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REVIEW ARTICLE

Xanthan-based chlorhexidine gel effects in non-surgical periodontal therapy? A meta-analysis

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Abstract

Objective: To carry out a systematic review and meta-analysis of randomized controlled clinical trials (RCTs) and controlled clinical trials (CCTs) comparing scaling and root planing (SRP) or placebo with subgingival application of xanthan-based CHX (chlorhexidine) gel as adjunct to SRP.

Materials and Methods: The literature search was carried out in PubMed/MEDLINE, EMBASE, and SCOPUS; primary outcomes were probing pocket depth (PPD) reduction and gain in clinical attachment level (CAL).

Results: Overall, 15 studies were included. Three studies were judged to be at moderate risk of bias while the remaining 12 were rated at high risk of bias. A significant improvement in PPD reduction (standardized mean difference, SMD, 0.87, 95% CI, 0.41–1.34) and CAL gain (SMD = 0.84, 95% CI, 0.36–1.33) emerged for the SRP + CXH gel compared to the SRP alone group, in the presence of significant high heterogeneity among the studies.

Conclusions: Our systematic review and meta-analysis showed that xanthan-based chlorhexidine gel as adjunct to non-surgical periodontal therapy gives benefit in terms of PPD reduction and CAL gain as compared to non-surgical periodontal therapy only. Since there was high heterogeneity among studies and the quality of the evidence is low, further studies characterized by a better methodology, adequate sample size and longer follow-up are warranted in the next future.

Registration: The protocol of this scoping review was registered in the International Prospective Register of Systematic Reviews (https://www.crd.york.ac.uk/PROSPERO) with ID: CRD42023391589.

KEYWORDS
non-surgical therapy, periodontitis, xanthan-based chlorhexidine gel

1 | INTRODUCTION

Nowadays periodontitis is defined as an infectious disease that, among other causal co-factors, is triggered by the dysbiosis of the subgingival microbiota. Due to their high prevalence, periodontal diseases are a significant global burden on public health (Carasol et al., 2016; Ferreira et al., 2017; Kassebaum et al., 2014; Sanz et al., 2018) and if left untreated, may lead to the tooth-supporting tissues destruction and, eventually, to tooth loss. Non-surgical periodontal therapy (NSPT), including subgingival debridement or scaling and root planing (SRP), is universally acknowledged as a milestone in periodontology since removing or controlling such pathogens is a pivotal component of the periodontal treatment (Badersten et al., 1981). Unfortunately, NSPT has showed drawbacks

and less than ideal results especially in certain patients or specific sites (Abraham et al., 2020; Baehni & Takeuchi, 2003; Bonito et al., 2005; Chauhan et al., 2013; Chitsazi et al., 2013; DerSimonian & Laird, 1986; Dhamecha et al., 2019; Dodwad et al., 2012; Egger et al., 1997; Faramarzi et al., 2017; Goodson et al., 1985; Gupta et al., 2008; Hanes & Purvis, 2003; Herrera et al., 2012, 2020; Higgins & Thompson, 2002; Jain et al., 2013; Jeffcoat et al., 1998; Jones, 1997; Karpinski & Szkaradkiewicz, 2015; Kaushik et al., 2011; Khan et al., 2003; Kranti et al., 2010; Matesanz et al., 2013; Mummolo et al., 2019; Munn et al., 2018; Nandan et al., 2022; Oosterwaal et al., 1990; Paolantonio et al., 2009; Paul et al., 2015; Phogat et al., 2014; PRISMA, 2021; Quirynen et al., 2000; Rams & Slots, 1996; Rusu et al., 2005; Sajna et al., 2021; Smiley et al., 2015; Soskolne, 1997; Soskolne et al., 1997; Tonetti et al., 2018; Unsal et al., 1994; Verma et al., 2012, 2022; Zhao et al., 2020). In this regard, limitations have been reported, among others, in case of patients affected by grade C periodontitis, smokers or posterior/multi-rooted teeth. To overcome these limitations, numerous antimicrobial agents (delivered by rinsing, irrigation, systemic administration and local devices Bonito et al., 2005; Goodson et al., 1985; Hanes & Purvis, 2003; Herrera et al., 2012; Kaushik et al., 2011; Matesanz et al., 2013; Paul et al., 2015; Soskolne, 1997) are used as adjunctive therapy for the control of the periodontal disease (Smiley et al., 2015).

Beyond fewer side effects, topical treatments offer additional advantages such as increase compliance and lowered risk of bacterial tolerance or resistance (Dodwad et al., 2012). Among antimicrobials, chlorhexidine (CHX) is considered as the gold standard with a long history in medicine (Jones, 1997; Karpinski & Szkaradkiewicz, 2015; Rams & Slots, 1996). In the field of dentistry, chlorhexidine is available in a multiplicity of vehicles and formulations such as mouthrinses, gels, sprays, tablets and varnishes. To solve the washing away by saliva and crevicular fluid problem, it is usually combined with different molecules/carriers in order to optimize its activity. The use of an injectable xanthan-based chlorhexidine gel formulation containing CHX digluconate (0.5%) and CHX dihydrochloride (1%) in a 1:2 ratio (Baehni & Takeuchi, 2003; Dhamecha et al., 2019; Rusu et al., 2005) has been investigated as an adjunct therapy to SRP in several studies.

The aim of this systematic review and meta-analysis is to summarize the effect of subgingival application of xanthan-based chlorhexidine gel after non-surgical periodontal therapy and highlighting the potential effects on clinical biometric parameters.

2 | MATERIALS AND METHODS

2.1 | Protocol and registration

This systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA, 2021) guidelines. The study protocol was registered in the International Prospective Register of Systematic Reviews (https://www.crd.york.ac.uk/PROSPERO) with ID: CRD42023391589.

2.2 | Focused question

A PICO framework (Population, Exposure, and Outcome) (Khan et al., 2003; Munn et al., 2018) was used to formulate the research question: "Do adjunctive subgingival application of xanthan-based chlorhexidine gel have any effect on clinical parameters after non-surgical periodontal therapy?"

(P) Patients: Patients affected by periodontitis.

(I) Intervention: Non-surgical periodontal therapy plus xanthan-based chlorhexidine gel.

(C) Comparison: Non-surgical periodontal therapy alone or plus placebo.

(O) Outcome: Probing pocket depth (PPD) reduction, gain in clinical attachment level (CAL), adverse events.

2.3 | Primary and secondary endpoints

The primary endpoints were probing pocket depth (PPD) reduction and the gain in clinical attachment level (CAL) within a period of 6 months after therapy. Studies reporting on complications were analyzed and adverse events were considered as secondary outcomes.

2.4 | Eligibility criteria

Inclusion criteria: Randomized controlled clinical trials (RCTs) and controlled clinical trials (CCTs) comparing scaling and root planing (SRP), full-mouth scaling and root planing (FMSRP), full-mouth disinfection (FMD) alone or placebo, hereafter defined SRP alone group (i.e., the "control arm"), and subgingival application of xanthan-based CHX gel as adjunct to scaling and root planing (SRP), full-mouth scaling and root planing (FMSRP), full-mouth disinfection (FMD), hereafter defined SRP + CXH gel (i.e., the "experimental arm"), were included in the systematic review and meta-analysis. In order to be included in the systematic review and meta-analysis, studies were required to (i) have a minimum follow-up period of no <2 weeks; (ii) have a sample size of at least 10 patients; (iii) be published in English and (iv) report data on the two aforementioned primary outcomes (PPD reduction, CAL gain or related indexes).

Exclusion criteria: All studies missing the inclusion criteria were excluded, as well as in vitro studies, animal studies, retrospective studies, observational studies, case reports and narrative or systematic reviews. At the same time, studies characterized by having a follow-up less than 2 weeks, reporting no clinical data or using xanthan-based chlorhexidine gel for other therapies were considered as ineligible.

2.5 | Information sources and search strategy

Two reviewers (AP & GG) conducted an electronic search in an independent and unblinded manner on three databases, namely, Pubmed/MEDLINE, Embase, and Scopus, to identify articles that addressed the focused PICO question. The search period spanned from January 2000 to November 2022, and the most recent search was conducted on December 9th, 2022. The bibliographic search consisted of a combination of MeSH (Medical Subject Headings) terms and free-text words combined through Boolean Operators (AND or OR). An example of the words used for the search process (Pubmed) is listed below: (periodontitis OR periodontal disease) AND ((((chlorhexidine, OR chlorhexidine gluconate, OR xanthan OR xanthan chlorhexidine) AND gel) AND (subgingival, OR subgingival curettage, OR dental scaling, OR root planing OR dental prophylaxis)) OR full mouth disinfection). Embase and Scopus were queried using the same search terms in accordance with their specific syntaxes. Furthermore, the reference lists of the retrieved articles were screened for potentially missing studies. Open Grey databases were also scrutinized for further relevant articles (https://opengrey.eu/; https://www.greynet.org/).

2.6 | Selection of sources of evidence

Mendeley, a free reference manager by Elsevier, was used to identify and remove duplicate publications. On the basis of the inclusion criteria, titles and abstracts were initially reviewed for eligibility by two reviewers (AP & GG). The retrieved full texts were then independently analyzed and the selected articles were compared. The whole search process was conducted by two calibrated reviewers, with calibration comprising two rounds in which the reviewers assessed the eligibility for inclusion of 20 of the retrieved references. At the end, the level of agreement for the included studies was computed (Cohen kappa coefficient, $k = 0.91$). Any controversy related to the eligibility of the including studies was resolved through discussion with a third reviewer (MR). In case of uncertainties and/or missing data within the articles, the corresponding authors of the included studies were contacted after the screening process.

2.7 | Data extraction

The following data were extracted using an ad-hoc form from the studies meeting the inclusion criteria: author names and study design, year of publication, number of patients, inclusion criteria, sample features (demographics: gender, mean age/range), types of CHX gel, timing and frequency of CHX gel application, median follow-up time, the primary endpoints PPD reduction and CAL gain together with their statistical significance and adverse events/complications (secondary endpoint)and.

2.8 | Quality evaluation

In case of non-randomized clinical trial (non-RCT or controlled clinical trial, CCT), the quality assessment of the included studies was performed through the tool "Risk of Bias In Non-randomized Studies of Intervention" (ROBINS-I: a tool for assessing risk of bias in non-randomized studies of interventions; BMJ, 2016). The risk of bias for the randomized clinical trials (RCTs) was evaluated by using the Risk of Bias (RoB). An overall appraisal of each included study was obtained as follows: (i) low risk of bias when the study showed no criticism or doubts according to the tools (ii) moderate risk of bias when the study missed less than two domains or in case the judgment was unclear in less two domains (iii) high risk of bias when the study missed multiple domains (two or more) or uncertain assessment was encountered in more than two domains. The evaluation was carried out by two independent reviewers (AP & GG). The 'robvis' tool was used to generate a visual representation of the assessment.

2.9 | Synthesis of results

The two primary endpoints – PPD reduction and CAL gain – were synthesized in terms of standardized mean difference (SMD). The SMD is the difference in PPD reduction and CAL gain means divided by the within-group standard deviation for the SRP + CHX as compared to the SRP alone group. When the standard deviation of the PPD reduction and/or CAL gain were not provided, the values were computed from the standard error of the mean (SEM), if available. Otherwise, we estimated the values by assuming a linear correlation coefficient of 0.5 between baseline and follow-up standard deviations. Such approach was also applied to a study (Jain et al., 2013) with implausible standard deviations of PPD reduction and CAL gain.

As between-study heterogeneity was anticipated, the pooled estimates for PPD reduction and CAL gain were computed using the random effect model with the Der Simonian and Laird moment estimator (Phogat et al., 2014). The Q test was used to measure data dispersion and the I^2 statistic was used to quantify between-study heterogeneity (DerSimonian & Laird, 1986).

For PPD reduction and CAL gain, a sensitivity analysis by omitting one study at a time was performed to assess the influence that each individual study had on the final pooled estimates.

A meta-regression model was then fitted to assess the possible effect of (i) the study design (split mouth vs parallel group) and of (ii) the imputation of the standard deviation when not provided in the original report on the pooled PPD reduction and CAL gain estimates.

Publication bias was assessed by visual inspection for the presence of the asymmetry of the funnel plot, and Egger test was carried out to evaluate the presence of asymmetry (Higgins & Thompson, 2002).

Statistical analyses were performed using the "metafor" package under the R version 4.2.1 (R Foundation for statistical computing, Vienna, Austria).

3 | RESULTS

3.1 | Study selection

The flowchart of the electronic search strategy and workflow is reported in Figure 1. A total of 1070 studies were identified through the literature review: 306 articles were identified in Pubmed/MEDLINE, 245 in EMBASE, and 519 in SCOPUS. Eleven (11) papers were found through the Open Grey databases. After duplicate removal ($n=213$), 868 articles were included in the screening phase of title and abstracts. A total of 12 articles were not included because they were written in other languages than English. After the selection phase through the evaluation of titles and abstracts, 786 articles were excluded and 82 papers were selected for thoroughly full-text reading. After full-text examination, 67 studies were further excluded (Figure 1), leading to 15 selected studies (Egger et al., 1997; Gupta et al., 2008; Paolantonio et al., 2009; Kranti et al., 2010; Verma et al., 2012; Matesanz et al., 2013; Chauhan et al., 2013; Chitsazi et al., 2013; Jain et al., 2013; Phogat et al., 2014; Faramarzi et al., 2017; Mummolo et al., 2019; Abraham et al., 2020; Sajna et al., 2021; Verma et al., 2022). A high level of concordance between investigators emerged ($\kappa=0.89$).

3.2 | Characteristics of included studies

Fifteen studies (Abraham et al., 2020; Chauhan et al., 2013; Chitsazi et al., 2013; Egger et al., 1997; Faramarzi et al., 2017; Gupta et al., 2008; Kranti et al., 2010; Jain et al., 2013; Matesanz et al., 2013; Mummolo et al., 2019; Paolantonio et al., 2009; Phogat et al., 2014; Sajna et al., 2021; Verma et al., 2012, 2022), whose results were published over a period ranging from 2008 to 2022, met the criteria and were included in the systematic review; 10 were performed in India, two in Italy, two in Iran and one in Spain. All but one (Abraham et al., 2020) were RCTs. Six studies had a parallel group design (Abraham et al., 2020; Matesanz et al., 2013; Mummolo et al., 2019; Phogat et al., 2014; Verma

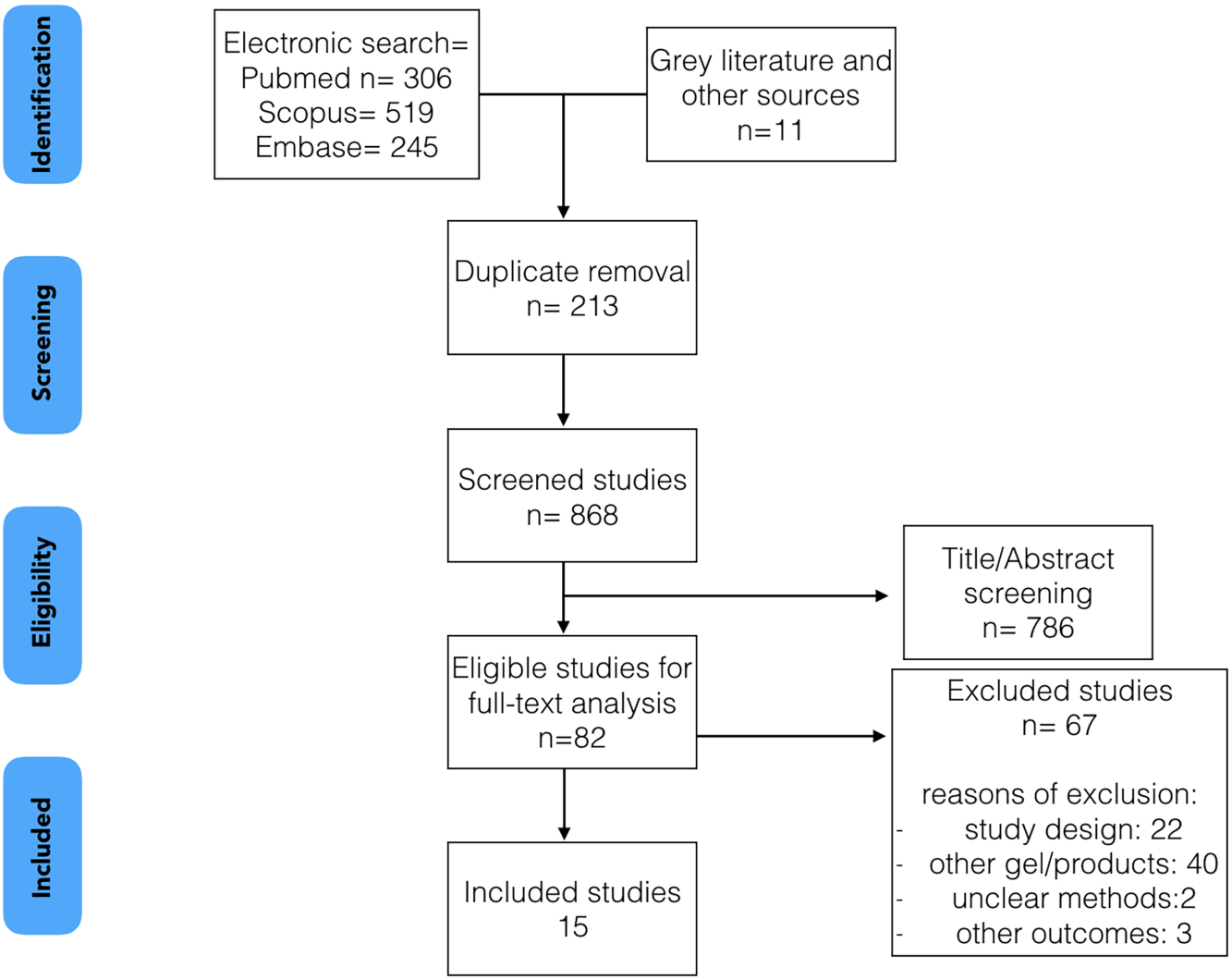


FIGURE 1 Flowchart of the electronic search strategy.

et al., 2012, 2022) while 9 had a split-mouth design (Chauhan et al., 2013; Chitsazi et al., 2013; Egger et al., 1997; Faramarzi et al., 2017; Gupta et al., 2008; Jain et al., 2013; Kranti et al., 2010; Paolantonio et al., 2009; Sajna et al., 2021). In two studies the control group was SRP + placebo drug (Paolantonio et al., 2009; Verma et al., 2012). The chlorhexidine concentration in the XAN-CHX gel was 1.5% in 13 studies and 2.5% in two studies (Faramarzi et al., 2017; Gupta et al., 2008). Among the included studies, sample size ranged between 10 and 98 patients. All aforementioned data and the features of the population samples are shown in Table 1. The main results about PPD reduction and CAL gain are summarized in Table 2.

3.3 | Adverse events

Only 4 out of 15 studies have mentioned adverse events after treatment (Chitsazi et al., 2013; Matesanz et al., 2013; Nandan et al., 2022; Verma et al., 2012). In this regard, no treatment-related side effects during the study period were reported.

3.4 | Risk of bias in individual studies

Overall, three RCTs were judged to be at moderate risk of bias (Kranti et al., 2010; Matesanz et al., 2013; Paolantonio et al., 2009) while the remaining 11 RCTs were rated at high risk of bias (Abraham et al., 2020; Chauhan et al., 2013; Chitsazi et al., 2013; Faramarzi et al., 2017; Gupta et al., 2008; Jain et al., 2013; Mummolo et al., 2019; Nandan et al., 2022; Phogat et al., 2014; Verma et al., 2012, 2022). The non-RCT study conducted by Sajna et al. was judged at high risk of bias (Sajna et al., 2021).

3.5 | Meta-analysis

Figures 2 and 3 show study-specific and pooled SMDs of PPD reduction and CAL gain, respectively. The forest-plot showed a significant improvement in PPD reduction for the SRP + CXH gel compared to the SRP alone group, with a SMD of 0.87 (95% CI, 0.41–1.34), in the presence of significant high heterogeneity among the studies ($I^2 = 91\%$, $p < 0.001$) (Figure 2). The leave-one-out sensitivity analysis revealed that none of the studies had a single influential effect on the PPD summary effect and between-study heterogeneity. However, the exclusion of the studies by Chauhan et al., 2013 (Chauhan et al., 2013) and Verma et al., 2022 (Verma et al., 2012) lead to a drop in between-study heterogeneity (SMD = 0.64, 95% CI, 0.41–0.87; $I^2 = 53.8\%$, $p = 0.02$). Similar results emerged when considering only the studies reporting results at three (12 studies, SMD = 1.02, 95% CI, 0.49–1.54; $I^2 = 92.8\%$, $p < 0.001$) and at 6 months (6 studies, SMD = 1.05, 95% CI, 0.40–1.69; $I^2 = 92.9\%$, $p < 0.001$).

The meta-regression revealed that the study design (split mouth vs parallel group) was not significantly associated with PPD reduction ($p = 0.64$). Studies whose standard deviation has been imputed showed a significantly ($p = 0.006$) lower SMD (0.50, 95% CI, 0.25–0.76; $I^2 = 38.5\%$) as compared to those who not (SMD = 1.56, 95% CI, 0.64–2.47; $I^2 = 94.5\%$).

The meta-analysis showed a significant CAL gain for the SRP + CXH gel compared to the SRP alone group, with a SMD of 0.84 (95% CI, 0.36–1.33), in the presence of significant high heterogeneity among the studies ($I^2 = 91.3\%$, $p < 0.001$) (Figure 3). The leave-one-out sensitivity analysis revealed that none of the studies had a single influential effect on the summary effect and between-study heterogeneity. Similar results emerged when considering only the studies reporting results at three (12 studies, SMD = 0.76, 95% CI, 0.33–1.19; $I^2 = 90.0\%$, $p < 0.001$) and at 6 months (6 studies, SMD = 0.91, 95% CI, 0.25–1.58; $I^2 = 93.5\%$, $p < 0.001$).

The meta-regression revealed that the study design (split mouth vs parallel group) was not significantly associated with CAL gain ($p = 0.30$). Studies whose standard deviation has been imputed showed a significantly ($p = 0.006$) lower SMD (0.30, 95% CI, −0.06-0.65; $I^2 = 64.5\%$, $p < 0.001$) as compared to those who reported it (SMD = 1.60, 95% CI, 1.04–2.16; $I^2 = 84.5\%$, $p < 0.001$).

Visual inspection of funnel plots (Figure 4) revealed a slight departure from symmetry for CAL gain, but the Egger test did not support the assumption of publication bias ($p = 0.60$ for PPD reduction, $p = 0.85$ for CAL gain) (Figure 5).

4 | DISCUSSION

The aim of this systematic review and meta-analysis was to investigate the role of xanthan-based chlorhexidine gel as additional treatment after non-surgical periodontal therapy. This gel consists of a combination of two CHX formulations: 0.5% chlorhexidine digluconate and 1.0% chlorhexidine dihydrochloride, which are incorporated in a saccharidic polymer, xanthan. The cross linking structure of xanthan enables the controlled release of the drugs, resulting in a near-zero order drug release pattern. Upon contact with water, the gel forms a three-dimensional pseudoplastic reticulum, which has the ability to suspend and retain various substances. The CHX xanthan-based gel undergoes a progressive process of imbibition and is physically removed in 10–30 days. Chlorhexidine digluconate is released within the first day and reaches a concentration greater than 100 μg/mL, which is maintained for an average of 6–9 days. This concentration exceeds the minimum inhibitory concentration for CHX (0.10 μg/mL). Chlorhexidine dihydrochloride is gradually released over the subsequent days, effectively sustaining both bacteriostatic and bactericidal concentrations for at least 2 weeks. This sustained released mechanism serves to impede recolonization and further microbial growth (Chitsazi et al., 2013).

TABLE 1 Characteristics of the included studies.

First author	Country	Year of publication	Study design	Participants (control/test)	Periodontal case definition	Systemic disease	Mean age/range
Gupta et al. (RCT)	India	2008	SC, RCT, SMD	30 (30/30/30)	At least 3 teeth, (at least one tooth apart), with PPD 5-8 mm and BOP+	No, no information on smoking	25–75 years
Paolantonio et al. (multicentric RCT)	Italy	2009	MC, RCT, SMD, B	98 (98/98)	At least two teeth with PPD ≥5 mm and BOP (+)	No, smoker excluded	24–58 years
Kranti et al. (RCT)	India	2010	RCT, SMD, BBB, PC	10 (10/10) (60 sites; 30/30)	At least 4 periodontal pockets with PPD 5–8 mm	No, smoker excluded	25–65 years
Verma et al. (RCT)	India	2012	RCT, SMD	46 (46/46)	At least two non-adjacent interproximal sites with PPD 5–8 mm and BOP(+)	No, smoker excluded	30–65 years
Matesanz P. et al. (RCT)	Spain	2013	RCT, PGD, PC	22 (12/10)	At least 16 teeth and at least 3 teeth per quadrant, 4–10 pockets with PPD >4 mm and BOP(+), or at a programmed supportive visit	No	Elder than 30 years
Chauhan et al. (RCT)	India	2013	RCT, PGD	40 (20/20/20)	At least 8 teeth with PPD 4–8 mm	No	30–65 years
Chitsazi et al. (RCT)	Iran	2013	RCT, SMD	24 (20/20; 4 drop-outs)	One site per quadrant with PPD ≥4 mm and BOP (+)	No	Mean 46.5 years
Jain et al. (RCT)	India	2013	RCT, SMD	30 (30/30)	Two sites located on the same side PPD between 5 to 7 mm	No, smoker excluded	30–60 years
Phogat et al. (RCT)	India	2014	RCT, SMD	30 (30/30)	At least 3 nonadjacent interproximal sites with PPD 4–8 mm	No	30–50 years

Description of gel	CHX gel application	Adverse events	Follow-up (months)	Recorded clinical parameters (indexes)	Non-surgical periodontal therapy (NSPT)	Comments
XAN-CHX1.5% CHX gel	One time at baseline	Not mentioned	1.3	PI, GI, PPD, CAL, GM	FM supra- and subgingival SRP using an ultrasonic scaler and curettes	Local drug therapy markedly improves the benefits of SRP, and by the use of these agents the threshold for surgical periodontal therapy might be moved towards deeper pockets
XAN-CHX2.5% CHX gel	One time at baseline	Not mentioned	3.6	PI, mGI, CAL, PPD, BOP, GR	Two sessions of SRP within 48 h	The results obtained showed that the adjunctive subgingival administration of a Xan-CHX gel significantly improved the positive therapeutic effects of extensive SRP on chronic periodontitis
XAN-CHX1.5% CHX gel	One time at baseline	Not mentioned	3.6	PI, GI, PPD, BOP, GM, CAL	SRP at selected sites	/
XAN-CHX1.5% CHX gel	One time 1 month after SRP	No adverse events	1.3	PI, GI, PPD, CAL	SRP using hand and ultrasonic scalers and periodontal curettes	/
XAN-CHX1.5% CHX gel	One time at baseline	No adverse events	1,3,6	PI, BOP, PPD, CAL, GR, FI, TM	Scaling of the selected sites by means of an ultrasonic device and Gracey curettes	The study was conducted on patients characterized by: Prior periodontal treatment (non-surgical) in the previous 6 months or patients in a supportive periodontal therapy for at least 1 year
XAN-CHX1.5% CHX gel	One time at baseline	Not mentioned	1.3	PI, GI, PPD, CAL	Complete SRP and subgingival debridement performed within 6 h	/
XAN-CHX1.5% CHX gel	One time at baseline	No adverse events	1.3	PPD, CAL, BOP, GR	SRP	/
XAN-CHX1.5% CHX gel	One time at baseline	Not mentioned	1.5,3,6	GI, sBI, PI, PPD, CAL	FM-SRP performed using ultrasonic instruments followed by hand instruments	/
XAN-CHX1.5% CHX gel	One time at baseline, 10 days and 20 days	Not mentioned	1.3	PI, GI, PPD, CAL	SRP	/

(Continues)

TABLE 1 (Continued)

First author	Country	Year of publication	Study design	Participants (control/test)	Periodontal case definition	Systemic disease	Mean age/range
Faramarzi et al. (RCT)	Iran	2017	RCT, PGD	68 (34/34)	At least eight teeth with PPD 4–8 mm	Type 2 Diabetes Mellitus, smoker excluded	30–60 years
Mummolo et al. (RCT)	Italy	2019	RCT, SMD	60 (120/120, quadrants), 30 M/30F	Patients affected by generalized (>30%) periodontitis	No, non-smoker patients	Mean age 54.1 ± 6.
Abraham et al. (RCT)	India	2020	RCT, PGD	60 (20/20/20)	Two or more non-adjacent teeth with PPD of at least 5 mm with BOP (+) or SUP	No, smoker excluded	30–55 years
Sajna et al. (CCT)	India	2021	CCT, PGD	40	CALof ≥3 mm. A minimum of three teeth with PPD ≥4 mm and BOP (+) in patients suffering from chronic periodontitis	No, smoker excluded	30–50 years
Verma et al. (RCT)	India	2022	RCT, SMD	26 (416 sites, 208 Test group, 208 Control group)	Chronic generalized periodontitis having (PPD) of ≥6 mm in mandibular posterior teeth	Not specified	≥30 years-...not spe
Nandan et al. (RCT)	India	2022	RCT, PGD	22 (11/11)	Aggressive periodontitis, PPD and CAL of >4 mm and <6 mm	No	25–55 years

Abbreviations: B, blinded; BB, double blinded; BBB, triple blinded; BOP, bleeding on probing; CAL, clinical attachment level; CCT, controlled clinical trial; CHX, chlorhexidine; FI, furcation involvement; FM, full-mouth; FMD, full-mouth disinfection; GI, Gingival index; GM, gingival margin location; GR, gingival recession; MC, multicentric; mGI, modified gingival index; mPI, modified plaque index; PC, placebo controlled; PGD, parallel group design; PI, plaque index; PPD, probing pocket depth; RCT, randomized controlled clinical trial; sBI, sulcus bleeding index; SC, single center; SMD, split-mouth design; SRP, scaling and root planing; SUP, suppuration; TM, tooth mobility; XAN, xanthan.

After a rigorous systematic review of the literature, we identified a total of 15 clinical studies (14 RCTs and 1 CCT) investigating the application of locally delivered Xanthan-based chlorhexidine gel as adjunct to non-surgical periodontal therapy over a period ranging from 2 weeks to 6 months. In all the selected articles it has been reported that XAN-CHX gel was applied at selected sites characterized by a PPD of at least 4 mm. Gupta et al. (2008) found statistically significant differences in PPD reduction and CAL gain from 1 to 3 months favoring the test group when compared with SRP alone. The authors suggested that enhanced healing may have occurred at the test sites in the absence or following reduction of microbial load during the critical initial phase of healing following NSPT. Furthermore, CAL gain was slightly greater when comparing xanthan-based chlorhexidine gel+ SRP versus doxycycline gel+SRP even though no statistically significant differences were reported. This effect has been attributed to the combination of fast releasing chlorhexidine digluconate with slow releasing chlorhexidine dihydrochloride. Paolantonio et al. reported that the adjunctive usage of XAN-CHX was particularly evident in deeper pockets (>7 mm). This finding is of utmost importance as a 2 mm pocket reduction could reduce the need for advanced and surgical periodontal treatment which lead to positive effect concerning time, costs and patient morbidity (Nandan et al., 2022). On the other hand, Oosterwaal et al. (Jeffcoat et al., 1998) found no difference when comparing the adjunctive usage of 2% chlorhexidine gel versus SRP alone or placebo. According to this, Unsal et al. (1994) (Oosterwaal et al., 1990) reported less CAL gain after SRP whereas Quirynen et al. (2000) reported negligible beneficial effects after one-stage full-mouth disinfection protocol. Both studies applied a 1% chlorhexidine gel as adjunct to NSPT. This was attributed to the mechanical interference of the CHX gel with the early healing process. However, the authors suggested that the aforementioned findings could be explained by low subgingival substantivity of the applied devices. In fact, the outflow of gingival crevicular fluid is 20 mL/h that, in turn, would be responsible for 1-min half-life of chlorhexidine gel within a periodontal pocket. The authors stated that bioadhesive properties of xanthan gum might partly explain the better outcomes. Furthermore, the cationic charges of chlorhexidine might interact with the anionic charges of the xanthan gum polymer, enhancing its gel structure and substantivity. All studies but one (Verma et al., 2022) used

Description of gel	CHX gel application	Adverse events	Follow-up (months)	Recorded clinical parameters (indexes)	Non-surgical periodontal therapy (NSPT)	Comments
XAN-CHX1.5% CHX gel	One time after 2nd SRP (baseline, 2 weeks after 1st SRP)	Not mentioned	3.6	PI, GI, CAL, PPD	FM-SRP using an ultrasonic device and standard Gracey periodontal curettes + second session of SRP after 2 weeks	/
XAN-CHX2.5% CHX gel	One time at baseline	Not mentioned	3 weeks	PI, BOP, PPD	One stage FMD under local anesthesia	/
XAN-CHX1.5% CHX gel	One time 1 week after SRP	Not mentioned	15 days, 1 month	PI, GI, PPD	SRP using hand and ultrasonic scalers and periodontal curettes	/
XAN-CHX1.5% CHX gel	One time at baseline	Not mentioned	1 month	GI, PPD, CAL	SRP using hand and ultrasonic scalers and periodontal curettes	/
XAN-CHX1.5% CHX gel	One time at baseline	Not mentioned	1,3,6	PI, GI, CAL, PPD	FM-SRP using ultrasonic instruments followed by hand instruments	/
XAN-CHX1.5% CHX gel	One time at baseline	No adverse events	1,2,3	PI, GI, PPD, CAL	SRP using a sterile scaler and Gracey curettes	/

XAN-CHX gel in patients affected by moderate or severe chronic periodontitis. Nandan et al. (2022) instead, used XAN-CHX gel in patients affected by aggressive periodontitis. Thirteen studies used xanthan gum chlorhexidine gel during active periodontal therapy. Gupta et al. (2008) used the adjunctive therapy both in untreated and treated sites showing recurrent disease. Verma et al., 2012 (Kranti et al., 2010) applied xanthan gum chlorhexidine gel at selected sites during supportive periodontal therapy. Improvements in PPD were observed, especially between the 1 and 3 months interval. The authors attributed this effect to the absence of microbial interference during the maturation phase of healing. Such finding is in line with previous studies featured by similar experimental design but using different devices (Quirynen et al., 2000). Matesanz et al. (2013) used xanthan-based chlorhexidine gel both in residual pockets after a first stage of non-surgical periodontal therapy and in patients undergoing supportive periodontal therapy. Fourteen studies recruited patients featured by good general health and most studies considered systemic diseases as exclusion criteria. Faramarzi et al. (2017), as instance, compared the clinical outcomes between SRP plus XAN-CHX gel and SRP alone for patients with diabetes mellitus type 2. No study reported significant side effects related to adjunctive usage of xanthan-based chlorhexidine gel. This is of clinical relevance as compared to systemic antibiotics especially in light of further advantages such as incidence of resistant bacteria or gastrointestinal disturbances. On the whole, limited additional benefits over SRP alone could be expected in patients with good systemic health and plaque control. Potential advantage of additional therapy could be more pronounced for compromised healthy patients, elderly patients, and also in more severe forms of periodontitis like aggressive periodontitis or periodontitis modified by systemic factors. Nevertheless, evidence is lacking and further studies regarding aforementioned conditions were advocated (Chauhan et al., 2013). Among the included studies, the application of XAN-CHX gel was different in terms of timing and frequency. Eleven studies reported the usage of XAN-CHX gel one time at baseline after NSPT. The remaining studies applied XAN-CHX gel as follows: one study applied XAN-CHX gel once one month after NSPT (Kranti et al., 2010), one study used XAN-CHX gel one time at baseline and repeated the procedure after 10 and 20 days of NSPT (Jain et al., 2013), one study applied XAN-CHX gel after the second step of NSPT (Phogat

TABLE 2 PPD reduction, CAL gain, Adverse events evidence summary (+ significant benefit for XAN-CHX; = no difference, − significant benefit for other groups than XAN-CHX).

	First author	Significance	Mean PPD reduction	Mean CAL gain	Adverse events
1	Gupta et al. (RCT)	+	Baseline vs. 1 month 1.76 ± 0.81, Baseline vs. 3 months 2.76 ± 1.25	Baseline vs. 1 month 1.33 ± 0.66, Baseline vs. 3 months 2.03 ± 1.12	Not mentioned
2	Paolantonio et al. (multicentric RCT)	+	Mean differences between the decreases for the treatments were 0.87 and 0.94 mm at 3 and 6 months, respectively	Mean differences between the gains for the treatments were 0.83 and 0.90 mm, respectively	Not mentioned
3	Kranti et al. (RCT)	+	Experimental group mean PPD reduction from baseline to 3 & 6 months 2.25 ± 0.58 & 3.11 ± 0.47 ($p < 0.0001$) CONTROL group mean PPD reduction from baseline to 3 & 6 months 1.68 ± 050 & 2.44 ± 0.55 ($p < 0.0001$)	Experimental group mean CAL gain to 3 & 6 months 2.24 ± 0.62 & 3.11 ± 0.65 ($p < 0.001$). CONTROL group mean CAL gain to 3 & 6 months 1.69 ± 1.03 & 2.44 ± 0.98 ($p < 0.001$)	Not mentioned
4	Verma et al., 2012 (RCT)	+	SRP + CHX group mean pocket depth reduction from 1 to 3 months 1.24 ± 0.82. Group A mean pocket depth reduction from 1 to 3 months 0.35 ± 0.67 ($p < 0.001$)	SRP + CHX mean attachment gain from 1 month to 3 months 0.85 ± 0.63. Group A mean attachment gain from 1 month to 3 months 0.22 ± 0.42 ($p < 0.001$)	No adverse events
5	Matesanz et al. (RCT)	=	TEST group mean reduction in PPD after 6 months 0.32 mm (±0.26 mm) PLACEBO group mean reduction in PPD after 6 months 0.22 mm (±0.52 mm) ($p < 0.147$).	TEST group mean reduction in CAL after 6 months 0.30 mm ($p < 0.380$) PLACEBO group no change in CAL observed at the end of the follow-up.	No adverse events
6	Chauhan et al. (RCT)	=	Group 1 mean change in PPD value from baseline to 3 months 1.60 ± 0.27 Group 2 mean change in PPD value from baseline to 3 months 2.50 ± 0.42 Group 3 mean change in PPD value from baseline to 3 months 2.48 ± 0.32 (p 0.005)	Group 1 mean change in CAL value from baseline to 3 months 0.55 ± 0.16 (p 0.004) GROUP 2 mean change in CAL value from baseline to 3 months 1.25 ± 0.20 (p 0.004) Group 3 mean change in CAL value from baseline to 3 months 2.48 ± 0.32 (p 0.005)	Not mentioned
7	Chitsazi et al. (RCT)	=	SRP group baseline mean PPD 4.90 ± 0.78 – after 3 months 3.25 ± 0.65 GEL groups baseline mean PPD 5.05 ± 0.79 in the SRP and gel groups – after 3 months 3.38 ± 0.79 ($p > 0.05$)	SRP group baseline mean CAL 3.9 ± 0.58 – after 3 months 3.4 ± 0.60 GEL groups baseline mean CAL 4.15 ± 0.67 – after 3 months 3.67 ± 0.65 p(0.001)	No adverse events
8	Jain et al. (RCT)	+	Control group baseline mean PPD value 5.20 ± 484 – after 6 months 3.00 ± 0.91 TEST group baseline PPD value 5.20 ± 484 - after 6 months 2.40 ± 0.675 (p 0.002)	Control group baseline mean CAL value 11.43 ± 2.750 – after 6 months 9.20 ± 0.508 (p 0.014). TEST group mean CAL 11.70 ± 2.806 – after 6 months 10.03 ± 2.977 (p 0.014)	Not mentioned
9	Phogat et al. (RCT)	+	Mean PPD change 0-1 months were 1.156 ± 0.055, 2.143 ± 0.009 and 1.588 ± 0.080 ($p < 0.001$) in control, group A(SRP + XAN) and group C(SRP + HB) respectively that decreased at 0–3 months to 2.264 ± 0.0.031, 3.764 ± 0.010 and 2.0.917 ± 0.082 ($p < 0.001$)	Mean CAL change 0-1 months were 2.037 ± 0.091, 2.410 ± 0.007 and 2.142 ± 0.009 ($p < 0.001$) in control, group A(SRP + XAN) and group C(SRP + HB) respectively that decreased at 0–3 months to 2.405 ± 0.0.079, 2.913 ± 0.051 and 2.0.784 ± 0.056 ($p < 0.001$)	Not mentioned
10	Faramarzi et al. (RCT)	=	Control group mean PD reductions from baseline to 3 and 6 months 1.74 ± 0.14 mm and 1.93 ± 0.26 mm ($p < 0.001$) TEST group mean PD reductions from a baseline to 3 and 6 months 1.93 ± 0.33 mm and 2.03 ± 0.31 mm ($p < 0.001$)	Control group mean CAL from baseline to 3 and 6 months 0.77 ± 0.09 and 0.87 ± 0.1 ($p < 0.05$). TEST group mean CAL from baseline to 3 and 6 months 0.87 ± 0.1 and 1.23 ± 0.22 ($p < 0.05$)	Not mentioned
11	Mummolo et al. (RCT)	?	No clinical data and statistical analysis available	No clinical data and statistical analysis available	Not mentioned
12	Abraham et al. (RCT)	+	XAN CHX group baseline mean PPD value 5.86 ± 0.28 – after 30 days 3.20 ± 0.08. METRONIDAZOLE GEL group baseline mean PPD value 5.58 ± 0.89 – after 30 days 3.18 ± 0.72. TETRACYCLINE group baseline mean PPD 5.66 ± 0.68 – after 30 days 3.12 ± 0.30 (p 0.001). No intergroup data analysis available	Data not available	Not mentioned
13	Sajna et al. (CCT)	+	SRP group baseline mean PPD 4.82 ± 0.66 – after 1 month 3.40 ± 0.66 ($p < 0.001$). SRP + XAN group baseline mean PPD 5.06 ± 0.64 a- after 1 month 3.07 ± 0.61 ($p < 0.001$)	SRP group baseline mean CAL 5.74 ± 0.77 – after 1 month 4.91 ± 0.78 ($p < 0.001$). SRP + XAN group baseline mean CAL 6.18 ± 0.67 – after 1 month 4.86 ± 0.69 ($p < 0.001$)	Not mentioned
14	Verma et al., 2022 (RCT)	+	SRP group baseline PPD value 6.98 ± 0.34 – after 6 months 4.63 ± 0.39. SRP + XAN group baseline PPD value 7.15 ± 0.18 – after 6 months 3.80 ± 0.30 ($p < 0.001$)	SRP group baseline CAL value 10.94 ± 0.41 – after 6 months 8.48 ± 0.18 SRP + XAN group baseline CAL value 11.02 ± 0.46 – after 6 months 7.90 ± 0.31 ($p < 0.001$)	Not mentioned
15	Nandan et al. (RCT)	=	SRP + XAN group baseline mean PPD 2.50 ± 0.25 – after 3 months 1.81 ± 0.18 (p 0.002). SRP + AMOXI+METRO group mean PPD 2.55 ± 0.14–3 months 1.88 ± 0.127 (p 0.127)	SRP + XAN group baseline mean CAL 3.43 ± 1.18 – after 3 months 2.41 ± 0.77 (p 0.001). SRP + AMOXI+METRO group baseline mean CAL 3.57 ± 1.21 – after 3 months 2.76 ± 0.95 (p 0.001)	No adverse events

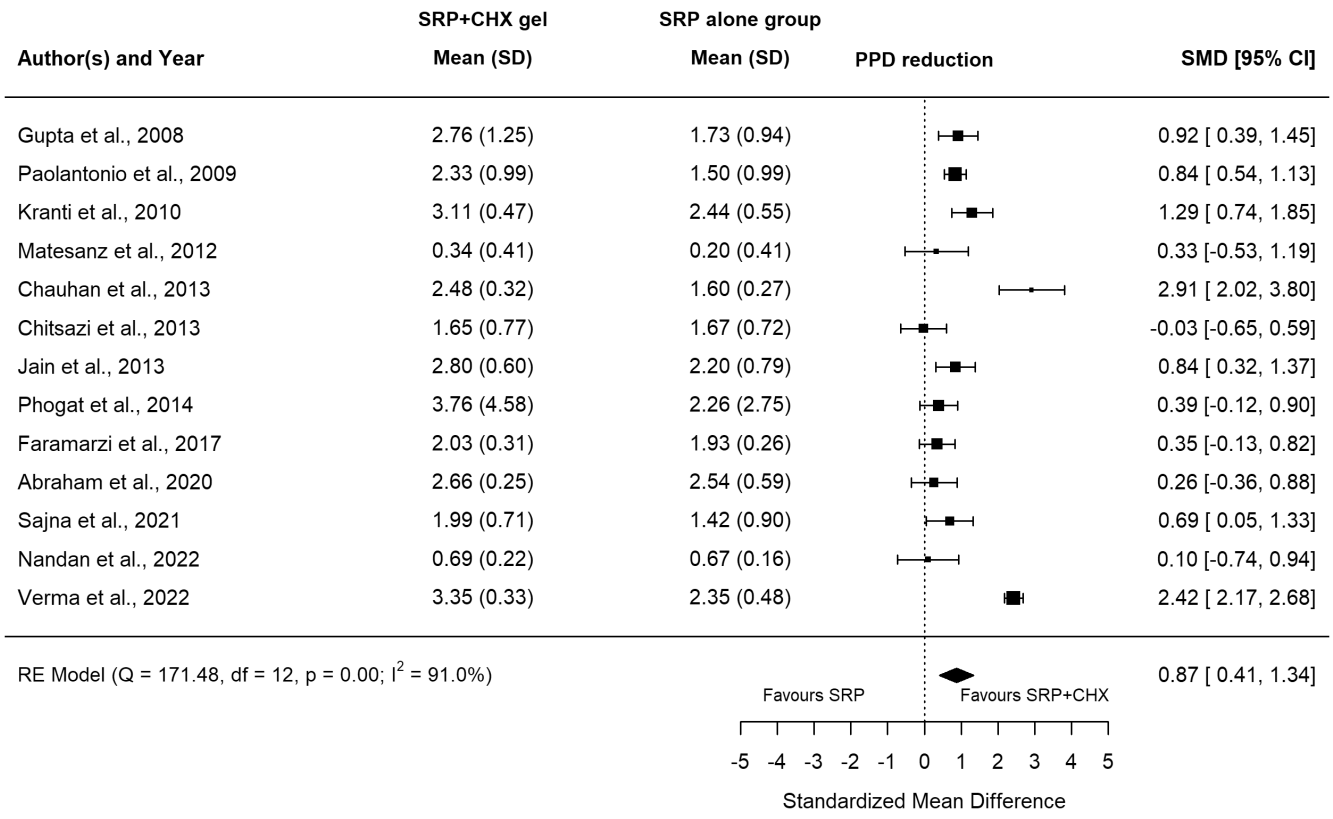


FIGURE 2 Forest-plot for probing pocket depth (PPD) reduction comparing the adjunctive use of chlorhexidine (CHX) gel to scaling and root planing (SRP) and SRP alone at last follow-up visit.

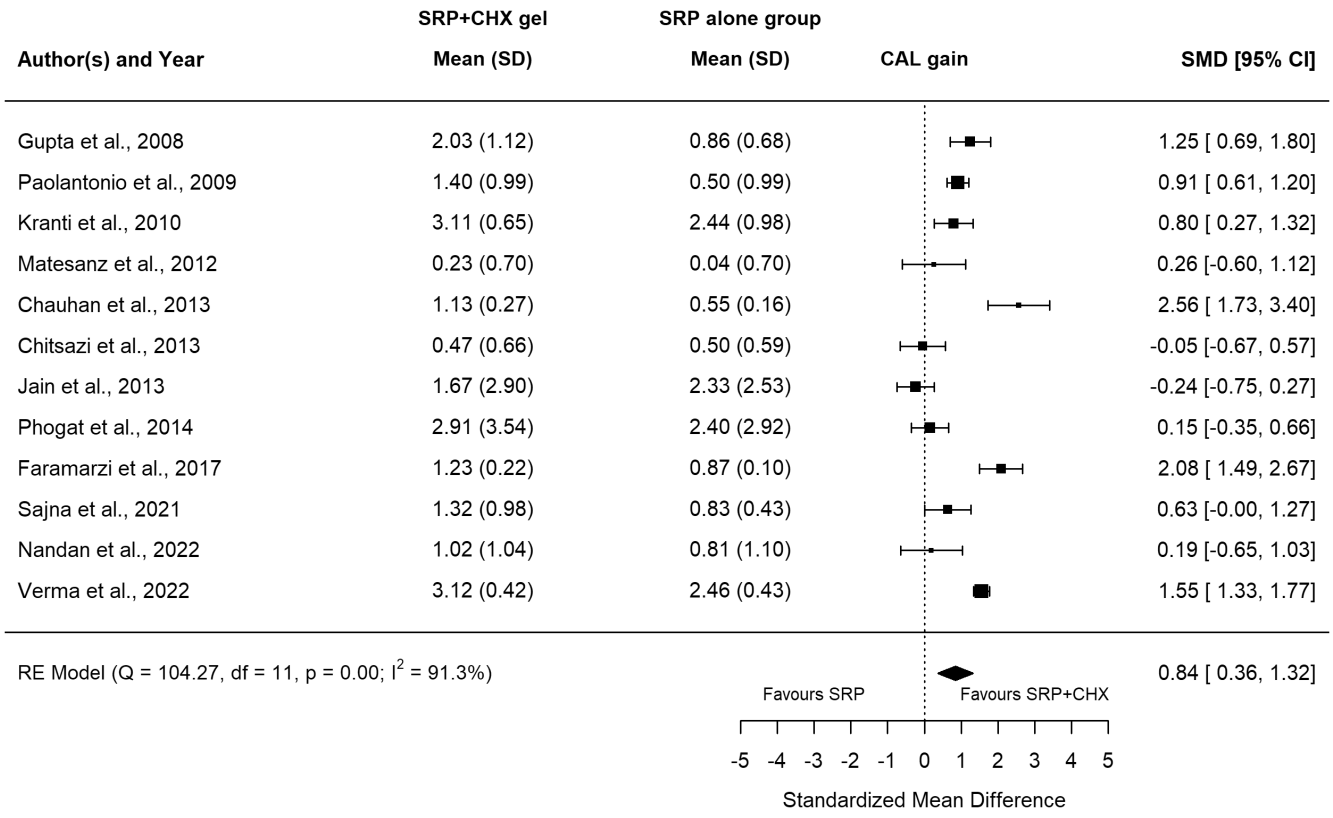


FIGURE 3 Forest-plot for clinical attachment level (CAL) gain comparing the adjunctive use of chlorhexidine (CHX) gel to scaling and root planing (SRP) and SRP alone at last follow-up visit.

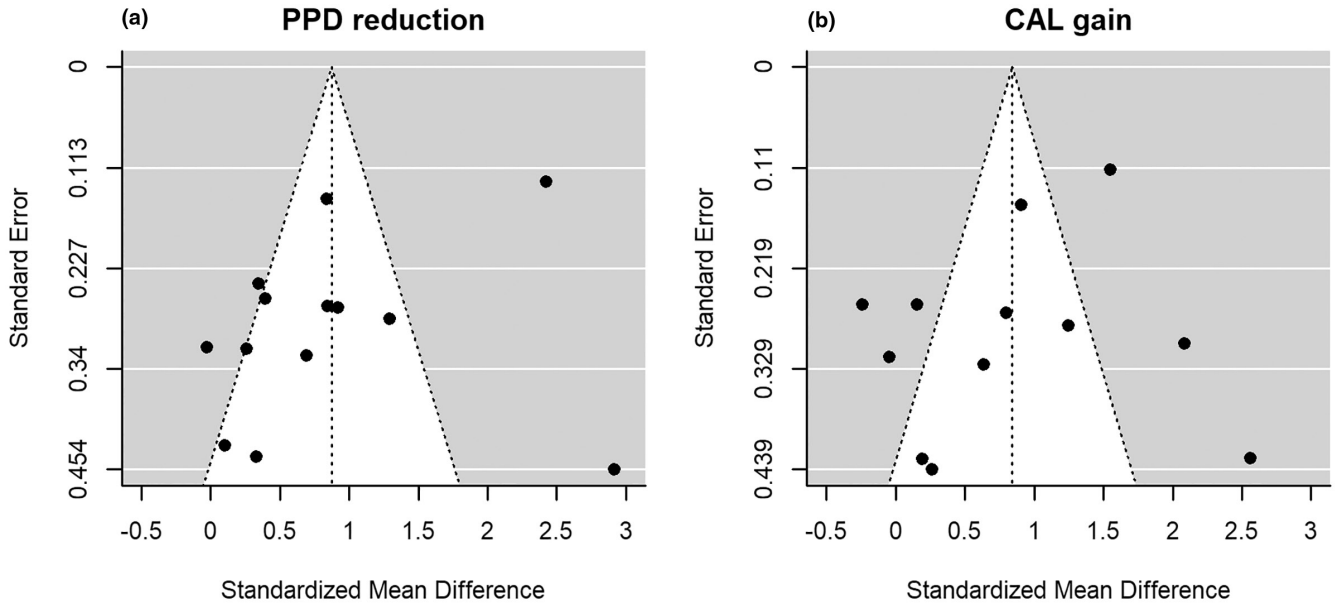


FIGURE 4 Funnel plot for probing pocket depth (PPD) reduction (panel A) and clinical attachment level (CAL) gain (panel B).

et al., 2014) and one study used XAN-CHX gel 1 week after NSPT (Mummolo et al., 2019). The follow-ups ranged from 2 weeks to 6 months. Twelve out of 15 included studies investigated the adjunctive usage of XAN-CHX gel in NSPT versus NSPT alone. Three studies had one or more additional arms investigating the adjunctive use in NSPT of, respectively: doxycycline gel (Egger et al., 1997), hyaluronan gel (Matesanz et al., 2013), tetracycline fibers and metronidazole gel (Mummolo et al., 2019). All studies excepting Abraham et al. had a control group. Non-clinical outcomes were investigated in 7 studies such as subgingival microbiologic evaluation in 4 studies (Chauhan et al., 2013; Gupta et al., 2008; Verma et al., 2012, 2022), biomarkers in gingival crevicular fluid (GCF) or saliva in 2 studies (Abraham et al., 2020; Gupta et al., 2008) and systemic outcomes in 2 studies. Chauhan et al. (2013) evaluated systemic/hematological parameters, total leucocyte count (TLC), differential leucocyte count (DLC), and C-reactive protein (CRP) whereas Faramarzi et al. (2017) reported data on fasting blood sugar (FBS) and glycated hemoglobin (HbA1c). In the end, a recent systematic review and meta-analysis by Zhao et al. (2020) concluded that adjunctive application of xanthan- based chlorhexidine gel at selected sites provided only a slight benefit in PPD reduction (mean 0.15 mm) when compared with non-surgical periodontal therapy (NSPT) alone. It is of utmost importance to highlight the statistically significant findings by Herrera et al. (2020) using meta-regression analysis. In contrast with our results, larger benefits were observed for split-mouth studies as compared with parallel-arm studies. In the same way, larger benefits were observed for partial mouth assessments, as compared with full-mouth evaluation. Studies on treated patients tended to achieve larger PPD reductions when compared with studies in untreated patients. Therefore, control group using placebo tended to achieve smaller benefits, as compared with those in which the control group was SRP alone.

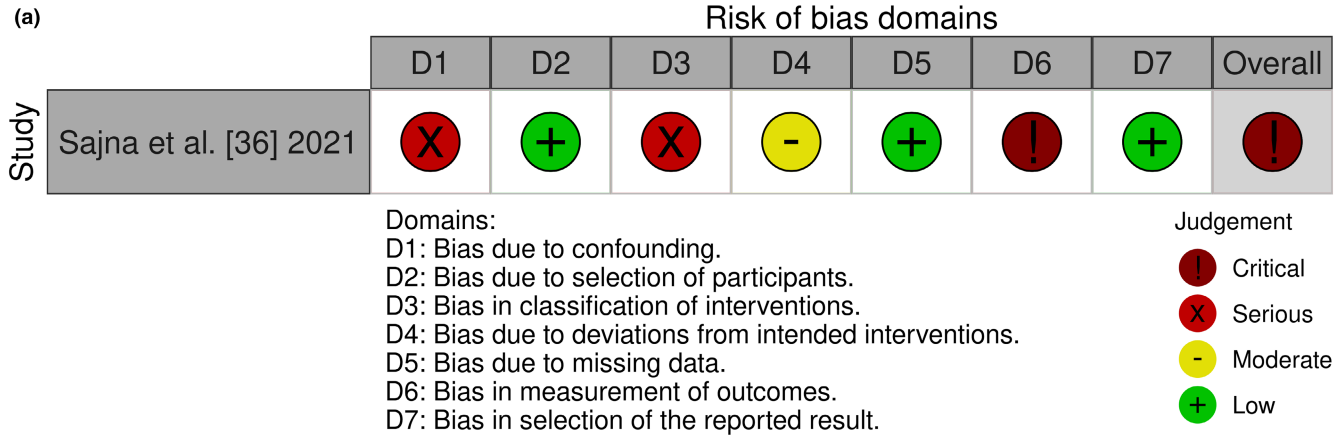
5 | LIMITATIONS

The main limitation of this systematic review and meta-analysis relies on the study quality. In fact, the risk of bias evaluation showed that three RCTs were judged to be at moderate risk of bias while the remaining 12 studies were rated at high risk of bias. Considerable heterogeneity across the studies included was noticed in terms of study design (split-mouth/parallel groups), number of centers (monocentric/multicentric), performed periodontal therapy (different timing, full mouth vs partial mouth approaches, different instruments e.g. mechanical, manual and or both), study duration and outcome assessment (partial mouth/full mouth). Moreover, only a few studies reported patient perception (Patient Related Outcome Measures, PROMs) and adverse events. Last, only articles published in English-language were selected.

6 | CONCLUSIONS

Although there was high heterogeneity among studies and the quality of the evidence is low, our systematic review and meta-analysis showed that xanthan-based chlorhexidine gel as adjunct to non-surgical periodontal therapy gives benefit in terms of PPD reduction and CAL gain as compared to non-surgical periodontal therapy only. Due to increased costs, treatment time and potential side effects (e.g. allergy to chlorhexidine and/or to other compounds within the topical device), its use should be based on a case-by-case selection of patients.

Due to limited scientific evidence at the time of writing, well-designed studies to evaluate effectiveness of xanthan-based chlorhexidine gel in aggressive periodontitis, severe periodontitis modified by systemic factors, peri-implant mucositis and peri-implantitis are



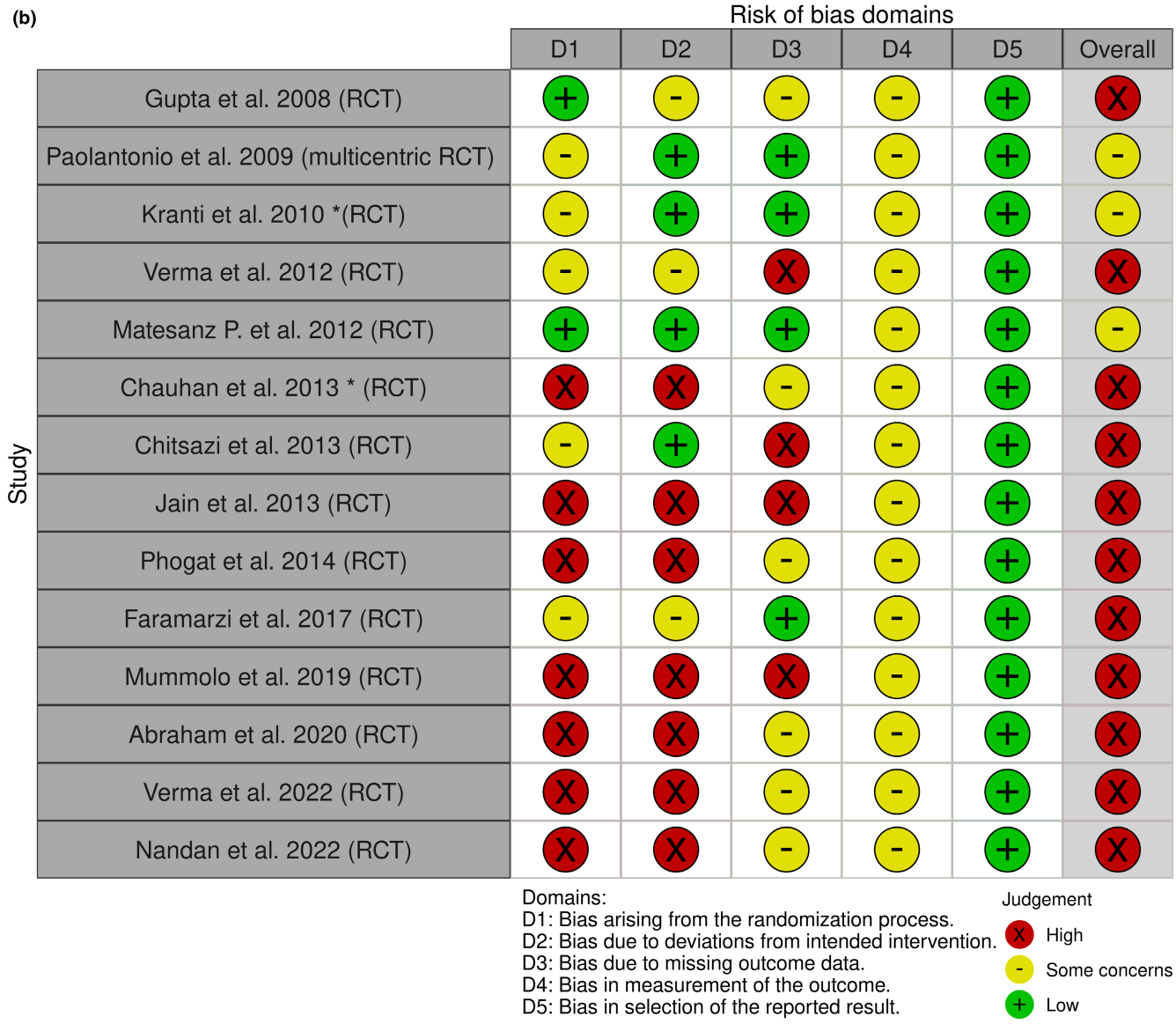


FIGURE 5 Visual representation of risk of bias evaluation with 'robvis' tool.

warranted in the next future. These should be characterized by a better methodology, adequate sample size and longer follow-up.

AUTHOR CONTRIBUTIONS

Mensi Magda: Conceptualization; project administration; supervision; resources. **Antonino Palazzolo:** Investigation; writing – original draft; writing – review and editing; data curation. **Gianluca Garzetti:** Writing – review and editing; investigation; writing – original draft; data curation. **Diego Lops:** Supervision. **Stefano Calza:** Supervision. **Matteo Rota:** Data curation; formal analysis; methodology.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest relevant to this study.

DATA AVAILABILITY STATEMENT

The data that supports the findings of this study are available in the supplementary material of this article.

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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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