



Major characteristics of the dental pulp regeneration process under the stimulation of biomaterials, bioactive Compounds, cells, and molecules: a systematic review

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Abstract

Introduction: Dental pulp regeneration is a challenging process that requires sophisticated cellular and molecular mechanisms, as well as biomaterials, to support the pulp's diverse functions, including immune defense, sensory perception, vascularization, and reparative dentinogenesis. Dental pulp contains stem cells with characteristics similar to mesenchymal stem cells. Dental pulp-derived stem cells (DPSC) can regenerate a variety of tissues. **Objective:** This was a systematic review to elucidate the main characteristics of the dental pulp regeneration process under the stimulation of biomaterials, bioactive compounds, cells, and molecules, as well as to present the main clinical outcomes. **Methods:** The systematic review rules of the PRISMA Platform were followed. The research was carried out from May to June 2025 in Scopus, Embase, PubMed, Science Direct, Scielo, and Google Scholar databases. The quality of the studies was based on the GRADE instrument, and the risk of bias was analyzed according to the Cochrane instrument. **Results and Conclusion:** A total of 114 articles were found, and 24 articles were evaluated in full, and 22 were included and developed in this systematic review study. Considering the Cochrane tool for risk of bias, the overall assessment resulted in 25 studies with a high risk of bias and 32 studies that did not meet GRADE and AMSTAR-2. According to the GRADE instrument, most studies presented homogeneity in their results, with $X^2=91.7\%>50\%$. It was concluded that dental pulp stem cells can promote nerve regeneration

through mitochondrial transfer, presenting a promising strategy for improving stem cell-based therapies for nerve injuries. Furthermore, hydrogels specifically developed to regulate the JAG1/Notch signaling pathway have demonstrated potential for pulp tissue regeneration. Mineral Trioxide Aggregate (MTA) is an excellent marginal sealer that prevents bacterial migration into the canal. It is a biocompatible cement that induces dentinogenesis, cementogenesis, and osteogenesis. Calcium hydroxide remains a standard material for use in pulp capping due to its bactericidal effect.

Keywords: Dental pulp regeneration. Biomaterials. Vascularization. Pulp-derived stem cells.

Introduction

Dental pulp regeneration is a challenging process that requires sophisticated cellular and molecular mechanisms, as well as biomaterials, to support the pulp's diverse functions, including immune defense, sensory perception, vascularization, and reparative dentinogenesis. Regeneration involves orchestrating the formation of soft connective tissues, neurons, blood vessels, and mineralized structures, which requires materials with tailored biological and mechanical properties [1], thereby supporting progress toward effective dental pulp regeneration strategies [2].

Despite their wide applications in various fields,

research on dental pulp organoids and their use in regenerative therapies is still in its early stages, presenting both opportunities and challenges. Innovative bioengineering strategies hold promise for future applications [3]. Furthermore, dental pulp contains stem cells with characteristics similar to mesenchymal stem cells. Dental pulp-derived stem cells (DPSC) can regenerate a variety of tissues, and their potential for clinical application in regenerative medicine is promising. DPSC express low levels of HLA-DR Class II (MHC) molecules, making them potential candidates for allogeneic transplantation without a match for donor tissue. The correlation between non-coding RNAs (microRNAs) and DPSC provides promising insights into the use of these cells in osteoblastogenesis and osteoclast differentiation [4].

Also, when the dental organ presents great destruction due to trauma or various processes, it is common for pulp tissue exposures to occur. In this event, one can directly opt for endodontic treatment. However, in the case of incomplete root formation or even economic factors, one can choose a more conservative treatment, maintaining pulp vitality. In this case, the indicated treatment is direct pulp capping [5,6].

Due to the intimate relationship between the cells that form the dental pulp and dentin, these two issues are considered a single functional entity, called the dentin-pulp complex [7]. Keeping a healthy and intact pulp is a desirable goal. In cases of teeth injured by carious injuries or trauma, maintaining the pulp vitality of the teeth is an essential requirement for successful treatment. This is why we are looking for more and more techniques and materials that contribute to achieving this result. For authors, if pulpal exposure occurs, materials should be used to repair the damaged tissue and provide for the formation of a hard tissue barrier or dentin bridge [3,4].

The greatest threats to pulp vitality are caries and traumatic damage. In the event of a pulp exposure, a pulp or pulpotomy cap should be performed to preserve pulp vitality, thus allowing normal root development [8]. The pulp-dentin complex is a system formed by the pulp and dentin together. Both are interconnected structures, and it is through the odontoblasts that the pulp tissue maintains an intimate relationship with the dental structure [9].

Therefore, the present study carried out a systematic review in order to elucidate the main characteristics of the dental pulp regeneration process under the stimulus of biomaterials, bioactive compounds, cells, and molecules, as well as present the main clinical outcomes.

Methods

Study Design

This study followed the international systematic review model, following the PRISMA (preferred reporting items for systematic reviews and meta-analysis) rules. Available at: <http://www.prisma-statement.org/?AspxAutoDetectCookieSupport=1>. Accessed at: 18/05/2025. The AMSTAR 2 (Assessing the methodological quality of systematic reviews) methodological quality standards were also followed. Available at: <https://amstar.ca/>. Accessed on: 18/05/2025.

Search Strategy and Search Sources

The literature search process was carried out from May to June 2025 and developed based on Web of Science, Scopus, Embase, PubMed, Lilacs, Ebsco, Scielo, and Google Scholar, covering scientific articles from various periods to the present day. The following descriptors were used in health sciences (DeCS/MeSH): "Dental pulp regeneration. Biomaterials. Vascularization. Pulp-derived stem cells", and the Boolean "and" was used between the MeSH terms and "or" between the historical findings.

Study Quality and Risk of Bias

Quality was classified as high, moderate, low, or very low regarding the risk of bias, clarity of comparisons, precision, and consistency of analyses. The most evident emphasis was on systematic review articles or meta-analyses of randomized clinical trials, followed by randomized clinical trials. Low quality of evidence was attributed to case reports, editorials, and brief communications, according to the GRADE instrument. The risk of bias was analyzed according to the Cochrane instrument by analyzing the Funnel Plot graph (Sample size versus Effect size), using Cohen's test (d).

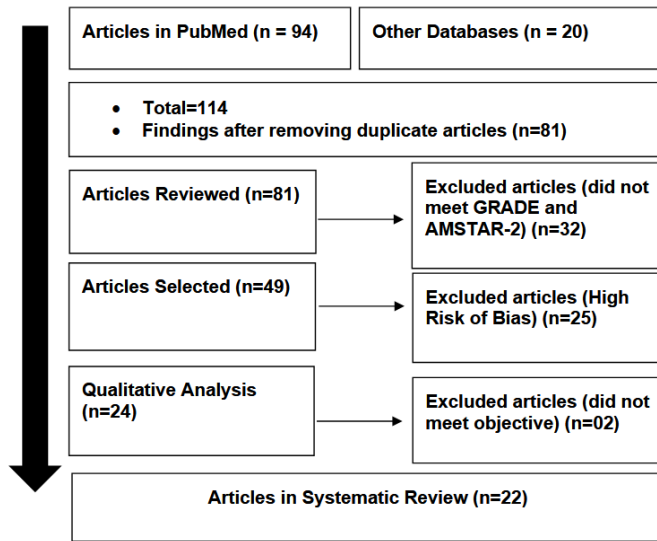
Results and Discussion

Summary of Findings

A total of 114 articles were found and submitted to eligibility analysis, with 22 final studies selected to compose the results of this systematic review. The listed studies were of medium to high quality (Figure 1), considering the level of scientific evidence of studies such as meta-analysis, consensus, randomized clinical, prospective, and observational. Biases did not compromise the scientific basis of the studies. According to the GRADE instrument, most studies presented homogeneity in their results, with $X^2=91.7\%>50\%$. Considering the Cochrane tool for risk of bias, the overall assessment resulted in 25 studies with a high

risk of bias and 32 studies that did not meet GRADE and AMSTAR-2.

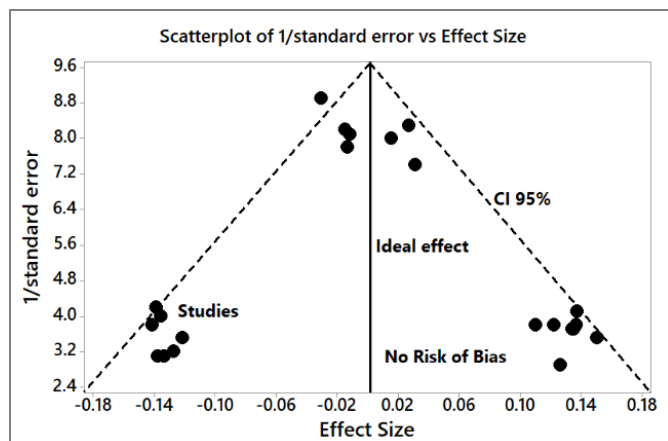
Figure 1. Flowchart showing the article selection process.



Source: Own Authorship.

Figure 2 presents the results of the risk of bias of the studies using the Funnel Plot, showing the calculation of the Effect Size (Magnitude of the difference) using Cohen's Test (d). Precision (sample size) was determined indirectly by the inverse of the standard error (1/Standard Error). This graph had a symmetrical behavior, not suggesting a significant risk of bias, both among studies with small sample sizes (lower precision) that are shown at the base of the graph and in studies with large sample sizes that are presented at the top.

Figure 2. The symmetrical funnel plot suggests no risk of bias among the studies with small sample sizes that are shown at the bottom of the graph. High confidence and high recommendation studies are shown above the graph (n= 22 studies).



Source: Own Authorship.

Major Outcomes

Dental pulp regeneration is promoted by revascularization and angiogenesis through the Jagged1(JAG1)/Notch signaling pathway. A Notch signaling hydrogel was developed by indirectly immobilizing JAG1, aiming to precisely target the regeneration of vascularized pulp tissue. Cultivation of DPSC and endothelial cells (ECs) in this hydrogel significantly increases the expression of Notch target genes and key proangiogenic markers. Three-dimensional (3D) culture assays demonstrate that Notch signaling hydrogels improve efficacy by facilitating the differentiation of encapsulated cells, enhancing their paracrine functions, and promoting capillary lumen formation. Furthermore, it effectively communicates with the Jagged1(JAG1)/Notch signaling pathway, creating an odontoinductive microenvironment for the formation of the pulpentin complex [10].

Furthermore, the authors Zheng et al. (2025) [11] analyzed how DPSC alleviate Schwann cell pyroptosis and restore mitochondrial homeostasis through intercellular mitochondrial transfer. In a monkey model, it was initially observed that DPSC-loaded nerve conduits significantly promoted long-term nerve regeneration, facilitating tissue proliferation and myelin recovery. Furthermore, a model of facial nerve injury was established in rats, showing that DPSC treatment reduced pyroptosis and mitochondrial ROS production in Schwann cells. One protective mechanism involved the transfer of mitochondria from DPSC to Schwann cells. TNF α secreted by pyroptosis-induced Schwann cells activated the NF- κ B pathway in DPSC, enhancing mitochondrial transfer and adaptive stress responses.

Liu et al. (2025) [12], further developments in the use of DPSC were observed, analyzing that DPSC can promote periodontal regeneration through a non-invasive procedure. A total of 132 patients with chronic periodontitis (158 teeth) were included. DPSC injection was safe and improved clinical outcomes compared to saline injection in patients with stage III periodontitis.

Regarding the use of biomaterials, the authors Alshahhoud et al. (2024) [13] evaluated pulp regeneration by comparing the application of native chitosan-based scaffolds with enzymatically modified chitosan-based scaffolds in mature teeth with apical lesions, using clinical and radiographic assessments. Participants aged 15 to 45 years, free of systemic diseases, and with necrotic single-rooted mature teeth with periapical lesions were included. A total of 30 teeth from 24 participants were included. The application of the enzymatically modified chitosan scaffold demonstrated superior results in pulp regeneration after six months, with a greater degree of healing observed compared to the control groups.

In this scenario, the pulp constitutes dental vitality. It contains all the innervation responsible for the painful sensitivity of dentin and pulp itself. The pulp has a morphofunctional organization capable of reacting to aggressions suffered and remodeling this nervous network, allowing it to recover and maintain its vitality [14]. The pulp has nutritive, sensitive, and defensive functions. It also produces the dentin and provides nutrition through the odontoblastic prolongations, which carry nutrients found in the tissue fluid [15].

Authors describe the constitution of the pulp as a gelatinous material called the extracellular matrix, which contains proteoglycans and glycoproteins, together with bundles of collagen fibers. This structure works as a defense against irritants and toxins. According to the author, defense cells, fibroblasts, ectomesenchymatic cells, and odontoblasts are the main pulp cells [16]. The dental pulp is formed by a loose, specialized connective tissue. It has several functions like the differentiation of cells in ameloblasts for enamel production; dentin production by odontoblasts; dentin nutrition and tissue defense [17].

The direct pulp capping consists of the protection of the pulp exposed with the use of a material that allows the repair of the pulp and the formation of dentin tissue, thus enabling pulp vitality to be maintained. According to the same authors, in the occurrence of pulp exposure, the following aspects should be taken into account: the general state of the pulp tissue and the prevention of pulp contamination during the operative procedures. If bacteria and inflammation are present, direct pulp capping may be impaired and may not achieve the expected success. In this way, the purpose of the capping is to promote the healing of the pulp, and the capping material should not affect the vitality of the pulp tissue and stimulate the production of calcified tissue [6].

Besides, direct pulp capping is indicated in cases where the exposures are small, so that there is a possibility of repair of the pulp. In order to perform the capping, factors such as pulp condition, patient age, pulp exposure size, and control of pulpal hemorrhage [7]. Dentin and pulp tissue form an integrated structure since they originate from the same embryological structure. For this reason, this structure is called the pulp dentin complex. The pulp tissue is responsible for all the physiological changes undergone by the dentin. In this way, the pulp dentine complex develops three defense mechanisms against the injuries suffered by this tissue in order to preserve the vitality of odontoblast cells and pulp tissue. Such mechanisms are inflammation and humoral response, intratubular dentin deposition, deposition of tertiary dentin [18].

Since 1756 a form has been studied for the

preservation of the exposed pulp, using a capping material to protect it. At this time, the exposed pulp tissue was protected with gold capsules. From the outset, what is expected with the application of a material on the exposed pulp tissue is that the formation of a mineralized dentine bridge occurs, thus maintaining the pulp vitality [8]. For the authors, factors such as patient age, periodontal condition, root formation stage, size, and nature of pulp exposure and local contamination will determine the success of direct pulp capping.

Calcium hydroxide

Calcium hydroxide products stimulate the formation of sclerosed dentin, thus protecting the pulp against the thermoelectric stimuli and the action of the toxic agents of some restorative materials. For these reasons, they are widely used as capping agents. As a direct capping agent, calcium hydroxide can be used by the professional as calcium hydroxide pastes and calcium hydroxide cement [15]. According to the author, the Calcium Hydroxide paste was first used by Hermann in 1920 for the protection of the pulp-dentin complex. This material differs from the cement in composition and consistency and consists of pro-analysis calcium hydroxide dissolved in distilled water, sodium chloride, potassium, calcium, and calcium carbonate, or else with the addition of barium sulfate, which makes the radiopaque paste. These pastes have the ability to form repairing dentin when placed on the pulp, which is why their use is indicated in cases of direct protection when accidental exposure occurs.

The calcium hydroxide cements present relative hardness and mechanical resistance. Dycal is an example of such products; it is in the form of two pastes, a base, and another catalyst. Its mechanical properties make it possible to indicate this protective agent as a single base in the case of indirect protection. In the case of direct protection, from a biological point of view, it seems to lead to satisfactory results when applied to small accidental pulp exposures. Calcium hydroxide is the most accepted pulp protection material in dental practice, due to its low cost, antibacterial action, and biocompatibility. This material acts on the pulp tissue, stimulating the formation of a mineralized tissue barrier. Therefore, it is an excellent option for performing direct pulp protection [19].

The calcium hydroxide Pro-Analysis (PA) is used in cases of direct protection of the pulp tissue, in which the stimulation of odontoblastic and mesenchymal cells is objectified to form a mineralized tissue barrier in the exposed region, associated with the control of inflammation, pH reduction, and elimination of invading microorganisms. Calcium hydroxide has excellent

antibacterial properties and a record of clinical success in periods of up to 10 years. However, it has some disadvantages: it does not have adhesion with dentin, and presents high solubility in aqueous medium, besides a low mechanical resistance [20].

Moreover, calcium hydroxide is the most used and accepted pulp protective material in dental practice. Its advantages are low cost, antibacterial action, and biocompatibility. It stimulates the formation of a mineralized layer on the pulp. In their studies, 80.2% of the analyzed cases were successful with the use of calcium hydroxide in direct pulp capping [21]. Silva et al (2012) [22] carried out a study in which calcium hydroxide cement (Dycal, Dentsply) was used for direct pulp protection in case of coronary fracture with small pulp exposure. By obtaining a positive pulpal response to the vitality test, we opted for fragment collage and direct pulp protection. The cement of calcium hydroxide stimulates the formation of the dentin barrier, which guarantees the success of the treatment.

In your research studies, Holland et al. (2015) [17] tested various materials in direct pulp protection and found that the best protection was exerted by $\text{Ca}(\text{OH})_2$, which is a product that stimulates pulpal repair through the formation of a bridge. hard tissue. $\text{Ca}(\text{OH})_2$ Dycal-based cement was tested on dog pulp and, in some cases, induced hard tissue bridge formation. The authors also performed an experimental work comparing the effect of $\text{Ca}(\text{OH})_2$ in paste form or powder form and observed that there was no difference in the percentage of success. In this work, the authors describe the technique to be used with the use of calcium hydroxide in the direct cap: After the isolation of the tooth in question, Otosporin is applied for 5 minutes, and then $\text{Ca}(\text{OH})_2$, on the pulp surface.

With an instrument, preferably, a little of the $\text{Ca}(\text{OH})_2$ paste is taken against the exposed portion of the pulp. This application must be made under pressure so that there is not an air bubble interposed between $\text{Ca}(\text{OH})_2$ and the pulp surface. According to studies by Filther et al (2016) [23], there is evidence that reactional dentinogenesis is only assisted and not stimulated when calcium hydroxide based materials are used for the protection of the dentinopulpar complex due to its adequate biocompatibility. However, for direct application to the pulp tissue, materials based on calcium hydroxide are still the materials of choice.

Mineral Trioxide Aggregate (MTA)

Tessare et al. (2005) [24] carried out research work on the MTA and found that it is an excellent marginal sealer that prevents bacterial migration into the canal. It is a cement with biocompatibility, an inducer of dentinogenesis, cementogenesis, and

osteogenesis. According to Freires and Cavalcanti (2011) [19], MTA was developed by the University of Loma Linda (USA) to seal the communication between the root canal system and the outer surface at all levels. The main characteristics of this material are biocompatibility, excellent sealing ability, antibacterial effect, the absence of mutagenic potential, low cytotoxicity, stimulus to the formation of mineralized tissue, and stimulus to tissue regeneration of the periodontium. Thus, the MTA is considered a suitable material for the protection of the pulp-dentin complex. However, as a disadvantage and limitation of use, it can be mentioned its high cost.

For Filther et al (2016) [23], the MTA forms a dentin bridge, obliterating the pulp exposure. This material was initially developed to seal communications between the tooth and the external periodontal surface. Its main characteristics are properties such as high alkalinity, low solubility, excellent marginal sealing, antimicrobial capacity, radiopacity, and high biocompatibility. However, the authors proved from clinical experiences with the material that it has a high prey time and with that, it is difficult at the time of insertion on the region of exposure. Another disadvantage relates to the high cost of the material, which means a major obstacle to its use.

Calcium Hydroxide vs. MTA

Rosa and Macedo (2003) [7] carried out studies on the protection of exposed dental pulp and concluded that calcium hydroxide forms the dentin barrier as long as the pulp presents favorable conditions for this repair. The MTA presents solutions similar to calcium hydroxide in the recovery of the pulp, stimulating the formation of a hard tissue bridge. However, in the same studies, they failed to present solutions with the use of adhesive systems as direct pulp protectors. As a result, they conclude that these materials still require evidence of pulpal repair stimulatory capacity.

Queiroz et al. (2005) [25] conducted research on the performance of MTA and calcium hydroxide to cover pulp. In these studies, calcium hydroxide, when placed in contact with the pulp, preserves its vitality without an inflammatory response and stimulates the formation of a barrier of mineralized tissue. The use of calcium hydroxide for direct pulp treatment has always been very successful, but other materials have begun to be tested as pulp protectors. Among these materials is the aggregate of mineral trioxide - MTA. Properties such as biocompatibility, high sealing capacity, antibacterial effects, low cytotoxicity, no alteration in cytomorphology of osteoblastic cells, stimulation of tissue mineralization formation, were identified in cases of direct pulp protection with the use of MTA. The

conclusion of the cases analyzed in these studies was that MTA and Calcium Hydroxide present similar results when used as a direct pulp capping.

Comparative studies between MTA and calcium hydroxide found that when using calcium hydroxide, this material releases calcium ions and creates an alkaline environment that provides tissue mineralization. However, it was found that the same material has poor long-term capacity against bacterial infiltration [27]. The MTA is a hygroscopic cement that has the ability not to be affected by the presence of blood and other fluids. Because it is a hydrophilic material, it has the capacity of a good marginal seal, thus inducing tissue repair. But it has a high cost and has a long prey time.

The authors conducted a randomized controlled trial for histological, ultrastructural, and qualitative evaluation of the human pulp response in front of the experimental cap with MTA and calcium hydroxide-based cement of calcium. Dental elements (third molars) of volunteers underwent iatrogenic pulpotomy and were treated with MTA or calcium hydroxide cement. MTA treatment was more effective than calcium hydroxide in tissue recovery at all times. Treatment with MTA resulted in a lower degree of inflammation, a greater stimulus to tissue regeneration, and a greater neoformation of mineralized dentin [19]. However, the authors affirm that further studies and monitoring over time are necessary with the use of MTA in the protection of the complex pulp-dentin to prove the efficacy and effectiveness of this material.

MTA is mainly composed of calcium oxide in the forms of tricalcium silicate, dicalcium silicate, and tricalcium aluminate. Many of its advantages and mechanisms of action are similar to calcium hydroxide. Including its antibacterial power, biocompatibility, high pH, radiopacity, and its ability to release bioactive molecules, however, the MTA provides a better sealing, and its main disadvantage over calcium hydroxide is the high cost [20]. According to the authors, when comparing the curing process of the pulp using calcium hydroxide or MTA, it is observed in most studies that the results presented by the two materials are similar. However, the authors emphasize that in the long run, calcium hydroxide shows a path of clinical success that has not yet been observed with the use of MTA and therefore, the studies must continue to prove the success of the MTA in the long term.

The author prescribes in his work on Protection of Complex Dentino Pulp that Calcium Hydroxide Pro-Analysis - PA is used in cases of direct protection of pulp tissue, in which the stimulation of odontoblastic and mesenchymal cells for barrier formation in the exposed region [9]. As for the MTA, the author describes that it is a material that forms a dentine

bridge, obliterating the pulp exposure. It has antimicrobial activity and releases hydroxyl ions, raising the pH and preventing the survival of the bacteria. However, it has the clinical disadvantage of a very long prey time.

Hydroxyapatite - HAp and Tricalcium Phosphate - β -TCP

Delfino et al (2010) [8] carried out work on the use of new materials for the direct pulp capping, hydroxyapatite (HAp and tricalcium phosphate - β -TCP). According to the authors, for having a bactericidal effect, calcium hydroxide still remains as a standard material for use in pulp capping. After the pulp capping with this alkaline agent, due to the high local pH, the adjacent pulp tissue is usually altered, forming an obliteration zone and, in the underlying tissue, more apical, there is a formation of a coagulation zone and necrosis. In other cases, the formation of a repairing dentin under calcium hydroxide and a mineralized dentin bridge, closing the pulp exposure, is observed.

The authors also cite other problems with the use of calcium hydroxide, such as accelerated degradation behavior, often being incompatible with the repair time; tunnel defects in the dentin bridge formed; intense caustic effect, and inadequate sealing property, allowing the microleakage of contaminants. Such problems led to the search for new capping materials. Several calcium phosphate ceramics have been tested as capping agents. Particularly noteworthy are the particulate ceramic materials, such as hydroxyapatite (HAp) and tricalcium phosphate (β -TCP), which are inducers of mineralization and, in other dental applications. Reasons why these materials can be a safe alternative for pulp capping.

Limitations

There is still a lack of randomized controlled clinical studies with larger sample sizes to demonstrate better clinical outcomes and more robust patient follow-up.

Conclusion

It was concluded that dental pulp stem cells can promote nerve regeneration through mitochondrial transfer, presenting a promising strategy for improving stem cell-based therapies for nerve injuries. Furthermore, hydrogels specifically developed to regulate the JAG1/Notch signaling pathway have demonstrated potential for pulp tissue regeneration. Mineral Trioxide Aggregate (MTA) is an excellent marginal sealer that prevents bacterial migration into the canal. It is a biocompatible cement that induces dentinogenesis, cementogenesis, and osteogenesis. Calcium hydroxide remains a standard material for use in pulp capping due to its bactericidal effect.

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Author contributions **Conceptualization-** Mariana Aguiar Alves da Silva, Julia Vasconcelos Perelli, Fábio Pereira Linhares de Castro; **Formal Analysis-** Mariana Aguiar Alves da Silva, Julia Vasconcelos Perelli, Fábio Pereira Linhares de Castro; **Investigation-** Mariana Aguiar Alves da Silva, Julia Vasconcelos Perelli; **Methodology-** Mariana Aguiar Alves da Silva, Julia Vasconcelos Perelli; **Project administration-** Mariana Aguiar Alves da Silva, Julia Vasconcelos Perelli, Fábio Pereira Linhares de Castro; **Supervision-** Fábio Pereira Linhares de Castro; **Writing - original draft-** Mariana Aguiar Alves da Silva, Julia Vasconcelos Perelli, Fábio Pereira Linhares de Castro; **Writing-review & editing-** Mariana Aguiar Alves da Silva, Julia Vasconcelos Perelli, Fábio Pereira Linhares de Castro.

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Conflict of Interest

The authors declare no conflict of interest.

Similarity Check

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Application of Artificial Intelligence (AI)

Not applicable.

Peer Review Process

It was performed.

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