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Clinical Efficacy of *Piper betle* L. Nanoemulgel as an Adjunct to Scaling and Root Planing in Chronic Periodontitis: A Randomized, Double-Blind, Placebo-Controlled Trial

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A B S T R A C T

This study evaluated the clinical efficacy of a *Piper betle* L. (betel leaf) nanoemulgel as an adjunct to scaling and root planing (SRP) in chronic periodontitis through a randomized, double-blind, placebo-controlled trial. Sixty-four patients with Stage III Grade B periodontitis were randomized to *P. betle* nanoemulgel (5% w/w ethanolic extract standardized to ≥30 mg/g hydroxychavicol; n = 32) or placebo gel (n = 32), applied subgingivally at baseline, week 2, and week 4 as adjuncts to SRP, at a private hospital in Palembang, Indonesia. The nanoemulgel had a mean droplet size of 78.4 ± 12.6 nm, polydispersity index 0.218, zeta potential −32.6 mV, and encapsulation efficiency 87.3%. Primary outcomes were probing pocket depth (PPD), clinical attachment level (CAL), bleeding on probing (BOP), and gingival index (GI) at 12 weeks. The intervention group showed significantly greater PPD reduction (−2.58 ± 0.68 vs −1.56 ± 0.74 mm; p < 0.001; Cohen d = 1.43), CAL gain (d = 1.23), BOP reduction (d = 1.12), and GI improvement (d = 1.25). Gingival crevicular fluid TNF-α decreased to 18.4 ± 8.2 versus 28.6 ± 10.4 pg/mL (p < 0.001; d = 1.09). Adverse events were limited to mild transient burning in 12.5% of patients. *Piper betle* nanoemulgel provided significant adjunctive clinical benefit in chronic periodontitis through anti-inflammatory and antimicrobial mechanisms, supporting its integration into evidence-based herbal periodontal therapy.

1. Introduction

Chronic periodontitis is a prevalent inflammatory disease of the tooth-supporting structures, affecting approximately 1.1 billion individuals globally in its severe form and ranking among the most prevalent chronic diseases worldwide.[1] The condition is driven by a dysbiotic subgingival biofilm dominated by gram-negative anaerobes including *Porphyromonas gingivalis*, *Tannerella forsythia*, and *Aggregatibacter actinomycetemcomitans*, which trigger an exaggerated host inflammatory response characterized by elevated pro-inflammatory cytokines (TNF-α, IL-1β, IL-6), matrix metalloproteinase activation, and RANKL-mediated osteoclastogenesis.[2] In Indonesia, periodontal disease remains a substantial oral health burden among adults, compounded by limited access to specialized periodontal care in many regions.[3]

Scaling and root planing (SRP) remains the cornerstone of non-surgical periodontal therapy; however, mechanical debridement alone may be insufficient to achieve complete resolution of inflammation in deep periodontal pockets and anatomically complex sites.[4,5] This limitation has

driven the development of adjunctive local drug delivery systems. While chlorhexidine and systemic antibiotics have been widely used, concerns regarding antimicrobial resistance, adverse effects, and the growing preference for natural therapeutic alternatives have stimulated interest in herbal adjunctive therapies.[6]

Piper betle L. (Piperaceae), commonly known as betel leaf or *daun sirih* in Indonesian traditional medicine, has been used for centuries in *jamu* preparations for oral hygiene and wound care.[3] Modern phytochemical analysis has identified hydroxychavicol, eugenol, chavibetol, allylpyrocatechol, and chavicol as the principal bioactive constituents of *P. betle* leaves.[3,7] Hydroxychavicol demonstrates potent anti-inflammatory activity through inhibition of the nuclear factor kappa-B (NF-κB) signaling pathway, suppression of cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS) expression, and reduction of pro-inflammatory cytokine production in lipopolysaccharide-stimulated macrophages.[8] Eugenol and chavibetol exhibit broad-spectrum antimicrobial activity against key periodontal and cariogenic pathogens, with minimum inhibitory concentrations comparable to chlorhexidine.[9,10] Phytochemicals of the chalcone and phenylpropanoid classes have further been shown to suppress RANKL-induced osteoclastogenesis through modulation of NFATc1 signaling, suggesting a mechanism relevant to the inhibition of alveolar bone resorption.[11]

However, the therapeutic potential of *P. betle* phytochemicals is limited by poor bioavailability, rapid clearance from the oral cavity, and inadequate penetration into the sulcular epithelium.[12] Nanoemulgel technology addresses these limitations by combining the enhanced drug loading and mucosal penetration of nanoemulsions (droplet size 20–200 nm) with the bioadhesive and sustained-release properties of hydrogel matrices.[4,13] This dual platform provides prolonged contact time in the periodontal pocket, improved penetration through disruption of the lipid barrier, and controlled release of phytochemicals.[14,15]

Despite promising preclinical evidence, no well-designed randomized controlled trial has evaluated the clinical efficacy of a nano-formulated *P. betle* extract specifically for subgingival periodontal delivery.[16] This study aimed to evaluate the clinical efficacy and safety of a *Piper betle* L. nanoemulgel as an adjunct to SRP in patients with chronic periodontitis through a randomized, double-blind, placebo-controlled trial.

2. Methods

This randomized, double-blind, placebo-controlled, parallel-group clinical trial was conducted at the Department of Periodontics of a private hospital in Palembang, Indonesia, between February 2024 and January 2025. The protocol adhered to the Declaration of Helsinki and the CONSORT 2010 statement and was approved by the CMHC Ethics Committee (Approval No. CMHC/EC/2024/0218). Written informed consent was obtained from all participants.

Plant material and extract preparation

Fresh mature leaves of *Piper betle* L. (Piperaceae) were collected from a cultivated plantation in South Sumatra, Indonesia, during the wet season (March 2024). Botanical identification was performed at the Department of Biology of a private university in Palembang, and a voucher specimen was deposited in the university herbarium. Leaves were washed, shade-dried at room temperature (25 ± 2 °C) for 7 days, and ground to a fine powder (mesh size 40). Extraction was performed by maceration in 70% ethanol (1:10 w/v) for 72 hours, followed by filtration and rotary evaporation at 40 °C under reduced pressure (yield 18.4% w/w). HPLC profiling (Shimadzu LC-20A, UV detection at 280 nm) confirmed hydroxychavicol (32.4 ± 1.8 mg/g), eugenol (18.7 ± 1.2 mg/g), chavibetol (12.3 ± 0.9 mg/g), and allylpyrocatechol (8.9 ± 0.6 mg/g). The extract was standardized to ≥30 mg/g hydroxychavicol.

Nanoemulgel formulation

The nanoemulsion was prepared by spontaneous emulsification. The *P. betle* ethanolic extract (5% w/w) was dissolved in clove oil (oil phase) with Tween 80 and Span 80 (surfactant:co-surfactant 3:1). The aqueous

phase was added dropwise under magnetic stirring (1000 rpm, 30 min), followed by ultrasonication (Vibra-Cell, Sonics; 40% amplitude, 5 min). The nanoemulsion was incorporated into a Carbopol 940 base (0.5% w/w) with triethanolamine and propylene glycol (10%). Characterization showed a mean droplet size of 78.4 ± 12.6 nm, PDI 0.218 ± 0.034, zeta potential −32.6 ± 3.8 mV, viscosity 12,450 ± 890 cP at 25 °C, pH 6.4 ± 0.2, and encapsulation efficiency 87.3 ± 2.1%. The placebo gel was identical in appearance, viscosity, and pH but contained no *P. betle* extract. Formulations were coded by an independent pharmacist for blinding.

Participants and sample size

Consecutive patients aged 30–65 years with Stage III Grade B periodontitis (2018 AAP/EFP classification)[17] were screened. Inclusion required at least one site with PPD ≥5 mm, CAL ≥4 mm, and radiographic bone loss. Exclusion criteria included systemic antibiotic or anti-inflammatory use within 3 months, periodontal treatment within 6 months, pregnancy or lactation, uncontrolled diabetes (HbA1c >8%), known allergy to *Piper betle*, immunosuppressive therapy, and fewer than 20 teeth. The sample size (G*Power 3.1) was based on an independent *t*-test to detect a 0.8 mm between-group difference in PPD reduction (SD = 0.9 mm, α = 0.05, power = 0.80), yielding 28 per group; with 15% dropout, 68 patients (34 per group) were targeted.

Randomization, procedures, and outcomes

Patients were randomly allocated (1:1; block size 4) using computer-generated numbers, with concealment via sequentially numbered opaque sealed envelopes. Both examiner and patients were blinded. Standardized SRP was delivered by a single periodontist within 2 visits; 0.5 mL of the assigned gel was applied subgingivally at baseline, week 2, and week 4. Parameters were recorded at baseline, 4, 8, and 12 weeks by a single calibrated examiner (ICC >0.90). Primary outcomes were PPD (UNC-15 probe, six sites/tooth), CAL, BOP, and GI (Löe–Silness). Secondary outcomes included PI (Silness–Löe), GCF TNF-α (ELISA, R&D Systems), patient satisfaction (VAS 0–10), and adverse events.

Statistical analysis

Data were analyzed with SPSS 28.0. Normality was assessed by the Shapiro–Wilk test. Between-group comparisons used independent *t*-tests; within-group comparisons used paired *t*-tests. Longitudinal changes were evaluated by two-way repeated-measures ANOVA (group × time) with Bonferroni correction. Categorical variables used chi-square or Fisher exact tests. Effect sizes were Cohen *d* with 95% CI. Bonferroni correction was applied for the 4 primary outcomes ($p < 0.0125$). All tests were two-tailed (α = 0.05).

3. Results and Discussion

Participant flow and baseline characteristics

Of 72 patients screened, 68 met the inclusion criteria and were randomized (34 per group). Four patients (2 per group) were lost to follow-up, yielding 64 patients (32 per group) for the final analysis (dropout 5.9%). The baseline demographic and clinical characteristics, detailed in Table 1, were well-balanced between groups (all $p > 0.05$).

The comparable baseline characteristics confirmed successful randomization and eliminated the need for covariate adjustment, consistent with recommendations for well-conducted randomized trials of herbal interventions.[16]

Probing pocket depth and clinical attachment level

The primary periodontal outcomes showed significantly greater improvement in the *P. betle* nanoemulgel group at all post-baseline time points, as summarized in Table 2. At 12 weeks, mean PPD in the intervention group decreased from 5.82 ± 0.94 to 3.24 ± 0.72 mm (change −2.58 ± 0.68 mm) versus 5.68 ± 0.88 to 4.12 ± 0.84 mm (change −1.56 ± 0.74 mm) in controls. The between-group difference of −1.02 mm (95% CI: −1.37 to −0.67; $p < 0.001$; Cohen $d = 1.43$) exceeded the clinically meaningful threshold of 0.5 mm and represented a large effect size, as illustrated in Figure 1.

Table 1. Baseline demographic and clinical characteristics (n = 64 patients).

Parameter	*P. betle* NEG (n = 32)	Placebo (n = 32)	p-value
Age (years)	44.8 ± 9.2	43.6 ± 10.1	0.612
Male, n (%)	14 (43.8)	15 (46.9)	0.802
Current smokers, n (%)	6 (18.8)	7 (21.9)	0.758
Diabetes mellitus, n (%)	3 (9.4)	4 (12.5)	0.689
PPD (mm)	5.82 ± 0.94	5.68 ± 0.88	0.528
CAL (mm)	4.96 ± 1.12	4.84 ± 1.08	0.658
BOP (%)	78.4 ± 14.2	76.8 ± 15.6	0.672
GI (Löe–Silness)	2.14 ± 0.42	2.08 ± 0.38	0.546
PI (Silness–Löe)	1.86 ± 0.48	1.82 ± 0.44	0.724
GCF TNF-α (pg/mL)	42.8 ± 14.6	40.2 ± 13.8	0.462

Notes: Values are mean ± SD or n (%). NEG = nanoemulgel; PPD = probing pocket depth; CAL = clinical attachment level; BOP = bleeding on probing; GI = gingival index; PI = plaque index; GCF = gingival crevicular fluid. Independent t-test for continuous and chi-square for categorical variables.

Table 2. Periodontal parameters at baseline and 12 weeks (primary outcomes).

Parameter	Baseline	12 Weeks	Change	Cohen d (95% CI)
***P. betle* Nanoemulgel + SRP (n = 32)**				
PPD (mm)	5.82 ± 0.94	3.24 ± 0.72	−2.58 ± 0.68	
CAL (mm)	4.96 ± 1.12	3.08 ± 0.88	−1.88 ± 0.72	
BOP (%)	78.4 ± 14.2	18.6 ± 8.4	−59.8 ± 12.6	
GI	2.14 ± 0.42	0.68 ± 0.32	−1.46 ± 0.38	
Placebo Gel + SRP (n = 32)				
PPD (mm)	5.68 ± 0.88	4.12 ± 0.84	−1.56 ± 0.74	
CAL (mm)	4.84 ± 1.08	3.82 ± 0.96	−1.02 ± 0.68	
BOP (%)	76.8 ± 15.6	32.4 ± 12.2	−44.4 ± 14.8	
GI	2.08 ± 0.38	1.12 ± 0.38	−0.96 ± 0.34	
Between-Group Comparison				
ΔPPD	−1.02 (−1.37 to −0.67)	p < 0.001	1.43 (0.90–1.96)	
ΔCAL	0.86 (0.51 to 1.21)	p < 0.001	1.23 (0.71–1.75)	
ΔBOP	−15.4 (−22.1 to −8.7)	p < 0.001	1.12 (0.60–1.64)	
ΔGI	−0.50 (−0.68 to −0.32)	p < 0.001	1.25 (0.73–1.77)	

Notes: All p-values remained significant after Bonferroni correction ($p < 0.0125$). Values are mean ± SD; between-group differences as mean (95% CI). Cohen d: small ≥0.2, medium ≥0.5, large ≥0.8. SRP = scaling and root planing.

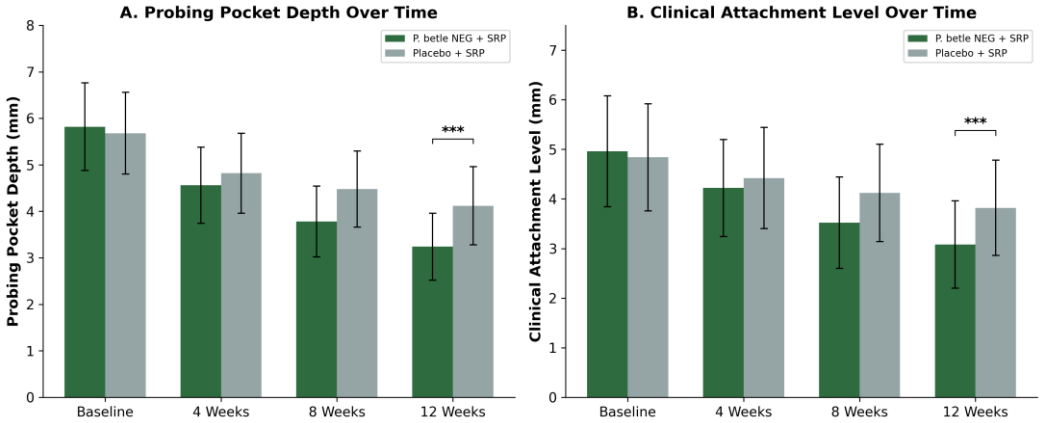

*Figure 1. Probing pocket depth (A) and clinical attachment level (B) over 12 weeks in the P. betle nanoemulgel and placebo groups. Error bars represent SD. ***p < 0.001 between groups at 12 weeks.*

The PPD reduction of 2.58 mm exceeds the 1.5–2.0 mm range typically reported with conventional herbal gels used as adjuncts to SRP.[18,19] This enhanced efficacy may be attributed to the nanoemulgel system, which provided sustained release of hydroxychavicol within the periodontal pocket. Hydroxychavicol inhibits NF-κB activation, reducing transcription of pro-inflammatory mediators including TNF-α, IL-1β, and MMP-8 that drive periodontal tissue destruction.[8] The nanoscale droplet size (78.4 nm) likely facilitated enhanced penetration through the sulcular epithelium, consistent with the improved tissue permeation reported by Abdallah et al. for optimized nanoemulgel systems.[13]

The CAL gain of 1.88 mm versus 1.02 mm in controls (between-group difference 0.86 mm; d = 1.23) is clinically meaningful and consistent with the magnitude reported by Mathew et al. for plant-derived nanoparticle formulations applied as adjuncts to SRP.[19] Sustained improvement through 12 weeks, despite gel application ceasing at week 4, suggests a disease-modifying rather than symptomatic effect, reflecting the multi-target activity of the whole *P. betle* extract on inflammation, microbial dysbiosis, and tissue remodeling.

Bleeding on probing and gingival index

BOP decreased markedly in both groups but significantly more in the intervention group (−59.8% vs −44.4%; p < 0.001; d = 1.12). GI scores decreased from 2.14 ± 0.42 to 0.68 ± 0.32 in the intervention group versus 2.08 ± 0.38 to 1.12 ± 0.38 in controls (p < 0.001; d = 1.25), as reported in Table 2. These findings are consistent with the antimicrobial activity of *P. betle* phytochemicals, particularly eugenol and 4-allylpyrocatechol, which show low minimum inhibitory concentrations against periodontal and cariogenic pathogens including *P. gingivalis* and *Streptococcus mutans*.[9,10] Okonogi et al. demonstrated that 4-allylpyrocatechol isolated from *P. betle* exerted strong activity against established oral biofilms, a mechanism that may explain the sustained anti-inflammatory effect observed beyond the active treatment period.[20]

Gingival crevicular fluid TNF-a

GCF TNF-α decreased significantly in both groups but with a markedly greater reduction in the intervention group, as shown in Figure 2. At 12 weeks, mean TNF-α was 18.4 ± 8.2 pg/mL in the intervention group versus 28.6 ± 10.4 pg/mL in controls (p < 0.001; d = 1.09, 95% CI: 0.57–1.61). The 57.0% reduction in the intervention group versus 28.9% in controls provides direct biochemical evidence for the anti-inflammatory mechanism at the site of disease.

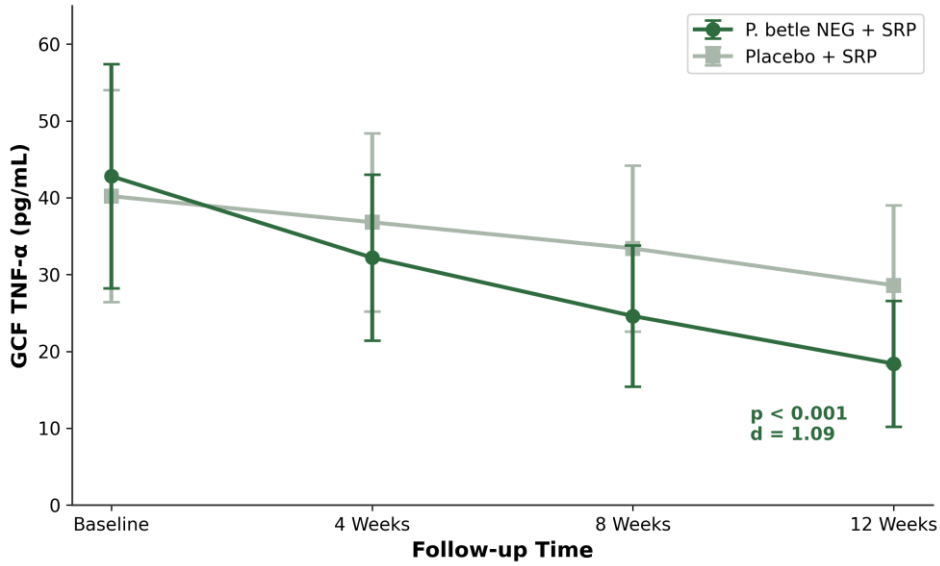

Figure 2. Gingival crevicular fluid TNF-a concentrations over 12 weeks in the P. betle nanoemulgel (green circles) and placebo (gray squares) groups. Error bars represent SD. p < 0.001, d = 1.09 at 12 weeks.

This finding aligns with the work of Seo et al., who demonstrated that the methanol extract of *P. betle*, rich in hydroxychavicol, suppressed NF-κB- and MAPK-dependent pro-inflammatory signaling, including TNF-α production, in LPS-stimulated macrophages.[8] The concurrent activation of the Nrf2 antioxidant pathway provides an additional mechanism by which *P. betle* phenolics may protect periodontal tissues from oxidative stress–induced damage.[8] Comparable antioxidant and antibacterial effects of betel-derived phenolics against oral pathogens have been documented by Prasetya et al., reinforcing the dual anti-inflammatory and antimicrobial basis for the observed benefit.[10]

Effect size analysis

The forest plot of effect sizes, presented in Figure 3, demonstrates consistently large effects across all outcome measures, with Cohen *d* values ranging from 0.77 (PI) to 1.43 (PPD). All primary outcomes exceeded the large-effect threshold ($d > 0.8$), and all 95% confidence intervals excluded zero, confirming the robustness of the treatment effect.

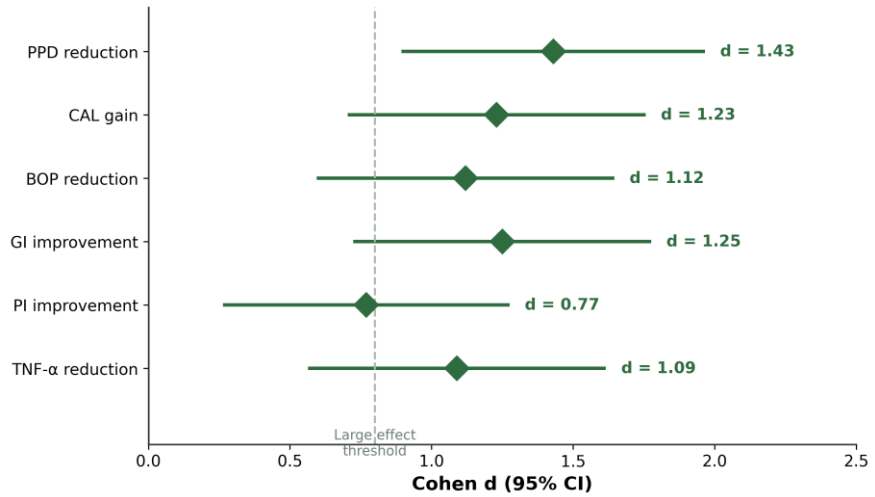

Figure 3. Forest plot of effect sizes (Cohen d with 95% CI) for all outcome measures. Green diamonds denote statistically significant outcomes; the dashed line marks the large-effect threshold (d = 0.8).

Safety and patient satisfaction

The safety profile of *P. betle* nanoemulgel was favorable, as detailed in Table 3. A mild transient burning sensation was reported by 4 of 32 patients (12.5%) in the intervention group and 2 of 32 (6.3%) in controls, resolving within 24 hours. No allergic reactions, mucosal ulceration, or serious adverse events occurred. Patient satisfaction was significantly higher in the intervention group (VAS 8.2 ± 1.4 vs 7.0 ± 1.6; $p = 0.002$), reflecting both perceived improvement and cultural familiarity with betel leaf as a traditional remedy in Indonesian communities.[3]

Table 3. Safety profile, secondary outcomes, and patient satisfaction.

Outcome	*P. betle* NEG	Placebo	*p*-value
PI at 12 weeks	0.54 ± 0.28	0.78 ± 0.34	0.003
GCF TNF-α at 12 wk (pg/mL)	18.4 ± 8.2	28.6 ± 10.4	<0.001
Mild burning, *n* (%)	4 (12.5)	2 (6.3)	0.672
Serious adverse events, *n* (%)	0 (0)	0 (0)	—
Satisfaction VAS (0–10)	8.2 ± 1.4	7.0 ± 1.6	0.002

Notes: NEG = nanoemulgel; PI = plaque index; GCF = gingival crevicular fluid; VAS = visual analogue scale. Continuous variables by independent t-test; categorical by chi-square or Fisher exact test.

Indonesian herbal context

These findings carry particular significance within Indonesian herbal medicine traditions. *Piper betle* has been an integral component of *jamu* formulations for oral health for centuries, and the demonstration of its clinical efficacy through rigorous randomized methodology bridges traditional knowledge and evidence-based practice.[3] The nanoemulgel system represents a modern innovation that enhances the therapeutic potential of this traditional plant, aligning with Indonesia's strategy for integrating traditional medicine into healthcare. Nayaka et al. highlighted the need for well-designed clinical trials to validate traditional herbal applications, and the present study contributes directly to this evidence base.[3]

Strengths and limitations

Strengths include the double-blind, placebo-controlled design with adequate power, a standardized HPLC-verified formulation, comprehensive clinical and biochemical assessment, and single-examiner calibration. The nanoemulgel was characterized according to international pharmaceutical standards, ensuring reproducibility. Limitations include the single-center design, a 12-week follow-up that may not capture long-term outcomes, the absence of microbiological confirmation of antimicrobial mechanisms, and the exclusion of patients with uncontrolled diabetes or aggressive periodontitis, which limits generalizability. Formal dose–response studies were not conducted. Future multicenter trials with longer follow-up, microbiological endpoints, and dose optimization are warranted.

4. Conclusion

Subgingival application of *Piper betle* L. nanoemulgel (5% w/w, standardized to ≥30 mg/g hydroxychavicol) as an adjunct to SRP produced statistically significant and clinically meaningful improvements in all primary periodontal parameters compared to placebo over 12 weeks, with superior PPD reduction (d = 1.43), CAL gain (d = 1.23), BOP reduction (d = 1.12), GI improvement (d = 1.25), and a 57% reduction in GCF TNF-α. The anti-inflammatory and antimicrobial mechanisms of hydroxychavicol, eugenol, and chavibetol, delivered through a sustained-release nanoemulgel platform, provide a pharmacologically plausible explanation for these benefits. The favorable safety profile and high patient satisfaction support clinical applicability, contributing to the validation of Indonesian traditional medicine through modern clinical research.

Declaration

Conflict of interest

The authors declare no conflict of interest.

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