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# Recent developments in bioactive pulp capping materials (direct and indirect): A review

**Dr. Asma Munir Khan**

Assistant professor, Department of Conservative dentistry and Endodontics, College of Dentistry, Qassim University, Buraydah, Saudi Arabia

**Abstract**---The field of dentistry is rapidly shifting its focus toward biologically active restorative materials. Bioactive materials are those capable of inducing and promoting the regeneration of the damaged tissue and remineralizing demineralized dentinal structure as a vital dental pulp is necessary for the long-term healthy survival of a tooth. Vital pulp therapy intends to protect and prevail the vitality of pulp tissue which gets compromised when subjected to mutilating factors like dental caries, trauma, and operative or restorative procedures. During the therapy, the said bioactive material initially forms a non-irritant protective bridge over the vital pulp and later stimulates the pulpal odontoblasts to produce a reparative dentinal barrier which later forms a barrier and protects the underlying pulp's vitality. The vitality of a tooth needs to be intact protected because the consensus reports that endodontically treated teeth, particularly molars, reportedly have a reduced survival probability than the vital teeth. [1] These factual arguments lead to the development of biologically active restorative materials. This review article intends to provide a review of the modern products introduced in the category of bioactive restorative materials.

**Keywords**---recent developments, bioactive pulp capping materials, direct, indirect.

## Introduction

Pulp vitality is an essential factor in determining the long-term health and survivability of a tooth. That is why vital pulp therapy (VPT) intends to retain and protect the vitality of the dental pulp tissue of a tooth, which is subjected to mutilating factors like dental caries, trauma, and operative or restorative procedures. [2]. Promoting the remineralization of hypo-mineralized and carious dentine is the primary challenge confronting restorative dentistry in the present day, therefore conserving and preserving pulp vitality. Deep caries treatment has always led to subsequent exposure of pulp resulting in the need for root canal

treatment (RCT). Mechanical caries removal using biologically-based therapeutic methods (by making use of biologically active material) has been advocated, but these procedures often lead to iatrogenic indirect or direct exposure of the dental pulp. In fact, complete carious excision is regarded an overtreatment according to current consensus reports, and evidence suggests that clinicians should opt for selective caries removal in situations when a carious lesion is in close contact with the pulp. [3] Moreover, endodontically treated teeth, particularly molars, are said to have a inferior rate of survival than the vital teeth.[1]

The morbidity linked to untreated pulpal infection typically needs root canal therapy or tooth extraction and replacement, both of which may require several sessions, substantial expenditures, and are not as cost-effective.[4] This continual shift toward a cautious, noninvasive approach is strongly linked to the profession's focus gradually changing to care for the senior adult population. [6, 7] The preservation of natural teeth is critical in these conditions. These developments are linked to the development of bioactive dental materials. [8] The bioactivity of a restorative substance typically refers to its biological action or activity. This characteristic denotes the capacity to encourage selective and deliberate mineral adherence to the dentine substrate.[9] The term "bioactive substance" refers to the "one that generates a surface layer of an apatite-like material in the presence of an inorganic phosphate solution" in restorative dentistry. As a result, dentine that has been demineralized may be remineralized by the production of inorganic mineral-like substances.[10] This review article intends to provide a review of the modern products introduced in the category of bioactive restorative materials and highlights their advantages and disadvantages.

### **Vital Pulp Therapy (VPT) in the Treatment of Advanced Caries**

#### **Vital pulp therapy**

Vital pulp therapy has been defined as “preserving and maintaining the pulp tissue that has been compromised but not destroyed by extensive dental caries, dental trauma, and restorative procedures or for iatrogenic reasons”[11, 12]

#### **Indirect pulp capping (IPC)**

IPC is needed when there is no direct exposure of the underlying coronal pulp, but the remaining dentine thickness is relatively less (2 to 3mm). This happens most commonly due to gross and deep carious cavities. [5] Despite the conventional concept of total caries removal until hard dentin is reached, partial caries removal coupled with IPC with a bioactive material (partial caries excavation concept) has been advocated in research. [13] This concept is further validated by the recent position statements of the European Society of Endodontics (ESE), so the total removal of the carious lesion is considered an aggressive treatment option.[14]

#### **Direct pulp capping (DPC)**

DPC deals with the placement of pulp capping bio-active material directly on the exposed pulp, which will form a dentine-like matrix formation by stimulating the

dental pulp stem cells. This matrix forms a protective barrier over the underlying dental pulp, thus protecting its vitality. [11]

Carious exposure may be treated with various procedures, ranging from conservative vital pulp treatments (VPT) like DPC and partial and total pulpotomy to more invasive procedures like pulpectomy and root canal therapy.[14]. While root canal therapy is a conventional option to treat and save teeth that have been exposed to gross caries, it is damaging and requires a high degree of professional skill. [14]. On the other hand, if the clinical diagnosis is reversible pulpitis, partial pulpotomies have a high success rate, which is comparatively less invasive than root canal therapy. [15-17] while DPC is an even more conservative option, as mentioned above, it uses a bioactive material to produce a dentine-like protective matrix to protect the pulp vitality.

Due to the persistence of bacterial contamination across the teeth in earlier investigations, the efficacy of DPC could not be established.[18] But with the latest advancements, researchers have started reporting promising results with DPC, especially newly introduced materials, for example, mineral trioxide aggregate (MTA) and calcium silicate cements like Biodentine (Septodont, France). These are bioactive materials, and their use in DPC for traumatically and cariously compromised teeth has shown promising results. [19, 20]

### **Pulpotomy**

Other than DPC or IPC, which does not remove any portion of the pulp that has been affected by the bacterial infection resulting in an inflamed pulpal portion, pulpotomy involves the amputation of a small inflamed pulpal portion (2 to 3mm), leaving healthy pulp underneath. [21] Afterwards, a bioactive pulp capping material may be applied to the exposed pulp surface.[22] Considering the fact that visual examination may not be accurate enough to differentiate amongst non-inflamed and inflamed pulp tissue poses the question of choosing the most suitable treatment. [21] Therefore as a convention, if the hemostasis is not achieved within the initial 5 minutes of partial pulpotomy, which indirectly indicates the inflammatory state of the pulp, pulpotomy leading to pulpectomy can be considered. [23]

### **Materials available for VPT (Conventional Materials)**

For the purpose of pulp capping, a variety of materials have been used. Besides bioactivity, the quality and stability of any dental material are critical components for a restoration's life in clinical situations; marginal adaptability and intimate contact at the interface with surrounding tissues are important qualities.

### **Calcium hydroxide (Ca(OH)<sub>2</sub>)**

The initial evidence of calcium hydroxide for the pulpal healing started emerging between 1934-41[24] which lead to calcium hydroxide becoming the gold standard for vital pulp therapy. However, calcium hydroxide, on the other hand, has the longest track record of reported success as compared to any other bioactive material.[23]

However, it does have poor adherence to dentinal walls, a high number of tunnel defects in induced dentin bridges, poor sealing capacity, and breaks down with time. In addition, the hydroxide ions contribute to the development of an enzymatic inhibition of the bacteria, which results in the antibiotic action of the substance. [25] Clinical research with long-term follow-ups has shown that Calcium hydroxide pulp capping has highly variable success rates, is usually unexpected, and frequently shows ineffective outcomes. [26, 27]

In fact, DPC with calcium hydroxide is no longer recommended. [28] Due to its high basicity, it causes an uncontrolled necrotic zone to form when it comes into contact with the pulp. This necrotic zone causes an inflammatory response that lasts for a long time or causes intra-pulpal calcifications. [23] A little amount of discomfort caused by firm necrosis prompts the pulp to protect and heal by differentiating its cells, secreting an extracellular matrix, and then mineralizing to create a dentin bridge. It was formerly thought that a dentin bridge was necessary for the clinical effectiveness of direct pulp-capping, however recent research found that 89 percent of monkey dentin bridges created using calcium hydroxide cement had tunnel defects.[27, 29, 30] These defects within the heterogeneous dentin bridge are unsuccessful in providing a long-lasting biological seal, and a durable barrier against bacterial infections. As a pulp capping agent, high solubility is the main drawback of its usage. Dissolution is another downside of calcium hydroxide as this could result in microleakage and the creation of dead space. [31] The failure to establish a lasting seal against bacterial infections is due to the material's disintegration and the formation defective dentin under the material in just under two years of its initial application. The formation of superficial necrosis is the first result of calcium hydroxide applied to exposed pulp.

### **Novel Materials for VPT**

The newly introduced materials for the VPT include:

- i. Mineral trioxide aggregate (MTA)
- ii. Calcium Silicate Based Materials
  - a. Biodentine (Septodont, France)
  - b. Endosequence Root Repair Material (ERRM)
  - c. TheraCal LC (TLC, Bisco Inc., USA)
- iii. Calcium aluminate based materials
  - a. Endobinder (Binderware, Brazil)
- iv. Materials containing bioactive proteins
  - a. Emdogain (Straumann, Switzerland)

### **Mineral-Trioxide-Aggregate (MTA)**

MTA, a cement based on calcium silicate, has been extensively researched as a material of DPC and demonstrated favorable therapeutic outcomes in clinical trials. [32, 33]. Significant advantages include strong radiopacity, biocompatibility, sealing ability, long-term stability, low solubility [34], and its role to impart resistance to bacterial invasion within the dental tissue. [34] Additionally, MTA has also been demonstrated to solubilize bioactive proteins

critical to tooth regeneration and reduce hyperemia, inflammation, and necrosis in the pulp tissue. [24] Furthermore, it is capable of setting and sealing in conditions that are damp or tainted with blood. [35]

MTA works like calcium hydroxide. When the pulp comes into contact with the calcium hydroxide that is leached out as a byproduct of MTA hydration, necrosis occurs. The calcium silicates in MTA powder hydrate when exposed to water during application, resulting in the formation of calcium hydroxide and a calcium silicate hydrate gel. As a result, MTA can be classified as a calcium-hydroxide-releasing substance, and it is anticipated to display some characteristics that are comparable to those previously observed for calcium hydroxide.[36] Biocompatibility, bioactivity, good sealability, and the ability to trigger tissue mineralization are considered advantages of MTA. Additionally, when compared to calcium hydroxide, MTA produces a less inflammatory response and less pulpal necrosis in addition to a more homogenous and thicker dentin bridge formation. [37, 38]

MTA exhibited antibacterial activity against some facultative bacteria but not against completely anaerobic microorganisms. [39] when compared to traditional calcium hydroxide-based cements and sealers, the antibacterial capabilities of MTA may be less effective when used alone. Tooth discolouration is another drawback observed with certain sealers, lining, and pulp capping materials. Investigations have shown the shreds of evidence of tooth discolouration with the use of MTA as a DPC material. [40, 41]. Studies have addressed that both white and grey MTA were shown to produce a change in tooth colour. [41, 42] Numerous variables have been implicated in the discolouring of teeth caused by white MTA: blood contamination [43], exposure to light and oxygen [44], interaction with sodium hypochlorite. [45] The discolouration may be triggered by the radio pacifier bismuth oxide. [42] But further research is needed to determine the root cause and the exact mechanism of tooth discolouration.

### **Calcium Silicate Based Materials**

#### **Biodentine**

Biodentine, a bioactive dentine substitute with a quick set time, was brought to the market in 2011. The fundamental core ingredient in biodentine is pure tricalcium silicate (80.1%), with zirconium oxide as a radioopacifier, calcium carbonate (14.9%) as a filler [46, 47], water, a setting accelerator of calcium chloride, and a water-reducing polymer make up the liquid. [48] Biodentine has no calcium sulfate, calcium aluminate, or bismuth oxide. As biodentine lacks bismuth oxide in its composition, it has proven to increase its properties [49], whereas bismuth oxide in MTA has been reported to slow setting [50], degrade biocompatibility [51], and more tooth discolouration [52]. Biodentine has proven to have superior mechanical properties [53, 54], superior colour stability [55], easier handling and manipulation; and Unlike MTA, it just needs 12-16 minutes to set up initially. [56]

Biodentine is an acceptable dentine alternative when filled with a composite resin restoration [57]. Biodentine has now become one of the most regularly used materials. Its clinical implications include DPC and IPC for the remineralization of

the damaged dentinal portion; placing direct restorations in the posterior teeth, especially in the treatment of deep palatogingival or palatoradicular grooves; in placing dressing after pulpotomy of primary teeth[58]; in the retrograde restorations due to its hydrophilic nature; in the teeth which under-went internal resorption as a sequelae to pulpitis and in cases of accidental furcation involvement during root canal therapy. [46, 59-61] Biodentine is the material of choice for many clinicians and serves the cause even better than MTA.[62] Its principal drawbacks are the low radiopacity and difficulty in establishing the required or tailored consistency. [63]

### **Endosequence Root Repair Material (ERRM )**

Endosequence Root Repair Material (ERRM; Brasseler USA, Savannah, GA) is also a novel material prepared for pulp capping purpose. This bio-ceramic material is radiopaque, hydrophilic, high pH, and aluminum-free. According to the investigations, ERRM showed the same antibacterial impact on *Enterococcus faecalis* as MTA. [64] Hirschman WR et al. examined the cytotoxicity of four pulp capping materials on cultured adult human skin fibroblasts. [65] They concluded that ERRM was superior to MTA, Dycal, and Ultra-blend Plus (resin-based calcium hydroxide liner) in terms of cell viability. [65]

### **TheraCal (resin modified calcium silicate-based liner)**

TheraCal LC (Bisco, USA) was created in 2011 to address the lack of adhesion between the resins and calcium silicate-based materials in final restorations. TheraCal LC is a calcium silicate filled, light curing liner used as a protective base/liner for restorations like amalgam, composite, cements, and other base materials in indirect and DPC. It provides insulation and a protective layer for the pulp-dentin combination. TheraCal LC releases calcium, which increases the development of hydroxyapatite and, consequently, dentinal bridges. Ghodduzi et al. [66] evaluated the physicochemical parameters of ProRoot MTA, TheraCal, and Dycal and determined that TheraCal had a greater calcium-releasing capacity and lower solubility than ProRoot MTA and Dycal. [67] According to a study, TheraCal demonstrated superior bonding capacity to composite or glass-ionomer cements than Biodentine.[68, 69] Although significant bioactivity, improved handling qualities, and superior bonding quality when used as a final restoration could confirm the use of this material as the IPC agent, additional in-vivo and in-vitro research is still necessary.

### **Calcium aluminate-based materials Endobinder**

EndoBinder (Binderware, So Carlos, SP, Brazil) is a novel calcium aluminate-based endodontic cement that was created to keep the qualities and therapeutic uses of MTA while removing its negative characteristics.[70] Endobinder varies from MTA in that it lacks magnesium oxide and calcium oxide, which contribute to the material's undesired expansion, and Ferric oxide, which is responsible for tooth discoloration. Aluminum oxide and calcium carbonate are desiccated by roasting and ground at 1315 to 1425°C. Bismuth oxide is used to achieve

radiopacity. Eliminating magnesium oxide, calcium oxide, and ferric oxide residues ensures purity. [70-72]

Another feature that makes endobinder a suitable bioactive material is that it showed better osteoblastic differential compared to MTA in the studies due to the lower calcium hydroxide release from its matrix.[73] On the basis of research data available so far, the overall impression of the material appears to be well advantageous to be used in VPT procedures. However, a lack of publications explaining and validating its biological and physiochemical properties[74] makes its use slightly doubtful to clinicians.

### **Materials containing bioactive proteins**

#### **Emdogain**

Emdogain is a synthetic gel containing an “Enamel Matrix Derivative” (EMD) which has been extracted from developing porcine teeth’s enamel matrix.[75] In the treatment of infrabony deficiencies due to periodontal disease, it has been shown to be effective in repairing periodontal tissues. Pulpal tissues, on the other hand, have less supporting data; preliminary studies in both animals and humans reveal that it is, at most, no better than calcium hydroxide or MTA.[76] Emdogain may offer certain benefits over conventional treatments for replacing gum tissue lost due to gum disease, such as fewer postoperative symptoms, but it has not been shown to preserve more affected teeth or that patients had any cosmetic benefits one year after application.[77] Comparing the aesthetic outcomes, even though patients did not detect any differences in the aesthetic outcomes, The study found that adding Emdogain regenerates one mm more gingival tissue than surgical debridement alone. However, it is uncertain to what degree this improvement is perceptible.[77]

### **Conclusion**

The newly developed materials, for example, TheraCal LC, Biodentine, ERRM etc., stimulate the pulp progenitor cells in an improved manner and eliminate prominent drawbacks of previous materials. On the other hand, researchers are working on improving the slightly older materials. For example, in the case of MTA, a prominent disadvantage of discoloration has now been addressed via modification into convention MTA compositions.

There is an ever-growing demand for new developments of bioactive materials for vital pulp treatment (VPT). The review concludes that besides materials like Emdogain (an enamel matrix derivative) are available. However, their long-term success, cytotoxicity, bond strength quality, and the quality of dentin-bridge formation are still needed to be supported by more experimental data via in-vitro and in-vivo studies.

### **References**

1. About I. Biodentine: from biochemical and bioactive properties to clinical applications. *Giornale Italiano di Endodonzia*. 2016;30(2):81-8.

2. Adl A, Javanmardi S, Abbaszadegan A. Assessment of tooth discoloration induced by biodentine and white mineral trioxide aggregate in the presence of blood. *Journal of Conservative Dentistry: JCD*. 2019;22(2):164.
3. Aguilar P, Linsuwanont P. Vital pulp therapy in vital permanent teeth with cariously exposed pulp: a systematic review. *J Endod*. 2011;37(5):581-7.
4. Al-Dlaigan YH. Pulpotomy medicaments used in deciduous dentition: an Update. *J Contemp Dent Pract*. 2015;16(6):486-503.
5. Alqaderi H, Lee CT, Borzangy S, Pagonis TC. Coronal pulpotomy for cariously exposed permanent posterior teeth with closed apices: A systematic review and meta-analysis. *J Dent*. 2016;44:1-7.
6. Arandi NZ, Thabet M. Minimal Intervention in Dentistry: A Literature Review on Biodentine as a Bioactive Pulp Capping Material. *BioMed research international*. 2021;2021.
7. Bajrami D, Stavileci M, Dragidella A, Sejfiija Z. In Vitro Antifungal Effect of Biodentine™ Against *Candida Albicans*. *Journal of International Dental and Medical Research*. 2020;13(1):57-60.
8. Bergenholtz G, Axelsson S, Davidson T, Frisk F, Hakeberg M, Kvist T, et al. Treatment of pulps in teeth affected by deep caries—A systematic review of the literature. *Singapore Dental Journal*. 2013;34(1):1-12.
9. Cao CY, Mei ML, Li Q-L, Lo ECM, Chu CH. Methods for biomimetic remineralization of human dentine: a systematic review. *International journal of molecular sciences*. 2015;16(3):4615-27.
10. Caplan DJ, Cai J, Yin G, White BA. Root canal filled versus non-root canal filled teeth: a retrospective comparison of survival times. *J Public Health Dent*. 2005;65(2):90-6.
11. Castro-Raucci LMSd, Oliveira IRd, Teixeira LN, Rosa AL, Oliveira PTd, Jacobovitz M. Effects of a novel calcium aluminate cement on the early events of the progression of osteogenic cell cultures. *Brazilian Dental Journal*. 2011;22:99-104.
12. Chailertvanitkul P, Paphangkorakit J, Sooksantisakoonchai N, Pumas N, Pairojamornyoot W, Leela-apiradee N, et al. Randomized control trial comparing calcium hydroxide and mineral trioxide aggregate for partial pulpotomies in cariously exposed pulps of permanent molars. *International Endodontic Journal*. 2014;47(9):835-42.
13. Cox C, Sübay R, Ostro E, Suzuki S, Suzuki S. Tunnel defects in dentin bridges: their formation following direct pulp capping. *Operative dentistry*. 1996;21(1):4-11.
14. Cox CF, Suzuki S. Re-evaluating pulp protection: calcium hydroxide liners vs. cohesive hybridization. *The Journal of the American Dental Association*. 1994;125(7):823-31.
15. Cushley S, Duncan HF, Lappin MJ, Tomson PL, Lundy FT, Cooper P, et al. Pulpotomy for mature carious teeth with symptoms of irreversible pulpitis: A systematic review. *J Dent*. 2019;88:103158.
16. Darade L, Ranjan S, Singh GB, Gangadhar B, Vandekar M, Rathi AG. Bioceramic a futuristic boon in endodontics-A.
17. Deepa V, Dhamaraju B, Bollu I, Balaji T. Shear bond strength evaluation of resin composite bonded to three different liners: TheraCal LC, Biodentine, and resin-modified glass ionomer cement using universal adhesive: An *in vitro* study. *Journal of Conservative Dentistry*. 2016;19(2):166-70.

18. Duncan HF, Galler KM, Tomson PL, Simon S, El-Karim I, Kundzina R, et al. European Society of Endodontology position statement: Management of deep caries and the exposed pulp. *Int Endod J*. 2019;52(7):923-34.
19. Elmsmari F, Ruiz XF, Miró Q, Feijoo-Pato N, Durán-Sindreu F, Olivieri JG. Outcome of Partial Pulpotomy in Cariously Exposed Posterior Permanent Teeth: A Systematic Review and Meta-analysis. *J Endod*. 2019;45(11):1296-306.e3.
20. Eren SK, Örs SA, Aksel H, Canay Ş, Karasan D. Effect of irrigants on the color stability, solubility, and surface characteristics of calcium-silicate based cements. *Restorative Dentistry & Endodontics*. 2022;47(1).
21. Esposito M, Grusovin MG, Papanikolaou N, Coulthard P, Worthington HV. Enamel matrix derivative (Emdogain®) for periodontal tissue regeneration in intrabony defects. *Cochrane database of systematic reviews*. 2009(4).
22. Esposito M, Grusovin MG, Papanikolaou N, Coulthard P, Worthington HV. Enamel matrix derivative (Emdogain(R)) for periodontal tissue regeneration in intrabony defects. *The Cochrane database of systematic reviews*. 2009;2009(4):Cd003875.
23. Estrela C, Sydney GB, Bammann LL, Felipe Júnior O. Mechanism of action of calcium and hydroxyl ions of calcium hydroxide on tissue and bacteria. *Brazilian dental journal*. 1995;6(2):85-90.
24. Gandolfi M, Siboni F, Prati C. Chemical–physical properties of TheraCal, a novel light-curable MTA-like material for pulp capping. *International endodontic journal*. 2012;45(6):571-9.
25. Garcia LdFR, Huck C, de Oliveira LM, de Souza PPC, de Souza Costa CA. Biocompatibility of new calcium aluminate cement: tissue reaction and expression of inflammatory mediators and cytokines. *Journal of Endodontics*. 2014;40(12):2024-9.
26. Ghoddusi J, Forghani M, Parisay I. New approaches in vital pulp therapy in permanent teeth. *Iranian endodontic journal*. 2014;9(1):15.
27. Ghoddusi J, Forghani M, Parisay I. New approaches in vital pulp therapy in permanent teeth. *Iran Endod J*. 2014;9(1):15-22.
28. Hanna SN, Perez Alfayate R, Prichard J. Vital Pulp Therapy an Insight Over the Available Literature and Future Expectations. *Eur Endod J*. 2020;5(1):46-53.
29. Hirschman WR, Wheeler MA, Bringas JS, Hoen MM. Cytotoxicity comparison of three current direct pulp-capping agents with a new bioceramic root repair putty. *Journal of Endodontics*. 2012;38(3):385-8.
30. Jacobovitz M, Vianna ME, Pandolfelli VC, Oliveira IR, Rossetto HL, Gomes BP. Root canal filling with cements based on mineral aggregates: an in vitro analysis of bacterial microleakage. *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontology*. 2009;108(1):140-4.
31. Jefferies SR. Bioactive and biomimetic restorative materials: a comprehensive review. Part I. *Journal of esthetic and restorative dentistry*. 2014;26(1):14-26.
32. Johari Y, Pungut NA, Yin VWX, Khamis MF, Yusoff MNM. Sealing Ability of Injectable Dental Composites, Biodentine and MTA in Repairing Furcal Perforation of Permanent Molar Teeth. *Journal of International Dental and Medical Research*. 2020;13(4):1428-34.
33. Kadali NS, Alla RK, AV R, MC SS, Mantena SR, RV R. An overview of composition, properties, and applications of Biodentine. *International Journal of Dental Materials*. 2021;3(4):120-6.

34. Kaur M, Singh H, Dhillon JS, Batra M, Saini M. MTA versus Biodentine: review of literature with a comparative analysis. *Journal of clinical and diagnostic research: JCDR*. 2017;11(8):ZG01.
35. Khedmat S, Ahmadi E, Meraji N, Fallah ZF. Colorimetric Comparison of Internal Bleaching with and without Removing Mineral Trioxide Aggregate (MTA) on Induced Coronal Tooth Discoloration by MTA. *International Journal of Dentistry*. 2021;2021.
36. Kim JR, Nosrat A, Fouad AF. Interfacial characteristics of Biodentine and MTA with dentine in simulated body fluid. *Journal of dentistry*. 2015;43(2):241-7.
37. Komabayashi T, Zhu Q, Eberhart R, Imai Y. Current status of direct pulp-capping materials for permanent teeth. *Dental materials journal*. 2016;35(1):1-12.
38. Koubi G, Colon P, Franquin J-C, Hartmann A, Richard G, Faure M-O, et al. Clinical evaluation of the performance and safety of a new dentine substitute, Biodentine, in the restoration of posterior teeth—a prospective study. *Clinical oral investigations*. 2013;17(1):243-9.
39. Kunert M, Lukomska-Szymanska M. Bio-Inductive Materials in Direct and Indirect Pulp Capping—A Review Article. *Materials*. 2020;13(5):1204.
40. Li Z, Cao L, Fan M, Xu Q. Direct Pulp Capping with Calcium Hydroxide or Mineral Trioxide Aggregate: A Meta-analysis. *J Endod*. 2015;41(9):1412-7.
41. Lim M, Song M, Hong C-U, Cho Y-b. The biocompatibility and mineralization potential of mineral trioxide aggregate containing calcium fluoride—An in vitro study. *Journal of Dental Sciences*. 2021;16(4):1080-6.
42. Lin LM, Ricucci D, Saoud TM, Sigurdsson A, Kahler B. Vital pulp therapy of mature permanent teeth with irreversible pulpitis from the perspective of pulp biology. *Australian Endodontic Journal*. 2020;46(1):154-66.
43. Lovato KF, Sedgley CM. Antibacterial activity of endosequence root repair material and proroot MTA against clinical isolates of *Enterococcus faecalis*. *Journal of endodontics*. 2011;37(11):1542-6.
44. Madani Z, Alvandifar S, Bizhani A. Evaluation of tooth discoloration after treatment with mineral trioxide aggregate, calcium-enriched mixture, and Biodentine® in the presence and absence of blood. *Dental Research Journal*. 2019;16(6):377.
45. Malkondu Ö, Kazandağ MK, Kazazoğlu E. A review on biodentine, a contemporary dentine replacement and repair material. *BioMed research international*. 2014;2014.
46. Marques Junior RB, Baroudi K, Santos AFCd, Pontes D, Amaral M. Tooth discoloration using calcium silicate-based cements for simulated revascularization in vitro. *Brazilian Dental Journal*. 2021;32:53-8.
47. Megantoro A, Djauharie RN, Margono A. The Effect of Biodentine™ Application in Affected Dentin Remineralization after Partial Caries Excavation In Vivo. *Journal of International Dental and Medical Research*. 2019;12(3):1117-22.
48. Mente J, Hufnagel S, Leo M, Michel A, Gehrig H, Panagidis D, et al. Treatment outcome of mineral trioxide aggregate or calcium hydroxide direct pulp capping: long-term results. *Journal of Endodontics*. 2014;40(11):1746-51.
49. Meraji N, Camilleri J. Bonding over dentin replacement materials. *Journal of endodontics*. 2017;43(8):1343-9.

50. Mutluay M, Mutluay AT. Sealing efficiency of MTA, accelerated MTA, Biodentine and RMGIC as retrograde filling materials. *Balkan Journal of Dental Medicine*. 2021;25(3):159-65.
51. Nair PN, Duncan HF, Pitt Ford TR, Luder HU. Histological, ultrastructural and quantitative investigations on the response of healthy human pulps to experimental capping with Mineral Trioxide Aggregate: a randomized controlled trial. 2008. *Int Endod J*. 2009;42(5):422-44.
52. Ochoa-Rodriguez VM, Tanomaru-Filho M, Rodrigues EM, Guerreiro-Tanomaru JM, Spin-Neto R, Faria G. Addition of zirconium oxide to Biodentine increases radiopacity and does not alter its physicochemical and biological properties. *Journal of applied oral science*. 2019;27.
53. Okiji T, Yoshiba K. Reparative dentinogenesis induced by mineral trioxide aggregate: a review from the biological and physicochemical points of view. *International journal of dentistry*. 2009;2009.
54. Parirokh M, Torabinejad M. Mineral trioxide aggregate: a comprehensive literature review—part III: clinical applications, drawbacks, and mechanism of action. *Journal of endodontics*. 2010;36(3):400-13.
55. Pereira TC, da Silva Munhoz Vasconcelos LR, Graeff MSZ, Ribeiro MCM, Duarte MAH, de Andrade FB. Intratubular decontamination ability and physicochemical properties of calcium hydroxide pastes. *Clinical oral investigations*. 2019;23(3):1253-62.
56. Pires MD, Cordeiro J, Vasconcelos I, Alves M, Quaresma SA, Ginjeira A, et al. Effect of different manipulations on the physical, chemical and microstructural characteristics of Biodentine. *Dental Materials*. 2021;37(7):e399-e406.
57. Prati C, Gandolfi MG. Calcium silicate bioactive cements: Biological perspectives and clinical applications. *Dental materials*. 2015;31(4):351-70.
58. Qureshi A, Soujanya E, Nandakumar P. Recent advances in pulp capping materials: an overview. *Journal of clinical and diagnostic research: JCDR*. 2014;8(1):316.
59. Rajasekharan S, Martens L, Cauwels R, Anthonappa RP. Biodentine™ material characteristics and clinical applications: a 3 year literature review and update. *European Archives of Paediatric Dentistry*. 2018;19(1):1-22.
60. Saghiri MA, Asatourian A, Garcia-Godoy F, Sheibani N. Effect of biomaterials on angiogenesis during vital pulp therapy. *Dental materials journal*. 2016:2015-332.
61. Schröder U. Effects of calcium hydroxide-containing pulp-capping agents on pulp cell migration, proliferation, and differentiation. *Journal of dental research*. 1985;64(4):541-8.
62. Schwendicke F, Frencken JE, Bjørndal L, Maltz M, Manton DJ, Ricketts D, et al. Managing carious lesions: consensus recommendations on carious tissue removal. *Advances in dental research*. 2016;28(2):58-67.
63. Shokouhinejad N, Alikhasi M, Khoshkhounejad M, Pirmoazen A. Effect of irrigation solutions on the coronal discoloration induced by mineral trioxide aggregate cements containing different radiopacifiers. *Dental Research Journal*. 2020;17(6):447.
64. Silva EJ, Herrera DR, Rosa TP, Duque TM, Jacinto RC, Gomes BP, et al. Evaluation of cytotoxicity, antimicrobial activity and physicochemical properties of a calcium aluminate-based endodontic material. *Journal of applied oral science : revista FOB*. 2014;22(1):61-7.

65. Simon S, Smith AJ, Lumley PJ, Cooper PR, Berdal A. The pulp healing process: from generation to regeneration. *Endodontic Topics*. 2012;26(1):41-56.
66. Slaboseviciute M, Vasiliauskaite N, Drukteinis S, Martens L, Rajasekharan S. Discoloration Potential of Biodentine: A Systematic Review. *Materials*. 2021;14(22):6861.
67. Spagnuolo G. Bioactive Dental Materials: The Current Status. *Materials*. 2022;15(6):2016.
68. Srinivasan S, Vengidesh R, Ramachandran A, Kadandale S. An Immature Traumatic Teeth Management With Apical Pathology Using the Novel Biodentine™ Obturation: A Case Report. *Cureus*. 2021;13(12).
69. Stencel R, Kasperski J, Pakieła W, Mertas A, Bobela E, Barszczewska-Rybarek I, et al. Properties of experimental dental composites containing antibacterial silver-releasing filler. *Materials*. 2018;11(6):1031.
70. Tamzini M, Albeshti R, Abdesalam A. Enamel Matrix Derivative (Emdogain®) for Wound Healing and Bone Regeneration: A Short-Review. *Libyan J Med Res*. 2022;16(1):107-13.
71. Tan SY, Yu VSH, Lim KC, Tan BCK, Neo CLJ, Shen L, et al. Long-term pulpal and restorative outcomes of pulpotomy in mature permanent teeth. *Journal of endodontics*. 2020;46(3):383-90.
72. Tripathi R, Cohen S, Khanduri N. Coronal tooth discoloration after the use of white mineral trioxide aggregate. *Clinical, Cosmetic and Investigational Dentistry*. 2020;12:409.
73. Vural UK, Kiremitci A, GÖKALP S. Which is the most effective biomaterial in indirect pulp capping? 4-year comparative randomized clinical trial. *European Oral Research*. 2022;56(1):35-41.
74. Widbiller M, Jeanneau C, Galler KM, Laurent P. Biocompatibility and Bioactive Properties of Biodentine TM. *Biodentine™: Springer*; 2022. p. 31-50.
75. Xu D, Mutoh N, Ohshima H, Tani-Ishii N. The effect of mineral trioxide aggregate on dental pulp healing in the infected pulp by direct pulp capping. *Dental Materials Journal*. 2021;40(6):1373-9.
76. Zhu C, Ju B, Ni R. Clinical outcome of direct pulp capping with MTA or calcium hydroxide: a systematic review and meta-analysis. *International journal of clinical and experimental medicine*. 2015;8(10):17055.
77. 박윤정, 강주희, 서현, 송호준, 박영준, 저자. Effect of compositional variation of dental MTA cements on setting time. *Korean Journal of Dental Materials-Vol*. 2021;48(2):99-118.