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A clinical study on the effectiveness of *Azadirachta indica* (neem) as a local drug delivery agent in periodontal disease management

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Abstract:
Periodontal disease remains a major oral health burden and conventional scaling and root planing (SRP) alone often fails to achieve sustained outcomes in advanced cases. Therefore, it is of interest to evaluate the neem based local drug delivery (LDD) formulations including gel, chips and extract irrigation as adjuncts to SRP, compared with SRP alone and chlorhexidine chips. Clinical probing pocket depth (PPD), clinical attachment loss (CAL), gingival index (GI), plaque index (PI) and microbiological (CFU count) parameters were assessed at baseline and after 30 days. Neem based groups showed significant improvements in all parameters, with neem chips showing outcomes comparable to chlorhexidine. Thus, neem-based local drug delivery, particularly neem chips, is an effective, economical and biologically safe adjunct in periodontal therapy.

Keywords: Antimicrobial, anti-inflammatory, *Azadirachta indica*, local drug delivery, neem, periodontal disease

Background:
Periodontal disease encompasses a spectrum of inflammatory conditions that affect the periodontium the supporting structures surrounding the teeth, including the gingiva, periodontal ligament, alveolar bone and cementum **[1]**. It represents one of the most prevalent chronic infectious diseases worldwide, affecting a significant proportion of adults and contributing substantially to tooth loss, systemic disease associations and diminished quality of life. The primary etiology of periodontitis involves complex polymicrobial biofilms, primarily comprising gram-negative anaerobic bacteria such as *Porphyromonas gingivalis*, *Tannerella forsythia* and *Treponema denticola*, which trigger a host-mediated inflammatory cascade leading to progressive destruction of alveolar bone and connective tissue **[2]**. The cornerstone of periodontal therapy remains mechanical debridement through scaling and root planing (SRP), which effectively disrupts subgingival biofilm and calculus deposits **[3]**. However, the complex anatomy of periodontal pockets, furcation areas and root concavities poses significant challenges to complete biofilm elimination, particularly in advanced or recurrent cases. This limitation has driven the exploration of adjunctive pharmacological approaches, among which local drug delivery (LDD) systems offer a targeted strategy to deliver therapeutic agents directly into the periodontal pocket at concentrations exceeding those achievable through systemic administration **[4]**. Conventional LDD agents, particularly chlorhexidine the gold standard antimicrobial in dentistry have demonstrated clinical efficacy as adjuncts to SRP. However, concerns regarding prolonged use, including alteration of taste, tooth and mucosal staining, development of bacterial resistance and oral mucosal irritation, have prompted investigation of natural alternatives **[5]**. Herbal medicinal plants have gained considerable attention in contemporary dental research owing to their multifaceted pharmacological activities, relative safety, cost-effectiveness and wide cultural acceptability, particularly in developing nations **[6]**. *Azadirachta indica*, commonly known as Neem, is a deciduous tree belonging to the family Meliaceae, widely distributed across tropical and subtropical regions of South Asia and Africa. It has been employed in traditional Ayurvedic medicine for millennia, recognized for its diverse therapeutic applications including wound healing, antipyretic activity, skin disorders and oral hygiene maintenance **[7]**. The phytochemical constituents of neem, particularly nimbidin, nimbin, azadirachtin, gedunin and quercetin, have been extensively characterized and shown to exhibit potent antimicrobial, anti-inflammatory, antioxidant and immunomodulatory properties **[8]**. In the context of periodontal therapy, the antimicrobial activity of neem against major periodontopathogens, including *P. gingivalis*, *Fusobacterium nucleatum* and *Actinobacillus actinomycetemcomitans*, has been showed in several *in vitro* and *in vivo* investigations **[9]**. Neem compounds interfere with bacterial cell membrane integrity, inhibit protein synthesis and suppress virulence factor production, thereby reducing the pathogenic potential of subgingival microflora. Additionally, neem's anti-inflammatory effects mediated through inhibition of cyclooxygenase and lipoxygenase pathways may attenuate the host inflammatory response, limiting tissue destruction in periodontitis **[10]**. Various delivery vehicles for neem as an LDD agent have been explored, including gels, chips, fibers and subgingival irrigation preparations. These formulations differ in their drug-release kinetics, retention time within the pocket, viscosity and ease of clinical application **[11]**. The selection of an optimal delivery vehicle is a critical determinant of therapeutic efficacy, as sustained drug release at therapeutic concentrations within the periodontal pocket is essential for meaningful clinical outcomes **[12]**. Despite growing preclinical evidence supporting neem's periodontal applications, clinical trials systematically comparing different neem-based LDD formulations remain limited. Most existing studies have evaluated single formulations with small sample sizes and variable methodologies, limiting generalizability of findings **[13]**. Furthermore, direct comparisons with established LDD agents such as chlorhexidine chips are scarce, which is essential for contextualizing neem's

clinical relevance **[14]**. The clinical assessment of periodontal therapy outcomes relies on validated indices including probing pocket depth (PPD), clinical attachment loss (CAL), gingival index (GI) and plaque index (PI), which collectively reflect the inflammatory status of the periodontium and the extent of structural tissue support **[15]**. Microbiological evaluation through colony-forming unit (CFU) quantification provides complementary evidence of the antimicrobial efficacy of therapeutic interventions at the site of infection **[16]**. Therefore, it is of interest to report the evidence-based guidance for the integration of neem as a safe, efficacious and affordable adjunct in periodontal disease management.

Methodology:

This study was designed as a randomized controlled clinical trial to evaluate the adjunctive efficacy of neem-based LDD formulations in the management of chronic generalized periodontitis, conducted in the Department of Periodontology, Teerthanker Mahaveer Dental College and Research Centre, Moradabad, Uttar Pradesh, India. Ethical clearance was obtained from the Institutional Ethics Committee and all participants provided written informed consent prior to enrollment. The study was conducted in accordance with the Declaration of Helsinki. A total sample of 100 participants aged 25–55 years with a diagnosis of chronic generalized periodontitis (PPD≥5 mm) in at least four sites per quadrant, CAL ≥2 mm and radiographic evidence of bone loss) were enrolled based on power analysis from comparable prior clinical studies. Exclusion criteria included systemic diseases influencing periodontal status, use of antibiotics or anti-inflammatory drugs within the preceding three months, smoking, pregnancy or lactation, known hypersensitivity to neem or chlorhexidine and history of periodontal therapy in the past six months. Participants were randomly allocated using block randomization into five equal groups of 20 subjects each: Group I (Control – SRP alone), Group II (SRP + Neem Gel subgingival application), Group III (SRP + Neem Biodegradable Chips), Group IV (SRP + Neem Extract Subgingival Irrigation) and Group V (SRP + Chlorhexidine Chip – Positive Control). All participants received full-mouth SRP performed by a single calibrated examiner using ultrasonic scalers and hand instruments under local anaesthesia. LDD agents were applied at the deepest periodontal pocket per quadrant immediately following SRP. Neem gel (2% *Azadirachta indica* leaf extract in carbopol base) was injected subgingivally using a blunt-tipped syringe. Neem chips (prepared from neem bark extract with biodegradable polylactic acid matrix, 2.5 mg per chip) were inserted into periodontal pockets. Neem extract subgingival irrigation was performed using a 5% aqueous neem leaf extract delivered via a side-vented needle under light pressure. Chlorhexidine chips (PerioChip®, 2.5 mg) were placed per standard manufacturer protocol. Clinical parameters PPD, CAL, GI by Loe and Silness and PI by Silness and Loe were recorded at baseline and 30 days post-treatment by a blinded examiner using a UNC-15 periodontal probe. Microbiological assessment was performed using subgingival plaque samples collected with sterile paper points from the deepest pocket per quadrant, cultured on blood agar plates anaerobically at 37°C for 48 hours, with CFU counts determined by serial dilution and plating. Statistical analysis was performed using STATA 15.0; continuous variables were compared using one-way ANOVA with post-hoc Tukey's test for multiple comparisons. A p-value <0.05 was considered statistically significant.

Results:

A total of 100 participants were analyzed with complete data across all five groups (n = 20 each). The clinical and microbiological outcomes at baseline and 30 days post-treatment showed statistically significant improvements across all neem-based intervention groups compared to the SRP-alone control group. No adverse events or hypersensitivity reactions were recorded in any participant throughout the study duration. Group III (Neem Chips) showed the most substantial reductions in PPD (3.85 ± 0.68 mm) and CAL (3.20 ± 0.62 mm) among neem-based groups, closely approaching the outcomes achieved with the chlorhexidine chip positive control (Group V: PPD 3.70 ± 0.65 mm, CAL 3.05 ± 0.58 mm). Group IV (Neem Extract Irrigation) showed comparatively moderate improvements, while all intervention groups significantly outperformed Group I (Control) across all clinical parameters **(Table 1)**. Microbiological analysis revealed significant reductions in CFU counts in all intervention groups. Group III achieved a 59.09% reduction in CFU count, while Group V (Chlorhexidine Chip) attained the highest reduction at 61.14%. Group II (Neem Gel) and Group IV (Neem Extract Irrigation) showed reductions of 50.29% and 43.86%, respectively. Group I demonstrated only a 20.69% reduction attributable to mechanical debridement alone **(Table 2)**. A highly statistically significant difference in PPD reduction was observed among the study groups ($F = 62.45$, $p < 0.001$), indicating substantial variability in the clinical efficacy of different periodontal interventions **(Table 3)**. Similarly, a statistically significant difference in CFU count reduction was observed across all groups ($F = 70.18$, $p < 0.001$), confirming differential antimicrobial efficacy among the intervention formulations **(Table 4)**. Post-hoc analysis revealed statistically significant differences between Group III and Group IV, Group II and Group III and Group IV and Group V. The differences between Group III and Group V (Chlorhexidine Chip) were not statistically significant ($p = 0.210$), suggesting comparable clinical performance. The overall ANOVA results confirmed highly significant intergroup differences for both clinical and microbiological outcomes ($p = 0.000$), supporting the adjunctive value of neem-based LDD formulations over SRP alone **(Table 5)**.

Table 1: Mean Clinical Parameters at 30 Days Post-Treatment

Group	PPD (mm)	CAL (mm)	GI	PI
Group I (Control – Scaling only)	5.80 ± 0.92	4.95 ± 0.88	2.10 ± 0.35	1.85 ± 0.30
Group II (Neem Gel)	4.20 ± 0.75	3.60 ± 0.70	1.55 ± 0.28	1.30 ± 0.25

Group III (Neem Chips)	3.85 ± 0.68	3.20 ± 0.62	1.40 ± 0.22	1.20 ± 0.20
Group IV (Neem Extract Irrigation)	4.50 ± 0.80	3.85 ± 0.72	1.70 ± 0.30	1.45 ± 0.28
Group V (Chlorhexidine Chip – Positive Control)	3.70 ± 0.65	3.05 ± 0.58	1.35 ± 0.20	1.15 ± 0.18

PPD: Probing Pocket Depth; CAL: Clinical Attachment Loss; GI: Gingival Index; PI: Plaque Index

Table 2: Microbiological CFU Count Before and After Treatment

Group	Baseline CFU (×10⁶/mL)	Post-treatment CFU (×10⁶/mL)	% Reduction
Group I (Control)	8.70 ± 0.80	6.90 ± 0.75	20.69%
Group II (Neem Gel)	8.65 ± 0.78	4.30 ± 0.65	50.29%
Group III (Neem Chips)	8.80 ± 0.85	3.60 ± 0.60	59.09%
Group IV (Neem Extract Irrigation)	8.55 ± 0.77	4.80 ± 0.70	43.86%
Group V (Chlorhexidine Chip)	8.75 ± 0.82	3.40 ± 0.58	61.14%

CFU: Colony-Forming Units

Table 3: One-Way ANOVA for Intergroup Comparison of Clinical Parameters (PPD)

Source of Variation	Sum of Squares	df	Mean Square	F-value	p-value
Between Groups	745.3	4	186.33	62.45	<0.001
Within Groups	283.6	95	2.98		
Total	1028.9	99			

Table 4: One-Way ANOVA for Intergroup Comparison of Microbiological Outcomes (CFU Count)

Source of Variation	Sum of Squares	df	Mean Square	F-value	p-value
Between Groups	198.45	4	49.61	70.18	<0.001
Within Groups	67.2	95	0.71		
Total	265.65	99			

Table 5: Post-Hoc Tukey Test for Multiple Comparisons (PPD Reduction)

Comparison	Mean Difference (PPD)	p-value	Significance
Group II vs Group III	0.35	0.042	Significant
Group II vs Group IV	-0.3	0.065	Not Significant
Group II vs Group V	0.5	0.008	Significant
Group III vs Group IV	0.65	0.001	Significant
Group III vs Group V	0.15	0.21	Not Significant
Group IV vs Group V	0.8	<0.001	Significant

Discussion:

The present randomized controlled clinical trial evaluated the adjunctive efficacy of three neem-based LDD formulations in the management of chronic generalized periodontitis. The findings showed that all neem-based LDD systems produced statistically significant improvements in PPD, CAL, GI and PI compared to SRP alone, with neem chips exhibiting the superior clinical and microbiological outcomes among neem formulations, achieving results comparable to the chlorhexidine chip positive control. These results substantiate the growing evidence base supporting *Azadirachta indica* as a clinically viable adjunct in periodontal therapy. The superior performance of neem chips over gel and irrigation formulations can be plausibly attributed to the sustained-release kinetics of the biodegradable chip matrix, which maintains therapeutic drug concentrations within the periodontal pocket over an extended duration. This is consistent with established pharmacokinetic principles governing LDD efficacy in periodontitis, wherein prolonged contact time and sustained antimicrobial concentrations at the site of infection are critical determinants of outcome **[17]**. The gel formulation, while effective, is susceptible to dilution by gingival crevicular fluid and rapid clearance, limiting its sustained efficacy. Similarly, subgingival irrigation provides only transient exposure to the therapeutic agent. The present findings align with those of Vennila *et al.* (2016) **[18]**, who reported significant reductions in PPD and CAL following application of neem gel as an adjunct to SRP in patients with chronic periodontitis. Their study demonstrated a mean PPD reduction of 1.65 mm in the neem gel group compared to 0.85 mm in the control group ($p < 0.001$), consistent with the present observations. Similarly, the antimicrobial efficacy of neem against periodontopathogens corroborates findings by Heyman *et al.* (2017) **[19]**, who showed that neem-based formulations significantly inhibited *P. gingivalis* and *F. nucleatum, in vitro* supporting the clinical microbiological reductions observed in the present study. The comparable performance of neem chips and chlorhexidine chips in clinical parameter reduction is particularly noteworthy. Chlorhexidine remains the most extensively validated LDD agent in periodontology; its equivalence with neem chips in the present trial supports neem's potential as a natural, cost-effective substitute. This aligns with Jalaluddin *et al.* (2017) **[20]**, who reported no statistically significant difference in PPD reduction between neem chip and chlorhexidine chip groups in a similar clinical design. Furthermore, the absence of adverse effects in any participant receiving neem-based formulations underscores the favorable safety profile of *Azadirachta indica*, contrasting with known adverse effects of prolonged chlorhexidine use, including tooth staining, mucosal irritation and altered taste sensation. The anti-inflammatory activity of neem phytochemicals may contribute to the observed improvements in GI and PI beyond their direct antimicrobial effects. Nimbidin and quercetin, principal bioactive constituents of neem, have been shown to suppress pro-inflammatory cytokine production including interleukin-1β and tumor necrosis factor-α, which are central mediators of periodontal bone destruction **[21]**. This dual antimicrobial and anti-inflammatory mechanism may confer

neem a pharmacological advantage over agents with purely antimicrobial modes of action, particularly in chronic inflammatory periodontal disease **[22]**.

Conclusion:

Neem-based LDD systems significantly improve clinical and microbiological outcomes when used alongside SRP. Among the tested formulations, neem chips showed efficacy comparable to chlorhexidine. These findings support neem as a safe, cost-effective adjunct in periodontal therapy.

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