

REGENERATIVE ENDODONTICS-SYSTEMATIC REVIEW**Padmapriya A¹, Kaviya Selvaraj¹, Dr. Rajasekar G²**¹Undergraduate resident, Department of Pediatric Dentistry, Saveetha Dental College and Hospitals, Saveetha Institute of Medical and Technical Sciences, 162, Poonamallee High Road, Velappanchavadi, Chennai-600077
152001072.sdc@saveetha.com, 152001052.sdc@saveetha.com²Senior Lecturer, Department of Pediatric Dentistry, Saveetha Dental College and Hospitals, Saveetha Institute of Medical and Technical Sciences, 162, Poonamallee High Road, Velappanchavadi, Chennai-600077Corresponding Author: rajasekarg.sdc@saveetha.com**Abstract:**

Regenerative endodontic materials represent a groundbreaking frontier in the field of dentistry, revolutionizing the way we approach the restoration of damaged tooth tissue. This innovative approach seeks not only to repair but also to regenerate dental pulp, a feat that was once considered elusive. This transformative approach heralds a new era in dentistry, where the goal is not just to fix teeth but to regenerate them, preserving oral health and function in the most biologically harmonious manner. Following PRISMA principles and the eligibility criteria, each reviewer independently screened the titles and abstracts of the retrieved publications. Between the two reviewers, disagreements or discrepancies were settled by consensus. Flowchart detailing the methodology used in the systematic review according to the standards provided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). This systematic review concluded that endodontic regenerative therapy showed better results in certain parameters such as increase in root wall lengthening and thickening, acute/chronic periapical lesions healing, and improved apical closure formation in the management of immature necrotic permanent teeth. This regenerative endodontic procedure (REP) proposes the use of a combination of antimicrobials and irrigants, no canal walls instrumentation, induced apical bleeding to form a blood clot and a tight seal into the root canal to promote healing. More clinical trials with a standardized protocol and defined clinical, radiographic, and histopathological outcomes with longer follow-up periods are warranted.

Keywords: Regenerative endodontics, Systematic review, pulp regeneration, MTA, medicine.**1. Introduction:**

Regenerative endodontic materials represent a groundbreaking frontier in the field of dentistry, revolutionizing the way we approach the restoration of damaged tooth tissue[1]. This innovative approach seeks not only to repair but also to regenerate dental pulp, a feat that was once considered elusive[2].

At the heart of regenerative endodontics lies a diverse array of materials carefully designed to stimulate the innate healing potential of the tooth. Bioceramics, for instance, have emerged as key players in this domain[1,3]. These materials, often composed of calcium silicates, possess exceptional biocompatibility and bioactivity[2,4]. When introduced into the root canal system, they create an environment conducive to tissue regeneration[5].

One of the remarkable features of bioceramics is their ability to set in the presence of moisture, ensuring effective sealing of the root canal[1,3,6]. This characteristic is particularly advantageous in clinical scenarios where maintaining a dry environment can be challenging.[7] The hermetic seal created by bioceramics prevents the ingress of bacteria, a crucial factor in promoting regeneration and preventing reinfection.[8]

Moreover, bioceramics exhibit bioinductive properties, meaning they can actively influence the surrounding cells to differentiate and participate in tissue regeneration.[9] This ability to recruit and guide the behavior of stem cells marks a significant departure from traditional endodontic materials, which focus primarily on the passive sealing of the root canal[10][11].

Complementing the role of bioceramics are growth factors, signaling molecules that orchestrate the complex process of tissue regeneration. [12] These factors, such as transforming growth factor-beta (TGF- β) and platelet-derived growth factor (PDGF), act as molecular messengers, communicating instructions to cells involved in tissue repair[13]. The strategic use of growth factors enhances the regenerative potential of the endodontic treatment, promoting the formation of functional pulp tissue.[1]

Regenerative endodontic procedures hold particular promise in cases involving immature teeth with underdeveloped roots.[6] Traditionally, these cases posed significant challenges, often resulting in compromised tooth strength and longevity.[14] However, regenerative approaches leverage the unique opportunity presented by the open apex of immature teeth to encourage the formation of vital pulp tissue, fostering root development and enhancing overall tooth resilience.[15] While the application of regenerative endodontic materials represents a leap forward in dental science, ongoing research endeavors seek to refine and expand the scope of these innovations[7]. Researchers explore novel biomaterials, delve deeper into the intricacies of cellular signaling, and investigate the long-term outcomes of regenerative treatments[16][11,17]. As our understanding deepens, regenerative endodontics holds the promise of becoming a standard of care, offering patients not only functional restorations but also the potential for biological repair.[18]

In conclusion, regenerative endodontic materials embody a paradigm shift in dental therapeutics, steering us towards a future where the restoration of damaged tooth tissue transcends mere repair[19]. Bioceramics and growth factors collaborate synergistically, guiding the natural healing processes within the tooth. [20] This transformative approach heralds a new era in dentistry, where the goal is not just to fix teeth but to regenerate them, preserving oral health and function in the most biologically harmonious manner[21][11,17,22].

2. Review's scope and a literature study:

A computerized search was conducted through PubMed, Scopus, and Web of Science. "Regenerative endodontics," "revascularization," "revitalization," and "immature teeth with pulp necrosis" were among the pertinent MeSh keywords. However, rather than doing a systematic review, a thorough narrative review covering the entire field of regenerative endodontics was carried out due to the size and complexity of the search.

2.1 Inclusion criteria:

Regardless of the scaffold types or techniques of disinfection, any procedure that tried to revascularize or regenerate a decaying immature permanent human tooth with the purpose of inducing root formation was included as RET in the current study. Root development, encompassing root thickening, root lengthening, and/or apical closure, was examined in isolation and quantified.

2.2 Criteria for Exclusion:

The following criteria were used to omit studies: Research on nonhuman subjects, The title and abstract don't fit the inclusion requirements, Article reviews, A case series or descriptive case report, Studies conducted outside of English, Primary or fully grown permanent teeth were included in the study. No whole article could be found.

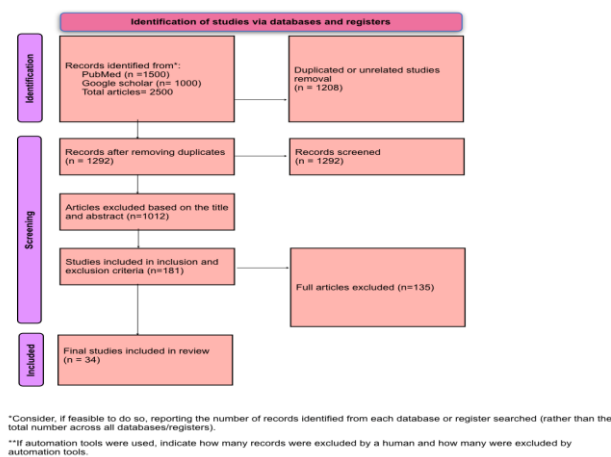
2.3 Critical Evaluation:

Following PRISMA principles and the eligibility criteria, each reviewer independently screened the titles and abstracts of the retrieved publications. Between the two reviewers, disagreements or discrepancies were settled by consensus.

3. Results and Discussion:

34 human studies that met the inclusion and exclusion criteria and were completed during the previous years were found through the search. The many parameters affecting the results of RET for successful patients were compared in this research. A total of 181 successful RET cases were sampled in the 34 included studies. The following categories of studies were covered in this systematic review: 10 case reports/case series, comprising 5 prospective investigations, 10 retrospective studies, and 9 randomized clinical trials (RCTs).

PRISMA 2020 flow diagram for new systematic reviews which included searches of databases and registers only



From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;372:n71. doi: 10.1136/bmj.n71

For more information, visit: <http://www.prisma-statement.org/>

Fig-1: Flowchart detailing the methodology used in the systematic review according to the standards provided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).

In order to achieve our study goal, a systematic review was carried out to evaluate and compile all noteworthy papers that have been published in the recent ten years. [23]The current systematic review sought to gather all available and current data on endodontic regeneration therapy in the treatment of immature permanent teeth with necrotic pulp, as well as the most popular and suitable protocols for this surgery in both human and animal studies[24]. Our analysis provides an extensive synthesis of data from 34 publications that satisfied our inclusion and exclusion standards[25].The majority of the retrieved studies about clinical protocols of endodontic regenerative treatment suggest their efficacy in the management of these types of teeth, according to Bucchi et al.'s systematic review.[25,26] However, the majority of the studies found support for particular irrigations and intracanal dressings to improve clinical, histological, and radiographic outcomes in endodontic regeneration for clinical studies involving humans and animals[27]. All 34 of the studies in our updated systematic review supported the use of various scaffolds in endodontic regeneration therapy for the treatment of permanently damaged, immature teeth.Conversely, although concentrating just on 11 studies concerning pulp revascularization,[28] Antunes et al.'s findings validate the procedure's clinical effectiveness. Additionally, this method can promote the thickness of radicular dentin and trigger the creation of apical closure; however, several clinical studies have not yet clarified the critical elements of tissue healing, the kind of tissue generated, or the long-term prognosis. [29]. On the other hand, most dentists eventually adjusted their treatment plans in light of their clinical opinion. Partial pulpotomy was shown to be effective in treating immature permanent teeth with partial pulp necrosis and symptomatic apical periodontitis.[30,31] This could be attributed to the pulp's strong disease resistance and repair function, which is a result of its distinct physiological and anatomical features[32]. Comparing these research to previously published systematic reviews, we were able to identify some evidence for the high success rates of endodontic regeneration therapy in the treatment of immature necrotic permanent teeth in both human and animal trials.[30]

Regarding the various kinds of pulpal space/barriers and intracanal medications used in this procedure, the majority of the investigations in this review used mineral trioxide aggregate (MTA) as the pulpal space/barrier and triple-antibiotic paste (TAP) as the intracanal medication because, when compared to other intracanal medications and pulpal space/barriers, MTA was more effective in treating immature necrotic permanent teeth through pulp revascularization[33]. As a result, in the majority of the included studies in this review, regenerative endodontic therapy demonstrated a considerable increase in dentinal wall thickness and root length, suggesting that it may induce the root maturation of necrotic immature permanent teeth.[32]

Regenerating pulp over the existing pulp tissue would be the most straightforward method of pulp tissue regeneration[34]. Nevertheless, attempts to regenerate pulp tissue in the presence of inflammation or partial necrosis have not been effective, and it is well acknowledged that direct pulp capping of infected tissue has a poor long-term prognosis and is not advised[35]. The pulp stem cells that make it through infection seem to be unable to mineralize and deposit a tertiary dentin bridge[36]. Consequently, the overwhelming body of research to date points to the failure of necrotic and diseased tooth pulp to recover[37][22]. Thus, before utilizing regenerative endodontic treatments in the near future, it will be required to clean the root canal systems and eliminate any contaminated hard and soft tissues in accordance with the previous study[38].

Acknowledgement: The authors are thankful to Saveetha Institute of Medical and Technical Sciences, Saveetha Dental College and Hospitals, Saveetha University for giving a platform to conduct the study.

Conflict of interest: The authors would like to declare no conflict of interest in the present study.

Funding:

The present project is funded by

- Saveetha Institute of Medical and Technical Sciences,
- Saveetha Dental College and Hospitals and Saveetha University
- Saveetha University
- Padmalaya Ayurveda Speciality Clinic

4. Conclusion:

This systematic review concluded that endodontic regenerative therapy showed better results in certain parameters such as increase in root wall lengthening and thickening, acute/chronic periapical lesions healing, and improved apical closure formation in the management of immature necrotic permanent teeth. This regenerative endodontic procedure (REP) proposes the use of a combination of antimicrobials and irrigants, no canal walls instrumentation, induced apical bleeding to form a blood clot and a tight seal into the root canal to promote healing. More clinical trials with a standardized protocol and defined clinical, radiographic, and histopathological outcomes with longer follow-up periods are warranted.

5. References:

1. Thomson A, Kahler B. Regenerative endodontics--biologically-based treatment for immature permanent teeth: a case report and review of the literature. *Aust Dent*

- J. 2010 Dec;55(4):446–52.
2. Deepyanti DR, Srishti DR, Ghosh DRM, Saha DRA. REGENERATIVE ENDODONTICS. DENTOMED PUBLICATION HOUSE; 2021. 61 p.
 3. Rao A. Principles and Practice Of Pedodontics. JP Medical Ltd; 2012. 529 p.
 4. Arora AS, Khinda VIS, Bajaj N. Regenerative Endodontics. LAP Lambert Academic Publishing; 2014. 156 p.
 5. Kumar SA, Kumar EP, Keerthi R, Krishnaprakash, Borthakur BJ, Varatharajan V. Radiographic evaluation of root canal treatments performed by undergraduate students at saveetha dental school. *CODS J Dent.* 2026 Feb 18;17(1):8–12.
 6. Nosrat A, Seifi A, Asgary S. Regenerative endodontic treatment (revascularization) for necrotic immature permanent molars: a review and report of two cases with a new biomaterial. *J Endod.* 2011 Apr;37(4):562–7.
 7. Reis-Prado AD, Toledo PTA, Nunes GP, Ferreira PAV, Rahimnejad M, Fabbro RD, et al. Citric acid conditioning as an alternative to EDTA for growth factors release and stem cell response in regenerative endodontics: A systematic review of in vitro studies. *J Endod [Internet].* 2023 Nov 18; Available from: <http://dx.doi.org/10.1016/j.joen.2023.11.006>
 8. Takimoto K, Widbiller M, Diogenes A. Expression of Toll-like Receptors in Stem Cells of the Apical Papilla and Its Implication for Regenerative Endodontics. *Cells [Internet].* 2023 Oct 21;12(20). Available from: <http://dx.doi.org/10.3390/cells12202502>
 9. Shivashankar VY, Johns DA, Maroli RK, Sekar M, Chandrasekaran R, Karthikeyan S, et al. Comparison of the Effect of PRP, PRF and Induced Bleeding in the Revascularization of Teeth with Necrotic Pulp and Open Apex: A Triple Blind Randomized Clinical Trial. *J Clin Diagn Res.* 2017 Jun;11(6):ZC34–9.
 10. Kınıkoğlu İ, Türkoğlu Kayacı Ş, Arslan H. Short fiber reinforced composite on fracture strength of immature permanent anterior teeth with simulated regenerative endodontic procedures: an study. *J Clin Pediatr Dent.* 2023 Nov;47(6):171–7.
 11. Swathi S, Solete P, Antony SDP, Sairaman S, Sandeep AH, Teja KV. Efficacy of various heat-treated rotary file systems on the removal of obturated material in single-rooted teeth using nanocomputed tomography. *Endodontology.* 2026 Jan;38(1):76–81.
 12. Sönmez IS, Akbay Oba A, Erkmen Almaz M. Revascularization/Regeneration performed in immature molars: case reports. *J Clin Pediatr Dent.* 2013 Spring;37(3):231–4.
 13. Sabeti M, Ghobrial D, Zanjir M, da Costa BR, Young Y, Azarpazhooh A. Treatment outcomes of regenerative endodontic therapy in immature permanent teeth with pulpal necrosis: A systematic review and network meta-analysis. *Int Endod J [Internet].* 2023 Nov 15; Available from: <http://dx.doi.org/10.1111/iej.13999>
 14. Duncan HF, Cooper PR. Clinical Approaches in Endodontic Regeneration: Current and Emerging Therapeutic Perspectives. Springer; 2018. 194 p.
 15. Hosseinpour S, Walsh LJ, Moharamzadeh K. Regenerative Approaches in Dentistry: An Evidence-Based Perspective. Springer Nature; 2021. 276 p.
 16. Cvek M. Prognosis of luxated non-vital maxillary incisors treated with calcium hydroxide and filled with gutta-percha. A retrospective clinical study. *Endod Dent Traumatol.* 1992 Apr;8(2):45–55.
 17. Patel T, Shivalingam C, Pandurangan KK, Ali S, Ganapathy DM, Teja KV, et al. Synthesis of hydroxyapatite from eggshells to be used in regenerative endodontics: An in vitro study. *Saudi Endod J.* 2025 Sep;15(3):252–9.
 18. Jiang X, Liu H. Analysis of the achievement of primary and secondary goals and influencing factors in single-rooted immature permanent teeth after regenerative endodontic procedures: a retrospective study. *BMC Oral Health.* 2023 Nov 11;23(1):851.
 19. Alghamdi FT, Alqurashi AE. Regenerative Endodontic Therapy in the Management of Immature Necrotic Permanent Dentition: A Systematic Review. *The Scientific World Journal [Internet].* 2020 Jul 13 [cited 2023 Nov 28];2020. Available from: <https://doi.org/10.1155/2020/7954357>
 20. Ding RY, Cheung GSP, Chen J, Yin XZ, Wang QQ, Zhang CF. Pulp revascularization of immature teeth with apical periodontitis: a clinical study. *J Endod.* 2009 May;35(5):745–9.
 21. Chogle SMA, Goodis HE. Regenerative Endodontics. *Clinics: Dentistry;* 2012.
 22. Website [Internet]. Available from: <https://doi.org/10.3389/fdmed.2025.1540038>
 23. McCabe P. Revascularization of an immature tooth with apical periodontitis using a single visit protocol: a case report. *Int Endod J.* 2015 May;48(5):484–97.
 24. Kontakiotis EG, Filippatos CG, Tzanetakakis GN, Agraftioli A. Regenerative Endodontic Therapy: A Data Analysis of Clinical Protocols. *J Endod.* 2015 Feb 1;41(2):146–54.
 25. Elnawam H, Abdelmougod M, Mobarak A, Hussein M, Aboualmakarem H, Girgis M, et al. Regenerative Endodontics and Minimally Invasive Dentistry: Intertwining Paths Crossing Over Into Clinical Translation. *Front Bioeng Biotechnol.* 2022 Feb 8;10:837639.
 26. Bucchi C, Rosen E, Taschieri S. Non-surgical root canal treatment and retreatment versus apical surgery in treating apical periodontitis: A systematic review. *Int Endod J.* 2023 Oct;56 Suppl 3:475–86.
 27. Betancourt P, Bucchi C, Arroyo-Bote S. Determination of crown discoloration and fluorescence induced by different medications used in regenerative endodontic procedures: An study. *J Clin Exp Dent.* 2021 Aug;13(8):e755–61.
 28. Shin SY, Albert JS, Mortman RE. One step pulp revascularization treatment of an immature permanent tooth with chronic apical abscess: a case report. *Int Endod J.* 2009 Dec;42(12):1118–26.
 29. Diogenes A, Ruparel NB, Shiloah Y, Hargreaves KM. Regenerative endodontics: A way forward. *J Am Dent Assoc.* 2016 May;147(5):372–80.
 30. Ajram J, Khalil I, Gergi R, Zogheib C. Management of an Immature Necrotic Permanent Molar with Apical Periodontitis Treated by Regenerative Endodontic Protocol Using Calcium Hydroxide and MM-MTA: A Case Report with Two Years Follow Up. *Dent J [Internet].* 2019 Jan 1;7(1). Available from: <http://dx.doi.org/10.3390/dj7010001>
 31. Yoo YJ, Lee W, Cho YA, Park JC, Shon WJ, Baek SH. Effect of conditioned medium from preameloblasts on regenerative cellular differentiation of the immature teeth with necrotic pulp and apical periodontitis. *J Endod.* 2014 Sep;40(9):1355–61.
 32. Cehreli ZC, Sara S, Uysal S, Turgut MD. MTA apical plugs in the treatment of traumatized immature teeth with large periapical lesions. *Dent Traumatol.* 2011 Feb;27(1):59–62.
 33. Torabinejad M. Mineral Trioxide Aggregate: Properties and Clinical Applications. John Wiley & Sons; 2014. 360 p.
 34. Fuks A, Peretz B. Pediatric Endodontics: Current Concepts in Pulp Therapy for Primary and Young Permanent Teeth. Springer; 2016. 164 p.
 35. Parirokh M, Torabinejad M. Mineral trioxide aggregate: a comprehensive literature review--Part III: Clinical applications, drawbacks, and mechanism of action. *J Endod.* 2010 Mar;36(3):400–13.
 36. Ulusoy AT, Cehreli ZC. Regenerative Endodontic Treatment of Necrotic Primary Molars with Missing Premolars: A Case Series. *Pediatr Dent.* 2017 May 15;39(3):131–4.
 37. Rizk HM, Al-Deen MSS, Emam AA. Regenerative Endodontic Treatment of Bilateral Necrotic Immature Permanent Maxillary Central Incisors with Platelet-rich Plasma versus Blood Clot: A Split Mouth Double-blinded Randomized Controlled Trial. *Int J Clin Pediatr Dent.* 2019 Jul-Aug;12(4):332–9.
 38. Lenzi R, Hernández SR, Alves FRF, Rôças IN, Siqueira JF. Regenerative Endodontic Therapy for Management of an Immature Permanent Tooth with Recurrent Post-treatment Apical Periodontitis: A Case Report. *J Int Soc Prev Community Dent.* 2022 Aug 29;12(4):468–73.