UNIVERSIDADE ESTADUAL DE CAMPINAS
FACULDADE DE ODONTOLOGIA DE PIRACICABA

LUCAS PEIXOTO DE ARAÚJO

TERAPIA FOTODINÂMICA EM ENDODONTIA: UMA SÍNTESE DE EVIDÊNCIAS

PHOTODYNAMIC THERAPY IN ENDODONTICS: AN EVIDENCE SYNTHESIS

Piracicaba
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Tese apresentada à Faculdade de Odontologia de Piracicaba da Universidade Estadual de Campinas como parte dos requisitos exigidos para a obtenção do título de Doutor em Clínica Odontológica, na Área de Endodontia.

Thesis presented to the Piracicaba Dental School of the University of Campinas in partial fulfillment of the requirements for the degree of Doctor in Clinical Dentistry in the Endodontics area.

Orientador: Prof. Dr. Caio Cezar Randi Ferraz.

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A Ata da defesa, assinada pelos membros da Comissão Examinadora, consta no SIGA/Sistema de Fluxo de Dissertação/Tese e na Secretaria do Programa da Unidade.

DEDICATÓRIA

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RESUMO

O uso da terapia fotodinâmica (PDT) na endodontia visa complementar a desinfecção do sistema de canais radiculares após o preparo químico-mecânico com a utilização de um agente fotossensibilizante ativado por uma fonte de luz com comprimento de onda específico. Entretanto, ainda há uma escassez de evidências sólidas quanto à eficácia dessa técnica nos principais desfechos clínicos. Assim, os objetivos desse trabalho foram: 1) mapear sistematicamente a literatura existente nesse escopo, sintetizar as principais evidencias de alto impacto disponíveis, e apontar direções futuras para pesquisa; 2) avaliar através de uma revisão sistemática de ensaios clínicos se a complementação com PDT é eficaz na redução microbiana na pulpectomia de dentes decíduos; e 3) avaliar através de uma revisão sistemática de estudos *in vitro* se a PDT pode causa alteração de cor em dentes tratados endodônticamente. Os resultados dos estudos mostraram que: 1) a maior parte da evidencia existente é laboratorial (74,5%), os principais desfechos clínicos investigados foram a redução da carga microbiana e dor pós-operatória, o periódico *Photodiagnosis and Photodynamic Therapy* foi o que mais publicou sobre o assunto e houve um crescimento exponencial na publicação destes estudos na última década; 2) Apenas um estudo mostrou que a complementação com PDT na pulpectomia de dentes decíduos diminui significativamente a carga microbiana, os demais discutiram os possíveis benefícios porém sem observar diferença estatística nesse desfecho; e 3) todos os agentes fotossensibilizantes tem o potencial de pigmentação dentária e nenhum método se provou eficaz na remoção desses agentes. Dentro das limitações da metodologia empregada, pode-se concluir que a quantidade de evidencias de alta qualidade sobre PDT na endodontia ainda é escassa e futuros estudos clínicos devem focar em investigar os efeitos dessa terapia à longo prazo no reparo periradicular, na taxa de sobrevivência, e no impacto estético e social de uma possível pigmentação dentária como efeito colateral.

Palavras-chave: Terapia fotodinâmica, Endodontia, Revisão sistemática

ABSTRACT

Photodynamic therapy (PDT) in endodontics aims to supplement the disinfection of the root canal system after chemo-mechanical preparation by using a photosensitizing agent activated by a light source with a specific wavelength. However, there is still a lack of solid evidence regarding the effectiveness of this technique on major clinical outcomes. Thus, the objectives of this work were: 1) to systematically map the existing literature in this scope, synthesize the main high-impact evidence, and point future directions for research; 2) to evaluate, through a systematic review of clinical trials, whether supplementation with PDT is effective in reducing microbial load in pulpectomy of primary teeth; and 3) to evaluate, through a systematic review of *in vitro* studies, whether PDT can cause discoloration in endodontically treated teeth. The results of the studies showed that: 1) most of the existing evidence is laboratory-based (74.5%), the main clinical outcomes investigated were the reduction of the microbial load and postoperative pain, the journal Photodiagnosis and Photodynamic Therapy was the one which most published on the subject, and there was an exponential growth in the publication of these studies in the last decade; 2) Only one study showed that supplementation with PDT in pulpectomy of primary teeth significantly decreases the microbial load, the others discussed its benefits but without observing a statistical difference in this outcome; and 3) all photosensitizing agents have the potential to stain teeth and no method has proven to be effective in removing these agents. Within the limitations of the methods employed, it can be concluded that the amount of high-quality evidence on PDT in endodontics is still scarce, and future clinical trials should focus on investigating the long-term effects of this therapy on periradicular repair, survival rate, and the aesthetic and social impact of tooth staining as a side effect.

Keywords: Photodynamic therapy, Endodontics, Systematic review

SUMÁRIO

1 INTRODUÇÃO

O objetivo primário do tratamento endodôntico é prevenir e tratar patologias pulpares e perirradiculares através da remoção químico-mecânica de tecidos orgânicos inflamados e/ou infectados do interior do sistema de canais radiculares, e assim, preservar a dentição natural em função (American Association of Endodontists 2018)

As patologias perirradiculares tem a colonização microbiana de dentes necrosados como principal fator etiológico (Siqueira & Rôças 2022). Estudos clássicos demonstraram a influência das bactérias na progressão da necrose pulpar e desenvolvimento de periodontite apical através da organização de espécies bacterianas em biofilme aderido às paredes dos canais radiculares (Kakehashi et al. 1965; Möller et al. 1981; Sundqvist et al. 1998). A remoção eficaz desse biofilme é realizada através do preparo químico-mecânico em toda a extensão do sistema de canais radiculares (Martinho & Gomes 2008; Gomes et al. 2022).

Diversos métodos suplementares ao preparo químico-mecânico para a desinfecção do sistema de canais radiculares foram propostos com a finalidade de melhorar os desfechos clínicos do tratamento endodôntico através da redução da carga microbiana remanescente (Meire et al. 2022). Entre eles, a terapia fotodinâmica (PDT) se apresenta como uma alternativa eficaz na redução dessa carga microbiana intracanal sem efeitos colaterais reportados (Pourhajibagher & Bahador 2019). O mecanismo de ação da terapia fotodinâmica consiste em uma reação fotoquímica induzida pela fotoativação de um agente fotossensibilizante (Plaetzer et al. 2009). Uma fonte de luz com um comprimento de onda apropriado é emitida em um agente fotossensibilizante com capacidade de absorver energia dessa luz, e em combinação com o oxigênio livre presente, essa interação formará espécies reativas de oxigênio como o oxigênio singleto, sendo essa eficaz na inativação e morte celular de bactérias, fungos e vírus (Wainwright 1998).

Os principais agentes fotossensibilizantes utilizados para realizar a PDT na endodontia são os do grupo dos corantes fenotiazínicos como o azul de metileno (Plotino et al. 2019). Esse grupo de agentes fotossensibilizantes tem o seu pico de absorção de energia na região de luz vermelha (i.e., 610 – 660 nm) e por isso são comumente associados à um laser de baixa potência configurado neste comprimento de onda para a realizar a fotoativação. Atualmente existem diversos protocolos de fotosensibilização e isso varia de acordo com o tipo de fotossensibilizante empregado.

A pesar de existirem evidências provenientes de ensaios clínicos randomizados que observam uma maior taxa de reparo periapical e menor dor pós-operatória quando a suplementação do preparo químico-mecânico é realizada com a PDT (de Miranda & Colombo 2018; Alves-Silva et al. 2022), ainda há uma escassez de estudos de alto impacto que possam validar essa técnica. Portanto, o objetivo do presente estudo foi de realizar uma coletânea de revisões sistemáticas no campo da terapia fotodinâmica em endodontia visando sintetizar as evidências de alto impacto disponíveis, assim como identificar os principais pesquisadores e suas linhas de pesquisa da área e apontar as lacunas do conhecimento a serem investigadas em futuros estudos.

2 ARTIGOS

2.1 ARTIGO 1

Global research trends on photodynamic therapy in endodontics: A bibliometric analysis

Artigo publicado no periódico *Photodiagnosis and Photodynamic Therapy* (Fator de impacto: 3.577; Qualis CAPES: A2) - (Anexo 1)

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Global research trends on photodynamic therapy in endodontics: a bibliometric analysis

Running title: Photodynamic therapy in endodontics and bibliometric analysis

Abstract

Background: Photodynamic therapy (PDT) is an adjunctive treatment that aims to inactivate microorganisms through an oxidative reaction produced by irradiating a photosensitizing agent. The never-ending quest for root canal disinfection predictability has always sought supplementary methods when performing chemomechanical procedures. From this perspective, PDT protocols were proposed as an auxiliary approach in endodontics. Thus, the aim of this study was to investigate publication metrics and research trends related to this scope. **Methods:** This review is reported in accordance with the PRISMA 2020 recommendations. Two blinded and independent reviewers systematically searched five electronic databases until December 2021. The acquired bibliometric parameters were analyzed through descriptive statistics and graphical mappings with VOSViewer software. **Results:** The search retrieved 342 studies from 84 journals originating from 33 countries. About 85% of the included studies were published over the last decade. Most of the available evidence is laboratory-based (74.5%), and the main clinical outcomes evaluated were microbiological load reduction and postoperative pain. Mayram Pourhajibagher is the researcher with the most publications as the first author (n = 16). Tehran University of Medical Sciences carried out the highest number of studies (n = 29), and *Photodiagnosis and Photodynamic Therapy* is the journal that most published on the theme (n = 111). **Conclusions:** This bibliometric analysis mapped and discussed the scientific progress and publication metrics in PDT in endodontic research. Additionally, future perspectives were highlighted and should focus on discovering new photosensitizer agents, standardizing optimal photoactivation protocols, and conducting more clinical-oriented research.

Keywords: Photodynamic Therapy, Endodontics, Root Canal Preparation, Bibliometrics, Review

1 *Introduction*

Photodynamic therapy (PDT) is an adjunctive treatment modality that aims to inactivate cells, microorganisms, or molecules through an oxidative reaction produced by irradiating a photosensitizing agent with a light of an appropriate resonant wavelength (1). Even though this approach has been investigated since the 1960s, it was not until the late 1990s that it gained adequate attention from medical specialties (2,3). In endodontics, the never-ending quest for root canal disinfection predictability has always sought supplementary methods when performing chemomechanical procedures. From this perspective, PDT protocols were proposed as an auxiliary approach for conventional root canal chemomechanical preparation in an attempt to reduce any residual bacteria on the root canal systems to the lowest possible level (4).

Several characteristics related to the effects of PDT on root canal treatment have been investigated in recent years; for instance, the intracanal bacteria reduction (5), tooth color change (6,7), and the bond strength of root canal sealers or glass-fiber post adhesiveness on radicular dentin previously treated with PDT (8,9). Although clinical trials are still scarce, there is evidence that PDT with phenothiazine salts light activated with a low-level laser decreases postoperative pain through its photobiomodulation effect (10,11) and may result in better periapical healing in a six-month time frame (12).

Bibliometric analysis is a widely used systematic method to evaluate research developments, publication trends, and their scientific impact in a specific area of knowledge over time (13). This type of study outlines the state of the art of a determined area, helps researchers understand literature gaps in underinvestigated topics, and highlights the most prominent authors, research institutions, and countries where major contributions have been made to the field. Furthermore, bibliometric analysis had already been explored in different scopes of endodontics (14–19), yet none investigated the publication metrics related to PDT. Thus, this study aims to conduct a bibliometric analysis to benefit both clinical and academic researchers by analyzing the past and understanding the present in this field to help develop further high-impact investigations on the use of PDT in endodontic therapies.

2 *Materials and Methods*

2.1 Protocol registration

This bibliometric review is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA 2020) recommendations (20). The study protocol was registered in the Open Science Framework due to the nature of the study design (e.g., bibliometric analysis), and it can be accessed through the following link: https://osf.io/3uzhf

2.2 Eligibility and exclusion criteria

Studies that investigated the different applications of photodynamic therapy in endodontics were included in this analysis; however, only studies written in the English language were considered. The publication period was limited up to the year 2021, and no study design restriction was applied. Exclusion criteria were studies that did not use any intracanal photosensitizing agent to perform PDT.

2.3 Search strategy

A comprehensive and systematic search strategy was adopted to yield the publication records related to PDT in endodontics from five different electronic databases: PubMed/MEDLINE, The Cochrane Library, SciVerse Scopus, EMBASE, and the Web of Science. The search descriptors used to carry out the search were selected based on the MEDLINE MeSH (Medical Subject Headings) terms, and they were adapted for the other databases (Supplementary file 1). All relevant studies retrieved by the search strategy were imported into Mendeley software (Elsevier, Amsterdam, NE) to remove duplicate records. Additionally, the pool of studies was improved by searching the references cited by the included studies, and those were hand examined for any further eligible study. Additionally, if the full article was unavailable through the database, the corresponding author of the included study was contacted via e-mail to retrieve the study. A second reminder e-mail was sent after two weeks in case of no response, and the study was excluded from the analysis if it could not be retrieved.

2.4 Selection process

Initially, a calibration exercise was performed through a discussion of the eligibility criteria with all reviewers. Then, the remaining articles were exported into the Rayyan web application (Qatar Computing Research Institute, Doha, QA) (21) to be screened by title and abstract by two blinded and independent reviewers (LPA and LBG). The articles that clearly met the eligibility criteria and those that were considered uncertain were obtained and selected for full-text analysis. If any disagreement between the two reviewers was observed, then consensus was achieved through discussion with a third reviewer with more experience in the field (CCRF).

2.5 Data collection process

Data of interest from the included studies were tabulated and interpreted by two independent reviewers (LPA and LBG) in an Excel spreadsheet (Microsoft Corporation, Redmond, WA, USA), and another reviewer (CCRF) double-checked it. In case of any missing information, the corresponding author of the included study was contacted via e-mail to retrieve any missing data. The parameters of interest included the year of publication, frequency of authorship, institutional affiliations, country of origin, journal of publication and its impact factor, citation count, level of evidence (LoE), and study design. Additionally, additional parameters were retrieved from the studies with the highest LoE (i.e., systematic reviews and randomized clinical trials), and those were the photosensitizing agent used, the light source, and the study's main findings.

The LoE of each study was determined based on a previous study that discussed the hierarchy of evidence in endodontics research (22). The institution and country of origin of the articles were identified through the first author's institutional affiliation, and the citation metrics were retrieved from the Google Scholar database. Moreover, the impact factors of journals with the highest number of publications on PDT in endodontics were extracted from the 2020 Journal Citation Reports™ (JCRs) (Clarivate Analytics, Philadelphia, PA, USA).

2.6 Bibliometric analysis

Bibliometric network maps were developed by importing the included studies into the Visualization of Similarities Viewer software (VOSViewer 1.6.8, Center for Science and Technology Studies, Leiden University, Leiden, NL). The software creates a distance-based map by performing bibliographic coauthorship and keyword cooccurrence analysis. The terms are arranged into clusters shown as colored circles, and the smaller the distance between the circles is, the stronger the collaborative relationship between them, while the thickness of the cluster indicates the strength of the links represented by the cluster.

The VOSViewer software was calibrated through van Eck and Waltman (2010) recommendations (23) by using a resolution value of '1.00' and a minimum cluster size value of '1'. Additionally, the minimum set of published articles was defined as '3' to allow a thorough examination of the bibliometric relationships between the authors; also, the minimum set of keyword co-occurrences was defined as '10'.

3 *Results*

3.1 Search strategy

The search strategy (last conducted on December 31st, 2021) retrieved 1434 potentially relevant records. Figure 1 is a schematic flowchart that delineates the selection process in accordance with the PRISMA 2020 statement (20). After removing the duplicate records, 1080 studies remained for the title and abstract screening using the web application Rayyan (Qatar Computing Research Institute). In the next phase, 655 studies were excluded because they did not clearly meet the inclusion criteria, leaving 425 studies for full-text analysis. Of these, 83 were excluded because 14 were trial protocols, 11 records were meeting abstracts, 43 were not related to endodontic procedures, 5 papers were written in languages other than English, 2 were book chapters, and 8 studies did not use any photosensitizing agent to perform PDT. The remaining 342 studies were in accordance with the inclusion criteria and were included in this bibliometric analysis.

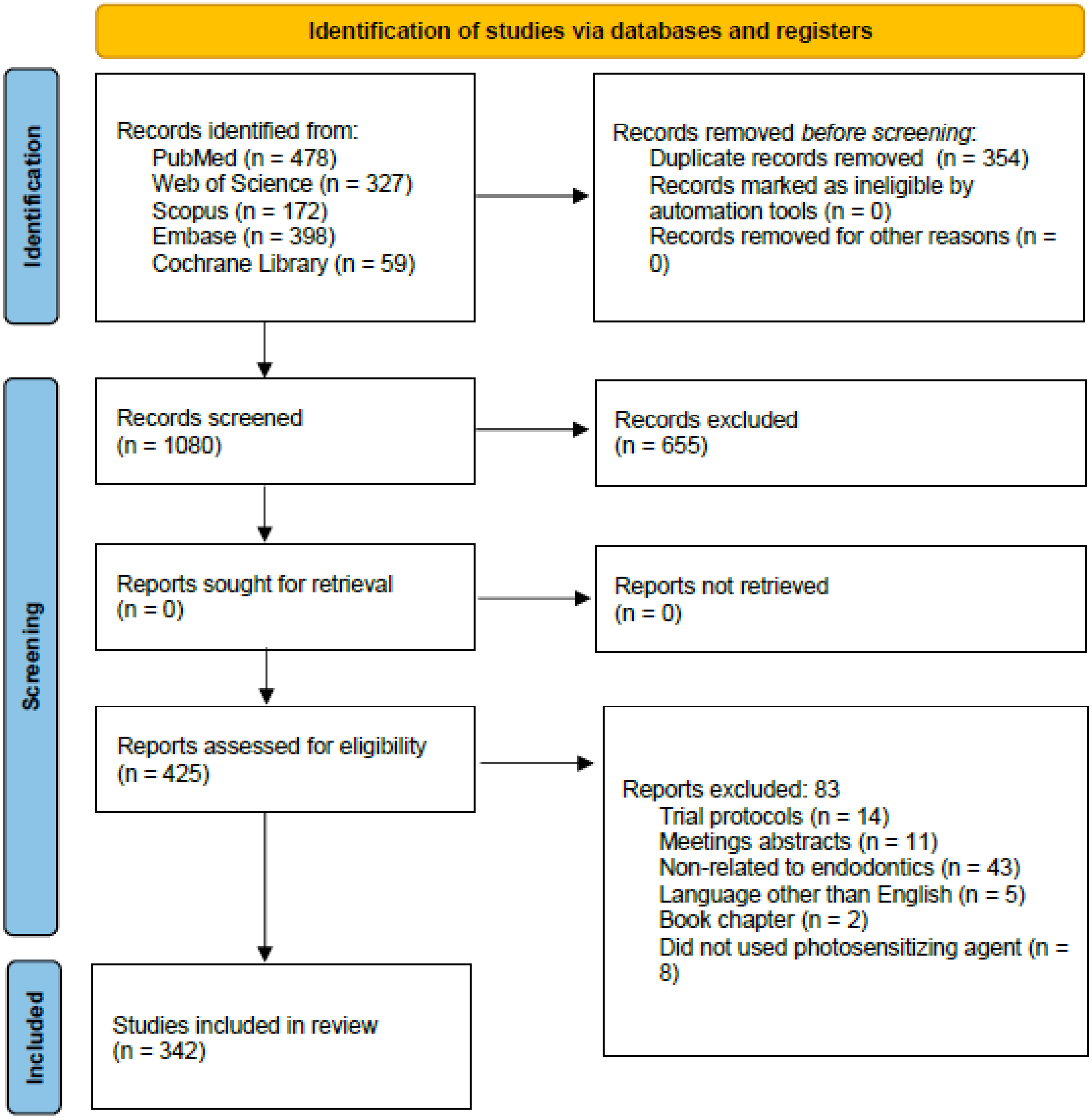

Figure 1. Flowchart showing search strategy based on the PRISMA 2020 statement.

3.2 Study characteristics

Of the total 342 included studies, 255 were laboratory assays, 32 were narrative reviews (LoE = 5), 17 were case reports (LoE = 5), 5 were case series (LoE = 4), 2 were observational studies (LoE = 3), 21 were randomized clinical trials (LoE = 2), and 10 were systematic reviews classified with the highest level of evidence (LoE = 1). Table 1 and Table 2 summarizes the main findings of the highest LoE studies and additional data regarding the PDT procedures. There is a consensus among the highest LoE studies that the most investigated photosensitizing agents are phenothiazine salts, such as methylene blue and toluidine blue, with absorption wavelengths of 600-660 nm, and the light source commonly used to activate these photosensitizing agents is a low-level diode. Other substances were also investigated as photosensitizers, including porphyrins, indocyanine green, rose bengal, curcumin, erythrosine, and polyethyleneimine-chlorin e6. Each class of photosensitizing agents has a specific photoactivation protocol according to their wavelength sensitivity.

Table 1. Main findings and additional data of the highest LoE studies

Author and Year	**Outcomes evaluated**	**Photosensitizing agents**	**Light source**	**Main findings**
Systematic Review and Meta-Analysis				
Pourhajibagher *et al.*, 2019	*In vivo* microbial reduction	Methylene blue, toluidine blue, indium gallium aluminum phosphide, polyethyleneimine-chlorin e6, and phenothiazinium chloride	Low-level diode laser	Although the PDT parameters may vary from one randomized clinical trial to the next, all studies found a significant reduction in microbial load with adjunctive use of PDT.
Systematic Review without Meta-Analysis				
Fransson *et al.*, 2012	*In vivo* microbial reduction	Polyethyleneimine-chlorin e6, and tolonium chloride	Low-level diode laser	All included studies were assessed as having low quality, which means that no conclusions can be drawn regarding the efficacy of laser as an adjunct to conventional chemo-mechanical treatment of infected root canals.
Siddiqui *et al.*, 2013	*In vitro* microbial reduction	Methylene blue and toluidine blue	Low-level diode laser	The efficacy of PDT in eliminating E. faecalis from infected root canals remains questionable. Further well-designed studies are needed to investigate the role of PDT as a valid approach in treating infected root canals.
Arneiro *et al.*, 2014	*In vitro* microbial reduction	Methylene blue, toluidine blue, and phenothiazinium chloride	Low-level diode laser	PDT was effective in reducing E. faecalis inside root canals. Therefore, the use of PDT as adjunctive therapy to current endodontic disinfection techniques is recommended.
Chrepa *et al.*, 2014	*In vivo* microbial reduction	Polyethyleneimine-chlorin e6, and tolonium chloride	Low-level diode laser	Limited clinical information is currently available on the use of PDT in root canal disinfection. If supported by future clinical research, PDT may have efficacy for additional root canal disinfection, especially in the presence of multidrug-resistant bacteria.
Abdelaziz Ali *et al.*, 2018	*In vitro* microbial reduction	Methylene blue, toluidine blue, rose bengal, indocyanine green, polyethyleneimine-chlorin e6, and porphyrin	Low-level diode laser and LED	Conventional root canal debridement using sodium hypochlorite irrigant can be enhanced by light activation of photosensitizer agents.
Anagnostaki *et al.*, 2020	Post-operative pain, periapical healing, and *in vivo* microbial reduction	Methylene blue, toluidine blue, and polyethyleneimine-chlorin e6	Low-level diode laser	The use of laser photonic energy of appropriate delivered parameters can be proposed as a useful adjunctive when considering optimal treatment modalities in endodontics.

Bordea *et al.*, 2020	*In vivo* and *in vitro* microbial reduction	Methylene blue and toluidine blue	Low-level diode laser	The combination of PDT with antimicrobial irrigants could provide a synergetic effect and can be considered as an alternative to the conventional disinfection methods for persistent root canal infections.
Vendramini *et al.*, 2020	*In vitro* microbial reduction	Methylene blue, toluidine blue, curcumin, and polyethyleneimine-chlorin e6	Low-level diode laser, LED, and UV light	PDT reduced bacterial counts in most studies, especially when used as an adjunct to the conventional endodontic technique to treat refractory infections.
Scoping Review				
Betancourt *et al.*, 2021	In vitro microbial reduction	Methylene blue, toluidine blue, indocyanine green, chitosan, rose bengal, erythrosine. Different nanoparticles encapsulated those photosensitizing agents	High and low-level diode laser, LED, and halogen lamp	The use of functionalized nanoparticles with photosensitizer agents in PDT has been shown to be effective in reducing the bacteria count, making it a promising alternative in endodontic disinfection.

Table 2. Characteristics of the included randomized clinical trials and their main findings.

Sample characteristics				Intervention characteristics			
Author and year	**Number of patients**	**Tooth group**	**Pulpal and perirradicular diagnosis**	**Light source**	**Photosensitizer agent**	**Photoactivation parameters**	**Main findings**
Bonsor *et al.*, 2006	64	Mostly molars	Irreversible pulpitis or perirradicular periodontitis	Low-level diode laser	Toluidine blue O	12J cm^2 light fluency, 100mW output power, and 635nm wavelength applied for 120s	Photodynamic therapy has been shown to be as effective as conventional chemomechanical techniques but is more biocompatible and could potentially decrease the time spent disinfecting the root canal system.
Johns *et al*., 2014	60	Single-rooted anterior teeth	Perirradicular periodontitis	Low-level diode laser	Toluidine blue O	Parameters were not reported	The study concluded that the PDT group was the most effective root canal disinfectant and aided in the healing of periapical lesions.
Asnaashari *et al.,* 2016	27	Single-rooted endodontically treated teeth	Perirradicular periodontitis	Low-level diode laser	0,005% mg/L of methylene blue	9J cm^2 light fluency, 1W output power, 660nm wavelength applied for 240s	Regarding the elimination of intraradicular microbiota, additional PDT may increase the effectiveness of conventional chemomechanical preparation in previously root-filled teeth accompanied by perirradicular periodontitis
Ahangari *et al.,* 2020	20	Endodontically treated single-rooted mandibular premolars	Perirradicular periodontitis	Ga-Al-As diode laser	0,005% mg/L of methylene blue	200mW output power, and 810nm wavelength applied for 10s	PDT and calcium hydroxide intracanal dressing therapy showed the same antimicrobial efficacy.
Asnaashari *et al.,* 2017	20	Endodontically treated molars	Perirradicular periodontitis	Low-level diode laser	0,005% mg/L of methylene blue	4J cm2 light fluency, 200mW output power, and 660nm wavelength applied for 60s	LED photodynamic therapy is a better disinfectant strategy than calcium hydroxide therapy. It can be concluded that PDT is capable of disinfecting the root canals in a single-visit root canal treatment.
Rabello *et al*., 2017	24	Single-rooted teeth	Perirradicular periodontitis	Low-level diode laser	0,010% mg/L of methylene blue	60mW output power, and 660nm wavelength applied for 120s	The photodynamic therapy optimized the disinfection of bacteria from root canals in one-visit but not for two-visit treatment modality with the accomplishment of calcium hydroxide medication.
da Silva CC *et al*., 2018	10	Single-rooted teeth	Perirradicular periodontitis	Gal-Al-As diode laser	0,010% mg/L of methylene blue	4J cm2 light fluency, 100mW output power, and 660nm wavelength applied for 40s	PDT may be used as an effective adjunct therapy in the endodontic treatment of permanent teeth, resulting in a significant reduction in the incidence of E. faecalis before root canal obturation

de Miranda RG *et al*., 2018	32	Mandibular molars	Perirradicular periodontitis	Low-level diode laser	0,005% mg/L of methylene blue	100mW output power, and 660nm wavelength applied for 300s	PDT resulted in better healing at 6-month follow-up compared to conventional endodontic treatment alone
Barciela *et al*., 2019	40	Single-rooted anterior teeth	Perirradicular periodontitis	Low-level diode laser	0,005% mg/L of methylene blue	100mW output power, and 660nm wavelength applied for 90s	The results of the study did not show any difference in pain symptoms between the groups at 24 h, 72 h, and 1 week.
Coelho *et al*., 2019	60	Single-rooted teeth	Perirradicular periodontitis	Low-level diode laser	0,005% mg/L of methylene blue	18J cm2 light fluency, 100mW output power, and 660nm wavelength applied for 180s	Within the limitations of this study, it can be concluded that PDT was efficient in reducing postoperative pain in single-visit root canal treatment of teeth with necrotic pulps.
Yoshinari *et a*l., 2019	10	Single-rooted teeth	Perirradicular periodontitis	Low-level diode laser	0,005% mg/L of methylene blue	18J cm2 light fluency, 100mW output power, and 660nm wavelength applied for 180s	The photodynamic therapy did not have advantages in controlling postoperative pain in endodontic treatments of asymptomatic teeth with apical periodontitis, since both groups showed low levels of pain in all patients evaluated.
Anand *et al*., 2020	20	Primary mandibular second molars	Necrotic pulp	Low-level diode laser	0,005% mg/L of methylene blue	0.5W output power, and 940nm wavelength applied for 10s	It was concluded that PDT, and Clotrimazole disinfection protocols for infected root canals of primary teeth are equally effective as an adjunct to standard irrigation protocol with no significant difference in the postoperative CFU of C. albicans.
Okamoto *et al*., 2020	30	Single-rooted anterior teeth	Necrotic pulp	Low-level diode laser	0,005% mg/L of methylene blue	4J cm2 light fluency, 100mW output power, and 660nm wavelength applied for 40s	The present findings demonstrated that the microbiological results achieved with conventional endodontic treatment combined with PDT using parameters employed in this study on primary teeth with a diagnosis of pulp necrosis were similar to those achieved with conventional treatment alone.
Bharti *et al*., 2021	54	Endodontically treated single-rooted anterior teeth	Perirradicular periodontitis	Blue LED	Toluidine blue O	200mW output power, 630nm wavelength applied for 60s	The use of PDT in endodontic retreatment led to a significant reduction of the remaining bacterial species. So, PDT can be used for routine endodontic disinfection in failed root canal cases.
Gueorgieva *et a*l., 2021	36	All teeth groups	Necrotic pulp and/or perirradicular periodontitis	Low-level diode laser	0,005% mg/L of methylene blue	200mW output power, 665nm wavelength applied for 60s	The disinfection with NaOCl has a stronger antimicrobial effect compared to PDT.
Guimarães *et al*., 2021	70	Single-rooted teeth	Perirradicular periodontitis	Low-level diode laser	0,010% mg/L of methylene blue	9J cm2 light fluency, 100mW output power,	PDT had no significant effect on postoperative pain, tenderness, edema, and the use of

						and 660nm wavelength applied for 90s	analgesics after root canal treatment with foraminal enlargement in single-rooted teeth with asymptomatic apical periodontitis in a single visit.
Moreira *et al.*, 2021	50	Incisors, canines and premolars	Necrotic pulp and/or perirradicular periodontitis	Low-level diode laser	0,005% mg/L of methylene blue	9J cm2 light fluency, 100mW output power, and 660nm wavelength applied for 90s	PDT did not promote better results in endodontic treatment, being similar to conventional treatment.
Souza *et al.*, 2021	40	Mandibular molars	Perirradicular periodontitis	Low-level diode laser	0,005% mg/L of methylene blue	9J cm2 light fluency, 100mW output power, and 660nm wavelength applied for 90s	Apical limit of instrumentation and PDT have no influence on the postoperative pain of lower molars with asymptomatic apical periodontitis.
Vilas-Boas *et al*., 2021	70	Molars	Perirradicular periodontitis	Low-level diode laser	0,015% mg/L of methylene blue	9J cm2 light fluency, 100mW output power, and 660nm wavelength applied for 180s	The findings of the present study led to the conclusion that PDT is efficient in decreasing postoperative pain in teeth presenting with symptomatic apical periodontitis. However, the pain perception was similar to the control group after 72 hours.
Dedania *et al.*, 2021	44	Single-rooted teeth	Necrotic pulp and/or perrirradicular periodontitis	Low-level diode laser	0,005% of methylene blue	200W output power, and 810nm wavelength applied for 10s	Both PUI and laser disinfection are equally effective in reducing postoperative pain and discomfort after single visit root canal treatment.
Alves-Silva *et al*., 2021	60	Single-rooted teeth	Necrotic pulp and perirradicular periodontitis	Low-level diode laser	0,005% of methylene blue	4J cm2 light fluency, 100mW output power, and 660nm wavelength applied for 40s	The findings of this study reported that photodynamic therapy had a significant effect on decreasing post-endodontic treatment pain in teeth with necrotic pulp and asymptomatic periapical lesions.

All primary outcomes investigated in the LoE 1 studies were regarding microbial reduction (5,24–32); however, a few studies also evaluated postoperative pain and periapical healing as secondary outcomes regardless of the data limitation. The main findings of the majority of these studies reported that PDT could have a synergic effect when used as an adjunctive treatment since it significantly reduced the microbial load from infected root canals. On the other hand, there is still very limited clinical evidence that this approach could lead to a more favorable outcome of periapical repair.

3.3 *Bibliometric analysis*

The included studies were published in 84 different scientific journals over a period of 19 years (2002-2021), with 46 (272 studies) of those journals with impact factors available at the 2020 JCR. The remaining 38 journals (70 studies) were not listed in any internationally recognized scientometric index that evaluates impact factors. Therefore, they were classified separately and are available in Supplementary file 2. The journal that had the most publications on the theme is *Photodiagnosis and Photodynamic Therapy* (n = 111), followed by *Journal of Endodontics* (n = 26), *Lasers in Medical Science* (n = 20), *Photomedicine and Laser Surgery* (n = 19), and the *International Endodontic Journal* (n = 15). Table 3 shows all the journals, number of published articles, impact factors, and journal categories according to the 2020 JCR.

Table 3. The top journals based on the number of publications, impact factor (IF), as well as the subject category and ranking in the 2020 Journal Citation Reports (Clarivate Analytics).

Journal	Articles (n)	JCR® IF 2020	Journal category (ranking)
Photodiagnosis and Photodynamic Therapy	111	3.631	Oncology (145/242) (Q3)
Journal of Endodontics	26	4.171	Dentistry, Oral Surgery & Medicine (16/92) (Q1)
Lasers in Medical Science	20	3.161	Engineering, Biomedical Sciences (46/89) (Q3)
International Endodontic Journal	15	5.264	Dentistry, Oral Surgery & Medicine (10/92) (Q1)
Photomedicine and Laser Surgery	15	2.796	Surgery (83/211) (Q2)
Photochemistry and Photobiology	9	3.421	Biochemistry & Molecular Biology (179/295) (Q3)
Journal of Dentistry	7	4.379	Dentistry, Oral Surgery & Medicine (14/92) (Q1)
Lasers in Surgery and Medicine	6	4.025	Dermatology (17/69) (Q1)
Clinical Oral Investigations	5	3.573	Dentistry, Oral Surgery & Medicine (21/91) (Q1)
Australian Endodontic Journal	5	1.659	Dentistry, Oral Surgery & Medicine
Journal of Photochemistry and Photobiology B-Biology	4	6.252	Biochemistry & Molecular Biology (61/295) (Q1)
Journal of Oral Science	4	1.556	Dentistry, Oral Surgery & Medicine (82/92) (Q4)
Frontiers in Microbiology	3	5.640	Microbiology (28/136)
Antibiotics	3	4.639	Infectious Diseases (34/118) (Q2)
Photobiomodulation, Photomedicine, and Laser Surgery	3	2.222	Surgery (118/211) (Q3)
Journal of Biophotonics	2	3.207	Biophysics (33/71) (Q2)
Applied Sciences	2	2.679	Chemistry, Multidisciplinary Sciences (101/178) (Q3)
Acta Odontologica Scandinavica	2	2.331	Dentistry, Oral Surgery & Medicine (53/92) (Q3)
Brazilian Oral Research	2	2.303	Dentistry, Oral Surgery & Medicine (54/92) (Q3)
Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontology	2	1.221	Not available (discontinued)
Journal of Biomedical Optics	1	3.170	Biochemical Research Methods (39/78) (Q2)

Photochemical and Photobiological Sciences	1	3.982	Biochemistry & Molecular Biology (142/295) (Q2)
Australian Dental Journal	1	2.291	Dentistry, Oral Surgery & Medicine (55/92) (Q3)
International Journal of Artificial Organs	1	1.595	Engineering, Biomedical Sciences (75/89) (Q4)
Nanomedicine: Nanotechnology, Biology, and Medicine	1	6.458	Medicine, Research and Experimental (28/140)
BMC Oral Health	1	2.757	Dentistry, Oral Surgery & Medicine (35/92) (Q2)
Nigerian Journal of Clinical Practice	1	0.968	Medicine, General & Internal (136/167) (Q4)
PloS One	1	3.240	Multidisciplinary Sciences (26/72) (Q2)
Advances in Clinical and Experimental Medicine	1	1.726	Medicine, Research & Experimental (118/140) (Q4)
Journal of Inorganic Biochemistry	1	4.155	Biochemistry & Molecular Biology (129/295) (Q2)
Saudi Journal of Biological Sciences	1	4.219	Biology (24/93) (Q2)
Laser Physics	1	1.366	Optics (78/99) (Q4)
Odontology	1	2.634	Dentistry, Oral Surgery & Medicine (41/92) (Q2)
Journal of Applied Oral Science	1	2.698	Dentistry, Oral Surgery & Medicine (38/92) (Q2)
IN VIVO	1	2.155	Medicine, Research & Experimental (113/140) (Q4)
Infection and Drug Resistance	1	4.003	Infectious Diseases (35/93) (Q2)
Materials	1	3.623	Chemistry, Physical Science (75/168) (Q2)
Journal of Prosthetic Dentistry	1	3.426	Dentistry, Oral Surgery & Medicine (25/92) (Q2)
International Journal of Oral Science	1	6.344	Dentistry, Oral Surgery & Medicine (4/92) (Q1)
International Journal of Nanomedicine	1	6.400	Nanoscience & Nanotechnology (37/106) (Q2)
Quintessence International	1	1.677	Dentistry, Oral Surgery & Medicine (77/92) (Q4)
Polymers	1	4.329	Polymer Science (18/90)
BioMed Research International	1	3.411	Biotechnology & Applied Microbiology (70/159) (Q2)
International Journal of Molecular Sciences	1	5.924	Biochemistry & Molecular Biology (67/295) (Q1)

Journal of Applied Biomaterials	1	1.075	Engineering, Biomedical Sciences (14/41) (Q2)
International Journal of Pharmaceutics	1	3.061	Pharmacology & Pharmacy (68/219) (Q2)

The first scientific publication related to the use of PDT in endodontics was an *in vitro* microbiological study conducted by Seal *et al*. (33) in 2002, and it was published in the *International Endodontic Journal*. Since then, a positive trend on the publication metrics has been seen, with an expressive cumulative growth beginning as of 2012 onward (Figure 2). The citation analysis demonstrated that the study with a higher citation count was published in 2004 by Wilson (34), and it had 420 citations with a mean of 24,7 citations per year. This classical study is one of the first to describe the general applications of PDT in the treatment of oral infections. Table 4 is a ranking with the top 10 cited studies, and they originated from 4 countries, namely, Brazil (n = 4), the United States of America (n = 3), the United Kingdom (n = 2), and Turkey (n = 1), with Aguinaldo Silva Garcez being the author with the most studies published on this ranking (n = 3).

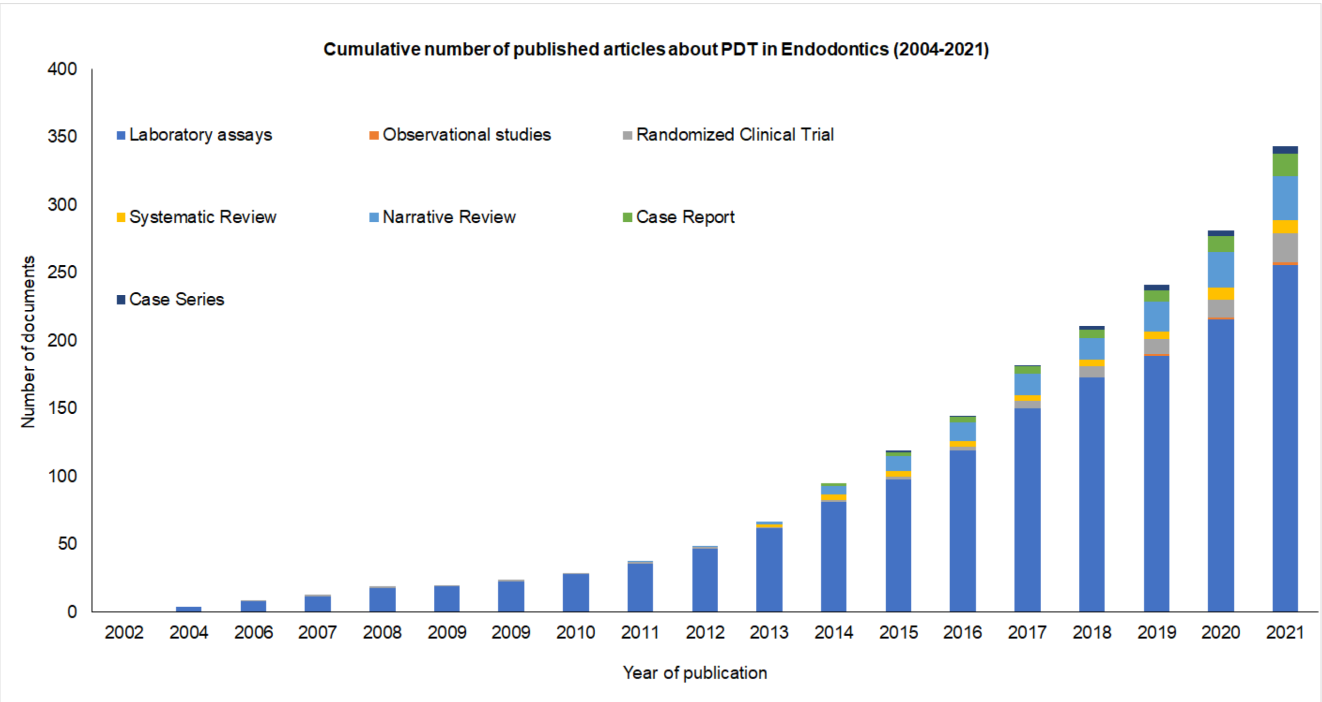

Figure 2. Cumulative number of published articles on PDT in endodontics in the period of 2004-2021.

Table 4. Top 10 articles regarding total citations and citations per year.

Rank	Article	Author's country	Citations	Citations per year
1	Wilson M. Lethal photosensitisation of oral bacteria and its potential application in the photodynamic therapy of oral infections. Photochem Photobiol Sci. 2004 May;3(5):412–8.	UK	420	24,70
2	Soukos NS, Chen PSY, Morris JT, Ruggiero K, Abernethy AD, Som S, et al. Photodynamic Therapy for Endodontic Disinfection. J Endod. 2006;32(10):979–84.	USA	388	25,86
3	Garcez AS, Ribeiro MS, Tegos GP, Nunez SC, Jorge AOC, Hamblin MR. Antimicrobial photodynamic therapy combined with conventional endodontic treatment to eliminate root canal biofilm infection. Lasers Surg Med. 2007;39(1):59–66.	Brazil	337	24,07
4	Garcez AS, Nunez SC, Hamblin MR, Ribeiro MS. Antimicrobial Effects of Photodynamic Therapy on Patients with Necrotic Pulps and Periapical Lesion. J Endod. 2008 Feb;34(2):138–42.	Brazil	336	25,84
5	Fimple JL, Fontana CR, Foschi F, Ruggiero K, Song X, Pagonis TC, et al. Photodynamic Treatment of Endodontic Polymicrobial Infection In Vitro. J Endod. 2008;34(6):728–34.	USA	311	23,92
6	Gursoy H, Ozcakir-Tomruk C, Tanalp J, Yılmaz S. Photodynamic therapy in dentistry: A literature review. Clin Oral Investig. 2013 May;17(4):1113–25.	Turkey	289	36,15
7	Pagonis TC, Chen J, Fontana CR, Devalapally H, Ruggiero K, Song X, et al. Nanoparticle-based Endodontic Antimicrobial Photodynamic Therapy. J Endod. 2010 Feb;36(2):322–8.	USA	251	22,81
8	Garcez AS, Nunez SC, Hamblin MR, Suzuki H, Ribeiro MS. Photodynamic therapy associated with conventional endodontic treatment in patients with antibiotic-resistant microflora: A preliminary report. J Endod. 2010 Sep;36(9):1463–6.	Brazil	244	22,18
9	Bonsor SJ, Nichol R, Reid TMS, Pearson GJ. Microbiological evaluation of photo-activated disinfection in endodontics (An in vivo study). Br Dent J. 2006 Mar;200(6):337–41.	UK	241	16,06
10	Souza LC, Brito PRR, Machado de Oliveira JC, Alves FRF, Moreira EJL, Sampaio-Filho HR, et al. Photodynamic Therapy with Two Different Photosensitizers as a Supplement to Instrumentation/Irrigation Procedures in Promoting Intracanal Reduction of Enterococcus faecalis. J Endod. 2010 Feb;36(2):292–6.	Brazil	225	20,45

Regarding demographic data, Brazil has the highest number of publications globally (n = 104), followed by Iran (n = 60), Saudi Arabia (n = 19), India (n = 19), and Germany (n = 13). A worldwide map chart of the countries involved in researching PDT applied to endodontics is shown in Figure 3. The institution that led the scientific knowledge growth on the theme is the Tehran University of Medical Sciences (n = 29), followed by São Paulo State University (n = 20), Shahid Beheshti University of Medical Sciences (n = 13), and the University of Passo Fundo (n = 10). Figure 4 is a graphical top 10 ranking of the most productive institutions on PDT in endodontics.

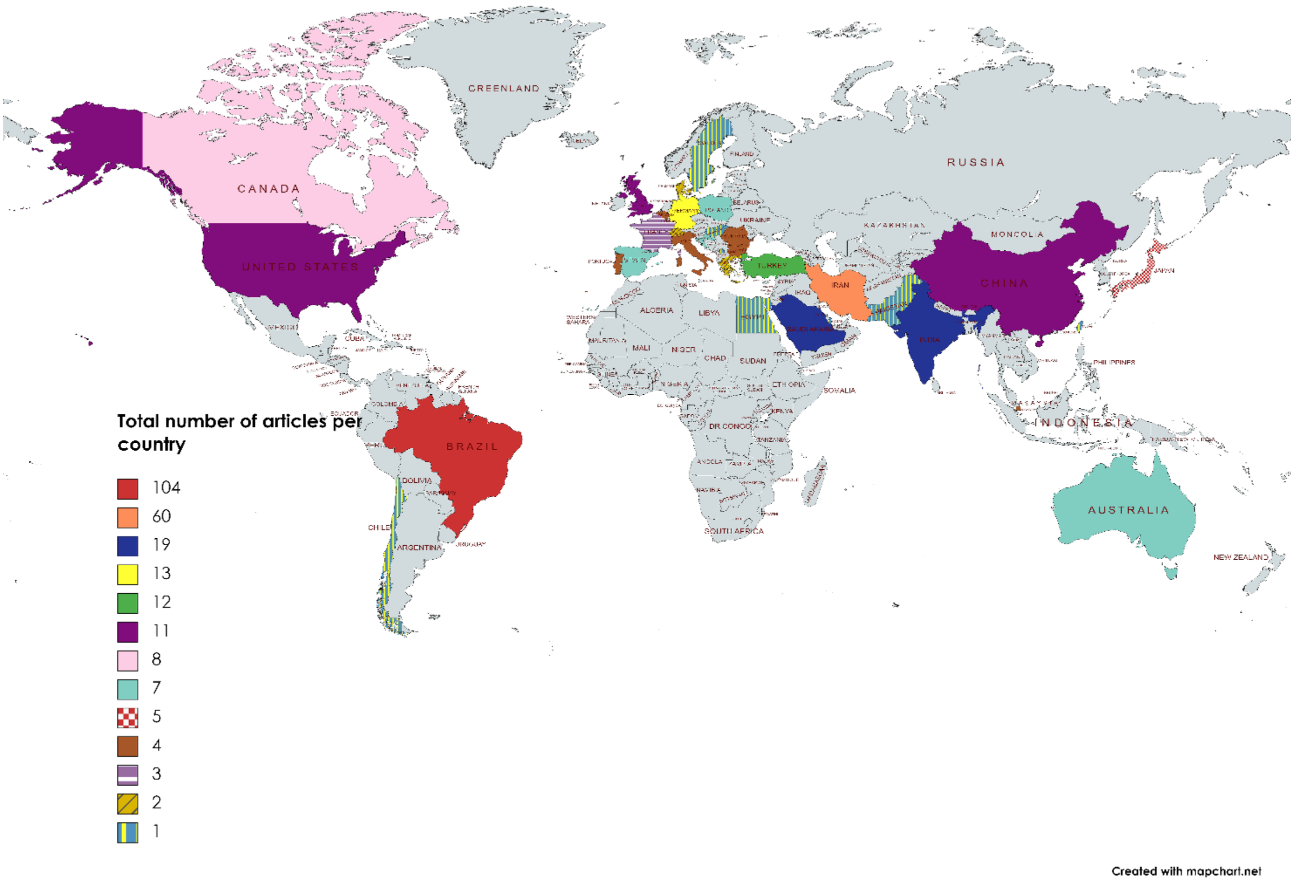

Figure 3. Geographic distribution for the countries undertaken PDT studies in endodontics

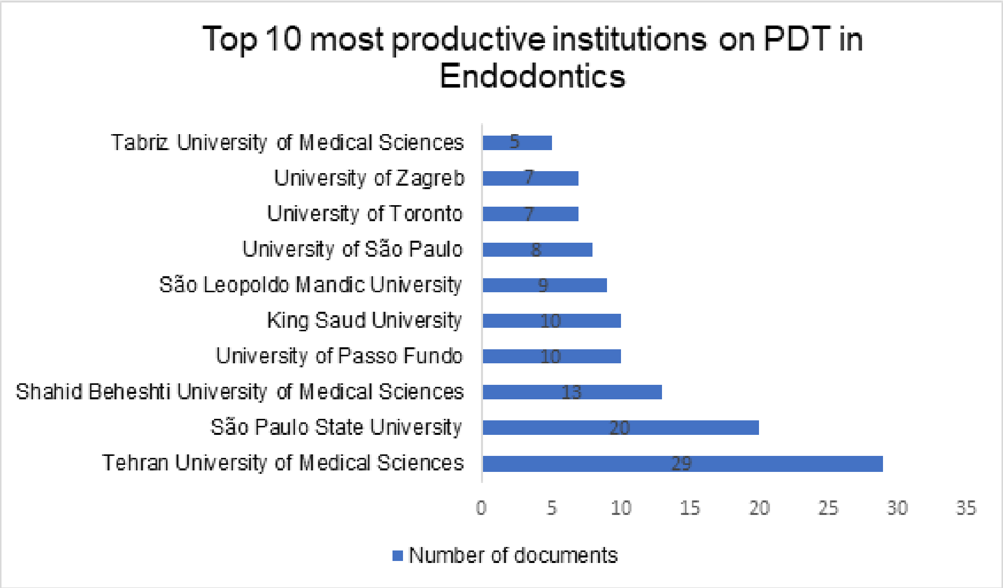

Figure 4. Top 10 most productive institutions on PDT in endodontic research.

A total of 1317 researchers appeared as authors or coauthors in the included studies. Table 5 is a top 5 ranking of researchers that collaborated with the highest number of articles on the theme. It is also important to acknowledge that Mayram Pourhajibagher is the researcher that had the most publications as first author (n = 16), followed by Aguinaldo Silva Garcez (n = 10) and Matheus Albino Souza (n = 8). In the coauthorship network map analysis (Figure 5), it was observed that Mayram Pourhajibagher was also the author with the highest number of links (n = 54), followed by Abbas Bahador (n = 52), Nasim Chiniforush (n = 42), Matheus Albino Souza (n = 30), Luciano Tavares Angelo Cintra and Gustavo Sivieri-Araujo (n = 29 each).

Table 5. Top 5 ranking of researchers on PDT in Endodontics.

Rank	Author	Institution	Country	Total articles	As the first author
1	Pourhajibagher M	Tehran University of Medical Sciences	Iran	26	16
	Bahador A	Tehran University of Medical Sciences	Iran	26	0
2	Chiniforush N	Tehran University of Medical Sciences	Iran	21	3
3	Anil K	University of Toronto	Canada	13	0
4	Asnaashari M	Shahid Beheshti University of Medical Sciences	Iran	11	7
5	Garcez AS	São Leopoldo Mandic University	Brazil	10	10
	Souza MA	University of Passo Fundo	Brazil	10	8
	Sivieri-Araujo G	São Paulo State University	Brazil	10	1
	Cintra LTA	São Paulo State University	Brazil	10	0
	Hamblin MR	University of Johannesburg	South Africa	10	0

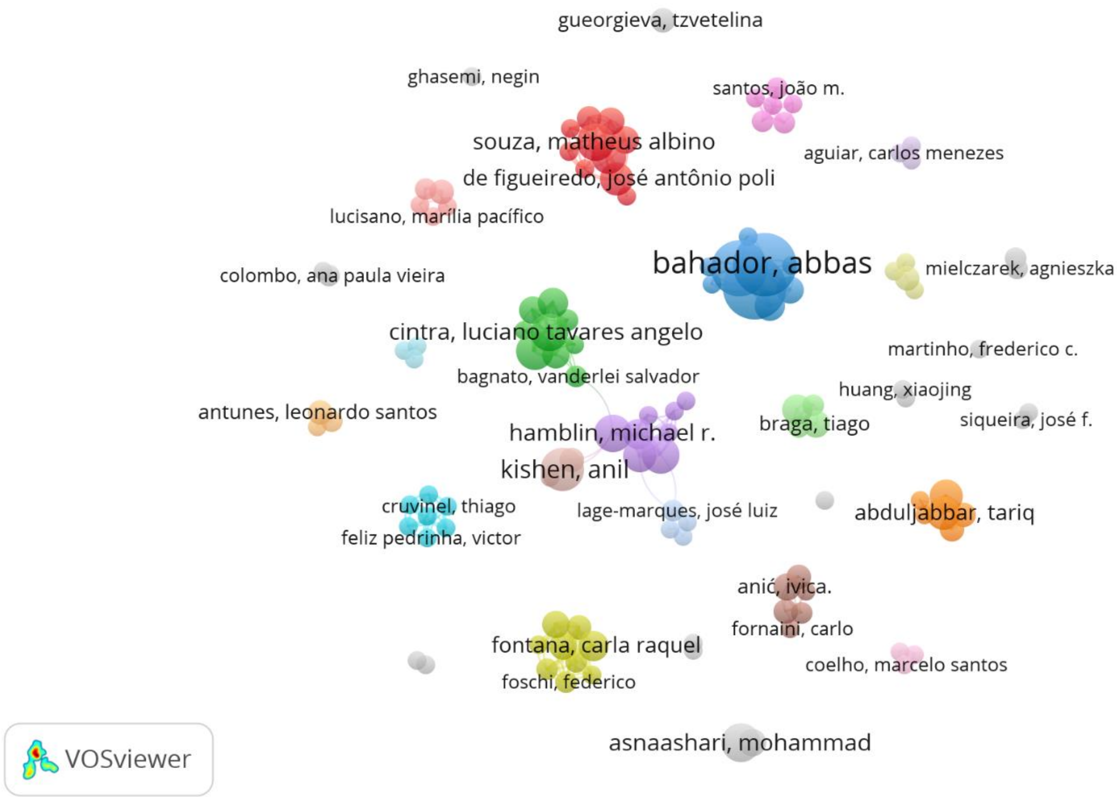

Figure 5. Co-authorship network map analysis.

The keyword co-occurrence analysis of the total included studies resulted in 850 keywords, a minimum of at least 10 occurrences was applied in this analysis, and 37 keywords met the threshold. The keyword co-occurrence network map (Figure 6) shows the existing links between them, and the central keywords are those with more occurrences and higher total link strength. The term “photodynamic therapy” appeared 161 times and had 313 total links, followed by “Enterococcus faecalis” with 95 occurrences and 282 links and “endodontics” with 53 occurrences and 132 links.

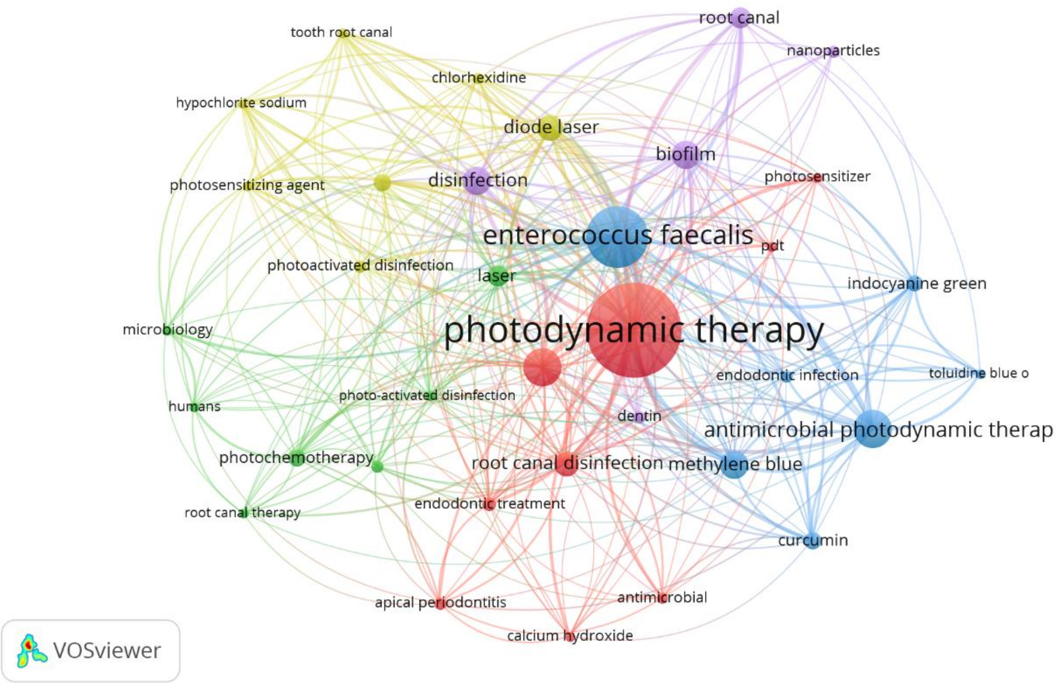

Figure 6. Density map of the most commonly used keywords based on co-occurrence analysis

4 *Discussion*

This bibliometric analysis presented a systematic overview of photodynamic therapy in endodontic research. In the last decade, there has been a significant worldwide interest growth in researching this topic. The steady scientific progress throughout time shows that PDT has a promising clinical approach that should be better investigated. Although the bulk of the available evidence was gathered in a laboratory environment (74.5% of the included studies), it is in the natural order of sound scientific knowledge construction to first exhaust fundamental laboratory assays and then slowly and gradually translate this knowledge to clinical applications through *in vivo* studies and clinical trials aiming to improve patient-care clinical protocols (35).

Even though the available laboratory studies were almost unanimous regarding the numerous benefits that PDT has on root canal disinfection, the limited clinical evidence showed conflicting datasets when adopting this approach as a supplementary method after conventional root canal preparation. The highest LoE study showed that PDT has an *in vivo* optimizing effect on intracanal bacterial load reduction (24); however, there are a few clinical trials that did not find any difference in the treatment outcome (36,37).

Most of the included clinical trials evaluated microbiological samples before and after the PDT procedure. Although endodontic infection is composed of a polymicrobial community, *Enterococcus faecalis* is the most common and prevalent pathogen in endodontic failures due to its resistance to conventional root canal preparation (38). Thus, most PDT studies in endodontic research focus on this bacterial species. Another clinical trial evaluated the *Enterococcus faecalis* reduction after single-visit root canal treatment associated with PDT compared to conventional two-visit treatments using calcium hydroxide intracanal dressing. The authors found that these two approaches were effective in root canal disinfection; however, in the single-visit/PDT group, the microbiological load was significantly lower (39).

Moreover, postoperative pain is another outcome that has been investigated due to the photobiomodulation effect caused by the low-level diode laser activation. However, there is no clear consensus, with a few studies arguing that PDT did not have advantages in controlling postoperative pain (40–43), while other trials found significant differences in pain modulation after PDT, especially in the first 8 to 72 hours (10,11,44,45). Also, no adverse side effects related to PDT in endodontics have been reported to date.

The main clinical outcome of interest in endodontics is periapical repair and tooth survival (46,47). In this context, PDT in endodontics has much to explore since there are only three randomized clinical trials evaluating periapical repair. One of them (37) performed a radiographic evaluation at 60 days posttreatment, showing no difference when compared to the control group; the other trial (12) also evaluated this outcome with a radiographic follow-up six months posttreatment, presenting a better healing score than the control group. Although the randomized clinical trial with the longest clinical and radiographic follow-up period (48) observed a statistically significant difference in the periapical index score between the PDT group and the control group at 18 months follow-up, special considerations have to be made regarding the methodological quality of this finding since in this study a low sample was used, and no sample size calculation was performed. For an intervention effect to be properly measured, the sample needs to be large enough to detect true differences (49), especially when it is trying to provide paradigm-shift results when compared to a very well-established outcome in the literature (e.g., the success rate in conventional root canal treatment). Moreover, it is feasible to say that the short-frame timeline presented in the other trials underestimates the dynamic rate of the periapical healing process, and long-term observation periods are crucial to determine posttreatment periapical health (50). From that standpoint, a recent retrospective study based on the analysis of clinical records (51) retrieved data regarding 214 teeth that underwent root canal treatment with or without supplementary PDT, and the findings of this study showed that even though PDT resulted in a shorter mean healing period for both primary infection and retreatments, the difference was not significant.

All the included clinical trials reported using phenothiazine salts, such as methylene blue (n = 18) and toluidine blue (n = 3) as photosensitizer agents. These agents have been extensively investigated regarding their ability to produce singlet oxygen, and they also present low cytotoxicity, chemical stability, and are approved for human use (52,53). Another significant issue related to PDT in endodontics is the photoactivation parameters and the currently available photosensitizer agents. A recent scoping review discussed that conventional photosensitizer agents have several setbacks regarding clinical performance, such as poor water solubility, uncontrollable drug-delivery systems, and poor microbial target selectivity (32). Additionally, this study highlighted that these agents could be engineered and encapsulated in nanostructured carriers to increase the photosensitizer penetrability in tubular dentin and allow a controlled release of this substance, thus possibly increasing its clinical applicability. Nevertheless, each photosensitizer agent requires a specific photoactivation protocol based on its wavelength absorption and energy fluency sensitivity. PDT is particularly dependent on optimal dosimetric parameters to predict its effectiveness in producing reactive oxygen species (54,55). Hence, different photoactivation protocols have been proposed to optimize these agents (56); however, no *in vivo* clinical evidence has determined the ideal parameters for each photosensitizer agent, and so far, there are highly variable parameters protocols in existing clinical trials (Table 2), which could be underestimating the antimicrobial effect of PDT on the microbiome of the root canal system of infected teeth.

Based on the number of articles published, the *Photodiagnosis and Photodynamic Therapy* journal published 34,5% of the included studies. It is also important to acknowledge that this journal has an impact factor of 3.631, which is higher than the mean impact factors of the journals included in Table 3 (mean IF = 3.275). The impact factor metric has been used to rank journals and, by extension, the authors that publish in these journals, so based on this assumption, high-quality studies can be expected in journals with higher impact factors due to this competitive selectivity (57).

Although most bibliometric studies retrieved data regarding the corresponding author of each study, we opted to classify these data through the first author since the authorship order usually signals the researcher's relative contribution to the work, and thus fair accreditation should be acknowledged to them (58,59). Furthermore, Mayram Pourhajibagher from the Tehran University of Medical Sciences is the researcher who contributed the most to this field, and thereby, it is highly expected that her research center is on the edge of world-class expertise in PDT in endodontic research. Additionally, special acknowledgments should be granted to Aguinaldo Silva Garcez for being the author with the most highly cited published studies.

Publication trends show that this field has rapidly developed since 2012, and a positive trend was observed in the last few years. However, this knowledge development has been concentrated mainly in Brazil and Iran, and therefore, other research centers throughout the world should be encouraged to further develop this line of research. PDT has numerous aspects that could be further explored in future studies, such as developing new photosensitizer agents with better drug delivery systems and optimizing the rate of singlet oxygen production. Additionally, light activation parameters such as the light source, light fluency, output power, wavelength, and irradiation time need to be better evaluated since there is no clear consensus regarding the most recommended activation protocol. Last, high-quality randomized clinical trials should be conducted to investigate the effects of PDT on periapical healing and tooth survival with more extended periods of follow-up.

5 *Conclusions*

This bibliometric analysis mapped and discussed the scientific progress and publication metrics in PDT in endodontic research. This study can help clinicians and researchers familiarize themselves with impactful research in the field, journals of publication, and recurring authors. Additionally, a critical perspective was highlighted regarding the future steps necessary to develop this line of research, which should focus on discovering new photosensitizer agents, standardizing photoactivation protocols, and performing more clinical trials with longer observation periods.

Acknowledgments

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References

1. Gursoy H, Ozcakir-Tomruk C, Tanalp J, Yılmaz S. Photodynamic therapy in dentistry: A literature review. Clin Oral Investig. 2013;17(4):1113–25.
2. Dougherty TJ, Gomer CJ, Henderson BW, Jori G, Kessel D, Korbelik M, et al. Photodynamic therapy. J Natl Cancer Inst. 1998;90(12):889–905.
3. Dougherty TJ. Photodynamic therapy an update on clinical applications. J Natl Cancer Inst. 2002;20(1):3–7.
4. Soukos NS, Chen PSY, Morris JT, Ruggiero K, Abernethy AD, Som S, et al. Photodynamic Therapy for Endodontic Disinfection. J Endod. 2006;32(10):979–84.
5. Vendramini Y, Salles A, Portella FF, Brew MC, Steier L, de Figueiredo JAP, et al. Antimicrobial effect of photodynamic therapy on intracanal biofilm: A systematic review of in vitro studies. Photodiagnosis Photodyn Ther. 2020;32.
6. Costa LM, Matos FDS, Correia AMYDO, Carvalho NC, Faria-E-Silva AL, Paranhos LR, et al. Tooth color change caused by photosensitizers after photodynamic therapy: An in vitro study. J Photochem Photobiol B Biol. 2016;160:225–8.
7. Figueiredo RA, Anami LC, Mello I, Carvalho EDS, Habitante SM, Raldi DP. Tooth discoloration induced by endodontic phenothiazine dyes in photodynamic therapy. Photomed Laser Surg. 2014;32(8):458–62.
8. Hashem M, El-Hejazi AA, Niaz MO, Alsadon O, Alolayani BM, Fouad H. Bond strength of root canal filling with radicular dentin previously treated with either photobiomodulation or photodynamic therapy: Effect of disinfection protocols. Photodiagnosis Photodyn Ther. 2020;30.
9. Souza MA, Bonacina LV, Ricci R, Padilha Rauber MG, Zuchi N, Hoffmann IP, et al. Influence of final irrigation protocols and type of resin cement on bond strength of glass fiber posts in root dentin previously treated with photodynamic therapy. Photodiagnosis Photodyn Ther. 2019;26:224–8.

10. Alves-Silva EG, Arruda-Vasconcelos R, Louzada LM, de-Jesus-Soares A, Ferraz CCR, de Almeida JFA, et al. The effect of photodynamic therapy on postoperative pain in teeth with primary endodontic infection. Photodiagnosis Photodyn Ther. 2021;102700.

11. Coelho MS, Vilas-Boas L, Tawil PZ. The effects of photodynamic therapy on postoperative pain in teeth with necrotic pulps. Photodiagnosis Photodyn Ther. 2019;27:396–401.

12. de Miranda RG, Colombo APV. Clinical and microbiological effectiveness of photodynamic therapy on primary endodontic infections: a 6-month randomized clinical trial. Clin Oral Investig. 2018;22(4):1751–61.

13. Choudhri AF, Siddiqui A, Khan NR, Cohen HL. Understanding bibliometric parameters and analysis. Radiographics. 2015;35(3):736–46.

14. Shamszadeh S, Asgary S, Nosrat A. Regenerative Endodontics: A Scientometric and Bibliometric Analysis. J Endod. 2019;45(3):272–80.

15. Ahmad P, Vincent Abbott P, Khursheed Alam M, Ahmed Asif J. A bibliometric analysis of the top 50 most cited articles published in the Dental Traumatology. Dent Traumatol. 2020;36(2):89–99.

16. Kodonas K, Fardi A, Gogos C, Economides N. Scientometric analysis of vital pulp therapy studies. Int Endod J. 2021;54(2):220–30.

17. Aksoy U, Küçük M, Versiani MA, Orhan K. Publication trends in micro-CT endodontic research: a bibliometric analysis over a 25-year period. Int Endod J. 2021;54(3):343–53.

18. Nosrat A, Dianat O, Verma P, Nixdorf DR, Law AS. Postoperative Pain: An Analysis on Evolution of Research in Half-Century. J Endod. 2021;47(3):358–65.

19. Silva EJNL, Pinto KP, Ajuz NC, Sassone LM. Ten years of minimally invasive access cavities in Endodontics: a bibliometric analysis of the 25 most-cited studies. Restor Dent Endod. 2021;46(3).

20. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: An updated guideline for reporting systematic

reviews. BMJ. 2021;372:n71–n71.

21. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan-a web and mobile app for systematic reviews. Syst Rev. 2016;5(1):1–10.

22. Haapasalo M. Level of evidence in endodontics: what does it mean? Endod Top. 2016;34(1):30–41.

23. van Eck NJ, Waltman L, Jan van Eck N, Waltman L. Software survey: VOSviewer, a computer program for bibliometric mapping. Scientometrics. 2010;84(2):523–38.

24. Pourhajibagher M, bahador A. Adjunctive antimicrobial photodynamic therapy to conventional chemo-mechanical debridement of infected root canal systems: A systematic review and meta-analysis. Photodiagnosis Photodyn Ther. 2019;26:19–26.

25. Fransson H, Larsson KM, Wolf E. Efficacy of lasers as an adjunct to chemo-mechanical disinfection of infected root canals: A systematic review. Int Endod J. 2013;46(4):296–307.

26. Siddiqui SH, Awan KH, Javed F. Bactericidal efficacy of photodynamic therapy against Enterococcus faecalis in infected root canals: A systematic literature review. Photodiagnosis Photodyn Ther. 2013;10(4):632–43.

27. Arneiro RAS, Nakano RD, Antunes LAA, Ferreira GB, Fontes KBFC, Antunes LS. Efficacy of antimicrobial photodynamic therapy for root canals infected with Enterococcus faecalis. J Oral Sci. 2014;56(4):277–85.

28. Chrepa V, Kotsakis GA, Pagonis TC, Hargreaves KM. The Effect of Photodynamic Therapy in Root Canal Disinfection: A Systematic Review. J Endod. 2014;40(7):891–8.

29. Abdelaziz Ali IA, Neelakantan P. Light activated disinfection in root canal treatment-a focused review. Dent J. 2018;6(3).

30. Anagnostaki E, Mylona V, Parker S, Lynch E, Grootveld M. Systematic review on the role of lasers in endodontic therapy: Valuable adjunct treatment? Dent J. 2020;8(3).

31. Bordea IR, Hanna R, Chiniforush N, Grădinaru E, Câmpian RS, Sîrbu A, et al. Evaluation of the outcome of various laser therapy applications in root canal disinfection: A systematic review. Photodiagnosis Photodyn Ther. 2020;29.

32. Betancourt P, Brocal N, Sans-Serramitjana E, Zaror C. Functionalized nanoparticles activated by photodynamic therapy as an antimicrobial strategy in endodontics: A scoping review. Antibiotics. 2021;10(9).

33. Seal GJ, Ng YL, Spratt D, Bhatti M, Gulabivala K. An in vitro comparison of the bactericidal efficacy of lethal photosensitization or sodium hyphochlorite irrigation on Streptococcus intermedius biofilms in root canals. Int Endod J. 2002;35(3):268–74.

34. Wilson M. Lethal photosensitisation of oral bacteria and its potential application in the photodynamic therapy of oral infections. Photochem Photobiol Sci. 2004;3(5):412–8.

35. Drolet BC, Lorenzi NM. Translational research: Understanding the continuum from bench to bedside. Transl Res. 2011;157(1):1–5.

36. Okamoto CB, Bussadori SK, Prates RA, da Mota ACC, Tempestini Horliana ACR, Fernandes KPS, et al. Photodynamic therapy for endodontic treatment of primary teeth: A randomized controlled clinical trial. Photodiagnosis Photodyn Ther. 2020;30:101732.

37. Moreira S de A, Nunes JB, Colombo FA, Fonseca N da SM, Viola NV. Radiographic and antimicrobial evaluation of enterococcus Faecalis and Actinomyces Israelii micro-organisms after photodynamic therapy (aPDT). Photodiagnosis Photodyn Ther. 2021;35.

38. Barbosa-Ribeiro M, Arruda-Vasconcelos R, Louzada LM, Lima AR, Marciano MA, Almeida JFA, et al. Microbiological investigation in teeth with persistent/secondary endodontic infection in different stages of root canal retreatment. Eur Endod J. 2020;5(3):219–25.

39. Asnaashari M, Ashraf H, Rahmati A, Amini N. A comparison between effect of photodynamic therapy by LED and calcium hydroxide therapy for root canal disinfection against Enterococcus faecalis: A randomized controlled trial. Photodiagnosis Photodyn Ther. 2017;17:226–32.

40. Barciela B, Da Silva Limoeiro AG, Bueno CE, Fernandes SL, Mandarini DR, Boer NC, et al. In vivo evaluation of painful symptomatology after endodontic treatment with or without the use of photodynamic therapy. J Conserv Dent. 2019;22(4):332–5.

41. Yoshinari FMS, Pereira KFS, Beraldo DZ, da Silva JCL, Zafalon EJ, da Silva PG. Influence of photodynamic therapy in the control of postoperative pain in endodontic treatment: A cross-sectional randomized clinical trial. Pesqui Bras Odontopediatria Clin Integr. 2019;19(1).

42. Guimarães L da S, da Silva EAB, Hespanhol FG, Fontes KBF da C, Antunes LAA, Antunes LS. Effect of photobiomodulation on post-operative symptoms in teeth with asymptomatic apical periodontitis treated with foraminal enlargement: A randomized clinical trial. Int Endod J. 2021;54(10):1708–19.

43. Souza MA, Bonacina LV, Trento A, Bonfante F do C, Porsch HF, Ricci R, et al. Influence of the apical limit of instrumentation and photodynamic therapy on the postoperative pain of lower molars with asymptomatic apical periodontitis. Photodiagnosis Photodyn Ther. 2021;36:102489.

44. Vilas-Boas L, Cozer V, Tawil PZ, Coelho MS. Effect of Photodynamic Therapy on Postoperative Pain in Posterior Teeth with Symptomatic Apical Periodontitis. Photodiagnosis Photodyn Ther. 2021;35:102348.

45. Dedania MS, Shah NC, Shah R, Bhadra D, Bajpai N, Pisal N, et al. Effect of Passive Ultrasonic Irrigation and Laser Disinfection in Single Visit Root Canal Therapy on Postoperative Pain. J Clin Diagnostic Res. 2021;15(11):ZC33–6.

46. Wu MK, Shemesh H, Wesselink PR. Limitations of previously published systematic reviews evaluating the outcome of endodontic treatment. Int Endod J. 2009;42(8):656–66.

47. Ng YL, Mann V, Gulabivala K. Tooth survival following non-surgical root canal treatment: A systematic review of the literature. Int Endod J. 2010;43(3):171–89.

48. Johns DA, Shivashankar VY, Krishnamma S, Johns M. Use of photoactivated disinfection and platelet-rich fibrin in regenerative Endodontics. Vol. 17, Journal of Conservative Dentistry. 2014. p. 487–90.

49. Lucena C, Souza EM, Voinea GC, Pulgar R, Valderrama MJ, De-Deus G. A quality assessment of randomized controlled trial reports in endodontics. Int Endod J. 2017;50(3):237–50.

50. Azarpazhooh A, Cardoso E, Sgro A, Elbarbary M, Laghapour Lighvan N, Badewy R, et al. A Scoping Review of 4 Decades of Outcomes in Nonsurgical Root Canal Treatment, Nonsurgical Retreatment, and Apexification Studies—Part 1: Process and General Results. J Endod. 2022;48(1):15–28.

51. Conejero MJ, Almenar A, Forner L, Sanz JL, Llena C. Retrospective clinical evaluation of root canal treatment with or without photodynamic therapy for necrotic teeth and teeth subjected to retreatment. J Oral Sci. 2021;63(2):163–6.

52. Wainwright M, Crossley KB. Methylene Blue - A therapeutic dye for all seasons? J Chemother. 2002;14(5):431–43.

53. Grizante Barião PH, Tonani L, Brancini GTP, Nascimento E, Braga GÚL, Wainwright M, et al. In vitro and in vivo photodynamic efficacies of novel and conventional phenothiazinium photosensitizers against multidrug-resistant Candida auris. Photochem Photobiol Sci. 2022;

54. Le Clainche T, Carigga Gutierrez NM, Pujol-Solé N, Coll JL, Broekgaarden M. Optimizing the Pharmacological and Optical Dosimetry for Photodynamic Therapy with Methylene Blue and Nanoliposomal Benzoporphyrin on Pancreatic Cancer Spheroids. Onco. 2022;2(1):19–33.

55. Pogue BW, Elliott JT, Kanick SC, Davis SC, Samkoe KS, Maytin E V., et al. Revisiting photodynamic therapy dosimetry: Reductionist & surrogate approaches to facilitate clinical success. Phys Med Biol. 2016;61(7):R57–89.

56. Yamamoto LY, Loureiro C, Cintra LTA, Leonardo R de T, Banci HA, Ribeiro APF, et al. Antibiofilm activity of laser ablation with indocyanine green activated by different power laser parameters compared with photodynamic therapy on root canals infected with Enterococcus faecalis. Photodiagnosis Photodyn Ther. 2021;35.

57. McKiernan EC, Schimanski LA, Nieves CM, Matthias L, Niles MT, Alperin JP. Use of the journal impact factor in academic review, promotion, and tenure

evaluations. Elife. 2019;8.

58. Helgesson G. Authorship order and effects of changing bibliometrics practices. Res Ethics. 2020;16(1–2):1–7.

59. International Committee of Medical Journal Editors. ICMJE recommendations [Internet]. Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals. 2015.

Supplementary table 1 – Search strategies

	Search Terms
Pubmed	
#3	Search #1 AND #2
#2	Seach (Photochemotherapies) OR (Photodynamic Therapy) OR (Therapy, Photodynamic) OR (Photodynamic Therapies) OR (Therapies, Photodynamic) OR (Antimicrobial Photodynamic Therapy) OR (Photodynamic Inactivation) OR (Photosensitization) OR (Photosensitizer) OR (PDT) OR (Photobiomodulation)
#1	Search (Tooth, Nonvital) OR (Tooth, nonvital) OR (Nonvital Tooth) OR (Tooth, Devitalized) OR (Devitalized Tooth) OR (Tooth, Pulpless) OR (Pulpless Tooth) OR (Teeth, Pulpless) OR (Pulpless Teeth) OR (Teeth, Devitalized) OR (Devitalized Teeth) OR (Teeth, Nonvital) OR (Nonvital Teeth) OR (Teeth, Endodontically-Treated) OR (Endodontically-Treated Teeth) OR (Teeth, Endodontically Treated) OR (Tooth, Endodontically-Treated) OR (Endodontically-Treated Tooth) OR (Tooth, Endodontically Treated) OR (Root canal therapy) OR (Canal Therapies, Root) OR (Canal Therapy, Root) OR (Root Canal Therapies) OR (Therapies, Root Canal) OR (Therapy, Root Canal) OR (Endodontics) OR (Endodontics) OR (Endodontology)
Embase	
#3	Search #1 AND #2
#2	Seach (Photochemotherapies) OR (Photodynamic Therapy) OR (Therapy, Photodynamic) OR (Photodynamic Therapies) OR (Therapies, Photodynamic) OR (Antimicrobial Photodynamic Therapy) OR (Photodynamic Inactivation) OR (Photosensitization) OR (Photosensitizer) OR (PDT) OR (Photobiomodulation)
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Web of Science	
#3	Search #1 AND #2

#2	TS=((Photochemotherapies) OR (Photodynamic Therapy) OR (Therapy, Photodynamic) OR (Photodynamic Therapies) OR (Therapies, Photodynamic) OR (Antimicrobial Photodynamic Therapy) OR (Photodynamic Inactivation) OR (Photosensitization) OR (Photosensitizer) OR (PDT) OR (Photobiomodulation))
#1	TS=((Tooth, Nonvital) OR (Tooth, nonvital) OR (Nonvital Tooth) OR (Tooth, Devitalized) OR (Devitalized Tooth) OR (Tooth, Pulpless) OR (Pulpless Tooth) OR (Teeth, Pulpless) OR (Pulpless Teeth) OR (Teeth, Devitalized) OR (Devitalized Teeth) OR (Teeth, Nonvital) OR (Nonvital Teeth) OR (Teeth, Endodontically-Treated) OR (Endodontically-Treated Teeth) OR (Teeth, Endodontically Treated) OR (Tooth, Endodontically-Treated) OR (Endodontically-Treated Tooth) OR (Tooth, Endodontically Treated) OR (Root Canal Therapy) OR (Canal Therapies, Root) OR (Canal Therapy, Root) OR (Root Canal Therapies) OR (Therapies, Root Canal) OR (Therapy, Root Canal) OR (Endodontics) OR (Endodontics) OR (Endodontology))
SciVerse Scopus	
#3	Search #1 AND #2
#2	TITLE-ABS-KEY ((“Photochemotherapies”) OR (“Photodynamic Therapy”) OR (“Therapy, Photodynamic”) OR (“Photodynamic Therapies”) OR (“Therapies, Photodynamic”) OR (“Antimicrobial Photodynamic Therapy”) OR (“Photodynamic Inactivation”) OR (“Photosensitization”) OR (“Photosensitizer”) OR (“PDT”) OR (“Photobiomodulation”))
#1	TITLE-ABS-KEY ((“Tooth, Nonvital”) OR (“Tooth, nonvital”) OR (“Nonvital Tooth”) OR (“Tooth, Devitalized”) OR (“Devitalized Tooth”) OR (“Tooth, Pulpless”) OR (“Pulpless Tooth”) OR (“Teeth, Pulpless”) OR (“Pulpless Teeth”) OR (“Teeth, Devitalized”) OR (“Devitalized Teeth”) OR (“Teeth, Nonvital”) OR (“Nonvital Teeth”) OR (“Teeth, Endodontically-Treated”) OR (“Endodontically-Treated Teeth”) OR (“Teeth, Endodontically Treated”) OR (“Tooth, Endodontically-Treated”) OR (“Endodontically-Treated Tooth”) OR (“Tooth, Endodontically Treated”) or (“Root Canal Therapy”) OR (“Canal Therapies, Root”) OR (“Canal Therapy, Root”) OR (“Root Canal Therapies”) OR (“Therapies, Root Canal”) OR (“Therapy, Root Canal”) OR (“Endodontics”) OR (“Endodontics”) OR (“Endodontology”))
The Cochrane Library	
#3	Search #1 AND #2
#2	TITLE-ABS-KEY (Photochemotherapies) OR (Photodynamic Therapy) OR (Therapy, Photodynamic) OR (Photodynamic Therapies) OR (Therapies, Photodynamic) OR (Antimicrobial Photodynamic Therapy) OR (Photodynamic Inactivation) OR (Photosensitization) OR (Photosensitizer) OR (PDT) OR (Photobiomodulation)
#1	TITLE-ABS-KEY (Tooth, Nonvital) OR (Tooth, nonvital) OR (Nonvital Tooth) OR (Tooth, Devitalized) OR (Devitalized Tooth) OR (Tooth, Pulpless) OR (Pulpless Tooth) OR (Teeth, Pulpless) OR (Pulpless Teeth) OR (Teeth, Devitalized) OR (Devitalized Teeth) OR (Teeth, Nonvital) OR (Nonvital Teeth) OR (Teeth, Endodontically-Treated) OR (Endodontically-Treated Teeth) OR (Teeth, Endodontically Treated) OR (Tooth, Endodontically-Treated) OR (Endodontically-Treated Tooth) OR (Tooth, Endodontically Treated) OR (Root canal therapy) OR (Canal Therapies, Root) OR (Canal Therapy, Root) OR (Root Canal Therapies) OR (Therapies, Root Canal) OR (Therapy, Root Canal) OR (Endodontics) OR (Endodontics) OR (Endodontology)

Supplementary table 2. Journals not listed on the 2020 Journal Citation Reports (Clarivate Analytics).

Journal	Articles (n)
Journal of Lasers in Medical Science	10
Dental and medical problems	5
Journal of Conservative Dentistry	5
Journal of Contemporary Dental Practice	4
Journal of IMAB	3
Journal of Clinical & Diagnostic Research	3
Journal of Clinical and Experimental Dentistry	3
International Journal of Dentistry	3
Iranian Endodontic Journal	3
Dentistry Journal	3
European Journal of Dentistry	2
Giornale Italiano di Endodonzia	2
Pesquisa Brasileira em Odontopediatria e Clínica Integrada	2
Romanian Journal of Oral Rehabilitation	2
Mechanisms for Low-Light Therapy III	1
ISRN Dentistry	1
Dental Research Journal	1
Journal of Dental Research, Dental Clinics, Dental Prospects	1
Dental Update	1
Acta Stomatologica Croatica	1
Brazilian Dental Journal	1
Acta Odontologica Latinoamericana	1
Laser Therapy	1
Journal of Investigative and Clinical Dentistry	1
European Endodontic Journal	1
Meandros Medical and Dental Journal	1
Brazilian Dental Science	1
Journal of Functional Biomaterials	1
Indian Journal of Public Health Research and Development	1
F1000 Research	1
Journal of Indian Society of Pedodontics and Preventive Dentistry	1
Balneo Research Journal	1
Journal of Advanced Oral Research	1
Brazilian Journal of Oral Sciences	1
International Journal of Dentistry and Oral Science	1
Journal of Dentistry Shiraz	1
International Journal of Burns and Trauma	1
Reviews and Research in Medical Microbiology	1

2.2 ARTIGO 2

Photodynamic therapy in the root canal treatment of primary teeth: a systematic review of clinical trials

Artigo publicado no periódico *International Journal of Paediatric Dentistry* (Fator de impacto: 3.264; Qualis CAPES: A2)

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Photodynamic therapy in the root canal treatment of primary teeth: a systematic review of clinical trials

Running title: Photodynamic therapy and primary teeth infections

Abstract

Dental caries is the most common oral disease worldwide, and it is estimated to affect 2.3 billion people, with at least 530 million of them being schoolchildren with decayed primary teeth. This condition can rapidly evolve into irreversible pulp inflammation and pulp necrosis and thus requiring endodontic intervention. Photodynamic therapy (PDT) is a supplementary method to conventional pulpectomy and is used to improve the disinfection protocol. Thus, the main objective of this study is to evaluate through a systematic review the efficacy of supplementary PDT on the pulpectomy of primary teeth. This review was registered *a priori* on the PROSPERO database (CRD42022310581). Two independent and blinded reviewers carried out a comprehensive search in five databases: PubMed, Cochrane, Scopus, Embase, and Web of Science. Eligible studies were randomized and nonrandomized clinical trials that evaluated *in vivo* microbiological load or clinical outcomes after using supplementary PDT in infected primary teeth. After the selection process, four studies met the inclusion criteria and were included in this study. Data regarding the sample characteristics and PDT protocols were retrieved. All included trials used phenothiazinium salts as photosensitizer agents. Only one study observed a significant difference in the *in vivo* microbiological load reduction outcome when performing PDT on primary teeth. The remaining studies all discussed the possible benefits of this intervention; however, none observed a significant difference in this outcome. In this systematic review, moderate to low certainty of the available evidence was observed, and thus, no significant conclusions can be drawn from the findings.

Keywords: Photodynamic Therapy, Endodontics, Root Canal Preparation, Primary Teeth, Systematic Review

1 Introduction

Dental caries is the most common oral disease worldwide, and it is estimated to affect 2.3 billion people, with at least 530 million of them being schoolchildren with decayed primary teeth [1]. When this condition is left untreated, it can rapidly evolve into more severe dental conditions, such as irreversible pulp inflammation and pulp necrosis [2]. In primary teeth, the transition from irreversible pulpitis to pulp necrosis is usually faster and symptomless than in the permanent dentition [3]. According to the American Academy of Pediatric Dentistry (AAPD) clinical practice guideline, the gold standard treatment choice in this situation is to perform a pulpectomy procedure [4].

Root canal treatment in children needs special consideration regarding the children's acceptance to receive the treatment [5]. Multiple visits may compromise the children's ability to stay calm and cooperate throughout this lengthy procedure, and thus, single-visit protocols should be preferred to avoid repeated mechanical trauma (e.g., local anesthesia and rubber dam isolation) and chemical trauma [6]. The overall microbiota composition of infected primary teeth is very similar to permanent teeth infections [7] and should be treated in the same perspective to achieve the objective of maintaining the tooth and restoring periradicular health by eliminating intracanal microbiota and their byproducts through cleaning and shaping of the root canal system [8].

Photodynamic therapy (PDT) is a supplementary method that uses a light source to induce the inactivation of microorganisms [9]. This approach involves exciting a nontoxic photosensitizer agent through light activation of a specific wavelength to produce highly reactive oxygen species and induce cell damage to the surrounding bacteria [10]. In endodontics, the optimization of root canal disinfection protocols has always been of significant concern among clinicians and scientists alike, and thus, PDT has been widely investigated in this specialty as a supplementary approach to conventional root canal preparation that could optimize the disinfection process [11].

A recent meta-analysis of randomized clinical trials evaluated the effects of PDT after conventional root canal preparation in the permanent infected dentition [12], and it was observed that every included study found a significant reduction in the intracanal microbial load after the use of PDT, suggesting that this approach may be valid in further controlling the endodontic infection. However, there is no systematic review to date addressing the same issue regarding primary teeth. Hence, the purpose of this systematic review was to critically analyze and answer whether PDT could be a valid supplementary method to reduce the microbial load in primary tooth infections when compared to conventional root canal preparation alone.

2 *Materials and Methods*

2.1. Protocol registration

The present review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA 2020) recommendations [13], and the study protocol was registered *a priori* at the PROSPERO database (CRD42022310581). The guiding question was formulated based on the PICO framework (Population (P), Intervention (I), Comparison (C), and Outcome (O)) and aimed to answer the following question: "Can supplementary PDT (I) reduce the microbial load (O) in primary teeth infections (P) over conventional root canal preparation alone (C)?"

2.2. Eligibility and exclusion criteria

Eligible studies were randomized and nonrandomized clinical trials that complied with our PICO question and investigated the effects of PDT on reducing the microbial load of primary teeth *in vivo* after conventional root canal preparation. The gender and age of the participants enrolled in the trials were not excluding factors as long as primary teeth were the intervention target. There were no restrictions regarding language or date of publication.

Exclusion criteria were case reports and case series, *in vitro* and *ex vivo* studies, animal studies, gray literature, narrative literature reviews, short commentaries, letters to the editor, and congress abstracts.

2.3. Information sources and search strategy

The search strategy was elaborated based on our PICO question and aimed to identify and retrieve studies related to PDT in root canal treatment of primary teeth. Our strategy was based on combined MeSH terms related to the theme, and they were adapted for the other databases, respecting their rules of syntax (Table 1). The initial search was performed on December 31st of 2021 on the following databases: Cochrane, Web of Science, Scopus, EMBASE and PubMed. The duplicate records of the retrieved studies were deleted using the Mendeley software software (Elsevier, Amsterdam, NE). Additionally, to improve the pool of included studies, a manual search was performed in the reference list of the included studies to retrieve any additional publication.

Table 1 – Search strategies

	Search Terms
Pubmed	
#3	Search #1 AND #2
#2	Seach (Photochemotherapies) OR (Photodynamic Therapy) OR (Therapy, Photodynamic) OR (Photodynamic Therapies) OR (Therapies, Photodynamic) OR (Antimicrobial Photodynamic Therapy) OR (Photodynamic Inactivation) OR (Photosensitization) OR (Photosensitizer) OR (PDT) OR (Photobiomodulation)
#1	Search (Tooth, Nonvital) OR (Tooth, nonvital) OR (Nonvital Tooth) OR (Tooth, Devitalized) OR (Devitalized Tooth) OR (Tooth, Pulpless) OR (Pulpless Tooth) OR (Teeth, Pulpless) OR (Pulpless Teeth) OR (Teeth, Devitalized) OR (Devitalized Teeth) OR (Teeth, Nonvital) OR (Nonvital Teeth) OR (Teeth, Endodontically-Treated) OR (Endodontically-Treated Teeth) OR (Teeth, Endodontically Treated) OR (Tooth, Endodontically-Treated) OR (Endodontically-Treated Tooth) OR (Tooth, Endodontically Treated) OR (Root canal therapy) OR (Canal Therapies, Root) OR (Canal Therapy, Root) OR (Root Canal Therapies) OR (Therapies, Root Canal) OR (Therapy, Root Canal) OR (Endodontics) OR (Endodontics) OR (Endodontology)
Embase	
#3	Search #1 AND #2
#2	Seach (Photochemotherapies) OR (Photodynamic Therapy) OR (Therapy, Photodynamic) OR (Photodynamic Therapies) OR (Therapies, Photodynamic) OR (Antimicrobial Photodynamic Therapy) OR (Photodynamic Inactivation) OR (Photosensitization) OR (Photosensitizer) OR (PDT) OR (Photobiomodulation)
#1	Search (Tooth, Nonvital) OR (Tooth, nonvital) OR (Nonvital Tooth) OR (Tooth, Devitalized) OR (Devitalized Tooth) OR (Tooth, Pulpless) OR (Pulpless Tooth) OR (Teeth, Pulpless) OR (Pulpless Teeth) OR (Teeth, Devitalized) OR (Devitalized Teeth) OR (Teeth, Nonvital) OR (Nonvital Teeth)

	OR (Teeth, Endodontically-Treated) OR (Endodontically-Treated Teeth) OR (Teeth, Endodontically Treated) OR (Tooth, Endodontically-Treated) OR (Endodontically-Treated Tooth) OR (Tooth, Endodontically Treated) OR (Root canal therapy) OR (Canal Therapies, Root) OR (Canal Therapy, Root) OR (Root Canal Therapies) OR (Therapies, Root Canal) OR (Therapy, Root Canal) OR (Endodontics) OR (Endodontics) OR (Endodontology)
Web of Science	
#3	Search #1 AND #2
#2	TS=((Photochemotherapies) OR (Photodynamic Therapy) OR (Therapy, Photodynamic) OR (Photodynamic Therapies) OR (Therapies, Photodynamic) OR (Antimicrobial Photodynamic Therapy) OR (Photodynamic Inactivation) OR (Photosensitization) OR (Photosensitizer) OR (PDT) OR (Photobiomodulation))
#1	TS=((Tooth, Nonvital) OR (Tooth, nonvital) OR (Nonvital Tooth) OR (Tooth, Devitalized) OR (Devitalized Tooth) OR (Tooth, Pulpless) OR (Pulpless Tooth) OR (Teeth, Pulpless) OR (Pulpless Teeth) OR (Teeth, Devitalized) OR (Devitalized Teeth) OR (Teeth, Nonvital) OR (Nonvital Teeth) OR (Teeth, Endodontically-Treated) OR (Endodontically-Treated Teeth) OR (Teeth, Endodontically Treated) OR (Tooth, Endodontically-Treated) OR (Endodontically-Treated Tooth) OR (Tooth, Endodontically Treated) OR (Root Canal Therapy) OR (Canal Therapies, Root) OR (Canal Therapy, Root) OR (Root Canal Therapies) OR (Therapies, Root Canal) OR (Therapy, Root Canal) OR (Endodontics) OR (Endodontics) OR (Endodontology))
SciVerse Scopus	
#3	Search #1 AND #2
#2	TITLE-ABS-KEY ((“Photochemotherapies”) OR (“Photodynamic Therapy”) OR (“Therapy, Photodynamic”) OR (“Photodynamic Therapies”) OR (“Therapies, Photodynamic”) OR (“Antimicrobial Photodynamic Therapy”) OR (“Photodynamic Inactivation”) OR (“Photosensitization”) OR (“Photosensitizer”) OR (“PDT”) OR (“Photobiomodulation”))
#1	TITLE-ABS-KEY ((“Tooth, Nonvital”) OR (“Tooth, nonvital”) OR (“Nonvital Tooth”) OR (“Tooth, Devitalized”) OR (“Devitalized Tooth”) OR (“Tooth, Pulpless”) OR (“Pulpless Tooth”) OR (“Teeth, Pulpless”) OR (“Pulpless Teeth”) OR (“Teeth, Devitalized”) OR (“Devitalized Teeth”) OR (“Teeth, Nonvital”) OR (“Nonvital Teeth”) OR (“Teeth, Endodontically-Treated”) OR (“Endodontically-Treated Teeth”) OR (“Teeth, Endodontically Treated”) OR (“Tooth, Endodontically-Treated”) OR (“Endodontically-Treated Tooth”) OR (“Tooth, Endodontically Treated”) or (“Root Canal Therapy”) OR (“Canal Therapies, Root”) OR (“Canal Therapy, Root”) OR (“Root Canal Therapies”) OR (“Therapies, Root Canal”) OR (“Therapy, Root Canal”) OR (“Endodontics”) OR (“Endodontics”) OR (“Endodontology”))
The Cochrane Library	
#3	Search #1 AND #2
#2	TITLE-ABS-KEY (Photochemotherapies) OR (Photodynamic Therapy) OR (Therapy, Photodynamic) OR (Photodynamic Therapies) OR (Therapies, Photodynamic) OR (Antimicrobial Photodynamic Therapy) OR (Photodynamic Inactivation) OR (Photosensitization) OR (Photosensitizer) OR (PDT) OR (Photobiomodulation)
#1	TITLE-ABS-KEY (Tooth, Nonvital) OR (Tooth, nonvital) OR (Nonvital Tooth) OR (Tooth, Devitalized) OR (Devitalized Tooth) OR (Tooth, Pulpless) OR (Pulpless Tooth) OR (Teeth, Pulpless) OR (Pulpless Teeth) OR (Teeth, Devitalized) OR (Devitalized Teeth) OR (Teeth,

Nonvital) OR (Nonvital Teeth) OR (Teeth, Endodontically-Treated) OR (Endodontically-Treated Teeth) OR (Teeth, Endodontically Treated) OR (Tooth, Endodontically-Treated) OR (Endodontically-Treated Tooth) OR (Tooth, Endodontically Treated) OR (Root canal therapy) OR (Canal Therapies, Root) OR (Canal Therapy, Root) OR (Root Canal Therapies) OR (Therapies, Root Canal) OR (Therapy, Root Canal) OR (Endodontics) OR (Endodontics) OR (Endodontology)

2.4. Selection process

The selection process was performed using the Rayyan web application (Qatar Computing Research Institute, Doha, QA) [14]. An initial calibration exercise was proposed for two reviewers (LPA and LBG) to discuss the eligibility criteria and apply them to a sample of 10% of the retrieved studies to determine the interexaminer agreement through Cohen's kappa coefficient. After a proper coefficient was achieved ($\kappa = 0.86$), the same two reviewers were blinded and performed a systematic screening of the studies by title and abstract. The eligibility criteria were applied and the records that were in accordance with the inclusion criteria and those that were considered uncertain were selected for full-text analysis. If any disagreement was observed, a third reviewer (CCRF) was consulted to achieve consensus and make a final decision.

2.5. Data collection process

Data of interest from the included studies, such as demographic data (author, year, country, institution where the research was conducted, and funding sources), sample characteristics (number of patients, gender, age range, tooth group, and preoperative pulpal diagnoses), intervention characteristics (photoactivation protocol parameters, type of light source, photosensitizer agent) and details of the reported outcomes, including the assessment methods, were extracted in an Excel spreadsheet (Microsoft Corporation, Redmond, WA, USA) and the obtained data were interpreted by two reviewers (LPA and LBG), and another reviewer (TSA) double-checked the accuracy of the data extraction.

2.6. Study risk of bias assessment

Two reviewers (LPA and LBG) independently used the Cochrane's Risk of Bias tool for randomized trials (ROB 2) and for nonrandomized studies of interventions

(ROBINS-I) to assess the methodological quality of the included trials [15]. Each tool consists of evaluating different sets of domains; the ROB 2 tool compromises judging five domains: (d1) bias arising from the randomization process; (d2) bias due to deviations from intended interventions; (d3) bias due to missing outcome data; (d4) bias in the measurement of the outcome; and (d5) bias in the selection of the reported result, while the ROBINS-I tool embraces seven domains: (d1) bias due to confounding; (d2) bias in the selection of participants into the study; (d3) bias in classification of interventions; (d4) bias due to deviations from intended interventions; (d5) bias due to missing data; (d6) bias in the measurement of outcomes; and (d7) bias in the selection of the reported result. Each of the signaling questions was judged according to the degree of risk of bias. Because of the nature of the intervention (laser application), blinding of personnel and patients was not considered to increase the risk of bias of the included trials.

2.7. Certainty assessment

To appraise the certainty of the body of evidence summarized from this study, two reviewers (LPA and LBG) used the Grading of Recommendations, Assessment, Development, and Evaluation approach (GRADEpro GDT; McMaster University, Ontario, CA) to rate the quality of the outcome analysis through the five GRADE domains: (d1) risk of bias, (d2) inconsistency, (d3) indirectness, (d4) imprecision and (d5) publication bias.

3 *Results*

3.1. Search strategy

The proposed search strategy (last updated on May 20th, 2022) yielded 1545 studies from all target databases (Figure 1). Subsequent to the removal of duplicate records, a total of 1152 studies were screened by title and abstract. Of these, 1139 were excluded for not meeting the review scope, and 13 were deemed relevant and were fully assessed for eligibility by two reviewers (LPA and LBG). After that, nine studies were excluded for having different study designs or evaluating other outcomes, and four studies met all the eligibility criteria and were included in this systematic review. A complete list of the excluded records is outlined in Supplementary file 1.

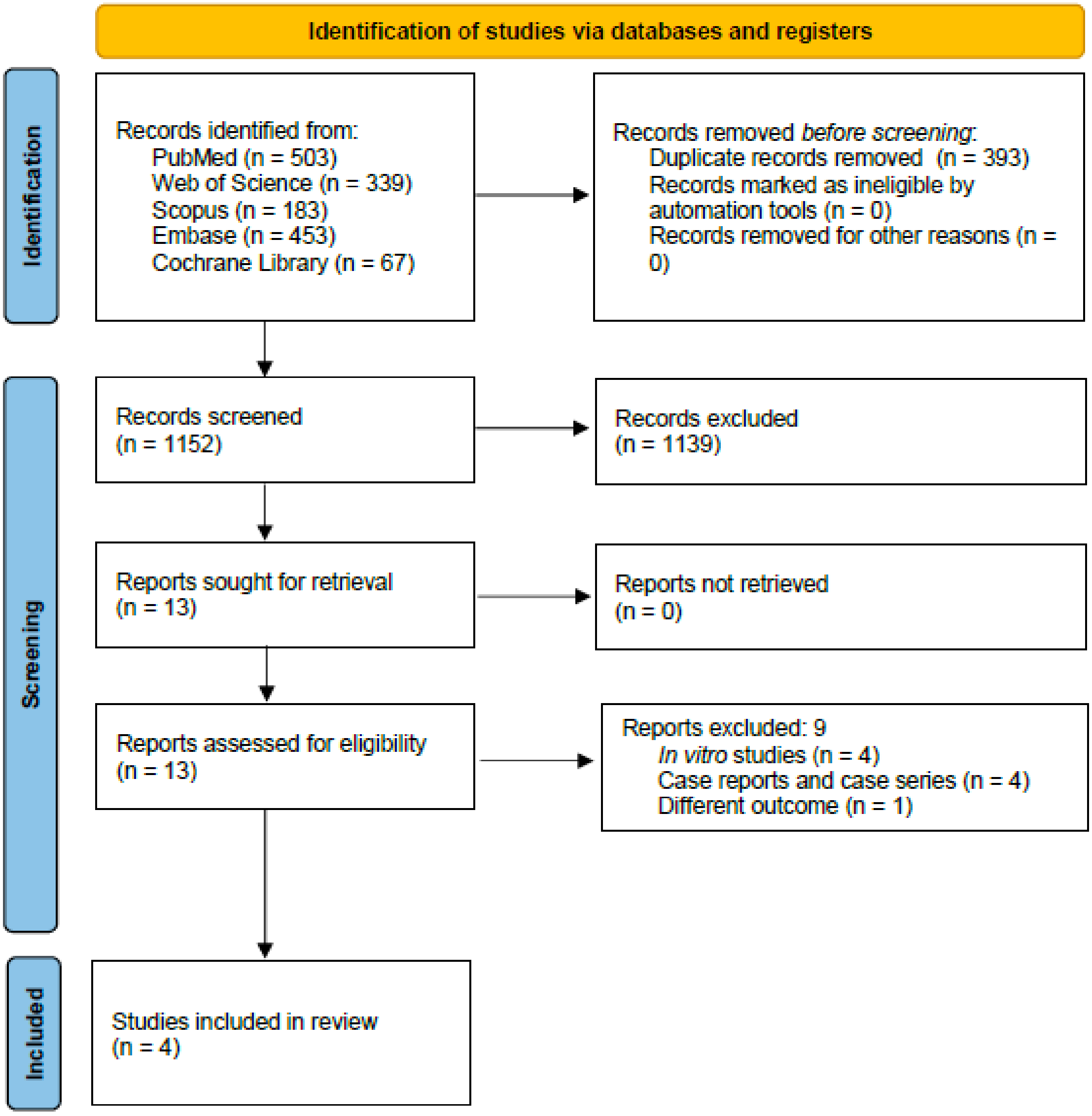

Figure 1. Flowchart showing search strategy based on the PRISMA 2020 Statement.

3.2. Study characteristics

A detailed overview of the methodology and main findings of the four clinical studies included in this review is described in Table 2. A total of 72 children were reported to have received the intervention, and the age range of the sample was 2-8 years old. All assessed primary teeth had a diagnosis of necrotic pulp, with two studies evaluating the microbiological load after PDT in primary anterior teeth [16,17], while the other two included studies evaluated the same outcome in primary molar teeth [18,19]. Three studies measured the intervention outcome on total viable bacteria in colony-forming units [16–18], whereas one study measured the viable fungal colony-forming units of *Candida albicans* [19]. Every study evaluated the viable colony-forming units through different cultivation methods. Additionally, the included studies differed regarding the study design, with only one study being a randomized clinical trial [17], while the remaining studies were nonrandomized clinical trials.

The photosensitizer agents used to perform PDT were phenothiazinium salts (i.e., methylene blue and toluidine blue O). One study [19] used a higher concentration of methylene blue dye (0,010% mg/L), and two studies [16,17] used it at a lower concentration (0,005% mg/L). The remaining study [18] used toluidine blue O at a 0,005% mg/L concentration. All studies reported having employed a pre-irradiation time of 3 minutes for the photosensitizer agents to diffuse inside the root canal system.

Regarding the light source and photoactivation parameters, every included study used a low-level diode laser. However, two different configuration settings were observed: three studies [16–18] used the laser at a 660 nm wavelength, 100 mW output power, and 4 J cm^2 setting for 40 seconds, while the other study [19] used it at a 940 nm wavelength, 200 mW output power, and 2 J cm^2 applied in three cycles of 10 seconds each. Only two studies reported having used intracanal optical fibers coupled to the diode lasers to activate the photosensitizer agents [16,19].

Just one study [18] found a statistically significant difference in the *in vivo* microbiological load reduction outcome when performing PDT on primary teeth. The remaining studies [16,17,19] all discussed the possible benefits of this intervention; however, none observed a significant difference in microbiological load reduction when compared to the control sample (i.e., conventional root canal preparation).

Table 2. Characteristics of the included trials and their main findings.

Sample characteristics					Intervention characteristics				
Author and year	**Number of patients**	**Age-range**	**Tooth group**	**Pulpal diagnosis**	**Light source**	**Photosensitizer agent**	**Photoactivation parameters**	**Assessment measure**	**Main findings**
Pinheiro *et al.,* 2008	10	4-7 years	Primary molars	Necrotic pulp	Low-level diode laser	0,005% mg/L of toluidine blue O	4J cm^2 light fluency, 100mW output power, and 660nm wavelength applied for 40s	Assessment of viable bacteria in colony-forming units (CFUs/mL)	Photodynamic therapy may be an additional resource for microbial reduction in primary teeth with necrotic pulp since, in this study, there was a significant difference of an additional 15.78% reduction in the total number of bacteria.
Anand *et al.,* 2020	20	5-8 years	Primary molars	Necrotic pulp	Low-level diode laser	0,010% mg/L of methylene blue	2J cm^2 light fluency, 200mW output power, 940nm wavelength applied in three cycles of 10s each	Assessment of viable fungal in colony-forming units of *Candida albicans* (CFUs/mL)	Postoperative CFUs values show no significant difference, which shows that all the protocols used for disinfection of root canals of primary teeth in this study were equally effective.
Okamoto *et al.,* 2020	32	2-5 years	Primary anterior teeth	Necrotic pulp	Low-level diode laser	0,005% mg/L of methylene blue	4J cm2 light fluency, 100mW output power, and 660nm wavelength applied for 40s	Assessment of viable bacteria in colony forming units (CFUs/mL)	The reduction in bacterial load was 93% in the control group and 99% in the PDT group, with no statistically significant difference.
Fernandes *et al.,* 2020	10	3-5 years	Primary anterior teeth	Nerotic pulp	Low-level diode laser	0,005% mg/L of methylene blue	4J cm2 light fluency, 100mW output power, and 660nm wavelength applied for 40s	Assessment of viable bacteria in colony forming units (CFUs/25mL)	No significant reduction in CFUs was observed using PDT after the conventional chemo-mechanical preparation of the root canal system

3.3. Study risk of bias and certainty assessment

Figure 2 shows the ROB 2 tool applied to the included randomized clinical trial [17], indicating a low risk of bias in all domains. Moreover, Table 3 summarizes the risk of bias in the nonrandomized studies. Of these, two studies [16,18] showed an overall low risk of bias, and in one study [19], a moderate risk of bias was detected in the classification of interventions domain for not thoroughly describing the intervention groups, and a serious risk was detected in the selection of the reported result domain since this study had not made a preclinical research protocol and there are suspicions that the reported outcome was selected based on a subset of the overall microbiological analysis.

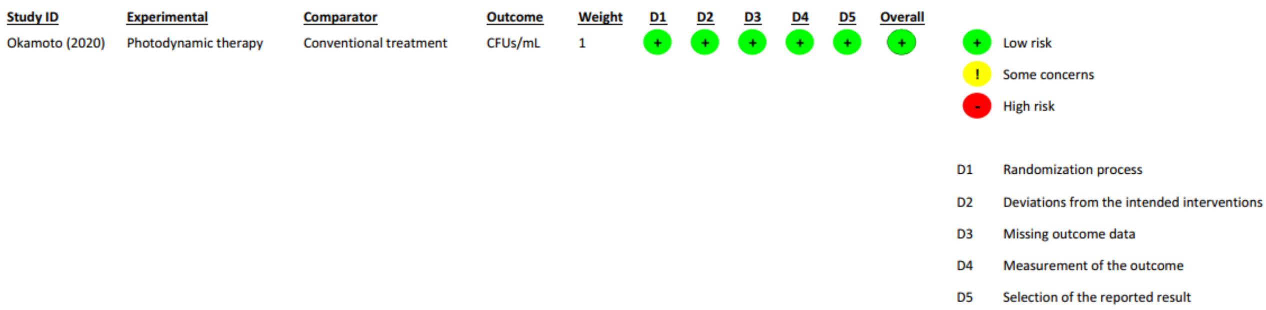

Figure 2. Risk of Bias assessment of the included randomized clinical trial

Table 3. Risk of bias in included trials based on Cochrane's ROBINS-I tool.

	Pinheiro *et al*., 2008	Arnand *et al*., 2020	Fernandes *et al*., 2020
Bias due to confounding	Low risk	Low risk	Low risk
Bias in selection of participants into the study	Low risk	Low risk	Low risk
Bias in classification of interventions	Low risk	Moderate risk	Low risk
Bias due to deviations from intended interventions	Low risk	Low risk	Low risk
Bias due to missing data	Low risk	Low risk	Low risk
Bias in measurement of outcomes	Low risk	Low risk	Low risk
Bias in selection of the reported result	Low risk	Serious risk	Low risk
Overall risk of bias	Low risk	Serious risk	Low risk

Since the data from the included studies could not be standardized and pooled together, a quantitative meta-analysis was contraindicated. The GRADE approach was carefully modified following specific recommendations to rate the certainty of the evidence [20]. The overall summary of evidence showed moderate certainty for the included randomized clinical trial and very low certainty for the nonrandomized trials (Table 4). A serious risk was observed in both categories in the 'publication bias' domain because all studies consisted of small samples, and thus, the intervention effect may be over- or underestimated [21]. In the nonrandomized trials category, serious risks were also observed in the 'risk of bias' and 'inconsistency' domains.

Table 4. Certainty of the available evidence based on the GRADEpro GDT tool.

Certainty assessment						Effect	Certainty
Number of studies	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**		
Randomized clinical trial **Outcome:** Microbiological load reduction (in CFUs/mL)							
1	Not serious	Not serious	Not serious	Not serious	Serious	No significant difference was observed in the primary outcome	⊕⊕⊕◯ Moderate
Non-randomized clinical trial **Outcome:** Microbiological load reduction (in CFUs/mL)							
3	Serious	Serious	Not serious	Not serious	Serious	Most studies did not observe significant differences in the primary outcome	⊕◯◯◯ Very low

4 *Discussion*

Root canal treatment in infected primary teeth is an essential step toward maintaining the teeth in the oral cavity until physiological exfoliation occurs, avoiding malocclusions, phonetic alterations, reduced masticatory force, and esthetic problems [22]. However, this type of treatment can be a challenging task for the clinician since primary teeth present physiological, morphological, and behavioral aspects such as root resorptions, complex root anatomy, and difficult patient management [23]. From this perspective, different supplementary methods for improving root canal disinfection in primary teeth have been investigated [24], and PDT has shown significantly positive *in vitro* results on microbiological load reduction [25–27]. Additionally, case reports on PDT application in primary teeth infections discussed some possible benefits, such as improving the outcome of traumatized primary teeth [28,29] and potentially reducing microbiological load, thus improving the therapy prognosis [30,31]. It is noteworthy that case reports represent the lowest evidence possible and should not be used to justify the use of an experimental intervention; however, they are helpful in developing a hypothesis to further investigate through controlled analytical studies [32].

The overall findings of this review were in contrast to a previous study that evaluated the outcome of PDT in reducing the microbiological load on infected permanent teeth [12]. Of the included trials, only one [18] reported a significant effect on this outcome; however, the sample size used in this study consists of a fundamental methodological limitation (only ten patients). The same limitation can be described for the remaining trials since none performed a sample size calculation and used small samples. Sample size underestimation may lead the intervention to be statistically nonsignificant or may overestimate the effect of the intervention [33]. It is also important to point out that all trials have activated the photosensitizer agents with an under-optimal irradiation time (10 - 40s), and in one trial [19], an incorrect wavelength was irradiated to methylene blue (940nm). Phenothiazinium salts have an optimal light absorbance peak at 665nm wavelength irradiated for 90 seconds [34,35]. Two trials [17,18] have not used an optical fiber coupled to the light source, which is crucial to properly activate the photosensitizer agents and produce reactive oxygen species in the apical region of the root canal system [36].

Additionally, all included trials have investigated microbiological load reduction through different first-generation cultivation methods for bacterial and fungal detection, and these methods are known for having several setbacks, such as low sensitivity and inability to detect certain species, resulting in an oversight of the overall endodontic pathogen microbiome [37]. Therefore, randomized clinical trials of PDT in primary tooth infections that aim to investigate microbiological load reduction should focus on optimal dosimetric light activation parameters, larger sample size, and next-generation sequencing technologies for identifying a more precise effect of this intervention on the endodontic microbiome.

Only one trial [17] evaluated the follow-up of the PDT intervention at 1- and 3-month intervals; however, this timeline is insufficient to evaluate any positive outcome related to clinical interventions in primary teeth infections. Thus, future high-quality clinical trials should make efforts to perform long-term clinical and radiographic follow-ups evaluating primary tooth survival and the exfoliation period when PDT is used as an additional disinfection method to conventional pulpectomy. In this way, a clinically significant outcome may be assessed regarding the potential benefits of PDT in root canal treatment of primary teeth In this systematic review, moderate to low certainty of the available evidence was observed, and thus, no significant conclusions can be drawn from the findings. Future studies should follow trial reporting guidelines such as the Consolidated Standards of Reporting Trials (CONSORT) [38] or the Preferred Reporting Items for RAndomized Trials in Endodontics (PRIRATE) [39] to improve the quality of the generated evidence.

Why this paper is important to paediatric dentists

- Even though there is still insufficient evidence to recommend the use of photodynamic therapy on the pulpectomy of primary teeth, this review provided clinicians with insights regarding the use of this supplementary disinfection technique.
- Future studies should also evaluate if laser-assisted photodynamic therapy affects children's behavior management.

References

1. James SL, Abate D, Abate KH, et al. Global, regional, and national incidence, prevalence, and years lived with disability for 354 Diseases and Injuries for 195 countries and territories, 1990-2017: A systematic analysis for the Global Burden of Disease Study 2017. *Lancet*. 2018;392(10159):1789-1858. doi:10.1016/S0140-6736(18)32279-7

2. Bjørndal L, Simon S, Tomson PL, Duncan HF. Management of deep caries and the exposed pulp. *Int Endod J*. 2019;52(7):949-973. doi:10.1111/iej.13128

3. Kritikou K, Imre M, Tanase M, et al. Assessment of Mineralization, Oxidative Stress, and Inflammation Mechanisms in the Pulp of Primary Teeth. *Appl Sci*. 2022;12(3):1554. doi:10.3390/app12031554

4. Kratunova E, Silva D. *Pulp Therapy for Primary and Immature Permanent Teeth: An Overview*. Vol 66.; 2018. Accessed February 11, 2022. http://www.aapd.org/media/Policies_Recommendations/G_VitalPulpTherapies

5. Carrotte P. Endodontic treatment for children. *Br Dent J*. 2005;198(1):9-15. doi:10.1038/sj.bdj.4811946

6. Tirupathi SP, Krishna N, Rajasekhar S, Nuvvula S. Clinical Efficacy of Single-visit Pulpectomy over Multiple-visit Pulpectomy in Primary Teeth: A Systematic Review. *Int J Clin Pediatr Dent*. 2019;12(5):453-459. doi:10.5005/jp-journals-10005-1654

7. Delikan E, Caliskan S, Cankilic MY, Aksu S, Kesim B, Ulger ST. Microbiota of Endodontically Infected Primary and Permanent Teeth. *Pediatr Dent*. 2021;43(2).

8. Chugal N, Mallya SM, Kahler B, Lin LM. Endodontic Treatment Outcomes. *Dent Clin North Am*. 2017;61(1):59-80. doi:10.1016/j.cden.2016.08.009

9. Gursoy H, Ozcakir-Tomruk C, Tanalp J, Yılmaz S. Photodynamic therapy in dentistry: A literature review. *Clin Oral Investig*. 2013;17(4):1113-1125. doi:10.1007/s00784-012-0845-7

10. Abdelkarim-Elafifi H, Parada-Avendaño I, Arnabat-Dominguez J. Photodynamic therapy in endodontics: A helpful tool to combat antibiotic resistance? a literature review. *Antibiotics*. 2021;10(9). doi:10.3390/antibiotics10091106

11. Plotino G, Grande NM, Mercade M. Photodynamic therapy in endodontics. *Int Endod J*. 2019;52(6):760-774. doi:10.1111/iej.13057

12. Pourhajibagher M, bahador A. Adjunctive antimicrobial photodynamic therapy to conventional chemo-mechanical debridement of infected root canal systems: A systematic review and meta-analysis. *Photodiagnosis Photodyn Ther*. 2019;26:19-26. doi:10.1016/j.pdpdt.2019.02.009

13. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *BMJ*. 2021;372:n71-n71. doi:10.1136/bmj.n71

14. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan---a web and mobile app for systematic reviews. *Syst Rev*. 2016;5(1):210.

doi:10.1186/s13643-016-0384-4

15. Sterne JA, Hernán MA, Reeves BC, et al. ROBINS-I: A tool for assessing risk of bias in non-randomised studies of interventions. *BMJ*. 2016;355. doi:10.1136/bmj.i4919

16. Fernandes ML da MF, Maia CA, Santos AMC, et al. Antimicrobial photodynamic therapy in the endodontic treatment of deciduous teeth: In vivo pilot study. *Pesqui Bras Odontopediatria Clin Integr*. 2020;20:1-9. doi:10.1590/pboci.2020.111

17. Okamoto CB, Bussadori SK, Prates RA, et al. Photodynamic therapy for endodontic treatment of primary teeth: A randomized controlled clinical trial. *Photodiagnosis Photodyn Ther*. 2020;30:101732. doi:10.1016/j.pdpdt.2020.101732

18. Pinheiro SL, Schenka AA, Neto AA, De Souza CP, Rodriguez HMH, Ribeiro MC. Photodynamic therapy in endodontic treatment of deciduous teeth. *Lasers Med Sci*. 2009;24(4):521-526. doi:10.1007/s10103-008-0562-2

19. Anand P, Mathur S, Sachdev V, Jain A. Inter-comparison of antimicrobial photodynamic therapy, LASER, and an antifungal agent as adjunct intracanal irrigation techniques to standard disinfection protocols in reducing Candida albicans counts in the root canals of primary teeth: A pilot study. *J Indian Soc Pedod Prev Dent*. 2020;38(3):304-310. doi:10.4103/JISPPD.JISPPD_286_20

20. Murad MH, Mustafa RA, Schünemann HJ, Sultan S, Santesso N. Rating the certainty in evidence in the absence of a single estimate of effect. *Evid Based Med*. 2017;22(3):85-87. doi:10.1136/ebmed-2017-110668

21. Guyatt GH, Oxman AD, Montori V, et al. GRADE guidelines: 5. Rating the quality of evidence - Publication bias. *J Clin Epidemiol*. 2011;64(12):1277-1282. doi:10.1016/j.jclinepi.2011.01.011

22. Parisay I, Ghoddusi J, Forghani M. A review on vital pulp therapy in primary teeth. *Iran Endod J*. 2015;10(1):6-15. Accessed March 6, 2022. /pmc/articles/PMC4293574/

23. Ahmed HMA. Anatomical challenges, electronic working length determination and current developments in root canal preparation of primary molar teeth. *Int Endod J*. 2013;46(11):1011-1022. doi:10.1111/iej.12134

24. Öter B, Topçuoglu N, Tank MK, Çehreli SB. Evaluation of Antibacterial Efficiency of Different Root Canal Disinfection Techniques in Primary Teeth. *Photomed Laser Surg*. 2018;36(4):179-184. doi:10.1089/pho.2017.4324

25. Maciel Martins CR, de Andrade MV, Carvalho AP, et al. Photodynamic therapy associated final irrigation in root canals of the primary teeth. *Photodiagnosis Photodyn Ther*. 2021;33. doi:10.1016/j.pdpdt.2021.102182

26. Pinheiro SL, da Silva JN, Gonçalves RO, Villalpando KT. Manual and rotary instrumentation ability to reduce enterococcus faecalis associated with photodynamic therapy in deciduous molars. *Braz Dent J*. 2014;25(6):502-507. doi:10.1590/0103-6440201302414

27. Attiguppe PR. Comparative Evaluation of Different Modes of Laser Assisted

Endodontics in Primary Teeth: An In vitro Study. *J Clin Diagnostic Res*. 2017;11(4):ZC124-ZC127. doi:10.7860/jcdr/2017/24001.9755

28. Meyfarth S, Torres AFC, Rodrigues AS, de Moraes JB, Antunes LS, Antunes LAA. Improvement on OHRQoL after endodontic treatment associated with aPDT in traumatized primary teeth: a 12-month follow-up case report. *Int J Burns Trauma*. 2021;11(3):251-259. http://www.ncbi.nlm.nih.gov/pubmed/34336392%0Ahttp://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC8310866

29. de Sant'Anna G. Photodynamic therapy for the endodontic treatment of a traumatic primary tooth in a diabetic pediatric patient. *J Dent Res Dent Clin Dent Prospects*. 2014;8(1):56-60. doi:10.5681/joddd.2014.010

30. da Silva Barbosa P, Duarte DA, Leite MF, de Sant’ Anna GR. Photodynamic Therapy in Pediatric Dentistry. *Case Rep Dent*. 2014;2014:1-5. doi:10.1155/2014/217172

31. Okamoto CB, Motta LJ, Prates RA, et al. Antimicrobial Photodynamic Therapy as a Co-adjuvant in Endodontic Treatment of Deciduous Teeth: Case Series. *Photochem Photobiol*. 2018;94(4):760-764. doi:10.1111/php.12902

32. Brighton B, Bhandari M, Tornetta P, Felson DT. Hierarchy of Evidence: From Case Reports to Randomized Controlled Trials. *Clin Orthop Relat Res*. 2003;413:19-24. doi:10.1097/01.blo.0000079323.41006.12

33. Wang X, Ji X. Sample Size Estimation in Clinical Research: From Randomized Controlled Trials to Observational Studies. *Chest*. 2020;158(1):S12-S20. doi:10.1016/j.chest.2020.03.010

34. Larasati NA, Ismiyatin K, Kunarti S. EFFECTIVENESS OF TIME IRRADIATION BY LASER DIODE 650 NM AND PHOTOSENSITIZER Methylene Blue ON DECREASING THE NUMBER OF MIXED BACTERIAL COLONIES FROM NECROTIC ROOT CANAL. *Conserv Dent J*. 2019;9(1):33. doi:10.20473/cdj.v9i1.2019.33-39

35. Rauf MA, Meetani MA, Khaleel A, Ahmed A. Photocatalytic degradation of Methylene Blue using a mixed catalyst and product analysis by LC/MS. *Chem Eng J*. 2010;157(2-3):373-378. doi:10.1016/j.cej.2009.11.017

36. Garcez AS, Ribeiro MS, Tegos GP, Núñez SC, Jorge AOC, Hamblin MR. Antimicrobial photodynamic therapy combined with conventional endodontic treatment to eliminate root canal biofilm infection. *Lasers Surg Med*. 2007;39(1):59-66. doi:10.1002/lsm.20415

37. Siqueira JF, Rôças IN. A critical analysis of research methods and experimental models to study the root canal microbiome. *Int Endod J*. Published online 2021. doi:10.1111/iej.13656

38. Schulz KF, Altman DG, Moher D. CONSORT 2010 Statement: Updated guidelines for reporting parallel group randomised trials. *BMJ*. 2010;340(7748):698-702. doi:10.1136/bmj.c332

39. Nagendrababu V, Duncan HF, Bjørndal L, et al. PRIRATE 2020 guidelines for reporting randomized trials in Endodontics: a consensus-based development.

Int Endod J. 2020;53(6):764-773. doi:10.1111/iej.13294

Supplementary file 1. Excluded studies and reasons for exclusion

***In vitro* studies. (n = 4)**

1. Pinheiro SL, da Silva JN, Gonçalves RO, et al. Manual and rotary instrumentation ability to reduce enterococcus faecalis associated with photodynamic therapy in deciduous molars. *Braz Dent J* 2014; 25: 502–507.

2. Attiguppe PR. Comparative Evaluation of Different Modes of Laser Assisted Endodontics in Primary Teeth: An In vitro Study. *J Clin Diagnostic Res* 2017; 11: ZC124–ZC127.

3. Öter B, Topçuoglu N, Tank MK, et al. Evaluation of Antibacterial Efficiency of Different Root Canal Disinfection Techniques in Primary Teeth. *Photomed Laser Surg* 2018; 36: 179–184.

4. Maciel Martins CR, de Andrade MV, Carvalho AP, et al. Photodynamic therapy associated final irrigation in root canals of the primary teeth. *Photodiagnosis Photodyn Ther*; 33. Epub ahead of print 2021. DOI: 10.1016/j.pdpdt.2021.102182.

Case report. (n = 3)

5. de Sant'Anna G. Photodynamic therapy for the endodontic treatment of a traumatic primary tooth in a diabetic pediatric patient. *Journal of Dental Research, Dental Clinics, Dental Prospects* 2014; 8: 56–60.

6. da Silva Barbosa P, Duarte DA, Leite MF, et al. Photodynamic Therapy in Pediatric Dentistry. *Case Rep Dent* 2014; 2014: 1–5.

7. Meyfarth S, Torres AFC, Rodrigues AS, et al. Improvement on OHRQoL after endodontic treatment associated with aPDT in traumatized primary teeth: a 12-month follow-up case report. *Int J Burns Trauma* 2021; 11: 251–259.

Case series. (n = 1)

8. Okamoto CB, Motta LJ, Prates RA, et al. Antimicrobial Photodynamic Therapy as a Co-adjuvant in Endodontic Treatment of Deciduous Teeth: Case Series. *Photochem Photobiol* 2018; 94: 760–764.

Different outcome. (n = 1)

9. Yavagal C, Lal A, Chavan Patil V, et al. Efficacy of laser photobiomodulation pulpotomy in human primary teeth: A randomized controlled trial. *J Indian Soc Pedod Prev Dent* 2021; 39: 436.

2.3 ARTIGO 3

Tooth color change after photodynamic therapy in endodontics: a systematic review

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ABSTRACT

Background: A smile is considered one of the most important soft skills in social interaction. It is known that some photosensitizer agents (PS) used in photodynamic therapy (PDT) during root canal treatment could play a significant role in tooth color change, and thus the main objective of this systematic review is to address whether performing PDT can influence tooth color change and to synthesize the most effective methods to remove PS from the root canal system. **Methods:** This study followed the PRISMA 2020 statement, and the protocol was registered at the Open Science Framework. Two blinded reviewers searched five databases up to November 20th, 2022: Web of Science, PubMed, Scopus, Embase, and the Cochrane Library. The eligibility criteria were studies that investigated tooth color change after PDT in endodontics. **Results:** A total of 1695 studies were retrieved, and 7 were included in the qualitative analysis. All the included studies were *in vitro* evidence and investigated five different PS: methylene blue, toluidine blue O, malachite green, indocyanine green, and curcumin. Besides curcumin and indocyanine green, the remaining agents all caused tooth color change, and no method employed was effective in fully removing these PS from inside the root canal system. **Conclusions:** Even though the findings showed that curcumin and indocyanine green did not influence tooth color change, the present evidence should be interpreted with caution since it is based on laboratory studies with questionable methods, and all efforts should be employed to avoid this undesirable side effect during clinical practice.

Keywords: Endodontics, Pigmentation, Photochemotherapy, Systematic review

1 Introduction

Apical periodontitis is an inflammatory disease that is the main consequence of a polymicrobial infection on the decayed tooth (1). The standard treatment consists of performing root canal therapy to chemo-mechanically remove infected and/or inflamed pulp tissue from the root canal system. It is estimated that half the world's population has at least one tooth with apical periodontitis (2).

Even though the success rate of primary root canal treatment is considered high (3), the endodontics specialty community has always chased enhanced disinfection methods to improve the treatment outcome (4). From this perspective, photodynamic therapy (PDT) has been investigated as an effective supplementary approach to improve the decontamination of the infected root canal system (5). Several benefits have been observed using PDT after the conventional root canal chemo-mechanical preparation, such as reduced intracanal bacterial load and reduced postoperative pain (6,7).

The science of PDT follows the principles of a photochemical reaction, in which three essential factors are required: a light source with the appropriate wavelength (8), a non-toxic dye (i.e., photosensitizer agent) with the ability to absorb energy from this light source and free oxygen. This photochemical reaction will produce highly reactive oxygen species, such as singlet oxygen which is effective against bacteria, viruses, and yeasts (9).

The photosensitizers most used in endodontics are phenothiazine salts, with no side effects reported to date (10). However, there is uneasiness among clinicians due to the fact that the current photosensitizer agents may have a pigmentation potential on tooth structure.

Dental aesthetics play a significant role in the psychosocial impact of patients undergoing oral treatments (11). And thus, tooth pigmentation caused by the current photosensitizer agents used in PDT could negatively impact the patient's self-awareness and self-esteem. Hence, the main goal of this systematic review is to address this issue and answer whether PDT can cause tooth color change on endodontically treated teeth and provide evidence regarding the optimal removal of the photosensitizer agent from the root canal system to avoid tooth staining.

2 Methods

2.1 Registration and research question

This systematic review is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA 2020) recommendations (12). The study protocol was registered in the Open Science Framework (https://osf.io/qx2e6/) due to the nature of the study design (e.g., a systematic review of *in vitro* studies). The main research question was formulated based on the PICO strategy: Can the photosensitizer agents used in photodynamic therapy during root canal treatment cause tooth color change?

2.2 Eligibility and exclusion criteria

Considering this paper's scope, all English-written studies that investigated tooth color change after performing PDT during root canal treatment and the methods used to remove photosensitizer agents from the root canal system were qualified for inclusion, all photosensitizer agents were considered, and no study design or publication period restrictions were applied. Exclusion criteria were studies that did not use any photosensitizing agent to perform PDT, investigated photodynamic tooth bleaching, or evaluated antimicrobial properties.

2.3 Search strategy

Five electronic databases (i.e., PubMed/MEDLINE, The Cochrane Library, SciVerse Scopus, EMBASE, and the Web of Science) were screened using a systematic search strategy elaborated based on search descriptors from MEDLINE MeSH (Medical Subject Headings) terms were used as common search descriptors and adapted for other database syntaxes (Supplementary file 1). All pertinent articles were imported into Mendeley software (Elsevier, Amsterdam, NE) to sort duplicate studies. If the article was inaccessible within these databases, the study's corresponding author was contacted via e-mail, aiming to retrieve the paper.

2.4 Selection process

Firstly, the assortment process was conducted through a discussion of all eligibility criteria among the reviewers. Then the remaining articles were exported into the Rayyan web application (Qatar Computing Research Institute, Doha, QA) (13) to be assessed by two blinded and independent reviewers (ARM and LPA), who had access to the article's information filtered by title and abstract The studies that were in accordance with the eligibility criteria, as well as those that were considered uncertain, were selected for a full-text analysis by the reviewers. In case of disagreement, a consensus was achieved through discussion with a third reviewer with more experience in the field (CCRF).

2.5 Data collection process

Data of interest from the included studies were tabulated and interpreted by two independent reviewers (ARM and LBG) in an Excel spreadsheet (Microsoft Corporation, Redmond, WA, USA), and another reviewer (LPA) double-checked it. In case of any missing information, the corresponding author of the included study was contacted via e-mail to retrieve any missing data. The parameters of interest included the year of publication, study design, the method used to investigate tooth color change, tooth group, photosensitizer agent used, photoactivation protocols (light source, energy fluency, and wavelength), the auxiliary chemical solution used, methods for removing the photosensitizer agent, and main findings. The complete database will be available at the *Open Science Framework* register.

2.6 Study risk of bias assessment

The methodological risk of bias in each included study was evaluated by two blinded and independent reviewers (LPA and ARM) using the revised Cochrane risk of bias tool. This tool was meticulously modified according to an adaptation made in a previously published systematic review of in vitro studies (14). The following parameters were used to assess the risk of bias: (1) *sample size calculation, (2) samples with similar dimensions, (3) sample groups were randomized, (4) well-described photosensitizer activation parameters, (5) color measurement following a standard system, (6) comprehensible reporting of the study design, (7) statistical analysis was carried out.*

3 Results

3.1 Search strategy

The proposed search strategy was lastly applied on November 20^{th,} 2022, and retrieved a total of 1695 studies. Figure 1 is a schematic flowchart underlining the search process according to the PRISMA 2020 guideline. After duplicate removals, 831 studies were screened by title and abstract, resulting in 10 potentially eligible studies which were analyzed through full-text reading. Of these, 1 was excluded because it was a randomized clinical trial that only discussed possible pigmentation effects without showing any data, 1 was a narrative review that also did not show any data regarding tooth pigmentation, and 1 was an *in vitro* study with a different outcome. Seven studies met the criteria and were included in the present systematic review. A complete list showing the excluded and included studies is available in Supplementary file 2.

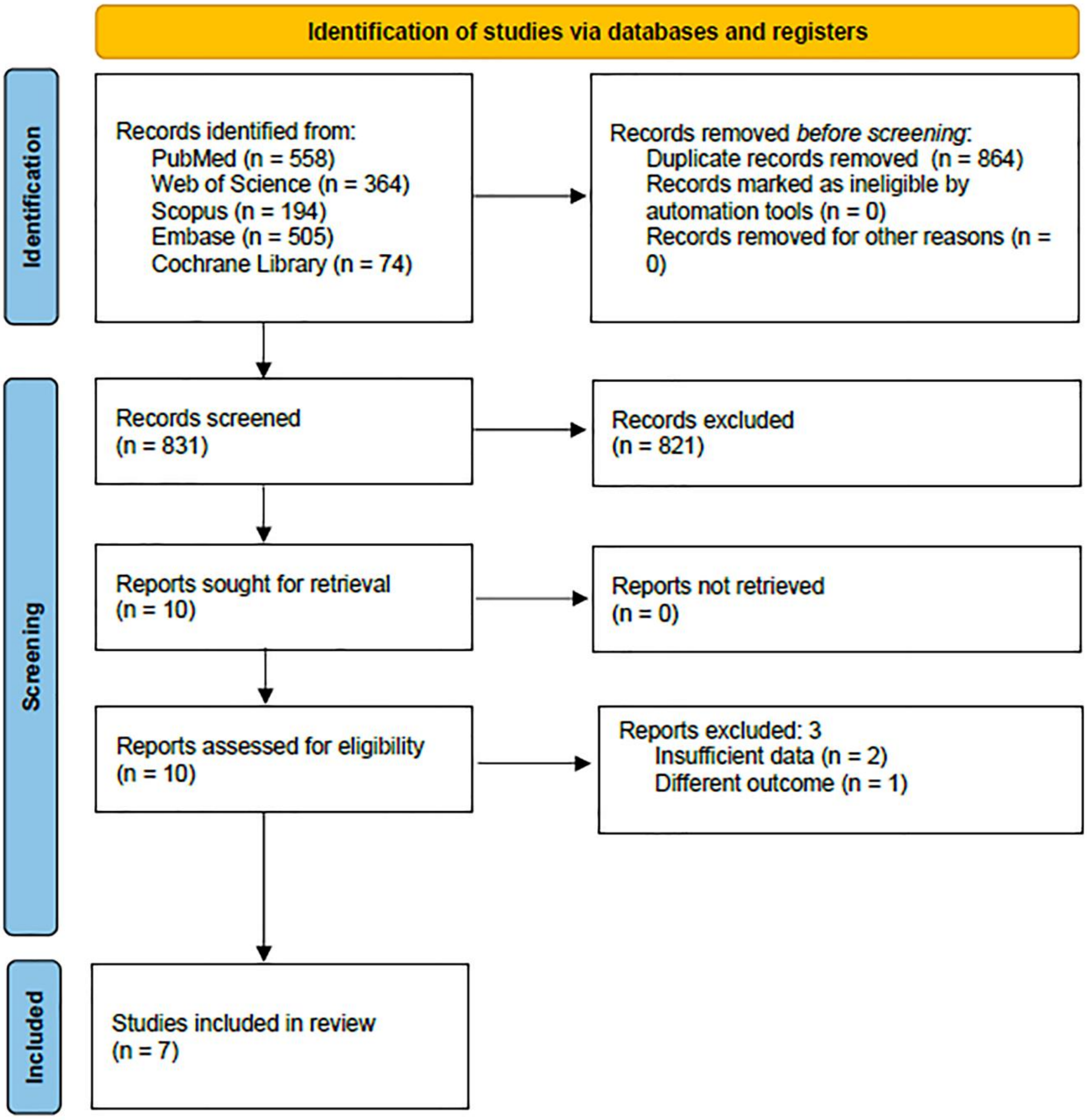

Figure 1. Search flowchart according to the PRISMA 2020 Statement.

3.2 Study characteristics

A total of five photosensitizer agents were investigated for tooth color change after endodontic PDT. Six studies evaluated methylene blue at a 0.01% concentration (15–20), other three studies investigated toluidine blue at a 0.01% concentration (15,19,20), one investigated malachite green at a 0.01% concentration (19), one evaluated indocyanine green at a 0.01% concentration (15), and two studies evaluated curcumin at 1000mg/L and 1500mg/L concentrations (16,21).

Every included study assessed tooth color change through *in vitro* spectrophotometer analysis following the CIELab color space system (22). Table 1 shows the method used, sample groups, photosensitizer agent used, and photoactivation parameters. A total of 160 single-rooted teeth, 180 resin-based composite discs, 30 bovine tooth enamel discs, and 60 intraradicular dentin blocks were used to evaluate color change. As light sources, the included studies used low-level diode lasers at two different settings to photoactivate methylene blue, toluidine blue, malachite green, and indocyanine green, while a blue LED light curing unit was used to photoactivate the curcumin photosensitizer.

Table 2 addresses the methods used to remove these photosensitizer agents and the outcome on tooth structure pigmentation. The methods employed varied from Endo-PTC cream (Asfer, São Caetano do Sul, São Paulo, Brazil) associated with 2.5% NaOCl (20), irrigation with 1% or 2.5% NaOCl (15,18,19), irrigation with different types of final irrigants such as 17% EDTA, QMix (Dentsply Sirona, Charlotte, NC, USA), and 17% Glycolic acid (17,18), passive ultrasonic irrigation (18), and irrigation with saline solution, deionized water and distilled water (16,18,21). No method was able to completely remove the photosensitizer agents; however, two studies observed no tooth color change when curcumin or indocyanine green was used as photosensitizer agents (15,21). The remaining agents all caused tooth color change beyond the clinically acceptable threshold.

Table 1. Study design and methods employed in the included studies

Study	Design	Method	Tooth group	Photosensitizer agent	Photoactivation parameters
Figueiredo et al., 2014	*In vitro*	Spectrophotometer analysis	40 Single-rooted teeth	Methylene blue and Toluidine blue at 0.01%	Diode laser set in 660nm wavelength at 40mW output power, 9J energy fluency, and irradiated for 3 minutes.
Costa et al., 2016	*In vitro*	Spectrophotometer analysis	40 Single-rooted teeth	Methylene blue, Toluidine blue, and Malachite green at 0.01%	Diode laser set in 660nm wavelength at 40mW output power, 9J energy fluency, and irradiated for 2 minutes.
Ramalho et al., 2017	*In vitro*	Spectrophotometer analysis	40 Single-rooted teeth	Methylene blue at 0.01%	Diode laser set in 660nm wavelength at 40mW output power, 9J energy fluency, and irradiated for 4 minutes.
Souza et al., 2021	*In vitro*	Spectrophotometer analysis	40 Single-rooted teeth	Methylene blue at 0.01%	Diode laser set in 660nm wavelength at 100mW output power, 9J energy fluency for 90 seconds.
Reina et al., 2021	*In vitro*	Spectrophotometer analysis	60 resin-based composite discs and 30 bovine tooth enamel	Curcumin	Blue LED at 455nm wavelength, 22mW output power, 18J energy fluency for 14 minutes.
Sivieri-Araujo et al., 2022	*In vitro*	Spectrophotometer analysis	60 Intraradicular dentin blocks from single-rooted teeth	Methylene blue at 0.01%, Curcumin 1000mg/L, and Curcumin 1500mg/L	Not applicable
Ozkocak et al., 2022	*In vitro*	Spectrophotometer analysis	120 resin-based composite discs	Methylene blue and Toluidine blue at 0.01%, and Indocyanine green at 0.5%	Diode laser set in 940nm wavelength, 1W output power for 1 minute

Table 2. Photosensitizer removal methods and main findings related to tooth pigmentation caused by these agents.

Study	Photosensitizer agent	Photosensitizer removal method	Main findings
Figueiredo et al., 2014	Methylene blue and Toluidine blue at 0.01%	Endo-PTC cream and irrigation with 2.5% NaOCl	Both photosensitizer agents cause tooth discoloration, and Endo-PTC cream associated with 2.5% NaOCl was able to reduce the discoloration potential.
Costa et al., 2016	Methylene blue, Toluidine blue, and Malachite green at 0.01%	Irrigation with 1% NaOCl	The photosensitizers Methylene Blue, Toluidine Blue, and Malachite Green, used in photodynamic therapy at a concentration of 0.01%, promoted tooth color change
Ramalho et al., 2017	Methylene blue at 0.01%	Irrigation with saline solution, 2.5% NaOCl, 17% EDTA, and passive ultrasonic irrigation	No removal method was completely effective in preventing dentin staining from the root canal
Souza et al., 2021	Methylene blue at 0.01%	Irrigation with 17% EDTA, QMix, and 17% Glycolic acid	No final irrigants were able to avoid the color change of the dentin structure
Reina et al., 2021	Curcumin	Irrigation with distilled water	Curcumin does not seem to have the potential to promote any esthetic or mechanical changes to the surface of tooth enamel and can be applied safely in clinical practice. However, the results on color change obtained for composite resins show that some negative effects can be produced.
Sivieri-Araujo et al., 2022	Methylene blue at 0.01%, Curcumin 1000mg/L, and Curcumin 1500mg/L	Irrigation with deionized water	The effects of methylene blue and curcumin photosensitizers on the color stability of endodontically treated intraradicular dentin exceeded the clinical acceptability threshold.
Ozkocak et al., 2022	Methylene blue and Toluidine blue at 0.01%, and Indocyanine green at 0.5%	Irrigation with 2.5% NaOCl	Methylene blue and toluidine blue caused color change on the resin-based composite, whereas indocyanine green was completely removed with 2.5% NaOCl and caused no color change

3.3 Quality assessment

Among the parameters established for the quality assessment of the included 7 *in vitro* studies, six of them scored poorly on '*Sample size calculation'* (16–21), while in 1 study, unclear risk of bias was detected on the '*Well-described photosensitizer activation parameters'* because the authors had not photoactivated the studied agents (16). The explanation for this issue is that the authors aimed to investigate the pigmentation effect of the agents themselves instead of the post-photoactivation effect. All studies scored a low risk of bias for the remaining parameters, and thus an overall low risk of bias can be considered for this *in vitro* evidence. Figure 2 shows the risk of bias graph of the included studies.

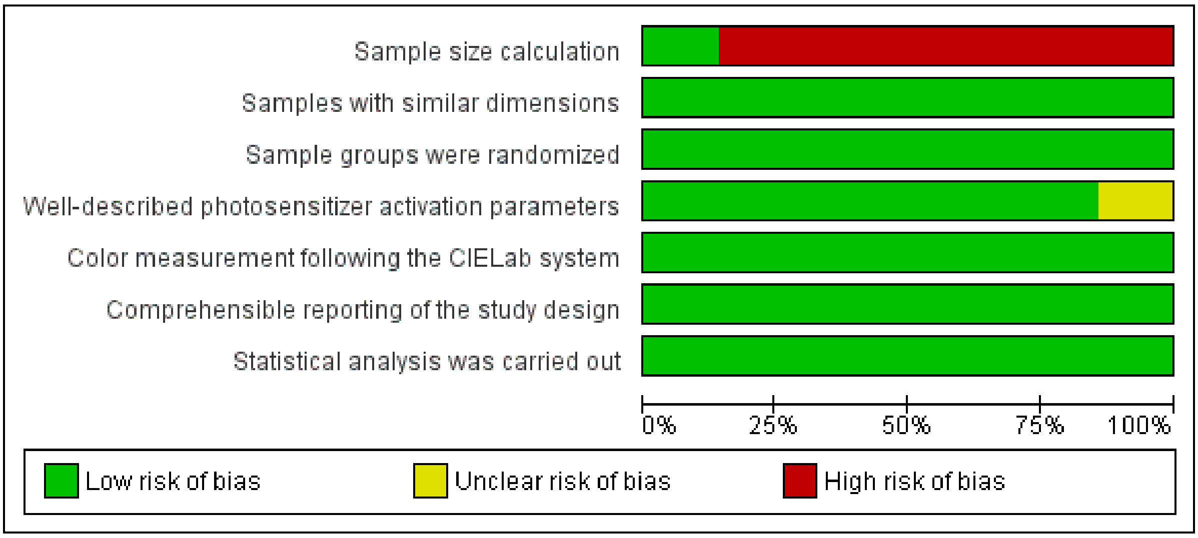

Figure 2. Review authors' judgments about each risk of bias item for each included in vitro study.

4 Discussion

Tooth color change induced by endodontic materials and procedures is well-known for the possibility of causing aesthetic issues and having a negative social impact on patients, mainly when it occurs on anterior teeth (23). It is a consensus that a good smile is considered to be among the most important soft skill to increase interpersonal and employability abilities (24,25), and thus all efforts should be made to avoid undesirable side effects on tooth color after endodontic procedures.

The findings from the present review suggest that tooth color change caused by the current photosensitizer agents is almost unavoidable. Only two studies found that curcumin and indocyanine green did not promote clinically-relevant color change (15,21); however, it is important to note that these studies have investigated the effects of photosensitizer agents on resin-based composites discs and thus may not represent the whole complexity of color change on natural tooth structure. Tooth color change is perceived by the way light penetrates and interacts by reflecting throughout tooth structure, such as the dentin-enamel junction. In restored teeth, the color stratification of resin-based composites is different from sound teeth and has an impact on light transmission characteristics when compared to dentin substracts (26) and; thereby, investigating color change only on the restorative materials is an underestimation of clinically perceived color change.

Moreover, no clinical trial to date has evaluated tooth color change after endodontic PDT, and thus the findings from this review are purely based on the qualitative synthesis of *in vitro* assays. Even though it is expected to have similar effects on clinical settings, the present findings should be interpreted with caution since several clinical trials investigated other outcomes related to PDT in endodontics (27–30), and none has described occurring tooth color changes in the patients. Also, systematic reviews of *in vitro* studies are still considered extremely complex to acquire reliable data that can be extrapolated to clinical environments, especially when there is a heterogeneity of the available data, and there is still no quality assessment guideline to evaluate the certainty of the generated evidence (31). Furthermore, a quantitative meta-analysis was not performed because even though the methods used to evaluate color change were the same, other variables, such as the investigated structure (i.e., human tooth, bovine tooth, and resin-based composite discs), the photosensitizer agents evaluated and the methods used to remove these agents differed from each study, making it impossible to pool the findings into homogenous subgroups, and thus a meta-analysis would mislead the true effect due to confounding bias (32).

Another issue observed in the included studies is that almost none performed a sample size calculation to determine a relevant effect of the intervention, and thus the studies may be over or underestimating the investigated outcome. Also, the included studies evaluated color change through spectrophotometer analysis using the CIELab color system to express the results. However, future studies should express the results through the CIEDE2000 formula, which is considerably more sophisticated and precise than its predecessor (33). This way, a more clinically relevant tooth color change can be better evaluated (34).

Regarding the photosensitizer removal methods, no method investigated by the included studies has proved to be sufficiently efficient to avoid tooth pigmentation (Table 2); however, it is feasible to recommend that all efforts should be made to increase its removal. Passive ultrasonic irrigation is a technique that is noted for better removal of debris and intracanal medicaments (35,36), and even though the only study that evaluated this technique on the removability of photosensitizer agents has found that it was not sufficient to completely avoid pigmentation, it was the method that removed them the most (18). The contemporary photosensitizer agents used in endodontics all have pigmentation side-effect; however, a recent scoping review has shown that incorporating these agents into bioengineered nanoparticle carriers could minimize this effect and increase its antimicrobial potential (37), favoring the clinical application of PDT in endodontics.

Future studies should focus on investigating the clinical effects of the current photosensitizer agents on the color stability of endodontically treated teeth, developing novel photosensitizer agents with reduced or none pigmentation side-effect, improving drug-delivery strategies such as nanoparticle incorporation, and investigating other methods to effectively remove remnants of the photosensitizer agent from the root canal system to successively overcome the undesirable pigmentation side-effect on clinical practice.

5 Conclusions

The available *in vitro* evidence indicates that the current photosensitizer agents have pigmentation potential beyond the clinically accepted threshold, and there is still no guaranteed method to remove these agents from inside the root canal system and completely avoid tooth color change. Future studies should assess this outcome in clinical settings, and efforts toward the technological development of novel photosensitizer agents should also address reducing the pigmentation side-effect.

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References

1. Siqueira JF, Rôças IN. Present status and future directions: Microbiology of endodontic infections. Int Endod J. 2022;55(S3):512–30.
2. Tibúrcio-Machado CS, Michelon C, Zanatta FB, Gomes MS, Marin JA, Bier CA. The global prevalence of apical periodontitis: a systematic review and meta-analysis. Int Endod J. 2021;54(5):712–35.
3. Ng YL, Mann V, Rahbaran S, Lewsey J, Gulabivala K. Outcome of primary root canal treatment: Systematic review of the literature - Part 1. Effects of study characteristics on probability of success. Int Endod J. 2007;40(12):921–39.
4. Siqueira JF, Rôças IN. Optimising single-visit disinfection with supplementary approaches: A quest for predictability. Aust Endod J. 2011;37(3):92–8.
5. de Araújo LP, da Rosa WL de O, Gobbo LB, da Silva TA, de Almeida JFA, Ferraz CCR. Global research trends on photodynamic therapy in endodontics: A bibliometric analysis. Photodiagnosis Photodyn Ther. 2022;40(July).
6. Pourhajibagher M, bahador A. Adjunctive antimicrobial photodynamic therapy to conventional chemo-mechanical debridement of infected root canal systems: A systematic review and meta-analysis. Photodiagnosis Photodyn Ther. 2019;26:19–26.
7. Alves-Silva EG, Arruda-Vasconcelos R, Louzada LM, de-Jesus-Soares A, Ferraz CCR, de Almeida JFA, et al. The effect of photodynamic therapy on postoperative pain in teeth with primary endodontic infection. Photodiagnosis Photodyn Ther. 2021;102700.
8. Plaetzer K, Krammer B, Berlanda J, Berr F, Kiesslich T. Photophysics and photochemistry of photodynamic therapy: Fundamental aspects. Lasers Med Sci. 2009;24(2):259–68.
9. Wainwright M. Photodynamic antimicrobial chemotherapy (PACT). J Antimicrob Chemother. 1998;42(1):13–28.
10. Plotino G, Grande NM, Mercade M. Photodynamic therapy in endodontics. Int Endod J. 2019;52(6):760–74.
11. Campos LA, Costa MA, Bonafé FSS, Marôco J, Campos JADB. Psychosocial impact of dental aesthetics on dental patients. Int Dent J. 2020;70(5):321–7.
12. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. BMJ. 2021;372:n71–n71.
13. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan-a web and mobile app for systematic reviews. Syst Rev. 2016;5(1):1–10.
14. Araújo LP De, Da Rosa WLDO, De Araujo TS, Immich F, Da Silva AF, Piva E. Effect of an Intraorifice Barrier on Endodontically Treated Teeth: A Systematic Review and Meta-Analysis of in Vitro Studies. Biomed Res Int. 2022;2022.
15. Ozkocak BBC, Ozkocak I, Agaccioglu M. Effects of dyes used in photodynamic

therapy on color stability of composite resins. J Oral Sci. 2022;64(3):194–7.

16. Sivieri-Araujo G, Strazzi-Sahyon HB, Jacomassi DP, dos Santos PH, Cintra LTA, Kurachi C, et al. Effects of methylene blue and curcumin photosensitizers on the color stability of endodontically treated intraradicular dentin. Photodiagnosis Photodyn Ther. 2022;37(July 2021):102650.
17. Souza MA, Trentini BM, Parizotto TF, Vanin GN, da Silva Piuco L, Ricci R, et al. Influence of a glycolic acid-based final irrigant for photosensitizer removal of photodynamic therapy on the microhardness and colour change of the dentin structure. Photodiagnosis Photodyn Ther. 2021;33(October 2020):102151.
18. Ramalho KM, Cunha SR, Mayer-Santos E, Eduardo C de P, Moreira de Freitas P, Aranha ACC, et al. In vitro evaluation of methylene blue removal from root canal after Photodynamic Therapy. Photodiagnosis Photodyn Ther. 2017;20(July):248–52.
19. Costa LM, Matos FDS, Correia AMYDO, Carvalho NC, Faria-E-Silva AL, Paranhos LR, et al. Tooth color change caused by photosensitizers after photodynamic therapy: An in vitro study. J Photochem Photobiol B Biol. 2016;160:225–8.
20. Figueiredo RA, Anami LC, Mello I, Carvalho EDS, Habitante SM, Raldi DP. Tooth discoloration induced by endodontic phenothiazine dyes in photodynamic therapy. Photomed Laser Surg. 2014;32(8):458–62.
21. Reina BD, Neto CS, Garcia PPNS, Chorilli M, Calixto GMF, Dovigo LN. Bioadhesive curcumin-mediated photodynamic inactivation and its potential to cause undesirable effects on dental and restorative surfaces. Pharmaceutics. 2021;13(9).
22. Robertson AR. The CIE 1976 Color-Difference Formulae. Color Res Appl. 1977;2(1):7–11.
23. Bosenbecker J, Barbon FJ, de Souza Ferreira N, Morgental RD, Boscato N. Tooth discoloration caused by endodontic treatment: A cross-sectional study. J Esthet Restor Dent. 2020;32(6):569–74.
24. Hattab FN, Qudeimat MA, Al-Rimawi HS. Dental discoloration: An overview. J Esthet Restor Dent. 1999;11(6):291–310.
25. Nickson D, Warhurst C, Commander J, Hurrell SA, Cullen AM. Soft skills and employability: Evidence from UK retail. Econ Ind Democr. 2012;33(1):65–84.
26. Lenherr P, Allgayer N, Weiger R, Filippi A, Attin T, Krastl G. Tooth discoloration induced by endodontic materials: A laboratory study. Int Endod J. 2012;45(10):942–9.
27. de Miranda RG, Colombo APV. Clinical and microbiological effectiveness of photodynamic therapy on primary endodontic infections: a 6-month randomized clinical trial. Clin Oral Investig. 2018;22(4):1751–61.
28. Okamoto CB, Bussadori SK, Prates RA, da Mota ACC, Tempestini Horliana ACR, Fernandes KPS, et al. Photodynamic therapy for endodontic treatment of primary teeth: A randomized controlled clinical trial. Photodiagnosis Photodyn Ther. 2020;30:101732.

29. Guimarães L da S, da Silva EAB, Hespanhol FG, Fontes KBF da C, Antunes LAA, Antunes LS. Effect of photobiomodulation on post-operative symptoms in teeth with asymptomatic apical periodontitis treated with foraminal enlargement: A randomized clinical trial. Int Endod J. 2021;54(10):1708–19.

30. Rabello DGD, Corazza BJM, Ferreira LL, Santamaria MP, Gomes APM, Martinho FC. Does supplemental photodynamic therapy optimize the disinfection of bacteria and endotoxins in one-visit and two-visit root canal therapy? A randomized clinical trial. Photodiagnosis Photodyn Ther. 2017;19:205–11.

31. Hammel C, Pandis N, Pieper D, Faggion CM. Methodological assessment of systematic reviews of in-vitro dental studies. BMC Med Res Methodol. 2022;22(1):110.

32. Sedgwick P. Meta-analyses: What is heterogeneity? BMJ. 2015;350.

33. Luo MR, Cui G, Rigg B. The development of the CIE 2000 colour-difference formula: CIEDE2000. Color Res Appl. 2001;26(5):340–50.

34. Athanassiadis B, Abbott P V., Walsh LJ. A critical analysis of research methods and experimental models to study tooth discolouration from endodontic materials. Int Endod J. 2022;55(S2):370–83.

35. Barbosa AFA, de Lima CO, Sassone LM, Fares RD, Fidalgo TKDS, Silva EJNL. Effect of passive ultrasonic irrigation on hard tissue debris removal: a systematic review and meta-analysis. Braz Oral Res. 2021;35.

36. Kim NY, Kim HJ, Min KS. The efficacy of three passive ultrasonic irrigation systems on intracanal medicament removal in a novel standardised three-dimensionally printed model. Aust Endod J. 2022;

37. Betancourt P, Brocal N, Sans-Serramitjana E, Zaror C. Functionalized nanoparticles activated by photodynamic therapy as an antimicrobial strategy in endodontics: A scoping review. Antibiotics. 2021;10(9):1064.

3 DISCUSSÃO

A desinfecção do sistema de canais radiculares é uma das etapas fundamentais para o sucesso do tratamento endodôntico, e métodos suplementares ao preparo-químico mecânico convencional sempre foi e sempre serão investigados a fim de melhorar os principais desfechos clínicos na endodontia (Siqueira & Rôças 2011). A terapia fotodinâmica em endodontia tem sido investigada através de estudos clínicos desde 2006 (Bonsor et al. 2006), e mesmo havendo um crescimento exponencial na última década de instituições acadêmicas e pesquisadores envolvidos em estudos publicados nesse escopo (Artigo 1) (de Araújo et al. 2022), ainda há uma lacuna no conhecimento científico referente à taxa de sucesso do tratamento endodôntico quando essa intervenção suplementar é aplicada, com apenas um estudo avaliando esse desfecho (de Miranda & Colombo 2018). A maior parte das evidências de alto nível (i.e., estudos clínicos e revisões sistemáticas) dissertam sobre a significância da terapia fotodinâmica na redução da carga microbiana de pacientes com dentes permanentes (Pourhajibagher & Bahador 2019) e decíduos (Artigo 2) (Araújo et al. 2023) ou na dor pós-operatória (Elafifi-Ebeid et al. 2020) e isso constituí como uma limitação da evidência disponível para estabelecer essa intervenção como prática recomendável.

Até o presente momento, não há quaisquer efeitos colaterais reportados em pacientes (Plotino et al. 2019), porém em uma síntese de estudos laboratoriais foi observado alteração de cor em dentes extraídos (Artigo 3) (de Araújo et al. 2023). Esse efeito colateral é associado ao agente fotossensibilizante utilizado, entretanto, nenhum estudo clínico ou relato de caso observou esse achado. Outro fator que influencia na efetividade da PDT é com relação ao sistema de entrega dos agentes fotossensibilizantes. Estudos atuais demonstram que o sistema de entrega pode ser otimizado através da incorporação de nanopartículas, aumentando a ação antimicrobiana de forma controlada e reduzindo possíveis efeitos colaterais como alteração de cor e citotoxicidade (Shrestha & Kishen 2016; Diogo et al. 2019).

CONCLUSÃO

A terapia fotodinâmica na endodontia é uma opção eficaz e segura na redução da carga microbiana intracanal. Porém, futuros estudos clínicos precisam esclarecer se essa redução microbiana é relevante clinicamente, aumentando a taxa de sucesso e sobrevivência dentária ao utilizar essa intervenção suplementar. Novos agentes fotossensibilizantes com maior atividade antimicrobiana e fototerapêutica, e sem efeitos colaterais como alteração de cor devem ser desenvolvidos e investigados clinicamente à longo prazo para recomendar essa suplementação de forma rotineira.

REFERÊNCIAS

Alves-Silva EG, Arruda-Vasconcelos R, Louzada LM, de-Jesus-Soares A, Ferraz CCR, Almeida JFA, Marciano MA, Steiner-Oliveira C, Bello-Silva MS, Shemesh H, et al. 2022. The effect of photodynamic therapy on postoperative pain in teeth with primary endodontic infection. Photodiagnosis Photodyn Ther. 37:102700.

American Association of Endodontists. 2018. Treatment Standards. Chicago, ILL.

Araújo LP de, Gobbo LB, Silva TA da, Rosa WL de O da, Almeida JFA de, Gomes BPF de A, Ferraz CCR. 2023 May 17. Photodynamic therapy in the root canal treatment of primary teeth: a systematic review of clinical trials. Int J Paediatr Dent.

de Araújo LP, Marchesin AR, Gobbo LB, da Rosa WL de O, Soares A de J, de Almeida JFA, Gomes BPF de A, Ferraz CCR. 2023 May 20. Tooth color change after photodynamic therapy in endodontics: a systematic review. Photodiagnosis Photodyn Ther.:103626.

de Araújo LP, da Rosa WL de O, Gobbo LB, da Silva TA, de Almeida JFA, Ferraz CCR. 2022. Global research trends on photodynamic therapy in endodontics: A bibliometric analysis. Photodiagnosis Photodyn Ther. 40(July).

Bonsor SJ, Nichol R, Reid TMS, Pearson GJ. 2006. Microbiological evaluation of photo-activated disinfection in endodontics (An in vivo study). Br Dent J. 200(6):337–341.

Diogo P, Faustino MFA, Neves GMPMS, Palma PJ, Baptista IP, Gonçalves T, Santos JM. 2019. An insight into advanced approaches for photosensitizer optimization in endodontics—a critical review. J Funct Biomater. 10(4).

Elafifi-Ebeid H, Betancourt P, Parada-Avendaño I, Arnabat-Domínguez J. 2020. Post-endodontic pain evaluation after different intracanal laser assisted disinfection techniques. A Systematic Review. J Clin Exp Dent. 15(2):0–0.

Gomes BPFA, Berber VB, Marinho ACS, Louzada LM, Arruda-Vasconcelos R, Passini MRZ, Lopes EM, Pecorari VGA, Chen T, Paster BJ. 2022. Chemomechanical preparation influences the microbial community and the levels of LPS, LTA and cytokines in combined endodontic-periodontal lesions: A clinical study. J Periodontal Res. 57(2):341–356.

Kakehashi S, Stanley HR, Fitzgerald RJ. 1965. The effects of surgical exposures of dental pulps in germ-free and conventional laboratory rats. Oral Surgery, Oral Med Oral Pathol. 20(3):340–349.

Martinho FC, Gomes BPFA. 2008. Quantification of Endotoxins and Cultivable Bacteria in Root Canal Infection before and after Chemomechanical Preparation with 2.5% Sodium Hypochlorite. J Endod. 34(3):268–272.

Meire MA, Bronzato JD, Bomfim RA, Gomes BPFA. 2022 Sep. Effectiveness of adjunct therapy for the treatment of apical periodontitis: A systematic review and meta-analysis. Int Endod J.

de Miranda RG, Colombo APV. 2018. Clinical and microbiological effectiveness of photodynamic therapy on primary endodontic infections: a 6-month randomized clinical trial. Clin Oral Investig. 22(4):1751–1761.

MÖLLER ÅJR, FABRICIUS L, DAHLÉN G, ÖHMAN AE, HEYDEN G. 1981. Influence on periapical tissues of indigenous oral bacteria and necrotic pulp tissue in monkeys. Eur J Oral Sci. 89(6):475–484.

Plaetzer K, Krammer B, Berlanda J, Berr F, Kiesslich T. 2009. Photophysics and photochemistry of photodynamic therapy: Fundamental aspects. Lasers Med Sci. 24(2):259–268.

Plotino G, Grande NM, Mercade M. 2019. Photodynamic therapy in endodontics. Int Endod J. 52(6):760–774.

Pourhajibagher M, bahador A. 2019. Adjunctive antimicrobial photodynamic therapy to conventional chemo-mechanical debridement of infected root canal systems: A systematic review and meta-analysis. Photodiagnosis Photodyn Ther. 26:19–26.

Shrestha A, Kishen A. 2016. Antibacterial Nanoparticles in Endodontics: A Review. J Endod. 42(10):1417–1426.

Siqueira JF, Rôças IN. 2011. Optimising single-visit disinfection with supplementary approaches: A quest for predictability. Aust Endod J. 37(3):92–98.

Siqueira JF, Rôças IN. 2022. Present status and future directions: Microbiology of endodontic infections. Int Endod J. 55(S3):512–530.

Sundqvist G, Figdor D, Persson S, Sjögren U. 1998. Microbiologic analysis of teeth with failed endodontic treatment and the outcome of conservative re-treatment. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 85(1):86–93.

Wainwright M. 1998. Photodynamic antimicrobial chemotherapy (PACT). J Antimicrob Chemother. 42(1):13–28.

Apêndice 1

Súmula curricular do candidato ao grau de Doutor em Clínica Odontológica com área de concentração em Endodontia

O candidato Lucas Peixoto de Araújo nasceu em 24 de outubro de 1994, na cidade de Rio Grande, Rio Grande do Sul, Brasil. No final do ano de 2012 ingressou na Faculdade de Odontologia da Universidade Federal de Pelotas, recebendo o título de Cirurgião-Dentista em 2018. No mesmo ano, iniciou o curso de Especialização em Endodontia no Instituto Educacional Odontológico do Mercosul (Pelotas/RS), finalizando o curso em dezembro de 2019 sob orientação da Prof.ª. Dr.ª. Fernanda Graziela Côrrea Signoretti e co-orientação do Prof. Dr. Alexandre Augusto Zaia. No período de março/2019 à fevereiro/2021 realizou Mestrado em Clínica Odontológica com ênfase em Endodontia na Universidade Federal de Pelotas sob orientação do Prof. Dr. Evandro Piva, e em março/2021 à presente data realiza Doutorado em Clínica Odontológica com área de concentração em Endodontia na Faculdade de Odontologia de Piracicaba na Universidade Estadual de Campinas (FOP/UNICAMP) sob orientação do Prof. Dr. Caio Cezar Randi Ferraz.

Ademais, como experiência docente, atuou como professor do curso de Especialização em Endodontia do Instituto Educacional Odontológico do Mercosul (IEOM - Pelotas/RS) no período de 2020 à 2021, e atualmente atua como professor no curso de Especialização em Endodontia no Instituto Orofacial das Américas (IOA - Pelotas/RS) desde 2022 e também como professor de Graduação em Odontologia atuando na área de Endodontia da Universidade Católica de Pelotas desde março de 2023 (UCPel – Pelotas/RS).

Em 2022 recebeu prêmio de melhor revisor *peer-reviewer* da revista internacional *Restorative Dentistry & Endodontics* e é associado efetivo da Sociedade Brasileira de Endodontia desde 2019.

ORCID ID: https://orcid.org/0000-0003-2893-1416

Produção bibliográfica do candidato:

1. da Silva TA, **Araújo LP De**, Gobbo LB, Soares ADJ, Gomes BPFA, Almeida JFA de, et al. Outcome of root canal treatment of teeth with chronic apical periodontitis treated with foraminal enlargement and 2% chlorhexidine gel: a retrospective cohort study. J Endod. 2023;

2. Kinalski MA, **Araújo LP**, Sarkis-Onofre R, Dos Santos MBF. Endodontic therapy in patients with inherited bleeding disorders: a scoping review. Gen Dent. 2023;71(3):28–34.

3. **Araújo LP de**, Gobbo LB, Silva TA da, Rosa WL de O da, Almeida JFA de, Gomes BPF de A, et al. Photodynamic therapy in the root canal treatment of primary teeth: a systematic review of clinical trials. Int J Paediatr Dent. 2023;

4. **de Araújo LP**, Marchesin AR, Gobbo LB, da Rosa WL de O, Soares A de J, de Almeida JFA, et al. Tooth color change after photodynamic therapy in endodontics: a systematic review. Photodiagnosis Photodyn Ther. 2023;103626.

5. **Araújo LP De**, Da Rosa WLDO, De Araujo TS, Immich F, Da Silva AF, Piva E. Effect of an Intraorifice Barrier on Endodontically Treated Teeth: A Systematic Review and Meta-Analysis of in Vitro Studies. Biomed Res Int. 2022;2022.

6. Moreira Pinto L, **Peixoto de Araújo L**, Pinto Carpena L, De Souza Ferreira N, Rolim de Sousa EL. Webseminários do Projeto Endo Z: experiência em meio à pandemia. Rev UFG. 2020;20.

7. Kinalski M de A, **de Araujo LP**, dos Santos MBF. Is there a difference in the oral health status of healthy patients and those with inherited bleeding disorders? A systematic review and meta-analysis of case-control studies. Dent Rev. 2022;2(2):100046.

8. Pinto LM, **Araújo LP de**, Coutinho RD, Ramson KP, Rolim de Sousa EL. Satisfação dos ouvintes dos seminários remotos do Projeto Endo Z. Rev UFG. 2022;22.

9. Moreira-Pinto L, **Peixoto-de-Araújo L**, Pinto-Carpena L, De-Souza-Ferreira N, Rolim-de-Sousa EL. Endodontic reintervention of a mandibular second premolar with four root canals: a case report. CES Odontol. 2022;35(1):47–59.

10. **Araújo LP de**, Xavier SR, Hartwig AD, Azevedo MS, Pappen FG, Romano AR. Endodontic treatment during pregnancy: case series and literature review Tratamento. Rev Gaucha Odontol. 2020;23–23.

11. Estivalet MS, **de Araújo LP**, Immich F, da Silva AF, Ferreira N de S, da Rosa WL de O, et al. Bioactivity Potential of Bioceramic-Based Root Canal Sealers: A Scoping Review. Life. 2022;12(11):1853.

12. **de Araújo LP**, da Rosa WL de O, Gobbo LB, da Silva TA, de Almeida JFA, Ferraz CCR. Global research trends on photodynamic therapy in endodontics: A bibliometric analysis. Photodiagnosis Photodyn Ther. 2022;40(July).

13. **Araújo LP de**, Rosa WL de O da, Carpena LP, Pinto LM, Falson LAS, Ferreira N de S, et al. Intentional foraminal enlargement: a systematic review with bibliometric analysis. Brazilian Dent Sci. 2022;25(4):e3506.

14. **de Araújo LP**, de Azevedo Kinalski M, Carpena LP, Ferraz CCR, Dos Santos MBF. One-year follow-up of endodontic retreatment in a patient with severe Hemophilia A. G Ital Endod. 2022;36(1):151–9.

ANEXOS

ANEXO 1 - Comprovante de publicação do Artigo 1

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Global research trends on photodynamic therapy in endodontics: A bibliometric analysis

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A R T I C L E I N F O

Keywords:
Photodynamic therapy
Endodontics
Root canal preparation
Bibliometrics
Review

A B S T R A C T

Background: Photodynamic therapy (PDT) is an adjunctive treatment that aims to inactivate microorganisms through an oxidative reaction produced by irradiating a photosensitizing agent. The quest for improved root canal disinfection has sought supplementary methods when performing chemomechanical procedures. From this perspective, PDT protocols were proposed as an auxiliary approach in endodontics. Thus, the aim of this study was to investigate publication metrics and research trends related to this scope.

Methods: This review is reported in accordance with the PRISMA 2020 recommendations. Two blinded and independent reviewers systematically searched five electronic databases until December 2021. The acquired bibliometric parameters were analyzed through descriptive statistics and graphical mappings with VOSViewer software.

Results: The search retrieved 342 studies from 84 journals originating from 33 countries. About 85% of the included studies were published over the last decade. Most of the available evidence is laboratory-based (74.5%), and the main clinical outcomes evaluated were microbiological load reduction and postoperative pain. Mayram Pourhajibagher is the researcher with the most publications as the first author (n = 16). Tehran University of Medical Sciences carried out the highest number of studies (n = 29), and *Photodiagnosis and Photodynamic Therapy* is the journal that most published on the theme (n = 111).

Conclusions: This bibliometric analysis mapped and discussed the scientific progress and publication metrics in PDT in endodontic research. Additionally, future perspectives were highlighted and should focus on discovering new photosensitizer agents, standardizing optimal photoactivation protocols, and conducting more clinical-oriented research.

ANEXO 2 - Comprovante de publicação do Artigo 2

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SYSTEMATIC REVIEW

INTERNATIONAL JOURNAL OF PAEDIATRIC DENTISTRY WILEY

Photodynamic therapy in the root canal treatment of primary teeth: A systematic review of clinical trials

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Coordenação de Aperfeiçoamento de Pessoal de Nível Superior

Abstract

Background: Dental caries is the most common oral disease worldwide, and it is estimated to affect 2.3 billion people, with at least 530 million of them being schoolchildren with decayed primary teeth. This condition can rapidly evolve into irreversible pulp inflammation and pulp necrosis and thus requiring endodontic intervention. Photodynamic therapy (PDT) is a supplementary method to conventional pulpectomy and is used to improve the protocol used for disinfection.

Aim: The main objective of this study was to evaluate through a systematic review the efficacy of supplementary PDT on the pulpectomy of primary teeth. This review was registered a priori on the PROSPERO database (CRD42022310581).

Design: Two independent and blinded reviewers carried out a comprehensive search in five databases: PubMed, Cochrane, Scopus, Embase, and Web of Science. Eligible studies were randomized and nonrandomized clinical trials that evaluated in vivo microbiological load or clinical outcomes after using supplementary PDT in infected primary teeth.

Results: After the selection process, four studies met the inclusion criteria and were included in this study. Data regarding the sample characteristics and PDT protocols were retrieved. All included trials used phenothiazinium salts as photosensitizer agents. Only one study observed a significant difference in the in vivo microbiological load reduction outcome when performing PDT on primary teeth. The remaining studies all discussed the possible benefits of this intervention; however, none observed a significant difference in this outcome.

Conclusion: In this systematic review, moderate-to-low certainty of the available evidence was observed, and thus, no significant conclusions can be drawn from the findings.

Anexo 3 – Comprovante de publicação do Artigo 3

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Tooth color change after photodynamic therapy in endodontics: A systematic review

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Systematic review
Photodynamic Therapy

ABSTRACT

Background: A smile is considered one of the most important soft skills in social interaction. And discolored teeth may effect this. It is known that some photosensitizer agents (PS) used in photodynamic therapy (PDT) during root canal treatment could play a significant role in tooth color change, and thus the main objective of this systematic review is to address whether performing PDT can influence tooth color change and to synthesize the most effective methods to remove PS from the root canal system.

Methods: This study followed the PRISMA 2020 statement, and the protocol was registered at the Open Science Framework. Two blinded reviewers searched five databases up to November 20th, 2022: Web of Science, PubMed, Scopus, Embase, and the Cochrane Library. The eligibility criteria were studies that investigated tooth color change after PDT in endodontics.

Results: A total of 1695 studies were retrieved, and 7 were included in the qualitative analysis. All the included studies were *in vitro* evidence and investigated five different PS: methylene blue, toluidine blue O, malachite green, indocyanine green, and curcumin. Besides curcumin and indocyanine green, the remaining agents all caused tooth color change, and no method employed was effective in fully removing these PS from inside the root canal system

Conclusions: Even though the findings showed that curcumin and indocyanine green did not influence tooth color change, the present evidence should be interpreted with caution since it is based on laboratory studies with questionable methods, and all efforts should be employed to avoid this undesirable side effect during clinical practice.

Anexo 4 – Relatório de similaridade

Tese Doutorado

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