SYSTEMATIC REVIEW

Endodontic Regeneration of Micro/ Nanoparticles-based Delivery System of the Triple Antibiotic Drug: A Systematic Review

Mahaboobshahul Hameed[1], S. Delphine Pricilla Antony[1], Rajeshkumar Shanmugam[2]

[1]Department of Conservative Dentistry and Endodontics, Saveetha Dental College and Hospitals, Saveetha Institute of Medical and Technical Sciences, Saveetha University, Chennai, Tamil Nadu, India, [2]Nanobiomedicine Laboratory, Saveetha Institute of Medical and Technical Sciences, Saveetha University, Chennai, Tamil Nadu, India

Abstract

Improved physicochemical properties of antimicrobial nanoparticles have attracted significant attention as an improved antimicrobial agent, especially in the multifaceted setting of the oral cavity. The present systematic review assesses the existing evidence regarding nanoparticle-based delivery systems loaded with triple antibiotic paste (TAP) that can be applied in the field of regenerative endodontics, in other words, in the treatment of root canal infections. The systematic review was carried out through a comprehensive search of the literature published in 2016–2021 in English in PubMed Central, Google Scholar, and in MEDLINE. Appropriate information regarding TAP, endodontic regeneration, and antimicrobial activity of the micro- and nanoparticle systems was retrieved and reviewed descriptively. Among 39 identified articles, 19 articles were found to be relevant after the screening process, and nine articles met the inclusion criteria to be included in the quantitative synthesis. The result reveals that biodegradable micro- and nanoparticle-based delivery systems retain the antibacterial effect of TAP and allow to control and release the compound locally and at low concentrations to promote regenerative effects where it is delivered. All in all, the included studies indicated that nanoparticulate systems have similar or even better efficacies in the management of root canal infections as compared to traditional antimicrobial methods, but the clinical evidence on the utilization of TAP-loaded local drug delivery systems is still limited, which explains the necessity of well-designed clinical trials to facilitate the standardization of the procedures in clinical practice.

Key words: Endodontics, innovative, product innovation, regeneration, triple antibiotic paste

INTRODUCTION

Endodontic therapy is mainly guided by the removal of microorganisms in the root canal system and root canal reinfection prevention, thus promoting periapical healing. Pulpal and periapical diseases have a microbial etiology, mostly which is complex polymicrobial biofilms which colonize the complex root canal system. Such biofilms are of high resistance to traditional chemomechanical preparation methods because of their organization and protective extracellular matrix, which makes total disinfection difficult.[1,2] In addition, anatomical complications such as lateral canals, apical ramifications, and dentinal tubules restrict the penetration of irrigants and intracanal medicaments, which lead to persistent infection and failure in treatment.[3]

Traditional root canal treatment emphasizes disinfection and obturation; however, it lacks any restoration of the biological vitality of pulp density complex. Regenerative endodontics has come up as a biologically oriented mode of treatment with a goal of restoring the vitality of the

Address for correspondence:
S. Delphine Pricilla Antony, Department of Conservative Dentistry and Endodontics, Saveetha Dental College and Hospitals, Saveetha Institute of Medical and Technical Sciences, Saveetha University,
Chennai, Tamil Nadu, India.
E-mail: delphy.priscilla@gmail.com

Received: 22-02-2026
Revised: 21-03-2026
Accepted: 31-03-2026

AQ1

pulp, stimulating further root growth, and strengthening the dentinal walls.[4] Regenerative endodontic procedures are grounded on principles of tissue engineering that uses stem cells, scaffolds, and signaling molecules. Effective disinfection is one of them, since any remaining microbial contamination may interfere with stem cell survival and regeneration.[5] Intracanal medicaments are essential toward this disinfection. Triple antibiotic paste (TAP) containing metronidazole, ciprofloxacin, and minocycline has become popular with its ability to be effective against the endodontic pathogens with a broad-spectrum antimicrobial activity.[6] Its synergistic effect allows it to be effective in the removal of aerobes and anaerobes, including resistant bacteria like Enterococcus faecalis.[7]

Recent evidence indicates that TAP is an important ingredient of the regenerative protocol, especially in revascularization surgery, because it can develop a good microenvironment to promote tissue regeneration.[8] Nevertheless, in spite of being effective, there are several limitations to conventional TAP delivery. It is reported that high levels of TAP work by inducing cytotoxic properties on the apical papilla (SCAP) stem cells that are vital to effective regeneration.[9] Furthermore, there is an esthetic issue regarding tooth coloration caused by minocycline usage, especially anterior teeth.[10] Its other disadvantages are uncontrollable release of drugs, poor penetration into dentinal tubules, and the possibility of antimicrobial resistance.[11]

New systematic reviews also highlight that TAP itself has high antimicrobial efficacy, although its clinical performance is a function of concentration, mode of delivery, and formulation.[12] To address these shortcomings, novel and superior drug delivery systems founded on micro- and nanotechnology have been considered. This is due to the fact that nanoparticles have distinct physicochemical characteristics such as a high surface area-volume ratio, increased penetration in biofilms and dentinal tubules, and controlled and sustained drug release.[13] Latest developments in antibacterial nanoformulations possess a high potential to enhance better endodontic disinfection due to biofilm resistance and anatomical obstacles.[14] The systems can be designed to proffer antimicrobial agents in a controlled and continuous fashion, thus enhancing effectiveness and decreasing cytotoxicity. Introduction of TAP in delivery systems based on micro/nanoparticles is also a promising strategy in regenerative endodontics. These systems permit the release of kinetic to be regulated, the antibiotics to be more stable, and the antimicrobial activity to be improved. Furthermore, nanoparticle scaffolds have the capability to serve as drug carriers and scaffolds, facilitating cell adhesion, proliferation, and differentiation.[15]

Recent findings indicate that nanoparticle-based scaffold and hydrogel are both effective in disinfection and regenerative functions, including stimulating angiogenesis, mineralization, and pulp-like tissue regeneration.[16] Moreover, newer research identifies the potency of the nano-enabled drug delivery systems to overcome the shortcomings of the traditional intracanal medicaments. With these systems, it is easy to penetrate deeper into the infected dentin, maintain antimicrobial action, and increase the contact with stem cells, which form a favorable microenvironment in which regeneration occurs.[14,17]

A combination of nanotechnology and regenerative endodontics can therefore be considered an important step toward ensuring that the endodontics profession will be able to guarantee predictable and biologically desirable outcomes. Due to the recent accumulation of evidence regarding nanoparticles, as the mediators of drug delivery and the proven application of TAP in the context of a regenerative procedure, a thorough assessment of these methods is required. This systematic review is expected to critically evaluate the efficacy, biocompatibility, and regenerative promise of micro/nanoparticle-based delivery system containing triple antibiotic drugs in endodontic regeneration.

MATERIALS AND METHODS

Study design

This systematic review was conducted in accordance with the preferred reporting items for systematic reviews and meta-analyses guidelines established in 2009.

Our objective in the review aimed to analyze the studies that reported the biomedical application of micro/nanoparticles with triple antibiotics in drug delivery systems for endodontic regeneration.

Eligibility and inclusion criteria

Intervention

TAP, comprising ciprofloxacin, metronidazole, and either minocycline, penicillin, or clindamycin.

Comparators

Absence of an intracanal medicament or the use of alternative intracanal medicaments other than TAP.

Outcomes

Assessment of antimicrobial effectiveness, cytotoxicity, and stem cell viability, potential for tooth discoloration, and the ability to support revascularization and regenerative outcomes.

Study designs

This was a *in vitro*, *in vivo,* and clinical trials.

AQ1

Exclusion criteria

Case reports and studies not published in English were excluded from the analysis. Additionally, studies in which TAP was employed as an irritant rather than as an intracanal medicament were not considered for inclusion.

Search strategy

The electronic search of the literature was conducted on the "PubMed Central, Google scholar, and MEDLINE" databases with the following MESH terms: "Triple antibiotic pastes or TAP," "Endodontic regeneration," "Antimicrobial efficacy," "Drug delivery" and "Nanoparticles" using Boolean operators (AND, OR).

In addition to database searching, the reference lists of the selected articles were manually screened to identify any additional relevant studies. Only publications available in English were considered for inclusion. The titles and abstracts retrieved from the three databases were initially screened to evaluate their relevance and eligibility. Subsequently, the abstracts of potentially eligible studies were examined in detail based on the predefined selection criteria. Studies that did not meet these criteria were excluded at this stage. Full-text articles of the remaining studies were then assessed thoroughly, and those with duplicate data or failing to meet the inclusion criteria were further excluded [Figure 1].

Data collection

The relevant studies were determined with the help of the identified keywords. Preference was made to data that covered antibacterial efficacy in both *in vitro* studies, *in vivo* studies, and clinical trials. The studies that included a quantitative analysis were only included because they gave strong and meaningful evidence which complied with the purpose of the review.

RESULTS

Search results

The electronic database search led to the identification of 39 articles. A total of 19 studies shortlisted on the basis of their relevance were thoroughly evaluated on the basis of their abstracts and the entire content. After this evaluation, 9 articles were found to be within the inclusion consideration and were finally included into the study. The constant research that is underway is based on designing greater drug delivery systems that would deliver therapeutic concentration accurately at the target site. Besides other factors like cellular uptake and release, cytotoxicity, and general efficacy of treatment, this review also intends to determine the biomedical potential of TAP as an intracanal medicament in micro- and nanoparticle-based systems to enhance periradicular healing.

Overall features of the study

All original research articles published in 2016–2021 were taken into account, and nine studies met the inclusion criteria that included both *in vitro* and *in vivo* studies. TAP is proved to be a good antimicrobial intracanal medication with a rather positive biocompatibility with stem cells in the periapical area compared to calcium hydroxide that can be used traditionally and can be cytotoxic to the stem cell. TAP concentration determines the viability of human dental pulp cells and the level of cytotoxicity of TAP. It is worthy to note that the synergistic combination exhibits higher cytotoxicity in comparison to the single antibiotics; this is probably because more hydrogen ions were released and therefore, the pH was reduced. Considering the constraints, much has been done on the development of innovative local drug delivery systems.

In these systems, the antibiotics are loaded in appropriate microcarriers, such that there is a burst release at the first 24 h, and then the therapeutic ability is maintained up to 14 days. The overall features of all nine studies that show the different devised lymphatic drug delivery systems employing a triple antibiotic mixture are shown in Table 1.

DISCUSSION

Antimicrobial resistance has become a major issue with regard to the treatment of infection. TAP, which contains metronidazole, ciprofloxacin, and minocycline, has been widely used in endodontics because of broad-spectrum antimicrobial effect and because it has the ability to effectively disinfect dentin.[18] Lovelace *et al*.[19] established that in addition to its action of disinfecting infected pulp, which is necrotic in nature, the induced bleeding step following TAP application in re-generating procedures promotes the migration of undifferentiated stem cells in the periapical area into the root canal space.[20] The lack of precise targeting capability in the diffusion of antibiotics within living organisms at the tissue level may be offset by the recent developments of using nanoparticles in biomaterial-based drug delivery systems of antimicrobial agents to ensure appropriate drug delivery levels at the target site of action, even under dynamic conditions.[21] These types of local drug delivery methods increase the efficacy and pharmacokinetic characteristics of the drugs over their traditional free states. Moreover, they allow the release of an antimicrobial agent in a sustained and controlled fashion, thus supporting the better infection control and promoting the regeneration of the dentin-pulp complex.[22]

Micro/Nanoparticles based delivery systems are a tool with a variety of applications, which include drug delivery in the biomedical field, tissue engineering, cell imaging, and intracellular sensing over biosensors and immunoassays, as well as heterogeneous biocatalysis.[23]

Table 1: Summary of studies examining the use of nanoparticles for drug delivery system

Study objective	Procedure	Physicochemical properties	Comparator	Main findings	References
To assess and compare the cytotoxic potential of TAP and an anti-inflammatory agent in both nanoparticle-based and conventional formulations, using calcium hydroxide as a control.	Cytotoxicity evaluated on human fibroblast cell lines using MTT assay followed by flow cytometric analysis of materials on apoptosis/necrosis	Reduced particle size may elicit different biological responses by production of reactive oxygen species and interruption of ATP synthesis causing DNA damage	Ca $(OH)_2$ and conventional TAP	Nano TAP had higher cytotoxic effect compared to conventional TAP	[30]
To assess the efficacy of PLGA coated ceramic microparticles to deliver modified triple antibiotics to the root canal system for use in endodontic application	PLGA-coated ceramic microparticles were synthesized using β-tricalcium phosphate and hydroxyapatite, followed by uniform dispersion within the drug solution. Drug release from these PPCMs was analyzed using a ultraviolet spectrophotometer. The antimicrobial efficacy of PPCMs was evaluated against *Enterococcus faecalis* and *Aggregatibacter actinomycetemcomitans* using agar plate diffusion testing, along with determination of minimum inhibitory concentration and minimum bactericidal concentration. Cytotoxicity was assessed through an MTT assay to determine cell viability in HGFs.	Ceramic microparticles was in the ideal range of drug delivery system (2 nm–1 μm) with a smooth surface, which results in less inflammatory response in the target sites/ tissues.	PLGA/ Chloroform solution without antibiotic	An initial rapid release of antibiotics from the PLGA matrix was observed, followed by a controlled and sustained release phase, likely governed by the combined effects of diffusion and polymer degradation. PPCMs maintained a neutral pH, enabled adequate drug release, demonstrated effective antibacterial activity against *E. faecalis* and *A. actinomycetemcomitans*, and showed good biocompatibility, with over 70% viability in HGF cells.	[31]
To develop clindamycin-modified triple antibiotic-loaded polymeric nanofibers and evaluate their *in vitro* antimicrobial efficacy, biocompatibility, and potential to cause dentin discoloration.	CLIN modified triple antibiotic nanofibers processed via electrospinning. The antimicrobial efficacy of electrospun nanofibers was evaluated against *Actinomyces naeslundii*, *E faecalis, A. actinomycetemcomians* and *Fusobacterium nucleatum*. Cytocompatibility was measured against human dental pulp stem cells hDPSCs	Clindamycin-containing triple antibiotic nanofibers are smaller in diameter, which could allow more drug release over time since they provide more surface area. Nanofibers have high tensile strength during dry and wet conditions and able to withstand handling, suggesting its potential to endure placement in clinical conditions.	Compared with clindamycin, chlorhexidine, and conventional TAP	CLIN-m nanofibers exhibited larger inhibition zones compared to chlorhexidine. It showed slight reduction in cell viability on hDPSCs about 50% and demonstrated stain free properties on tooth dentin compared to conventional TAP	[32]

(Contd...)

AQ1

Table 1:*(Continued)*

Study objective	Procedure	Physicochemical properties	Comparator	Main findings	References
To assess the antibacterial efficacy of triple antibiotics incorporated within a nitric oxide-releasing biomimetic nanomatrix gel.	The gel synthesized from PAs and antibiotics was encapsulated in the biomimetic nanomatrix gel, and tested on fourteen endodontic species	The biomimetic nanomatrix gel is a biocompatible peptide-based material with self-assembled PA matrix which enhances structural integrity and eliminate concerns regarding inflammatory responses, and exhibits potential for bio-absorbable stent coating applications	Compared with $Ca(OH)_2$, TAP without NO releasing nanomatrix gel	*In vivo* findings indicated that a nitric oxide-releasing biomimetic nanomatrix gel loaded with antibiotics facilitated tooth revascularization and supported root canal maturation at a concentration of 0.125 μg/mL.	[33]
To design and fabricate a three-dimensional tubular construct capable of delivering triple antibiotics in a controlled manner for effective intracanal drug delivery.	The antimicrobial properties of the tubular 3D constructs were determined *in vitro* and *in vivo* using an infected (*A. naeslundii*) dentin tooth slice model and a canine method of periapical disease	Young's modulus of electrospun nanofibers were high at dry state suggesting that the antibiotics did not compromise rigidity characteristics of the fibers. After hydration reduced modulus indicates that tubular 3D construct allows the fibers to progressively degrade to ensure their antimicrobial effect.	Antibiotic-free polymer nanofibers	The three-dimensional tubular construct designed for sustained release of triple antibiotics promoted apical closure and facilitated the formation of a thin layer of osteodentin-like tissue within the root canal.	[34]
This study aimed to evaluate the antimicrobial effectiveness of nanofibers loaded with a triple antibiotic combination against a dual-species biofilm, while also assessing the capacity of dental pulp stem cells to attach and proliferate on dentin following exposure to these nanofibers.	Seven-day-old dual-species biofilm established on dentin specimens. Bacterial viability assessed using the LIVE/DEAD assay. Cyto-compatibility evaluated for cell adhesion and spreading by actin-phalloidin staining.	Triple antibiotic-containing polymer nanofibers demonstrate a kinetic release property with a favorable burst in 24 h while sustaining its effects up to 14 days.	Antibiotic free polymer nanofibers	After 7 day exposure of dentin biofilm TAP nanofibers promote bacterial death with no damaging effects on stem cell attachment and viability. TAP nanofibers in acidic pH promotes significant reduction in dentin microhardness	[27]
An *in vitro* study was undertaken to assess the effects of a polymer-based nanofibrous scaffold mimicking TAP on dentin biofilms infected with *Porphyromonas gingivalis* (Pg).	TAP polymer solution of 25 mg/mL concentration spun into scaffolds using a custom-made electrospinning system	Antibiotic-containing nanofibrous-based polymer scaffolds contain 3 mg/mL concentration of antibiotics to avoid root canal reinfection and residual bacterial proliferation	Conventional TAP	Scanning electron microscopy analysis of the TAP-mimic scaffold and TAP solution demonstrated the attachment of non-viable bacteria to the dentin surface. This was attributed to surface irregularities and porosities in the scaffold membrane, as well as the formation of small, insoluble aggregates deposited over the dentin.	[35]

(Contd...)

AQ1

Table 1:*(Continued)*

Study objective	Procedure	Physicochemical properties	Comparator	Main findings	References
An *in vitro* investigation was conducted to evaluate the antimicrobial efficacy of three-dimensional (3D), tubular-shaped nanofibrous constructs loaded with triple antibiotics against a multispecies biofilm established on human dentin.	Polydioxanone polymer solutions incorporated with TAP, electrospun into 3D tubular-shaped constructs. After 7 day exposure, the infected dentin slices was assessed for cell viability using fluorescent LIVE/DEAD assay.	3D tubular construct contains 1 mg/mL drug concentration which closely adapts to the root canal wall of the dentin slices posing minimal risk of dentinal tubules blockage and, allow release of dentin growth factors upon ethylenediaminetetraacetic acid irrigation	Conventional TAP	Tubular three-dimensional antibiotic-eluting nanofibers, designed for disinfecting immature teeth with pulpal necrosis, enable close adaptation to the root dentin walls and support regeneration of the pulp-dentin complex.	[36]
To assess the efficacy of PLGA microspheres containing a triple antibiotic mixture	Triple antibiotic loaded on PLGA microspheres using the double emulsion technique. Cytotoxicity evaluated using MTT bromide assay.	The diameter and surface morphology of microspheres shows deformation and hydrolytic degradation after incubation for 8–12 days. the drug-release from PLGA microspheres mainly depends on the polymer mass degradation	Antibiotic-free polymer microspheres	The lower cytotoxicity and minimized adverse effects can be linked to the controlled and sustained release of therapeutic agents from the microspheres. Additionally, the viability of human dental pulp cells and the degree of cytotoxicity were observed to be influenced by both the concentration of the agents and the duration of exposure.	[37]

TAP: Triple antibiotic paste, PLGA: Poly-lactic-co-glycolic acid, PPCMs: Polymer-ceramic microparticles, MTT: 3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide, PA: Peptide amphiphile, hDPSCs: Human dental pulp stem cells, HGF: Human gingival fibroblast

AQ1

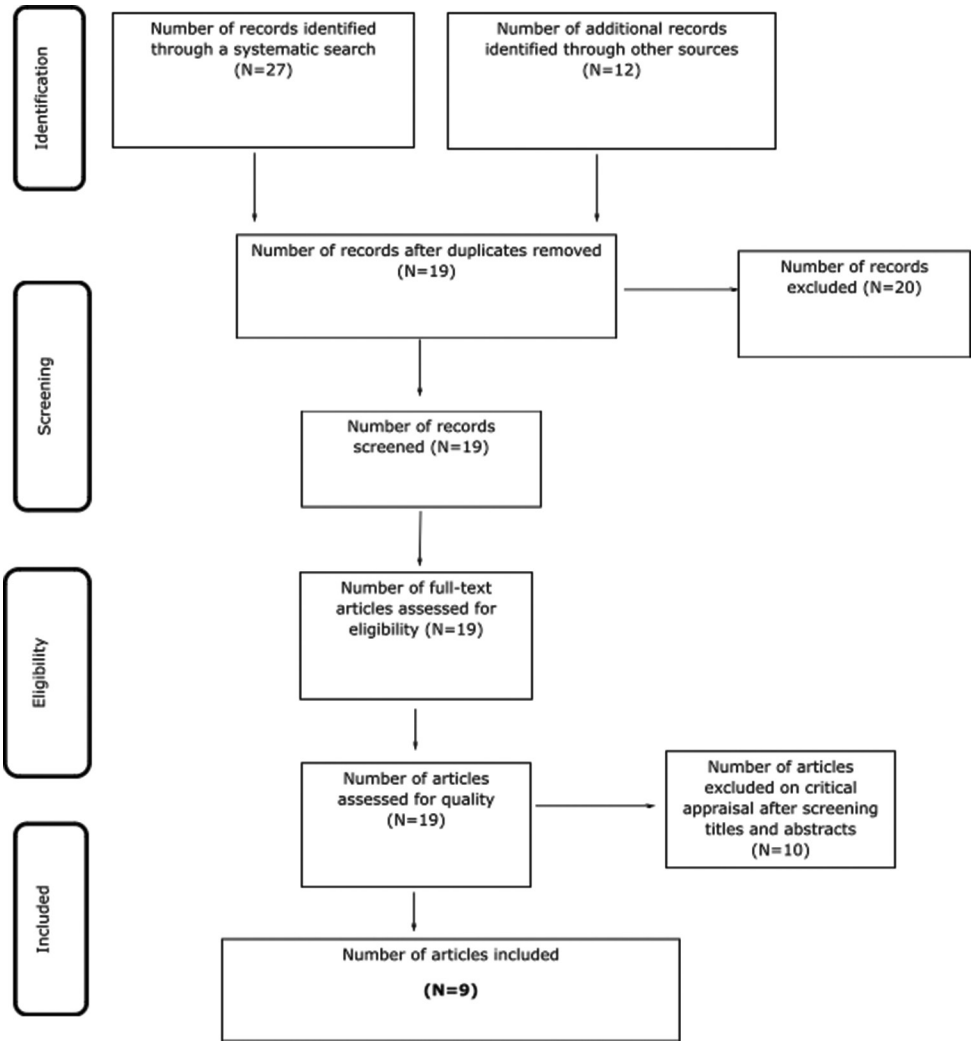

Figure 1: Preferred reporting items for systematic reviews and meta-analyses flow chart showing the identification and selection process of articles included

This hybrid design maintains flexibility to the surface modification with particle chemistry, whereby encapsulation of covalent-conjugated protein immobilization can be conducted in the synthesis to produce active biohybrid nanomaterials. Nanoparticles are also receiving much attention due to their distinctive antibacterial properties, including damaging of cell walls and membranes, interference with protein production, and interference with DNA. Such properties render them useful in the fight against bacterial infection.[24]

This paper seeks to assess the biomedical importance of micro-/nanoparticles based drug delivery system that incorporates triple antibiotics to be used in endodontic regeneration. Nanoparticles, which have low mass density and are relatively larger, are porous, which facilitates deposition to occur in the apical region. The incorporation of drug-containing nanoparticles into these systems would provide a good solution to the delivery of antimicrobials in the periradicular infections by integrating the benefits of micro- and nanoscale delivery vehicles to develop a system that offers prolonged release of nanoparticles containing antimicrobial drugs when deposited in the root dentin and exposed to the polymicrobial environment. This localized and prolonged delivery increases the efficacy of treatment and facilitates better clinical outcome.

Similarly, penicillin-modified TAP encapsulated with appropriate microcarriers has shown successful results against endodontic infections. Recently, an innovative local delivery system of bioceramic microparticles, made from hydroxyapatite and β-tricalcium phosphate, coated with a biopolymer, that is, polylactic glycolic acid (PLGA), loaded with triple antibiotics to the root canal system (target drug delivery) has exhibited successful outcomes to remove dominant intracanal microorganisms.[25]

The prolonged application period (1–4 weeks) and viscous nature of intracanal medicaments, compared to irrigating solutions, make them effective disinfectants capable of influencing stem cell behavior within the root canal system, including their attachment, proliferation, and

AQ1

differentiation.[26] Furthermore, dentin serves as a natural reservoir of bioactive molecules such as vascular endothelial growth factor and transforming growth factor-beta 1, which play a crucial role in supporting the survival, proliferation, and differentiation of dental stem cells.

Alghilan *et al*.[27] reported that dentin treated with TAP and double antibiotic paste in regenerative protocols demonstrated enhanced attachment of dental pulp stem cells, attributed to the demineralizing effect of TAP and the resulting increase in dentin surface roughness consequently, the results of Pankajakshan *et al*.[28] suggested that TAP can have a negative effect on the release of growth factors, the main cause being the lack of complete elimination of the TAP. Furthermore, the growth of stem cells on treated dentin has been limited by the presence of the residual paste, which obstructs the dentinal tubules, which in turn limits the release of the embedded growth factors. TAP is a product that is acidic in nature (pH = 2.9) and has been reported to cause a significant reduction in the dentin microhardness.[29]

An all-inclusive analysis of preclinical research shows that delivery systems based on biodegradable micro- and nanoparticle-based antibiotic delivery methods can be used to sustain the antimicrobial effects of the drugs contained as well as achieve controlled and localized delivery of TAP. These systems lead to a continuous and predictable low concentration release (around 1 mg/mL or 0.1 mg/mL) along the dentinal walls.

The evidence presented indicates that such intracanal delivery systems have a promising clinical application in regenerative endodontics. They have benefits such as successful antimicrobial activity, lower cytotoxicity, low chances of tooth discoloration, and possible aid in angiogenesis. Taken together, these results offer solid ground toward the establishment of standard clinical procedures and subsequent human testing.[30-37]

CONCLUSION

The current systematic review reveals the potential beneficial effect of micro- and nanoparticle-based drug delivery systems containing TAP in promoting endodontic regeneration. Such novel delivery systems have shown great benefits compared to traditional intracanal delivery medicaments because they allow sustained, controlled, and site-influenced release of antimicrobial drugs. More to the point, by being included in biodegradable micro/nanocarriers, TAP does not impair its antibacterial activity; on the contrary, it enhances the bioavailability of drugs, as well as supporting therapeutic levels in the target location throughout a prolonged period.

The evidence examined in this paper continues to suggest that nanoparticulate systems possess either high or equal effectiveness in killing endodontic pathogens in comparison to conventional delivery methods. They possess increased physicochemical properties such as greater surface area, greater penetration into dentinal tubules, and greater disruption of biofilms, which is why they are more effective in disinfecting the complex root canal. Besides, these systems assist in regenerative effects by reducing cytotoxicity related to high levels of antibiotics and by providing an appropriate microenvironment to allow the survival, proliferation, and differentiation of the stem cells. Although such positive findings have been made, the existing literature is largely *in vitro* based, and only a few studies have been done *in vivo*, and there is a significant lack of well-conducted randomized clinical trials.

Fluctuations in nano-particle composition, drugs concentration, and delivery procedures also hamper the capacity to have uniform clinical guidelines. Thus, although the micro/nanoparticle-mediated TAP delivery can be considered an important breakthrough in the area of regenerative endodontics, additional high-grade, large-scale clinical trials are needed to establish the long-term safety, effectiveness, and applicability of this technology in the translational environment. To sum up, TAP delivery systems based on nanoparticle is a clinically relevant and biologically favorable method of providing effective root canal debridement and tissue regeneration, yet its common clinical use needs more significant justification and standardization of protocols.

REFERENCES

1. Choudhari S, Ramesh S, Shah TD, Teja KV. Diagnostic accuracy of artificial intelligence versus dental experts in predicting endodontic outcomes: A systematic review. Saudi Endod J 2024;14:153-63.
2. Choudhari S, Ramesh S, Rossi-Fedele G, Teja KV. Comparative evaluation of pain and bacterial reduction in one-visit and two-visit retreatment of single-rooted teeth: A randomized clinical trial. J Conserv Dent Endod 2025;28:1252-7.
3. Manobharathi G, Raghu S, Krishnan A. Antimicrobial efficacy of modified gutta-percha for obturation - A systematic review. J Conserv Dent Endod 2025;28:2-9.
4. Murray PE, Garcia-Godoy F, Hargreaves KM. Regenerative endodontics: A review of current status and a call for action. J Endod 2007;33:377-90.
5. Hargreaves KM, Diogenes A, Teixeira FB. Treatment options: Biological basis of regenerative endodontic procedures. J Endod 2013;39:S30-43.
6. Sato I, Kurihara-Ando N, Kota K, Iwaku M, Hoshino E. Sterilization of infected root-canal dentine by topical application of a mixture of ciprofloxacin, metronidazole and minocycline *in situ*. Int Endod J 1996;29:118-24.
7. Mohammadi Z, Jafarzadeh H, Shalavi S. Antimicrobial efficacy of chlorhexidine as a root canal irrigant: A literature review. Iran Endod J 2014;9:149-55.
8. Panchal KG, Virani K, Patel V, Ali Khan A,

Pettiwala A, Puranik SS, *et al*. Triple antibiotic paste: A game changer in endodontics. J Pharm Bioallied Sci 2024;16 Suppl 3:S1913-5.
9. Ruparel NB, Teixeira FB, Ferraz CC, Diogenes A. Direct effect of intracanal medicaments on survival of stem cells of the apical papilla. J Endod 2012;38:1372-5.
10. Kim JH, Kim Y, Shin SJ, Park JW, Jung IY. Tooth discoloration of immature permanent incisor associated with triple antibiotic therapy: A case report. J Endod 2010;36:1086-91.
11. Iwaya SI, Ikawa M, Kubota M. Revascularization of an immature permanent tooth with apical periodontitis and sinus tract. Dent Traumatol 2001;17:185-7.
12. Barve A, Lakade L, Shah P, Chaudhary S, Jajoo S, Joshi G. Antibiotic paste as an intracanal medicament in infected primary teeth: A systematic review. Cureus 2025;17:e82876.
13. Shrestha A, Kishen A. Antibacterial nanoparticles in endodontics: A review. J Endod 2016;42:1417-26.
14. Dionísio T, Brandão P, Machado V, Botelho J, Mendes JJ, Fonte P. Recent advances in antibacterial nanoformulations for endodontic applications. Expert Opin Drug Deliv 2025;22:1117-36.
15. Bottino MC, Pankajakshan D, Nör JE. Advanced scaffolds for dental pulp and periodontal regeneration. Dent Clin North Am 2017;61:689-711.
16. Galler KM, D'Souza RN, Federlin M, Cavender AC, Hartgerink JD, Hecker S, *et al*. Dentin conditioning codetermines cell fate in regenerative endodontics. J Endod 2011;37:1536-41.
17. Zhao J. Progress of research on the application of triple antibiotic paste and hydrogel scaffold materials in endodontic revascularization: A systematic review. Evid Based Complement Alternat Med 2022;2022:3610461.
18. Taneja S, Kumari M. Use of triple antibiotic paste in the treatment of large periradicular lesions. J Investig Clin Dent 2012;3:72-6.
19. Lovelace TW, Henry MA, Hargreaves KM, Diogenes A. Evaluation of the delivery of mesenchymal stem cells into the root canal space of necrotic immature teeth after clinical regenerative endodontic procedure. J Endod 2011;37:133-8.
20. Lagler H, Zeitlinger M. Tissue penetration of antibiotics. Does the treatment reach the target site? Med Klin Intensivmed Notfmed 2014;109:175-81.
21. Li J, Esteban-Fernández De Ávila B, Gao W, Zhang L, Wang J. Micro/nanorobots for biomedicine: Delivery, surgery, sensing, and detoxification. Sci Robot 2017;2:eaam6431.
22. Parhizkar A, Asgary S. Local drug delivery systems for vital pulp therapy: A new hope. Int J Biomater 2021;2021:5584268.
23. Gomes MC, Cunha A, Trindade T, Tomé JP. The role of surface functionalization of silica nanoparticles for bioimaging. J Innov Opt Health Sci 2016;9:1630005.
24. Fahmy SH. The effect of amorphous calcium phosphate nanoparticles loaded in chlorhexidine as an intracanal medicament on radicular dentin microhardness (an *in vitro* study). Ain Shams Dent J 2021;23:7-14.
25. Torshabi M, Nojehdehian H, Tabatabaei FS. *In vitro* behavior of poly-lactic-co-glycolic acid microspheres containing minocycline, metronidazole, and ciprofloxacin. J Investig Clin Dent 2017;8:e12201.
26. Galler KM, Buchalla W, Hiller KA, Federlin M, Eidt A, Schiefersteiner M, *et al*. Influence of root canal disinfectants on growth factor release from dentin. J Endod 2015;41:363-8.
27. Alghilan MA, Windsor LJ, Palasuk J, Yassen GH. Attachment and proliferation of dental pulp stem cells on dentine treated with different regenerative endodontic protocols. Int Endod J 2017;50:667-75.
28. Pankajakshan D, Albuquerque MT, Evans JD, Kamocka MM, Gregory RL, Bottino MC. Triple antibiotic polymer nanofibers for intracanal drug delivery: Effects on dual species biofilm and cell function. J Endod 2016;42:1490-5.
29. Berkhoff JA, Chen PB, Teixeira FB, Diogenes A. Evaluation of triple antibiotic paste removal by different irrigation procedures. J Endod 2014;40:1172-7.
30. Bottino MC, Yassen GH, Platt JA, Labban N, Windsor LJ, Spolnik KJ, *et al*. A novel three-dimensional scaffold for regenerative endodontics: Materials and biological characterizations. J Tissue Eng Regen Med 2015;9:E116-23.
31. Nashaat Y, Sabry H, Hassan SA. Evaluation of the cytotoxicity and apoptotic effects of nano triple antibiotic paste with nano anti-inflammatory drug as an intracanal medicament. Eur Endod J 2021;6:82-9.
32. Parhizkar A, Nojehdehian H, Tabatabaei F, Asgary S. An innovative drug delivery system loaded with a modified combination of triple antibiotics for use in endodontic applications. Int J Dent 2020;2020:8859566.
33. Karczewski A, Feitosa SA, Hamer EI, Pankajakshan D, Gregory RL, Spolnik KJ, *et al*. Clindamycin-modified triple antibiotic nanofibers: A stain-free antimicrobial intracanal drug delivery system. J Endod 2018;44:155-62.
34. Moon CY, Nam OH, Kim M, Lee HS, Kaushik SN, Cruz Walma DA, *et al*. Effects of the nitric oxide releasing biomimetic nanomatrix gel on pulp-dentin regeneration: Pilot study. PLoS One 2018;13:e0205534.
35. Bottino MC, Albuquerque MT, Azabi A, Münchow EA, Spolnik KJ, Nör JE, *et al*. A novel patient-specific three-dimensional drug delivery construct for regenerative endodontics. J Biomed Mater Res Part B Appl Biomater 2019;107:1576-86.
36. Albuquerque MT, Evans JD, Gregory RL, Valera MC, Bottino MC. Antibacterial TAP-mimic electrospun polymer scaffold-effects on P. gingivalis-infected dentin biofilm. Clin Oral Investig 2016;20:387-93.
37. Albuquerque MT, Nagata J, Bottino MC. Antimicrobial efficacy of triple antibiotic-eluting polymer nanofibers against multispecies biofilm. J Endod 2017;43:S51-6.

Source of Support: Nil. **Conflicts of Interest:** None declared.

Author Queries???
AQ1: Kindly provide running title