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SYSTEMATIC REVIEW

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Efficacy of chemical approaches for implant surface decontamination in conjunction with sub-marginal instrumentation, in the non-surgical treatment of peri-implantitis: A systematic review

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Abstract

Aim: To answer the following PICOS question: In adult patients with peri-implantitis, what is the efficacy of sub-marginal instrumentation combined with chemical surface decontamination in comparison with sub-marginal instrumentation with or without placebo, in terms of changes in probing depth (PD) and/or bleeding on probing, as reported in prospective randomized controlled trials, non-randomized controlled trials, or prospective cohort studies, with a minimum of 6-month "follow-up".

Materials and Methods: A systematic literature search was performed in PubMed, Web of Science, Embase, Scopus, Ovid Medline, and The Cochrane Library of the Cochrane Collaboration (CENTRAL) for articles published until March 2022. Data addressing the primary and secondary outcomes were extracted.

Results: The search gave 2033 results of which 3 fulfilled the inclusion criteria. Two studies investigated the use of anti-microbial photodynamic therapy as adjunct to sub-marginal instrumentation and the third study assessed the adjunctive use of a desiccant material. A meta-analysis was not deemed meaningful because of the large heterogeneity among the studies. All three studies showed favourable results in terms of PD reduction for chemical surface decontamination over control approaches, but were inconsistent or showed no differences for the other outcome variables.

Conclusions: Adjunctive chemical approaches for implant surface decontamination may offer an advantage over sub-marginal instrumentation alone, in terms of improved PD.

KEYWORDS
decontamination, dental implant, peri-implantitis, systematic review, therapy

Clinical Relevance

Scientific rationale for study: It is currently unknown if a single application of chemical decontaminants, in conjunction with sub-marginal instrumentation, can be of benefit in improving the outcomes of non-surgical peri-implantitis treatment.

Principal findings: Treatment approaches including chemical surface decontamination resulted in more favourable pocket depth reductions over control approaches. However, the results should be interpreted with caution because of the small number of studies identified and the considerable heterogeneity between studies.

Practical implications: Chemical decontamination of the implant surface may be of merit for the non-surgical treatment of peri-implantitis.

1 | INTRODUCTION

Peri-implantitis is characterized by inflammation of the peri-implant soft tissues and loss of the supporting bone. Since a major factor in peri-implantitis is the biofilm established on the various implant components, treatment strategies employed over the years derive primarily from traditional anti-infective treatment regimens for periodontitis (Schwarz et al., 2018; Wang, Li, et al., 2019; Wang, Renvert, et al., 2019). Thus, peri-implantitis treatment includes customarily a non-surgical phase, including oral hygiene adjustment and assessment/adjustment of the prosthetic reconstruction when needed, as well as debridement/instrumentation of the implant surface. Non-surgical debridement/instrumentation of implants may be performed by either hand or power-driven instruments (Wang, Li, et al., 2019; Wang, Renvert, et al., 2019). However, non-surgical instrumentation in peri-implantitis patients is often challenging when compared to that in natural teeth, as the presence of threads and the complex/structured implant surface hinder effective biofilm removal (Renvert & Polyzois, 2017).

Non-surgical instrumentation results, in general, in decreased probing depths (PD) and reduced signs of inflammation, expressed as reduced tendency for bleeding on probing (BOP) and/or suppuration (SUP), but as yet it has not been proven to be a reliable treatment option (Wang, Li, et al., 2019; Wang, Renvert, et al., 2019). Only occasionally, and primarily at the early stages of the disease, can non-surgical treatment be effective in resolving inflammation and establishing healthy conditions. Thus, non-surgical treatment is primarily seen as a way of improving peri-implant tissue conditions by reduction of inflammation while observing the patient's motivation and oral hygiene practices and the possible effect of other variables such as the prosthetic supra-structure (Karring et al., 2005; Renvert et al., 2009; Renvert & Polyzois, 2017; Wang, Li, et al., 2019; Wang, Renvert, et al., 2019). In advanced cases, resolution of the disease is unlikely, and surgical procedures need to be considered (Klinge et al., 2018; Polyzois, 2019).

A number of mechanical means, that is, specially designed scalers and ultrasonic tips, various types of brushes, and airflow devices, have been suggested to reduce/avoid the damage that may be caused to the implant and/or implant abutment surface during sub-marginal instrumentation (Ruhling et al., 1994; Matsubara et al., 2020). Although these instruments indeed cause less surface alteration compared with conventional stainless steel curettes and ultrasonic tips, they have also been proven ineffective in completely eliminating the biofilm (Yang et al., 2015; Wang, Li, et al., 2019; Wang, Renvert, et al., 2019). Indeed, there is large variation in terms of the amount of residual biofilm, as demonstrated in several in vitro studies, depending, among others, on the instrument used, pocket depth, defect angle, accessibility due to the prosthetic reconstruction, and other factors (Ronay et al., 2017; Iatrou et al., 2021). Therefore, the adjunctive use of chemical/photochemical therapy, such as anti-bacterial solutions, local antibiotics, acid application, and anti-microbial photodynamic therapy (aPDT), has been considered.

Recommendations from recent workshops regarding the assessment of peri-implantitis treatment suggest that treatment results should be based on composite outcomes indicative of inflammation resolution and that studies should have a follow-up of a minimum of 6 months (Sanz & Chapple, 2012; Jepsen et al., 2019). For example, in a recent consensus report, it was stated that sub-marginal instrumentation alone often provides clinical improvements of up to 50% in reducing bleeding tendencies and sometimes pocket reduction of ≤1 mm compared with baseline. Interestingly, adjunctive use of chemical approaches provided only minimal additional improvements in the above-mentioned clinical parameters (Renvert et al., 2019). Furthermore, a recent systematic review evaluated the efficacy of sub-marginal instrumentation with various adjunctive measures against conventional non-surgical treatment of peri-implant diseases. In that review, adjunctive use of single application of local antiseptics/antibiotics did not lead to significant improvements for a number of outcomes when compared to sub-marginal instrumentation alone (Ramamauskaite et al., 2021). Thus, there is currently no reliable evidence supporting the use of local antibiotics/antiseptics or anti-infective therapy as an adjunct to sub-marginal instrumentation. In this context, there is currently no comprehensive appraisal of only high-quality studies in the literature as to whether non-surgical therapy with or without chemical implant surface decontamination can lead to disease resolution and for how long.

The objective of the present systematic review was therefore to answer the following PICOS question: "In adult patients with peri-implantitis (P), what is the efficacy of sub-marginal instrumentation combined with chemical surface decontamination (I) in comparison

with sub-marginal instrumentation with or without placebo (C), in terms of changes in probing depths (PD) and/or bleeding on probing (BOP) (O), as reported in randomized clinical trials (RCTs), non-randomized controlled clinical trials (CCTs), or prospective cohort studies, with a minimum of 6-month "follow-up" (S)?

2 | MATERIALS AND METHODS

2.1 | Protocol and registration

Prior to starting the systematic review, the protocol was approved by the committee for the XVIII European Workshop and registered in the International Prospective Register of Systematic reviews PROSPERO (CRD42022327124).

2.2 | Eligibility

2.2.1 | Population

Patients over 18 years with peri-implantitis based on case definitions used in the selected studies.

2.2.2 | Intervention

For the test group, sub-marginal instrumentation combined with surface decontamination with chemical approaches (e.g., antiseptic, local antibiotic but not as a sustained-release device, acid treatment, antimicrobial photodynamic therapy, or any combination of the above).

2.2.3 | Comparison

Control groups received sub-marginal instrumentation with or without a placebo.

2.2.4 | Outcome

Primary outcome was changes in PD and/or BOP. Secondary clinical outcomes were also registered: disease resolution, implant/implant-supported prosthesis loss/survival, changes in suppuration on probing (SOP), mucosal recession, radiographic marginal bone loss (MBL), composite outcomes including PD, BOP/SOP ± MBL, patient-reported outcome measures (PROMs), and side effects.

2.2.5 | Study design and duration

RCTs or CCTs with a minimum of 6 months follow-up and at least 10 patients in each treatment group at randomization. Prospective cohort studies (PCs) that included a control group, if they had ≥50 treated patients in total and 6 months' follow-up.

2.3 | Information sources and search

Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) (Liberati et al., 2009; Moher et al., 2009) was used for reporting the results, based on clinical studies published in English language until 28 March 2022.

The articles were identified from searching the following databases: PubMed, Web of Science (WOS), Embase, Scopus, Ovid Medline, and The Cochrane Library of the Cochrane Collaboration (CENTRAL). Finally, a forward search via Science Citation Index of the selected papers was added.

The search strategy was a combination of MESH terms (i.e., Medical Subject Headings) and free text words, with the filter "clinical trial": The following PubMed search terms were used and their combination.

"treatment" OR "nonsurgical treatment" OR "non-surgical treatment" OR "therapy" OR "nonsurgical therapy" OR "non-surgical therapy" OR "submarginal instrumentation" OR "antiseptic treatment" OR "antibiotic treatment" OR "adjunctive treatment" OR "antiseptic therapy" OR "antibiotic therapy" OR "adjunctive therapy" OR "photochemical treatment" OR "photodynamic therapy" OR "laser treatment" OR "laser" AND "peri-implant disease" OR "periimplant disease" OR "peri-implant infection" OR "periimplant infection" OR "Periimplantitis" (MeSH) OR "peri-implantitis".

This systematic review, together with a number of other systematic reviews undertaken at the same time by different authors, will be used as the basis for generating guidelines for peri-implant therapy during the XVIII European Workshop of Periodontology. As a result, they must be conducted in a very strict period of time and under instructions generated by the methodology consultant. Therefore, no hand-search was performed, and only publications written in English were included. In an effort to identify potential articles for inclusion, grey literature was searched in clinicaltrials.gov and trialsearch.who.int.

2.4 | Study selection

Titles and abstracts of relevant studies obtained from the electronic libraries were saved in EndNote (Clarivate Analytics, Philadelphia, PA, USA), and duplicates were removed. The remaining studies were uploaded to the Covidence systematic review software (Himmelfarb health sciences Library, Washington DC, USA) for screening. Initial calibration of reviewers was achieved by multiple online discussion sessions. Three reviewers (Y.W., I.P., L.W.) independently screened titles and abstracts, and, when necessary, full texts were obtained and screened. Any ambiguity was resolved with discussion with a fourth author (A.S.). All eligible articles were reviewed and evaluated by four reviewers (Y.W., I.P., L.W., A.S.). Again, any ambiguity was resolved

through discussion. All articles excluded and the reason for their exclusion were recorded.

2.5 | Data collection and extraction process

Data collection was done in a specifically designed EXCEL sheet and included aspects related to material and methods and results from the selected studies. Data addressing the primary and secondary outcomes were extracted in duplicate by two independent reviewers (Y. W. and L.W.) for analysis. Two reviewers (I.P. and A.S.) cross-checked the data recorded for accuracy. The following data were extracted: (1) author, (2) publication year, (3) study design, (4) population characteristics, (5) case definition, (6) study duration, (7) interventions, and (8) outcomes. When data was missing, an attempt was made to contact the corresponding authors.

Calculations of clinical variables such as the number of implants, position, number of implants per patient, and enrolment into supportive therapy, were attempted.

Additional information such as the country, setting, and source of funding was recorded.

2.6 | Risk of bias in individual studies

Risk-of-bias assessments were performed by two independent review authors (I.P. and A.S.). If there was disagreement, a third reviewer (L.W.) was consulted to reach an agreement. The Cochrane risk-of-bias tool for randomized trials (RoB 2) was used to assess the risk of bias (Sterne et al., 2019). In the first domain of the instrument, the risk of bias arising from the randomization process was evaluated (selection bias). In the second domain, the risk of bias due to deviations from the intended interventions was evaluated (effect of assignment and adhering to the intervention). The risk of bias due to missing outcome data was assessed in the third domain, risk of bias in measurement of the outcome in the fourth domain, and finally, the risk of bias in the selection of the reported result in the fifth domain.

2.7 | Data synthesis and analyses of the results

Quantitative analysis was performed for the clinical and radiographic outcomes (primary outcomes: BOP, PD; secondary outcomes: mucosal recession, radiographic MBL, composite outcomes, implant loss, PROMs, and side effects).

3 | RESULTS

3.1 | Study selection

Electronic search identified 6290 publications and, following the removal of duplicates in EndNote (Clarivate Analytics, Philadelphia, PA, USA), 2033 publications were uploaded into the Covidence systematic review software (Himmelfarb health sciences Library, Washington DC, USA) for screening. From those, 2016 were considered irrelevant based on their title or abstract. From the 17 publications selected for full-text review, 14 were excluded for reasons described in Table 1. Three publications (all RCTs) were included. The PRISMA chart can be seen in Figure 1.

TABLE 1 Reasons for exclusion of 14 full texts

Study (year)	Reason for exclusion
Crespi et al. (2019)	Intervention not matching the definition of "submarginal instrumentation"
Alqahtani et al. (2019)	Lack of a clear case definition of peri-implantitis
Abduljabbar (2017)	Lack of a clear case definition of peri-implantitis
Ahmed et al. (2020)	Lack of a clear case definition of peri-implantitis
Al Amri et al. (2016)	Lack of a clear case definition of peri-implantitis
Birang et al. (2017)	Lack of a clear case definition of peri-implantitis and follow-up <6 months
Alqutub (2022)	Lack of a clear case definition of peri-implantitis
John et al. (2015)	Sub-marginal instrumentation protocol not consistent across groups
Sahm et al. (2011)	Sub-marginal instrumentation protocol not consistent across groups
Romeo et al. (2016)	Lack of a clear case definition of peri-implantitis
Esposito et al. (2013)	Lack of a clear case definition of peri-implantitis; intervention a mix of surgical and non-surgical procedures
Cheng et al. (2020)	Publication not in English language
Labban et al. (2021)	Study employing repeated non-surgical treatment; intervention not an adjunct to sub-marginal instrumentation
Javed et al. (2016)	Lack of a clear case definition of peri-implantitis

3.2 | Study characteristics

3.2.1 | Study design

The characteristics of the selected studies can be found in Table 2. There were some differences in study design (parallel, in groups, and two-factorial) and the type of clinical settings (private and hospital), but for each one of the studies only one centre was involved. One study was carried out in China, one in Italy, and one in Saudi Arabia. The duration for all three studies was 6 months

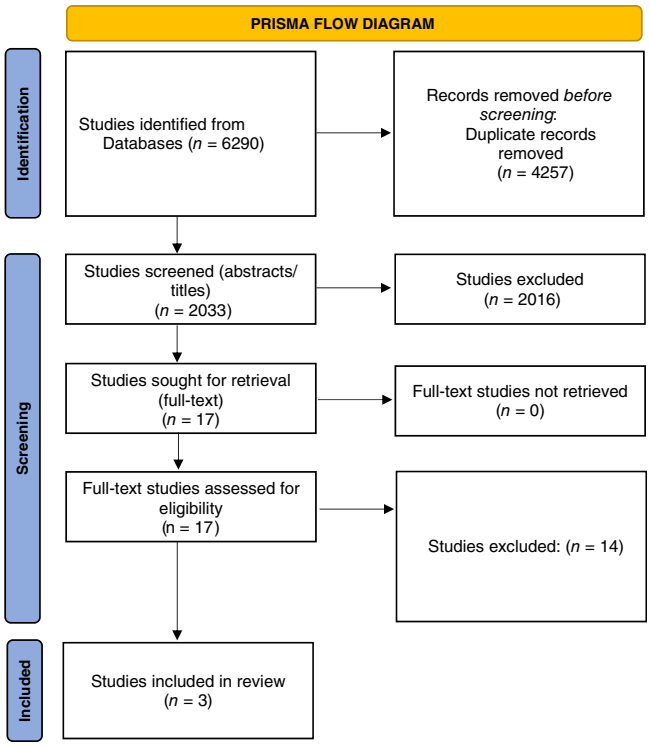

FIGURE 1 PRISMA flow diagram

(Wang, Li, et al., 2019; Wang, Renvert, et al., 2019; Merli et al., 2020; Alasqah, 2022).

3.2.2 | Disease definition

Peri-implantitis was defined differently in all three studies by using composite clinical and radiographical measurements. In the study by Wang, Li, et al. (2019) and Wang, Renvert, et al. (2019), peri-implantitis was defined as sites with obvious inflammatory symptoms, at least one implant site with PD ≥6 mm, visible plaque, and clinical attachment loss (CAL) ≤3 mm. Additionally, radiographic bone loss had to be evident. In the study by Merli et al. (2020), peri-implantitis was defined as implants exhibiting sites with PD in range 5–8 mm, BOP or SUP, and radiographic bone loss beyond crestal bone-level changes resulting from initial bone remodelling (but infraosseous defect component ≤5 mm and radiographic suprabony component of defect ≤4 mm). In the third study, a simpler definition was given for peri-implantitis and included implants with PD ≥4 mm, bone loss ≥3 mm and BOP ≥30% of the implant sites (Alasqah, 2022) (Table 2).

3.2.3 | Further characteristics

The three publications selected were reporting on RCTs with 51–131 patients each at follow-up. In one study (Alasqah, 2022), all smokers were excluded, and in the other two studies smokers were included and their proportion ranged from 12% to 31.8% (Wang, Li, et al., 2019; Wang, Renvert, et al., 2019; Merli et al., 2020). In the study by Alasqah (2022), only obese patients were included but only small differences were observed in the distribution of age and gender among the study groups (Table 2).

3.3 | Risk of bias in studies

The risk-of-bias assessment of the included studies is presented in Appendices I and II. Two studies were judged to have a low risk of bias (Wang, Li, et al., 2019; Wang, Renvert, et al., 2019; Merli et al., 2020). The study of Alasqah (2022) was considered to have some risk of bias, mainly due to an unclear randomization process and an inconsistent selection of the reported results.

3.4 | Outcome assessment

The interventions and outcomes of the included studies are reported in Tables 3 and 4. All included studies reported on changes in PD and BOP. Other variables (secondary outcomes) that were reported in either one or two studies were CAL (two studies), MBL (two studies), recession, implant loss, side effects (two studies), and PROMs (pain, satisfaction, and OHIP-14). A composite outcome (treatment success, defined as no PD >5 with BOP/SUP + no further bone loss) was reported only in one study (Merli et al., 2020).

3.4.1 | Adjunctive anti-microbial photodynamic therapy

Two studies investigated the use of anti-microbial photodynamic therapy as adjunct to sub-marginal instrumentation, using either toluidine blue (Wang, Li, et al., 2019; Wang, Renvert, et al., 2019) or methylene blue (Alasqah, 2022) as photosensitizer (Table 3). Sub-marginal instrumentation was performed with glycine powder air-polishing (Wang, Li, et al., 2019; Wang, Renvert, et al., 2019) or plastic curettes (Alasqah, 2022). Both studies reported significantly lower mean PDs at 6 months for the test groups compared to the control groups. In addition, Wang, Li, et al. (2019) and Wang, Renvert, et al. (2019) reported significantly lower BOP at 6 months, while Alasqah (2022) found no difference in BOP between the test and control groups at 6 months. No significant differences were noted for any of the other outcome variables (CAL, MBL, side effects).

3.4.2 | Adjunctive antiseptic solutions

One study investigated the adjunctive use of a desiccant material consisting of a gel of a concentrated aqueous mixture of hydroxybenzenesulfonic and hydroxymeth oxybenzene acids and sulfuric acid (Merli et al., 2020) (Table 4). A two-factorial study design was employed to

TABLE 2 Characteristics of included studies

Publication	Study design	Location	Setting	Source of funding	Population	Case definition	Study duration
Wang, Li, et al. (2019), Wang, Renvert, et al. (2019)	RCT, parallel, single-centre	Beijing, China	Hospital	None	132 patients (unknown number of implants) randomized to two intervention groups: *Control*: 66 patients, mean age 42.6 ± 13.0 years, 62.1% female, 31.8% with smoking history. One patient lost to follow-up, 65 patients included in analysis. *Test*: 66 patients, mean age 44.1 ± 9.8 years, 64.6% female, 20.0% with smoking history	PD ≥6 mm + BOP + visible plaque + CAL ≤3 mm + radiographic bone loss	6 months
Merli et al. (2020)	RCT, two-factorial, single-centre	Rimini, Italy	Private practice	The study desiccant material was provided by the industry. No other source of funding reported	64 patients (one implant per patient selected) randomized to four intervention groups (two control groups, two test groups): *Control* 1: 16 patients, mean age 64.5 ± 8.3, 56% female, 19% smokers *Test* 1: 16 patients, mean age 60.3 ± 10.7, 75% female, 25% smokers. 1 patient lost to follow-up, 15 patients included in analysis *Control* 2: 16 patients, mean age 66.4 ± 9.4, 56% female, 12% smokers. One patient lost to follow-up, 2 patients with implant failure due to progressive peri-implantitis, 13 patients included in analysis *Test* 2: 16 patients, mean age 60.3 ± 8.5, 62% female, 25% smokers. 2 patients lost to follow-up, 14 patients included in analysis	PD in range 5–8 mm + BOP or suppuration + radiographic bone loss beyond crestal bone-level changes resulting from initial bone remodelling (but infraosseous defect component ≤5 mm + radiographic suprabony component of defect ≤4 mm)	6 months
Alasqah (2022)	RCT, 3 groups, single-centre	Riyadh, Saudi Arabia	Specialist dental centre	Not reported	74 obese patients (BMI ≥30) (with 91 implants) were randomized to three intervention groups. Only two intervention groups are included in current systematic review: *Control*: 25 patients/30 implants, mean age 40.5 (30–51) years *Test*: 26 patients/33 implants, mean age 42.1 (34–55) years Smokers were excluded	PD ≥4 mm + bone loss ≥3 mm + BOP ≥30% of implant sites	6 months

Abbreviations: BMI, body mass index; BOP, bleeding on probing; CAL, clinical attachment level; PD, pocket depth; RCT, randomized controlled trial.

TABLE 3 Included studies on photodynamic therapy as adjunct to sub-marginal instrumentation

Publication	Test	Control	Outcomes	Conclusion
Wang, Li, et al. (2019), Wang, Renvert, et al. (2019)	OHI/full mouth cleansing 2 weeks prior to therapy + sub-gingival glycine powder airpolishing (Air-flow Master, EMS, Nyon, Switzerland) + aPDT (Helbo Photodynamic Systems, Wels, Austria) using toluidine blue as photosensitizer with a LED light source (wavelength: 635 nm, power 750 mW, 3D irradiation, minimum 60 mW/cm^2)	OHI/full mouth cleansing 2 weeks prior to therapy + sub-gingival glycine powder airpolishing + irrigation with sterile saline	Subject level *PD: mean of 6 sites per implant (SD)* Control: Baseline 5.07 ± 0.72 mm, 6 months: 4.62 ± 0.45 mm, $p < .05$ Test: Baseline 4.93 ± 1.07 mm, 3.06 ± 0.29 mm, $p < .05$ Significantly lower mean PPD in the test group, $p < .001$, at 6 months *BOP (recalculated from SBI data: SBI 2,3,4, or 5 versus SBI 0 or 1): No. of subjects (%)* Control: Baseline: 66 (100%); 6 months: 66 (100%) Test: Baseline: 65 (100%); 6 months: 3 (4.6%) Significantly lower BOP in the test group, $p < .001$, at 6 months *CAL: mean of 6 sites per implant (SD)* Control: Baseline 1.49 ± 0.67 mm, 6 months: 1.49 ± 0.67 mm, not significant Test Baseline 1.85 ± 0.86 mm, 1.32 ± 0.43 mm, $p < .05$ No significant difference between test and control, $p = .07$, at 6 months Side effects: No adverse events related to the treatment were observed	Adjunctive aPDT significantly improved PD and BOP over control at 6 months
Alasqah (2022)	Non-surgical debridement with plastic curettes + aPDT, using methylene blue photosensitizer and a diode laser (wavelength: 670 nm, power 150 mW)	Non-surgical debridement with plastic curettes alone.	Subject level *PD; mean of six sites per implant (range)* Control: Baseline 5.1 (4.2–6.0) mm, 6 months: 3.7 (3.3–4.5) mm Test: Baseline 4.8 (4.0–5.7) mm, 3.1 (2.7–3.6) mm Significantly lower mean PD in the test group, $p < .05$, at 6 months *BOP: mean % (range)* Control: Baseline 44.3 (35.1–55.3)%, 6 months 15.5 (11.4–20.0)% Test: Baseline 43.3 (36.1–52.8)%, 6 months 11.0 (7.0–14.1)% No significant difference between groups at 6 months *Marginal bone loss: mean of mesial and distal site per implant (range)* Control: Baseline 2.0 (1.2–2.7) mm, 6 months 2.4 (1.7–2.7) mm Test: Baseline 2.3 (1.5–2.7) mm, 6 months 2.1 (1.5–2.4) mm No significant difference between groups at 6 months	Adjunctive aPDT significantly improved PD over control at 6 months

Abbreviations: aPDT, anti-microbial photodynamic therapy; BOP, bleeding on probing; CAL, clinical attachment level; LED, light-emitting diode; OHI, oral hygiene instructions; PD, pocket depth; SBI, sulcular bleeding index; SD, standard deviation.

investigate two different adjunctive therapies (glycine powder air-polishing and a desiccant material) and their combinations to sub-marginal instrumentation with an ultrasonic scaler. Patients were allocated to receive no adjunctive intervention, one or the other, or both, resulting in four different treatment groups. PD and CAL reduction were greater in patients treated with the desiccant material ($p = .023$ and $p = .025$, respectively), regardless of the sub-marginal debridement method (ultrasonic scaler alone or combined with glycine powder air-polishing). There were no significant differences for any of the other outcomes reported (BOP, marginal bone level, recession, treatment success, implant loss, complications, pain after 6 months, satisfaction, or OHIP-14), except for the amount of pain experienced during treatment, which was higher for patients treated with glycine powder air-polishing ($p = .006$) but not for those treated with the desiccant material. Overall treatment success ranged from 14% to 43%, with no significant differences between the treatment groups.

4 | DISCUSSION

The current systematic review identified only three RCTs investigating the efficacy of adjunctive chemical approaches for implant surface decontamination in conjunction with sub-marginal instrumentation for the non-surgical management of peri-implantitis

TABLE 4 Included study on acid treatment as adjunct to sub-marginal instrumentation

Publication	Test	Control	Outcomes	Conclusion
Merli et al. (2020)	Test group 1: OHI/non-surgical debridement with ultrasonic scaler and desiccant material[a]	Control group 1: OHI/non-surgical debridement with ultrasonic scaler alone	Subject level *PD: mean of 4 sites per implant* (*SD*) Control 1: Baseline 4.4 ± 1.1 mm, 6 months 4.2 ± 1.3 mm, mean reduction 0.2 ± 0.7 mm Test 1: Baseline 5.0 ± 1.2 mm, 6 months 4.5 ± 1.2 mm, mean reduction 0.5 ± 0.9 mm Control 2: Baseline 5.1 ± 1.5 mm, 6 months 4.8 ± 1.3 mm, mean reduction 0.1 ± 0.8 mm Test 2: Baseline 4.9 ± 1.1 mm, 6 months 4.0 ± 1.2 mm, mean reduction 0.8 ± 0.8 mm Pocket depth reduction was greater in patients treated with desiccant material, $p = .023$, at 6 months *BOP: mean no. of bleeding sites per implant* (*out of 4 sites measured*) Control 1: Baseline 3.3 ± 0.8, 6 months 2.9 ± 0.8, mean reduction 0.4 ± 0.9 Test 1: Baseline 2.9 ± 1.3, 6 months 2.5 ± 1.7, mean reduction 0.5 ± 1.8 Control 2: Baseline 3.6 ± 0.8, 6 months 2.8 ± 1.3, mean reduction 0.7 ± 1.3 Test 2: Baseline 3.6 ± 0.8, 6 months 2.7 ± 1.3, mean reduction 0.8 ± 1.2 No significant difference between groups at 6 months *CAL: mean of four sites per implant* (*SD*) Control 1: Baseline 4.4 ± 1.0 mm, 6 months 4.3 ± 1.3 mm, mean reduction 0.1 ± 0.6 mm Test 1: Baseline 5.4 ± 1.2 mm, 6 months 4.9 ± 1.3 mm, mean reduction 0.6 ± 0.9 mm Control 2: Baseline 5.4 ± 1.6 mm, 6 months 5.2 ± 1.5 mm, mean reduction 0.1 ± 0.9 mm Test 2: Baseline 5.0 ± 0.9 mm, 6 months 4.2 ± 1.0 mm, mean reduction 0.7 ± 0.8 mm CAL reduction was greater in patients treated with desiccant material, $p = .025$, at 6 months *Marginal bone level: mean of mesial and distal site per implant* (*SD*) Control 1: Baseline 3.3 ± 1.2 mm, 6 months 3.1 ± 1.5 mm, mean reduction 0.2 ± 0.8 mm Test 1: Baseline 3.9 ± 1.2 mm, 6 months 4.0 ± 1.8 mm, mean reduction −0.1 ± 0.9 mm Control 2: Baseline 3.6 ± 1.7 mm, 6 months 4.0 ± 1.8 mm, mean reduction −0.2 ± 1.0 mm Test 2: Baseline 3.6 ± 0.9 mm, 6 months 3.5 ± 1.0 mm, mean reduction −0.1 ± 0.7 mm No significant difference between groups at 6 months *Recession: mean of 4 sites per implant* (*SD*) Control 1: Baseline 0.1 ± 0.1 mm, 6 months 0.1 ± 0.2 mm, mean reduction 0.0 ± 0.2 mm Test 1: Baseline 0.4 ± 0.5 mm, 6 months 0.3 ± 0.5 mm, mean reduction 0.1 ± 0.3 mm Control 2: Baseline 0.2 ± 0.9 mm, 6 months 0.3 ± 0.7 mm, mean reduction 0.0 ± 0.4 mm Test 2: Baseline 0.1 ± 0.2 mm, 6 months 0.2 ± 0.4 mm, mean reduction −0.1 ± 0.3 mm No significant difference between groups at 6 months *Treatment Success* (*no PD≥5 mm with BOP/suppuration + no further bone loss*): Control 1: $n = 6$ (37%); Test 1: $n = 3$ (25%); Control 2: $n = 2$ (14%); Test 2: $n = 6$ (43%) No significant difference between groups at 6 months *Implant loss* Control 1: $n = 0$ (0%); Test 1: $n = 0$ (0%); Control 2: $n = 2$ (13%); Test 2: $n = 0$ (0%) *Side effects* (*complications*)	Adjunctive use of desiccant material significantly improved PD and CAL regardless of non-surgical debridement method
	Test group 2: OHI/non-surgical debridement with ultrasonic scaler and glycine powder air-polishing (Airflow, EMS) and desiccant material[a]	Control group 2: OHI/non-surgical debridement with ultrasonic scaler and glycine powder airpolishing (Airflow, EMS)		
	[a]A gel of concentrated aqueous mixture of hydroxybenzenesulfonic and hydroxymeth oxybenzene acids and sulfuric acid (HybenX, Epien Medical Inc.) After treatment all patients (test and control groups) used chlorhexidine mouthrinse (0.12%) twice a day for 15 days. All patients were seen at 1 week, 1, 3 and 6 months for maintenance with supragingival prophylaxis			

(Continues)

TABLE 4 (Continued)

Publication	Test	Control	Outcomes	Conclusion
			Control 1: $n = 1$ (6%); Test 1: $n = 3$ (20%); Control 2: $n = 4$ (27%); Test 2: $n = 2$ (14%) No significant difference between groups at 6 months *PROMs* VAS pain (during treatment): Control 1: 2.1 ± 2.1; Test 1: 3.3 ± 2.7; Control 2: 3.9 ± 2.7; Test 2: 5.0 ± 2.5 VAS pain during treatment was higher for patients treated with glycine powder, $p = .006$, but not significant for patients treated with desiccant material VAS pain (after 6 months): Control 1: 0.7 ± 1.5; Test 1: 0.5 ± 2.1; Control 2: 0.2 ± 0.4; Test 2: 0.5 ± 1.4 No significant difference between groups at 6 months VAS satisfaction (after 6 months): Control 1: 6.9 ± 2.6; Test 1: 7.8 ± 2.6; Control 2: 7.5 ± 3.0; Test 2: 8.2 ± 2.5 No significant difference between groups at 6 months OHIP-14 reduction: Control 1: 1.8 ± 6.1; Test 1: 0.1 ± 4.2; Control 2: 4.0 ± 6.4; Test 2: 0.0 ± 5.6 No significant difference between groups at 6 months	

Abbreviations: BOP, bleeding on probing; CAL, clinical attachment level; OHI, oral hygiene instructions; OHIP, Oral Health Impact Profile; PD, pocket depth; PROM, patient-reported outcome measure; SD, standard deviation; VAS, Visual Analogue Scale.

with ≥6 months' follow-up. Two studies investigated the adjunctive decontamination efficacy of photodynamic therapy with toluidine blue/methylene blue (Wang, Li, et al., 2019; Wang, Renvert, et al., 2019; Alasqah, 2022), while one study investigated the decontamination efficacy of a desiccant material consisting of a gel of a concentrated aqueous mixture of hydroxybenzenesulfonic and hydroxymeth oxybenzene acids and sulfuric acid as adjunct to mechanical decontamination my means of ultrasonic tips with and without air-polishing (Merli et al., 2020). The trials reported greater pocket depth reductions for chemical decontamination of the implant surface as an adjunct to mechanical sub-marginal instrumentation over only mechanical sub-marginal instrumentation control groups, but were inconsistent or showed no differences with regard to the other clinical parameters.

Wang, Li, et al. (2019) and Wang, Renvert, et al. (2019) found that adjunctive photodynamic therapy significantly improved PD and BOP over control at 6 months (Wang, Renvert,et al., 2019; Wang, Li, et al., 2019). In agreement with this study, Alasqah (2022) reported that adjunctive photodynamic therapy significantly improved PD over control at 6 months. However, there was no difference in BOP or MBL between groups (Alasqah, 2022). Merli and co-workers (2020), reported that using an adjunctive desiccant material significantly improved PD and CAL outcomes versus control groups. There was no significant differences between test groups and control groups in the other parameters investigated, including BOP, MBL, recession, treatment success, and implant loss (Merli et al., 2020).

A meta-analysis was not performed because of the significant heterogeneity in the study design interventions, populations studied, and reported outcomes. The small number of studies identified in this systematic review and the significant heterogeneity in study designs highlight the need for further studies to draw a stronger conclusion regarding the potential benefit of adjunctive chemical approaches for implant surface decontamination in conjunction with sub-marginal instrumentation for the non-surgical management of peri-implantitis.

Heterogeneity between studies in the current systematic review may also be related to varying approaches with regard to the intervention. It may be incorrect to discuss the overall efficacy of "adjunctive chemical approaches" because different approaches are likely to have specific pharmacokinetic or pharmacodynamic effects. Even with regard to the two studies we included investigating adjunctive photodynamic therapy, both interventions were subtly different. Alasqah performed photodynamic therapy using a diode laser with 670 nm wavelength and power 150 mW with methylene blue as the photosensitiser (Alasqah, 2022), whereas Wang and colleagues performed photodynamic therapy with a light-emitting diode (LED) light source with wavelength 635 nm and power 750 mW using toluidine blue as the photosensitizer (Wang, Li, et al., 2019; Wang, Renvert, et al., 2019). Whether these subtle differences in photodynamic therapy methodology results in any significant clinical difference is unclear.

The main limitation of the current systematic review is the lack in quantity and quality of appropriately conducted research. This limits our ability to provide a definite conclusion or recommend a clinical protocol for adjunctive chemical approaches in the non-surgical management of peri-implantitis. Although the overall risk of bias was deemed low in two studies (Wang, Li, et al., 2019; Wang, Renvert, et al., 2019; Merli et al., 2020) and moderate in one study (Alasqah, 2022), study design heterogeneity prevented data synthesis

in the form of a meta-analysis to calculate an overall absolute effect. The study populations also varied significantly, with one study limited to obese patients (BMI >30 kg/m^2) with a mean age of ~40 years from Saudi Arabia (Alasqah, 2022), another study was carried on patients from a private centre in Italy with mean age of 60.3 (SD 8.3) years (Merli et al., 2020), and the third study was carried out in a group of Han Chinese adults with a mean age of 43.4 (SD 11.5) years (Wang, Li, et al., 2019; Wang, Renvert, et al., 2019). It is therefore unclear which patient profile in particular might benefit from adjunctive chemical approaches. Furthermore, participants who smoked were excluded altogether in one study (Alasqah, 2022), whereas one study excluded participants who smoked ≥20 cigarettes per day (Merli et al., 2020) and another study excluded participants with a history of "long smoking" (Wang, Li, et al., 2019; Wang, Renvert, et al., 2019). Given the close relationship between the peri-implant microbiome and smoking (Tsigarida et al., 2015), these differences in design may have implications when assessing response to non-surgical peri-implant treatment. Other factors such as the availability of products in national markets or the added economic cost and the cost/benefit ratio were also not investigated. In this context, implant surface microstructure, implant platform, and the type of prosthetic connection likely influence the potential of the various clinical approaches to exert a relevant effect on the biofilm (Garaicoa-Pazmino et al., 2021; Schwarz et al., 2021). Additionally, as defect depth can also play a role, it would be important to remember that mainly moderately deep sites were treated in the three studies included in this systematic review.

The findings of the current systematic review are broadly in agreement with the relevant sections of previous systematic reviews (Schwarz et al., 2015; Ramamauskaite et al., 2021; Shahmohammadi et al., 2022). Schwarz and colleagues reported that "alternative/adjunctive measures may improve the efficacy over/of conventional non-surgical treatments at peri-implantitis sites" (Schwarz et al., 2015). However, this conclusion was based mainly on studies in which the adjunctive measures concerned antibiotic therapy and not restricted to chemical approaches as in the current systematic review. More recently, another systematic review and meta-analysis, which specifically investigated the adjunctive use of photodynamic therapy, reported a significant benefit in terms of both PD and plaque index at 3-month follow-up over mechanical debridement alone (Shahmohammadi et al., 2022).

Adhering to previous recommendations, studies of 1 year or longer, which include both short-term (1–3 months) and long-term evaluation times (6 and 12 months), are the preferred ones to be included for analysis (Sanz & Chapple, 2012). A minimum follow-up period of 6 months was used here as an inclusion criterion, as this timeframe is considered necessary for adequately judging soft tissue and bone changes in the case of successful non-surgical peri-implant treatment. Among the studies of shorter duration, Park and co-workers assessed the adjunctive use of antibiotic ointments (non-sustained release) for surface decontamination in combination with non-surgical treatment of peri-implantitis in a large multicentre RCT setting (118 subjects with peri-implantitis). Adjunctive use of either a metronidazole-minocycline ointment or a minocycline ointment resulted in significantly higher treatment success rates, using a composite outcome including the absence of bleeding or SOP and PD ≤5 mm. Furthermore, the use of metronidazole–minocycline ointment resulted in a significantly greater reduction in PD compared to the use of minocycline ointment alone (Park et al., 2021). In a smaller RCT, with a split-mouth design, Karimi et al. (2016) investigated the adjunctive benefit of photodynamic therapy to mechanical debridement for peri-implant disease management in a group of 10 people. Adjunctive photodynamic therapy resulted in significantly favourable outcomes in terms of PD, CAL, and BOP over mechanical debridement alone. While these 3-month studies may broadly support the findings of the 6-month studies included in the current systematic review, it should be noted that not all studies report that adjunctive chemical decontamination has significant benefits over mechanical therapy alone. Roos-Jansåker et al. (2017) carried out a 3-month RCT investigating adjunctive implant decontamination utilizing chloramine (Roos-Jansåker et al., 2017) but found no demonstrable benefit. The inconsistency in findings again highlights the need for further studies.

Finally, the scope of what constitutes an "adjunct chemical approach" is clearly broad, ranging from antiseptic solutions, acid treatments, and antibiotic solutions (without sustained release) to photodynamic therapy. It is unlikely that all interventions would have similar efficacies, which again highlights the need for further well-designed clinical trials. Sustained-release antibiotics/antiseptics or repeat disinfection procedures may offer additional benefits over one-off procedures. This, however, is beyond the scope of the current systematic review and is explored in another systematic review as part of this series.

5 | CONCLUSIONS

Within the limitations of this systematic review, the following conclusions can be drawn:

- Adjunctive chemical approaches for implant surface decontamination in conjunction with sub-marginal instrumentation for the non-surgical management of peri-implantitis may offer an advantage over sub-marginal instrumentation approaches alone, in terms of improved PD with adjunct chemical approaches. There were no reported adverse effects of adjunct chemical approaches.
- Significant heterogeneity was observed between studies. This was evident in terms of study populations, study designs, interventions performed, and outcomes reported.
- The small number of studies identified in this systematic review and the significant heterogeneity between studies highlight the need for further studies to draw a stronger conclusion regarding the potential benefit of adjunctive chemical approaches for implant surface decontamination in conjunction with sub-marginal instrumentation for the non-surgical management of peri-implantitis.

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CONFLICT OF INTEREST

The authors declare no conflict of interests.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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