UNIVERSIDADE FEDERAL DO PARANÁ

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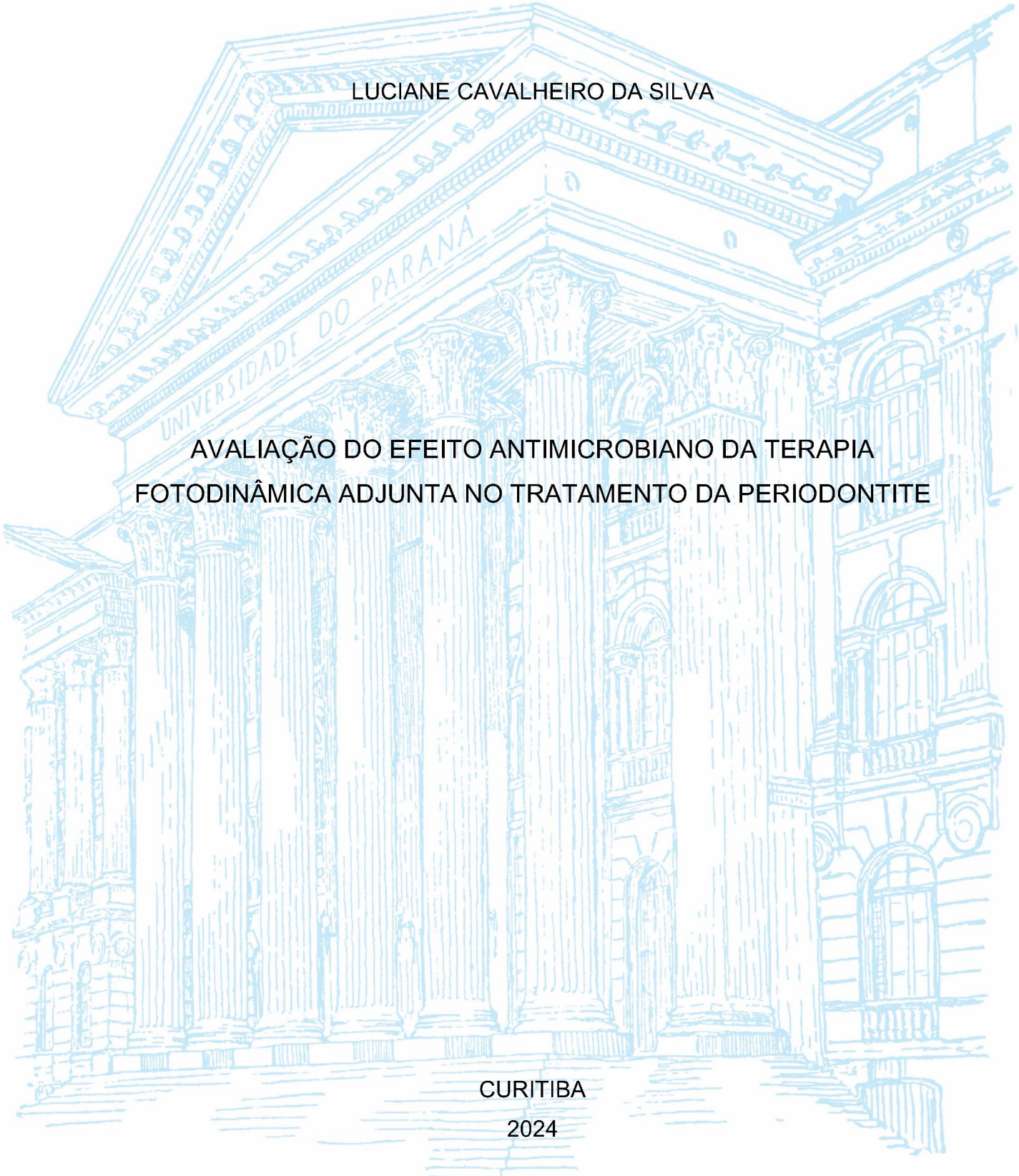

AVALIAÇÃO DO EFEITO ANTIMICROBIANO DA TERAPIA FOTODINÂMICA ADJUNTA NO TRATAMENTO DA PERIODONTITE

CURITIBA

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Dissertação apresentada ao Programa de Pós-Graduação em Odontologia, Área de concentração Clínica Odontológica, nível Mestrado, Setor de Ciências da Saúde, Universidade Federal do Paraná, como requisito parcial à obtenção do título de Mestre em Odontologia.

Orientadora: Prof(a). Dr(a). Geisla Mary Silva Soares

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TERMO DE APROVAÇÃO

Os membros da Banca Examinadora designada pelo Colegiado do Programa de Pós-Graduação ODONTOLOGIA da Universidade Federal do Paraná foram convocados para realizar a arguição da dissertação de Mestrado de **LUCIANE CAVALHEIRO DA SILVA** intitulada: **Avaliação do efeito antimicrobiano da terapia fotodinâmica adjunta no tratamento da periodontite**, sob orientação da Profa. Dra. GEISLA MARY SILVA SOARES, que após terem inquirido a aluna e realizada a avaliação do trabalho, são de parecer pela sua Aprovação no rito de defesa.

A outorga do título de mestra está sujeita à homologação pelo colegiado, ao atendimento de todas as indicações e correções solicitadas pela banca e ao pleno atendimento das demandas regimentais do Programa de Pós-Graduação.

CURITIBA, 19 de Dezembro de 2024.

GEISLA MARY SILVA SOARES
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Dedico este trabalho ao meu Deus, fonte de toda sabedoria e força, que me capacitou e sustentou em cada passo desta jornada. Ao meu amado esposo, cujo apoio incansável e amor constante foram fundamentais para que eu chegasse até aqui. E aos meus queridos pais, que com imenso carinho, dedicação e esforço, sempre lutaram para que eu pudesse alcançar meus objetivos e realizar meus sonhos.

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A sabedoria é a árvore que dá vida a quem a abraça; quem a ela se apega será abençoado.

(Provérbios 9:10)

RESUMO

A periodontite é uma doença crônica, que afeta mais de um bilhão de pessoas ao redor do mundo e, portanto, é considerada um problema de saúde pública. A definição de periodontite é de doença inflamatória crônica, associada a um biofilme disbiótico, que resulta na destruição do periodonto de sustentação e, quando não tratada, pode levar à perda dentária. O biofilme dental disbiótico contém contagens e proporções aumentadas de bactérias periodontopatogênicas, que levam a uma resposta inflamatória exacerbada do hospedeiro. Quando essa inflamação não é controlada ela leva à reabsorção óssea periodontal. O tratamento padrão da periodontite inclui orientação de higiene, motivação para o controle do biofilme, remoção de fatores de retenção do biofilme e a remoção do biofilme e cálculo supra e subgengivais, além do controle de fatore sistêmicos associados à doença, como fumo e diabetes. Casos avançados da periodontite podem não ser resolvidos somente com o tratamento padrão e, nesses casos, terapias adjuntas podem ser utilizadas. Dentre as terapias auxiliares, a terapia fotodinâmica antimicrobiana (aPDT), composta por uma fonte de luz e um fotossensibilizador, tem sido investigada para auxiliar na redução de patógenos periodontais e, consequentemente, nas melhoras clínicas. Estudos *in vitro* tem demostrado uma capacidade antimicrobiana da aPDT em biofilmes, bem como em patógenos periodontais, tais como *Aggregatibacter actinomycetemcomitans Fusobacterium nucleatum; Porphyromonas gingivalis.* Alguns estudos clínicos demostram esta mesma efetividade antimicrobiana, contudo há uma heterogeneidade entre os estudos realizados quanto ao protocolo de aplicação da aPDT, o que leva a um resultado controverso. Assim, o presente estudo teve como objetivo analisar sistematicamente as evidências científicas de estudos clínicos sobre o efeito antimicrobiano da aPDT na terapia periodontal. Para a revisão sistemática, 8 bases de dados foram utilizadas, e delas, foram selecionados apenas estudos clínicos randomizados. O risco de viés dos estudos incluídos foi avaliado pela ferramenta RoB 2 Assessment Form e todos os dados foram sumarizados em 2 tabelas, contendo as principais informações dos estudos. Um total de 4.044 artigos foram encontrados, e destes, 32 artigos foram incluídos para a revisão sistemática. Dentre os estudos, 50% observaram maior redução de patógenos periodontais quando a terapia mecânica não cirúrgica foi realizada junto com aPDT, em comparação com raspagem e alisamento radicular sozinha ($p<0,05$). Entre os patógenos periodontais avaliados, 11 estudos relataram redução significativa em *Porphyromonas gingivalis*, 7 estudos observaram reduções *Aggregatibacter actinomycetemcomitans,* 6 estudos observaram reduções em *Tannerella forsythia* e 5 estudos relataram redução em *Treponema denticola.* Além disso, quanto ao tipo de laser e fotossensibilizador mais utilizados, estão o mais laser de diodo no comprimento de 660 nm e o fotossensibilizador azul de toluidina. Assim, conclui-se que, apesar dos resultados promissores da aPDT na saúde periodontal, não se pode afirmar que esta seja mais eficaz do que a raspagem e alisamento radicular isoladamente.

Palavras-chave: periodontite; fotoquimioterapia; fármacos fotossensibilizadores; ação antimicrobiana; revisão sistemática.

ABSTRACT

Periodontitis is a chronic disease that affects over one billion people worldwide, making it a public health issue. The definition of periodontitis is a chronic inflammatory disease associated with a dysbiotic biofilm, which results in the destruction of the supporting periodontium and, when untreated, can lead to tooth loss. The dysbiotic dental biofilm contains increased counts and proportions of periodontopathogenic bacteria, which trigger an exacerbated host inflammatory response. When this inflammation is not controlled, it leads to periodontal bone resorption. The standard treatment for periodontitis includes hygiene guidance, motivation for biofilm control, removal of biofilm retention factors, and supra- and subgingival biofilm and calculus removal, as well as the management of systemic factors associated with the disease, such as smoking and diabetes. Advanced cases of periodontitis may not be resolved with standard treatment alone, and in these cases, adjunctive therapies may be used. Among the adjunctive therapies, antimicrobial photodynamic therapy (aPDT), which consists of a light source and a photosensitizer, has been investigated to help reduce periodontal pathogens and, consequently, improve clinical outcomes. In vitro studies have demonstrated the antimicrobial capacity of aPDT on biofilms as well as on periodontal pathogens, such as *Aggregatibacter actinomycetemcomitans*, *Fusobacterium nucleatum*, and *Porphyromonas gingivalis*. Some clinical studies have shown the same antimicrobial effectiveness, but there is heterogeneity among the studies regarding the aPDT application protocol, leading to controversial results. Thus, the present study aimed to systematically analyze the scientific evidence from clinical studies on the antimicrobial effect of aPDT in periodontal therapy. For the systematic review, 8 databases were used, and only randomized clinical trials were selected. The risk of bias of the included studies was assessed using the RoB 2 Assessment Form, and all data were summarized in 2 tables, containing the main information from the studies. A total of 4,044 articles were found, and 32 articles were included in the systematic review. Among the studies, 50% observed a greater reduction of periodontal pathogens when non-surgical mechanical therapy was performed together with aPDT, compared to scaling and root planing alone ($p<0.05$). Among the periodontal pathogens evaluated, 11 studies reported significant reduction in *Porphyromonas gingivalis*, 7 studies observed reductions in *Aggregatibacter actinomycetemcomitans*, 6 studies reported reductions in *Tannerella forsythia*, and 5 studies reported reductions in *Treponema denticola*. Additionally, regarding the type of laser and photosensitizer most commonly used, the diode laser at a wavelength of 660 nm and the toluidine blue photosensitizer were the most frequent. In conclusion, despite the promising results of aPDT in periodontal health, it cannot be stated that it is more effective than scaling and root planing alone.

Keywords: periodontitis; photochemotherapy; photosensitizing drugs; antimicrobial action; systematic review.

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aPDT	- Terapia fotodinâmica antimicrobiana
PICOT estudo	- População; intervenção; comparador; desfecho(outcome); tipo de
RoB	- Risk of Bias (risco de viés)

SUMÁRIO

1 INTRODUÇÃO

As doenças periodontais são condições de saúde que afetam a qualidade de vida da população pois tem estreita relação com outras doenças sistêmicas, tais como: doenças cardiovasculares, diabetes, câncer, entre outras. Sobretudo, a presença da periodontite impacta diretamente no bem-estar e na condição socioeconômica do indivíduo devido aos custos gerados para o tratamento desta doença (DOLINSKA et al, 2022).

Estima-se que a prevalência das doenças periodontais seja de 20% a 50% da população no mundo, afetando mais de um bilhão de pessoas (LAZUREANU et al, 2022). Dentre as doenças periodontais, de acordo com o Global Burden of Disease Study (2017), a periodontite avançada é a 11ª condição mais prevalente representando cerca de 753 milhões de indivíduos e sua incidência aumenta conforme o passar da idade.

A saúde periodontal baseia-se na definição de saúde da Organização Mundial da Saúde na qual, quando avaliado clinicamente, constata-se ausência de doença, mesmo em pacientes com histórico de gengivite ou periodontite, não apresentando sinais clínicos de inflamação gengival (CHAPPLE et al, 2018). Já a periodontite é definida como uma doença inflamatória crônica, associada a um biofilme disbiótico que resulta na destruição progressiva dos tecidos periodontais de proteção e sustentação e, quando não tratada, pode levar à perda dentária. Suas características clínicas incluem a perda de inserção clínica e perda óssea alveolar avaliada radiograficamente, inflamação gengival, presença de bolsa periodontal, sangramento à sondagem, mobilidade e migração patológica (PAPAPANOU et al, 2018).

A periodontite pode ser classificada de acordo com sua severidade e sua evolução. O estadiamento da doença envolve 4 estágios sendo o estágio I uma periodontite mais leve e o estágio IV uma periodontite mais avançada. Além disso, o risco de progressão da doença se dá em três graus: A, B e C (baixo risco, risco moderado e alto risco de progressão, respectivamente). A classificação da doença permite ao dentista tratar o paciente a fim de, não somente eliminar a doença, mas

modificar seus hábitos e também fatores ambientais que afetam diretamente o desenvolvimento e progressão da periodontite (CATON et al, 2018).

O desenvolvimento da doença acontece devido a uma complexa interação entre o hospedeiro e seus mecanismos de defesa, fatores ambientais e patógenos bacterianos específicos (KWON; LAMSTER e LEVIN, 2021). A inflamação crônica é resultante de um biofilme disbiótico, constituído principalmente de espécies bacterianas anaeróbias gram-negativas caracterizadas como complexo vermelho na qual são, predominantemente, encontradas em bolsas periodontais profundas (SOCRANSKY e HAFFAJE, 2005).

Em estado de saúde ou simbiose, os microrganismos orais estão em quantidades e proporções compatíveis com a saúde, mas em disbiose as contagens e proporções dos patógenos periodontais aumentam, o que gera uma resposta inflamatória exacerbada, que levará às alterações clínicas periodontais, como perda de inserção clínica, aumento da profundidade de sondagem, sangramento à sondagem, formação de bolsas periodontais, e por último, à perda do dente (BOSSHARDT, 2018). Dentre as espécies bacterianas periodontopatogênicas se destacam *Aggregatibacter actinomycetemcomitans Fusobacterium nucleatum; Porphyromonas gingivalis; Prevotella intermedia; Treponema denticola* (SOCRANSKY e HAFFAJE, 2005).

Dentre os principais objetivos no tratamento da periodontite está a interromperrupção da progressão da doença preservando condições periodontais saudáveis e estáveis, bem como reduzir ou eliminar as espécies patogênicas que causam as doenças periodontais (RAMANAUSKAITE e MACHIULSKIENE, 2020). Para tanto todos os pacientes com periodontite devem ser tratados com a terapia básica já instituída: conscientização e eliminação dos fatores de risco, instruções de higiene para o paciente, remoção mecânica do biofilme e raspagem supragengival e subgengival (SANZ et al, 2020). Para casos graves, a terapia periodontal não cirúrgica associada a terapias adjuvantes, como o uso de antibióticos, está indicada (YANG et al, 2021).

Na reavaliação, espera-se que o paciente não apresente bolsas periodontais maiores que 4 mm com sangramento à sondagem ou bolsas profundas maiores que 6 mm. Em casos não responsivos a estes objetivos terapias auxiliares,

juntamente com a raspagem, como o uso de antimicrobianos sistêmicos ou locais, agentes físicos ou químicos e moduladores do hospedeiro, estão indicadas. Estas terapias podem contribuir para uma melhora clínica, na resposta do hospedeiro e na eliminação de microrganismos patógenos locais (CALCIOLARI et al, 2022).

Dentre as terapias adjuvantes, o laser de baixa potência e a terapia fotodinâmica antimicrobiana (traduzida de Antimicrobial Photodinamic Therapy - aPDT) tem sido investigada para auxiliar na instrumentação mecânica não cirúrgica, principalmente em locais com acesso prejudicado como em bolsas profundas e áreas de furca (SALVI et al, 2020). É uma terapia não invasiva e, dentre suas vantagens destaca-se a capacidade de atingir seletivamente as bactérias periodontais, evitando assim, efeitos adversos (HAAG, STEIGER-RONAY e SCHMIDLIN, 2015).

A aPDT consiste na associação de uma fonte de luz visível, ou infravermelho próximo ao comprimento de onda apropriado, combinado com um corante, sensível à luz, chamado de fotossensibilizador. Este fotossensibilizador irradiado com luz resulta na formação de radicais livres de oxigênio singlete que leva à oxidação de vários componentes celulares e inativação celular dos microrganismos (KWIATKOWSKI et al, 2018).

Os fotossensibilizadores são substâncias capazes de absorver a luz, cada qual em diferentes comprimentos de onda variando entre 630 e 700 nm, desencadeando reações fotoquímicas ou fotofísicas (KWIATKOWSKI et al, 2018). Dentre os fotossensibilizadores, os principais utilizados na Odontologia são derivados de hematoporfirina, fenotiazina, como azul de toluidina e azul de metileno, cianina, benzoporfirina, agentes fitoterápicos e hialocianinas (MEISEL e KOCHER, 2005). Já as fontes de luz utilizadas na terapia fotodinâmica podem ser lasers, LEDs, lâmpadas de arco ou fontes de luz fluorescentes, sendo os mais comuns os lasers de hélio-neon (633 nm), os lasers de diodo de gálio-alumínio-arsenieto (630–690, 830 ou 906 nm) e os lasers de argônio (488–514 nm) (GURSOY et al, 2013).

Atualmente, aPDT é amplamente utilizada em diversas áreas da Odontologia, todavia, seu uso deu-se início na área da Medicina com as observações de Raab em 1900 que constatou a morte de protozoário mediante a um corante de laranja de acridina. Em 1907 Von Tappeiner, em conjunto com Jodlbauer observaram que o oxigênio tinha papel fundamental no mecanismo de

ação da aPDT (MACCORMACK, 2006). Mais tarde, Dr. Friedrich Meyer-Betz testou a eficácia da associação de um fotossensibilizador com uma fonte de luz e presença de oxigênio na área da dermatologia e assim a terapia fotodinâmica se difundiu para outras áreas como ginecologia e urologia (PRAZMO et al, 2016).

Na Odontologia a aPDT é considerada uma modalidade de tratamento inovador pela sua capacidade de estímulo celular, controle de dor, e anti-infecciosa, e sendo muito utilizada como terapia de diversas condições como tumores, lesões orais ou pré-malignas, doenças autoimunes e no controle e/ou eliminação de infeções fúngicas, virais e bacterianas (GURSOY et al, 2013; HU et al, 2018). Com o uso abusivo de antibióticos e o surgimento de bactérias multirresistentes, a aPDT tornou-se uma terapia atraente devido ao seu efeito antimicrobiano local (GHOLAMI et al, 2023).

A ação antimicrobiana da aPDT no microrganismo acontece por meio de um dano celular principalmente por três mecanismos: dano à membrana celular, dano ao DNA e inativação de proteína/enzima (HAMBLIN e HASAN, 2004). A aPDT demonstrou eficácia contra bactérias gram-positivas e gram-negativas, contudo, seu efeito é maior em bactérias gram-positivas devido à estrutura da parede celular de peptidoglicano quando comparada às bactérias Gram-negativas (WARRIER et al, 2021).

Para patógenos periodontais, a aPDT demonstra um potencial efeito em reduzir ~~apresenta redução significativa~~ a quantidade de espécies como *P. gingivalis*, *A. actinomycetemcomitans* e *F. nucleatum*, porém, em um menor grau para a cepa de *A. actinomycetemcomitans* (HAAG, STEIGER-RONAY e SCHIDLIN, 2015). Além disso, a aPDT foi eficaz na erradicação de cepas bacterianas tanto em sua forma planctônica quanto em biofilme (SONGCA e ADJEI, 2022). Todavia, sua efetividade é maior quando as bactérias estão em fase planctônica do que quando estão organizadas em um biofilme (STREET, PEDIGO e LOEBEL, 2010). Sobretudo, a terapia fotodinâmica tem papel fundamental na redução e eliminação de patógenos periodontais através do estresse oxidativo induzido por oxigênio reativo, enfraquecimento da matriz do biofilme, perda de adesão e alterações de componentes estruturais, podendo auxiliar no tratamento periodontal (MANG et al, 2016).

1.1 JUSTIFICATIVA

Diversos estudos *in vitro* e estudos clínicos randomizados sugerem o uso da terapia fotodinâmica como terapia antimicrobiana adjuvante no tratamento da periodontite. Contudo, os estudos apresentam grande diversidade entre protocolos utilizados, na qual o tipo do laser, tipo do fotossensibilizador e tempo de aplicação são variados; poucas avaliações do efeito da terapia no perfil microbiológico periodontal e consequentemente resultados clínicos controversos. O principal questionamento sobre a aPDT é qual protocolo pode causar os melhores e duradouros efeitos. Mais especificamente, falta confirmar se há uma superioridade e um verdadeiro efeito antimicrobiano da terapia fotodinâmica em espécies bacterianas periodontais que beneficíe um resultado clínico significativo no tratamento periodontal.

1.2 OBJETIVOS

Analisar sistematicamente as evidências científicas de estudos clínicos sobre efeito antimicrobiano na terapia periodontal.

1.2.1Objetivos específicos

- Verificar a efetividade antimicrobiana da terapia fotodinâmica comparado à terapia periodontal básica;
- Identificar quais espécies sofreram maior ação antimicrobiana da terapia fotodinâmica;
- Identificar qual protocolo utilizado obteve melhores resultados na redução de microrganismos patogênicos.

2 ARTIGO

Apresentado de acordo com as normas da Revista Pesquisa Brasileira em Odontopediatria e Clínica Integrada

THE ANTIMICROBIAL EFFECT OF PHOTODYNAMIC THERAPY IN THE TREATMENT OF PERIODONTITIS: A SYSTEMATIC REVIEW

ABSTRACT

Objective: The aim of this study was to answer if adjunctive photodynamic therapy have an antimicrobial effect on periodontal therapy.
Methods: This systematic review was conducted according to Cochrane guidelines. The protocol was registered in PROSPERO database (CRD42024521843). The PICOT strategy was built based on the question "Does adjunctive photodynamic therapy have an additional antimicrobial effect in periodontal therapy compared to subgingival mechanical therapy alone?" The articles were assessed for risk of bias using the Cochrane Risk of Bias tool, and all data were summarized in two tables for comparison and analysis.
Results: Results were reported according to PRISMA checklist. Thirty two articles published between 2000 and 2024 were selected for qualitative analysis. The follow-up range was just after therapy–1 year. After analysis about the risk of bias 4 studies were considered to have a low risk; 17, unclear; and, 11 studies have been considered with a high risk of bias. 50% of the studies found statistically significant higher reduction in counts or detection of specific periodontal pathogens using scaling and root planing (SRP) and aPDT than SRP alone. Bacterial species analysis included a significant reduction of *Porphyromonas gingivalis* by 11 studies, *Aggregatibacter actinomycetemcomitans*, by 7 studies; *Tannerella forsythia*, by 6 studies and 5 studies reported significant reduction of *Treponema denticola*.
Conclusion: Significant higher antimicrobial effect with the adjunctive use of aPDT compared to scaling alone was observed. However, the heterogeneity among studies limits the ability to assert the superiority in terms of a greater antimicrobial effect when add aPDT to the periodontal therapy.

Keywords: Periodontitis; Photodynamic therapy; Antimicrobial.

INTRODUCTION:

Periodontitis is an infectious inflammatory disease associated with a dysbiotic biofilm. Clinically, periodontitis causes a progressive destruction of the dental support apparatus, with gingival inflammation, periodontal attachment loss, periodontal pockets, bleeding on probing and dental mobility[1] and, when it is untreated, can lead to tooth loss. The onset of this disease happens with complex interaction between the host, environmental factors, and specific periodontal pathogens[2,3], when the simbiosis among these factors is lost

and the immune system has an exacerbated answer leading to the periodontal attachment loss[4].

Periodontitis treatment should be applied as early as possible, involving awareness and elimination of risk factors, oral hygiene instructions, professional mechanical biofilm removal, and supragingival and subgingival scaling[5] in order to control supragingival biofilm, remove dental calculus, as well as to eliminate periodontal pockets and bleeding on probing. It is expected that, upon re-evaluation, the patient will not have periodontal pockets greater than 4 mm with bleeding on probing or deep pockets greater than 6 mm[5].

The efficacy of non-surgical periodontal therapy with scaling and root planing (SRP) is well substantiated[6], but it has limitations, particularly for severe cases characterized by teeth mobility, several periodontal deep pockets and furcation lesions[2,7]. In such scenarios SRP with some frequency fails to induce the ecological changes required to achieve and sustain the desired clinical outcomes over the long term[8]. When the treatment fails in closing deep pockets, the presence of these residual sites can accelerate disease progression. Therefore, residual sites have been used as clinical signs of incomplete periodontal treatment[10] and guiding the use of adjunctive therapies, such as anti-infective surgical therapy, local or systemic antimicrobial therapy[9], laser therapy, and photodynamic therapy[11].

Antimicrobial photodynamic therapy (aPDT) has been investigated to assist in non-surgical mechanical instrumentation, especially in areas with limited access such as deep pockets and furcation areas[12]. The laser therapy can modulate cellular metabolism in surrounding tissues of periodontal wounds, promoting healing and regeneration of debrided and decontaminated tissues. Furthermore, low-intensity diode lasers, in conjunction with a photosensitizer, have a phototoxic action that can reduce or eliminate periodontal pathogens present in periodontal pockets, thus assisting in the treatment of patients with periodontitis[13]. Moreover, photosensitizer is stimulated to form singlet oxygen free radicals, leading to the oxidation of various cellular components and rapid cell inactivation of microorganisms by weakening of the biofilm matrix, loss of adhesion, and alterations of structural components[14,15].

The type of photosensitizer, the energy density of the light, and the maturity of the biofilm are directly linked to the effectiveness of aPDT over the biofilm[16]. Although various randomized clinical trials have shown promising results using aPDT, including clinical

improvements and reductions in periodontal pathogens, it frequently does not provide additional clinical improvements when compared with conventional mechanical therapy[13]. The heterogeneity of aPDT protocols and study designs makes it difficult to determine the scientific evidence of clinical improvements. It remains unclear whether the limitations in clinical benefits are attributable to the absence of an ideal protocol or to the therapy's failure to induce sufficient ecological changes necessary for achieving and sustaining the desired clinical outcomes.

Therefore, the aim of the present systematic review was to investigate the antimicrobial effects of aPDT in the treatment of periodontitis?

MATERIALS AND METHODS

Protocol and registration

This systematic review was designed according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) checklist[17] and the Cochrane guidelines[18]. The systematic review protocol was registered in the PROSPERO database CRD42024521843.

Focused question and eligibility criteria for inclusion and exclusion studies

The PICOT strategy for systematic review was constructed to answer the research question: “Does photodynamic therapy have an antimicrobial effect on periodontal therapy?” Thus, the PICOT strategy was:

Population: patients with any type of periodontitis that received mechanical periodontal therapy.

Intervention: non-surgical mechanical periodontal treatment with application of antimicrobial photodynamic therapy (aPDT).

Comparison: non-surgical mechanical periodontal treatment alone.

Outcome: antimicrobial effect, by means of changing in counts or proportion of specific periodontal microorganisms or in microbial profile.

Type of studies: clinical studies and randomized clinical trials.

Search strategy

Publications were searched on the database Embase, Web of Science, PubMed, Scopus, and LILACS. To avoid biases, grey literature was also consulted: OpenGrey, ProQuest, and Google Scholar. The search strategy used was constructed by the Embase platform using Health Sciences Descriptors (DeCS), and their synonyms, for selection of keywords and the Boolean operators "AND" and "OR". Thus, the following search strategy was obtained: "periodontal disease" AND "photodynamic therapy" AND "anti-infective agent". For other databases, the search strategy was adapted accordingly. The entire list is on Supplemented Table 1. The search for studies was conducted by a single operator (LCS) and began in December 2023, restricted to publications written in English, Portuguese, and Spanish, and articles published after the year 1999. The records obtained were exported to the Mendeley Reference Management Software for detection and exclusion of duplicates.

Eligibility criteria

Studies were not included if: (1) they were not related to the topic; (2) studies of literature reviews, letters to the editor, book chapters, thesis, abstracts and editorials; (3) studies that used the photodynamic therapy technique on microorganisms not associated with periodontal disease; (4) tested the photodynamic therapy technique alone in periodontal treatment, without a mechanical therapy; (5) did not have a control group receiving only SRP.

All studies included in this review were randomized clinical trials; therefore, the risk of bias was assessed using the Cochrane Risk of Bias tool for randomized trials (RoB 2 Assessment Form). The RoB 2 tool consists of six domains: randomization process, bias arising from period and carryover effects, deviations from intended interventions, missing outcome data, outcome measurement, and selection of reported outcomes. Each domain is classified as low risk, some concerns, or high risk. This process was performed by two independent authors (LC and WBV).

Summary measures and data-synthesis

For summary of results, the information from the articles was summarized in two tables, consolidating the main information into a single table, which included: microbiological analysis, microorganisms identification before and after scaling and aPDT and follow up.

As for complementary information, a second table was created with: sample size, classification of periodontitis, periodontal treatment protocol, photodynamic therapy treatment protocol, photosensitizer and laser used, time and number of aPDT sessions and the clinical parameter results.

RESULTS

Study selection

An electronic search identified 4.044 studies. Of these, 364 studies were selected by reading the title, in different databases. Duplicates were excluded and 210 records remained for abstract screening. After excluding 146 articles that did not meet the eligibility criteria, 64 articles remained for full text evaluation. Then, 32 articles were excluded for the following reasons: articles on peri-implatitis (3); applied laser as the only therapy (1); article not complete for reading (6); article on gingivitis (1); retrospective article (1); articles with periodontal surgery (3); thesis (1); without complete microbiological data (1); articles that used aPDT associated to the use of chlorhexidine mouthrinse (3); article that used aPDT associated with systemic antibiotics (1); articles without the control group receiving only with scaling (10); and article removed from publication (1). Thus, 32 articles remained and were included for qualitative and quantitative analysis (Figure 1).

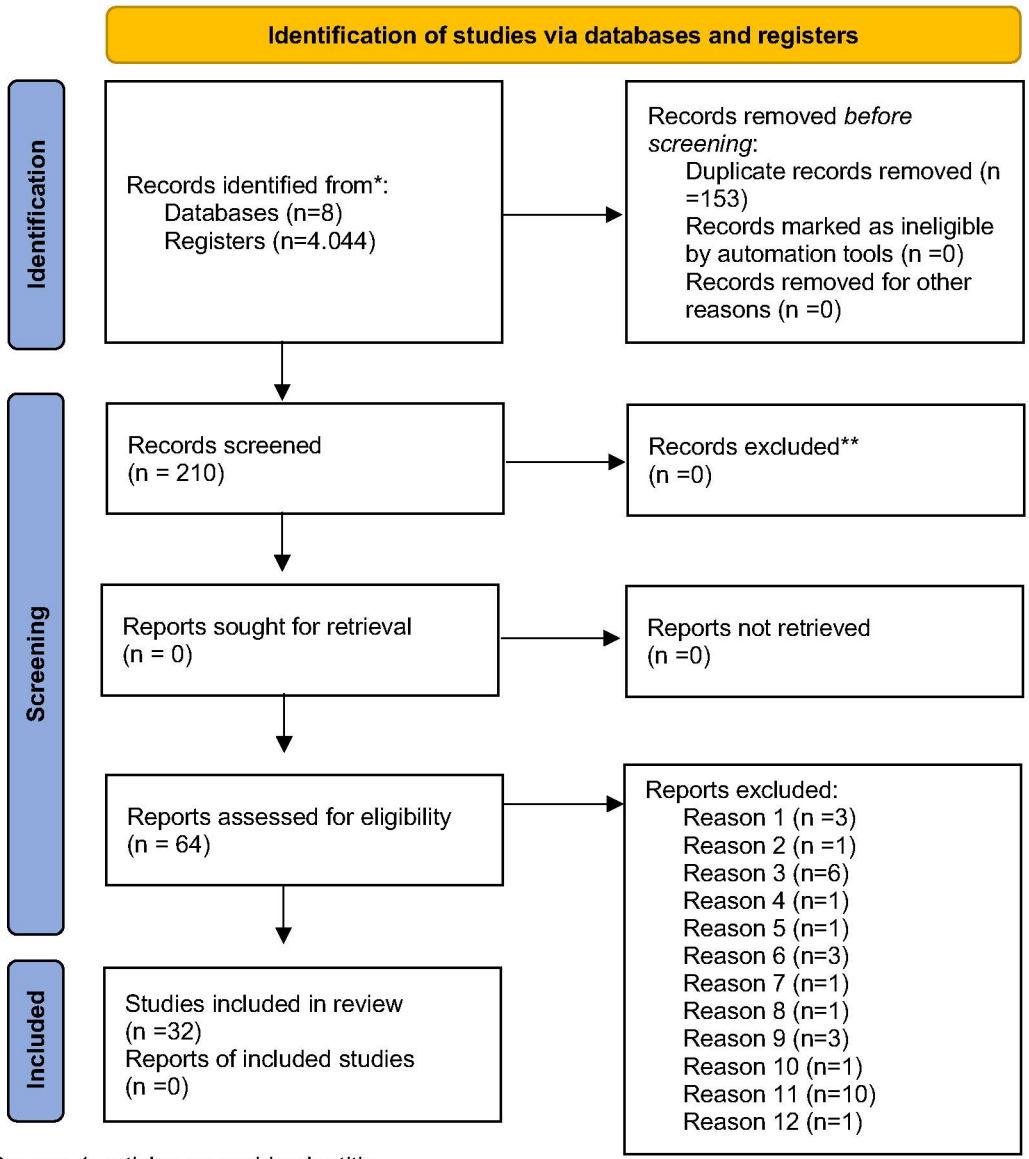
Characteristics of included studies

Articles conducted in several countries were included, such as from Brazil, India, Saudi Arabia, Germany, Iran, Poland, Italy, Romania, Egypt, Austria, Serbia and Switzerland. A total of 1.021 patients were included in the studies, with 410 male participants and 437 female participants. Six studies did not specify the number of participants by gender, only the total number.

Risk of bias assessment

The summary of bias risk assessment is in Figure 2. Four studies were considered to have a low risk of bias[19,20,21,22]. Seventeen studies were deemed to have an unclear risk of bias[23,24,25,26,27,28,29,30,31,32,33,34,35,36,37,38,39]. And, 11 studies have been considered with a high risk of bias[40,41,42,43,44,45,46,47,48,49,50]. The methods of blinding and random allocation were not thoroughly described in all studies. The domain five of the Cochrane Risk of Bias tool, about the clinical study protocol with a pre-specified analysis plan to be compared to the outcomes reported in the article, was the most prevalent cause for some concerns studies classification.

Figure 1: Flowchart of study selection for systematic review based on the PRISMA guidelines.



Reason 1: articles on peri-implantitis
Reason 2: laser-only articles
Reason 3: article not complete for reading
Reason 4: article on gingivitis
Reason 5: retrospective article
Reason 6: used aPDT with periodontal surgery
Reason 7: thesis
Reason 8: without microbiological data
Reason 9: used aPDT with chlorhexidine
Reason 10: used aPDT with antibiotics
Reason 11: absence of a control group, using only scaling
Reason 12: article removed from publication

Synthesis of microbiological results

Microbial samples were processed by different techniques, 18 studies accessed the microbiological content using real-time PCR methodology to detect specific periodontophatogens[21,22,23,24,25,26,27,30,32,34,36,37,38,40,41,43,49,50]; bacterial culture and colonies form counting method was applied in six studies[31,42,45,48,47,48]; micro-IDENT was used by one study[28]; one study used DNA probe kit[20]; Checkerboard DNA-DNA hybridization was used by four studies[19,29,39,44]; and Molecular-biological test system hybridization with RNA was applied in other two studies[33,35].

Of the 32 studies, 12 evaluated microbiological effects up to three months after treatment; 13, up to six months, one study re-examined up to 12 months, and the other 6 studies performed shorter re-evaluation times.

Sixteen studies did not find statistically significant reduction of periodontopathogen species among SRP alone or associated with aPDT[19,20,21,22,24,29,30,33,35,38,39,40,41,43,45,49,50]. From them , 4 articles were considered with low risk of bias[19,20,21,22]; 7 studies, with some concerns[24,29,30,33,35,38,39]; and 6, with high risk[40,41,43,45,49,50]. While, from the articles of which did find significant differences between groups, 10 reached some concerns[23,25,26,27,28,31,32,34,36,37], and 6, got high risk of bias[40,42,44,46,47,48].

Considering only the articles with some concerns and low risk of bias, 5 studies performed repeated sessions of aPDT and still did not find significant differences between groups[19,24,33,38,39]; however out of the 10 studies with significant differences among group, 3 applied more than once aPTD session, and achieved better results than SRP alone[23,26,37].

The bacterial species sought were *Aggregatibacter actinomycetemcomitans, Porphyromonas gingivalis, Treponema denticola, Tannerella forsythia, Prevotella intermedia, Fusobacterium nucleatum, Eubacterium nodatum, Parvimonas micra, C. gingivalis, C. rectus, Eubacterium corrodens and Filifactor allocis.* And, four studies analyzed 40 bacterial species grouped into bacterial complexes[19,29,39,44]. For instance, the bacterial specie most reported reducing by aPDT therapy was *P. gingivalis*[23,25,26,27,28,32,34,36,37,42,46]; followed by A. *actinomycetemcomitans*[27,32,34,37,44,46,48]; *T.*

forsythia[23,25,26,27,36,37]; *T. denticola*[23,27,36,37,40]; and, *P. intermedia*[23,27,32,40,43]. The increased counts of *P. gingivalis* and *T. forsythia* after aPDT was reported by one article[22].

The light source used by 23 studies was diode laser[19,22,23,25,29,30,31,32,33,34,35,36,37,38,39,40,41,42,44,45,48,49,50], with wavelength ranging from 628 to 810 nm, predominantly using a wavelength of 660 nm (27% of the studies). Five studies used LED light[20,24,27,28,43], with wavelengths ranging from 628 to 630 nm. Two articles reported the use of InGaIP (aluminum gallium indium phosphorus) diode laser with wavelengths ranging from 635 to 685 nm[21,26]. One study used blue light with a wavelength of 470 nm[46] and one study used GaAlAs (Gallium Aluminium Arsenide) diode laser with a wavelength of 810 nm[47]. The photosensitizer used by twelve studies was toluidine blue[20,22,23,24,27,28,32,38,43,48,49,50]; 7 articles used indocyanine green[30,31,33,40,42,45,47], 6 used phenothiazine chloride[19,29,34,35,39,44], 4 studies reported the use of methylene blue[21,36,37,41]; two studies used chloroaluminum italocyanine[25,26] and, one study used curcumin gel[46] (Table 3).

Clinical parameters were described by 29 studies, including periodontal pocket depth (PPD), bleeding on probing (BOP), plaque index (PI), clinical attachment level CAL), gingival index (GI), and full-mouth plaque score (FMPS). From them, 12 studies observed better clinical parameters improvements with adjunctive aPDT application than with mechanical treatment alone[19,23,25,27,31,33,36,37,43,45,46,47](Table 3). Out of the 10 studies that reported better microbiological results ($p<0.05$) adding aPDT to the periodontal therapy, 6 of them either had some better clinical results[23,25,27,31,36,37], 3 of them reported no significant clinical emprovents[26,32,34], and one did not report clinical results[28] (Table 3).

DISCUSSION

Photodynamic therapy has been extensively studied as an adjunctive periodontal treatment, mainly due to its fast action, painlessness and minimal risks and adverse effects[51,52]. However, despite numerous studies, the applied methodologies and results remain heterogeneous, which raises concerns regarding its practical implications and clinical indications[12]. After an extensive literature search 32 studies were included in this systematic review, of which 16 observed a significant reduction in periodontopathogen microorganisms after adjunctive aPDT therapy. Out of these 16 articles, 10 reached some concerns of risk of bias, and 6, high risk. For the ones with some concerns it was mainly about the domains 1 and 5. Domain 1, due to the lack of subjects blindness; and 5, because they did not present

a pre-specified analysis plan. Considering the aPDT methodology, one can understand that these concerns did not reduce the evidence of results. The bacterial species reported by these studies, as the most affected by aPDT therapy was *P. gingivalis,* followed by A. *actinomycetemcomitans, T. forsythia, T. denticola*, and, *P. intermedia*. The improvements in microbiological results were followed by clinical benefits in 6 of these 10 studies.

The effectiveness of aPDT in reducing pathogenic microorganisms has been studied for some time[12,53,54]. *In vitro* studies have shown its capacity to reduce bacteria closely associated with periodontal disease[55]. However, limitations in clinical trials achieving similar *in vitro* results have been attributed to challenges in using aPDT in periodontal pockets, since it contains gingival fluid, bleeding, exudate proteins, which may limit the absorption of photosensitizers. Additionally, the depth of the pocket has been considered restrictive to the penetration of light from the light source and oxygen consumption, as deep pockets often have a microenvironment with low oxygen tension[16]. Another factor that may change the outcomes is the diameter of the laser fiber, which affects the energy distribution modifying the amount of energy applied to the tissue.[21] However, according to the above mentioned results, those barriers did not block aPDT action.

Although previous clinical and *in vitro* data related beneficial microbiological results of aPDT[55,56], the heterogeneity of the treatment applied has been emphasized, for instance Alasqah (2024)[57], Souza et al., (2024)[58], Sales et al., (2022)[55], Salvi et al., (2020)[12], and the present data show great variability regarding the type of light source used, its wavelength, the type of photosensitizer and its concentration, as well as the number of PDT sessions. This limits its true assessment across studies due to the lack of established protocols for treatment implementation.

The diode laser was the light source of 72% of the studies included in this systematic review. Yu and colleagues (2021)[59], in another systematic review, observed that diode laser showed better clinical outcomes compared to scaling alone. The principles of aPDT are characterized by the use of a visible or near-infrared light source at an appropriate wavelength, combined with a light-sensitive dye (photosensitizer). Among the 32 included studies, 6 different types of photosensitizers were used, the most frequently used was toluidine blue, with concentrations ranging from 0.005% to 0.1% and from 0.1 mg/ml to 1 mg/ml. Its good absorption and safety has been demonstrated (Jao et al., 2023[52], Park et al., 2020[65]). Takasaki et al., (2009)[60] state that toluidine blue demonstrates greater effectiveness with higher elimination of *A. actinomycetemcomitans, P. gingivalis,* and *F. nucleatum* compared to methylene blue. Similar results were observed in the present review by Grzech-

Leśniak et al., (2019)[23], Mongardini et al., (2014)[27], Munteanu et al., (2022)[28], Theodoro et al., (2012)[32] and Annaji et al., (2016)[48].

A significant reduction of periodontopathogen species was achieved by using methylene blue as photosensitizer, studies by, Elsadek et al., (2020)[36] and El Makaky et al., (2021)[37] observed in periodontopathogen bacteria *A. actinomycetemcomitans, T. denticola, P. gingivalis,* and *T. forsythia* with the use of aPDT. The use of the photosensitizer indocyanine green (ICG) was already investigated, Bashir and colleagues (2021)[62] demonstrated that ICG improves periodontal clinical parameters and, ts antimicrobial capacity, as shown in by Nagahara et al., (2013)[63], was considered high, particularly against *P. gingivalis*. This finding is supported by articles included in this systematic review, which also noted a significant reduction of pathogens using indocyanine green[31,42,47], which assess microbial effects through colony-forming units (CFU) counting, and did not specific the antimicrobial effects.

Given the main objectives in the treatment of periodontitis, which are to halt disease progression and reduce or eliminate pathogenic species causing periodontal diseases[64], aPDT represents a viable alternative due to its antimicrobial capacity. In a study by Park et al., (2020)[65], which compared the effectiveness of aPDT with the use of Amoxicillin and Metronidazole (main antibiotics indicated in the treatment of periodontitis), aPDT showed a bactericidal rate equivalent to that of antibiotic combination therapy, and where more specific in reduce periodontopathogens.

The effectiveness of single or multiple applications of aPDT was tested in 12 articles[19,22,23,24,26,33,37,38,39,43,46,48] that employed multiple applications, from them, seven did not observe a significant improvement in reduction of microorganisms when compared with SRP alone[19,22,24,33,38,39,43], and five studies observed better results with 2 or three applications than control group. Three studies compared the number of aPDT sessions, two of them observed higher reduction of. *A. actinomycetemcomitans* with 3 sessions than with only one[46,48]; Lafzi et al., (2014)[43], did not observe significant differences between 1 or 2 sessions and, Annaji et al., (2016)[48], boths studies with 3 months follow up. Conversely, Mocanu et al., (2021)[68] argued that the possibility of not obtaining statistically different results for the reduction of microorganisms between aPDT and scaling therapy alone could be explained by the number of therapy applications, since only one application would not result in a significant improvement, while with 3 applications of aPDT was observed a significant reduction of *A. actinomycetemcomitans*, *P. gingivalis* and *T. forsythia*, and *T. denticola*. A

systematic review (Ramanauskaite et al., 2021)[67] till add that multiple applications of aPDT do not lead to superior clinical results compared to single application.

The application time of the photosensitizer reveals considerable variation in protocols, as well as in the impacts on clinical outcomes. Most studies used an application time of one to three minutes. Nineteen protocols applied the light under the photosensitizer during one minute, but results are varied, with statistically significant evidence between the test and control groups[27], but also with studies showing no differences between these groups[40]. The same happens with the eight studies that exposed photosensitizers for three minutes, with reports of significant improvements[42] or not[48]. In the two studies that applied the photosensitizer for five minutes, it is not possible to draw conclusions about this time because, in addition to only one of them showing differences, the conclusion of this statistical difference is attributed to the number of applications that followed three times, rather than necessarily the time[46]. Moreover, two minutes[33] and ten minutes[47] were tested as well, and showed no superior effets than the control group. No study directly compared different aPDT exposure times. Available systematic reviews on this topic do not mention whether the variation in photosensitizer time is a determining factor in the results. Franco et al. (2018)[69] states that better effects may be more related to the type of photosensitizer used and the wavelength of the laser, rather than the exposure time itself.

As limitations of the present review the methodology heterogeneity among studies, including different stages of periodontitis, systemic subjects' condition as smokers and diabetic, and aPDT protocols highlight the need of consistent clinical trials in order to directly compare the most beneficial conditions already tested.

CONCLUSION

Sixteen out of 32 studies included in this systematic review observed significant higher antimicrobial effect with the adjunctive use of aPDT compared to scaling alone. However, the heterogeneity among the studies limits the ability to assert the superiority in terms of a greater antimicrobial effect when add aPDT to the periodontal therapy.

Author contributions: **Luciane Cavalheiro da Silva:** Conceptualization, Methodology, Validation, Formal analysis, Investigation, Data curation, Writing – original draft, Writing – review & editing, Visualization. **Wellington Bruno Venâncio**: Methodology, Formal analysis, Data curation. **Tuany Rayra Pinto Lisboa Dias**: Methodology, Formal analysis, Data curation. **Maria Ângela Naval Machado:** Writing – review & editing, Visualization. **Geisla Mary Silva Soares:** Conceptualization, Methodology, Formal analysis, Re- sources, Data curation, Writing – original draft, Writing – review & editing, Supervision, Project administration, Funding acquisition.

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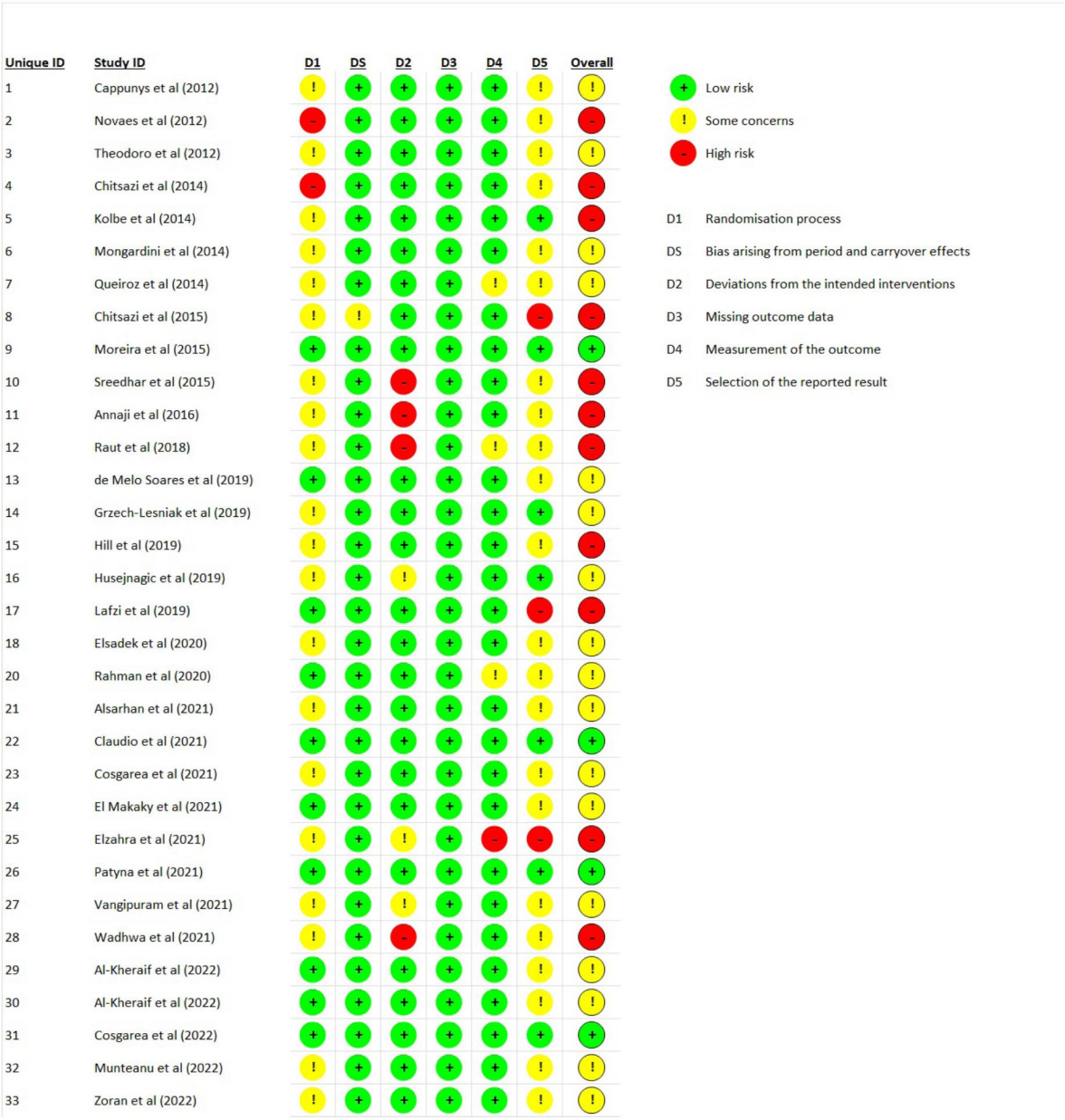
Conflict of Interest: All authors declare no conflicts of interest.

Figure 2 – The risk of bias assessed with Cochrane Risk of Bias tool for randomized trials according to the six domains:



Unique ID	Study ID	D1	DS	D2	D3	D4	D5	Overall
1	Cappunys et al (2012)	!	+	+	+	+	!	!
2	Novaes et al (2012)	-	+	+	+	+	!	-
3	Theodoro et al (2012)	!	+	+	+	+	!	!
4	Chitsazi et al (2014)	-	+	+	+	+	!	-
5	Kolbe et al (2014)	!	+	+	+	+	+	-
6	Mongardini et al (2014)	!	+	+	+	+	!	!
7	Queiroz et al (2014)	!	+	+	+	!	!	!
8	Chitsazi et al (2015)	!	!	+	+	+	-	-
9	Moreira et al (2015)	+	+	+	+	+	+	+
10	Sreedhar et al (2015)	!	+	-	+	+	!	-
11	Annaji et al (2016)	!	+	-	+	+	!	-
12	Raut et al (2018)	!	+	-	+	!	!	-
13	de Melo Soares et al (2019)	+	+	+	+	+	!	!
14	Grzech-Lesniak et al (2019)	!	+	+	+	+	+	!
15	Hill et al (2019)	!	+	+	+	+	!	-
16	Husejnagic et al (2019)	!	+	!	+	+	+	!
17	Lafzi et al (2019)	+	+	+	+	+	-	-
18	Elsadek et al (2020)	!	+	+	+	+	!	!
20	Rahman et al (2020)	+	+	+	+	!	!	!
21	Alsarhan et al (2021)	!	+	+	+	+	!	!
22	Claudio et al (2021)	+	+	+	+	+	+	+
23	Cosgarea et al (2021)	!	+	+	+	+	!	!
24	El Makaky et al (2021)	+	+	+	+	+	!	!
25	Elzahra et al (2021)	!	+	!	+	-	-	-
26	Patyna et al (2021)	+	+	+	+	+	+	+
27	Vangipuram et al (2021)	!	+	!	+	+	!	!
28	Wadhwa et al (2021)	!	+	-	+	+	!	-
29	Al-Kheraif et al (2022)	+	+	+	+	+	!	!
30	Al-Kheraif et al (2022)	+	+	+	+	+	!	!
31	Cosgarea et al (2022)	+	+	+	+	+	+	+
32	Munteanu et al (2022)	!	+	+	+	+	!	!
33	Zoran et al (2022)	!	+	+	+	+	!	!

+ Low risk
! Some concerns
- High risk

D1 Randomisation process
DS Bias arising from period and carryover effects
D2 Deviations from the intended interventions
D3 Missing outcome data
D4 Measurement of the outcome
D5 Selection of the reported result

Table 2: Summary of the microbiological data of the included studies

Article	Microbiological analysis	Before treatment (Mean ± SD)		After last follow up (Mean ± SD)		Follow up
		Control group	aPDT group	Control group	aPDT group	
Cappuyns et al (2012)	Hybridization with RNA probes method for detection the mean counts ± SD of *A. actinomycetemcomitans*, *P.s gingivalis*, *T. forsythi*a, *T. denticola*, and total bacterial load (TBL) on subgingival plaque samples	TBL $\times 10^6$: 38±27	TBL $\times 10^6$: 40±31	TBL $\times 10^6$: 28±20	TBL $\times 10^6$: 33±21 .	2 weeks, 2 and 6 months
Novaes et al (2012)	Checkerboard DNA-DNA hybridization technique for mean counts ±SD of 40 bacterial species	*A. actinomycetemcomitans* 0.33× 10^5±0.30 *P. gingivalis* ≅30× 10^5	*A. actinomycetemcomitans* 0.27× 10^5±0.25 *P. gingivalis* ≅20× 10^5	*A. actinomycetemcomitans* 0.26× 10^5±0.25 *P. gingivalis* ≅10× 10^5	*A. actinomycetemcomitans* 0.02× 10^5±0.01* *P. gingivalis* ≅30× 10^5*	-7days, baseline and 3 months
Theodoro et al (2012)	PCR method for detection the % of sites positive to *A. actinomycetemcomitans*, *P. gingivalis*, *P. intermedia*, *T. forsythia*, and *P. nigrescens* on subgingival plaque samples * (p<0,05)	*100% of sites positive for all bacterial species*	*100% of sites positive for all bacterial species*	*A. a*: 84% *P. gingivalis*: 64% *P. intermedia*: 92% *P. nigrescens*: 96% *T. forsythia*: 72%	*A. a*: 74%* *P. gingivalis*: 43%* *P. intermedia*: 52%* *P. nigrescens*: 87%* *T. forsythia*: 43%*	2, 3, and 6 months
Chitsazi et al (2014)	Real-time PCR method for detection the counts of *A. actinomycetemcomitans* on subgingival plaque samples	*A.a*: 129880	*A. a*: 161610	*A.a*: 2703	*A. a*: 1707	3 months

Kolbe et al (2014)	Real-time PCR method for detection of mean and standard error of the mean (mean±SEM) of *A. actinomycetemcomitans*, *P. gingivalis*, and *T. forsythia* on subgingival plaque samples	*A.a:* 2.7 ± 3.1 *P. gingivalis*: 1.6 ± 1.4 *T. forsythia*: 4.9 ± 3.6	*A.a*: 2.5 ± 2.4 *P. gingivalis*: 2.3 ± 1.9 *T. forsythia*: 4.4 ± 2.8	*A.a:* 2.7 ± 2.5 *P. gingivalis*: 1.0 ± 1.4 *T. forsythia*: 4.7 ± 3.8	*A. as*: 2.2 ± 1.8 *P. gingivalis*: 1.6 ± 1.9 *T. forsythia*: 3.7 ± 2.6	3 and 6 months
Mongardini et al (2014)	Real-time PCR method for detection and cell counts (Mean±SD) the relative proportion (towards the total bacterial count) and the total number of the "red complex bacteria" (RCB) of *A. actinomycetemcomitans, P. gingivalis, T. denticola, T. forsythia*, *F. nucleatum* spp., and *P. intermedia* on subgingival plaque samples.	TBC:$5{,}16\times10^{7}\pm5{,}26\times10^{7}$ RCB:$4.11\times10^{6}\pm5.23\times10^{6}$	TBC:$5{,}01\times10^{7}\pm4{,}98\times10^{7}$ RCB:$5.2\times10^{6}\pm7.7\times10^{6}$	TBC:$3{,}42\times10^{7}\pm5{,}26\times10^{7}$ RCB: 1.69×10^{6}	TBC:$3{,}94\times10^{7}\pm5{,}2\times10^{7}$ RCB: 3.2×10^{6}*	One week
Queiroz et al (2014)	Checkerboard DNA-DNA hybridization technique for mean counts ($\times 10^{5}$) of 40 bacterial species on subgingival plaque samples (Socransky et al., 1998; Socransky and Haffajee, 2002)	*Actinomyces sp*:17; Purple:5; Yellow: 8; Green: 3; Orange: 25; Red: 39	*Actinomyces sp*:13; Purple:6; Yellow: 5; Green: 7; Orange: 20; Red: 40	*Actinomyces sp*:23; Purple:10; Yellow: 5; Green: 8; Orange: 15; Red: 44	*Actinomyces sp*:18; Purple:6; Yellow: 6; Green: 7; Orange: 15; Red: 40	1, 4, and 12 weeks
Chitsazi et al (2015)	Real-time PCR method for detection the counts of *P. gingivalis* on subgingival plaque samples	Data not reported	Data not reported	P. gingivalis counts decreased significantly	P. gingivalis counts decreased significantly	3 months
Moreira et al (2015)	Checkerboard DNA-DNA hybridization technique for counts of 40 bacterial species on subgingival plaque samples distributed across bacterial complexes (Socransky et al., 1998; Socransky and Haffajee, 2002) in two different types of pockets (moderate and deep)	Moderate Pocket: *Actinomyces sp*:10.00%; Purple:5.89%; Yellow: 6.99%; Green: 7.30%; Orange: 28.13%; Red: 24.60% Deep Pocket: *Actinomyces sp*: 3.04% Purple: 2.94%; Yellow: 2.74%; Green: 5,72%	Moderate Pocket: *Actinomyces sp*: 6.89%; Purple: 3.94%; Yellow: 4.71%; Green: 7.55% Orange: 32.65%; Red: 29.99% Deep Pocket: *Actinomyces sp*: 3.50%; Purple: .06%; Yellow: 3.05%; Green: 11.77%	Moderate Pocket: *Actinomyces sp*: 25.09%; Purple: 7.10%; Yellow: 6.13%; Green: 6.05% Orange: 28.61%; Red: 10.61% Deep Pocket: *Actinomyces sp*: 11.86%; Purple: 2.81%; Yellow: 4.21%; Green: 6.67%	Moderate Pocket: *Actinomyces sp*: 29.42%; Purple: 7.05%; Yellow: 5.16%; Green: 6.78% Orange: 23.67%; Red: 9.63% Deep Pocket: Blue: 33.06%; Purple: 11.72%; Yellow: 8.34%; Green: 6.46%	1 and 3 months

		Orange: 37.41%; Red: 38.11%	Orange: 30.69%; Red: 26.85%	Orange: 42.19%; Red: 13.58%	Orange: 13.31%; Red: 3.78%	
Sreedhar et al (2015)	Microbial culture analysis for bacterial colony counts the Mean ± SD of *A. actinomycetemcomitans* and black-pigmented *bacteroides* (BPBs- *P. gingivalis* and *P. intermedia)* on subgingival plaque samples, after 1x or 3x aPDT application	*A. a*: 137.00 ± 12.247 BPBs: 133.00 ± 15.888	1x)*A. a*: 144.33 ± 9.044 BPBs: 133.60 ± 11.242 3x)*A. a*: 140.53 ± 6.706 BPBs: 134.20 ± 12.306	*A. a*: 108.13 ± 7.726 BPBs: 101.53 ± 13.855	1x)*A. a*: 93.13 ± 9.395 BPBs: 89.33 ± 8.014 3x)*A. a*: 81.66 ± 8.723* BPBs: 81.20 ± 6.857*	3 months
Annaji et al (2016)	Culture analysis for Mean Colony Forming Counting (CFU) ± SD of *A. actinomycetemcomitans* and black-pigmented *bacteroides* (BPBs) on subgingival plaque samples, after 1x or 3x aPDT application	*A.a* 143.07±14.85 BPB: 132.67±15.81	*A. a*: 1x) 144.53±11.82 3x) 136.00±11.63 BPB: 1x) 133.27±11.48 3x) 127.27±11.82	*A. a*: 122.73±8.52 BPB: 104.20±12.81	*A. a*: 1x) 93.40±8.79* 3x) 80.67±9.58 BPB: 1x) 88.60±7.73 3x) 79.40±10.34	1 and 3 months
Raut et al (2018)	Morphological and Microscopic Identification for Colony Counting (CFU) the log on subgingival plaque samples. Not specified the species studied	CFU: 6,00 × 10^6 /ml	CFU:6,11× 10^6 ml	CFU:3,57× 10^5 /ml	CFU: 2,15 × 10^5 /ml	6 months
de Melo Soares et al (2019)	Checkerboard DNA-DNA hybridization technique for mean counts the % of 40 bacterial species on subgingival plaque samples distributed across bacterial complexes (Socransky et al., 1998; Socransky and Haffajee, 2002)	*Actinomyces sp.*: 10% Purple: 12% Yellow: 5% Green: 6% Orange: 41% Red: 16%	*Actinomyces sp.*: 10% Purple: 15% Yellow: 5% Green: 6% Orange: 34% Red: 18%	*Actinomyces sp.*: 12% Purple: 15% Yellow: 6% Green: 8% Orange: 36% Red: 9%	*Actinomyces sp.*: 12% Purple: 12% Yellow: 5% Green: 9% Orange: 37% Red: 8%	1 and 3 months

Grzech-Leśniak et al (2019)	Real-time PCR method for the detection of *F. nucleatum, P. intermedia, P. gingivalis, T. forsythia, A. actinomycetemcomitans, E. nodatum, P. micra, C. gingivalis* and total bacterial count on subgingival plaque samples	Data not presented	Data not presented	Decrease the numbers of *P. gingivalis*, *T. denticola* and *T. forsythia* ($p<0.05$)	Decrease the number of all tested bacteria, except *A. actinomycetemcomitans*	6 months
Hill et al (2019)	Real-time PCR method for detection the % of *A. actinomycetemcomitans, P. gingivalis P. intermedia, T. forsythia*, and *T. denticola* on subgingival plaque samples	*A.a:* 0.25% *P. gingivalis*: 1.40% *P. intermedia*: 0.70% *T. forsythia*: 2.00% *T. denticola*: 1.45%	*A.a:* : 0.40% *P. gingivalis*: 0.90% *P. intermedia*: 0.55% *T. forsythia*: 1.90% *T. denticola*: 1.20%	*A a* 0.20% *P. gingivalis*: 1.45% *P. intermedia*: 0.90% *T. forsythia*: 1.90% *T. denticola*: 1.15%	*A. a.:* 0.19% *P. gingivalis*: 0.95% *P. intermedia*: 0.50%* *T. forsythia*: 1.90% *T. denticola*: 0.90%*	2 weeks, 3 months, and 6 months
Husejnagic et al (2019)	PCR method for detection the %, *A. actinomycetemcomitans, P. gingivalis, T. forsythia, T. denticola, P. intermedia, P. micros, F. nucleatum, C. rectus, Eubacterium nodatum, E. corrodens, Capnocytophaga sp.*, on subgengival plaque samples	P. gingivalis ≅ *70%* *T. forsythia* ≅ *95%* *T. denticola* ≅ *35%*	P. gingivalis ≅ *70%* *T. forsythia* ≅ *90%* *T. denticola* ≅ *39%*	P. gingivalis ≅ *70 %* *T. forsythia* ≅ *80%* *T. denticola* ≅ *30%*	P. gingivalis ≅ *50 %* *T. forsythia* ≅ *90%* *T. denticola* ≅ *20%*	12 weeks
Lafzi et al (2019)	Real-time PCR method for detection of the mean±SD of band intensities for *F. nucleatum*. No information about the type of sample used. Four groups: 1: SRP at baseline / 2: SRP at baseline and one month later. / 3: aPDT at baseline. / 4: aPDT at baseline and one month later	*F. nucleatum* 1: 45355,88±9736,47 2: 47249,61±12230	*F. nucleatum* 3: 42945,94±9150,43 4: 42909,07±10780	*F. nucleatum* 1: 41653,00±13896,55 2: 41679,16±11656,53	*F. nucleatum* 3: 42215,50±11485,11 4: 39222,47±10376,38	3 months
Elsadek et al (2020)	PCR method for detection the % of *P. gingivalis*, *T. forsythia*, and *T. denticola* on subgingival plaque samples	*P. gingivalis*: 78% *T. forsythia*: 49% *T. denticola*: 60%	*P. gingivalis*: 70% *T. forsythia*: 40% *T. denticola*: 48%	*P. gingivalis*: 80% *T. forsythia*: 50% *T. denticola*: 59%	*P. gingivalis*: 60%* *T. forsythia*: 30%* *T. denticola*: 28%*	3 months

Rahman et al (2020)	Real-time PCR method for detection the mean±SD of *P. gingivalis* on subgingival plaque samples	*P. gingivalis*: 6.85 ± 0.98	*P. gingivalis*: 7.38 ± 1.14	*P. gingivalis*: 7.38 ± 1.14	*P. gingivalis*: 4.53 ± 2.95	3 months
Alsarhan et al (2021)	Sequencing of 16S rRNA for reads of *Porphyromonas, Tannerella, Treponema* on subgengival plaque samples	does not present numerical data before and after scaling .	does not present numerical data before and after scaling	Log10 *Porphyromonas:* 4.4 *Tannerella: 3.75* *Treponema: 4.1*	Log10 *Porphyromonas:* 4.2 *Tannerella:* 3.65 *Treponema:* 3.85	After the treatment.
Claudio et al (2021)	Real time PCR method for detection the mean±SD of *P. gingivalis* and *P. intermedia* on subgengival plaque samples	*P. gingivalis*: 0.001 ±0.0015 *P. intermedia*: 0	*P. gingivalis* : 0.008 ±0.021 *P. intermedia*: 0.0003 (±0.0012)	*P. gingivalis*: 0.0014 ±0.003 *P. intermedia*: 0	*P. gingivalis*: 0.0003 ±0.001 *P. intermedia*: 0	3 and 6 months
Cosgarea et al (2021)	Real time PCR method for detection the mean±SD of *A. actinomycetemcomitans, P. gingivalis, T. forsythia, P. intermedia, T. denticola, F. nucleatum, C. rectus*, and *F. allocis* on subgengival plaque samples	*A. a*: 0.63 ± 1.79 *P. gingivalis*: 3.84 ± 2.83 *T. denticola*: 3.63 ± 2.50 *T. forsythia*: 4.61 ± 2.68 *P. intermedia*: 2.33±2.88 *F. nucleatum*: 6.49 ±1.28 *C. rectus*: 3.66 ± 3.02 *F. allocis*: 4.92 ± 2.74	*A. a*: 0.74 ± 1.67 *P. gingivalis*: 3.45 ±2.97 *T. denticola*: 3.78 ± 2.96 *T. forsythia*: 4.88 ± 2.36 *P. intermedia*: 2.96±3.00 *F. nucleatum*: 6.87 ±0.98 *C. rectus*: 4.35 ± 2.78 *F. allocis*: 5.23 ± 2.38	*A. a*: 0.20 ± 1.07 *P. gingivalis*:4.26 ±3.11 *T. denticola*:4.11±2.55 *T. forsythia*: 5.14 ± 2.29 *P. intermedia*:2.19±2.95 *F. nucleatum*:6.99±0.95 *C. rectus*: 4.48± 3.02 *F. allocis*: 5.37 ± 2.55	*A. a*:0.31 ± 1.15 *P. gingivalis*:3.74 ±2.96 *T. denticola*:3.66±2.78 *T. forsythia*: 5.04 ± 2.32 *P. intermedia*:3.88±2.93 *F. nucleatum*: 6.71±1.03 *C. rectus*: 3.99 ± 3.07 *F. allocis*: 4.99 ± 2.72	3 and 6 months
El Makaky et al (2021)	PCR method for detection the % of sites positive for *P. gingivalis, T. forsythia, A. actinomycetemcomitans*, and *T. denticola* on subgingival plaque samples	*P. gingivalis*: 100% *A. a*:33.3% *T. forsythia*: 100% *T. denticola*: 100%	*P. gingivalis*: 100% *A. a*: 40% *T. forsythia*: 100% *T. denticola*: 100%	*P. gingivalis*: 40% *A. a*:13.3% *T. forsythia*: 26.7% *T. denticola*: 40%	*P. gingivalis*: 6.7%* *A. a*:6.7%* *T. forsythia*: 6.7%* *T. denticola*: 26.7%*	1, 3, and 6 months
Elzahra et al (2021)	Morphological and Microscopic Identification for Colony Counting (CFU) the mean±SD of *P. gingivalis* and *P. intermedia* on gingival crevicular fluid samples	*P.gingivalis*: 49,13±10,75 *P.intermedia*: 45,2 ± 3,08	*P.gingivalis*: 49,53 ± 9,11 *P.intermedia*: 45,73 ± 2,91	*P. gingivalis*: 11,6 ± 2,79 *P.intermedia*: 5,47 ± 1,25	*P. gingivalis*: 22,87± 1,85* *P.intermedia*: 13,87 ± 1,55*	6 weeks
Patyna et al (2021)	DNA probe kit (IAI Pado test) for identification (Mean ± SD) of A. *actinomycetemcomitans*:, *T. forsythia*, *P. gingivalis*, and *T.*	*T. forsythia*: 3.43 ± 2.64 *P. gingivalis*: 3.55 ± 4.33 *T. denticola*: 1.20 ± 1.44	*T. forsythia*: 2.68 ± 2.37 *P. gingivalis*: 4.27 ± 3.44 *T. denticola*: 9.27 ± 1.11	*T. forsythia*: 2.65 ± 1.87 *P. gingivalis*: 2.11± 1.92 *T. denticola*: 0.83± 0.91	*T. forsythia*: 2.86± 2.50 *P. gingivalis*: 3.41± 3.55 *T. denticola*: 1.53± 1.87	3 and 6 months

	denticola on subgingival plaque samples					
Vangipuram et al (2021)	Microbial culture analysis for bacterial counts the Mean ± SD on subgingival plaque samples	CFU: 9.05±0.31	CFU: 9.08±0.27	CFU: 8.45±0.23	CFU: 6.03±0.82*	3 months
Wadhwa et al (2021)	Morphological and Microscopic Identification for Mean Colony Forming Counting (CFU) ±SD on subgingival plaque samples	CFU: 36,56 ± 7,67	CFU: 37,72 ± 7,36	CFU: 21,20 ± 6,30	CFU: 15,08 ± 4,32*	3 and 6 months
Al-Kheraif et al (2022)	Real-time PCR for detection the counts of *P. gingivalis* and *T. forsythia* on subgingival biofilm samples on periodontitis stage II patients	*P. gingivalis* Smokers: 5000 Never-smokers: 10000 *T. forsythia* Smokers: 10000 Never-smokers: 2000	*P. gingivalis* Smokers: 6000 Never-smokers: 2000 *T. forsythia* Smokers: 10000 Never-smokers: 2000	*P. gingivalis* Smokers: 4000 Never-smokers: 2000 *T. forsythia* Smokers: 2000 Never-smokers: 1000	*P. gingivalis* Smokers: 3000* Never-smokers: 1000 *T. forsythia* Smokers: 1000* Never-smokers: 700	3 and 6 months
Al-Kheraif et al (2022)b	Real-time PCR for detection the counts of *P. gingivalis* and *T. forsythia* on subgingival biofilm samples from periodontitis stage III patients	*P. gingivalis* Smokers: 5000 Never-smokers: 1900 *T. forsythia* Smokers: 10000 Never-smokers: 2000	*P. gingivalis* Smokers: 6000 Never-smokers: 2000 *T. forsythia* Smokers: 10000 Never-smokers: 2000	*P. gingivalis* Smokers: 4000 Never-smokers: 2000 *T. forsythia* Smokers: 2000 Never-smokers: 900	*P. gingivalis* Smokers: 2500* Never-smokers: 1000 *T. forsythia* Smokers: 1000* Never-smokers: 500	3 and 6 months
Cosgarea et al (2022)	Real time PCR method for detection the mean counts±SD of *A. actinomycetemcomitans, P. gingivalis, T. forsythia, P. intermedia, T. denticola, F. nucleatum, C. rectus*, and *F. allocis* on subgingival plaque samples	*A. actinomycetemcomitans*: 0.63 ± 1.79 *P. gingivalis*: 3.84 ± 2.83 *T. denticola*: 3.63 ± 2.50 *T. forsythia*: 4.61 ± 2.68 *P. intermedia*: 2.33±2.88 *F. nucleatum*: 6.49 ± 1.28 *C. rectus*: 3.66 ± 3.02 *F. allocis*: 4.92 ± 2.74	*A. actinomycetemcomitans*: 0.74 ± 1.67 *P. gingivalis*: 3.45 ± 2.97 *T. denticola*: 3.78 ± 2.96 *T. forsythia*: 4.88 ± 2.36 *P. intermedia*: 2.96±3.00 *F. nucleatum*: 6.87 ± 0.98 *C. rectus*: 4.35 ± 2.78 *F. allocis*: 5.23 ± 2.38	*A. actinomycetemcomitans*: 0.14 ± 1.70 *P. gingivalis*: 3.84 ± 2.76 *T. denticola*: 2.38 ± 2.60 *T. forsythia*: 4.56 ± 2.68 *P. intermedia*: 3.13±3.19 *F. nucleatum*: 6.76 ± 1.17 *C. rectus*: 3.53 ± 3.17 *F. allocis*: 3.11 ± 3.35	*A. actinomycetemcomitans*: 0.15 ± 0.78 *P. gingivalis*: 3.66 ± 2.95 *T. denticola*: 3.35 ± 2.88 *T. forsythia*: 5.30 ± 2.02 *P. intermedia*: 3.18±2.86 *F. nucleatum*: 7.07 ± 1.14 *C. rectus*: 3.68 ± 3.45 *F. allocis*: 3.96 ± 3.37	12 months
Munteanu et al (2022)	Micro-IDENT for detection the mean of *P. gingivalis, A. actinomycetemcomitans, P. intermedia, T. denticola* and *T. forsythia* on subgingival biofilm samples	*P. gingivalis* 24%, *A.a* 23%, *P. intermedia* 20%, *T. forsythia* 22%, *T. denticol*a 11%	*P. gingivalis* 24%, *A. a* 23%, *P. intermedia* 20%, *T. forsythia* 22%, *T. denticol*a 11%	*P. gingivalis* 2.1 *A. a* 2.0 *P. intermedia* 1.7 *T. forsythia* 1.3 *T. denticol*a 1.6	*P. gingivalis* 1.4* *A. a* 1.4* *P. intermedia* 1.3 *T. forsythia* 1.4 *T. denticol*a 1.4	After treatment

Zoran et al (2022)	PCR method for detection the % of A. *actinomycetemcomitans*, *P. gingivalis*, and *T. denticola* on subgingival plaque samples	A. *a*:36,0% *P. gingivalis*: 56,0% *T. denticola*: 98,0%	A. *a*:34,0% *P. gingivalis*: 44,0% *T. denticola*: 94,0%	A. *a*:18,0% *P. gingivalis*: 40,0% *T. denticola*: 67,3%	A. *a*:4,0%* *P. gingivalis*: 8,0%* *T. denticola*: 24,0%*	3 months

Table 3. Summary of the general characteristics of the included studies.

Article	Sample size Man / Woman	Periodontitis diagnose	Treatment protocol Control group	Treatment protocol Test group	Photosensitizer	Time and number of aPDT sessions	Laser	Clinical results
Cappuyns et al (2012)	32 patients (ns/ns)	Chronic periodontitis	SRP with Gracey curette. N=32	Photosensitizer was instilled into the pockets with a blunt cannula. After 1 min it was rinsed and irradiated with a diode laser during 1 min. Laser was applied subgingivally through a sterile optical fiber. N=32	Phenothiazine chloride (100 µg/ml)	1 min / 1	Diode laser with a wavelength of 810 nm	Both groups resulted in a significant and clinically relevant improvement in PPD and BOP. p>0,05
Novaes et al (2012)	10 patients (2 / 8)	Generalized aggressive periodontitis	SRP with Gracey curettes. N= 10	Photosensitizer was applied at the bottom of the periodontal pocket during 1 min, rinsed. Laser was applied with a flexible optical fiber tip into six sites per tooth. N= 10	Phenothiazine chloride (does not specify concentration)	1 min / 1	Diode laser with a wavelength of 660 nm	Without information regarding clinical parameters
Theodoro et al (2012)	33 patients (12 / 21)	Chronic periodontitis	SRP with manual curettes. N= 33	The periodontal sites were irrigated with photosensitizer using a syringe and insulin needle. After 1 min, the laser was positioned parallel and in contact with the selected site for 150s. N= 33.	Toluidine Blue O (1ml)	1 min / 1	Low-intensity laser with a wavelength of 660 nm	No clinical parameter showed significant differences between the groups
Chitsazi et al (2014)	24 patients (9 / 15)	Aggressive periodontitis	SRP with piezoelectric ultrasonic handpiece. N= 24	Photosensitizer was applied using an insulin needle, from the bottom of the pocket to cover the root surface. After 1 min, it was rinsed. Laser was applied around each tooth for 2 min. N= 24	Toluidine blue (does not specify concentration)	1min / 1	Diode laser with a wavelength of 670–690 nm	All groups showed statistically significant improvements of clinical parameters. The control group achieved lower BOP compared to the test group. p<0,05

Kolbe et al (2014)	22 patients (10 / 12)	Chronic periodontitis	SRP with curettes and ultrasonic instruments. N= 22	Photosensitizer was applied in the periodontal pocket. After 1 min, it was rinsed and soft diode laser light was applied once using corresponding sterile optical fiber, from the bottom of the pocket through the coronal direction for 1 min. N= 22	Methylene blue (10 mg/ mL)	1 min / 1	Diode laser with a wavelength of 660 nm	All therapies promoted similar improvements in clinical parameters throughout the study. However, BOP was not reduced in the aPDT group
Mongardini et al (2014)	30 patients (13 / 17)	Severe chronic periodontitis	SRP with Gracey curettes. N= 30	Photosensitizer was applied into the bottom of the pocket. After 1 min, it was rinsed. The LED was applied with a short blunt tip outside of the periodontal pocket touching the gingiva and inserting the periodontal tip inside the pocket till the bottom and irradiating for 10 s. N= 30	Toluidine blue O (0.1 mg/ml)	1 min / 1	LED with a wavelength of 628 nm	Mean BOP values decreased to 73% with BOP still positive at control sites and to 27% at sites with aPDT. The decrease in mean values of PPD was statistically significant in both groups, aPDT group had significantly reduction ≥2 mm. $p<0.05$
Queiroz et al (2014)	23 patients (11 / 9)	Chronic periodontitis	SRP with Gracey curettes and the ultrasonic instrument. N= 23	Photosensitizer was applied to the bottom of the periodontal pocket for 1 min, and rinsed. The laser was applied for 10 s, at six sites per tooth. N= 23	Phenothiazine (10mg/ml)	1 min / 1	Diode laser with a wavelength of 660 nm	Without information regarding clinical parameters
Chitsazi et al (2015)	22 patients (10 / 12)	Moderate and severe chronic periodontitis	Subgingival instrumentation with sonic scaler. N= 22	Photosensitizer was applied with walking motion throughout the pocket space, and left there for 60 s. The laser was applied into the deepest part of the pocket, followed by irradiation for 120 s. N= 22	Toluidine chloride (does not specify concentration)	1 min / 1	Diode laser with a wavelength of 638 nm	PPD, CAL, and gingival recession, were similar in both groups $p>0.05$. BOP were statistically significant differences after three months in the aPDT group compared to the SRP group
Moreira et al (2015)	20 patients (2 / 18)	Generalized aggressive periodontitis	SRP with Gracey curettes and ultrasonic scaling and a simulated irradiation	Photosensitizer was applied at the bottom of the periodontal pockets, and after 1 min, they were rinsed. A laser was used subgingivally. The light was applied at six locations on each tooth for 10 s	Phenothiazine chloride (10 mg/mL)	1 min / 4	Diode laser with a wavelength of 670 nm	All therapies led to a significant decrease in all clinical parameters. The Test Group showed a reduction in PPD and a gain in CAL that was significantly different from the Control Group at 90

			procedure. N= 20	each. The aPDT was repeated after 2, 7, and 14 days. N= 20				days. The frequency of residual periodontal pockets was significantly lower in the Test Group
Sreedhar et al (2015)	15 patients (7 / 8)	Periodontitis	Scaling using an ultrasonic scaler. N= 15	G1: Photosensitizer was applied during 5 min + blue halogen curing light for 5 min on baseline. N= 15 G2: aPDT on baseline, at 7, and 21 days. N= 15	Curcumin gel (10 mg/g)	5 min / 3	Blue halogen curing light with wavelength 470 nm	There was a higher significant reduction in BOP and PPD with multiple applications of aPDT compared to the other groups. This same group showed the greater reduction in CAL after 3 months .p<0.05
Annaji et al (2016)	15 patients (6 / 9)	Aggressive periodontitis	Scaling with ultrasonic scaler. N= 15	Photosensitizer was applied to the periodontal pocket with the aid of an applicator. After 3 min, was rinsed and exposed to the laser, which was repeated on the 7th and 21st day for the quadrant 4 site. N= 15	Toluidine blue-O (1mg/ml)	3 min / 3	Diode laser with a wavelength of 810 nm	There was a statistically significant reduction in all clinical parameters but without statistical difference between the test and control groups p>0.05
Raut et al (2018)	50 patients (28 / 22)	Chronic periodontitis	SRP with Curettes and ultrasonic scaler. Placebo diode laser with saline solution. N= 25	Photosensitizer was applied using a blunt needle. After 60 s, it was thoroughly rinsed. The diode laser was placed at the pocket depth and moved circumferentially around the tooth for 1 min. N= 25	Indocyanine green (5mg/m)	1 min / 1	Diode laser with a wavelength of 810 nm.	At 6 months, BOP showed statistically significant improvement.The PI had no difference between the two groups. And, there was a significant reduction in PPD and CAL gain after 6 months in the test group compared to the control group p<0.05
de Melo Soares et al (2019)	22 patients (6 / 14)	Generalized chronic periodontitis	SRP with curetts and an ultrasonic device. Placebo aPDT on contralateral selected teeth. N= 22	Photosensitizer was applied for 1 min into the periodontal pocket, and, then, it was rinsed. A soft diode laser light was applied at six sites per tooth for 10 s each. The protocol was repeated after 2, 7, and 14 days. N= 22	Phenothiazine chloride (10 mg/mL)	1 min / 4	Diode laser with a wavelength of 660 nm	All groups showed reduction in the clinical parameter, but no significant differences between the groups.p>0.05
Grzech-Lesniak et al (2019)	40 patients (15 / 25)	Chronic periodontitis	One SRP session using curettes and	The photosensitizer was applied into the periodontal pockets. After one minute it was washed. The	Toluidine Blue (0.1%)	1 min / 3	Diode laser with a	FMPS, PPD and CAL improved statistically significantly in both groups.

			ultrasonic instruments. N= 20	laser was applied during 30 s. 2ª session: after 7 days. 3ª session: after 14 days. N= 20			wavelength of 635 nm.	aPDT group had lower BOP scores compared to treatment with SRP alone (p<0,05)
Hill et al (2019)	20 patients (3 / 17)	Chronic periodontitis	SRP manually and with a piezoelectric ultrasonic system. N= 20	Photosensitizer was applied, and rinsed off after an exposure time of 60 s. Laser irradiation was performed using an intrasulcular fiber for 20 s. N= 20	Indocyanine green (0.1 mg/ml)	1 min / 1	Diode laser with a wavelength of 808 nm	Median values for BOP, Relative attachment level, PPD, decreased significantly in both groups after three months of treatment p>0.05
Husejnagic et al (2019)	24 patients (ns/ns)	Generalized or localized periodontitis , in stage II, III or IV, with grade B or C	SRP with, curettes, and ultrasonic instruments. N= 24	The photosensitizer was applied, and rinsed after 60 s. The area was irradiated with light for 60 s per location. This group received two sessions. N= 24	Tolonium chloride (0.01%)	1 min / 2	LED with a wavelength of 635 nm	At three months, both treatment groups showed significant improvements of BOP, PPD and CAL compared to baseline, with no significant difference between control and treatment group p>0.05
Lafzi et al (2019)	20 patients (11 / 9)	Moderate to severe chronic periodontitis	Group 1: scaling using manual and ultrasonic instruments. Group 2: SRP at baseline and one month later. N= 20	Photosensitizer was injected into the pocket until it was filled. 3 min after the excess was rinsed and activated for light irradiation 10 s for pockets shallower than 5 mm and 20 s for pockets deeper than 5 mm. Group 3: received aPDT at baseline, and group 4 , at baseline and one month later. N= 20	Toluidine blue O (0.1 mg/mL)	3 min / 2	LED with wavelength of 620-640 nm	A significant reduction in clinical parameters of periodontal health was observed in all groups compared to baseline values. At three months, the difference in PPD between groups 1 and 3 was statistically significant. The differences in CAL between groups 2 and 4 at three months were statistically significant
Elsadek et al (2020)	60 patients (32 / 28)	Generalized stage III grade C periodontitis	Four sessions of SRP using curettes and ultrasonic scaler. N= 19	The photosensitizer was applied directly into the worst pocket using a blunt-tipped side-vented irrigation needle. A diode laser was used with flexible fiber optic cable for access to the periodontal pocket, for 60 s per site. The tip was gently moved from the apical to coronal direction in the pocket. N= 19	Methylene Blue (0.005%)	Not informati on / 1	Diode laser with a wavelength of 670 nm	All groups showed statistically significant improvements in terms of clinical parameters. However, the proportion of PPD with ≥4 mm and ≥5 mm showed a statistically significant reduction for test group compared control group

Rahman et al (2020)	11 patients (ns/ns)	Periodontitis	Supragingival scaling and, after 2 weeks SRP using piezoelectric scalers and 1 curettes. N= 11	Photosensitizer was applied subgingivally using a syringe with a blunt cannula. After 3 min, it was rinsed. The pocket was exposed to laser light using an optical fiber for 10 s at six sites per tooth. N= 11	Indocyanine green (does not specify concentration)	3 min / 1	Diode laser with a wavelength of 810 nm	All groups showed a significant reduction in clinical parameters after 3 months of follow-up, p>0.05
Alsarhan et al (2021)	14 patients (12 / 2)	Mild or moderate chronic periodontitis	SRP using curettes and piezoelectric ultrasonic. Control sites underwent a placebo diode laser without ICG, at the initial appointment. . N= 14	Photosensitizer was injected with a fine cannula into the deep periodontal pockets followed by a rest period of 1 to 2 min. It was to rinseed to remove excess. Irradiation was performed using a 300 µm laser fiber tip in pulsed wave mode. The protocol was repeated one and two weeks after. N= 14	Indocyanine green (0.1 mg/ml)	2 min / 2	Diode laser with a wavelength of 808 nm	Significant reduction was observed in BOP and the residual periodontal pocket at 3-months post-therapy for the aPDT group. PPD and CAL were significantly higher in the test group. At 1 month, there was a significant favorable reduction in both PPD, CAL at both groups
Claudio et al (2021)	34 patients (22 / 12)	Stage III and IV periodontitis	SRP using manual curettes and ultrasonic scaler. N= 17	The sites were irrigated with photosensitizer using an insulin syringe and a non-beveled needle. After 1 min, they were irradiated for 50 s. N= 17	Methylene blue (10 mg/ml)	1 min / 1	InGaAlP diode laser with a wavelength of 660 nm	At 90 and 180 days, there was no difference between the groups in any clinical parameters
Cosgarea et al (2021)	105 patients (41 / 54)	Periodontitis stages I-IV, grade A/B/C	Scaling using ultrasonic instruments. N= 35	The photosensitizer was applied at 6 sites per tooth from the bottom to the top of the pocket, and left in situ for 3 min. Was rinsed, and each site of the treated tooth was exposed to laser light for 10 s. After 1 week, aPDT was repeated. N= 35	Toluidine blue (does not specify concentration)	3 min / 2	Laser with a wavelength of 660 nm	The PPD, CAL and BOP in the test teeth showed statistically significant reductions from baseline to 6 months in all treatment groups, with no statistically significant differences between the groups
El Makaky et al (2021)	30 patients (16 / 14)	Localized or generalized stage I, II, and III periodontitis	SRP using an ultrasonic scaler and Gracey curettes. N= 15	The photosensitizer was applied using a blunt needle at the base of the periodontal pocket and incubated for 1 min, followed by irrigation to remove excess. Was irradiated by the laser using a flexible tip applicator for 60 s. The	Methylene Blue (0.01%)	1 min / 2	Diode laser with a wavelength of 635 nm	In the test group showed significantly better results than the control group in the periodontal parameters improvement (PI, GI, PPD and gain CAL) p>0.05

				protocol was performed twice, once after SRP and again after 2 weeks. N= 15				
Elzahra et al (2021)	30 patients (ns/ns))	Chronic periodontitis	SRP. N=15	A blunt tip syringe was used to fill the pocket with the photosensitizer, and rinsed after 3 min to remove excess. The laser was positioned deeply into the pocket and moved circumferentially around the tooth for 30 s N=15	Indocyanine green (does not specify concentration)	3 min / 1	Diode laser with a wavelength of 810 nm	All clinical parameters were revealed statistically significant difference after six weeks of treatment among both groups
Patyna et al (2021)	48 patients (20 / 28)	Stage II and III Grade B periodontitis	SRP using ultrasonic devices and manual curetts. N= 16	A photosensitizer was applied into the periodontal pockets and left for 60 s. After, an LED device was used subgingivally to irradiate for 10 s on each side of the tooth and rinsed to remove the photosensitizer. N= 16	Toluidine Blue O (does not specify concentration)	1 min / 1	LED with a wavelength of 628 nm	PPD and CAL did not show significant differences between the treatment groups at 3 and 6 months. Secondary clinical parameters (BOP, GI and Plaque Control Record) improved in all three groups but did not show significant differences between the groups
Vangipuram et al (2021)	34 patients (ns/ns))	Chronic periodontitis	SRP using Gracey curettes and ultrasonic instrumentation. N= 34	Photosensitizer was applied, after 3 min the area was rinsed. Then, the laser with a probe tip was placed in the pocket and moved around the tooth for 1 min. N= 34	Indocyanine green 1 mg/ml	3 min / 1	Diode laser with a wavelength of 810 nm	The difference between the groups was statistically significant for modified sulcular bleeding index, PPD, CAL, PI and GI with much lower values in Group aPDT
Wadhwa et al (2021)	30 patients (22 / 8)	Generalized chronic periodontitis	Supragingival scaling with piezoelectric ultrasonic and curettes. . Subgingival instrumentation with Gracey curettes. N= 30	A photosensitizer was applied with a syringe loaded with the solution and applied to the experimental sites for 10 min. A laser was used to move circumferentially in the pockets and additional areas of bifurcation and trifurcation in the case of molars. N= 30	Indocyanine green (250 µg/ml)	10 min / 1	GaAlAs diode laser with a wavelength of 810 nm	The mean PI scores, GI scores, sulcus bleeding index scores, PPD scores, relative attachment level scores were significantly lower at experimental sites as compared to the control sites
Al-Kheraif et al (2022)	29 patients (23 / 6)	Stage III chronic periodontitis	SRP with Gracey curettes	The photosensitizer was introduced together with a gel-based medication. Then,	Chloro-aluminum	Not information / 1	Diode laser with a	PI, PPD and CAL showed significant reductions in both groups. BOP in the non-

			and ultrasonic scaling. N= 29	periodontal pockets were irradiated. N= 29	phthalocyanine (25mg/ml)		wavelength of 685 nm	smoker group had a significant reduction in both treatment groups at 3 and 6 months, while aPDT in smokers had significant reduction only at six months. Only marginal bone loss in the aPDT group within the non-smoker group showed a significant decrease at 6 months. $p<0.05$
Al-Kheraif et al. (2022b)	26 patients (23 / 3)	Stage II generalized chronic periodontitis	SRP with Gracey curettes and ultrasonic scaling. N= 26	The photosensitizer was applied into the periodontal pockets. After rinsing for 5 min, the periodontal pockets were irradiated. Procedure was repeated twice, every 3 days. N= 26	Chloro-aluminum phthalocyanine (30 mg/ml)	5 min / 2	InGaAlP diode laser with a wavelength of 685 nm	PI, BOP, PPD and CAL showed statistically significant reductions in both groups. Without significant difference treatment groups
Cosgarea et al (2022)	105 patients (41 / 54)	Periodontitis stages I-IV, grade A/B/C	Scaling using ultrasonic instruments.N= 35	The photosensitizer was applied at 6 sites per tooth from the bottom to the top of the pocket, and left in situ for 3 min. Was rinsed, and each site of the treated tooth was exposed to laser light for 10 s. After 1 week, aPDT was repeated. N= 35	Toluidine blue (does not specify concentration)	3 min / 2	Laser with a wavelength of 660 nm	No clinical parameter showed significant differences between the groups
Munteanu et al (2022)	18 patients (ns/ns)	Localized chronic periodontitis	SRP using Gracey curettes and ultrasonic instruments. N= 18	The photosensitizer was applied with a blunt needle in the periodontal pocket for 1 min. Was rinsed and the laser light at a wavelength 635 nm, performing 3 repetitions of 10 s each, with apico-coronal oscillatory movements. N= 18	Toluidine Blue Gel (0,005%)	1 min / 1	Red light laser with a wavelength of 635 nm	Without information regarding clinical parameters
Zoran et al (2022)	25 patients (13 / 12)	Chronic periodontitis	SRP with ultrasonic scaler and Gracey curettes. N= 25	Photosensitizer was rinsed on periodontal pockets up to 5 mm after 1 min, and for larger pockets of six mm after 3 min. Laser a power of 100 mW was applied for	Phenothiazine chloride (does not specify concentration)	3 min / 1	Diode laser with a wavelength of 660 nm	There was a statistically significant reduction in all clinical parameters, but without statistical difference

				1 min (10 s at a time at 3 points on the buccal surface and 3 points on the oral surface). N= 25				between the test and control groups

Supplemented Table 1: Database search strategy used:

Databases	Search strategy
Embase	("periodontal disease" OR "peridontal tissue disease" OR "periodontal infection") AND ("photodynamic therapy" OR "photodynamic treatment" OR "photosensitization" OR "therapeutic photosensitization") AND ("antiinfective agent" OR "anti bacterial agent" OR "anti infective agents" OR "anti-bacterial agents" OR "anti-infective agents" OR "antibacterial" OR "antibacterial agent" OR "antibacterial spectrum" OR "antiinfective agent").
Web of Science and Scopus	("periodontal disease" OR "peridontal tissue disease" OR "periodontal infection") AND ("photodynamic therapy" OR "photodynamic treatment" OR "photosensitization" OR "therapeutic photosensitization") AND ("antiinfective agent" OR "anti bacterial agent" OR "anti infective agents" OR "anti-bacterial agents" OR "anti-infective agents" OR "antibacterial" OR "antibacterial agent" OR "antibacterial spectrum" OR "antiinfective agent").
LILACS	('periodontitis' OR 'periodontal disease') AND ('photodynamic therapy' OR 'photodynamic therapy' OR 'photodynamic treatment' OR photosensibilisants OR 'photosensitizing agent' OR 'photosensitivity agent' OR 'photosensitizer' OR 'photosensitizers') AND ('antiinfective agent' OR 'anti bacterial agent' OR 'anti bacterial agents' OR 'anti infective agents' OR 'anti-infective agents' OR 'antibacterial' OR 'antibacterial agent' OR 'antiinfective agent').
Pubmed, ProQuest, and Google Scholar	('periodontal disease' OR 'peridontal disease' OR 'peridontal tissue disease' OR 'periodontal attachment loss' OR 'periodontal disease' OR 'periodontal diseases' OR periodontal infection') AND ('photodynamic therapy' OR 'photodynamic therapy' OR 'phtodynamic treatment' OR 'photosensitisation (intentional)' OR photosensitization (intentional)' OR 'therapeutic photosensitisation' OR 'therapeutic photosensitization' OR 'therapy, photodynamic') AND 'periodontal treatment' AND ('antiinfective agent' OR 'anti bacterial agent' OR 'anti bacterial agents' OR 'anti infective agents' OR 'anti-bacterial agents' OR 'anti-infective agents' OR 'antibacterial' OR 'antibacterial agent' OR 'antibacterial spectrum' OR 'antiifective agent').
OpenGrey	(periodontitis OR periodontitis OR periodontitis) AND (photochemotherapy OR chemophototherapy OR “photo-actived chemotherapy” OR “photo-chemotherapy” OR “photoactived chemotherapy” OR photochemotherapy OR

	"photosensitizing agent" OR "photosensitivity agent" OR photosensitizer OR photosensitizers OR photosensitizing OR "photosensitizing agent" OR "photosensitizing agents" OR "tolunium chloride" OR "3 amino 7 dimethylamino 2 methylphenazathionium chloride" OR "dimethyltoluthionine chloride" OR "tolinium chloride" OR "toloniu chloride" OR tolonium chloride" OR "toluidin blue" OR "toluidine blue" OR "toluidine blue o" OR "toluidineblue o") AND ("antiinfective agent" OR "anti-bacterial agent" OR "anti-bacterial agents" OR ("anti infective agents" OR "anti-bacterial agents" OR ("anti-infective agents" OR "antibacterial" OR "antibacterial agent" OR "antibacterial drug" OR "antibacterial soap" OR "antibacterial spectrum" OR "antibacterial" OR "antiinfective agent" OR antimicrobial agent" OR "antibacterial compound" OR "antibacterial drug" OR "antibacterial factor" OR "microbiological agent")

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3 CONSIDERAÇÕES FINAIS

A ação antimicrobiana da terapia fotodinâmica sobre patógenos periodontais tem sido demonstrada por diferentes protocolos de estudo, incluindo tipos de laser, comprimento de onda e potência, diferentes fotossensibilizadores, tempos de exposição, áreas expostas e quantidades de aplicações. Da mesma forma, diferentes condições já foram estudadas sobre a possiblidade de serem auxiliadas na busca de bons resultados clínicos, incluindo estudos com participantes fumantes e portadores de Diabetes e com diferentes estágios de periodontite. Os estudos *in vitro* ajudaram a construir um direcionamento sobre a capacidade de ação e sobre os melhores protocolos. No entanto, mesmo com alguns direcionamentos, se observa a ausência de consistência nos estudos. Na presente revisão sistemática buscou-se incluir o maior número possível de estudos clínicos que tenham investigado a ação antimicrobiana da aPDT, para tanto critérios de inclusão e exclusão pouco restritos foram empregados. O que resultou, primeiramente na inclusão de estudos com risco de viés elevado, devido a falhas metodológicas ou de relato de resultados. Considerando os estudos com moderado ou baixo risco de viés, observamos dados importantes, com direcionamento de protocolos com superioridade de efeito, como fotossensibilizador azul de toluidina, que teve melhor ação sobre espécies periodontopatogênicas; múltiplas sessões não resultaram em melhores efeitos, mas o tempo de aplicação entre 3 e 5 minutos sim.

Alguns pontos importantes que se observaram foram falta de dados na literatura sobre longos períodos de avaliação e alteração na microbiota não patogênica. O tempo de acompanhamento em estudos clínicos é fundamental para se avaliar a manutenção dos benefícios a longo prazo. Alterações a curto prazo podem vir a ser perdidas, o que contra-indicaria a utilização da terapia, ainda mais em terapia periodontal, onde a alteração da microbiota patogênica para uma compatível com saúde precisa ser re-estabelecida para se manter a condição de saúde. Alterações a curto prazo podem nem vir a resultar em melhoras clínicas. Já alterações que são mantidas a longo prazo podem levar a melhoria dos efeitos benéficos mesmo a longo prazo. Sobre a microbiota não patogênica, há de se considerar que a busca pelo re-equíbrio em condição de saúde envolve toda a ecologia da cavidade oral, considerando todos os sítios, rasos ou profundos;

tecidos, incluindo dentes, gengiva e mucosa; e fluidos gengival e saliva. Dessa forma, embora a aPDT seja proposta para ser aplicada em sítios específicos, o objetivo não é alterar somente espécies bacterianas específicas, mas sim, contribuir para o re-estabelecimento de uma microbiota compatível com saúde. Dessa maneira, análises que possam avaliar tanto microrganismos patogênicos quanto compatíveis com saúde podem contribuir de forma mais ampla para o entendimento e direcionamento para metodologia.

Portanto, apesar do grande número de estudos clínicos que avaliaram esta forma de tratamento, as metodologias aplicadas, bem como os resultados obtidos, ainda são muito heterogêneos, o que leva à necessidade de condução de estudos mais padronizados, com análises microbiológicas mais amplas e de acompanhamento a longo prazo, para se ter dados mais consistentes sobre sua indicação clínica.

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ANEXO 1 – NORMAS DA REVISTA

NORMAS DA REVISTA Pesquisa Brasileira em Odontopediatria e Clínica Integrada

INSTRUÇÕES PARA OS AUTORES

O periódico Pesquisa Brasileira em Odontopediatria e Clínica Integrada endossa a declaração PRISMA para o relato de revisões sistemáticas e metanálises, ensaios clínicos (CONSORT), a declaração STROBE para relato de estudos epidemiológicos, relatos de caso (CARE), estudos de acurácia em testes diagnósticos (STARD) e a declaração RECORD (REporting of studies Conducted using Observational Routinely-collected Data) para o relato de estudos conduzidos utilizando dados de saúde observacionais coletados rotineiramente. O periódico recomenda que todos os artigos submetidos cumpram com os padrões de qualidade editorial estabelecidos nos Requisitos Uniformes para Manuscritos Submetidos a Revistas Biomédicas. Os autores devem verificar o EQUATOR Network para obter instruções sobre relatórios e mais informações.

Forma e preparação de manuscritos

O periódico só aceita a submissão e faz a publicação de manuscritos em inglês.

O manuscrito enviado para publicação deve ser original e a submissão simultânea a outro periódico, brasileiro ou estrangeiro, não é permitida.

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Autoria

Todos os inscritos como autores devem atender aos critérios de autoria padrão Contributor Roles Taxonomy (CRediT). Esperamos que todos os autores assumam publicamente a responsabilidade pelo conteúdo do manuscrito submetido à PBOCI. As contribuições de todos os autores devem ser descritas na página do título.

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O manuscrito deve ser escrito em inglês, de forma clara, concisa e objetiva. Entre em contato com a PBOCI pelo e-mail apesb@terra.com.br para obter informações sobre as empresas de tradução recomendadas. Revisões linguísticas realizadas por empresas que não fornecem o certificado mencionado não serão aceitas.

O texto deve ser fornecido como um arquivo do Word para Windows (doc), usando uma fonte tamanho 12 Times New Roman, tamanho de página A4, com espaçamento 1,5 e margens de 2,5 cm. A extensão do manuscrito é limitada a 16 páginas, incluindo referências, tabelas e figuras.

Página de Título (dados obrigatórios): Título, Autor (es) [Nomes de todos os autores escritos na íntegra, incluindo os respectivos números de telefone e endereços de e-mail para correspondência] e Autor para correspondência. Dados de afiliação institucional / profissional de todos os autores, incluindo Departamento, Faculdade / programa, Universidade (ou outra instituição), Cidade, Estado e País. NÃO INCLUIR os títulos do autor (DDS, MSc, Ph.D., etc.) ou cargo (Professor, Estudante de Graduação, etc.).

Exemplos:

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[3]Department of Child Dental Health, Obafemi Awolowo University Teaching Hospitals Complex, Ile-Ife, Nigeria.

Texto Principal

Resumo: Máximo de 280 palavras. O resumo deve ser estruturado com as seguintes divisões: Objetivo, Métodos, Resultados e Conclusão.

Palavras-chave: Variando de 3 (três) a 5 (cinco) cinco palavras-chave, escolhidas entre as palavras-chave registradas no Medical Subject Headings da U.S. National Library of Medicine (https://meshb.nlm.nih.gov)

Introdução: Declare o propósito e resuma a justificativa para o estudo ou observação. O (s) objetivo (s) e / ou a hipótese do estudo devem ser declarados no último parágrafo. Evite a apresentação de uma revisão extensiva do campo.

Material e Métodos: Descreva o desenho do estudo, bem como a seleção dos participantes para os estudos observacionais ou experimentais (pacientes ou animais de laboratório, incluindo controles) claramente, incluindo critérios de elegibilidade e exclusão e uma descrição da população. Identifique os métodos, equipamentos (nome e endereço – cidade, estado e país, do fabricante entre parênteses) e procedimentos com detalhes suficientes para permitir que outros pesquisadores reproduzam os resultados. Os autores devem ter considerado os aspectos éticos de suas pesquisas e devem assegurar que o projeto foi aprovado por um comitê de ética apropriado, que deve ser declarado. O tipo de análise estatística deve ser descrito de forma clara e cuidadosa, mencionando inclusive o software utilizado.

Resultados: Devem ser apresentados em uma sequência lógica no texto, tabelas e ilustrações, destacando as descobertas principais ou mais importantes.

Discussão: Esta é a única seção apropriada para comentários subjetivos e referência à literatura anterior. Inferências, deduções e conclusões devem ser limitadas aos resultados do estudo (generalização conservadora).

Conclusão: Deve explicitar claramente a(s) principal (ais) conclusão (ões) do trabalho, ressaltando sua importância e relevância.

Contribuições do autor: As contribuições individuais dos autores ao manuscrito devem ser especificadas nesta seção. As declarações CRediT devem ser fornecidas durante o processo de submissão e aparecerão acima da seção de reconhecimento do artigo publicado como mostrado: Conceituação, Metodologia, Software, Validação, Análise Formal, Investigação, Recursos, Curadoria de Dados, Redação - Rascunho Original, Redação - Revisão e Edição,

Visualização, Supervisão, Administração de Projetos, Aquisição de Financiamento.

Exemplo:

- Conceptualization, Writing - Original Draft, Writing - Review and Editing, Supervision and Project Administration.

Suporte financeiro: Qualquer tipo de apoio financeiro (financiamento, subsídios, patrocínio) que você tenha recebido deve ser informado (agência e número de concessão).

Exemplos:

- Fundação de Amparo à Pesquisa e Inovação do Estado de Santa Catarina – Grant Number 06/2017
- This study was supported by the Coordination of Improvement of Higher Education Personnel (Capes) and the National Council for Scientific and Technological Development (CNPQ), Brazil.

Conflito de Interesse: Os autores devem declarar não haver conflitos de interesse.

Agradecimentos: Quando apropriado, reconheça a assistência técnica, conselhos e contribuições dos colegas. As pessoas que contribuíram para o trabalho, mas não se encaixam nos critérios para os autores, devem ser listadas na seção Agradecimentos, juntamente com suas contribuições.

Disponibilidade de dados: A PBOCI encoraja ou exige o fornecimento de declarações de disponibilidade de dados.

Tabelas: As tabelas devem ser enviadas no Word (.doc) ou Excel (.xls), não como imagens. Devem ser numeradas consecutivamente com algarismos arábicos e devem ter um título explicativo. Cada tabela deve ser digitada em uma página separada com relação à proporção da coluna / página impressa e conter apenas linhas horizontais.

Figuras e ilustrações: Cada figura deve ter uma legenda.

Citação de Autores no Texto

As referências devem ser citadas em ordem crescente dentro do parágrafo.

Exemplo:

In Brazil, the association between socioeconomic conditions and higher levels of dental caries has been more evident among brown/black people [9], females [10], low-income and less educated groups [10]. Socioeconomic factors, such as income and schooling [11], are described as determinants in the development of dental caries [12,13].

Referências

- Todas as referências devem ser citadas no texto; caso contrário, essas referências serão removidas automaticamente.
- Os autores são responsáveis por garantir que as informações em cada referência sejam completas e precisas. No máximo 50 referências devem ser numeradas consecutivamente na ordem em que aparecem no texto (modelo Vancouver).
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- Material não referenciado e, se possível, publicações em outros idiomas que não o inglês devem ser evitadas. Resumos de congressos, artigos não aceitos, observações não publicadas e comunicações pessoais não podem ser colocados na lista de referências.
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Ayub A, Ali S, Issrani R, Sethi A, Khattak O, Iqbal A. Burnout among dental students of private and public dental colleges in Pakistan - A cross-sectional study. Pesqui Brasileira Odontopediatria Clín Integr, 2024, 24:e220176. https://revista.uepb.edu.br/PBOCI/article/view/3100

Livro na íntegra. Autores, título do livro, edição, cidade, editora, ano.

Moursi AM, Truesdale AL. Clinical Cases in Pediatric Dentistry. 2nd. ed. New Jersey: Wiley-Blackwell; 2020. 432p.

Capítulo de livro. Autores, Título do capítulo, Editores, Título do livro, Edição, Cidade, Editor, Ano, número das Páginas do capítulo.

Bardow A, Vissink A. Saliva and caries development. In: Fejerskov O, Nyvad B, Kidd E. Dental Caries: The Disease and its Clinical Management. 4th. ed. London: Wiley-Blackwell; 2015.

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