Nanoparticles As A Local Drug Delivery System: A Scoping Review

ABSTRACT

Background: Periodontitis is a condition affecting the supportive structures of the teeth by inflammation and can lead to tooth loss if left untreated. Conventional treatments often do not fully eliminate periodontal pathogens. Local drug delivery used alongside conventional treatments has been employed to target and eliminate bacteria at the site of infection. Nanoparticles present a promising solution for local drug delivery, potentially enhancing therapeutic outcomes.

Objective: To comprehensively review and analyse the findings of in vivo studies on the use of nanoparticles as local drug delivery systems in the treatment of periodontitis.

Methods: This scoping review was conducted by searching electronic databases like PubMed, Medline, and Web of Science for in vivo studies evaluating the effectiveness of nanoparticle-based local drug delivery systems in managing periodontitis. A total of nine studies met the inclusion criteria and were analysed.

Results: Most studies reported significant improvements in pocket depth and clinical attachment level with the use of nanoparticles compared to control groups. Some studies also noted reductions in bleeding on probing and inflammation markers.

Conclusion: The reviewed in vivo studies suggest that nanoparticles as local drug delivery systems offer significant benefits in treating periodontitis. They demonstrate enhanced clinical outcomes, good safety profiles, and improved drug delivery efficiency.

Keywords: in vivo study; local drug delivery; nanotechnology; nanoparticles; periodontitis; targeted therapy.

1. INTRODUCTION

Periodontitis is a complex and multifactorial disease affecting the teeth' supporting structures, including the gingiva and bone. Despite the advancements in oral hygiene practices, completely eliminating the pathogens causing periodontitis and controlling the clinical findings remains a formidable challenge. The primary goal of treatment is often to achieve remission and effectively manage the disease (Lal et al., 2021).

For over a century, one of the fundamentals of periodontal therapy has been scaling, a procedure that involves the removal of plaque and calculus from the teeth mechanically (Budală et al., 2023). While scaling is effective in reducing bacterial load and inflammation, it

may not always lead to the complete eradication of pathogens, resolution of all symptoms and preventing recurrence (Holpuch et al., 2010; Puri & Puri, 2013).

In recent years, there has been a shift towards more targeted and localised therapeutic approaches, particularly in the form of local drug delivery systems (Ficai et al., 2017). These systems allow for the direct application of antimicrobial agents to the periodontal pockets, where bacteria thrive and contribute to disease progression. By delivering medications directly to the site of infection, local drug delivery can enhance the effectiveness of treatment while minimising systemic side effects (Nguyen & Hiorth, 2015; Oliveira de Sousa et al., 2014).

One of the latest advancements in local drug delivery is the incorporation of nanoparticles into therapeutic formulations (Garg et al., 2018). Nanoparticles offer several advantages, including improved drug stability, controlled release kinetics, enhanced tissue penetration, and the ability to target specific pathogens or inflammatory processes (Elizabeth et al., 2019). The incorporation of nanoparticles into local drug delivery systems has gained considerable interest in the field of periodontics due to their unique properties and potential therapeutic benefits (Higino & França, 2022).

While several studies have explored this area in the past, there is a growing need for a comprehensive overview to synthesise existing knowledge and identify current trends and future directions (Yıldırım et al., 2023).

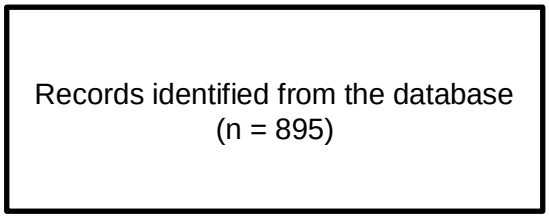
To address this gap, a scoping review was done to gather and analyse studies related to nanoparticle-based periodontal drug delivery systems in clinical research, in order to offer insights into their potential clinical utility, challenges, and avenues for further research and development. The primary objective was to identify and report on the various approaches and formulations involving nanoparticles for delivering therapeutic agents to periodontal tissues. The secondary objective was to observe the change in clinical and microbiological parameters.

2. METHODOLOGY

Only English-language reports were included in the literature search. Randomised clinical trials evaluating the efficacy of nanoparticle-based local drug delivery systems as an adjunct to non-surgical periodontal treatment in patients with periodontal disease were included in this review. In-vitro studies, animal studies, and narrative reviews were excluded.

The following electronic databases, PubMed, Medline, and Web of Science, were searched using a combination of free text search terms and Boolean operators (AND/OR). The search terms included were nanoparticle, nanotechnology, “local drug delivery”, “drug delivery system”, periodontitis, and “periodontal disease”. During the above-described database searches, 895 studies were identified. PRISMA-SCR guidelines were followed for the selection of the study (Fig. 1). Of the above-found literature, 184 were duplicates and were excluded. From reading their titles and abstracts, 620 articles were excluded as they were irrelevant to this review. After the remaining 91 records were thoroughly screened, 82 were removed for not meeting the eligibility criteria, leaving 9 studies to be included in the review.

Two experienced researchers are selected to independently conduct literature searches based on predefined inclusion and exclusion criteria. Each observer performed a comprehensive literature search using predetermined search terms and databases relevant to the research question. After completing the search, the observers compiled their findings and compared the retrieved articles. Any discrepancies in the included articles were resolved through discussion with the third author. The third author’s decision was considered final.



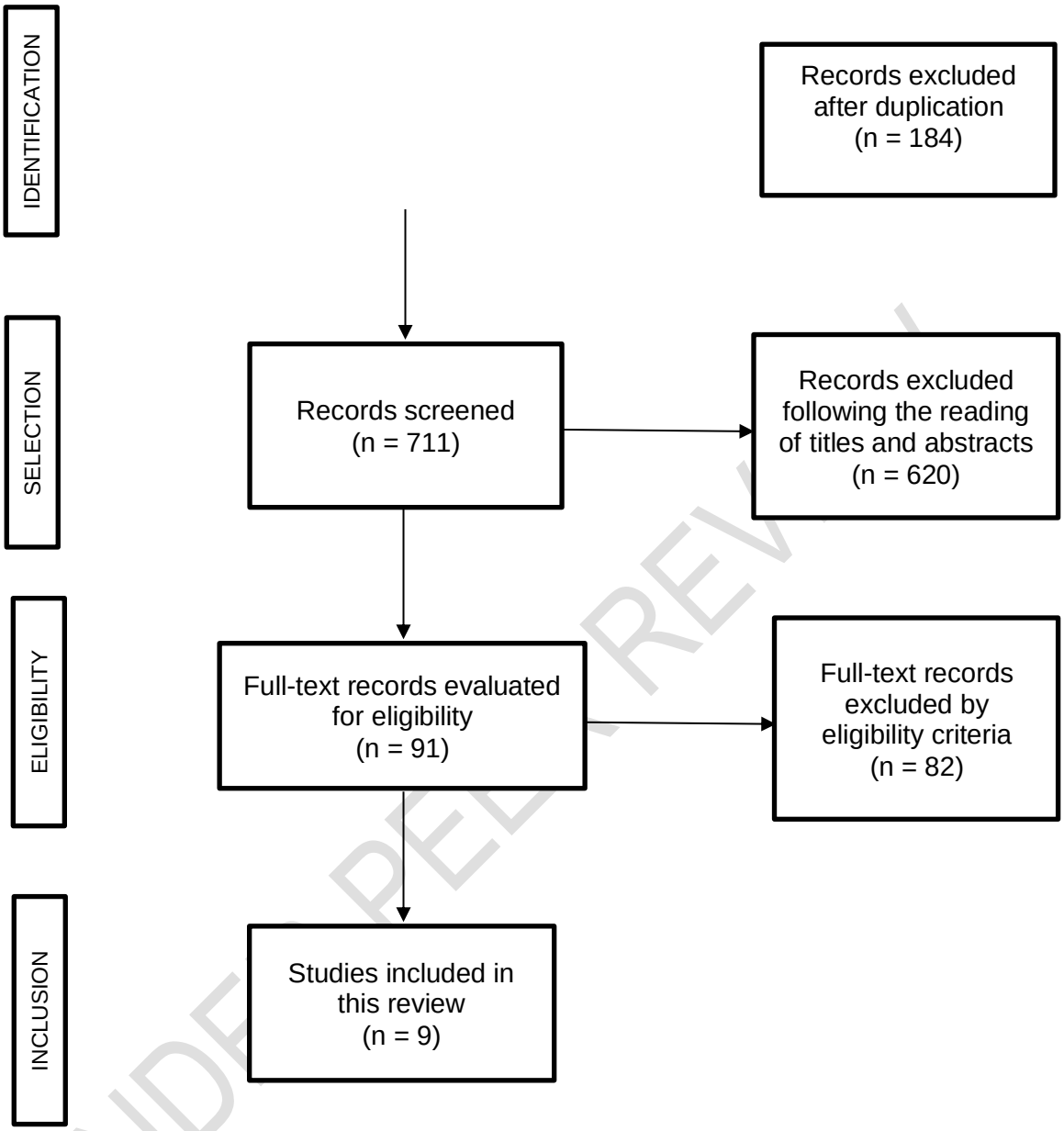


Fig. 1. Flowchart for Article Selection according to the PRISMA-SCR checklist.

3. RESULTS

3.1 Descriptive analysis

The sample sizes varied greatly, spanning from 6 to 60 cases. Patients' age ranges from 18 to 65 years. The studies showed different methods of delivering drugs, like nanoparticles, nanocarriers, nano-bioinfusion, and nanospheres. The following nanoparticle-delivering systems have been researched:

a) Nano-Bio Fusion composed of Propolis, Vitamin C and Vitamin E,
b) Nano-structured Doxycycline gel (nDOX),

c)PLGA nanospheres loaded with doxycycline,
d) Curcumin-loaded PLGA nanoparticles,
e) 2% Curcumin powder as nanocarrier-Pluronic F127,
f) 5% Tetracycline gel Hydroxypropyl methylcellulose (HPMC) powder & Silver nanoparticles,
g) 0.25% Satranidazole gel in Ganglioside polymeric nanoparticles (G-PNP),
h) Propolis as nanoparticle solution.

The gingival index (GI), plaque index (PI), probing pocket depth (PPD), and clinical attachment level (CAL) were found to be the preferred method of evaluation for assessing the periodontal status. The concentration of cytokines like IL-6, IL-1α, IL-10, and TNF-α and the microbiological analysis were also evaluated in a few studies. (Debnath K (2016), Lecio G (2018), Guru SR (2020), Kadam (2020), Kesarwani S (2022)). The above studies have collected data across various time frames as shown in Table 1. In this review, focus was given solely to the time that yielded the greatest result.

3.2 Clinical criteria

On average, the change in mean gingival index (GI) score ranged from 0.167±0.01 (Kesarwani S, 2022) to 0.88 (Guru SR, 2020) at 21 days. The change in mean plaque index (PI) from 20.0 ± 15.7 (Lecio G, 2018) at 6 months to 3.13 (Pérez-Pacheco CG, 2021) at 3 months.

The mean Papillary bleeding index value was 0.638 (Sneha V, 2014). The mean Sulcus bleeding index value at 6 weeks was 0.48 (Debnath K, 2016). The mean gingival bleeding index was 2.10 ± 2.02 at 1 month and the mean GR at 6 months was 0.91 ± 1.06 (Pérez-Pacheco CG, 2021). The mean GMP at 3 months was 1.3 ± 0.8 (Lecio G, 2020).

The mean difference of GCF IL-6 values ranges from 1.63± 0.33 (Marwa Madi, 2017) to 2.6 ± 3.6 (Lecio G, 2018) at 3 months. The mean difference of GCF TNF-α values ranges from 1.20 ± 0.41 (Marwa Madi, 2017) at 3 months to 1.7 ± 1.8 (Lecio G, 2018) at 1 month. The levels of GCF IFN-γ were recorded as 2.3 ± 2.6 at 1 month, while GCF IL-10 levels were 5.4 ± 12.2, GCF IL-17 levels were 1.9 ± 3.0 and GCF IL-4 were 9.5 ± 26.2 at the same time point. The GCF IL-1β levels were 46.5 ± 60.5 at 6 months. The GCF IL-8 levels were measured as 202.3 ± 88.3 at the 6-month, while GCF MMP-9 levels were 5.5 ± 5.9 at 6 months (Lecio G, 2018).

The study by Pérez-Pacheco CG et al in 2021, showed that the levels of inflammatory mediators in GCF were represented in the graph where IL-6 varied from 1.1 ng/µl at baseline to 0.2 ng/µl at 15th day. IL-1α levels varied from 0.2 ng/µl at baseline to 0.5 ng/µl on the 15th day. IL-10 varied from 1.3 ng/µl at baseline to 0.5 ng/µl on the 15th day. TNF-α varied from 0.3 ng/µl at baseline to 0.5 ng/µl on the 15th day. There was not much of a change observed at the end of 15 days when compared with the control group.

Debnath K et al (2016) observed the growth of aerobic bacteria in nutrient agar and Kadam P et al (2020) observed the growth of anaerobic bacteria in Thioglycollate medium (0.1 ml) with the blood agar through the mean colony-forming units. Guru SR, (2020) identified the presence of Aggregatibacter actinomycetemcomitans (Aa), Porphyromonas gingivalis (Pg), and Tannerella forsythia (Tf) and Kesarwani S, (2022) identified the presence of Porphyromonas, Fusobacterium, Tannerella, and Bacteroides through PCR. Lecio G, (2020) observed the levels of Porphyromonas gingivalis (Pg), Aggregatibacter actinomycetemcomitans (Aa), Tannerella forsythia (Tf), and Fusobacterium nucleatum (Fn) through quantitative polymerase chain reaction (qPCR). The Checkerboard DNA-DNA hybridization technique by Pérez-Pacheco CG, (2021) showed all subgingival microbial complexes including Actinomyces species, yellow, orange, and red complexes.

Table 1. Results of selected articles

AUTHOR & YEAR	STUDY DESIGN	NATURE OF NANOPARTICLE USED	DRUG DELIVERED	TARGET	PARAMETERS RECORDED	CONCLUSIONS
V.Sneha, 2014	A Clinical study	Nano-Bio Fusion (NBF) Gingival Gel	Propolis, Vitamin C and Vitamin E	Stage II and stage III gingivitis subjects	Indexes recorded 1. Gingival index, 2. Papillary bleeding index.	Nanoemulsion significantly reduced inflammation.
Koel Debnath,2016	A Clinico-Microbiological Study	Nano-Bio Fusion (NBF) gingival gel	Propolis, Vitamin C and Vitamin E	Six chronic periodontitis patients comprising 76 sites	-Indexes recorded 1. Plaque index, 2. Gingival index, 3. Sulcus bleeding index(SBI). -Clinical Parameters 1. Probing Pocket Depth, 2. Clinical attachment level (CAL). -Supragingival microbial plaque analysis was done.	NBF gel has improved the clinical parameters of the patients.
Marwa Madi, 2018	A Clinical Study	Nano-structured Doxycycline gel (nDOX)	Doxycycline (DOX)	45 patients suffering from moderate chronic periodontitis	- Indexes recorded 1. Plaque Index 2. Gingival Index -Clinical Parameters 1. Probing Pocket Depth, 2. Clinical attachment level (CAL). The concentration of IL-6 and TNF-α markers in the GCF samples was determined.	It is safe and improves both clinical parameters and 5nflammatory markers(3 months).
Giovana Lecio, 2019	A parallel, double-blind, randomized, placebo-controlled clinical trial immune	PLGA nanospheres	20% Doxycycline-loaded PLGA nano-spheres	Chronic periodontitis in 40 individuals with type-2 diabetes mellitus	- Clinical Parameters 1. Probing Pocket Depth, 2. Clinical attachment level (CAL), 3. Bleeding on probing,	Reduce pockets and bleeding on probing in chronic periodontitis individuals with type-2 DM.

	and microbiologic-al trial				4. Gingival margin position (GMP). - Levels of the cytokines were determined in GCF. - Periodontal pathogen quantification was analysed.	
Cindy Grace Pérez-Pacheco, 2020	Randomized, placebo-controlled, double-blind split-mouth clinical trial	PLGA/PLA nanoparticles	Curcumin loaded nanoparticles	Patients with generalized periodontitis with stage III and Grade A	- Clinical Parameters 1. Probing pocket depth (PPD), 2. Clinical attachment level (CAL), 3.Gingival recession (GR), 4. Bleeding on probing (BOP). - Indexes recorded 1. Plaque Index 2. Gingival Bleeding Index - Inflammatory cytokines 1.IL-6 2. TNF-α - Bacterial counts in colour-coded complexes.	The nano-encapsulated curcumin had no significant additional benefits.
Sanjeela Rakshith Guru, 2020	A pilot randomized controlled clinical trial	Nanocarrier-Pluronic F127	2% Curcumin powder	Patients with localized or generalized mild-to-moderate chronic periodontitis	- Clinical Parameters 1. Probing pocket depth (PPD), 2. Clinical attachment level (CAL). -Microbiological analysis - Indexes recorded 1. Plaque Index 2. Gingival Index.	There was an improvement and reduction in all clinical parameters and microbiological parameters.
Pooja Kadam, 2020	A clinico-microbiological study	Hydroxypropyl methylcellulose (HPMC) powder&Silver	5% Tetracycline gel	Subjects with chronic periodontitis	- Clinical Parameters 1. Probing pocket depth (PPD), 2. Clinical attachment level (CAL).	CFU showed a statistically significant reduction due to the antimicrobial activity of silver

		nanoparticles			-Microbiological analysis - Indexes recorded 1. Plaque Index 2. Gingival Index.	nanoparticles.
Shivam Kesarwani,2022	A split-mouth randomized clinical trial.	Gangliosside polymeric nanoparticles (G-PNP).	0.25% satranidazole gel.	Subjects with localized/ generalized mild-to-moderate chronic periodontitis.	- Clinical Parameters 1. Probing pocket depth (PPD), 2. Clinical attachment level (CAL), 3. Bleeding on probing (BOP). - Indexes recorded 1. Plaque Index 2. Gingival Index -Subgingival plaque samples were collected	Satranidazole gel consistently produced better results compared to metronidazole gel.
Sushree Ambika Sahu, 2023	The study was a prospective, double-blind, randomized clinical trial of parallel design	Nanoparticle solution	Propolis	Patients diagnosed with periodontitis	- Clinical Parameters 1. Probing pocket depth (PPD), 2. Relative attachment level (RAL), 3. Bleeding on probing (BOP). - Indexes recorded 1. Plaque Index 2. Gingival Index	Propolis nanoparticles with SRP resulted in significant reductions in GI, BOP, PPD, and RAL compared with the control sites.

The mean difference in Colony forming unit/ml ranges from 0.021 at 6 weeks (Debnath K, 2016) to 2873.7±418.11 (Kadam, 2020) at 3 months. The mean levels of Aggregatibacter actinomycetemcomitans ranged from 2.7 ± 1.6 (Lecio G, 2020) at 6 months to 560.1 (Guru SR, 2020) at 45 days. The mean levels of Porphyromonas gingivalis ranged from 3.6 ± 1.3 (Lecio G, 2020) at 3 months to 240.5 (Guru SR, 2020) at 45 days. The mean levels of Tannerella forsythia were 1.1 ± 1.9 (Lecio G, 2020) at 3 months to 848.9 (Guru SR, 2020) at 45 days. The levels of Fusobacterium nucleatum were 2.0 ± 1.8 at 6 months (Lecio G, 2020). The mean bacterial proportion of red complex organisms at 15 days was 7% when compared to the baseline which was 19% (Pérez-Pacheco CG, 2021).

4. DISCUSSION

Most of the studies were done on patients with chronic periodontitis, except one which was conducted on patients with gingivitis. A total of 257 subjects were included in this review. These studies considered the number of patients, except Kadam P et al (2020), who considered only the sites.

According to Sneha V et al (2014), which is the first published clinical research on this title, used Nano-Bio Fusion (NBF) Gingival Gel with propolis sulcularly in patients with gingivitis.

The same gel was investigated by Debnath K et al (2016) in subjects with chronic periodontitis which showed better results both clinically and microbiologically.

This review observed that different kinds of drugs/herbal extracts were incorporated with nanoparticles. That includes propolis, vitamin C, vitamin E, doxycycline (DOX), curcumin, satranidazole, and tetracycline.

Various clinical parameters were evaluated in this review such as probing pocket depth (PPD) clinical attachment level (CAL), bleeding on probing (BOP), relative attachment level (RAL), gingival margin position (GMP), and gingival recession (GR). Out of nine, seven articles have assessed PPD and CAL in common.

The results of clinical parameters and periodontal indices obtained from every article showed statistically significant differences between the groups.

In the course of six studies, researchers conducted microbiological analyses utilizing a variety of traditional methods. While these methods have historically served as valuable tools in scientific inquiry, recent advancements in technology and methodology have presented us with more sophisticated options. Contemporary techniques, such as next-generation sequencing (NGS) metagenomics, and MALDI-TOF (matrix-assisted laser desorption/ionization time-of-flight) mass spectrometry provide rapid and accurate identification of microorganisms and offer a wealth of advantages over traditional approaches.

The effects observed in this study prompted a question regarding whether they were caused by the drug itself or its nanoparticle formulation. This uncertainty arises because the study did not compare it with conventional drug delivery. The results do not definitively indicate whether the observed effects result from the drug's mode of delivery (nanoparticles) or the drug alone, given that the control group received standard treatment.

Nanoparticles demonstrated enhanced efficacy when compared with conventional treatment. This underscores the complexity of periodontal disease which involves multiple factors, indicating that examining these elements individually may not be comprehensive enough.

The impact of nanoparticles appears limited due to short observation periods, small sample sizes, and the absence of standardized study protocols. To achieve favourable outcomes, longer study periods and larger sample sizes are necessary.

5. CONCLUSION

Nanoparticles have shown considerable promise in various medical fields due to their unique properties and versatile applications in diagnosis, treatment, and disease management, with ongoing research exploring new possibilities and refining existing techniques. Nanoparticle-based local drug delivery represents a valuable approach to the comprehensive management of periodontal diseases. By delivering therapeutic agents directly to the affected areas, nanoparticles enhance the efficacy of these agents compared to systemic administration. This targeted approach increases drug concentration at the site of action, leading to improved outcomes in managing periodontitis. Despite the promising results, more research is needed to fully understand the long-term effects of nanoparticle-based drug delivery in periodontal treatment. Studies should focus on determining optimal dosing strategies, evaluating potential side effects, and assessing the durability of treatment effects over time.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc.) and text-to-image generators have been used during the writing or editing of this manuscript.

CONSENT AND ETHICAL APPROVAL

It is not applicable.

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ABBREVIATIONS

Prisma-SCR - Preferred Reporting Items for Systematic Reviews And Meta-Analyses Extension For Scoping Review.

APPENDIX

Supplementary data to this article can be found in Supporting Information File 1.pdf