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Effectiveness of chlorhexidine, hyaluronic acid, and anti-discoloration mouthrinses on periodontal wound healing: A systematic review and meta-analysis.

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Abstract

Periodontal wound healing following surgical or non-surgical therapy remains a clinical challenge, and adjunctive mouthrinses are commonly prescribed to enhance tissue repair and control biofilm accumulation. Chlorhexidine is considered the gold standard for chemical plaque control; however, adverse effects such as tooth staining have prompted the development of modified formulations, including hyaluronic acid and anti-discoloration systems (ADS). This systematic review and meta-analysis aimed to compare the effectiveness of chlorhexidine-based mouthwashes, hyaluronic acid formulations, and anti-discoloration systems versus other rinses on periodontal healing outcomes. A comprehensive electronic search was conducted in accordance with PRISMA 2020 guidelines, and randomized controlled trials were included. The protocol was prospectively registered in PROSPERO (CRD42024616667). Risk of bias was assessed using the Cochrane RoB 2 tool, and certainty of evidence was evaluated with the GRADE approach. Of 339 records screened, five trials involving 242 participants met the eligibility criteria. Outcomes included gingival healing indices, plaque index, bleeding scores, and dental pigmentation. While individual studies reported clinical improvements within intervention groups, pooled analyses showed small and non-statistically significant effects across healing, plaque, and bleeding outcomes. Overall certainty of evidence ranged from low to moderate due to heterogeneity and limited sample sizes. Current evidence suggests comparable short-term effectiveness among these formulations, without clear superiority of any specific regimen for periodontal healing.

Keywords: Chlorhexidine, Hyaluronic Acid, Mouthwashes, Periodontal Diseases, Wound Healing.

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Introduction

Periodontal diseases are chronic inflammatory conditions affecting the supporting tissues of the teeth, including gingivitis and periodontitis. Gingivitis represents the initial and reversible stage, characterized by gingival inflammation and bleeding, whereas untreated disease may progress to periodontitis, leading to irreversible attachment loss and alveolar bone destruction [1]. Periodontitis is highly prevalent, affecting approximately 40% of adults in the United States, with severe forms impacting nearly 11% of the global population [2]. Beyond tooth loss, periodontal disease significantly compromises quality of life and represents a substantial public health burden.

The primary goal of periodontal therapy is to control infection and reduce inflammation through a stepwise approach that includes supragingival biofilm control, subgingival instrumentation, and, when necessary, surgical intervention [3]. In the postoperative phase, optimal wound healing is critical, particularly during the first week, when tissue stability and primary closure determine clinical success [4,5]. Early healing begins within 12–24 hours through keratinocyte migration and restoration of epithelial continuity, protecting the surgical site from microbial and mechanical challenges [6]. However, mechanical plaque control is often limited during this period, increasing the risk of biofilm accumulation and postoperative complications [7–9]. Therefore, adjunctive chemical agents are frequently prescribed to support biofilm control and enhance wound healing [10].

Chlorhexidine (CHX) remains the gold standard antiseptic due to its ability to reduce plaque formation by 30–80% [11]. Nevertheless, its prolonged use is associated with adverse effects such as tooth staining, taste alteration, and mucosal irritation. To overcome these limitations, alternative formulations incorporating hyaluronic acid (HA) and anti-discoloration systems (ADS) have been developed. Hyaluronic acid has demonstrated bacteriostatic, anti-inflammatory, anti-edematous, osteoinductive, and proangiogenic properties, promoting fibroblast proliferation, collagen maturation, and extracellular matrix remodeling during oral wound healing [12-18]. Although several randomized clinical trials have evaluated these agents, their comparative effectiveness on periodontal healing outcomes remains unclear, and no consensus has been established regarding their superiority.

The objective of this study was to compare the effectiveness of chlorhexidine-based mouthwashes, hyaluronic acid formulations, and anti-discoloration systems versus other rinses on periodontal healing outcomes through a systematic review and meta-analysis. This research is justified by its contribution to the clinical and methodological understanding of adjunctive chemical plaque control during periodontal healing, with direct implications for evidence-based periodontal practice.

Methods

Study Design and Protocol Registration

This study was conducted as a systematic review and meta-analysis of randomized controlled trials (RCTs). The protocol was prospectively registered in the International Prospective Register of Systematic Reviews (PROSPERO; CRD42024616667). The manuscript was prepared in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) statement.

Eligibility Criteria

Randomized controlled trials evaluating the effectiveness of mouthwashes containing chlorhexidine (CHX), hyaluronic acid (HA), and/or anti-discoloration systems (ADS) on periodontal healing outcomes were included. No restrictions were applied regarding language or year of publication.

Studies were excluded if they were observational designs (cohort, case-control, cross-sectional), case reports, case series, conference abstracts, editorials,

letters to the editor, or non-peer-reviewed publications.

The primary outcome was periodontal wound healing, assessed through validated clinical indices such as the Early Wound Healing Index (EHI; Wachtel classification). Secondary outcomes included plaque index (PI), bleeding scores, gingival inflammation parameters, and dental pigmentation when reported.

Information Sources and Search Strategy

A comprehensive electronic search was conducted in PubMed/MEDLINE, Scopus, Web of Science, Embase, and the Cochrane Central Register of Controlled Trials from database inception until November 2024. The search strategy combined Medical Subject Headings (MeSH) terms and free-text keywords related to periodontal surgery, chlorhexidine, hyaluronic acid, wound healing, and randomized controlled trials, using Boolean operators. The complete search strategy for each database is available in the Supplementary Material.

Study Selection

Two reviewers independently screened titles and abstracts according to predefined eligibility criteria. Potentially relevant studies underwent full-text assessment. Disagreements were resolved by discussion or consultation with a third reviewer. The screening process was managed using Rayyan systematic review software.

Data Extraction

Data were independently extracted by two reviewers using a standardized data collection form. Extracted information included study characteristics (author, year, country), participant characteristics, sample size, type and concentration of mouthwash, control intervention, follow-up duration, and reported clinical outcomes.

When required data were missing or unclear, attempts were made to contact the corresponding authors. When standard deviations were not directly reported, they were calculated from available statistics where possible.

Risk of Bias Assessment and Certainty of Evidence

The methodological quality of included trials was assessed using the Cochrane Risk of Bias 2.0 (RoB 2) tool. Each domain was classified as low risk, some concerns, or high risk of bias. Two reviewers performed the assessment independently, and discrepancies were resolved through consensus.

The certainty of evidence for each outcome was evaluated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.

Statistical Analysis

Meta-analyses were performed using Review Manager (RevMan) version 5.4 (Cochrane Collaboration). Random-effects models were applied using the DerSimonian–Laird method to account for anticipated clinical and methodological heterogeneity.

For continuous outcomes measured using different scales, standardized mean differences (SMD) were calculated. When outcomes were measured using the same scale, mean differences (MD) were used. For dichotomous outcomes, risk ratios (RR) were calculated. All effect estimates were reported with 95% confidence intervals (CI).

Statistical heterogeneity was assessed using the I^2 statistic and interpreted as low (0–30%), moderate (30–60%), or high (>60%). Subgroup analyses were conducted according to follow-up duration when applicable. Statistical significance was set at $p < 0.05$.

Due to the limited number of included studies (<10 per outcome), publication bias was not formally assessed using funnel plots or regression tests.

Ethical Considerations

As this study synthesized data exclusively from previously published studies, ethical approval and

informed consent were not required. The study adhered to the principles of the Declaration of Helsinki. [19]

Results

Study Selection

The electronic search identified 339 records across PubMed (n = 312), Web of Science (n = 1), Embase (n = 10), and Cochrane (n = 12). After removal of 16 duplicates, 323 records underwent title and abstract screening.

A total of 313 records were excluded. Ten full-text articles were assessed for eligibility; one was not retrieved and four were excluded for not meeting inclusion criteria. Five randomized controlled trials were included in the qualitative and quantitative synthesis (Figure 1).

Characteristics of Included Studies

The five included randomized controlled trials were published between 2014 and 2024. Four studies were conducted in Italy and one in India, comprising a total of 242 participants. Sample sizes ranged from 33 to 82 participants.

All trials evaluated chlorhexidine-based mouthwashes alone or in combination with hyaluronic acid and/or anti-discoloration systems compared with control rinses or placebo. Follow-up periods ranged from 2 days to 30 days. Outcomes assessed included Early Wound Healing Index (EHI), plaque index (PI), bleeding scores, and gingival inflammation parameters (Table 1).

Rik of Bias

Risk of bias assessment using the Cochrane RoB 2 tool demonstrated predominantly low risk across domains related to randomization and allocation concealment. Concerns were identified in blinding of participants and personnel in some studies, and one study showed high risk of bias in performance bias. The overall risk-of-bias assessment is presented (Figure 2).

Quantitative ynthesis

Gingival Healing Index

Three studies were included in the meta-analysis. The pooled standardized mean difference (SMD) was −0.26 (95% CI −1.92 to 1.40; p = 0.76), with heterogeneity I^2 = 94%.

Plaque Index

Three studies contributed to this analysis. The pooled effect estimate was SMD −0.27 (95% CI −1.09 to 0.55; p = 0.52), with I^2 = 74%.

Bleeding Score

Three studies were included. The pooled SMD was −0.36 (95% CI −0.78 to 0.07; p = 0.10), with I^2 = 9%.

Forest plots summarizing the pooled estimates are presented (Figure 3).

Certainty of Evidence

According to the GRADE assessment, certainty of evidence was rated as low for gingival healing index and plaque index due to inconsistency and imprecision. Certainty for bleeding score was rated as moderate (Table 2).

Discussion

This systematic review and meta-analysis aimed to compare the effectiveness of chlorhexidine-basedmouthrinses, alone or combined with hyaluronic acid and/or anti-discoloration systems, versus other rinsing protocols on periodontal healing outcomes following surgical or dental procedures. Based on pooled evidence from five randomized controlled trials (242 participants), no statistically significant differences were observed across gingival healing, plaque index, or bleeding outcomes. Although individual trials reported improvements within intervention groups, the overall effect estimates were small and imprecise. Given the substantial global burden of periodontal

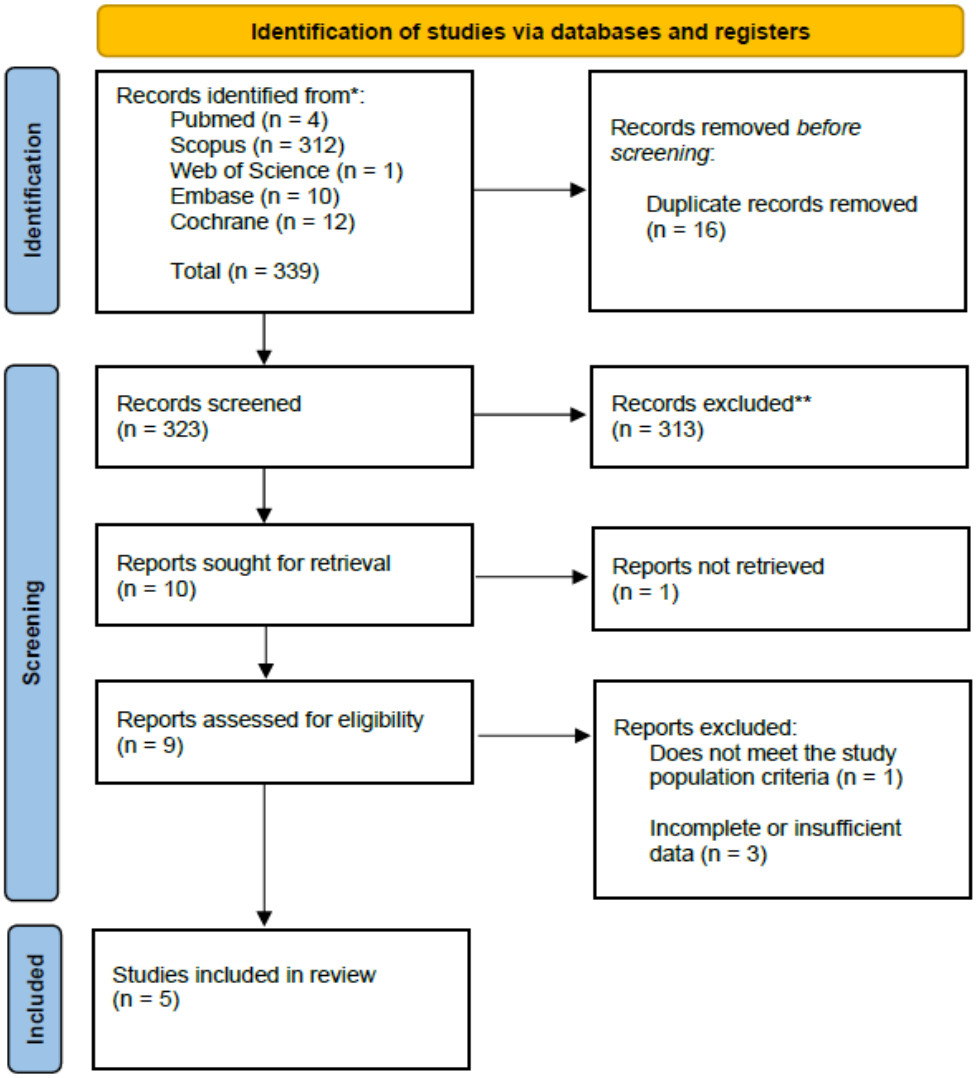

Figure 1. PRISMA 2020 flow diagram of the study selection process.

disease and its clinical and socioeconomic impact, the identification of adjunctive therapies capable of enhancing postoperative healing remains a relevant objective in contemporary periodontal care. [1,2]

The absence of clear pooled superiority likely reflects the biological complexity of periodontal wound healing and methodological variability across studies. Periodontal repair involves sequential inflammatory, proliferative, and remodeling phases, characterized by epithelial migration, angiogenesis, fibroblast proliferation, collagen maturation, and extracellular matrix remodeling. [4,5,7,8,20-26] Differences in follow-up intervals, surgical contexts, and outcome definitions across trials may have limited comparability and contributed to heterogeneity. Early postoperative plaque control is critical for flap stability and prevention of microbial colonization, supporting the rationale for adjunctive chemical plaque control during periods when mechanical hygiene is restricted. [9,10]

With in the broader literature, chlorhexidine remains the reference standard for chemical plaque control due to its documented antiplaque efficacy across concentrations. [11] However, its known adverse effects—including staining and taste alteration—have driven the development of modified formul ations incorporating anti-discoloration systems and adjunctive agents. [9,27] Hyaluronic acid has biological plausibility as an adjunct owing to its roles in tissue homeostasis, inflammation modulation, angiogenic signaling,

Table 1. Characteristics of Included Randomized Controlled Trials

Author	Year	Country	Study Design	Sample Size (n)	Intervention	Control	Patient Characteristics	Clinical Parameters	Follow-up	Main Findings
Graziani et al.[20]	2024	Italy	Randomized controlled trial	33	Chlorhexidine (CHX) 0.2% + anti-discoloration system (ADS) + hyaluronic acid (HA) 0.2%	No mouthrinse prescribed	Patients aged 18–70 years with chronic periodontitis undergoing conservative or resective periodontal surgery	Early Healing Index (EHI), Bleeding Index (BI), Gingival Inflammation Index	3, 7, and 14 days	CHX+ADS+HA showed significantly better early wound closure and reduced gingival inflammation compared to control ($p<0.01$).
Shah et al.[28]	2024	India	Randomized controlled clinical trial	50	CHX 0.2% + HA 0.1%	Placebo (saline solution)	Patients aged 18–50 years undergoing surgical extractions in multiple clinical centers	Healing Index (HI), Percent Healing Index (PHI), Pain, Inflammation, Bleeding	3, 7, 15, and 30 days	CHX+HA group demonstrated significantly improved healing indices and reduced pain and inflammation compared to placebo.
Trombelli et al.[21]	2018	Italy	Randomized controlled trial	37	CHX 0.2% + HA 0.2% + ADS	CHX 0.2%	Adults requiring periodontal flap surgery in a university research center	Gingival Healing Index (GHI), Plaque Index (PI), Gingival Index (GI), Angulated Bleeding Score (AngBS), Tooth Pigmentation	7 and 21 days	Both groups showed similar healing outcomes; no statistically significant superiority of CHX+HA+ADS over CHX alone.
Genovesi et al.[29]	2015	Italy	Randomized controlled single-blind trial	40	CHX 0.12% + HA 0.1%	CHX 0.12%	Adults undergoing periodontal surgical procedures at an academic center	Edema, Pain, Plaque Index (PI), Gingival Bleeding Index (GBI), Staining Index (SI)	3 hours, 2, 7, and 15 days	No significant differences between groups; slight trend toward reduced edema in CHX+HA group.
Lorenzini et al.[30]	2014	Italy	Randomized controlled trial	82	CHX 0.2% + ADS + HA	CHX 0.2% with ads	Adults >18 years undergoing oral biopsy procedures	Inflammation, Edema, Pain, Visual Analog Scale (VAS), Wound Stabilization	3, 7, and 14 days	Reduced inflammation and pain in CHX+ADS+HA group at early time points; similar healing at 14 days.

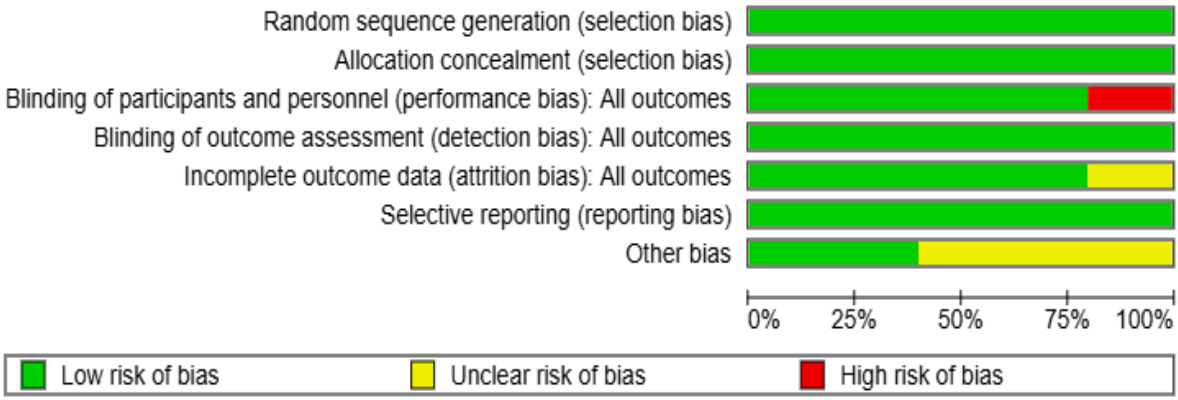

Figure 2. Bar chart of bias risk assessment.

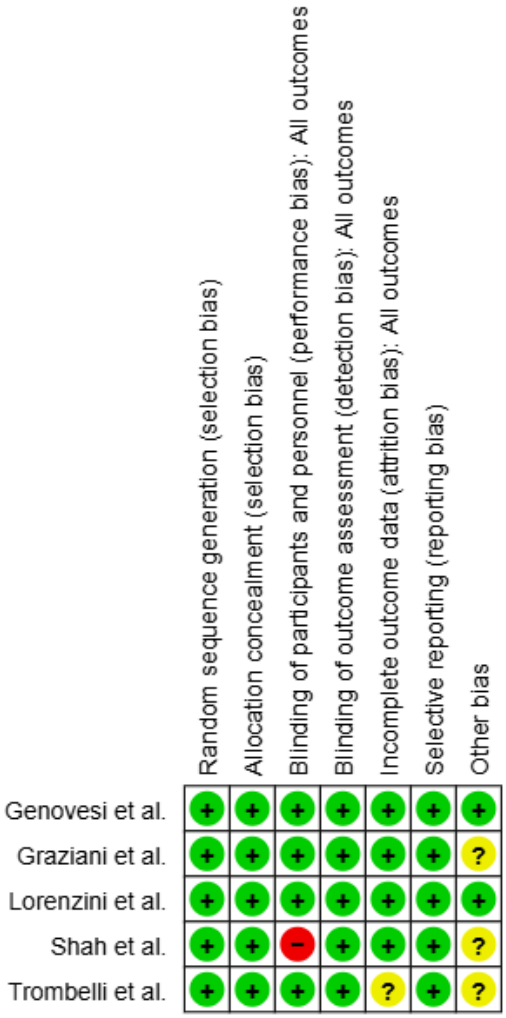

Figure 3. Detailed assessment of the risk of bias in individual studies

and extracellular matrix interactions. [16–19,31,32] Nevertheless, while individual trials have suggested potential benefits of specific CHX/HA/ADS combinations in early healing contexts, these effects appear context-dependent and are not consistently confirmed when data are pooled. [20,21] Thus, current evidence does not demonstrate clear additive clinical superiority over conventional chlorhexidine regimens in short-term healing outcomes.

From a clinical perspective, these findings support a pragmatic, patient-centered approach to postoperative mouthrinse selection. In the absence of demonstrated pooled superiority, clinicians may reasonably consider tolerability, esthetic impact, patient adherence, and cost when selecting formulations. Chemical adjuncts should be regarded as complementary to structured periodontal therapy pathways centered on diagnosis, staged treatment, and sustained biofilm control rather than as independent determinants of healing success. [2,3,22,23] This interpretation aligns with contemporary principles of evidence-based periodontal practice, in which therapeutic decisions integrate best available evidence, clinical expertise, and patient values.

This review presents methodological strengths, including prospective registration, comprehensive searching without language restrictions, duplicate screening, and structured appraisal of risk of bias and certainty of evidence. However, important limitations must be acknowledged. The number of eligible randomized trials was limited, sample sizes were modest, intervention protocols varied in concentration and combination, and outcome definitions and follow-up schedules were not standardized. Some studies presented concerns regarding blinding, potentially influencing subjective clinical measures, and substantial heterogeneity in certain pooled outcomes reduces

Table 2. Summary of findings, certainty of evidence GRADE

Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Control	**Risk with mouthwash containing chlorhexidine and hyaluronic acid, with or without anti-discoloration agents**				
Gingival Healing Index	-	SMD **0.58 higher** (0.72 lower to 1.87 higher)	-	109 (3 RCTs)	⨁⨁◯◯ Low[a,b]	Mouthwash containing chlorhexidine and hyaluronic acid, with or without anti-discoloration agents may increase gingival Healing Index.
Plaque Index	-	SMD **0.34 lower** (0.97 lower to 0.29 higher)	-	97 (3 RCTs)	⨁⨁◯◯ Low[c,d]	The evidence suggests mouthwash containing chlorhexidine and hyaluronic acid, with or without anti-discoloration agents reduces plaque Index slightly.
Bleeding score	-	SMD **0.36 lower** (0.78 lower to 0.07 higher)	-	97 (3 RCTs)	⨁⨁⨁◯ Moderate[e]	Mouthwash containing chlorhexidine and hyaluronic acid, with or without anti-discoloration agents likely reduces bleeding score slightly.

CI: confidence interval; **SMD:** standardised mean difference, **Moderate certainty:** we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different, **Low certainty:** our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect; [a]High heterogeneity (I^2 = 94%) with significant differences in effect directions across studies (Shah favors experimental, while Graziani and Trombelli favor control). [b]Wide confidence intervals include clinically non-significant effects (-1.92 to 1.40). [c]Moderate heterogeneity (I^2 = 74%), with variation in effect sizes across studies (mixed effects in plaque index values). [d]Wide confidence intervals (-1.09 to 0.55), limiting certainty in the interpretation of results. [e]Confidence intervals include clinically non-significant effects (-0.78 to 0.07), although heterogeneity is low and results are consistent.

confidence in precise effect estimation. [20,21] Furthermore, formal assessment of publication bias was not feasible due to the small number of trials per outcome.

Future research should prioritize adequately powered randomized trials with harmonized outcome measures, standardized postoperative evaluation intervals aligned with wound-healing biology, and transparent reporting of adherence and co-interventions. Trials should also clarify whether the principal value of anti-discoloration systems lies in improved tolerability rather than enhanced healing efficacy, and incorporate patient-reported outcomes and longer-term endpoints to determine clinically meaningful benefits. Such efforts would strengthen the evidence base guiding adjunctive chemical plaque control in periodontal surgery and

contribute to more precise clinical recommendations.

Conclusions

Within the limitations of the available evidence, chlorhexidine-based mouthrinses, hyaluronic acid formulations, and anti-discoloration systems demonstrate comparable short-term effectiveness in periodontal wound healing following therapy. No statistically significant superiority of any specific formulation was identified across gingival healing, plaque control, or bleeding outcomes. However, the overall certainty of evidence ranges from low to moderate due to methodological heterogeneity and limited sample sizes. Well-designed, adequately powered randomized clinical trials with standardized outcome measures are required to clarify the potential clinical advantages of combined formulations in periodontal post-therapy care.

Author Contributions Statement (CRediT)

JOE: Formal analysis, Data curation, Validation, Visualization, Conceptualization, Methodology, Supervision, Writing – Original Draft, Writing – Review & Editing. **MVE:** Investigation, Resources, Project administration, Writing – Review & Editing. **AAA:** Investigation, Resources, Project administration, Writing – Review & Editing.

All authors critically reviewed the intellectual content and approved the final version of the manuscript for publication.

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Conflict of Interest

The authors declare no financial, institutional, or personal conflicts of interest that could have influenced the conduct or publication of this study.

Data Availability

The datasets generated and analyzed during the current study are available from the corresponding author upon reasonable request.

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