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Review

Is antimicrobial photodynamic therapy a useful therapeutic protocol for oral decontamination? A systematic review and meta-analysis

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ABSTRACT

Background: The aim of the present systematic review and meta-analysis was to assess the efficacy of antimicrobial photodynamic therapy (aPDT) as a therapeutic protocol for oral decontamination.

Methods: In order to address the focused question: Is aPDT a useful therapeutic protocol for oral decontamination?, an electronic search without time or language restrictions was conducted up to July 2017 in indexed databases using the combination of different key words including photochemotherapy, lasers, photodynamic therapy, disinfection, mouth, saliva and oral. The exclusion criteria included reviews, case-reports, case-series, commentaries, letters to the editor, interviews, and updates. Four randomized control trials were included and processed for data extraction.

Results: All studies reported that aPDT was effective in reducing the overall oral microbial load in saliva. Considering the effects of aPDT + photosensitizer (PS) compared with PS alone, there was no heterogeneity noticed for aPDT + PS (Q value = 0.15, P = 0.69, I^2 = 0%). The overall mean difference for bacterial count in CFU/ml between aPDT + PS and PS alone was also not significant (weighted mean difference = −0.41, 95% CI = −1.12 to 0.29, p = 0.24) at follow-up.

Conclusion: The efficacy of aPDT for oral decontamination remains unclear. Further well-designed randomized clinical trials assessing the efficacy of aPDT reducing the oral microbial load are need.

1. Introduction

Antimicrobial photodynamic therapy (aPDT) is a modern disinfection protocol that involves interactions between a light source (630–880 wavelength) and a photosensitizer (PS) such as methylene blue, toluidine blue and curcumin [1,2]. The PS-light reaction produces reactive oxygen species (singlet oxygen and toxic radicals) capable of oxidizing organic molecules by a lipid peroxidation process, resulting in localized photodamage and microbes death [3]. This innovative therapeutic method has been widely used in different fields of medicine for the treatment of cancer and dermatological conditions [4,5]. In dentistry, aPDT has been proven to be efficient in the reduction of microbes load from oral biofilm (bacteria, virus, fungus and yeasts) in teeth and soft tissues surfaces. Therefore, aPDT has been used for the treatment of periodontal and peri-implant diseases (as adjunctive therapy to mechanical debridement) [6–10], disinfection of root canals [11,12], management of halitosis [13,14] and for the treatment of denture stomatitis or dentures disinfection [15,16]. Other uses of aPDT in dentistry include the treatment of herpes labialis and malignant and non-malignant oral lesions [17–19].

The oral cavity is a complex system that presents a diversity of biological surfaces, secretions and nutrients that provide a favorable habitat to more than 700 microbial species [20,21]. Although dental materials such as amalgam and composite restorations, porcelain crowns and veneers and orthodontic appliances are evidence-based treatments routinely used in dental settings; such materials may also support more biofilm growth than enamel structure [22–24]. Therefore, it is challenging to achieve aseptic conditions in the mouth. Conventionally, antiseptic mouthwashes, such as chlorhexidine are used for the reduction of the overall oral flora load (mucosa, tongue, saliva, teeth) [25–27]; however, this may result in complications including alteration in taste, oral mucosa desquamation, and staining of teeth and restorative materials [28].

A limited number of studies [29–32] have assessed the efficacy of aPDT for oral decontamination. For example, in the study by Panhoca et al. [31], oral decontamination using aPDT showed similar results

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compared with chlorhexidine in terms of reducing the oral microbial load. To our knowledge, there are no studies in indexed literature that have systematically reviewed the efficacy of aPDT in oral decontamination. Therefore, the aim of the present systematic review and meta-analysis was to assess the efficacy of aPDT as a useful therapeutic protocol for oral decontamination.

2. Material and methods

2.1. Focused question

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were used to conduct this systematic review [33]. A specific question was developed according to the Participants, Interventions, Control, and Outcomes (PICO) format. The addressed focused question was "Is aPDT a useful therapeutic protocol for oral decontamination?"

2.2. Eligibility criteria

A study was considered eligible for inclusion if it met the following criteria: (a) randomized controlled clinical trials; (b) presence of control group; and (c) interventions evaluating efficacy aPDT as therapeutic protocol for oral decontamination. The exclusion criteria included qualitative and/or quantitative reviews, laboratory (*in vitro)* and experimental (animal models) studies, case reports, case-series, commentaries, letters to the editor, interviews, updates, and studies with an ex-vivo design (saliva samples receiving aPDT outside the mouth).

2.3. Literature search protocol

The international database of Prospectively Registered Systematic Reviews in Health and Social Care (PROSPERO) and the Cochrane Register of Systematic Reviews were searched (SVK) in July 2017, and presented no existing or current review protocols assessing the efficacy of aPDT for oral decontamination. In order to identify studies relevant to the focused question, two authors (FJ and SVK) conducted a structured and logical electronic search without time or language limitations up to July 2017 in PubMed (National Library of Medicine), Scopus, EMBASE, and MEDLINE (OVID). The following Medical Subject Headings (MeSH) were used: (1) photochemotherapy, (2) lasers, (3) disinfection, (4) mouth and (5) saliva. Other related non-MeSH terms were used in the search strategy to detect additional articles discussing the efficacy of aPDT in the decontamination of oral cavity. These included: (6) photodynamic therapy and (7) oral. Boolean operators (OR, AND) were used to combine the key words mentioned above: (a) 1 or 2 or 6 and 3 and 4 or 5 or 7. To minimize the potential for reviewer bias; titles and abstracts of studies identified using the above-described protocol were independently screened by 2 reviewers (FJ and SVK) and checked for agreement. Full-texts of studies judged by title and abstract to be relevant were read and independently evaluated for the stated eligibility criteria. Reference lists of original studies were hand searched to identify any articles that could have been missed during the initial search. Hand searching of the following journals was performed: Photomedicine and Laser Surgery; Journal of Lasers in Medical Science; Journal of Photochemistry and Photobiology; and Photodiagnosis and Photodynamic Therapy. Any disagreements in the study selection were resolved via discussion and consensus. Cohen's kappa value [34] was used to determine the inter-reviewer reliability between the 2 reviewers. The kappa coefficient for inter-reviewer agreement was 1. Authors of the studies included were contacted via electronic mail in case data was missing or additional information regarding their studies was required.

2.4. Quality assessment

In an attempt to increase the strength of the present systematic review the studies that were included underwent a quality assessment following the recommendations of the CONSORT statement [35]. The CONSORT tool uses a systematic approach based on 7 specific criteria which are: (A) sample size calculation (minimum number of participants required to detect a significant difference among compared groups); (B) randomization and allocation concealment methods; (C) clear definition of inclusion and/or exclusion criteria; (D) complete follow up; (E) experimental and control groups comparable at study baseline; (F) presence of masking; and (G) appropriate statistical analysis. After determining the scores, an overall estimation of risk of bias (low, moderate or high) was estimated for each selected study. When all the criteria were met, a low risk of bias was estimated; those studies which partly met one or more criteria were estimated as moderate risk of bias; and the risk of bias was estimated as high when one or more criteria were not met [36]. Quality assessment of studies included was conducted independently by two authors (FJ and SVK) using the above-described tool. Qualitative analyses were checked for disagreement via discussion among the authors. (Kappa score = 0.88).

2.5. Quantitative analysis

In order to answer the focused question, meta-analysis was conducted for bacterial CFU/ml. The mean differences between the test and control groups were estimated as the effect size measures. Heterogeneity among the included studies for each outcome was assessed using Q-statistics and I^2 statistic. Meta-analysis of 2 studies [31,32] which reported CFU/ml means values were conducted. Statistical analyses were carried out by specialized statistical software (MedCalc Software- B-8400 Ostend v 15.11.04, Belgium).

3. Results

3.1. Study selection

Four hundred and eleven potential articles were initially identified, out of which 410 were identified thru electronic database searching and 1 article with hand searching. After title and abstract screening 399 publications, which were duplicates or did not fulfill the eligibility criteria were excluded. In the second step, 8 more articles were excluded (Appendix A). A total of 4 studies [29–32] were included for qualitative analysis (Fig. 1).

3.2. General characteristics

All studies [29–32] were conducted in Brazil under university settings between 2012 and 2016. All studies were randomized control trials with a parallel design. The number of study participants ranged between 13 and 50 individuals, with age ranging between 18 years and 50 years. In total 114 systemically healthy individuals were included in these primary studies [29–32], and confounding variables including pregnancy and lactation, antibiotics medication prior enrollment, and/or recent periodontal treatment were assessed. Panhóca et al. [31] studied the efficacy of aPDT for oral decontamination in patients with orthodontic appliances. Three studies [29,30,32] excluded smokers, and in 1 study [31] the inclusion/exclusion of smokers remains unclear. In all studies [29–32], the follow-up period ranged from immediate after laser irradiation and 24 h (Table 1).

3.3. Photosensitizer parameters

Araujo et al. [29] assessed the efficacy of aPDT with curcumin in reducing bacterial load in unstimulated whole saliva (UWS) compared with PS alone; whereas, Leite et al. [32] studied bacterial CFU/ml

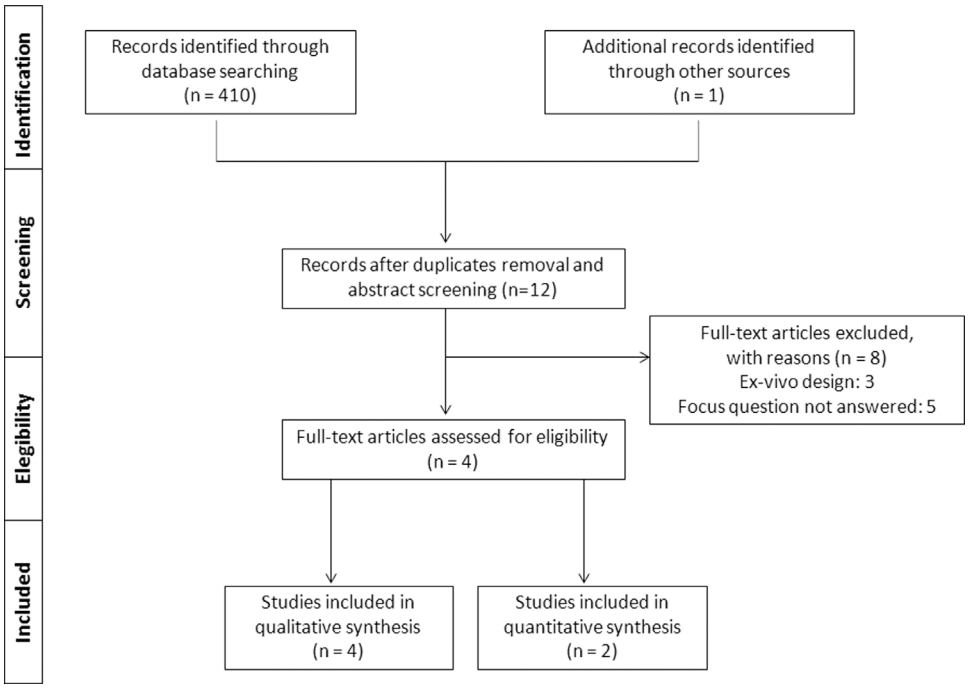

Fig. 1. Article selection flow chart for the systematic review according to PRISMA guidelines.

reduction in saliva after aPDT decontamination with curcumin compared with laser or PS alone. Panhóca et al. [31] assessed the efficacy of aPDT with curcumin for oral decontamination using 2 different aPDT protocols (aPDT + PS, aPDT + PS + surfactant Sodium Dodecyl Sulfate [SDS]), compared with laser treatment alone and chlorhexidine rinses. Ricci Donato et al. [30] studied microbial CFU/ml reduction in UWS by aPDT with 2 different photosensitizers (curcumin and photogem®) and 2 different concentrations (25 and 100 μg/ml) compared with water rinses and laser or PS alone. In 3 studies [29,31,32], patients in aPDT group rinsed once (rinsing duration ranged between 2 min and 5 min) with the PS solution prior irradiation. In the study by Donato Ricci et al. [30] the patients underwent 3 PS mouthwash for 1 min each prior laser exposure (Table 2).

3.4. Laser parameters

In all studies [29–32], diode lasers with wavelengths ranged between 450 nm and 630 nm were used. Three studies [29,30,32] used intra-oral irradiation, out of which, 2 studies [29,32] used a single laser unit, and 1 study [30] used 2 different diode lasers: a device emitting in the range of blue light at 450 nm for patients exposed to curcumin, and a device emitting in the red light at 630 nm for patients treated with Photogem®. Panhoca et al. [31] used intra-oral and extra-oral irradiation, using two different LED-based devices emitting blue light (450 nm). All the studies [29–32] conducted a single aPDT session, with an irradiation time ranged between 5 min and 9 min.

3.5. Main outcomes

All studies [29–32] reported that aPDT was effective reducing salivary microbial CFU. One study [31] showed that aPDT with curcumin and surfactant SDS results in similar reduction of salivary microbial load compared with chlorhexidine rinses. One study [30] reported that aPDT with curcumin as PS is more effective maintaining low bacterial CFU in saliva after 24 h (higher substantivity) compared with aPDT with Photogem®.

3.6. Quality assessment

All the included studies [29–32] in the present systematic review were randomized controlled trials. Quality score of the studies [29–32] ranged from 7 to 9 according to CONSORT guidelines. Quality assessment identified that in general, comparability of control and test group at baseline for salivary bacterial CFU load, recruitment of the patients, and appropriate statistical analysis were adequately performed in these studies [29–32]. The most common limitation was the short term and the incomplete follow-up (up to 24 h) of the experimental groups. Randomization was reported in 3 studies [30–32], out of which only 2 studies [31,32] reported the methodology for randomization (random computer number generation). In 1 study [29] randomization remains unclear. All the studies [29–32] were catalogued as high risk of bias because one or more criteria were not met. Quality assessment of the included studies is summarized in Table 3.

3.7. Data analysis results

Two studies [31,32] presented available data in CFU/ml to be included in the meta-analysis considering the effects of aPDT + PS (intervention) and PS alone (control) on bacterial CFU; one study [29] presented bacterial count outcome data using CFU values for aPDT + PS and PS alone where 2 studies [29,30] did not report the mean and standard deviation values and hence these studies were excluded from the meta-analysis. Considering the effects of aPDT + PS compared with PS alone, there was no heterogeneity noticed for aPDT + PS (Q value = 0.15, P = 0.69, I^2 = 0%, Fig. 2). The overall mean difference for bacterial count in CFU/ml between aPDT + PS and PS alone was also not significant (weighted mean difference (WMD) = −0.41, 95% CI = −1.12 to 0.29, p = 0.24) at follow-up.

4. Discussion

Results from all studies [29–32] reported that aPDT is effective in reducing the overall oral microbial load in saliva. Therefore, it is tempting to contemplate that aPDT is an efficient therapeutic protocol for oral decontamination. However, these results should be interpreted with extreme caution for a number of reasons. The meta-analysis did

Table 1
General characteristics of included studies.

Investigators (Country, year)	Sample size	Age range in years	Study groups	Sample and times of collection	Main outcomes
Araujo et al. [29] (Brazil, 2012)	13	25–50	Group 1: PS alone; Group 2: PS + PDT	2 ml UWS; BR, IPI	Bacterial CFU was significantly lower in group 2 compared with group 1.
Leite et al. [32] (Brazil, 2014)	27	20–35	Group 1: PS + PDT; Group 2: PDT alone; Group 3: PS alone	Saliva; BR, IPI, 1 h PI, 2 h PI	Bacterial CFU/ml was significantly lower in group 1 compared with groups 2 and 3.
Panhóca et al. [31] (Brazil, 2016)	24	18–50	Group 1: PDT alone; Group 2: PS + PDT; Group 3: PS + SDS 0.1% + PDT; Group 4: CHX	3 ml UWS; BR, AR, IPI	Bacterial CFU/ml was significantly lower in groups 2,3 and 4 compared with group 1. Group 3 presented similar CFU/ml reduction compared with group 4
Ricci Donato et al. [30] (Brazil, 2016)	50	18–40	Group 1: Water; Group 2: PS; Group 3: PDT; Group 4: PS 25 mg/ml + PDT; Group 5: PS 100 mg/ml + PDT	1 ml saliva samples; BR, IPI, 24 h PI	Bacterial CFU was significantly lower in group 5 compared with groups 1 and 2 IPI. Group 5 with curcumin presented significantly lower bacterial CFU 24 h PI compared with other curcumin and photogem groups.

PS: photosensitizer PDT: photodynamic therapy UWS: unstimulated whole saliva CFU: Colony forming units
BT: before rinsing IPI: immediately post-irradiation PI: post-irradiation AR: after rinsing CHX: chlorhexidine
SDS: surfactant Sodium Dodecyl Sulfate

Table 2
Laser and photosensitizer parameters of included studies.

	Type of laser	Fiber (D in mm)	Wavelength (nm)	Energy (J)	Energy Fluence (J/cm^2)	Power (W)	Power density (mW/cm^2)	Duration of laser irradiation (minutes)	Number of laser applications	Type of PS (Concentration in g/L)	Duration of PS rinsing (minutes)
Araujo et al. [29]	Diode	NR	450	NR	20.1	NR	67	5	1	20 ml of Curcumin (1.5)	5
Leite et al. [32]	Diode	6.73	455	NR	200	0.4	600	5	1	20 ml of Curcumin (1.5)	5
Panhóca et al. [31]	Diode for teeth	NR	450	36	14	0.2	80	6	1	Curcumin (1)	2
	Diode for oral cavity	24	450	216	85	1.2	472	3	1		
Ricci Donato et al. [30]	Diode	NR	630	NR	NR	NR	NR	6	1	15 ml of Photogem (25 and 100 μg/ml)	3
	Diode	NR	450	NR	NR	NR	NR	6	1	15 ml of Curcumin (0.025 and 0.1)	3

NR: not reported D: diameter PS: photosensitizer

Table 3
Quality assessment of included studies following CONSORT statement.

Investigators	A (0–2)	B (0–2)	C (0–1)	D (0–1)	E (0–2)	F (0–2)	G (0–2)	Total score	Estimated risk of bias
Araujo et al. [29]	1	0	1	0	2	1	2	7	High
Leite et al. [32]	1	2	1	0	2	1	2	9	High
Panhóca et al. [31]	1	2	1	0	2	1	2	8	High
Ricci Donato et al. [30]	1	1	1	1	2	1	2	9	High

(A) sample size calculation (minimum number of participants required to detect a significant difference among compared groups); (B) randomization and allocation concealment methods; (C) clear definition of inclusion and/or exclusion criteria; (D) complete follow-up; (E) experimental and control groups comparable at study baseline; (F) presence of masking; and (G) appropriate statistical analysis

not find a statistically significant difference for bacterial count in CFU/ml among patients treated with aPDT + PS compared with PS alone. Several factors may have influenced these results. Firstly, the intrinsic anatomical and morphological complexity of teeth and oral cavity structures might have influenced the PS activation. The oral cavity presents major habitats including buccal mucosa, dorsum of the tongue, tooth surfaces and crevicular epithelium [37]. The microbiome varies depending of the colonization niche. For example, teeth pits and fissures are colonized by a higher number of bacteria than smooth surfaces. Similarly, the subgingival plaque microbiota varies compared with the supragingival plaque (due to the gingival crevicular fluid that provides nutrients to obligate anaerobes microorganisms) [37–39]. Next, from the literature reviewed, it is noteworthy that in 75% of the included studies [29,30,32] the position of the laser diffuser tip remained unclear or was central type (supported in the tongue and in contact with the palate). This might have influenced the uniform light diffusion across the oral cavity and its absorption by the PS in different oral habitats such as vestibular surfaces of teeth and buccal mucosa. It is hypothesized that a protocol including equal light distribution into the oral cavity results in an effective PS activation and increase the aPDT bactericidal effect. Therefore, additional well-designed clinical studies using a standardized irradiation protocol, capable to excite the PS efficiently and equally in the different oral habitats are needed.

In all the studies [29–32] that met our eligibility criteria, aPDT was performed once. The authors of the present systematic review perceive that the primary factor that should determine the frequency of aPDT is the total microbial load. It is hypothesized that patients with higher microbial loads require multiple treatments using aPDT. Moreover, the maximum follow-up duration in the included studies in the present systematic review was 24 h. The long-term efficacy of aPDT in oral decontamination remains unclear. Therefore, further studies with particular emphasis on the frequency of aPDT with longer follow-up are needed. The authors of the present systematic review highlight that aPDT should be accompanied with regular follow-up and reinforcement of oral hygiene and patient education. Furthermore, it is pertinent to mention that all the studies [29–32] included were conducted in one country with relatively small samples. We believe that is hard to extrapolate these findings to the whole population. Hence, additional prospective multi-center studies including larger samples, different ethnicities and oral habits are needed.

Although the statistical analysis did not show a statistically significant reduction in terms of CFU/ml among the patients exposed to aPDT, the authors of the present review perceive that oral decontamination with aPDT is a suitable technique with important clinical applications. These include the reduction of the bacterial load in the aerosol generated from patient's mouth during common dental procedures in order to minimize cross-contamination and occupational hazard [2]. Likewise, the use of aPDT previous oral surgeries in order to temporarily reduce the oral bacterial load might reduce the risks of postoperative infections [32]. Moreover, a protocol including oral decontamination with aPDT prior surgeries offer several advantages compared with traditional therapeutics techniques including prophylactic antibiotic therapy (associated with allergic reactions, gastrointestinal disturbances and development of resistance) and the use of oral antiseptics such as chlorhexidine (associated with staining of teeth and restorative materials and taste alterations) [28,40–42]. Further studies are needed to test these hypotheses.

5. Conclusion

The efficacy of aPDT for oral decontamination remains unclear. Further well-designed randomized clinical trials assessing the efficacy of aPDT reducing the oral microbial load are need.

Conflict of interests

none

Funding

none

Ethical approval

not required

Acknowledgement

None

Appendix A. List of excluded articles

a. Al-Ahmad A, Tennert C, Karygianni L, Wrbas KT, Hellwig E, Altenburger MJ. Antimicrobial photodynamic therapy using visible light plus water-filtered infrared-A (wIRA). Journal of medical microbiology. 2013;62(Pt 3):467-73. (Focus question not answered)

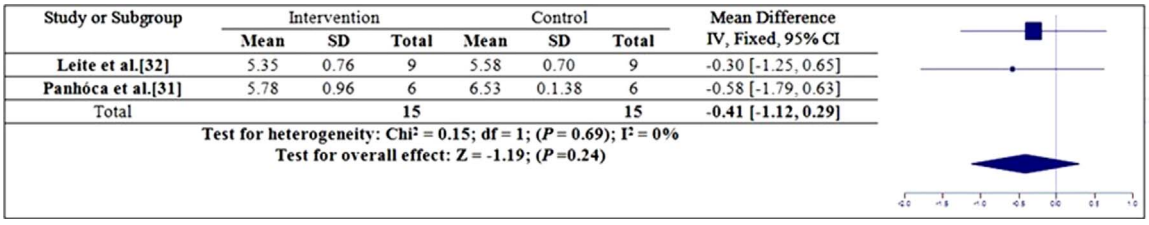

Fig. 2. Forest plots presenting mean difference (MD) for bacterial count in CFU/ml between test and control groups.

b. Fekrazad R, Seraj B, Chiniforush N, Rokouei M, Mousavi N, Ghadimi S. Effect of antimicrobial photodynamic therapy on the counts of salivary streptococcus mutans in children with severe early childhood caries. Photodiagnosis and photodynamic therapy. 2017. (Ex-vivo design)

c. Graciano TB, Coutinho TS, Cressoni CB, Freitas Cde P, Pierre MB, Pereira SA, et al. Using chitosan gels as a toluidine blue O delivery system for photodynamic therapy of buccal cancer: In vitro and in vivo studies. Photodiagnosis and photodynamic therapy. 2015;12(1):98-107. (Focus question not answered)

d. Hafner S, Ehrenfeld M, Storz E, Wieser A. Photodynamic Inactivation of Actinomyces naeslundii in Comparison With Chlorhexidine and Polyhexanide–A New Approach for Antiseptic Treatment of Medication-Related Osteonecrosis of the Jaw? Journal of oral and maxillofacial surgery: official journal of the American Association of Oral and Maxillofacial Surgeons. 2016;74(3):516-22. (Exvivo design)

e. Pinto EH, Longo PL, de Camargo CC, Dal Corso S, Lanza Fde C, Stelmach R, et al. Assessment of the quantity of microorganisms associated with bronchiectasis in saliva, sputum and nasal lavage after periodontal treatment: a study protocol of a randomised controlled trial. BMJ open. 2016;6(4):e010564. (Focus question not answered)

f. Santezi C, Tanomaru JM, Bagnato VS, Junior OB, Dovigo LN. Potential of curcumin-mediated photodynamic inactivation to reduce oral colonization. Photodiagnosis and photodynamic therapy. 2016;15:46-52. (Focus question not answered)

g. Voos AC, Kranz S, Tonndorf-Martini S, Voelpel A, Sigusch H, Staudte H, et al. Photodynamic antimicrobial effect of safranine O on an ex vivo periodontal biofilm. Lasers in surgery and medicine. 2014;46(3):235-43. (Ex-vivo design)

h. Shephard SE, Zogg M, Burg G, Panizzon RG. Measurement of 5-methoxypsoralen and 8-methoxypsoralen in saliva of PUVA patients as a noninvasive, clinically relevant alternative to monitoring in blood. Archives of dermatological research. 1999;291(9):491-9. (Focus question not answered)

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