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BEST-EVIDENCE CONSENSUS

Efficacy of biologics in root coverage and gingival augmentation therapy: An American Academy of Periodontology best evidence systematic review and network meta-analysis

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Abstract

Background: The aim of this systematic review was to assess the efficacy of three biologics, namely autologous blood-derived products (ABPs), enamel matrix derivatives (EMD) and recombinant human platelet-derived growth factor BB (rhPDGF-BB), in root coverage and gingival augmentation therapy.

Methods: The protocol of this PRISMA 2020-compliant systematic review was registered in PROSPERO (CRD42021285917). After study selection, data of interest were extracted. A network meta-analysis (NMA) was conducted to assess the effect of different surgical interventions on the main clinical outcomes of interest (i.e., mean root coverage [MRC%], complete root coverage [CRC%], keratinized tissue width [KTW], gingival thickness [GT] change, and recession depth [RD] reduction).

Results: A total of 48 trials reported in 55 articles were selected. All studies reported on the treatment of gingival recession defects for root coverage purposes. Forty-six treatment arms from 24 trials were included in the NMA. These arms consisted of treatment with coronally advanced flap (CAF) alone, EMD + CAF, platelet-rich fibrin (PRF) + CAF, and subepithelial connective tissue graft (SCTG) + CAF. Regarding MRC%, SCTG+CAF was associated with a significant higher estimate (13.41%, 95% CI [8.06–18.75], $P < 0.01$), while EMD+CAF (6.68%, 95% CI [−0.03 to 13.4], $P = 0.061$) and PRF+CAF (1.03%, 95% CI [−5.65 to 7.72], $P = 0.71$) failed to show statistically significant differences compared with CAF alone (control group) or with each other. Similarly, only SCTG+CAF led to a significantly higher CRC% (14.41%, 95% CI [4.21 to 24.61], $P < 0.01$), while treatment arms EMD + CAF (13.48%, 95% CI [−3.34 to 30.32], $P = 0.11$) and PRF+CAF (−0.91%, 95% CI [−15.38, 13.57], $p = 0.81$) did not show significant differences compared with CAF alone or with each other. Differences in the CI of PRF+CAF (symmetrical around a zero adjunctive effect) and EMD+CAF (non-symmetrical) suggest that EMD could have some additional value compared with PRF. Treatment with SCTG+CAF led to a statistically significant higher RD reduction (−0.39 mm, 95% CI [−0.55 to 0.22], $P < 0.01$), however EMD+CAF

(−0.13 mm, 95% CI [−0.29 to 0.01], $P = 0.08$) and PRF+CAF (−0.06 mm, 95% CI [−0.23 to 0.09], $P = 0.39$) failed to show significant differences compared with CAF or with each other. While SCTG+CAF was associated with a statistically significant higher gain of KTW (0.71 mm, 95% CI [0.48 to 0.93], $P < 0.01$), EMD+CAF (0.24 mm, 95% CI [−0.02 to 0.51], $P = 0.08$) and PRF+CAF (0.08 mm, 95% CI [−0.23 to 0.41], $P = 0.58$) did not result into significant changes compared with CAF alone or with each other. Regarding the use of rhPDGF–BB+CAF, although available studies have reported equivalent results compared with SCTG+CAF, evidence is very limited.

Conclusions: The use of ABPs, EMD, or rhPDGF-BB in conjunction with a CAF for root coverage purposes is safe and generally promotes significant improvements respective to baseline clinical parameters. However, the adjunctive use of ABPs and EMD does not provide substantial additional improvements in terms of clinical outcomes and patient-reported outcome measures to those achieved using CAF alone, when baseline KTW is >2 mm. Both PRF+CAF and EMD+CAF rendered inferior MRC%, CRC%, RD reduction, and KTW gain compared with SCTG+CAF, which should still be considered the gold-standard in root coverage therapy. Although some studies have reported equivalent results for rhPDGF-BB+CAF compared with the gold-standard intervention, limited evidence precludes formal comparisons with CAF or SCTG+CAF that could be extrapolated to guide clinical practice.

KEYWORDS
biologics, gingival recession, mucogingival deformities, periodontal plastic surgery

1 | INTRODUCTION

Periodontal plastic surgery (PPS) is frequently indicated for the correction of mucogingival deformities. Depending on their primary therapeutic goal, PPS interventions can be broadly classified into two categories: root coverage (RC) or gingival augmentation (GA).[1–7] Most RC and GA interventions involve the use of soft tissue grafts. Among them, autogenous grafts, namely subepithelial connective tissue grafts (SCTG) and free gingival grafts (FGG), are generally acknowledged as the gold standard for the treatment of sites presenting gingival recession defects (GRDs)[1–5] and keratinized tissue width (KTW) deficiency (i.e., <2 mm),[6,7] respectively. For the treatment of GRDs, bilaminar techniques involving the use of SCTG in combination with a displaced flap are generally associated with superior cost-to-benefit ratio and clinical outcomes, such as complete root coverage (CRC), mean root coverage (MRC), and KTW increase, compared with other alternatives.[1–3] In sites where KTW augmentation is priority over RC, the use of FGG usually leads to higher amounts of KTW gain compared with other modalities of treatment.[6,7] Alternatively, the use of soft tissue graft substitutes may be considered a viable alternative in cases where autogenous grafts cannot be harvested due to anatomical limitations, medical contraindications, or because of patient preferences.[1–3,8]

Whether autogenous grafts, graft substitutes or even no grafts are used (e.g., monolaminar techniques for RC), the adjuvant therapeutic application of biologics, also known as biologic agents or biologic mediators, can actively promote tissue healing and regeneration. Autologous blood-derived products (ABPs), enamel matrix derivative (EMD), and recombinant human platelet-derived growth factor-BB (rhPDGF-BB) are available biologics currently indicated for the treatment of mucogingival deformities. In alignment with the purpose of the American Academy of Periodontology (AAP) Best Evidence Consensus (BEC) on the use of biologic mediators in contemporary clinical practice, the aim of this systematic review was to assess the efficacy of biologics in the context of PPS by addressing the following focused question: "What is the effect of using biologics (i.e., ABPs, EMD, and rhPDGF-BB) on the outcomes of root coverage and gingival augmentation therapy?".

2 | MATERIALS AND METHODS

The protocol of this study was designed according to the guidelines enclosed in the Cochrane Handbook for Systematic Reviews of Interventions.[9] This systematic review is compliant with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) 2020 guidelines,[10] and it was registered in the National Institute for Health Research PROSPERO database (CRD42021285917). The following sections provide a description of the specific PICO (population, intervention, comparison, and outcome) framework used to address the focused question of this review.

2.1 | Eligibility criteria

Only randomized clinical trials (RCTs) were included in the qualitative and quantitative assessment of this systematic review. Articles reporting RCTs were considered for inclusion if they met the following criteria:

1. Surgical treatment of adult patients (aged ≥18 years) presenting single or multiple mucogingival deformities defined as sites presenting GRD[11,12] and/or KTW deficiency (i.e., <2 mm).[11]
2. Minimum of 10 participants per study arm.
3. Minimum follow-up of 6 months.
4. At least one study arm must involve the use of a biologic agent (i.e., ABPs, EMD, or rhPDGF-BB), either as a monotherapy, in addition to the compared therapy (control group) or combined with other modalities of treatment.
5. For gingival augmentation procedures, autogenous gingival grafts or soft tissue graft substitutes (e.g., acellular dermal matrices or xenogeneic collagen matrices) were considered.
6. For root coverage procedures, eligible therapies included the use of any monolaminar approach involving flap displacement, such as laterally positioned flaps (LPF) and coronally advanced flaps (CAF), or bilaminar techniques using autogenous SCTG or soft tissue graft substitutes. Moreover, different types of LPF or CAF (e.g., pedicle flap, envelope flap, tunnel flap) were considered eligible.

In addition, RCTs that indistinctly pooled data from single and multiple GRD in the analysis, that did not have at least one group that involved the use of biologics, or that did not clearly describe the study in terms of design and/or number of patients allocated per treatment arm were not eligible.

2.2 | Outcome measures

Clinical, digital imaging, esthetic, histologic, safety, and patient-reported outcome measures (PROMs) were assessed as follows:

1. Clinical outcomes were defined as structural and biological assessments performed by the investigators either directly, during a clinical examination, or indirectly (e.g., using intraoral photographs or stone casts). For root coverage procedures, relevant outcomes included number and percentage of sites in which CRC was achieved, percentage of MRC, changes in gingival recession depth (RD), and clinical attachment level (CAL) gain. In addition, changes in KTW and in mucosal thickness were assessed for both gingival augmentation and root coverage procedures.
2. Digital imaging outcomes were defined as linear (e.g., soft tissue thickness change), profilometric, and volumetric assessments of dimensional changes of the periodontal soft tissue performed by the investigators using standard or advanced digital imaging files (e.g., Standard Tessellation Language [STL] files).
3. Esthetic outcomes were defined as esthetic assessments (e.g., color match, surface texture, etc.) performed by the investigators either directly (i.e., clinical examination) or indirectly (e.g., using standardized intraoral photographs) through subjective evaluation or using pre-established indices or scores.
4. Histologic outcomes were defined as descriptive histologic, histomorphometric, and immunohistochemical assessments of periodontal soft tissue samples obtained after a variable healing time following mucogingival therapy performed by the investigators.
5. Safety outcomes were defined as assessments made by the investigators to monitor the occurrence of complications and adverse events at different time points during the study.
6. PROMs were defined as quality-of-life assessments made by the patients regarding different aspects of therapy, such as overall satisfaction, preferences, perceived pain/discomfort, occurrence of adverse events, esthetics, and function using standardized methods of assessment (e.g., visual analogue scale [VAS] or questionnaires).

For all types of outcome measures, when deemed feasible, the follow-up period was categorized as short-term

(6–12 months after the surgical intervention), medium-term (13–59 months), or long-term (≥60 months).

2.3 | Information sources and search strategy

Detailed search strategies were modeled for MEDLINE (via PubMed), Embase, and Cochrane Central Register of Controlled Trials (CENTRAL) databases to identify articles published in English language from January 1, 2000 to September 30, 2021, as follows:

#1 gingival recession
#2 mucogingival defect OR mucogingival deformity
#3 keratinized tissue deficiency
#4 (recession NEAR gingiva*) OR (recession NEAR defect*) OR "recession-type defect*"
#5 (exposure NEAR root*) OR (gingiva* NEAR defect*)
#6 denude* NEAR "root surface*"
#7 #1 or #2 or #3 or #4 or #5 OR #6
#8 "connective tissue graft*" OR "connective-tissue graft*"
#9 periodont* AND "plastic surgery"
#10 "soft tissue graft*" OR "soft tissue substitute"
#11 "coronally advanced flap*" OR "laterally positioned flap"
#12 #8 OR #9 OR #10 OR #11
#13 autologous blood-derived products OR platelet-rich plasma OR platelet-rich fibrin OR leukocyte–platelet-rich fibrin OR plasma rich in growth factors OR PRP OR PRF OR L-PRF OR PRGF
#14 platelet-derived growth factor OR PDGF
#15 enamel matrix protein OR EMD
#16 #13 OR #14 OR #15
#17 #7 OR #12
#18 #16 AND #17

The reference lists of all articles reviewed in full-text were searched to identify eligible articles that may have not been previously identified. Additionally, a hand search of articles published from January 1, 2000 to September 30, 2021 in four relevant journals (*Journal of Periodontology, Journal of Clinical Periodontology, Journal of Periodontal Research*, and *International Journal of Periodontics and Restorative Dentistry*) was conducted.

2.4 | Article selection process

Two independent reviewers (L.C. and S.B.) read the title and abstract of the entries obtained from the electronic search and performed the hand search. After completing the initial screening, both reviewers assessed the full-text version of potentially eligible articles and established a final selection. Disagreements between the review authors were resolved by open discussion. If no consensus could be reached, a third author (G.A.) was consulted. Any missing information that could contribute to this systematic review was requested to the corresponding author(s) via email communication.

2.5 | Data extraction

The following data were extracted and recorded in duplicate by two independent reviewers (L.C. and S.B.): 1) citation, publication status, and year of publication; 2) country(ies) and type of setting (e.g., private practice, university, military, or dental hospital); 3) type of procedure: root coverage or gingival augmentation; 4) characteristics of participants (i.e., sample size [initial and final number of participants per arm], sex, and age distribution per arm); 5) characteristics of interventions: test and control groups; 6) methodological quality; 7) outcome measures of interest; 8) main conclusions; and 9) source of funding.

2.6 | Methodological quality and risk of bias assessment

The assessment of methodological quality and risk of bias of each included RCT was performed in duplicate, using version 1 of the Cochrane risk-of-bias tool for RCTs (RoB1).[13] RoB1 individual domains address the following types of bias: 1) sequence generation (selection bias); 2) allocation concealment (selection bias); 3) masking of participants and personnel (performance bias); 4) blinding of outcome assessment (detection bias); 5) incomplete outcome data (attrition bias); 6) selective outcome reporting (reporting bias); and 7) other bias. Risk of bias was categorized as follows:

1. Low risk of bias (plausible bias unlikely to seriously alter the results) if all domains were at low risk of bias;
2. Unclear risk of bias (plausible bias that raises some doubt about the results) if one or more domains were at unclear risk of bias; or
3. High risk of bias (plausible bias that seriously weakens confidence in the results) if ≥1 domains were at high risk of bias.

2.7 | Data synthesis

Data were gathered into evidence tables and displayed according to the type of biologic. A frequentist mixed-modeling approach to network meta-analysis (NMA)[14,15]

was adopted with the aim of statistically comparing the extracted evidence regarding the employed biologic relative to a negative (i.e., treatment with a coronally advanced flap alone) and a positive control group (considering the utilization of an autogenous graft as the gold standard). This was planned for the outcomes of MRC%, CRC%, RD changes in millimeters (computed as measurements of RD after treatment minus baseline measures), KTW gain in millimeters, and gingival thickness (GT) change in millimeters. CRC was estimated as the difference in the percentage of reported "completed coverage" among treatment arms of different trials, and therefore estimated as a continuous variable, despite its binary nature at the individual-site level. Baseline demographics and clinical characteristics of the treated population cohorts in all treatment arms were gathered in a single spread sheet, along with the clinical outcomes and information on design-driven aspects of the studies. To evaluate the transitivity assumption underlying the NMA, the distribution of baseline clinical and reported methodological variables were assessed across treatment trials relative to their impact on the outcomes of interest.[16] Specifically, we looked for vast differences across study arms for variables that could potentially act as effect modifiers relative to the primary outcome of root coverage, such as duration of the study and the reporting of outcomes at different follow-up time points, baseline severity of the treated sites, their location in the oral cavity, recession type, etc. Further details pertaining to this methodological aspect are available as supplementary information (see supplementary Appendix in online *Journal of Periodontology*).

Since the focus of this review was to explore the potential benefit of the adjunctive use of biologics and, thus the immediate results therapies, due to the relative scarcity of data beyond the 1-year time point among treatment arms, as well as for a more homogenized data pool, only results pertaining to the short-term follow-up (including a time range of 6–12 months) were considered for this analysis. For the same reason, study arms exploring other therapies (e.g., guided tissue regeneration for root coverage) or those using combination therapies (i.e., the application of biologics with a carrier or in addition to a scaffold) were also not included. Consequently, only studies that would contribute to the data set with both a control (i.e., a treatment arm that does not involve the use of biologics) and a test group (i.e., involving the use of biologics) were included in the NMA.

The construction of the NMA model involved testing various specifications of random and fixed effects through a series of model structures with the purpose of identifying the model that best explained the data, capturing as much heterogeneity as possible and controlling for confounders. Akaike Information criterion (AIC) was used as evidence for an objective and data-driven approach for selection of the model that best fit the data.[17] The tested random effects included unique intercepts for study, study arm, and time. The considered fixed effects included study arm level aggregates such as mean age, percentage of females, site features (single or multiple GRD), inclusion of smokers, and other study design covariates (accounting for multicenter studies, split- vs. parallel-arm design, etc.). Methodological appraisal of the quality of reports, including the risk of bias assessment (as previously described), along with information on corporate study sponsorship (categorical variables), was also accounted in all models. Interactions between the different variables were tested to explore their effect on the outcomes. Study arms were weighted by their analyzed sample size at the terminal follow-up time point (i.e., the number of treated sites that the aggregate data at that specific time point), and clustered by the treated population (for multiple publications that reported on the same patient population).

The robustness of the relationships between changes in the outcomes of interest and different arms in the final models were tested through sensitivity analyses to detect any vast and meaningful changes in the results. Additional sensitivity analyses included direct pairwise contrasts between the available evidence for the primary outcome MRC (see results in supplementary Appendix in online *Journal of Periodontology*). Linearity assumption was also tested by including quadradic terms to identify any evidence of non-linearity. For all outcomes, the reference category for the initial comparisons was set as treatment with CAF alone (without any addition of a graft or biologic), and contrasts were recorded to quantify differences based on the model estimates (standard errors and *P* values). Confidence intervals (CIs) were produced, and a *P* value threshold of <0.05 was assumed as statistically significant. Statistical analyses were conducted by a review author with experience in performing network meta-analyses and using mixed-models (S.B.), using a software program (RStudio, Version 1.3.959) and the following statistical packages lme4,[18] lmerTest,[19] dplyr,[20] and tidyr.[21] The igraph[22] and ggplot2[23] packages were used for producing the geometry of the network plot to illustrate the existing direct relationships among treatment arms.

Moreover, based on the extracted data and results of the aforementioned analyses, strength of clinical recommendation was established for the treatment of GRD and KTW deficiencies using biologics. These recommendations were set according to a modified version[24–26] of the criteria enclosed in the *American Dental Association (ADA)*

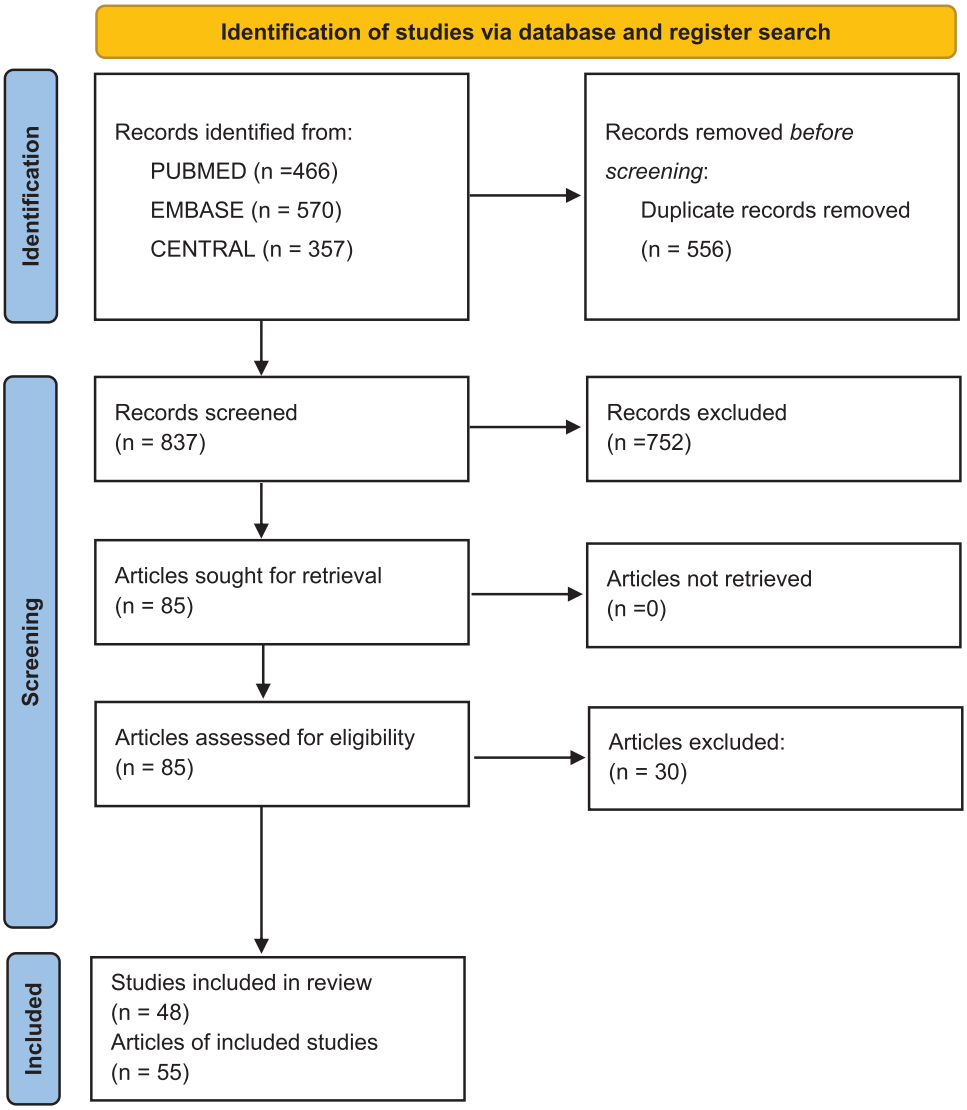

FIGURE 1 PRISMA 2020 search flow diagram

Clinical Practice Guidelines Handbook[27] (see Tables S1–S3 in online *Journal of Periodontology*), as follows:

1. **Clinical comparisons and main findings**: Description of the comparisons (i.e., therapies involving the use of biologics vs. controls) and outcomes of interest, based on the main findings of individual studies and pooled estimates, if available.
2. **Adverse events and complications**: Relevant adverse events and complications.
3. **Net benefit rating (benefit-harm estimation)**: Whether the expected benefits outweigh the potential for harm.
4. **Level of certainty**: Assessment of the extent to which there is confidence in the estimate of the effect of therapy considering the best available evidence. Briefly, this assessment is dictated by the following domains: a) risk of methodological bias; b) applicability of evidence; c) inconsistency or unexplained heterogeneity of results; d) imprecision (e.g., wide confidence intervals); and e) high probability of publication bias (e.g., selective reporting).[28] Level of cenrtainty may be classified as: high, moderate, or low (Tables S1 and S2 in online *Journal of Periodontology*).[24–27]
5. **Strength of clinical recommendation**: This assessment reflects the extent to which one can be confident that adherence to the treatment recommendation will be more beneficial than harmful, considering the strengths and weaknesses of the best available evidence. Strength of clinical recommendation may be classified as: strong, in favor, weak, expert opinion for/supports, expert opinion questions the use, expert opinion against, or against (Table S3 in online *Journal of Periodontology*).[24–27]

3 | RESULTS

3.1 | Description of studies

3.1.1 | Search results

A total of 1393 records were identified after electronic and hand searching (Figure 1). Following the removal of duplicates, 837 records were screened for eligibility, and of them, 752 were excluded based on title and/or abstract. Subsequently, the full text version of 85 articles was assessed.[29–113] Thirty of them did not meet the eligibility criteria.[29–58] The list of excluded articles and reasons for exclusion are reported in Table S4 in the online *Journal of Periodontology*.

3.1.2 | Included studies

A total of 48 trials reported in 55 articles[59–113] were included in this systematic review (Tables 1–3). Of them, 24 provided data for the conduction of network meta-analyses.[59–62,65,70,71,74,77,78,84,87–89,92,94,99,100,102,104,105,107,109,113] All included RCTs pertained to the efficacy of root coverage procedures, as no RCTs on the topic of gingival augmentation involving the use of the biologics of interest for this BEC were identified in our search. The findings of seven studies (i.e., different follow-up periods or clinical vs. patient-reported outcomes) were split into two individual publications (Tables 2 and 3).[63,66,67,80,81,84,85,94–97,104,105] To avoid confusion, these articles were grouped in the tables under a single study name. Eighteen studies were conducted according to a parallel arms design, whereas 30 had a split-mouth design. Most trials were university-based ($n = 43$) and single-center ($n = 45$). Regarding geographic location, trials were conducted in Australia ($n = 1$), Brazil ($n = 5$), Germany ($n = 1$), Greece ($n = 1$), Hungary ($n = 2$), India ($n = 13$), Iran ($n = 1$), Italy ($n = 4$), Mexico ($n = 1$), Poland ($n = 1$), Serbia ($n = 1$),Turkey ($n = 13$), and United States ($n = 4$). The majority of trials ($n = 41$) reported short-term outcomes (6–12 months), while five included medium-term follow-ups (13–59 months),[59,71,74,84,98] and two reported long-term data (≥5 years).[95,97] Of the 48 included RCTs, only four studies were completely or partially supported by companies that manufactured/marketed the products that were used in the trial.[84,85,94–97,108] A total of 1114 participants were treated, of whom 759 presented single GRD in 31 RCTs and 355 received treatment for multiple GRD in 17 RCTs. All trials include information on clinical outcomes (i.e., GR change, CAL change, KTW change, GT change, MRC, and CRC), 17 on PROMs (35.41%),[72,79–81,83,88,89,92–97,98,102,104–106,108,110,111,113] nine on esthetic outcomes (18.75%),[68,78–81,92,93,96,97,102,104,105,110] two on histologic outcomes (4.17%),[70,96] and only one on digital imaging outcomes (2.08%).[102]

3.2 | Methodological quality of included studies

Figure 2 displays the results of the risk of bias assessment. Only four trials were at a low risk of bias.[79–81,98,104,105] Lack of allocation concealment and masking of participants were the most common reasons for classifying studies in the high risk of bias category. Moreover, evidence of selective reporting (i.e., the lack of reporting of mean values of collected outcome measures)[62,68,76,77,93,111] and other sources of bias (i.e., differences between study groups at baseline)[100,102,106] were identified.

3.3 | Pooled estimates, individual study outcomes, and clinical recommendation for root coverage procedures involving biologics

The main findings reported in all included studies (Tables 1–5), as well as the outcomes of the NMA (Table 6) were combined to estimate, assess, and interpret the level of evidence available for root coverage procedures treating single and multiple GRD in function of the treatment approach (i.e., with or without the use of biologics). Relative to the treatment arms, for ABPs, only platelet-rich fibrin (PRF) protocols (i.e., PRF and leucocyte-PRF [L-PRF]) were considered in the NMA. Other modifications or preparations of ABPs (e.g., platelet-rich plasma [PRP], titanium prepared [T]-PRF and concentrated growth factors [CGF]) could not be included due to inadequacy or singularity of the data (T-PRF group only in one study,[111] PRP only in one trial,[83] and CGF in two reports[69,93]). Except for two trials,[79,106] CAF was the only flap type used across all included studies. For that reason, other types of flaps were not included in the NMA.

3.3.1 | Quantitative results of the NMA

Transitivity assessment

In essence, the goal of transitivity assessment is to ensure that all analyzed participants in the NMA, and all the treated sites, could have likely received any of the included treatment groups in the model (whether test or control) and that all patients could have equally been randomized to any treatment/procedure that is being analyzed. For this purpose, we inspected the main design of the

TABLE 1 Characteristics of included studies – ABP

Study	Participants and methods	Interventions	Outcome measures	Notes
Aroca et al.[65]	20 participants, 15 females, 22 to 47 years University-based (Hungary), single center, split-mouth design, multiple GRD, Miller Class I or II, RD NR, 6 months duration	PRF + CAF CAF	GRD reduction, CAL gain, KTW gain, GT gain, MRC, and CRC	Baseline KTW was >2.5 in both groups Baseline GT of 1.1 mm in both groups
Bozkurt Dogan et al.[69]	20 participants, 12 females, 20 to 45 years University-based (Turkey), single center, split-mouth design, multiple GRD, Miller I and II, RD ≥ 2 mm, 6 months duration	CGF + CAF CAF	GRD reduction, CAL gain, KTW gain, GT gain, MRC and CRC	Baseline KTW of 2.5 mm in both groups Baseline GT of 1.10 mm in both groups
Debnath and Chatterjee[73]	20 participants, number of males/females NR, 20 to 50 years University-based (India), single center, split-mouth, single GRD, Miller Class I, RD NR, 6 months duration five participants did not complete the 6 months follow-up	PRF + CAF Periosteum eversion technique + CAF	GRD reduction, CAL gain, KTW gain and MRC	It is described in the text that Miller Class I and II were included, but it is also stated that "individuals with ≥1 mm of width of keratinized gingiva", thus only Class I defects were actually included
Dixit et al.[77]	12 participants, 5 females, 18 to 50 years University-based (India), single center, split-mouth, single GRD, Miller Class I, RD ≥2 mm, 6 months duration	PRF + CAF CAF	GRD reduction, CAL gain, GT gain and MRC	Baseline KTW ≥3 mm in both groups Baseline GT of 0.5 mm in the test group and of 0.57 mm in the control group The authors stated that both Class I and II defects were considered eligible, but only Class I defects were included
Eren and Atilla[78]	University-based (Turkey), single center, split-mouth design, single GRD, Miller I and II GR, RD ≥2 mm, 6 months duration[88] 5 participants did not complete the 6 months follow-up	PRF + CAF SCTG + CAF	GRD reduction, CAL gain, KTW gain, MRC, and CRC	Baseline KTW >2.4 mm in both groups Baseline GT ≥ 0.8 mm
Huang et al.[83]	24 participants, 17 females, 24 to 63 years University-based (USA), single center, parallel design, single GRD, Miller Class I (KTW ≥2 mm), RD ≥2 mm, 6 months durationone participant did not complete the 6 months follow-up	PRP + CAF CAF	GRD reduction, CAL gain, KTW gain, GT gain, MRC, CRC, and PROMs (adverse events)	Baseline KTW of 2.7 mm in both group Baseline GT of 1.1 mm in both groups
Jain et al.[86]	30 participants, 15 females, 18 to 55 years University-based (India), single center, parallel design, single GR, Miller Class I or II, RD NR, 6 months duration	PRF + CAF Amniotic membrane + CAF	GRD reduction, KTW gain and MRC	Baseline KTW was >2.5 mm in both groups

(Continues)

TABLE 1 (Continued)

Study	Participants and methods	Interventions	Outcome measures	Notes
Jankovic et al.[88]	15 participants, 10 females, 19 to 47 years University-based (Serbia), single center, split-mouth design, single GRD, Miller Class I, RD ≥2 mm, 6 months duration	PRF + CAF SCTG + CAF	GRD reduction, CAL gain, KTW gain, MRC, CRC, PROMs (pain/discomfort) and healing index	Baseline KTW >1.3 in both groups
Joshi et al.[89]	15 participants, number of males/females NR, 18 to 40 years University-based (India), single center, split-mouth design, single GRD, Miller Class I, RD NR, 6 months duration	PRF + CAF SCTG + CAF	GRD reduction, CAL gain, KTW gain, MRC and PROMs (pain/discomfort)	Baseline KTW >1.80 in both groups
Keceli et al.[90]	40 participants, 30 females, 18 to 60 years University-based (Turkey), single center, parallel design, single GRD, Miller Class I or II, RD ≥3 mm, 12 months durationfour participants did not complete the 12 months follow-up	PRP + SCTG + CAF SCTG + CAF	MRC and CRC	
Keceli et al.[91]	40 participants, 27 females, 22 to 50 years University-based (Turkey), single center, parallel design, single GRD, Miller Class I or II, RD ≥3 mm, 6 months duration four participants did not complete the 12 months follow-up	PRF + SCTG + CAF SCTG + CAF	GRD reduction, CAL gain, KTW gain, GT gain, MRC and CRC	Baseline KTW >2.5 mm in both groups Baseline GT of 0.85 mm in the test groups and of 0.83 mm in the control group
Kuka et al.[92]	24 participants, 16 females, 21 to 41 years University-based (Turkey), single center, parallel design, multiple GRD, Miller Class I, RD ≥3 mm, 12 months duration	PRF + CAF CAF	GRD reduction, CAL gain, KTW gain, GT gain, MRC, CRC, Esthetics, and PROMs (overall satisfaction)	Baseline KTW was >2.5 in both groups Baseline GT of 0.78 mm in the test group and of 0.73 mm in the control group
Kumar and Murthy[93]	12 participants, number of males/females NR, 18 to 60 years University-based (India), single center, split-mouth design, single GRD, Miller Class I or II, RD ≥2 mm, 12 months duration	PCG + CAF SCTG + CAF	GRD reduction, CAL gain, KTW gain, MRC, esthetics and PROMs (pain/discomfort)	Data on baseline KTW not reported
Padma et al.[100]	15 participants, number of males/females NR, 18 to 35 years University-based (India), single center, split-mouth design, single GRD, Miller Class I or II, RD NR, 6 months duration	PRF + CAF CAF	GRD reduction, CAL gain, KTW gain, MRC and CRC	Baseline KTW ≥2.4 mm in both groups

(Continues)

TABLE 1 (Continued)

Study	Participants and methods	Interventions	Outcome measures	Notes
Potey et al.[102]	20 participants, 16 females, 22 to 47 years University-based (India), single center, parallel design, multiple GRD, Miller Class I, RD NR, 6 months duration	PRF + CAF CAF	GRD reduction, CAL gain, KTW gain, MRC, CRC, esthetics, PROMs (overall satisfaction, pain/discomfort and esthetics) and digital imaging outcomes (linear and volumetric)	The authors reported that both MillerClass I or II GR were included, but theinclusion criteria clearly states that GR must present "with ≥1 mm of attached gingiva" Baseline KTW was ≥2.5 in both groups
Subbareddy et al.[106]	20 participants, 7 females, 18 to 60 years University-based (India), single center, parallel design, multiple GRD, Miller Class I or II, RD NR, 6 months duration	PRF + CATF SCTG + CATF	GRD reduction, CAL gain, KTW gain, GT gain, MRC, CRC and PROMs (overall satisfaction, pain/discomfort and esthetics) GRD, CAL, KTW, and GT Baseline mean values were statistically different between groups	Baseline KTW was ≥2 mm in both groups
Thamaraiselvan et al.[107]	20 participants, 2 females, 21 to 47 years University-based (India), single center, parallel design, single GRD, Miller Class I or II, RD NR, 6 months duration	PRF + CAF CAF	GRD reduction, CAL gain, KTW gain, GT gain, MRC, and CRC	Baseline KTW ≥2.3 mm in both groups Baseline GT of 0.9 mm in both groups
Tunali et al.[109]	10 participants, 6 females, 25 to 52 years University-based (Turkey), single center, split-mouth, multiple GRD, Miller Class I or II, RD ≥ 3 mm, 12 months duration	L-PRF + CAF SCTG + CAF	GRD reduction, CAL gain, KTW gain, MRC and CRC	Baseline KTW was >2 mm in both groups
Ucak et al.[110]	72 participants, number of males/females NR, 19 to 58 years University-based (Turkey), single center, parallel design, single GRD, Miller Class I or II, RD ≥3 mm, 6 months durationseven participants did not comply with control visits	I-PRF + SCTG + CAF SCTG + CAF	GRD reduction, CAL gain, KTW gain, GT gain, MRC, CRC, Esthetics and PROMs (pain/discomfort, adverse events and esthetics)	Baseline KTW of 2.0 mm in both groups Baseline GT of 0.8 mm in the test group and of 0.9 mm in the control group
Uzun et al.[111]	34 participants, 19 females, 25 to 69 years University-based (Turkey), single center, parallel design, multiple GRD, Miller Class I or II, RD NR, 12 months duration	T-PRF + CAF SCTG + CAF	GRD reduction, CAL gain, KTW gain, GT gain, MRC, CRC, PROMs (pain/discomfort) and healing scores	Baseline KTW >2.8 mm in both groups Baseline GT of 1.21 mm in the test group and of 1.32 mm in the control group One of the authors holds intellectual property related to T-PRF.
Çetiner et al.[112]	12 participants, 4 females, 20 to 67 years University-based (Turkey), single center, split-mouth, multiple GRD, Miller Class I or II, RD ≥3 mm, 12 months duration	PRP + ADMG + CAF ADMG + CAF	GRD reduction, CAL gain, KTW gain, MRC and CRC	Baseline KTW of 1.2 mm in both groups

(Continues)

TABLE 1 (Continued)

Study	Participants and methods	Interventions	Outcome measures	Notes
Öncü[113]	20 participants, 11 females, 20 to 60 years University-based (Turkey), single center, split-mouth, multiple GRD, Miller Class I or II, RD ≥3 mm, 6 months duration	PRF + CAF SCTG + CAF	GRD reduction, CAL gain, KTW gain, GT gain, MRC, CRC and PROMs (pain/discomfort)	Baseline KTW was >2.6 mm in both groups Baseline GT of 0.7 mm in the test group and of 0.85 mm in the control group

ADMG, acellular dermal matrix graft; C, control; CAF, coronally advanced flap; CATF, coronally advanced tunnel flap; CAL, clinical attachment level; CMb, collagen membrane; CRC, complete root coverage; EMD, enamel matrix derivative; GT, gingival thickness; GR, gingival recession; KTW, keratinized tissue width; MRC, mean root coverage; NR, not reported; PROMs, patient-reported outcomes; RD, recession depth; sCAF, semilunar coronally advanced flap; SCTG, subepithelial connective tissue graft; T, test; XCM, xenogeneic collagen membrane.

included RCTs, as well as the distribution of variables before treatment that could act as effect modifiers (those which we assumed, based on previous evidence, would have an impact on the primary outcome of individual RCTs, as well as the outcomes of this review). For more details, see supplementary Appendix in the online *Journal of Periodontology*.

In summary, our inspection revealed that there were no vast differences among the included treatment arms relative to study duration, baseline defect characteristics, and jaw location. All recession types reported were RT1 defects. We also did not notice a major variability in sex or age distribution. Therefore, the results of our assessment indicate that there were no clear violations of the transitivity assumption across comparisons.

Results of the mixed-model NMA

Figure 3 displays the generated network plot illustrating the existing comparisons among treatment arms of included RCTs. A total of 46 eligible treatment arms from 24 trials were included in the NMA.[59–62,65,70,71,74,77,78,84,87–89,92,94,99,100,102,104,105,107,109,113] These arms consisted of treatment with CAF alone (n = 13),[65,70,71,74,77,84,87,92,99,100,102,104,105,107] EMDs + CAF (n = 12),[59–62,70,71,74,84,87,94,99,104,105] PRF + CAF (n = 11),[65,77,78,88,89,92,100,102,107,109,113] and SCTG + CAF (n = 10).[59–62,78,88,89,94,109,113] Due to insufficient data among treatment arms regarding GT, its assessment through the NMA was not feasible. NMA estimates for MRC%, CRC%, RD, and KT changes are reported in the following sections (Table 6). Further details on the selection of the final model for the NMA based on AIC results are available as supplementary information (see online *Journal of Periodontology*).

MRC%

Based on the final model for the outcome of mean root coverage, with CAF as the reference group, only SCTG + CAF was associated with a statistically significant higher estimate (13.41%, 95% CI [8.06 to 18.75], $P < 0.01$), while EMD + CAF (6.68%, 95% CI [−0.03 to 13.4], $P = 0.061$), and PRF + CAF (1.03%, 95% CI [−5.65, 7.72], $P = 0.71$) failed to show statistically significant differences compared with CAF alone, and with each other, as noted by changing the reference arm in the model (estimate of –5.64%, 95% CI [−13.86 to 2.56], $P = 0.17$) for PRF + CAF, with EMD + CAF as reference category).

CRC%

With CAF as the reference group, like MRC%, only SCTG + CAF (14.41%, 95% CI [4.21 to 24.61], $P < 0.01$) led to a significantly higher CRC%. Treatment arms EMD + CAF (13.48%, 95% CI [−3.34 to 30.32], $P = 0.11$) and PRF + CAF (–0.91%, 95% CI [−15.38 to 13.57], $P = 0.81$) did not show significant differences compared with CAF alone, or with each other as shown by a model estimate of −14.39%, 95% CI [−34.55 to 5.76], $P = 0.16$) with EMD + CAF as reference.

RD changes

Relative to CAF as the reference category, it was observed that treatment with SCTG + CAF led to a statistically significant higher RD reduction (–0.39 mm, 95% CI [−0.55 to −0.22], $P < 0.01$), while EMD + CAF (–0.13 mm, 95% CI [−0.29 to 0.01], $P = 0.08$) and PRF + CAF (–0.06 mm, 95% CI [−0.23 to 0.09], $P = 0.39$) failed to show significant differences compared with CAF and with each other as shown by a model estimate of 0.07 mm (95% CI [−0.11 to 0.24], $P = 0.43$) with EMD + CAF as reference. The model also revealed that RD at baseline had a significant effect on the results (0.18 mm, 95% CI [0.05 to 0.31], $P < 0.01$) suggesting that greater reduction at the follow-up time points was observed in sites with higher RD at baseline.

KTW gain

Compared with CAF as the reference category, only SCTG + CAF was associated with a statistically significant higher gain of KTW (0.71 mm, 95% CI [0.48 to 0.93], $P < 0.01$). The treatment groups of EMD + CAF (0.24 mm, 95% CI [−0.02 to 0.51], $P = 0.08$), and PRF + CAF (0.08 mm, 95% CI [−0.23 to 0.41], $P = 0.58$) did not provide significant

TABLE 2 Characteristics of included studies – EMD

Study	Participants and methods	Interventions	Outcome measures	Notes
Abolfazli et al.[59]	12 participants, 8 females, 28 to 51 years Practice-based (Iran), single center, split-mouth design, single GRD, Miller Class I, RD ≥3 mm, 24 months duration	EMD + CAF SCTG + CAF	GRD reduction, CAL gain, KTW gain, MRC, and CRC	Baseline KTW >2.5 mm in both groups
Alexiou et al.[60]	12 participants, 6 females, 23 to 60 years University-based (Greece), single center, split-mouth design, multiple GRD, Miller Class I, RD ≥2 mm, 6 months duration	EMD + CAF SCTG + CAF	GRD reduction, CAL gain, KTW gain, MRC, and CRC	Baseline KTW ≥2.3 mm in both groups Baseline RD of 2.15 (T) and 2.25 mm (C) The authors stated that both Class I and II were included, but they also stated that "situations where no keratinized tissue apical to the recession defect was detected were also excluded from the study," Thus, only Class I defects were included.
Alkan and Parlar[61]	12 participants, 7 females, 23 to 42 years University-based (Turkey), single center, split-mouth design, single GRD, Miller Class I, RD ≥2 mm, 12 months duration	EMD + CAF SCTG + CAF	GRD reduction, CAL gain, KTW gain, MRC, and CRC	Baseline KTW >2.1 in both groups Baseline GT of 1.0 mm in both groups (measured only at baseline)
Alkan and Parlar[62]	12 participants, 6 females, 35 to 53 years University-based (Turkey), single center, split-mouth design, single GRD, Miller Class I or II, RD ≥2 mm, 12 months duration	EMD + CAF SCTG + CAF	GRD reduction, CAL gain, KTW gain, MRC, and CRC	Baseline KTW of 1.6 mm in both groups Baseline RD of 3.54 (T) and 3.29 mm (C)
Alves et al./Costa et al.[63,64]	20 participants, 12 females, 30 to 50 years University-based (Brazil), single center, split-mouth design,single GRD, Miller Class I or II, RD ≥3 mm, 12 months duration Only heavy smokers (10 or more cigarettes/day over 5 years) were included 1 participant was lost on follow-up and did not return for clinical evaluation at 6 months.	EMD + ADMG + CAF ADMG + CAF	GRD reduction, CAL gain, KTW gain, GT gain, MRC, and CRC	Baseline KTW of 3.5 mm in both groups Baseline GT of 1.0 mm in both groups
Aroca et al.[66,67]	20 participants, number of males/females NR, mean age 31.7 years University-based (Hungary), single center, split-mouth design, multiple GRD, Miller Class III, RD ≥2 mm, 12 months duration	EMD + SCTG + CATF SCTG + CATF	GRD reduction, CAL gain, KTW gain, MRC, and CRC	Baseline KTW ≥2.5 mm in both groups

(Continues)

TABLE 2 (Continued)

Study	Participants and methods	Interventions	Outcome measures	Notes
Aydinyurt et al.[68]	19 participants, 10 females, 18 to 55 years University-based (Turkey), single center, split-mouth design, single GRD, Miller Class I or II, RD ≥2 mm, 12 months duration	EMD + SCTG + CAF SCTG + CAF	GRD reduction, CAL gain, KTW gain, MRC, CRC, and esthetics	Baseline KTW not reported in the study
Castellanos et al.[70]	22 participants, 13 females, 28 to 71 years University-based (Mexico), single center, parallel design, single GRD, Miller Class I or II, RD ≥2 mm, 12 months duration	EMD + CAF CAF	GRD reduction, CAL gain, KTW gain, MRC, CRC, and histologic outcomes	Baseline KTW ≥3.3 in both groups
Cordaro et al.[71]	10 participants, number of males/females NR, 19 to 60 years University-based (Italy), single center, split-mouth design,multiple GRD, Miller Class I or II, RD ≥2 mm, 24 months duration	EMD + CAF CAF	GRD reduction, CAL gain, KTW gain, MRC, and CRC	Baseline KTW of 2.7 in both groups
Del Pizzo et al.[74]	15 participants, 11 females, 18 to 56 years University-based (Italy), single center, split-mouth design,single GRD, Miller Class I or II, RD ≥3 mm, 24 months duration	EMD + CAF CAF	GRD reduction, CAL gain, KTW gain, MRC, and CRC	Baseline KTW ≥1.5 mm in both groups
Dias et al.[76]	16 participants, 9 females, mean age 42.7 years University-based (Brazil), single center, split-mouth design,single GRD, RT1, RD NR, 6 months duration	EMD + SCTG + CAF SCTG + CAF	GRD reduction, CAL gain, KTW gain, MRC, and CRC	Baseline KTW of 3.6 mm in test and of 2.6 mm in control groups (median values… means not reported)
França-Grohmann et al.[79]	30 participants, 22 females, 23 to 45 years University-based (Brazil), single center, parallel design, single GRD, Miller Class I, RD ≥2 mm or ≤4 mm), 12 months duration	EMD + sCAF sCAF	GRD reduction, CAL gain, KT gain, GT gain, MRC, CRC, esthetics and PROMs (esthetics and function)	Baseline KTW >3.2 mm in both groups Baseline GT of 1.1 mm in both groups
Górski et al.[80,81]	20 participants, 13 females, 21 to 38 years University-based (Poland), single center, split-mouth design, multiple GRD, RT1 or RT2 (Millers Class I, II or II), RD ≥1 mm, 12 months duration Two participants were lost to follow-up between 6 and 12 months	EMD + SCTG + CAF SCTG + CAF	GRD reduction, CAL gain, KTW gain, GT gain, MRC, CRC, esthetics, PROMs (pain/discomfort, adverse events and esthetics)	Baseline KTW ≥ 2.5 mm in both groups Baseline GT of 1.1 6 and 1.18 in test and control groups, respectively Data of GR with and without interproximal tissue loss were combined in the same analyses
Henriques et al.[82]	12 participants, 9 females, 35 to 52 years Practice-based (Brazil), single center, split-mouth design,single GRD, Miller Class III, RD ≥2 mm, 12 months duration	EMD + SCTG + CAF SCTG + CAF	GRD reduction, CAL gain, KTW gain, MRC, and CRC	Baseline KTW ≥3 mm in both groups

(Continues)

TABLE 2 (Continued)

Study	Participants and methods	Interventions	Outcome measures	Notes
Hägewald et al./Spahr et al.[84,85]	37 participants, 17 females, 22 to 62 years University-based (Germany), multicenter, split-mouth design,single GRD, Miller Class I or II, RD ≥3 mm, 24 months duration 1 participant was lost in 6 and 12 months follow-ups7 participants did not complete the 2-year follow-up	EMD + CAF Placebo (propylene glycol alginate) + CAF	GRD reduction, CAL gain, KTW gain, MRC, and CRC	Baseline KTW >2.0 mm in both groups Supported by BIORA AB (which was acquired by Straumann)
Jaiswal et al.[87]	20 participants, 8 females, 25 to 46 years University-based (India), single center, parallel design, multiple GRD, Miler Class I or II, RD ≥ 3 mm, 6 months duration	EMD + CAF CAF	GRD reduction, CAL gain, KTW gain, MRC and CRC	Baseline KTW >3.2 mm in both groups, thus not only Class II defects were included (as reported in the paper) It is reported in the study that only Class II defects were included, but baseline KTW and figures clearly indicates that Class I were also included
McGuire and Nunn/McGuire et al.[94,95]	20 participants, 10 females, 23 to 62 years Practice-based (USA), single center, split-mouth design,single GRD, Miller Class II, RD ≥4 mm, 12 months duration 1 participant did not return for the 6-month visit, 3 participants for the 12-month visit, and 11 participants for the 10-year follow-up	EMD + CAF SCTG + CAF	GRD reduction, CAL gain, KTW gain, MRC, CRC and PROMS (overall satisfaction and function)	Baseline KTW ≥2.4 mm in both groups Supported by BIORA AB (which was acquired by Straumann)
Mercado et al.[98]	42 participants, 70% females, mean age 43 years Practice-based (Australia), single center, parallel design, multiple GRD, Miller Class III and IV (lower anterior teeth only), RD NR, 36 months duration 1 participant was lost to follow-up	EMD + SCTG + CAF SCTG + CAF	GRD reduction, CAL gain, KTW gain, MRC, CRC, and PROMs (pain/discomfort)	Baseline KTW ≥1.5 mm in both groups (Class III GR) Baseline KTW >1.1 mm in both groups (Class IV GR)
Modica et al.[99]	12 participants, 5 females, 20 to 50 years University-based (Italy), single center, split-mouth design,single GRD, Miller Class I or II, RD NR, 6 months duration	EMD + CAF CAF	GRD reduction, CAL gain, KTW gain, MRC, and CRC	Baseline KTW of 1.36 mm in control group and 1.71 mm in test group
Pourabbas et al.[101]	15 participants, 8 females, 26 to 63 years University-based (India), single center, split-mouth design,single GRD, Miller Class I or II, RD ≥2.0 mm, 6 months duration	EMD + ADMG + CAF ADMG + CAF	GRD reduction, CAL gain, KTW gain, MRC, and CRC	Baseline KTW >2.0 mm in both groups

(Continues)

TABLE 2 (Continued)

Study	Participants and methods	Interventions	Outcome measures	Notes
Rasperini et al.[103]	56 participants, 39 females, mean age 35.5 years University-based (Italy), multicenter, parallel design, single GRD, Miller Class I or II, RD ≥3 mm, 12 months duration	EMD + SCTG + CAF SCTG + CAF	GRD reduction, CAL gain, KTW gain, MRC, and CRC	Baseline KTW values were statistically different between groups (0.5/1.4 mm)
Sangiorgio et al./Rocha Dos Santos et al.[104,105]	51 participants, number of males/females NR (for the 3 included groups), 18 to 60 years University-based (Brazil), multicenter, parallel design,single GRD, Miller Class I or II, RD ≥3 mm, 6 months duration This study included 4 treatment arms, but only three were eligible for inclusion in this review	EMD + CAF EMD + XCM + CAF CAF	GRD reduction, CAL gain, KTW gain, GT gain, MRC, CRC, esthetics, and PROMs (overall satisfaction and function)	Baseline KTW ≥2.3 mm in the three groups Baseline GT of 0.9 mm in the three groups This study included another group, but these data were not of interest for this review
Trabulsi et al.[108]	26 participants, 14 females, 20 to 65 years. University-based (USA), single center, parallel design,single GRD, Miller Class I or II, RD ≥2.5 mm, 6 months duration	EMD + CMb + CAF CMb + CAF	GRD reduction, CAL gain, KTW gain, GT gain, MRC, and CRC	Baseline KTW ≥3.3 mm in both groups Baseline GT of 1.00 mm in the test and of 1.1 mm in the control group EMD and membranes were donated by their manufacturers

changes with respect to CAF alone, or with each other as shown by a model estimate of −0.15 mm (95% CI [−0.54 to 0.22], $P = 0.41$) for PRF + CAF compared with EMD + CAF.

3.3.2 | Individual study outcomes and clinical recommendations

The summaries of evidence and strength of clinical recommendation for therapeutic use of ABP, EMD, and rhPDGF-BB of procedures are outlined below:

ABP

Clinical comparisons and main findings: Twenty-two RCTs involved the clinical application of ABPs (Table 1), with a follow-up ranging from 6 to 12 months. Twelve studies had a split-mouth design and 10 a parallel design. Single GRD (342 participants) were treated in 13 studies and multiple GRD (180 participants) in nine trials:

1. Concentrated growth factors (CGF) – multiple GRD (one RCT): *CGF + CAF vs. CAF*;[69]
2. Injectable platelet-rich fibrin (i-PRF) – single GRD (one RCT): *i-PRF + SCTG + CAF vs. SCTG + CAF*;[110]
3. Platelet-concentrated graft (PCG) – single GRD (one RCT): *PCG + CAF vs. SCTG + CAF*;[93]
4. Platelet-rich fibrin (PRF) – single GRD (nine RCTs): *PRF + CAF vs. Amniotic membrane + CAF* (one RCT);[86] *PRF + CAF vs. CAF* (three RCTs);[77,100,107] *PRF + CAF vs. Periosteum eversion + CAF* (one RCT);[73] *PRF + CAF vs. SCTG + CAF* (three RCTs);[78,88,89] and *PRF + SCTG + CAF vs. SCTG + CAF* (one RCT).[91]
5. Platelet-rich fibrin (PRF) – multiple GRD (six RCTs): *PRF + CAF vs. CAF* (three RCTs);[65,92,102] and *PRF + CAF vs. SCTG + CAF* (three RCTs).[106,109,113]
6. Platelet-rich plasma (PRP) – single GRD (2 articles): *PRP + CAF vs. CAF* (one RCT);[83] and *PRP + SCTG + CAF vs. SCTG + CAF* (one RCT).[90]
7. Platelet-rich plasma (PRP) – multiple GRD (one RCT): *PRP + ADMG + CAF vs. ADMG + CAF*.[112]
8. Titanium platelet-rich fibrin (t-PRF) – multiple GRD (one RCT): *t-PRF + CAF vs. SCTG + CAF*.[111]

Overall, outcomes reported in individual studies showed that all ABPs led to significant improvements in RD and CAL compared with baseline (Table S5 in online *Journal of Periodontology*), but the majority of trials failed to demonstrate superiority in terms of RD reduction, CAL and KTW gain when compared with CAF and SCTG + CAF. In fact,

TABLE 3 Characteristics of included studies – PDGF

Study	Participants and methods	Interventions	Outcome measures	Notes
Dandu and Murthy[72]	15 participants, 5 females, mean age 36.13 years University-based (India), single center, split-mouth design, multiple GRD, Miller Class I or II, RD ≥2 mm, 9 months duration	PDGF + CMb + CATF Periosteal pedicle graft + CATF	GRD reduction, CAL gain, KTW gain, and MRC	Baseline KTW >2.5 mm in both groups
Deshpande et al.[75]	36 participants, number of males/females NR, 19 to 39 years University-based (India), single center, parallel design, multiple GRD, Miller Class I or II, RD ≥2 mm, 6 months duration	PDGF + B-TCP + CAF SCTG + CAF CAF	GRD reduction, CAL gain, KTW gain, MRC, and CRC	Baseline KTW ≥2.3 mm in all groups
McGuire et al.[96,97]	30 participants, 26 females, 18 to 70 years Practice-based (USA), single center, split-mouth design, single GRD, Miller Class II, RD ≥3 mm, 5 years duration 10 participants were lost to follow-up and did not returnfor clinical evaluation at 5 years	PDGF + B-TCP + CAF SCTG + CAF	GRD reduction, CAL gain, KTW gain, MRC, CRC, Esthetics, histologic outcomes, PROMs (overall satisfaction, pain/discomfort, adverse events, esthetics and function)	Baseline KTW of 1.9 mm in both groups Supported by Osteohealth

B-TCP, beta tricalcium phosphate; CAF, coronally advanced flap; CATF, coronally advanced tunnel flap; CAL, clinical attachment level; CMb, collagen membrane; CRC, complete root coverage; GRD, gingival recession defect; KTW, keratinized tissue width; MRC, mean root coverage; NR, not reported; PDGF, platelet-derived growth factor; PROMs, patient-reported outcomes; RD, recession depth; SCTG, subepithelial connective tissue graft.

ABPs displayed similar (vs. CAF alone) or inferior (vs. CAF + SCTG) outcomes compared with other interventions. Compared with CAF alone, two trials showed that ABPs promoted significant KTW gain,[69,100] three studies showed that ABP led to superior GT,[69,77,92] and only one trial showed that ABPs led to superior RD reduction.[100] Notably, most studies ($n = 15$, 68.18%) reported mean values of baseline KTW ≥2 mm.

Adverse events and complications: Some degree of pain may occur within the first days following the surgical procedure, but it seems to be mainly related to flap preparation. The use of ABPs did not lead to the occurrence of adverse events or complications in the treated sites. Within studies reporting on PROMs (Table 6), PRF did not show superiority compared with CAF alone. Although PRF protocols were associated with statistically significant less discomfort and improved wound healing up to 1-week follow-up, these PROMs did not correlate with different final RC outcomes.

Net benefit rating (benefit-harm estimation) compared with other RC procedures: Outcomes reported in individual studies suggest that the marginal to modest additional clinical benefits provided by the use of ABPs, mainly PRF, when used in conjunction with CAF outweigh potential for harm. PRF may promote some additional clinical benefits, KTW and GT gain, compared with CAF alone. However, there was evidence of inconsistency of findings and plausible methodological bias across individual studies (i.e., selective reporting and differences in baseline mean values between test and control groups).[77,100] Pooled estimates derived from the NMA showed that PRF + CAF was not superior to SCTG + CAF, EMD + CAF, or CAF alone in terms of CRC%, MRC%, and KTW gain, and RD reduction. The limited sample size of some studies precludes the formal assessment of specific types of ABPs (CGF, PCG, and PRP) for RC. Also, none of the studies reported information on treatment costs.

1. **Level of certainty**: Low (CGF + CAF, PCG + CAF, or PRP + CAF) to moderate (CAF + PRF protocols).
2. **Strength of clinical recommendations of ABPs for the treatment of GRDs**: 1) CGF + CAF, PCG + CAF, or PRP + CAF – Expert opinion questions the use (evidence is lacking and the level of certainty is low, thus expert opinion questions implementing the routine use of these ABPs for RC); 2) PRF protocols + CAF – In favor (evidence supports its use).

FIGURE 2 Risk of bias assessment summary

EMD

Clinical comparisons and main findings: Twenty-three RCTs involved the clinical application of EMD, with a follow-up ranging from 6 months to 10 years. Seven studies had a split-mouth design and 16 had a parallel arms design. Single GRD (387 participants) were treated in 17 trials and multiple GRD (124 participants) were managed in six studies:

1. EMD – single GRD (15 RCTs reported in 19 articles): *EMD + ADMG + CAF vs. ADMG + CAF* (one RCT/two articles);[63,64] *EMD + ADMG + CAF vs. ADMG + CAF* (one RCT);[101] *EMD + CAF vs. CAF* (four RCTs/six articles);[74,84,85,99,104,105] *EMD + semilunar CAF vs. semilunar CAF* (one RCT);[79] *EMD + CAF vs. SCTG + CAF* (three RCTs/four articles);[59,61,94,95] *EMD + Collagen membrane (CM) + CAF vs. CM + CAF* (one RCT);[108] and *EMD + SCTG + CAF vs. SCTG + CAF* (four RCTs).[68,76,82,103]
2. EMD – multiple GRD (8 RCTs reported in 10 articles): *EMD + CAF vs. + CAF* (three RCTs);[70,71,87] *EMD + CAF vs. SCTG + CAF* (two RCTs);[60,62] and *EMD + SCTG + CAF vs. SCTG + CAF* (three RCTs/five articles).[66,67,80,81,98]

Similar to ABP, results reported in individual studies suggest that EMD + CAF promoted statistically significant RD reduction and CAL gain compared with baseline values (Table S6 in online *Journal of Periodontology*). However, the use of EMD + CAF was inferior to SCTG + CAF in terms of KTW gain,[59,60,94,95] and equivalent to CAF in terms of RD, CAL, and KTW changes. Evidence suggests that the adjunctive use of EMD to different RC modalities (i.e., SCTG + CAF, xenogeneic collagen matrix (XCM) + CAF and ADMG + CAF) may promote statistically significant improvements in RD reduction[63,64,76,82,104,105] and CAL gain,[80–82] as well as improved MRC% and CRC%.[68,76,82,103] It should be noted that 73.91% (n = 17) of the studies reported mean values of baseline KTW ≥2 mm. Interestingly, histologic evaluation of a tooth extracted with attached buccal gingiva 12 months after RC via EMD + CAF showed that the junctional epithelium ended at a level coronal to the original depth of the treated GRD, as well as partial regeneration of periodontal structures.[70]

Adverse events and complications: Some degree of pain/discomfort may occur within the first days following the surgical procedure, but it is mainly related to flap preparation. However, the occurrence of adverse events or complications associated to EMD were not reported. Regarding PROMs (Table 5), EMD seems to reduce early postoperative discomfort in sites treated with SCTG + CAF,[98] as well as enhance patient's esthetic perception at 6 months.[80,81]

Net benefit rating (benefit-harm estimation) compared with other RC procedures: Outcomes reported in individual studies suggest that the modest clinical benefits associated with the use of EMD in combination with

TABLE 4 Root coverage outcomes (i.e., mean root coverage [MRC%] and complete root coverage [CRC%])

Study	Interventions	MRC% (test/control)	CRC% (test/control)
ABP			
Aroca et al.[65]	PRF + CAF/CAF	6 months (80.7/91.5)	6 months (52.23/74.62)
Bozkurt Dogan et al.[69]	CGF + CAF/CAF	6 months (86.67/82.02)	6 months (45.8/56.7)
Debnath and Chatterjee[73]	PRF + CAF/Periosteum eversion technique + CAF	6 months (75.01/61.1)	NR
Dixit et al.[77]	PRF + CAF/CAF	6 months (82.87/79.50)	NR
Eren and Atilla[78]	PRF + CAF/SCTG + CAF	6 months (92.7/94.2)	6 months (72.7/77.3)
Huang et al.[83]	PRP + CAF/CAF	6 months (81.0/83.5)	6 months (63.6/58.3)
Jain et al.[86]	PRF + CAF/Amniotic membrane + CAF	6 months (48.77/64.28)	6 months (NR)
Jankovic et al.[88]	PRF + CAF/SCTG + CAF	6 months (88.68/91.96)	6 months (75.85/79.56)
Joshi et al.[89]	PRF + CAF/SCTG + CAF	6 months (70.64/93.33)	NR
Keceli et al.[90]	PRP + SCTG + CAF/SCTG + CAF	6 months (88.1/86.4) 12 months (86.4/86.4)	6 months (35/35) 12 months (35.3/42.1)
Keceli et al.[91]	PRF + SCTG + CAF/SCTG + CAF	6 months (89.6*/79.9)	6 months (55/35)
Kuka et al.[92]	PRF + CAF/CAF	12 months (88.36/74.63)	12 months (52/33)
Kumar and Murthy[93]	PCG + CAF/SCTG + CAF	6 months (86.0/85.0) 12 months (77.0/83.0)	NR
Padma et al.[100]	PRF + CAF/CAF	6 months (100/68.4)	6 months (100/NR)
Potey et al.[102]	PRF + CAF/CAF	6 months (95.68/93.17)	6 months (82.66/78.66)
Subbareddy et al.[106]	PRF + CATF/SCTG + CATF	Data were not reported because baseline RD mean values were statistically different between groups	Data were not reported because baseline RD mean values were statistically different between groups
Thamaraiselvan et al.[107]	PRF + CAF/CAF	6 months (74.16/65.0)	6 months (50/50)
Tunali et al.[109]	L-PRF + CAF/SCTG + CAF	6 months (74.61/74.13) 12 months (76.63/77.36)	6 months (18.2/9.1) 12 months (13.6/18.2)
Ucak et al.[110]	I-PRF + SCTG + CAF/SCTG + CAF	6 months (97.1/94.6)	6 months (88.2/80.6)
Uzun et al.[111]	T-PRF + CAF/SCTG + CAF	6 months (91.06/92.04) 12 months (99.29/93.22)	6 months (NR/NR) 12 months (76.57/72.54)
Çetiner et al.[112]	PRP + ADMG + CAF/ADMG + CAF	6 months (80.9/75.5) 12 months (77.9*/69.4)	NR
Öncü[113]	PRF + CAF/SCTG + CAF	6 months (77.1/84*)	6 months (50/60)
EMD			
Abolfazli et al.[59]	EMD + CAF/SCTG + CAF	12 months (77.7/83.4) 24 months (76.9/93.1)	12 months (NR) 24 months (25.0/66.6)
Alexiou et al.[60]	EMD + CAF/SCTG + CAF	6 months (81.7/79.7)	6 months (63/55.6)
Alkan and Parlar[61]	EMD + CAF/SCTG + CAF	6 months (91.0/89.0) 12 months (92.0/89.0)	6 months (NR) 12 months (75.0/58.3)
Alkan and Parlar[62]	EMD + CAF/SCTG + CAF	6 months (82.77/90.27) 12 months (85.87/92.4)	NR
Alves et al./Costa et al.[63,64]	ADMG + EMD + CAF/ADMG + CAF	6 months (55.4/44.0) 12 months (59.7/52.8)	6 months (15.8/5.3) 12 months (15.8/5.3)

(Continues)

TABLE 4 (Continued)

Study	Interventions	MRC% (test/control)	CRC% (test/control)
Aroca et al.[66,67]	EMD + SCTG + CATF/SCTG + CATF	6 months (NR) 12 months (82/83)	6 months (NR) 12 months (40.0/40.0) Site-based analysis (i.e., all GR contained in a site should have displayed CRC)
Aydinyurt et al.[68]	EMD + SCTG + CAF/SCTG + CAF	12 months (65.72/52.72)	12 months (68.0/52.0)
Castellanos et al.[70]	EMD + CAF/CAF	12 months (86.6/62.2)	12 months (54.4/36.3)
Cordaro et al.[71]	EMD + CAF/CAF	6 months (82.8/80.7) 24 months (74.8/71.0)	6 months (44.83/31.03) 24 months (17.24/24.14)
Del Pizzo et al.[74]	EMD + CAF/CAF	6 months (94.0/93.9) 12 months (93.67/88.33) 24 months (90.67/86.67)	6 months (73.33/73.33) 12 months (80.0/66.67) 24 months (77.33/60.0)
Dias et al.[76]	EMD + SCTG + CAF/SCTG + CAF	6 months (86/66)	6 months (75.0/43.8)
França-Grohmann et al.[79]	EMD + sCAF/sCAF	6 months (91.06/87.38) 12 months (90.86/79.76)	6 months (66.7/60.0) 12 months (66.7/33.3)
Górski et al.[80,81]	EMD + SCTG + CAF/SCTG + CAF	6 months (87.49/90.93) 12 months (95.0/91.0)	6 months (86.7/85.3) 12 months (90.0/86.0)
Henriques et al.[82]	EMD + SCTG + CAF/SCTG + CAF	6 months (60.88/52.23) 12 months (70.0/54.8)	NR
Hägewald et al./Spahr et al.[84,85]	EMD + CAF/Placebo + CAF	6 months (80.0/79.0) 12 months (80.0/79.0) 24 months (84.0/67.0)	6 months (NR) 12 months (NR) 24 months (53.0/23.0)
Jaiswal et al.[87]	EMD + CAF/CAF	6 months (86.3/79.56)	NR
McGuire and Nunn/McGuire et al.[94,95]	EMD + CAF/SCTG + CAF	6 months (NR) 12 months (95.1/93.8) 10 years (89.8/83.3)	6 months (NR) 12 months (89.5/79.0) 10 years (77.8/55.6)
Mercado et al.[98]	EMD + SCTG + CAF/SCTG + CAT	12 months Class III (72.92/77.57) Class IV (64.76/64.96) 24 months Class III (69.37/70.37) Class IV (60.58/65.86) 36 months Class III (69.85/59.29) Class IV (61.60/52.08) Tooth-level analysis	12 months Class III (22.22/18.46) Class IV (0/0) 24 months Class III (17.45/12.30) Class IV (0/0) 36 months Class III (17.45/10.76) Class IV (0/0) Tooth-level analysis
Modica et al.[99]	EMD + CAF/CAF	6 months (91.2/80.9)	6 months (64.28/50.0)
Pourabbas et al.[101]	EMD + ADMG + CAF/ADMG + CAF	6 months (84.9/89.5)	NR
Rasperini et al.[103]	EMD + SCTG + CAF/SCTG + CAF	12 months (90.0/80.0)	12 months (62.0/47.0)
Sangiorgio et al./ Rocha Dos Santos et al.[104,105]	EMD + CAF/EMD + XCM + CAF/CAF	6 months (88.77†/91.59†/68.04) †Compared with CAF	6 months (70.59†/58.82†/23.53) †Compared with CAF
Trabulsi et al.[108]	EMD + CMb + CAF/CMb + CAF	6 months (63.0/75.0)	NR

(Continues)

TABLE 4 (Continued)

Study	Interventions	MRC% (test/control)	CRC% (test/control)
PDGF			
Dandu and Murthy[72]	PDGF + CMb + CATF/PPG + CATF	9 months (87.37/71.84)	NR
Deshpande et al.[75]	PDGF + B-TCP + CAF/SCTG + CAF/CAF	6 months (87.8/91.3/68.8)	6 months (71.4†/72.7†/40.6) †Compared with CAF
McGuire et al.[96,97]	PDGF + B-TCP + CAF/SCTG + CAF	6 months (90.8/98.6) 5 years (74.1/89.3)	6 months (NR/NR) 5 years (60.0/75.0)

ADMG, acellular dermal matrix graft; B-TCP, beta tricalcium phosphate; CAF, coronally advanced flap; CATF, coronally advanced tunnel flap; CMb, collagen membrane; CRC, complete root coverage; EMD, enamel matrix derivative; L-PRF, leukocyte and platelet-rich fibrin; MRC, mean root coverage; NR, not reported; PCG, platelet concentrated graft; PDGF, platelet-derived growth factor; PRF, platelet-rich fibrin; PRP, platelet-rich plasma; PPG, periosteal pedicle graft; RD, recession depth; sCAF, semilunar coronally advanced flap; SCTG, subepithelial connective tissue graft; T-PRF, titanium prepared platelet-rich fibrin; XCM, xenogeneic collagen membrane.
*Indicates statistically significant differences between groups - superior group.

CAF outweigh potential for harm. Evidence of conceivable methodological bias was identified in some individual studies (i.e., selective reporting).[62,68,76]

Notably, the impact of EMD on clinical outcomes after treatment of GRD in sites presenting baseline KTW <2 mm could not be assessed. Pooled estimates derived from the NMA indicate that EMD + CAF did not lead to superior CRC%, MRC%, RD, and KTW changes compared with SCTG + CAF, PRF + CAF, or CAF alone. Also, none of the selected studies presented information on treatment costs.

1. **Level of certainty**: Moderate
2. **Strength of clinical recommendations of EMD for the treatment of GRDs**: In favor (evidence supports the use).

rhPDGF-BB

Clinical comparisons and main findings: Three clinical trials involved the use of rhPDGF-BB, with a follow-up ranging from 6 to 5 years. Two studies had a split-mouth design and one had a parallel arms design. Single GRD were treated in one study (30 participants) and multiple GRD were treated in two studies (51 participants):

1. rhPDGF-BB – single GRD (one RCT/2 articles): *rhPDGF-BB + beta tricalcium phosphate (B-TCP) + CAF vs. SCTG + CAF*;[96,97]
2. rhPDGF-BB – multiple GRD (two RCTs): *rhPDGF-BB + B-TCP + CAF vs. SCTG + CAF* (one RCT);[75] and *rhPDGF-BB + Collagen membrane + CAF vs. Periosteal pedicle graft + CAF* (one RCT).[72]

Overall, changes in RD, CAL, and KTW observed in the arms involving the use of rhPDGF-BB were similar to those achieved by SCTG + CAF (Table S7 in online *Journal of Periodontology*).[76,96,97] The single trial comparing the use of rhPDGF-BB to CAF showed that PDGF + B-TCP + CAF led to significant changes in RD, CAL, and KTW.[76] The three included studies reported baseline KTW mean values ≥1.9 mm. Histologic evaluation of a sample obtained 9 months after grafting with rhPDGF-BB + b-TCP showed robust coronal bone and cementum regeneration with a uniformly dimensioned PDL space.[96,97]

Adverse events and complications: Some degree of pain/discomfort may occur within the first few days following the surgical procedure, but it is mainly related to flap preparation. No significant adverse events or complications associated to use of rhPDGF-BB were reported. Regarding PROMs (Table 5), there were no significant differences in esthetics (esthetic satisfaction questionnaire and clinical rating of color/texture of the tissues), pain/discomfort and adverse events in sites treated with rhPDGF-BB compared with SCTG + CAF.[96,97]

Net benefit rating (benefit-harm estimation) compared with other RC procedures: Outcomes reported in the three selected studies suggest that the clinical benefits associated with the use of rhPDGF-BB outweigh potential for harm. Evidence of conceivable methodological bias was identified (i.e., selective reporting).[62,68,76] Evidence of inconsistency of findings could not be identified, due to the very restricted number of studies and total sample size. As it was the case with ABPs and EMD, the impact of baseline KTW <2 mm on clinical outcomes after the use of rhPDGF-BB could not be evaluated. The reduced number of studies and the different types of treatment protocols used across the three different trials precluded a formal assessment of evidence via NMA. Also, none of the studies presented information on treatment costs.

1. **Level of certainty**: Low
2. **Strength of clinical recommendations of rhPDGF-BB for the treatment of GRDs**: Expert opinion for

TABLE 5 PROMs and other outcomes

Study	Interventions	Outcomes
ABP		
Huang et al.[83]	PRP + CAF/CAF	Wound healing index (WHI) was recorded after surgery using the following criteria: score 1 = uneventful healing with no gingival edema, erythema, suppuration, patient discomfort, or flap dehiscence; score 2 = uneventful healing with slight gingival edema, erythema, patient discomfort, or flap dehiscence, but no suppuration; and score 3 = poor wound healing with significant gingival edema, erythema, patient discomfort, flap dehiscence, or any suppuration. The WHI at 2 weeks was 1.3 in the CAF group and 1.2 in the PRP + CAF group; both groups returned to 1 after 1 month.
Jankovic et al.[88]	PRF + CAF/SCTG + CAF	One patient in the PRF group experienced severe postoperative pain compared with 7 patients in the CTG group. All 15 patients indicated a greater discomfort in the CTG group. The subjects' overall postoperative pain was assessed in the first 7 days using a horizontal visual analog scale, with the left endpoint marking no pain (0), middle point marking pain (1), and right endpoint marking severe pain (2): Day 1 - 0.46/1.46*; Day 2 - 0.40/1.33*; Day 3 - 0.33/1.20*; Day 4 - 0.33/1.06*; Day 5 - 0.26/0.80*; Day 6 - 0.25/0.60*; Day 7 - 0.20/0.46* Healing Index - A score of 1 to 5 was given, with 1 associated with very poor healing and 5 being excellent. 1 week - 3.11*/2.25; 2 weeks - 4.20*/3.05; 3 weeks - 4.51/4.29
Joshi et al.[89]	PRF + CAF/SCTG + CAF	PROMs - Postsurgical patient discomfort (VAS) at 1 week and 2 weeks postoperatively: 1 week - 0.13/1.27*; 2 weeks - 0/0
Kuka et al.[92]	PRF + CAF/CAF	Esthetics: RES (7.8/7.0) PROMs (overall satisfaction) - 18.0/18.0 (the scale used for patients' overall satisfaction assessment was not reported)
Kumar and Murthy[93]	PCG + CAF/SCTG + CAF	The Esthetic evaluation included color match, tissue texture and contour of the surgical area in comparison with the adjacent tissue. The scoring was from 1 (most favorable) to 4 (least favorable): the PCG group yielded a clinically better gingival texture and contour. No statistically significant difference could be detected in color match between the two groups (means were not reported). A VAS (0-5) form, with "0" indicating negligible discomfort and "5" indicating unbearable pain, was completed by the patients: Baseline (0.17/0.92); 1 week (0/0.58); 1 months (0/0)
Potey et al.[102]	PRF + CAF/CAF	Esthetics: RES (8.84/8.69) PROMs (pain/discomfort): VAS - 1 week (65.0/70.0) PROMS (esthetics): VAS (75.0/72.5)
Subbareddy et al.[106]	PRF + CATF/SCTG + CATF	PROMS (overall satisfaction): All patients in both groups felt it was worth undergoing the treatment and responded that they would recommend the treatment to others having similar problems. PROMs (pain/discomfort): Most patients in both groups did experience mild to moderate pain after the surgery but did not complain of severe pain causing disability to carry out their routine. PROMs (esthetics): 9 out of 10 patients treated with PRF felt that their esthetics considerably improved after the surgery, whereas all the patients (n=10) treated with SCTG felt that their esthetics considerably improved following the treatment.
Ucak et al.[110]	I-PRF + SCTG + CAF/SCTG + CAF	Esthetics: VAS (9.6/9.2) PROMs (pain/discomfort): VAS – 1 week (8.1/8.5*) PROMS (adverse events): VAS – 1 week (8.0/7.9) PROMs (esthetics): VAS – (9.7/9.5)
Uzun et al.[111]	T-PRF + CAF/SCTG + CAF	PROMs (pain/discomfort) - Postoperative pain or tenderness significantly decreased on days 3 and 7 compared with that on day 1. However, no significant difference was observed between the groups. Healing scores, which were obtained from each tooth at 14 days post-surgery, showed no significant difference between groups.

(Continues)

TABLE 5 (Continued)

Study	Interventions	Outcomes
Öncü[113]	PRF + CAF/SCTG + CAF	PROMs (pain/discomfort): VAS scores during the first postoperative week were significantly lower in the test group ($P < .001$).
EMD		
Aydinyurt et al.[59]	EMD + SCTG + CAF/SCTG + CAF	Esthetics: RES (8.93/8.37)
Castellanos et al.[70]	EMD + CAF/CAF	One of the teeth in the experimental group was extracted with the attached buccal gingiva after the 12-month evaluation for orthodontic reasons. The findings demonstrated that the junctional epithelium ended at a level coronal to the treated recession, as indicated by the level of root instrumentation. Furthermore, the regeneration of the periodontal support was evident coronal to this area.
França-Grohmann et al.[79]	EMD + semilunar CAF/Semilunar CAF	Esthetics: Qualitative Cosmetic Evaluation (QCE) - QCE (20.75/18.82); QCE - scar tissue (2.67*/1.88); QCE - texture (2.85/2.57) PROMs (esthetics): VAS 6 months (9.13/9.20); VAS 12 months (9.47/8.20) PROMs (hypersensitivity): VAS 6 months (0/0); VAS 12 months (0/0)
Górski et al.[80,81]	EMD + SCTG + CAF/SCTG + CAF	Esthetics (RES): 6 months (9.25*/8.71); 12 months (9.62*/8.51) PROMs (pain/discomfort):VAS - 1st day (3.54/3.63); 2nd day (3.47/3.69); 4th day (2.63/2.95); 7th day (1.70/2.13); 14 day (0/0) Post-operative pain was reported by 13 patients in the test group and 17 patients in the control group. PROMs (adverse events): VAS Edema - 1st day (4.56/4.76); 2nd day (4.56/5.25); 4th day (2.63/3.66); 7th day (1.20/2.43); 14th day (0/3.5) Post-operative swelling was reported by 17 patients in the test group and 19 patients in the control group. PROMs (esthetics): VAS (6 months) - Gingival color (81.5/83.8); Gingival contour (80.2/81.3); Recession coverage (75.8/80.8) "How satisfied are you with the results of the surgery?" (83.0/81.5) "Would you decide again to go for the treatment performed?" (84.2/83.7) "Would you recommend the treatment to another person?" (80.8/81.9)
McGuire and Nunn/McGuire et al.[94,95]	EMD + CAF/SCTG + CAF	PROMs (Esthetics): 10 years after surgery patients were asked to respond to questions related to esthetic satisfaction. Six patients had no preference for a particular type of treatment, 2 favored esthetic results with the test treatment (i.e., EMD + CAF), and 1 favored the result obtained after the control treatment (SCTG + CAF) ($P = 0.564$) Superior healing was observed in test sites after 1 week compared with control sites ($P = 0.011$)
Mercado et al.[98]	EMD + SCTG + CAF/SCTG + CAT	PROMs (pain/discomfort): VAS - 2 days (5.08/6.29*); 7 days (2.25/3.24); 14 days (0.80/1.52).
Sangiorgio et al./Rocha Dos Santos et al.[104,105]	EMD + CAF/EMD + XCM + CAF/CAF	Esthetics: 7.82 (RES) and 9.0 (VAS)/8.47 (RES) and 8.82 (VAS)/7.71 (RES)/8.29 (VAS) PROMs (overall satisfaction): VAS - 9.24/9.38/9.62 PROMs (hypersensitivity): VAS - From baseline to 6 months, there were no differences between groups.
PDGF		
Dandu and Murthy[72]	PDGF + CMb + CATF/PPG + CATF	PROMs - Postsurgical discomfort levels were noted at the end of 1 day, 1 week, and 1 month using a subjective pain scale ranging from 0 (no pain) to 5 (worst possible pain). PROMs - Postsurgical discomfort levels (PSDL) were assessed at day 1, at the end of 1 week, and at the 1-month follow-up in both sites. In the VISTA group on day 1, 10 subjects had a PSDL score of 2; 4 subjects scored 1, and 1 subject scored 3. At 1 week, 11 subjects scored 0 and 4 subjects scored 1. At the end of 1 month, all 15 subjects scored 0. In the PPG group on day 1, 9 subjects scored 3, 4 subjects scored 5, and 2 subjects scored 2. At 1 week, 10 subjects scored 1, 4 subjects scored 2, and 1 subject scored 3. At the end of 1 month, 11 subjects scored 0 and 4 subjects scored 1.

(Continues)

TABLE 5 (Continued)

Study	Interventions	Outcomes
McGuire et al./McGuire et al.[96,97]	PDGF + B-TCP + CAF/SCTG + CAF	Histologic outcomes: Nine months after CTG, no evidence of periodontal regeneration was observed (no change in the level of the osseous crest. A LJE extends apically, ending just superior to the original osseous crest. Abundant connective tissue without evidence of bone or cementum regeneration is seen coronal to the osseous crest. Nine months after grafting with rhPDGF-BB + B-TCP, robust coronal bone, and cementum regeneration with a uniformly dimensioned PDL space was observed. In addition, regeneration of cellular cementum as well as a uniform PDL space between the newly formed bone and the adjacent tooth surface were seen (connective tissue fibers were inserted directly into newly regenerated adjacent tissue). PROMs (Esthetics): At 6 months, on a 10-cm VAS, no statistically significant differences were observed between the treatments in response to an esthetic satisfaction questionnaire. At the 5-year follow-up out of the 20 test and 20 control sites, 14 sites for each group were rated as "very satisfied." In the test group, four sites were rated as "satisfied," one as "unsatisfied," and one as "very unsatisfied." In the control group, the remaining six sites were rated as "satisfied" with the esthetic results 5 years after the grafting procedure. PROMs (pain/discomfort): The subjects rated postoperative discomfort, which included bleeding, swelling, and sensitivity, as similar for the two treatment sites. All subjects had mild or no discomfort due to bleeding, swelling, and sensitivity and continued to improve from weeks 1 through 4. No statistically significant difference in pain scores was observed between the study treatments using a VAS. At the 24-week postoperative visit, 97% of the subjects commented that they experienced no difference in discomfort between the two treatment sites. PROMs (adverse events): With regard to the safety results, 25 (78.1%) subjects experienced 75 adverse events (AEs) during the study. All AEs were mild or moderate in severity. The most common AE was mild contusion, occurring in 16 (50.0%) subjects, followed by face swelling in 13 (40.6%) subjects. There were no serious AEs during the study. PROMs (Esthetics): At 6 months, patients' esthetic rating by a VAS did not identify differences in the clinical rating of color/texture of the tissues observed between the treatments. At 5 years, of the 20 test and 20 control sites, 14 sites for each were rated as 'very satisfied.' In the test group, 4 sites were rated as 'satisfied,' 1 as 'unsatisfied,' and 1 as 'very unsatisfied.' In the control group, the remaining 6 sites were rated as 'satisfied'. PROMs (hypersensitivity): At the end of 5 years, there was no statistically significant differences between test and control groups in terms of root dentin hypersensitivity.

ADMG, acellular dermal matrix graft; CAF, coronally advanced flap; CATF, coronally advanced tunnel flap; CAL, clinical attachment level; CGF, concentrated growth factor; GT, gingival thickness; I-PRF, injectable platelet-rich fibrin; KTW, keratinized tissue width; L-PRF, leukocyte and platelet-rich fibrin; LJE, long junctional epithelium; NR, not reported; PCG, platelet concentrated graft; PRF, platelet-rich fibrin; SCTG, subepithelial connective tissue graft; T-PRF, titanium prepared platelet-rich fibrin.

* Indicates statistically significant differences between groups - superior group.

evidence is lacking and the level of certainty is low, thus expert opinion guides this recommendation.

4 | DISCUSSION

4.1 | Summary of main results

The findings of this systematic review indicate that all biologics assessed (i.e., ABPs, EMD, and rhPDGF-BB) can be safely used for the treatment of GRD. Individually, all trials demonstrated that the use of biologics promoted statistically and clinically significant reductions in baseline RD and CAL (Tables 1–4 and online Tables S5–S7). Moreover, outcomes reported in individual studies had suggested potential KTW (PRF and rhPDGF-BB) and GT gain (PRF), and that the use of PRF and EMD may lead to superior PROMs, specifically pain/discomfort reduction during early postoperative stages, but such outcomes did not have a direct positive impact on the final clinical outcome measures, when compared with the gold standard therapy (SCTG + CAF). Limited histologic evidence suggests that EMD and rhPDGF-BB could contribute to achieve periodontal regeneration (Table 5). Additionally, limited data available on EMD and rhPDGF-BB suggest that short-term outcomes (6–12 months) could be maintained long-term (≥5 years), specifically gingival margin stability over time.

Nevertheless, considering the results of our NMA, which are based upon a mixed model with data derived from 24 eligible clinical trials, we found that the biologic

TABLE 6 NMA results - improvements due to adjunctive use of either EMD, PRF, or the SCTG to CAF for the four clinical outcomes

Measure	SCTG	95 CI	*P* value	EMD	95 CI	*P* value	PRF	95 CI	*P* value
Treatment arms, n	13			12			11		
MRC%	13.41%	8.06 to 18.75	$P < 0.01$	6.68%	0.03 to 13.40	$P = 0.061$	1.03%	−5.65 to 7.72	$P = 0.71$
CRC%	14.41%	4.21 to 24.61	$P < 0.01$	13.48%	−3.34 to 30.32	$P = 0.11$	−0.91%	−15.38 to 13.57	$P = 0.81$
RD	−0.39 mm	−0.55 to −0.22	$P < 0.01$	−0.13 mm	−0.29 to 0.01	$P = 0.08$	−0.06 mm	−0.23 to 0.09	$P = 0.39$
KTW	0.71 mm	0.48 to 0.93	$P < 0.01$	0.24 mm	−0.02 to 0.51	$P = 0.08$	0.08 mm	−0.23 to 0.41	$P = 0.58$

CI, confidence interval; EMD, enamel matrix derivative; KTW, keratinized tissue width; PRF, platelet-rich fibrin; RD, recession depth; SCTG, subepithelial connective tissue graft.

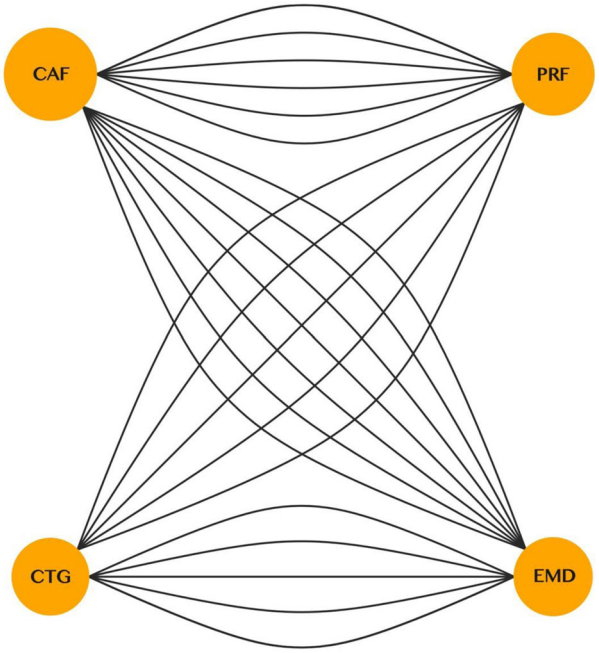

FIGURE 3 Network meta-analysis plot showing the treatment groups assessed (orange nodes), and the existing comparisons among the included randomized clinical trials (black edges). The node size is proportional to the total number of analyzed sites in that treatment arm, while distances are for plot clarity. Note that for studies with data on multiple time points (i.e., both 6- and 12-month data) only one edge per study is illustrated. CAF refers to treatment solely with a coronally advanced flap, CTG for treatment with coronally advanced flap and autogenous connective tissue graft, EMD for treatment with coronally advanced flap and enamel matrix derivatives, and PRF for treatment with coronally advanced flap and platelet-rich fibrin

treatment arms of PRF and EMD when used in conjunction with a CAF (without addition of other grafts/graft substitutes) do not render statistically significant superior outcomes compared with treatment with CAF alone (Table 6). It was also observed that SCTG + CAF, which is widely recognized as the gold standard root coverage therapy, consistently led to superior results compared with any of the other investigated treatments (CAF alone, EMD + CAF, and PRF + CAF) in terms of MRC, CRC, RD reduction, and KTW gain. Furthermore, there were no statistically significant differences between the outcomes of EMD + CAF and PRF + CAF. Among the findings of the NMA, a statistically significant inverse correlation between baseline RD and final RD was noticed (the deeper the baseline RD, the more RD reduction).

4.2 | Quality of the evidence

Of the 48 RCTs included in this review, only four (8.33%) presented a low risk of bias. This information was included in the NMA models for the outcomes of MRC, CRC, and RD. Despite of the high number of trials considered to be at an unclear or high risk of bias, NMA failed to demonstrate positive correlations between outcomes and quality of included studies. This may be explained by the evolution of methodological design according to the CONSORT statement guidelines, as well as refinements in flap design and preparation, among other critical aspects of the clinical curve of learning.[114,115] This is in line with data from Tattan et al.[114] who found that risk of bias did not have an impact on effect size (i.e., MRC% and CRC%) after SCTG-based procedures. Moreover, as demonstrated by previous medical[116–120] and dental[114,121,122] studies, the impact of deficient trial design (i.e., inadequate randomization and/or allocation concealment) on clinical outcomes remains controversial. In general terms, even with the application of the most rigorous methodological standards during the design and conduction of a clinical study, these measures cannot completely avoid per se the introduction of other inherent biases associated to the condition of interest.[114,123] Yet, the unintentional introduction of different types of biases can lead to under or overestimation of the outcomes of RC therapy,[114,123] which can largely affect or disqualify formal meta-analytical comparison of studies.[123] It should be noted that, apart from the methods used to randomize and allocate patients, other factors such as absence of reporting important outcome variables commonly used to assess the efficacy of treatment and the disparity of baseline parameters (probably because of an imbalanced randomization) certainly may impact

treatment result estimates and the assessment of quality of individual studies.

4.3 | Limitations and potential biases in the review process

This review was designed to provide an estimate ("big picture") of the outcomes of RCTs that evaluated the efficacy of biologics for the treatment of mucogingival deformities. Unfortunately, two issues precluded a more comprehensive assessment: 1) the lack of eligible RCTs on the topic of gingival augmentation or gingival phenotype modification; and 2) "only" half of the selected trials could be included in the NMA due to the vast amount of heterogeneity among treatment arms, which subsequently precluded the analysis of other treatments in the model, and did not allow for the assessment of GT changes after RC therapy (due to low number of studies that reported this outcome). The first issue, or limitation, may be partially explained by surgical preferences in contemporary practice as it is generally acknowledged that covering the biologic with a flap would likely render better outcomes. Also, there is robust clinical evidence that the sole application of autogenous grafts (mainly free gingival grafts) and soft tissue substitutes (ADM and XCM) can predictably modify the gingival phenotype (KTW and thickness gain) in sites where root coverage is not priority.[14] Regarding the second issue, it should be noted that not all RCTs available for ABP ($n = 22$) and EMD ($n = 23$) could be included in the NMA due to the variety of ABP types used (CGF, PCG or PRP, PRF, i-PRF, L-PRF, and T-PRF). Merging all of them within a single group was not considered methodologically appropriate due to substantial differences in preparation protocols and their potential influence on the outcomes of interest. Another limitation could be the impossibility of performing additional NMA assessments, such as evaluating the influence of other anatomic- and surgery-related factors, due to insufficient available data in the selected literature.

In addition, and as shown in Table S4 in the online *Journal of Periodontology*, other potentially relevant trials for the focused question of interest in this systematic review could not be included because these studies were not transparent or clear in their methodology or the exact number of treated patients and sites. This methodological aspect unfortunately precluded a formal assessment in the NMA model of the outcomes in different defects, because it could introduce important "anatomical" and "surgical" biases (associated to flap design) that affect data interpretation. Although all these aspects should be taken into consideration when critically evaluating the pooled estimates and outcomes reported in individual studies, these issues per se do not seem relevant to alter the main conclusions of this systematic review.

4.4 | Agreements and disagreements with other studies or reviews

The findings hereby reported appear to be in line with the information enclosed in previous systematic reviews and AAP consensus reports that addressed the effect of biologics on the outcomes of mucogingival therapy.[1,3,124–128] All these studies share in common the main conclusion that the use of biologics is safe and leads to clinical benefits, but they also unanimously position SCTG + CAF as the primary treatment choice (i.e., the gold-standard for RC therapy). However, it must also be acknowledged that there are limited data on the potential benefit of biologics when used as adjuncts to SCTG + CAF, or when added to other biomaterials and graft substitutes, and it must be noted that these could not be incorporated into the NMA. It is plausible to infer that in specific clinical scenarios in which unfavorable local and systemic factors are present, the addition of a biologic agent to the "gold-standard" therapy or to non-autogenous graft substitutes may contribute to maximize the outcomes and reduce the occurrence of postoperative complications by enhancing the initial healing response.

It is also important to highlight that 72.91% ($n = 35$) of the studies included in this review reported baseline KTW mean values ≥2 mm. This may partially explain the lack of differences between biologics + CAF and CAF alone, or differences between treatments involving the use of EMD and PRF. Key advancements in the understanding of successful flap preparation in the context of root coverage therapy have occurred in recent decades:[1,115] the importance of a minimum flap thickness in the application of CAF alone (>0.8 mm);[131,132] the maximum tension a flap may withstand (≤0.4 g)[133] optimal flap positioning upon suture (≈2 mm coronal to the cemento-enamel junction);[134] the development of flap designs without or with minimal vertical incisions;[135–138] the use of multiple/combined flap thickness;[136] the minimum KTW required for a CAF to be used alone;[139] the introduction and routine use of microsurgical instruments;[1,115,140] the use of reduced size and less reactive suture materials;[115,140] and the use of magnification equipment.[1,115,140,141] Among other therapeutic elements, progress in all these domains has contributed to improve flap design and management, which is essential for the success of root coverage therapy. In fact, minimally traumatic flap dissection and stabilization are key to accomplish favorable results.[115] Proper stabilization of the blood clot in the early stages of wound healing largely contributes to obtaining successful outcomes and may partially explain the reduced or negligible differences between

the use of a CAF alone or in combination with a biologic (i.e., EMD or PRF), particularly in sites presenting favorable phenotypic characteristics.[115] This notion is in agreement with previous evidence from an overview of 75 RCT (115 treatment groups) that concluded that "the methods/ways used to prepare and manage the flap will reflect on the final root coverage outcomes, regardless of the use of SCTG or other soft tissue substitutes/biomaterials".[115]

Another clinically relevant finding from the NMA was the fact that sites with deeper gingival recession at baseline exhibited greater RD reduction after therapy. It could be argued that, everything else being equal, the outcomes of RC therapy would be superior in sites presenting deeper recession. However, such an assumption may not be clinically realistic because the amount of RD reduction is displayed in millimeters and not based on the percentage of gains/root coverage accomplished with therapy. There is solid evidence indicating that mean changes from baseline are larger in sites presenting deep gingival recession (≥4 mm), which may have a direct impact in the conduction and interpretation of meta-analyses.[1,3,124] Consequently, assessments of MRC and CRC using percentage values better reflects the real amount of defect coverage independently of the unit of analysis.[1,3] Hence, this specific finding of our NMA result is not surprising, as higher changes in baseline values are clinically expected within deeper defects, but the amount of change in millimeters does not reflect necessarily on treatment predictability.

Unfortunately, it was not possible to perform a critical assessment of the long-term stability of the gingival margin in sites treated with biologics-based procedures. The information reported in two studies that collected data at 5-[96,97] and 10-year[94,95] follow-up visits suggests that the outcomes achieved in the short-term after using EMD and rhPDGF-BB may be satisfactorily maintained long-term. Evidence from long-term studies demonstrates that gingival margin stability and GRD recurrence are directly associated with deficient KTW (<2 mm).[4,5,7,142,143] Such observation were corroborated by the findings of a recent systematic review on periodontal phenotype modification conducted as part of the previous AAP BEC.[14]

Finally, it is worth highlighting the additional statistical gains (RD[63,64,76,82,104,105] and CAL[80–82]) reported by some studies that evaluated the use of EMD as an adjunct to SCTG and soft tissue graft substitutes. These outcomes shed a light on the potential beneficial role of this biologic in the early stages of the wound healing process. These findings might be explained by the angiogenic properties of this agent, that promote endothelial cell proliferation, increase the number of local blood vessels, and promotes capillary-like sprout formation.[144–146] These biologic events related to early revascularization can positively influence graft incorporation, as well as the overall wound healing process in both non-smoking[76,80–82,104,105] and heavy smoking patients, whose healing is typically compromised.[63]

5 | CONCLUSIONS

Based on the outcomes reported in the articles selected in this systematic review and the findings of the NMA, it can be concluded that:

1. The use of biologics (i.e., ABPs, EMD, and rhPDGF-BB) in conjunction with CAF for root coverage purposes may promote statistically and clinically significant improvements in RD, CAL, and KTW. Notably, KTW gains were more evident within sites treated with ABP or rhPDGF-BB.
2. The adjunctive use of ABPs and EMD in the treatment of RT1/GRD-I does not provide substantial additional improvements in terms of clinical outcomes and PROMs to those achieved by CAF alone, when baseline KTW is >2 mm.
3. Both PRF + CAF and EMD + CAF rendered inferior MRC%, CRC%, RD reduction, and KTW gain compared with SCTG + CAF, which should still be considered the gold-standard in RC therapy. Regarding the use of rhPDGF-BB + CAF, although available studies have reported equivalent results compared with the gold-standard intervention, limited evidence precludes formal comparisons with CAF or SCTG + CAF.

5.1 | Implications for clinical practice

Without reservations, PRF, EMD, and rhPDGF-BB may be safely used in RC therapy. Although some studies have reported favorable outcomes, evidence supporting the routine clinical application of biologics to optimize the outcomes of mucogingival therapy is limited. Clinical benefits derived from the use of biologics may be directly related to the baseline phenotypic characteristics of the site.

5.2 | Implications for future research

Future RCTs aimed at evaluating the efficacy of biologics in mucogingival therapy, including root coverage and gingival augmentation interventions, should involve large populations and long-term follow-ups (>5 years). Future studies should report periodontal phenotype characteristics at baseline and different timepoints, and conduct subgroup analyses when appropriate, to further understand the influence that these variables have on the outcomes of

therapy. Also, future research should explore the potential of soft tissue graft substitutes as carriers for molecular biologics. Data on the performance of biologics in combination with the gold-standard therapy (SCTG + CAF) versus the gold-standard alone are warranted to elucidate the full therapeutic potential of these adjunctive treatments, particularly in challenging clinical scenarios. These data are expected to allow more precise estimations, via standard or NMA, in future reviews of the literature with the goal of guiding clinical practice.

AUTHOR CONTRIBUTIONS

Leandro Chambrone and Gustavo Avila-Ortiz designed the study and led the writing; Leandro Chambrone and Shayan Barootchi screened the initial entries, selected the articles, collected the data, and also assessed the risk of bias; and Shayan Barootchi contributed to the design, analyzed the data, and critically revised the manuscript.

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CONFLICTS OF INTEREST

The authors report no conflicts of interest related to this systematic review.

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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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