	56 (only referenced 53 studies)	NR	Not evaluated	Jan 1st of 2011 – Jun 30th of 2016	More well-designed randomized controlled trials, including pediatric patient populations and patients treated with chemotherapy, are needed to clarify the promising potential of PBM in the management of OM in cancer patients.	None
Danwiek et al. (2023) [39] (Indonesia)	Adults	NR	47 (only referenced 43 studies)	PRISMA	Cochrane ROB and JBI Tools	Before Jun 2021	LLLT is most effective in reducing OM degree and associated pain.	NR
Peng et al. (2020) [34] (China)	Children and adults	hematological and head and neck	29	NR	Jadad scale	1946 - Dec 2018	Prophylactic LLLT is effective in preventing OM, reducing severity duration. Need to determine the optimal setting for LLLT.	Sichuan University Post-Doctoral Research and Development Fund (grant No. 19 XJ0008)

Table 2 (continued)

Authors, Year and Country	Population	Cancer type(s)	Studies (*n*)	Guideline / Guidance	Risk of Bias tool	Search period	Main conclusions	Funding
Figueiredo et al. (2013) [23] (Brazil)	NR	hematological, head and neck and osteossarcoma	12	NR	Jadad scale	1997–2011	Laser therapy is effective, especially with OM 3 grade or higher	NR
Oberoi et al. (2014) [24] (Canada)	Children and adults	hematological, head and neck, breast cancer, multiple myeloma	18	PRISMA	Cochrane ROB tool	1946- Feb 2014	Prophylactic LLLT reduces severe OM and pain.	None
Chan et al. (2023) [40] (SIngapore)	Adults	Hematological	18	PRISMA	Cochrane ROB tool	NR	Both PBM and OC were effective nonpharmacological OM prophylaxis and analgesia among chemo-conditioned HSCT patients, without significant difference in effectiveness.	NR
Khalil et al. (2023) [41] (Syria)	Children and adults	Leukemia, lymphoma solid tumors, breast cancer and solid tumors	6	PRISMA	ROB2	Until Mar 2023	PBM effectively prevents OM when applied to healthy tissue.	Damascus University
Cruz et al. (2023) [42] (Brazil)	Children and adults	Leukemia, Lymphoma, solid tumors, HSCT, oropharynx, hematological, Digestive and colon cancer	6	Cochrane Handbook	Cochrane ROB tool	Until Sep 2021	PBM significantly reduces the severity and pain in OM	NR

NR Not reported, *PRISMA* Preferred Reporting Items for Systematic Reviews and Meta-Analyses, *HSCT* Hematopoietic stem cell transplantation, *LLLT* low-level laser therapy, *CASPe* Critical Appraisal Skills Program Español, *ROB* Risk of bias, *OM* Oral mucositis, *PBM* Photobiomodulation, *OC* Oral cryotherapy

Table 3 Methodological quality assessment using AMSTAR2

Study	Overall Score	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Bjordal et al. (2011) [22]	Critically Low	Y	PY	N	Y	N	N	N	N	Y/Y	Y	Y/Y	N	N	N	N	Y
Migliorati et al. (2013) [12]	Critically Low	N	N	N	N	Y	Y	N	N	N/N	N	NA	NA	N	NA	NA	N
Figueiredo et al. (2013) [23]	Critically Low	Y	Y	N	PY	Y	Y	N	PY	Y/Y	N	Y/Y	N	N	N	N	Y
Oberoi et al. (2014) [24]	Low	Y	PY	N	PY	Y	Y	N	PY	Y/Y	N	N/N	N	N	N	N	Y
Carneiro-Neto et al. (2016) [25]	Critically Low	Y	PY	N	N	Y	Y	N	PY	Y/Y	N	Y/Y	Y	N	N	N	Y
He et al. (2018) [26]	Low	Y	PY	N	PY	Y	Y	N	N	Y/Y	N	Y/Y	Y	Y	Y	Y	Y
Anschau et al. (2019) [27]	Low	Y	Y	N	PY	Y	Y	Y	PY	Y/Y	N	N/N	N	Y	Y	Y	Y
Mazhari et al. (2019) [28]	Critically Low	Y	PY	N	N	Y	Y	N	Y	Y/Y	N	Y/Y	N	N	N	N	Y
Zadik et al. (2019)	Critically Low	Y	N	N	N	Y	Y	N	PY	N/N	N	NA	NA	N	NA	NA	Y
de Lima et al. (2020) [30]	Low	Y	Y	N	Y	Y	N	Y	PY	Y/Y	N	N/N	N	N	N	N	Y
Campos et al. (2020) [31]	Critically Low	Y	Y	N	N	N	N	N	PY	Y/Y	N	N/N	N	Y	Y	Y	Y
Cronshaw et al. (2020) [33]	Critically Low	Y	N	N	N	N	N	N	N	Y/Y	N	NA	NA	N	NA	NA	Y
Peng et al. (2020) [34]	Critically Low	Y	PY	N	N	Y	Y	N	PY	Y/Y	N	N/N	N	N	N	N	Y
Al-Rudayni et al. (2021) [35]	Critically Low	Y	Y	Y	N	Y	Y	Y	N	Y/Y	N	Y/Y	N	Y	Y	Y	Y
de Oliveira et al. (2021) [36]	Critically Low	Y	PY	N	N	Y	Y	N	Y	Y/Y	N	Y/Y	N	Y	Y	Y	Y
Redman et al. (2022) [37]	Low	Y	PY	N	PY	Y	Y	N	N	Y/Y	N	Y/Y	N	Y	Y	Y	Y
Sánchez-Martos et al. (2023) [38]	Critically Low	Y	PY	Y	N	Y	Y	N	N	Y/Y	N	NA	NA	N	NA	NA	Y
Danwiek et al. (2023) [39]	Critically Low	Y	PY	N	N	Y	Y	N	N	Y/Y	N	NA	NA	N	NA	NA	Y
Chan et al. (2023) [40]	Critically Low	Y	Y	N	PY	Y	Y	N	PY	Y/Y	N	N/N	N	Y	Y	Y	Y
Khalil et al. (2023) [41]	Low	Y	PY	N	PY	Y	Y	N	N	Y/Y	N	NA	NA	N	NA	NA	Y
Cruz et al. (2023) [42]	Critically Low	Y	PY	N	N	Y	Y	N	PY	Y/Y	N	N/N	N	Y	Y	Y	Y

1 – PICO elements; 2 – Review methods established a priori; 3 – Selection of the study designs explained; 4 – comprehensive literature search strategy; 5 – study selection in duplicate; 6 – data extraction in duplicate; 7 – List of excluded studies with justification; 8 – Adequate included study details description; 9 – Satisfactory technique for assessing the risk of bias; 10 – Sources of funding for the studies included reported; 11 – Appropriate methods for meta-analysis; 12 - Impact of risk of bias in meta-analysis; 13 – Account for risk of bias when interpreting/ discussing the results of the review; 14 – Satisfactory explanation for, and discussion of, any heterogeneity; 15 – Adequate investigation of publication bias; 16 – Conflict of interest and funding statements

Y Yes, *PY* Partial Yes, *N* No, *NA* Not applicable

Analysing the overlap values, the covered area was 12.14% and the corrected covered area was 7.75%, indicating moderate overlap. We then examined the pairwise CCA grid to determine which combinations of paired reviews had the highest overlap (Fig. 2). Overall, the level of overlap between SRs was not significant, with only 4 having very high overlap and one having high overlap.

Among the meta-analyses with weak evidence, the FSN was higher than the number of studies included in 20.0% of the meta-analyses ($n=8$), which means that the statistical significance of the summary estimates is very unlikely to change if more studies are added in the future.

Discussion

Summary of main findings

This is the first umbrella review to comprehensively evaluate the level evidence of SRs of PBMs effect on the prevention and treatment of OM in patients undergoing CT and/or radiotherapy. We identify 21 SRs suggesting key factors that can inform and improve future research on the effect of PBM on patients with OM secondary to chemo- and radiotherapy. Although a significant number of SRs were included, both the methodological and meta-analytic domains show low consistency and validity, respectively.

AMSTAR 2, overlapping and meta-analytic appraisal

The AMSTAR tool has been designed to critically assess the quality of SRs, taking into account their critical and non-critical weaknesses [14]. Of the 16 domains evaluated in AMSTAR 2, domains 3 (Did the review authors explain their selection of study designs for inclusion in the review?), 7 (Did the review authors provide a list of excluded studies and justify the exclusions?) and 10 (Did the review authors report the sources of funding for the studies included in the review?) were not addressed in more than 85% of the included SRs. Regarding domain 3, 90.5% of the SRs didn't specify the followed search strategy, with the included studies and justifications [14]. Concerning domain 7, 85.7% of the SRs didn't provide a list of excluded items with the corresponding reasons, thus increasing bias. [14]. in domain 10, 95.2% of the included trials did not report the source of funding, which is of great concern, as

Values in percentage (%)	Migliorati et al. (2013)	Figueiredo et al. (2013)	Oberoi et al. (2014)	Carneiro et al. (2017)	He et al. (2018)	Anschau et al. (2019)	Mazhari et al. (2019)	Zadik et al. (2019)	de Lima et al. (2020)	Campos et al. (2020)	Cronshaw et al. (2020)	Peng et al. (2020)	Al-Rudayni et al. (2021)	de Oliveira et al. (2021)	Redman et al. (2022)	Sánchez-Martos et al. (2023)	Danwiek et al. (2023)	Chan et al., 2023	Khalil et al. (2023)	Cruz et al. (2023)
Bjordal et al. (2011)	7,2%	6,4%	5,6%	0,0%	2,4%	2,4%	1,6%	8,0%	0,0%	0,0%	5,6%	7,2%	2,4%	0,0%	0,8%	0,0%	0,0%	2,4%	0,8%	0,8%
Migliorati et al. (2013)	-	6,4%	4,8%	0,0%	2,4%	1,6%	1,6%	18,4%	0,0%	2,4%	8,0%	8,8%	1,6%	0,0%	0,8%	0,0%	0,0%	3,2%	0,8%	1,6%
Figueiredo et al. (2013)	-	-	6,4%	0,8%	2,4%	0,8%	1,6%	9,6%	0,8%	1,6%	8,0%	8,0%	0,8%	0,0%	0,8%	0,8%	0,8%	3,2%	0,8%	1,6%
Oberoi et al. (2014)	-	-	-	0,0%	0,8%	0,0%	0,8%	10,4%	2,4%	3,2%	8,8%	11,2%	0,0%	0,0%	1,6%	3,2%	1,6%	4,0%	1,6%	0,0%
Carneiro et al. (2017)	-	-	-	-	0,0%	0,0%	0,0%	0,8%	0,0%	0,8%	0,8%	0,0%	0,0%	0,0%	0,0%	0,0%	2,4%	0,0%	0,0%	0,0%
He et al. (2018)	-	-	-	-	-	1,6%	3,2%	4,8%	0,0%	0,0%	3,2%	4,8%	1,6%	0,0%	2,4%	0,0%	0,0%	0,0%	1,6%	2,4%
Anschau et al. (2019)	-	-	-	-	-	-	1,6%	3,2%	0,0%	0,0%	1,6%	2,4%	4,0%	0,0%	1,6%	0,0%	0,0%	0,0%	0,0%	2,4%
Mazhari et al. (2019)	-	-	-	-	-	-	-	3,2%	0,0%	0,0%	1,6%	2,4%	1,6%	0,0%	1,6%	0,0%	0,0%	0,0%	1,6%	1,6%
Zadik et al. (2019)	-	-	-	-	-	-	-	-	2,4%	8,0%	19,2%	17,6%	3,2%	0,0%	3,2%	4,0%	4,0%	7,2%	2,4%	4,0%
de Lima et al. (2020)	-	-	-	-	-	-	-	-	-	3,2%	2,4%	1,6%	0,0%	0,0%	0,0%	3,2%	0,8%	0,0%	0,0%	0,0%
Campos et al. (2020)	-	-	-	-	-	-	-	-	-	-	5,6%	4,0%	0,0%	0,0%	0,0%	4,8%	3,2%	0,0%	0,0%	0,0%
Cronshaw et al. (2020)	-	-	-	-	-	-	-	-	-	-	-	15,2%	1,6%	0,0%	1,6%	4,0%	3,2%	7,2%	0,8%	3,2%
Peng et al. (2020)	-	-	-	-	-	-	-	-	-	-	-	-	2,4%	0,0%	4,0%	3,2%	3,2%	6,4%	1,6%	4,0%
Al-Rudayni et al. (2021)	-	-	-	-	-	-	-	-	-	-	-	-	-	0,0%	1,6%	0,8%	0,0%	0,0%	0,0%	2,4%
de Oliveira et al. (2021)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	0,0%	0,0%	0,8%	0,0%	0,0%	0,0%
Redman et al. (2022)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	0,0%	0,0%	0,8%	0,8%	1,6%
Sánchez-Martos et al. (2023)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	2,4%	0,8%	0,0%	0,0%
Danwiek et al. (2023)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	0,0%	0,0%	0,8%
Chan et al. (2023)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	0,0%	0,8%
Khalil et al. (2023)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	0,0%

Fig. 2 Overlap diagram in percentage (%) according to each included SR and year (Green cells indicate low overlap, yellow cells indicate moderate overlap, orange cells indicate high overlap and red cells indicate very high overlap)

reporting the source of funding is important because commercially funded trials are known to be more likely to produce results in favour of the sponsoring product than independently funded trials [14]. Given the limitations and potential biases present in these studies, the validity and reliability of their findings may be called into question.

The overlap interpretation also showed worrying results due to low percentiles (Fig. 2). A large number of SRs are published each year and duplication of reviews on similar topics is common, and overlap may occur if they include one or more identical primary studies, such as RCTs [21]. Hence, it was expected that reviews published in the same year would have a high overlap, since they would have included the same studies, however, this isn't in line with our findings. For example, two SRs, Zadik et al. (2019) and Cronshaw et al. (2020), had an overlap of 19.7%, which was the higher value obtained, while de Lima et al. (2020) and Heiskanen et al. (2020) had an overlap of 0.0%, as mentioned above. This leads us to believe that there might be a lack of consistency in the search strategy, which we also came across in the AMSTAR assessment.

The meta-analytic results go in line with the scarcity of quality evidence. Regarding the number of participants, only one study included more than 1000 participants, being the only "Highly suggestive" [34] whereas the remaining had a median number of 258 participants and were classified as "Weak". This concern suggests that RCTs are failing in terms of numbers of participants and that their conclusions are not robust. Another important aspect to consider is the potential for bias in heterogeneity statistics, also due to small meta-analysis. It's important to assess the homogeneity and heterogeneity of a trial because we can predict whether or not the effect of a particular treatment will be similar when applied to new people [44]. However heterogeneity is difficult to predict, especially in small meta-analyses [44] as presented in our results. Hence, larger studies of intervention, as RCTs, need to be conducted to have more predictable and reliable results.

Implications for practice and research

The findings of the analysis reveal considerable disparities in the quality of evidence, as the bulk of the studies incorporated were assessed as critically low and low. The results of this study align with those of a recent umbrella review [45], and raise doubts about the methodological proficiency of the groups responsible for the SRs and the quality of their review procedures.

Although the included studies have concluded that PBM is effective in reducing pain and severe OM, this can be questioned by the low quality of the included studies as we have identified. This is a major concern not only in clinical practice, where there's a lack of robust evidence to support treatment outcomes, but also in research, where existing SRs are not rigorous, and the methodology is unreliable.

PBMs have been suggested by several authors to have a long-term carcinogenic effect, although long-term follow-up studies of patients treated with PBMs for OM prevention have not shown an increase in cancer recurrence. [10, 29, 46–48]. Hence, it's crucial that the clinician informs the patient of the potential risks of PBM.

In addition, many of the included SRs mention the absence of guidelines and the need to define laser parameters [24, 29, 33, 34, 36, 37, 42]. RCTs are conducted according to their own protocol and do not have standardised parameters, which increases the variability of results. There is therefore an urgent need for more high-quality evidence that follows the latest guidelines and works to improve them so that patients receive the safest and most effective treatment.

Strengths and limitations

This umbrella review followed a strict protocol and the most recent tools available to evaluate the quality evidence of the included studies enhancing the trustworthiness of our findings.

There are limitations to this umbrella review that are worth mentioning. The fact that an overview synthesizes the results and conclusions of SRs, it does not provide an analysis of the primary studies included, preventing any conclusion regarding primary data. Yet, upon examining the meta-analytical strength, two significant constraints hinder the attainment of higher validity ranks: the low number of participants (< 1000 participants) and the bias potential of heterogeneity statistic due to small meta-analyses [44]. As such, the number of studies available contain still a very low number to provide more robust meta-analytical consistency and for this reason, this umbrella review support the need for larger studies of intervention, preferably randomized trials.

Conclusion

The level of evidence for the efficacy of PBM in chemo- and radiotherapy-induced oral conditions is constituted by SRs with inconsistent methodological quality, and the meta-analytical strength of which is low. This umbrella review underscores the salient aspects that warrant improvement in subsequent primary and secondary research pertaining to this subject matter.

Supplementary Information

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Supplementary Material 1.

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Authors' contributions
Inês Rodrigues: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Writing - original draft; Writing - review & editing. Vanessa Machado: Methodology; Resources; Software; Writing - original draft; Writing - review & editing. Luísa Bandeira Lopes: Writing - review & editing. Pedro Trancoso: Writing - review & editing. António Mano Azul: Writing - review & editing. José João Mendes: Supervision, Writing- Reviewing and Editing. Carlos Zagalo: Supervision, Writing- Reviewing and Editing. João Botelho: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Resources; Software; Supervision; Validation; Writing - original draft; Writing - review & editing.

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Availability of data and materials
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Declarations

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