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Is antimicrobial photodynamic therapy an effective treatment modality for aggressive periodontitis? A systematic review of *in vivo* human randomized controlled clinical trials

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ABSTRACT

Background: Limitations of scaling and root planing (SRP) have directed research to utilize additional therapies to enhance conventional techniques. The present systematic review was conducted to evaluate and present a comprehensive overview on effectiveness of antimicrobial photodynamic therapy (aPDT) in the management of aggressive periodontitis (AgP).

Methodology: The PRISMA statement guidelines and Cochrane Collaboration recommendations were followed to conduct this systematic review. The review protocol is registered in PROSPERO (CRD 42019143316). A structured electronic and manual search strategy was implied to gather the relevant published data on *in vivo* human RCTs from their earliest records until 31st October 2019. Relevant data was extracted from the eligible studies, analysed and impartially appraised for its quality.

Results: Eleven papers met the eligibility criteria and included in this review. The data on standardized study protocol, ideal photosensitizer (PS) dye-wavelength combination, optimal parameters was inconclusive and a high risk of bias in majority of the studies noted, which are fundamental in establishing a standardized and replicable protocol.

Conclusion: Ultimately researchers should conduct well-designed and robust RCTs performed by trained clinicians in order to determine the effectiveness of aPDT, if any, after acknowledging the drawbacks highlighted in this systematic review.

1. Introduction

Aggressive Periodontitis (AgP) is a disease of the periodontium, which is characterized by a rapid debilitation of periodontal tissues [1]. It is further subclassified as; localized or generalized forms of periodontitis, depending on the extent of the disease in the oral cavity [1]. The resultant bacterial infection that is predominantly composed of gram negative (Gram^{-ve}) anaerobic bacteria, can trigger a host immuno-inflammatory response [2,3]. Also, AgP presents with an altered of the host immune responses: phagocyte abnormalities, impaired polymorphonuclear neutrophil (PMN) functions, and a self-limiting disease pattern, which differentiate AgP entity from chronic periodontitis (CP) [3].

Non-surgical periodontal therapy (NSPT) is the most sought-after approach for disease management [4]. However, it produces only a modest and transient reduction in bacterial load [4,5]. This hampers disease resolution and recurrence can be prophesied. Furthermore, several study protocols utilizing adjunctive antibiotic therapy (AB), which either administered systemically or locally have been assessed. However, several shortcomings have been reported such as; development of antibiotic resistance, challenges in achieving patient compliance, and adverse effects of AB (gastro-intestinal disturbances) [6,7]. Locally delivered antibiotics have a better acceptance rate than their systemic counterparts. However, they have several limitations such as; difficulties in product manipulation, high chances of dislodgement, expensive and require patience compliance in order to facilitate

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successful outcomes [8]. Consequently, alternative or exclusive antibacterial therapeutic strategies have evolved, as methods to control microbial growth in the oral cavity [9].

Antimicrobial photodynamic therapy (aPDT) is a form of phototherapy, which involves light activation of a photosensitizer (PS) dye in the presence of molecular oxygen in order to elicit cell death [10]. Photo-excitation occurs when a PS is illuminated by a light of a matched wavelength, resulting in a pronounced antimicrobial action at the treatment site [10–12]. Various PS dye-wavelength combinations have been studied to assess the utilization of aPDT, as a monotherapy or as an adjunct to scaling and root planing (SRP) for the treatment of AgP [8, 13–19]. Of these 3 systematic reviews [14–16] and 1 systematic review and meta-analysis [17], have been conducted solely to assess aPDT role in cohort diagnosed with AgP. However, several inconsistencies such as; low sample size, older search strategy timelines and methodological differences in review protocol, have been noted in the available scientific literature [8,13–19]. Since the role of aPDT in the treatment of AgP remains unresolved and imperative, the present systematic review was conducted to provide an updated, critical and systematic assessment of the pertinent literature. Objectives of the present systematic review were to evaluate the outcome of various wavelengths, their equivalent PS and range of the laser parameters utilized for aPDT in AgP patients in order to deduce an ideal treatment protocol for forthcoming scientific investigations.

2. Materials and methods

2.1. Protocol and registration

The present systematic review was conducted as per Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) Statement guidelines and Cochrane Collaboration recommendations (Appendix 1) [20,21] and a protocol is published in Prospective Register of Systematic Reviews (PROSPERO) (www.crd.york.ac.uk/PROSPERO/; ref CRD 42019143316).

2.2. Population (P), Intervention (I), Comparison (C) and Outcomes (O)—PICO

- **Population:** Patients diagnosed with AgP
- **Intervention:** aPDT-monotherapy or as an adjunct to SRP
- **Comparison:** SRP alone or SRP + AB therapy
- **Outcome:** Clinical and/or microbiological and/or immunological profiles

2.3. Focused research question

"In AgP patients, is aPDT-monotherapy or as an adjunct to SRP more efficacious than conventional SRP or with adjunctive AB therapy, in terms of clinical or microbiological or immunological profiles?"

2.4. Search strategy

Cochrane MEDLINE filters for controlled trials of interventions were utilized to connect relevant free text keywords and Medical subject Heading (Mesh) terms. Electronic databases such as; MEDLINE (NCBI PubMed and PMC), Cochrane Central Register of Controlled Trials (CCRCT), Scopus, ScienceDirect, Google Scholar, EMBASE and EBSCO were accessed from their earliest records until 31st October 2019. A manual hand search of the following journals was performed; Journal of Photochemistry and Photobiology B: Biology, Photodiagnosis and Photodynamic Therapy, Photobiomodulation, Photomedicine and Laser Surgery, Journal of Periodontology, Photochemistry and Photobiology, Journal of Clinical Periodontology, Journal of Dental Research, Lasers in Medicine and Surgery and Lasers in Medical Science. Reference lists of all identified articles were searched for further studies. In order to detect unpublished studies, conference abstracts, as well as, grey literature sources were screened. In order to obtain additional information related to some papers, an attempt was made to establish a communication with the corresponding authors without any success. The search strategy was performed by two independent blinded reviewers (SD and RH). Inter-reviewer reliability analysis was assessed using Kappa (κ) statistics and a minimum value of $\kappa = 0.8$ was considered acceptable [22]. In case of disagreements in between reviewers, the matter was resolved by discussion with a third author (SB).

2.5. Search algorithms

"Antimicrobial photodynamic therapy" **OR** "photochemotherapy"

AND

"Scaling" **OR** "Root planing" **OR** "non-surgical periodontal therapy"

AND

"Aggressive Periodontitis" **OR** "Early Onset Periodontitis"

AND

"Randomized controlled clinical trials"

2.6. Eligibility criteria

2.6.1. Inclusion criteria

1 Fit and healthy subjects, age group >18 years whom diagnosed with AgP according to 1999 AAP Classification of Periodontal diseases and conditions [1].
2 *In-vivo* human RCT's comparing the efficacy of aPDT monotherapy or adjunctive to SRP compared to SRP alone or in combination with AB.
3 Parallel group (PG) and split-mouth (SM) studies.
4 No language restrictions for search strategy.
5 No restrictions on PS dye (any dose and incubation period) and laser wavelength combination.
6 At least one of the following parameters was an outcome variable; probing pocket depth (PPD), loss of clinical attachment level (CAL), bleeding on probing (BOP), plaque index (PI), gingival index (GI), microbiological profile or immunological profile.
7 Minimum follow-up duration was 3 months after treatment.

Studies conducted from their earliest records until 31st October 2019.

2.6.2. Exclusion criteria

1 Significant medical history of systemic diseases, periodontal and/or antibiotic therapy in last 6 months prior RCT enrolment.
2 Utilization of aPDT for residual pockets or in supportive periodontal therapy (SPT)
3 Studies that have utilized light emitting diodes (LEDs) as a light source
4 Pregnant females
5 Smokers
6 No outcome variable of interest
7 Literature/systematic reviews, case reports/series, *in vitro/in vivo* animal studies, abstracts, commentaries, interviews or updates.

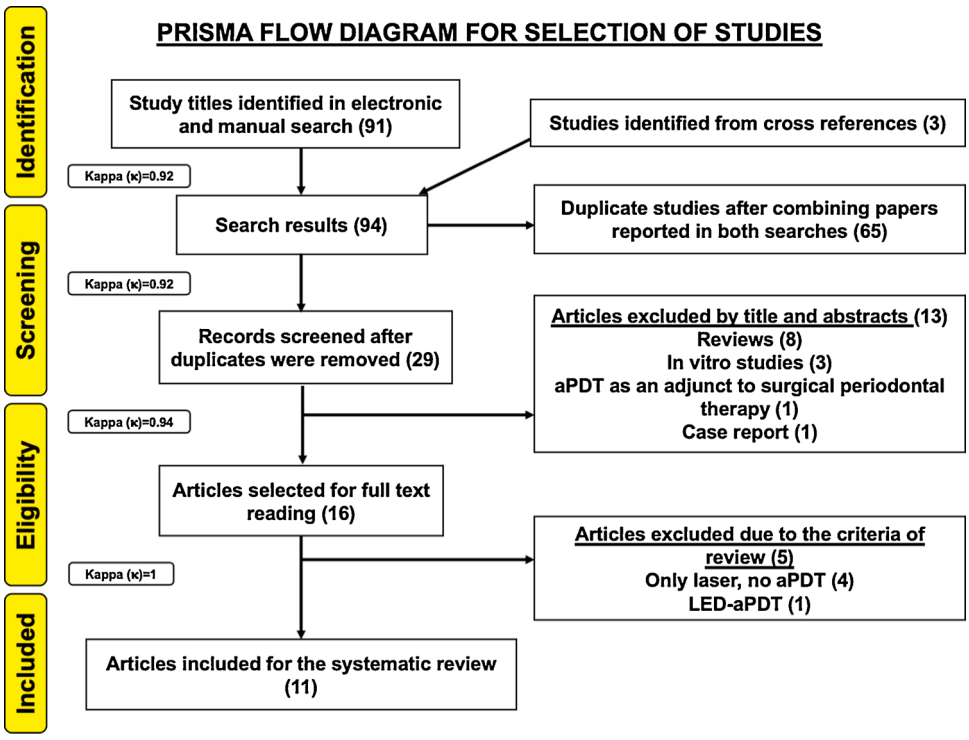

Fig. 1. PRISMA flow diagram of the study selection criteria.

2.7. Systematic review outcomes

2.7.1. Primary outcome

1 Clinical parameters such as; changes in PPD, CAL, GR, BOP, PI and GI.
2 Microbiological profile or immune-histological parameters obtained through gingival crevicular fluid (GCF) samples or biopsy specimens.

2.7.2. Secondary outcome measures

To derive the ideal dye-laser combination, a pre-specified laser protocol, dose of PS and number of aPDT sessions required to obtain optimum results in post-operative healing, for the utilization of aPDT in the management of AgP.

2.8. Data extraction

Study selection, data extraction, review, assessment was performed by two independent and blinded reviewers [SD and RH]. All eligible studies were given their unique identification with name of the first author, year of publication and origin. Additional relevant information such as; impact factor of journal, study design and sample size, demographics, intervention and comparator groups, PS used and its dosage, laser parameters, number of aPDT sessions, follow-up duration, study results and conclusions were tabulated.

2.9. Qualitative analysis

The Revised Cochrane Risk of Bias (RoB) tool for randomized trials, Version 2.0 (RoB 2) was utilized to perform the qualitative analysis by two independent and blinded reviewers [SD and RH] [23–25]. RoB was estimated under the following categories: 1. Bias arising from the randomization process; 2. Bias due to deviations from intended interventions; 3. Bias due to missing outcome data; 4. Bias in measurement of the outcome; 5. Bias in selection of the reported result. Each study were deemed as low, moderate or high RoB. Consensus for inter-reviewer disagreements was obtained by discussion with a third author (SB) as well as, use of 'discrepancy check' feature in RoB 2 tool.

3. Results

3.1. Study selection

Ninety-one study titles were obtained from a combined electronic and manual search. Three study titles were obtained from cross-references. Therefore, a total of 94 study titles were included from all databases, in the preliminary screening (inter-reviewer agreement, $\kappa = 0.92$). Sixty-five articles were excluded, due to duplication and the remaining 29 records were further evaluated (inter-reviewer agreement, $\kappa = 0.92$). Thirteen articles were excluded based on their titles and abstracts, mainly due to an inappropriate study design (inter-reviewer agreement, $\kappa = 0.94$) [8,13–19,26–30]. Thus, 16 articles were assessed for their eligibility. These articles were evaluated based on eligibility criteria. Additionally, 5 studies were excluded since there was only a laser group without aPDT [31–34] whereas 1 study was excluded for utilization of LED-aPDT [35] (inter-reviewer agreement, $\kappa = 1$). Hence out of 16 full text articles, 11 articles were included and analysed in the present systematic review [36–46]. All included articles were *in vivo* human studies. Fig. 1 depicts the PRISMA flow diagram for search strategy utilized in the present systematic review. During study selection, the list of eligible studies was discussed with a third author (SB) to draw a conclusion.

3.2. Study characteristics

3.2.1. Country of origin

Distribution of studies based on country of origin is as follows: 6 in Brazil [36–39,43,46], 3 in Poland [40,41,44], whereas one study each in Iran [42] and India [45] (Table 1).

Table 1
Tabular representation of eligible *in vivo* human studies in terms of demography, study design, intervention groups, methods of assessment, evaluation period, and outcomes. Refer to Appendix 2 for list of abbreviations.

Study, Year, Origin and Citation	Journal name/ Impact Factor (IF)	Study design	Type of Periodontitis	Sample size (n)	Gender M/F	Age (years) (mean ± SD)	Intervention groups		Evaluation period	Parameters assessed	Conclusion
De Oliveira et al., 2007, Brazil [36]	Journal of Periodontology IF 2020: 3.742 IF 2007: 2.426	SM-RCT	AgP (A minimum of 20 teeth (mean, 26 teeth) with at least one tooth in each posterior sextant and at least one posterior sextant with a minimum of three natural teeth; ≥ 5 mm of attachment loss around at least seven teeth involved, excluding first molars and central incisors)	10	2/8	18–35 Mean: 31.01 ± 4.43	SRP (Hand instruments) (10 teeth)	aPDT (10 teeth)	Baseline, 3 months	PD, RCAL, GR, PI, GI, BOP	Similar clinical results were noted in both groups in the nonsurgical treatment of AgP.
De Oliveira et al., 2009, Brazil [37]	Journal of Periodontology IF 2020: 3.742 IF 2009: 2.580	SM-RCT	AgP (A minimum of 20 teeth (mean, 26 teeth) with at least one tooth in each posterior sextant and at least one posterior sextant with a minimum of three natural teeth; ≥ 5 mm of attachment loss around at least seven teeth involved, excluding first molars and central incisors)	10	2/8	18–35 Mean: 31.01 ± 4.43	SRP (Hand instruments) (10 teeth)	aPDT (10 teeth)	−7 (baseline), 0 (immediately after interventions), +1, +7, +30, and +90 days.	TNF-α and RANKL assessment	Similar effects were noted for both groups for crevicular TNF-α and RANKL levels in the nonsurgical treatment of AgP.
Garcia et al., 2011, Brazil [38]	Revista Periodontia IF 2020: NA IF 2011: NA	SM-RCT	AgP (Bone loss first molars and incisors, and other teeth adjacent, with PPD ≥5 mm and loss of CAL ≥ 2 mm)	10	4/6	39.3 ± 5.84	SRP (Hand and ultrasonic instruments)	SRP + aPDT	Baseline, 3 months	PD, RCAL, furcation involvement, tooth mobility	Both groups showed similar clinical results in the nonsurgical treatment of AgP.
Novaes et al., 2012, Brazil [39]	Lasers in Medical Science IF 2019: 2.574 IF 2012: 2.645	SM-RCT	AgP (A minimum of 20 teeth (mean, 26 teeth) with at least one tooth in each posterior sextant, and at least one posterior sextant with a minimum of three natural teeth; ≥ 5 mm of attachment loss around at least seven teeth involved, excluding first molars and central incisors)	10	2/8	18–35 Mean: 31	SRP (Hand instruments)	aPDT	−7, 0 (Baseline and 3 months	Plaque sample analysis for estimation of 40 subgingival species using DNA-DNA hybridization.	aPDT was more effective in reducing the counts of *A.a* whereas, SRP reduced red complex bacteria. Combination of both treatment methods would be beneficial for the non-surgical treatment of AgP
Arweiler et al., 2013, Poland [40]	Schweiz Monatsschr Zahnmed IF 2020: NA IF 2013: NA	PG- RCT	AgP (At least 3 sites with PD ≥ 6 mm)	35 SRP + aPDT: 17 SRP + AB: 18	12/24 SRP + aPDT: 7/10 SRP + AB: 5/13	23–55 SRP + aPDT: 37.3 ± 8.0 SRP + AB: 34.7 ± 9.0	SRP + AB 141 sites AB: 375mg 375 mg AMX + 250 mg MTZ, TDS for 7 days (starting from day of SRP) (Hand and ultrasonic instruments)	SRP + aPDT 137 sites	Baseline, 3 months	PD, CAL, GR, PI, BOP, FMPI, FMBOP	SRP + AB showed significant differences in PD reduction and lower number of deep pockets ≥ 7 mm as compared to SRP + aPDT at 3 months
Arweiler et al., 2014, Poland [41]	Clinical Oral Investigations IF 2019: 2.903 IF 2014: 2.704	PG- RCT	AgP (At least 3 sites with PD ≥ 6 mm)	35 SRP + aPDT: 17 SRP + AB: 18	12/24 SRP + aPDT: 7/10 SRP + AB: 5/13	23–55 SRP + aPDT: 37.3 ± 8.0 SRP + AB: 34.7 ± 9.0	SRP + AB 141 sites AB: 375 mg AMX + 250 mg MTZ, TDS for 7 days (starting from day	SRP + aPDT 137 sites	Baseline, 6 months	PD, CAL, GR, PI, BOP, FMPI, FMBOP	SRP + AB showed significant differences in PD reduction and lower number of deep

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Table 1 (*continued*)

Study, Year, Origin and Citation	Journal name/ Impact Factor (IF)	Study design	Type of Periodontitis	Sample size (n)	Gender M/F	Age (years) (mean ± SD)	Intervention groups				Evaluation period	Parameters assessed	Conclusion
							of SRP) (Hand and ultrasonic instruments)						pockets ≥7 mm as compared to SRP + aPDT at 6 months
Chitsazi et al., 2014, Iran [42]	Journal of Dental Research, Dental Clinics, Dental Prospects IF 2020: 0.69 IF 2014: 1.30	SM-RCT	AgP (Minimum of 12 teeth with at least 3 teeth in each quadrant with ≥ 4 mm of probing depth)	24	9/15	29	SRP (Piezo-electric ultrasonic instruments)		SRP + aPDT		Baseline, 3 months	PD, CAL, GR, PI, GI, BOP, Microbiological analysis for A.a	No additional benefits of adjunctive aPDT in the nonsurgical management of AgP
Moreira et al., 2015, Brazil [43]	Journal of Periodontology IF 2020: 3.742 IF 2015: 3.159	SM-RCT	AgP (A minimum of 20 teeth and two pairs of single rooted contralateral teeth with proximal sites presenting PD and CAL ≥ 5 mm)	20	2/18	18–35 30.6 ± 4.25	SRP + sham procedure (Hand and ultrasonic instruments) 40 teeth/128 sites		SRP + aPDT 40 teeth/135 sites		Baseline, 3 months	PD, CAL, GR, PI, BOP Microbiological analysis for counts of 40 bacterial species using DNA- DNA Hybridization Immunological evaluation for GCF levels of IL-1β, IL-10 and TNF-α.	aPDT multiple sessions after SRP have several benefits over SRP alone in management of AgP.
Skurska et al., 2015, Poland [44]	BMC Oral Health IF 2019: 1.911 IF 2015: 1.605	PG- RCT	AgP (At least 3 sites with PD ≥ 6 mm)	35 SRP + AB: 17 SRP + aPDT:18	12/24 SRP + aPDT: 7/10 SRP + AB: 5/13	23–55 SRP + aPDT: 37.3 ± 8.0 SRP + AB: 34.7 ± 9.0	SRP + AB 141 sites AB: 375 mg AMX + 250 mg MTZ, TDS for 7 days, starting on the day of SRP (Hand and ultrasonic instruments)		SRP + aPDT 137 sites		Baseline, 3 and 6 months	MMP-8 and MMP-9 assessment	SRP + AB is more effective in reducing GCF MMP-8 levels compared to SRP + aPDT
Annaji et al., 2016, India [45]	Journal of Clinical and Diagnostic Research IF 2020: 0.81 IF 2016: NA	SM-RCT	AgP	15	6/9	18–35 Males: 27.83 ± 3.71 Females: 27.33 ± 2.29	SRP (ultrasonic)	SRP + Laser	SRP + 1 session of aPDT	SRP + 3 sessions of aPDT	Baseline, 3 months	PD, RAL, BOP, PI, Microbiological analysis (Bacterial culturing) for *A.a*, *P.g* and *P.i*	aPDT as an adjunct to SRP has an antibacterial action which is magnified by multiple sessions of aPDT.
Bechara et al., 2018, Brazil [46]	Photodiagnosis and Photodynamic Therapy IF 2020: 2.894 IF 2018: 2.624	PG- RCT	AgP (Single-rooted teeth in multiple quadrants, with both PPD and CAL ≥ 5 mm, and with BOP)	36 patients (72 sites)	CLM group: 1/17 Placebo group: 1/17	< 35 years CLM group: 33.11 ± 4.26 Placebo group: 31.26 ± 4.73	CLM group (n = 18) Clarithromycin 500 mg BD for 3 days UPD + CLM (18 sites)	UPD + CLM + aPDT (18 sites)	Placebo group (n = 18) UPD (18 sites)	UPD + aPDT (18 sites)	Baseline, 3 and 6 months	PD, CAL, BOP, GR	SRP + AB has more clinical advantages than SRP + aPDT. Combined SRP + AB + aPDT therapy has no additional benefits.

Table 2
Tabular representation of PS dye and laser parameters utilized for aPDT in the selected eligible *in vivo* human studies. Refer to Appendix 2 for list of abbreviations.

Study, Year, Origin and Citation	Photosensitizer (PS) used and its concentration	Pre-irradiation exposure time to PS (min)	LED/ Laser wavelength utilized	Emission mode Contact/ No contact Tip initiation	Energy (J)	Power outpour (W)	Pulse length (duration), Pulse interval	Use of Power meter	Distance from target	Spot size/ fibre-tip diameter/ spot diameter	Energy density [Fluence] (J/cm^2)	Power Density [Irradiance] (W/cm^2)	Exposure time to laser irradiation [Minute (min)/ second (sec)]	No. of aPDT applications
De Oliveira et al., 2007, Brazil [36]	Phenothiazine chloride (10 mg/ mL)	1 min	660 nm diode laser	Contact mode, fibre tip was place at the entrance of the gingival sulcus	NI	NI	NI	NI	NI	Tip diameter: 600μm	NI	60 mW/cm^2	10 s/site (6 sites = 1 min/ tooth)	1
De Oliveira et al., 2009, Brazil [37]	Phenothiazine chloride (10 mg/ mL)	1 min	660 nm diode laser	Contact mode, fibre tip was place at the entrance of the gingival sulcus	NI	NI	NI	NI	NA	Tip diameter: 600μm	NI	60 mW/cm^2	10 s/site (6 sites = 1 min/ tooth)	1
Garcia et al., 2011, Brazil [38]	Methylene blue (0.005%)	5 min	660 nm diode laser	NI	NI	40 mW	NI	NI	NI	NI	120 J/cm^2	NI	120 s/site	1
Novaes et al., 2012, Brazil [39]	Phenothiazine chloride	NI	660 nm diode laser	Contact mode, fibre tip was place at the entrance of the gingival sulcus	NI	NI	NI	NI	NI	Tip diameter: 600μm [8.5 cm long optic fibre with 60° angulated tip] Spot size: 0.06	212.23 J/cm^2	60 mW/cm^2	10 s/site (6 sites/tooth) 60 s/tooth	1
Arweiler et al., 2013, Poland [40]	Phenothiazine chloride	3 min	660 nm diode laser	NI	NI	NI	NI	NI	NI	NI	120 J/cm^2	60 mW/cm^2	60 s/site	2 (0 and 7th day)
Arweiler et al., 2014, Poland [41]	Phenothiazine chloride	3 min	660 nm diode laser	NI	NI	NI	NI	NI	NI	NI	120 J/cm^2	60 mW/cm^2	60 s/site	2 (0 and 7th day)
Chitsazi et al., 2014, Iran [42]	Toluidine Blue	1 min	670–690 nm diode laser	Contact mode	NI	75mW	NI	NI	NA	NI	NI	NI	120 s/site	1
Moreira *et al.*, 2015, Brazil [43]	Phenothiazine chloride (10 mg/ mL)	1 min	670 nm diode laser	NI	NI	75mW	NI	NI	NI	Tip diameter: 600μm	Fluence/ site: 2.49 J/cm^2 Fluen ce/ tooth: 14.94 J/cm^2	0.25 W/cm^2	10 s/site	4 (0,2nd,7th and 14th day)

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Table 2 (*continued*)

Study, Year, Origin and Citation	Photosensitizer (PS) used and its concentration	Pre-irradiation exposure time to PS (min)	LED/ Laser wavelength utilized	Emission mode Contact/ No contact Tip initiation	Energy (J)	Power outpour (W)	Pulse length (duration), Pulse interval	Use of Power meter	Distance from target	Spot size/ fibre-tip diameter/ spot diameter	Energy density [Fluence] (J/cm^2)	Power Density [Irradiance] (W/cm^2)	Exposure time to laser irradiation [Minute (min)/ second (sec)]	No. of aPDT applications
Skurksa et al., 2015, Poland [44]	Phenothiazine chloride	3 min	660 nm diode laser	NI	NI	NI	NI	NI	NI	NI	120 J/cm^2	60 mW/cm^2	60 s/site	2 (0 and 7th day)
Annaji et al., 2016, India [45]	Toluidine Blue O (1 mg/mL)	3 min	810 nm diode laser	Continuous wave	NI	100 mW	NI	NI	NI	NI	NI	NI	NI	1 session: 0 day 3 sessions: 0,7th,21st day
Bechara et al., 2018, Brazil [46]	Methylene Blue (10 mg/mL)	1 min	660 nm diode laser	NI	NI	60 mW	NI	NI	NI	NI	129 J/cm^2	NI	60 s/tooth (2 sites/tooth)	1

3.2.2. Study design

This review included 7 SM studies [36–39,42,43,45] and 4 PG studies [40,41,44,46] (Table 1).

3.2.3. Documentation of aPDT protocol parameters

Table 2 describes various dye-wavelength combinations as well as, laser dosimetry which were utilized to perform aPDT in all eligible studies. Ten out of 11 studies utilized a laser wavelength in the range of 660−690 nm [36–44,46] to perform aPDT, while 1 study utilized a 810 nm laser wavelength [45] (Table 2). Only 1 study reported the emission mode, which was 'continuous wave' [45]. Four out of 11 used the laser fibre tip in 'contact mode' with the periodontal pocket in order to perform aPDT [36,37,39,42]. Power output was reported in the range of 30 mW-1W in only 5 studies included in this review [38,42,43,45,46] and none of the studies reported the use of a power meter to measure the therapeutic power output, reaching the target tissues. Fibre tip diameter was mentioned in 4 studies [36,37,39,43] and a 600 μm fibre tip was used in all these studies. Energy density (fluence) was calculated in 7 out of 11 studies [38–41,43,44,46] and its value ranged from 14.94 to 212.23 J/cm^2. Power density (irradiance) was calculated in 7 studies [36,37,39,40,41,43,44] values ranged from 0.25 W/cm^2-60 mW/cm^2. Exposure time for laser irradiation was mentioned in all included studies except only one study [45] and values ranged from 10−120 sec/site amongst included studies. The total energy was overlooked in all eligible studies. Majority of studies utilized phenothiazine chloride PS [36,37, 39,39,40,41,43,44] while 2 studies each employed methylene blue (MB) [38,46] and toluidine blue O (TBO) [42,45]. The PS concentration was specified in 6 studies [36–38,43,45,46]. Interestingly, only 1 study failed to report the pre-radiation exposure time to PS [39] and this parameter ranged from 1 to 5 min amongst the included studies.

3.2.4. Utilization of aPDT as a mono-therapeutic or an adjunctive therapeutic agent

While 8 out of 11 eligible studies utilized SRP + aPDT, aPDT monotherapy was performed in 3 studies [36,37,39] (Table 1).

3.2.5. Comparison in between SRP + aPDT versus SRP + AB

Four out of 11 eligible studies compared efficacy of SRP + aPDT *versus* SRP + AB [40,41,44,46] (Table 1).

3.2.6. Number of aPDT sessions

A single session of aPDT was applied in 6 out of 11 included studies [36–39,42,46], while multiple aPDT sessions were performed in 5 studies [40,41,43–45]. None of the eligible studies compared single *versus* multiple sessions of aPDT (Table 2).

3.2.7. Follow-up assessment

A follow-up assessment at 3 months from baseline visit was performed in 8 out of 11 eligible studies [36–40,42,43]. One study conducted a follow-up at 6 months from baseline [41]. Two studies conducted 3- and 6-months follow-up assessment [44,46]. All eligible studies were lacking in a long-term follow-up of a minimum 1 year from baseline visit.

3.3. Qualitative assessment

Qualitative assessment was performed using the RoB 2 tool, designed for *in vivo* human RCTs, as depicted in Figs. 2 and 3. The most recent version of this tool was utilized to perform a qualitative assessment for both PG and SM human RCTs [23–25]. Fig. 2 represents a risk of bias assessment summary of all eligible studies. Fig. 3 is a graphical representation of percentage RoB score for each risk domain, which has been evaluated, using abovementioned tool. Overall, 80 % studies reported a high risk of bias and 20 % studies had a low risk of bias. None of the included studies fell under the category of 'some concerns' according to the summary of data generated from RoB 2 tool. The 80 % of included

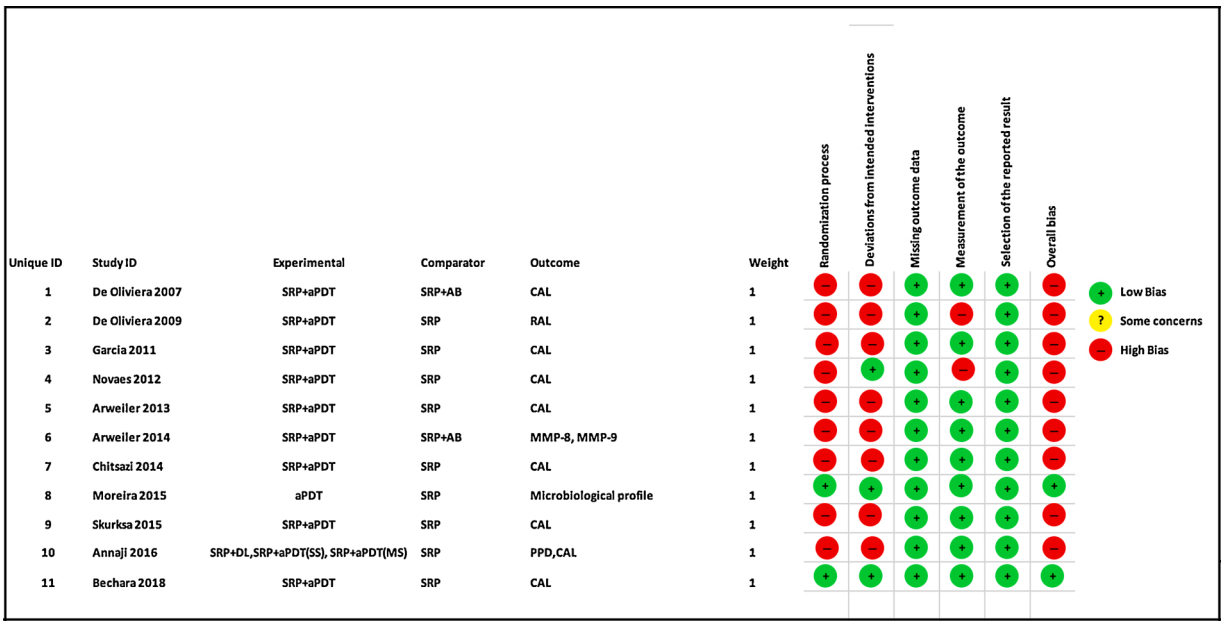

Fig. 2. Summary of Risk of Bias assessment for included studies based on the consensual answers across two individual assessors (SD and RH).

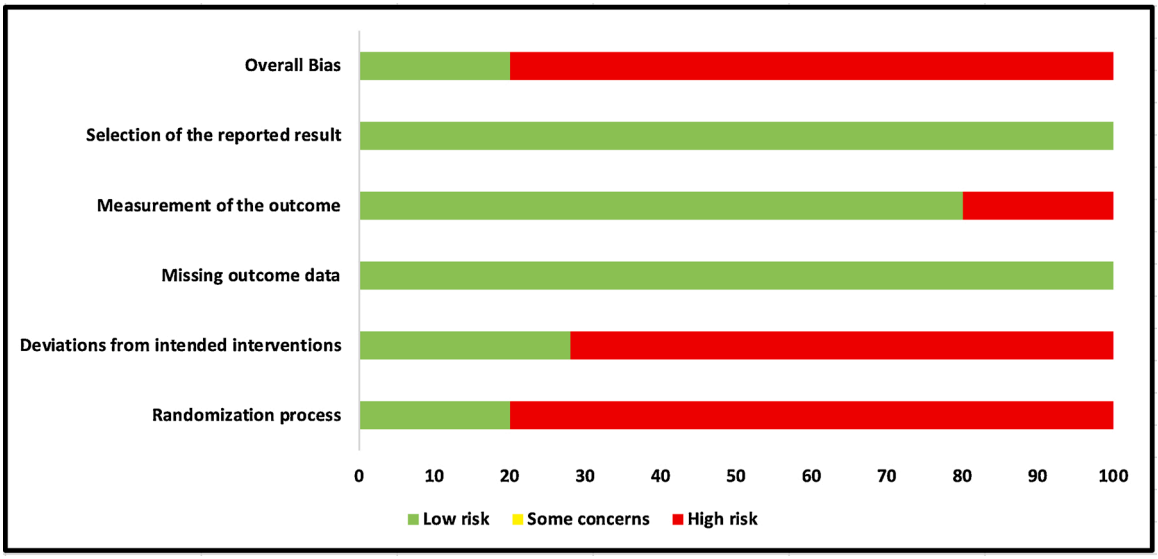

Fig. 3. Graphical representation of Risk of Bias assessment of the included studies expressed as percentages, based on the consensual answers across two individual assessors (SD and RH).

trials were at a high risk of inadequate randomization, whereas 20 % studies were at a low risk. The 72 % of included studies were at a high risk of deviations from intended interventions, whereas 28 % of them were at a low risk. All included papers were at a low risk for reporting substantial evidence and no missing outcome data (100 %). In terms of measurement of the outcome, 80 % studies were at a low risk and 20 % of studies at high risk. All included papers were at a low risk of selective reporting of the results (100 %). All the information provided in these figures represents the consensual answers verified using 'discrepancy check' feature of RoB 2 tool, across two independent reviewers [SD and RH] (inter-reviewer agreement, $\kappa = 0.94$).

4. Discussion

A thorough literature search resulted in the inclusion of 11 RCTs in the present systematic review [36–46]. Based on the hypothesis that SRP + aPDT or aPDT monotherapy can enhance the treatment outcome in AgP patients compared to SRP alone, or SRP + AB, a methodical appraisal of available scientific evidence was undertaken. The inconsistent and striking conclusions made by the various authors (Table 1), are a result of the heterogeneity in their methodology as well as, reported outcomes, which has made it impossible to conduct a meta-analysis of the included papers. Till date, 3 systematic reviews [14–16] and 1 meta-analysis [17] have been exclusively conducted to assess aPDT efficacy in AgP patients. However, owing to notable differences in their review protocol, limited sample size and contrasting results, the present systematic review was conducted. A comprehensive investigation of the pertinent literature was performed, which has been subsequently described.

All eligible studies have provided a tabular representation of relevant baseline characteristics in treatment arms of the trial, indicating the absence of an impartial baseline evaluation and absence of 'selection

Table 3
Tabular representation describing the assessment of clinical parameters used for the selected eligible *in vivo* human studies. Refer to Appendix 2 for list of abbreviations.

Study, Year, Origin and Citation	PPD		CAL/RAL		BOP/ SBI		PI		GI		GR	
	Statistically significant Y/ N/NI/NS	Not statistically significant Y/ N/NI/NS	Statistically significant Y/ N/NI/NS	Not statistically significant Y/ N/NI/NS	Statistically significant Y/ N/NI/NS	Not statistically significant Y/ N/NI/NS	Statistically significant Y/ N/NI/NS	Not statistically significant Y/ N/NI/NS	Statistically significant Y/ N/NI/NS	Not statistically significant Y/ N/NI/NS	Statistically significant Y/ N/NI/NS	Not statistically significant Y/ N/NI/NS
De Oliveira et al., 2007, Brazil [36]	N	Y	N	Y	N	Y	N	Y	N	Y	N	Y
Garcia et al., 2011, Brazil [38]	N	Y	N	Y	NS	NS	NS	NS	NS	NS	NS	NS
Arweiler et al., 2013, Poland [40]	N	Y	N	Y	N	Y	N	Y	NS	NS	N	Y
Arweiler et al., 2014, Poland [41]	N	Y	N	Y	N	Y	N	Y	NS	NS	N	Y
Chitsazi et al., 2014, Iran [42]	N	Y	N	Y	N	Y	N	Y	N	Y	N	Y
Moreira *et al.*, 2015, Brazil [43]	Y	N	Y	N	Y	N	Y	N	NS	NS	Y	N
Annaji et al., 2016, India [45]	N	Y	N	Y	N	Y	N	Y	NA	NA	NA	NA
1 session of aPDT 4 sessions of aPDT	N	Y	N	Y	Y	N	N	Y	NA	NA	NA	NA
Bechara et al., 2018, Brazil [46]	Y	N	Y	N	Y	N	NS	NS	NS	NS	Y	N

bias' for all the included studies [47,48]. Substantial evidence on the adverse effects of the smoking in hampering postoperative healing as well as the inter-relationship of periodontitis and systemic diseases, exists in the literature and hence resulted in the exclusion of the above mentioned confounders in this systematic review [49–52].

In order to determine the success of aPDT, a reduction in the inflammatory component of the diseased periodontium is quintessential. Periodontal inflammation is directly proportional to the severity of clinical, microbiological and immune-histological parameters [53–55]. Hence, these parameters were the outcome variables to be assessed in this systematic review. At baseline evaluation, heterogeneity in pre-treatment values of PPD and CAL across eligible studies was noted (Table 1) which resulted in post-operative variations in levels of significance across these clinical parameters (Table 3). As mentioned earlier, long-term follow-up assessment was overlooked in all the included studies. Other factors which govern the treatment outcome are; careful monitoring of post-operative healing, absence of post-operative complications, role of supportive periodontal therapy (SPT), provision of oral hygiene instructions and patient compliance to treatment [56–58]. Consequently, a noteworthy inconsistency in representation of treatment outcomes was evident amongst majority of the studies included in this systematic review.

For aPDT reaction to occur, the two vital elements are PS dye and a compatible wavelength. Hence appropriate reporting of laser-PS parameters is crucial for affirming the reliability of an aPDT protocol followed in the studies. However, several parameters which have been overlooked across the eligible studies are; emission mode, contact/non-contact mode, energy/treated site, power output, use of power meter spot size/fibre diameter, fluence and irradiance. Valle et al., 2019 conducted an *in vitro* analyses of the phenothiazine group of dyes associated with red laser and LED, on elimination of a suspension of *A.a.* The authors concluded that both blue dyes; TBO and MB at a concentration of 10 mg/mL, alone or associated with laser and LEDs, caused 100 % of *A.a* death [59]. In this systematic review, all included studies have utilized the blue PS dyes for aPDT (Table 2). However, information on the PS concentration which facilitates its' binding capacity to target commonly encountered periopathogens in AgP such as *A.a,* was lacking in majority of the included studies. With regards to the PS incubation time, pertinent research suggests that shorter pre-irradiation time is ideal to avoid patient discomfort [60]. This fact has been abided by majority of the included studies. Then again, there are no clinical studies till date, which have determined a minimal duration of PS incubation time, as well as, its role against periopathogens. Hence, research in this direction is required. Since bacterial re-colonization post-SRP occurs after three weeks [61], the utilization of multiple aPDT sessions is believed to impede this pathological process. This concept was implied in 5 out of 11 eligible studies, however, with contrasting results [40,41,43–45]. Only one study [45] has performed a comparative evaluation of 3 sessions (0, 7th and 21st day) *versus* a single session (0 day) of aPDT and concluded that the group receiving multiple sessions demonstrated superior treatment outcomes. Additionally, data regarding number of sites receiving aPDT application per tooth was inconsistent amongst eligible studies (Table 2). The voids which have been highlighted above, question the legitimacy of the included studies and this has consequently hampered the rational use of aPDT in the management of AgP.

Furthermore, all eligible studies were subjected to a qualitative assessment, in order to verify the respective study protocol and methodology. The results of this assessment have indicated that 80 % of the studies had an overall high RoB, which comprised of 9 out of 11 studies [36–42,44,45] whereas 20 % of the studies had an overall low RoB [43, 46]. A vast majority of the bias was raised from inadequate randomization and deviations from intended interventions (Figs. 2 and 3). Owing to the disparity in qualitative assessment of studies, their results are questionable and the methodology of studies with high risk of bias cannot be relied upon.

Although a qualitative systematic appraisal of eligible studies was

conducted, a quantitative data consolidation to perform a meta-analysis could not be performed owing to the heterogeneity in numerical representation of the presented facts. Majority of the included studies have assessed the efficacy of adjunctive aPDT in comparison to aPDT monotherapy, which has certainly influenced the results. Owing to limited number of studies assessing aPDT efficacy in AgP patients, the former was monitored in systemically healthy non-smokers only and it's benefits in their immunocompromised counterparts could not established in this systematic review. The studies also lacked in providing comprehensive information for aPDT protocol as well as long-term follow-up results in order to determine the stability in healing after aPDT. Owing to the aforementioned drawbacks, secondary outcome of this review could not be fulfilled. Future investigations should attempt to mitigate the limitations, which have been listed above. Adequate emphasis on long-term assessment of treatment outcomes in terms of patient related outcomes should be made. Above all, it remains imperative to conduct future research using a robust methodology with balanced baseline characteristics, performed by well trained, masked and calibrated clinicians.

5. Conclusion

Based on the available scientific evidence and within the limits of the present systematic review, aPDT efficacy in the non-surgical management of AgP remains inconclusive. Only a limited number of studies have acknowledged the benefits of aPDT while the remaining studies have failed to report the same. Upon careful evaluation and qualitative assessment of eligible studies, several noteworthy shortcomings were encountered which consequently result in an inability to reproduce their methodology. The data on aPDT protocol and parameters was incoherent amongst the included studies along with a high RoB in majority studies. Hence, future research should aim for well-designed, robust RCTs following an apposite local laser safety protocol and while considering the drawbacks highlighted in this systematic review.

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Authors contributions

1 **Snehal Dalvi:** Conceptualization, Methodology, Supervision, Investigation, Writing- Original draft preparation, Writing- Reviewing and Editing, Validation, Visualization, Data curation, Formal analysis.
2 **Stefano Benedicenti:** Resources, Project administration, Software, Validation, Supervision.
3 **Reem Hanna:** Conceptualization, Methodology, Supervision, Validation, Investigation, Writing-Reviewing and Editing, Visualization, Data curation, Formal analysis.

Declaration of Competing Interest

All authors have read the journal's authorship agreement and policy on disclosure of potential conflicts of interest and have declared that they have no known conflicts of interest.

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Appendix A. Supplementary data

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