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Materiais dentários bioativos: Estado da arte e prospecção tecnólogica

Wellington Luiz de Oliveira da Rosa

Pelotas, 2016

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Materiais dentários bioativos:
Estado da arte e prospecção tecnológica

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“Você nunca irá tropeçar com o inesperado se ficar somente com o que é familiar”

Ed Catmull

Notas Preliminares

A presente dissertação foi redigida segundo o Manual de Normas para Dissertações, Teses e Trabalhos Científicos da Universidade Federal de Pelotas de 2013, adotando o Nível de Descrição 3 – estrutura em “Capítulos convencionais”, descrita no Apêndice D do referido manual. <http://sisbi.ufpel.edu.br/?p=documentos&i=7> Acesso em: 20 de janeiro de 2016.

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Resumo

DA ROSA, Wellington Luiz de Oliveira. **Materiais dentários bioativos: Estado da arte e prospecção tecnológica.** 2015. 122f. Dissertação (Mestrado em Odontologia) – Programa de Pós-Graduação em Odontologia. Universidade Federal de Pelotas, Pelotas, 2016.

Materiais bioativos são capazes de promover uma resposta fisiológica induzida e programada nos tecidos vivos, organismos ou células. O complexo dentino-pulpar possui uma série de moléculas biologicamente ativas em sua composição, como os fatores de crescimento transformadores-β1 (TGF-β1) e as proteínas morfogenéticas ósseas-7 (BMP-7), que atuam em eventos de reparo e regeneração dental. A melhor compreensão dessas proteínas pode permitir explorar novos tratamentos com materiais destinados a terapias biologicamente ativas. Esse trabalho visou inicialmente analisar o estado da arte e da técnica dos tratamentos para polpa vital de modo a avaliar os avanços recentes e as perspectivas futuras no setor. A busca na literatura foi conduzida nas bases de dados de artigos (PubMed, Lilacs, IBECS, BBO, Web of Science, Scopus, SciELO and The Cochrane Library) e de patentes (no sistema Questel Orbit, USPTO, EPO, JPO, INPI e Patentscope). Foram analisados 799 documentos referentes à materiais para proteção do complexo dentino-pulpar, que mostraram que os cimentos de hidróxido de cálcio e mineral trióxido agregado (MTA) foram os mais estudados ao longo dos anos. Avanços recentes nos materiais derivados do MTA (cimento de silicato de cálcio, aluminato de cálcio, fosfato de cálcio) e nos materiais bioativos contendo proteínas dentárias apresentaram resultados promissores que poderiam melhorar os tratamentos para polpa vital no futuro. Além disso, foi feita uma revisão sistemática nas bases de artigos com o propósito de avaliar a eficácia do uso de moléculas dentinárias bioativas nos tratamentos para polpa vital. Um total de 32 experimentos em animais foram incluídos na análise. De maneira geral, o uso de moléculas bioativas potencializou a formação de dentina terciária no capeamento pulpar direto e indireto, promovendo uma menor resposta inflamatória inicial. Os materiais bioativos apresentararam potencial aplicação para novas abordagens terapêuticas com foco nos processos de reparo e regeneração do órgão dental.

Palavras-chave: capeamento da polpa dentária; fatores de crescimento transformadores; agentes de capeamento da polpa dentária; materiais dentários.

Abstract

DA ROSA, Wellington Luiz de Oliveira. **Materiais dentários bioativos: Estado da arte e prospecção tecnológica.** 2016. 122f. Dissertation (Master degree in Dentistry). Graduate Program in Dentistry. Federal University of Pelotas, Pelotas, 2016.

Bioactive materials are able to promote an induced and programmed physiological response in living tissue, cells or organisms. The dentin-pulp complex has a number of biologically active molecules in its composition, such as transforming growth factor-β1 (TGF-β1) and bone morphogenetic protein-7 (BMP-7) that acts in repair and regeneration events of teeth. A better understanding of dentin matrix proteins may allow exploring new treatments with materials for biologically based therapies. Initially, this study aimed to analyze the state of the art and technique of treatments for vital pulp in order to assess the recent advances and future prospects in the sector. A literature search was conducted in papers (PubMed, Lilacs, IBECS, BBO, Web of Science, Scopus, SciELO and The Cochrane Library) and patents databases (Questel Orbit, USPTO, EPO, JPO, the INPI and Patentscope). It was analyzed 799 documents related to materials for dentin-pulp complex protection, which showed that calcium hydroxide cement and mineral trioxide aggregate (MTA) have been the most studied over the years. Recent advances in MTA derived materials (calcium silicate, calcium aluminate, calcium phosphate cements) and bioactive materials containing proteins showed promising results that could improve treatments for vital pulp in the near future. In addition, a systematic review was conducted to evaluate the efficacy of deliver bioactive dentin molecules in vital pulp treatments. A total of 32 animal experiments were included in the analysis. In general, the use of bioactive proteins potentiated tertiary dentin formation in direct and indirect pulp capping, promoting a lower initial inflammatory response. Bioactive materials showed potential use for new therapeutic approaches focused on repair and regeneration processes of dental organ.

Key-words: dental pulp capping; transforming growth factor; pulp capping agents; dental materials.

Sumário

1 Introdução

A odontologia conservadora tem como objetivo prevenir danos ao complexo dentino-pulpar por meio da preservação dos tecidos dentais. Essa abordagem foi possível a partir do melhor entendimento da fisiologia dos tecidos dentários, bem como o surgimento de novas técnicas e materiais biocompatíveis e biologicamente ativos (RICKETTS, 2001, SCHWENDICKE; STOLPE, 2014, THOMPSON et al., 2008). Os materiais bioativos são descritos como aqueles que promovem uma resposta biológica nos tecidos vivos, organismos ou células, tais como a indução da formação de tecidos, como o pulpar ou dentinário (ANUSAVICE; SHEN; RAWLS, 2013). O cimento de hidróxido de cálcio e o mineral trióxido trióxido agregado (MTA) seriam considerados bioativos por estimularem a formação de dentina terciária (TOMSON et al., 2007). Nesse contexto, recentes avanços têm emergido a fim de desenvolver biomateriais que estimulem a mais benéfica resposta tecidual de interesse no indíviduo, de maneira a potencializar a bioatividade e a biocompatibilidade, sem acarretar em efeitos danosos aos tecidos orais (SMITH et al., 2016).

Apesar da odontologia conservadora e minimamente invasiva ser atualmente preconizada, a exposição da polpa pode ocorrer por injúrias de origem cariosa ou traumática, ou decorrente de acidentes durante preparos cavitários para o tratamento restaurador (SMITH, et al., 2016). A proteção da polpa pode ser necessária especialmente em casos de capeamento pulpar direto (quando há exposição pulpar), capeamento pulpar indireto (em casos em que não há exposição pulpar, mas há proximidade com a polpa) e pulpotomia (com a remoção parcial ou total de tecido pulpar coronário) (MIYASHITA et al., 2007). Um material de proteção pulpar ideal é descrito como aquele capaz de se aderir à estrutura dental, manter um selamento marginal eficiente, ser resistente à infiltração bacteriana, insolúvel aos fluidos teciduais, dimensionalmente estável, não reabsorvível, radiopaco, biocompatível. Além disso, deve ser bioativo, sendo capaz de estimular o tecido pulpar remanescente a manter a função e vitalidade da polpa (CAMILLERI; PITT FORD, 2006, ROBERTS et al., 2008, TORABINEJAD; PARIROKH, 2010).

Uma série de materiais têm sido usados para proteção da polpa, como o

cimento de hidróxido de cálcio e, mais recentemente, o MTA. O hidróxido de cálcio, apesar do longo histórico de sucesso clínico, não se adere aos substratos dentários, não permite um vedamento eficiente, e as formulações autoativadas são solúveis e sujeitas a dissolução ao longo do tempo (BARRIESHI-NUSAIR; QUDEIMAT, 2006, MARQUES; WESSELINK; SHEMESH, 2015). Por outro lado, o MTA apresenta biocompatibilidade, estabilidade a longo prazo e é também capaz de induzir a formação de dentina terciária. No entanto, a descoloração dos dentes, especialmente para dentes anteriores, a maior citotoxicidade imediatamente após manipulação, o maior pH durante a presa, a dificuldade de manipulação, e o elevado custo são suas principais desvantagens (BOGEN; KIM; BAKLAND, 2008, HILTON, 2009, TAWIL; DUGGAN; GALICIA, 2015). Atualmente, nenhum agente para proteção da polpa é capaz de satisfazer todos os requisitos de um material ideal (ROBERTS, et al., 2008).

O mecanismo de proteção pulpar após a aplicação de materiais capeadores envolve constituintes da matriz dentinária capazes de responder às injúrias por deposição de tecido mineralizado, com formação de dentina terciária ou esclerose dentinária (obliteração dos túbulos dentinários) (MIYASHITA, et al., 2007). De um modo geral, a matriz dentinária é um reservatório de moléculas secretadas pelos odontoblastos e fibroblastos da polpa (SMITH et al., 2012). Essas moléculas atuam como estimuladores e/ou inibidores em eventos que envolvem a modulação do desenvolvimento embriogênico, a diferenciação celular, a imunorregulação, o processo de reparo e regeneração tecidual. Os principais componentes presentes nessa matriz estão sumarizados na Tabela 1 (GOLDBERG; SMITH, 2004, PIVA; SILVA; NOR, 2014, SMITH, et al., 2012).

A incorporação de moléculas biologicamente ativas em materiais odontológicos pode possibilitar tratamentos mais biológicos com a indução de eventos que envolvem o reparo ou a regeneração de tecidos de interesse, como a formação de dentina terciária, a esclerose dentinária (mineralização intratubular), o controle do processo inflamatório, a formação de tecido mineralizado. Por causa disso, os materiais bioativos poderão representar novas alternativas de tratamentos para capeamento pulpar, pulpotomia, reparo de lesões de furca e perfurações, retro-obturação, apicigênese ou apicificação, hipersensibilidade dentinária, reabsorção radicular, reparo e regeneração óssea, entre outros.

Tabela 1 – Relação das principais moléculas bioativas presentes na matriz dentinárias com os respectivos efeitos no complexo dentino-pulpar*

Proteínas	Funções principais
TGF-β1	Capacidade de estimular processos de regeneração dentinária, com propriedades anti-inflamatórias e está envolvido na formação de dentina terciária
BMP-7 (OP-1)	Capacidade de estimular processos de regeneração dentinária, está envolvido na formação de dentina terciária
IGF-1	Envolvido na morfogênese dentária e diferenciação dos odontoblastos durante a embriogênese
FGF-2	Envolvido na morfogênese dentária e diferenciação dos odontoblastos durante a embriogênese
BMP-2	Capacidade de estimular processos de regeneração dentinária, diferenciação de odontoblastos e a atividade da fosfatase alcalina
DMP-1	Envolvido nos processos de mineralização dentinária e síntese de interleucinas (IL-6 e IL-8) a partir de fibroblastos da polpa
DPP	Envolvido no processo de mineralização dentinária
DSP	Envolvido na morfogênese dentária e capacidade de promover crescimento, migração e diferenciação odontoblástica
PDGF	Capacidade de estimular a angiogênese e modular diferenciação odontoblástica
VEGF	Capacidade de estimular a angiogênese
EGF	Envolvido na diferenciação neurogênica de células-tronco da polpa dentária

*Adaptado de Smith et al. (2012), Piva et al. (2014) e Smith et al. (2016)

Devido a isso, a presente dissertação está dividida em dois capítulos que abordam o estado da arte e da técnica de materiais bioativos na odontologia.

1.2 Objetivos

O objetivo do primeiro capítulo foi avaliar o estado atual e as perspectivas futuras de desenvolvimento de materiais para proteção do complexo dentino-pulpar, como os materiais bioativos. No segundo capítulo, foi analisado estudos em animais para avaliar a eficácia do uso de proteínas dentinárias bioativas em tratamentos para polpa vital.

2 Capítulo 1

State of the art and future perspectives of dental pulp capping materials: a systematic review[1]

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Abstract

The aim of this systematic review was to analyze the current trends and future perspectives of dental pulp capping materials through an analysis of scientific and technological data. This study is reported in accordance with the PRISMA Statement. Eight papers databases were screened: PubMed (MedLine), Lilacs, IBECS, BBO, Web of Science, Scopus, SciELO and The Cochrane Library. Additionally, the search of patent applications was conducted in Questel Orbit (Paris, France), USPTO, EPO, JPO, INPI and Patentscope. A total of 716 papers and 83 patents were included. Calcium hydroxide was the main type of material studied, especially for direct pulp capping, followed by MTA. Patents related to adhesives or resins increased from 1998 e 2008, while in the last years it was observed a major increase in bioactive materials (containing bioactive proteins), MTA and MTA derived materials (calcium silicate, calcium phosphate and calcium aluminate based cements). It was possible to obtain a scientific and technological overview of pulp capping materials. MTA have showed favorable results in vital pulp therapy that seems to surpass the disadvantages of calcium hydroxide. Recent advances in bioactive and MTA derived materials have showed promising results that could improve biomaterials used in vital pulp treatments.

Keywords: Dental pulp capping; Pulp capping agents; Pulpotomy; Dental materials; Review.

1 Introduction

Conservative dentistry aims to promote preservation of the tooth structure in an effort to avoid damage to dentin-pulp complex. Therefore, there are several techniques available for the management of teeth affected by caries or traumatic injuries in order to preserve pulp vitality, such as direct and indirect pulp capping [1, 2]. According to the American Association of Endodontists (AAE), dental pulp capping is defined as a treatment of an vital pulp by using biomaterials that enhance the formation of tertiary dentin and consequently maintenance of tooth vitality. Dental pulp capping involves the application of a protective material to the remaining thin layer of dentin over a nearly exposed pulp (indirect capping), over an exposed pulp (direct capping) or over a partially removed coronal pulp tissue (pulpotomy) [3]. The morbidity associated with non-treating pulp often requiring either root canal treatment or tooth extraction with further replacement, which could require multiple appointments, considerable expenses and it is less cost-effective [4, 5].

Vital pulp therapy has been practiced for more than 200 years. The first procedure described was the application of a cap of lead foil to an exposed pulp performed by Pfaff in 1756 [6, 7]. About 100 years later, materials containing calcium hydroxide for treating exposed pulp were first described. However, the use of calcium hydroxide gained importance only after publication of Hermann in 1930, and since then, this material has been one of the most commonly employed in vital pulp therapy [7, 8]. In the last decades, mineral trioxide aggregate (MTA), a Portland cement-based formulation, has gained attention in dentistry. It was first described in the literature in 1993 initially as dental root-end filling material [9, 10]. Only in 1998, MTA received approval for clinical use by the U.S. and Drug Administration (FDA), and it is until nowadays indicated for vital pulp therapy (direct/indirect pulp capping, pulpotomy) [11, 12].

In order to find an ideal pulp capping agent, over the years other biomaterials have been suggested in the literature, such as zinc oxide and eugenol cement, glass ionomer cement, dental bonding agents, formocresol, ferric sulfate, resin composites and MTA derived materials, such as calcium silicate, calcium phosphate and calcium aluminate based cements [2, 9, 11, 12]. Moreover, an ideal pulp capping should adhere to tooth substrate, maintain a sufficient seal, be insoluble in tissue fluids, dimensionally stable, non-resorbable, nontoxic, noncarcinogenic, nongenotoxic, radiopaque, and exhibit biocompatibility and bioactivity [9, 10, 13]. Unfortunately,

none of available biomaterials have been able to satisfy the total requirements of an ideal one [13].

Thus, since the evolution of dentistry, various dental materials have been developed to obtain maximum benefit from them generating the most beneficial tissue response [14, 15]. With the better understanding of dentin-pulp complex repair and regeneration process, the advances of biomaterials to maintain pulp vitality using minimal invasive dentistry has emerged [16]. Thus, the aim of this sistematic review was to analyze the scientific and technological information related to dental pulp capping materials in order to obtain the state of the art of this area. Additionaly, we aimed to verify the current trends and future perspectives in the development of new biomaterials for vital pulp treatments.

2 Methods

The report from this systematic review was adapted from the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement [17].

2.1 Electronic searches

The reviewers performed the literature search until November of 2015. Eight papers databases were selected to conduct the search: PubMed (MedLine), Web of Science, The Cochrane Library, Scopus, Scielo, Ibecs, Lilacs, BBO, and Lilacs. Additionally, the search and analysis of patent applications was conducted by the online system Questel Orbit (Paris, France), which allows the patent search over 80 authorities. Other patents databases screened were USPTO (United States Patents and Trademark Office), EPO (European Patent Office), JPO (Japan Patent Office), INPI (National Institute of Intellectual Property of Brazil) and Patentscope. Search strategy used in PubMed (MedLine) was adapted for other databases (Table 1).

Furthermore, a preliminary patent search was performed to identify relevant International Patent Classification (IPC) in order to optimize the patent search process. The aim of identifying these codes was to create a specific tool for patent search, and the following codes were crossed with the search terms to enhance the retrieval of relevant patents: A61K (preparations for medical, dental, or toilet purposes); A61K 6/02 (use of preparations for artificial teeth, for filling or for capping teeth) and A61C 5/00 (filling or capping teeth). The papers were imported to the

software Endnote X7 (Thompson Reuters, USA) to remove duplicates.

2.2 Screening and study selection

Studies and patents were initially analyzed through a screening of titles and abstracts. Reviewers selected only studies and patents related do dental pulp capping materials in accordance with the eligibility criteria (Table 2). There was no limit of publication year. Documents that appearing to meet the inclusion criteria or had insufficient data in the title and abstract to make a clear decision were selected for full analysis. Any disagreement regarding the inclusion of studies was resolved through discussion and consensus. Thus, only documents that fulfilled all of the eligibility criteria were admitted.

2.3 Data extraction

The scientific and technological data of interest were tabulated by reviewers (ARC, TMS, LCM, ADG), and another reviewer revised all data (WLOR). The following data from included studies were tabulated: type of study (*in vitro*, clinical and/or animal study), year of publication, country of corresponding author, vital pulp treatment (direct/indirect pulp capping, pulpotomy), type of material evaluated. The type of teeth evaluated by clinical studies was also analyzed (permanent/primary teeth). Moreover, the characteristics of the included patents, such as priority and publication year, priority and deposit country, type of depositor (personal, university, company, public foundation) and type of material patented were also tabulated in order to obtain the technological information. The materials were classified according to their main compositions, as described in Table 3.

3 Results

3.1 Documents selection

Figure 1 represents the document selection process. Of the 4149 papers initially select from all databases, 1956 were excluded after title and/or abstract examination. Thirty-seven articles were eliminated because they not evaluated the materials as pulp capping agents (23 studies) or they were literature reviews (14 studies). A total of 716 papers were included in the qualitative analysis.

Furthermore, from 367 patents initially identified from all databases, 216 were excluded since they were not related to pulp capping materials. Seventeen patents

were further excluded because were related to root canal sealers (5 patents) or were not related to pulp capping agents (12). Eighty-three patents could be included in the analysis of technological data. In this systematic review, a total of 799 documents were included in scientific and technological analysis.

3.2 Descriptive analysis

Figure 2 summarizes the vital pulp treatments related to the respective main biomaterials studied. Out of the studies included, 24% were *in vitro*, 38% animal experiments and 38% clinical trials. Scientific production of pulp capping materials related to different treatment protocols are represented in Figure 3. The number of papers published was higher than patents deposited or published annually in almost all period analyzed (Figure 3a). Moreover, animal experiments were predominant in direct pulp capping analysis, while clinical studies were the main study design to indirect pulp capping and pulpotomy. On the other hand, permanent teeth were evaluated by clinical studies mainly in direct pulp capping, while for pulpotomy and indirect pulp capping, primary teeth were the most analyzed (Figure 3b). The United States and Japan were the main countries with patents deposited related to pulp capping materials, respectively with 25 and 22 patents (Figure 4), and were also the main origin countries of patents related to this area. Besides, Brazil (24%), United States (15%) and Japan (8%) had the majority of papers published in this research field.

Figure 5 represents the main type of biomaterial studied and patented. Regarding annual technological production, calcium hydroxide based materials were the most patented for a long time in the past (Figure 5a). Patents related to adhesives or resins as pulp capping agents increased especially from 1998 e 2008. While in the last decade, it was observed a major increase in bioactive materials (containing bioactive proteins), MTA and MTA derived materials (calcium silicate, calcium aluminate, calcium phosphate based cements). Calcium hydroxide was the biomaterial most studied, followed by MTA (Figure 5b). While for indirect pulp capping, the majority of studies evaluated calcium hydroxide and adhesives/resins. Meanwhile for pulpotomy, many studies were related to calcium hydroxide, formocresol and MTA. Additionally, the main patent depositors were companies (36%) and universities (33%). The personal deposit represented 26% of all patents deposited, and public foundations the last 8%.

4 Discussion

This review allowed to map the knowledge available of pulp capping materials through a scientific and technological analysis. There was a gradual increase in studies and patents related to these biomaterials over the years, which reflects the constant evolution in treatments in this research field. Besides, patent is an important source of technological information [18, 19], and the scientific and technological scenario observed was different as regarding the main types of materials studied and patented, which means that only the search and analysis of papers might show a limited overview of this area. Furthermore, within each vital pulp therapy, several biomaterials were found, which will be hereafter discussed in order to present their current trends, recent advances and future perspectives.

4.1 Current trends in vital pulp treatments

4.1.1 Indirect pulp capping

There are different clinical procedures to preserve pulp vitality in teeth with deep caries: with total carious tissue removal or partial caries removal, either at the same appointment (complete caries excavation) or in one or more treatment steps (stepwise excavation) [20]. The complete removal of all carious substrate is no longer seen as mandatory, and in recent years indirect pulp capping with partial caries removal has been advocated in studies [21, 22]. The preservation of carious dentin along the pulpal floor is the goal of contemporary conservative dentistry based on retaining healthy tooth tissues. By leaving the deepest layer of carious dentin undisturbed, the risk of pulp exposure and post-operative pulpal symptoms is significantly reduced, and favourable clinical results have been reported with the remineralization of residual dentin [8, 20-22]. Moreover, a biological barrier is formed protecting the pulp from external irritations, being an adequate marginal seal critical to inhibit bacteria infiltration [23, 24].

Calcium hydroxide was also the main material evaluated in indirect pulp capping, probably because its important biological and antimicrobial properties. Adittionaly, it has the longest track record of clinical success [4]. It has been believed that calcium hydroxide’s high alkalinity causes irritation of the pulp tissue when in contact, which could stimulate repair process through the release of bioactive molecules sequestered within dentin [25]. There are a variety of proteins into dentin

matrix [26-28], and especially two of them, bone morphogenic protein-7 (BMP-7) and transforming growth factor-β1 (TBF-β1), have been show the ability to stimulate tertiary dentin formation [28-30]. Despite the wide use of calcium hydroxide, this material provides a poor seal, does not adhere to tooth substrates, and the self-cure formulations are soluble [6, 31]. Besides, this material has no adhesion to dentin and to composite resins used in restorative procedures, and as a consequence may occur solubilization over time in a cavity not properly sealed [31]. It is reported that the presence of a liner (i.e. calcium hydroxide cement, glass ionomer cement, zinc oxide and eugenol) could influence the longevity of restorations [32]. Therefore, adhesive properties are an important factor to considerate in vital pulp capping, once the adequate seal with a restorative material is imperative to pulp protection.

To overcome calcium hydroxide disadvantages, dental adhesive systems were suggested for use as a potential pulp capping about 20 years ago [33], which probably have led to a further increase in patent deposition observed especially from 1998 to 2008. Although adhesion to teeth substrates could improve cavity seal with restorative materials, the sound dentin is not the substrate most frequently found in clinical situations in deep carious lesions, but sclerotic, caries-infected or caries-affected dentin [34]. It is reported that the bond strength of adhesives to caries-affected dentin is lower than that to sound dentin [35-37]. Furthermore, the components of adhesive systems have been shown to be cytotoxic to pulp cells, and they are not currently reccomended to direct pulp capping [38-40]. It must be taken into consideration that these effects are dependent of how deep the carious lesion is, which could affect the clinical sucess of this treatment [8]. There is still no consensus on how much carious teeth substrates needs to be removed [20]. Furthermore, the therapy of deep cavitated lesions should require less focus on complete carious removal than on adequate seal with restorations [20, 41, 42].

4.1.2 Direct pulp capping

Direct pulp capping treatment has been suggested when occurs pulp exposure due to caries, traumas or accidents during cavity preparation, without the presence of irreversible pulp inflamation [4, 43, 44]. The biomaterial used should have some fundamental properties to maintain tooth vitality, such as stimulate tertiary dentin formation, provide an adequate bacterial seal and then promote pulp healing [4]. Our review demonstrated that calcium hydroxide based materials and MTA were

the two most studied materials in pulp exposures. Furthermore, it is important to emphasize that the outcome of these treatment not depends only on the biomaterial applied, but also on the type of pulp exposure (carious or mechanical), the length of follow-up [45], the area of pulp to which the capping material is applied (coronally or cervically) [46], the time elapsed to placement of a definitive restoration [45], the presence of bacteria infection [46], as well as the age of the patients [7]. It is reported that a tooth can present better prognosis if the initial exposure is due to mechanical reasons rather than caries [46, 47]. Besides, one critical principle that is the key to pulp vitality is the placement of a well-sealed restoration [4, 45, 48-51].

In direct pulp capping, calcium hydroxide has been considered the “gold standard” for years, due its excellent antibacterial effect, and the ability to induce tertiary dentin formation as previously mentioned. In recent years, MTA has been investigated as a material for direct pulp capping, and it has been shown promising results in clinical trials [44, 52]. The major benefits include good biocompatibility, radiopacity, sealing ability, low solubility, stability for long-term, prevention of bacterial infiltration, and the dentinogenic and osteogenic potentials [12]. Besides, MTA could reduce inflammation, hyperemia and necrosis levels of pulp [6, 53], and could also solubilize bioactive proteins involved in tooth repair process [54]. However, MTA presents disadvantages such as discoloration [55], which is critical in anterior teeth; the presence of toxic elements (i.e. arsenic) in the material composition [56], higher cytotoxicity in its freshly mixed state [57], long setting time [58], high pH during setting [59], and difficult handling characteristics [60]. Moreover, MTA has a considerable high cost [6], and about one gram of its powder costs the same as 24 grams of calcium hydroxide based material [4]. However, a recent study showed that MTA was more cost-effective than calcium hydroxide for direct pulp capping once expensive retreatments can be avoided with its use [61].

The main MTA components are tricalcium silicate, dicalcium silicate, tricalcium aluminate [62, 63]. The most reactive phase of MTA is tricalcium silicate which comprises about 68% of the Portland cement component [59]. Calcium hydroxide is the main reaction product of MTA hydration with water [10, 12, 62], which probably it is responsible to its similar effects to calcium hydroxide in vital pulp. During the setting process, MTA has an initial pH of 10.2, which increases to up to 12.5 during the first few hours [58] and it is comparable with the alkalinity achieved by calcium hydroxide [64]. Nowadays, MTA is the current reference control

recommended by ISO 7450 (2008) [65] or ANSI/ADA no. 41 [66]. Moreover, recent studies have demonstrated that MTA presented higher clinical success rates than calcium hydroxide in direct pulp capping [44, 52]. MTA presented a overall success rates of 80.5% compared to 59% of calcium hydroxide in up to 123 months [44], and it seems to be currently the best indicated biomaterial to this therapy.

4.1.3 Pulpotomy

In the presence of pulpal inflammation, teeth can be clinically managed either by an attempt to preserve the tissue in cases of reversible pulpitis, or remove it and seal the root canal in irreversible pulpitis. Considerable controversy exists on this issue, and pulpotomy should be considered to treat few affected teeth in which the pulp exposure occurred through sound dentin or through carious lesions in symptom-free teeth [8, 16, 31, 67]. Pulpotomy consists of the surgical amputation of coronally inflamed pulp [67], and the surface of the remanescent radicular pulp may be treated with a medicament or pulp capping agent in a tentative to maintain vitality [68].

Furthermore, pulpotomy is a widely accepted treatment for pulp exposures in immature teeth to ensure continued root development, which require an special clinical care [69, 70]. For them, the apexogenesis consists in continuing the root formation and apical closure in vital teeth. Unlike apexification, vital pulp therapy with pulpotomy allows the development a normal thickness of dentin and root length, which leads to apical closure, stronger root structure, and a greater structural integrity [70, 71]. The loss of tooth vitality before complete root formation leaves a weak root with thin dentin walls more susceptible to fracture. Therefore, pulpotomy was mainly observed in studies with primary teeth, and it is in fact commonly indicated to these acutely inflamed teeth [72], once dental pulp in young subjects is more able to recover from injuries. Besides, studies have demonstrated that in teeth with complex crown fractures, the exposed pulp can maintained its vitality for up to 7 days, and only a partial removal of the most superficial pulp inflamed can be an adequate treatment [73].

Some clinicians are reluctant in indicate pulpotomy due technical difficulties, once proper assessment of the affected tooth using radiographic evaluation and vital pulp testing is critical in determining an accurate diagnosis. Previous studies reported that even the concomitant presence of all three classical signs of pulp necrosis,

coronal discoloration, loss of pulp sensitivity and periapical radiolucency, can in rare cases be followed by pulp repair [73, 74]. Furthermore, immature teeth are frequently associated with child patients, and pulp testing in these subjects is a complex and subjective procedure [73]. The radiographic interpretation of the periapical area may be also mistaken by the unmineralized radiolucent zone around dental papilla [74, 75].

The main biomaterials that have been evaluated for pulpotomy include formocresol, ferric sulfate, zinc oxide and eugenol, calcium hydroxide, MTA. Their clinical success have differed from each pulp capping depending on biological compatibility, healing capabilities, cytotoxicity, histological response and repair potential [67]. Hence, the need arises to develop a pulpotomy biomaterial that potentiates the natural pulp healing process, is biocompatible, and is cost-effective.

Despite the long history of calcium hydroxide in vital pulp therapy, the issue is still controversial for pulpotomy in primary teeth, due its caustic actions [31]. There have been attempts to find other materials that permit tertiary dentin formation without the detrimental effects of calcium hydroxide [31], and one of biomaterials most commonly used for pulpotomy was formocresol. This pulp capping agent was introduced in 1904 by Buckley for the treatment of the putrescent pulp in animal teeth. Later, he introduced a commercial formula that consisted of 19% formaldehyde, 35% cresol and glycerin in distilled water [67]. Although formocresol has long been considered the gold standard in pulpotomy, researchers have been questioning its use due to possible toxic effects [76].

Other biomaterial evaluated was ferric sulphate, which has been used as a coagulative and a hemostatic agent [77, 78]. The agglutination of blood proteins result from the reaction of blood with ferric and sulphate ions, as well as with the acidic pH of the material [79]. It was reported that ferric sulphate could prevent problems arising from clot formation after the removal of the coronal pulp and produce a local and reversible inflammatory response [80]. A systematic review reported that primary molar teeth with pulp exposure by caries or trauma subjected to pulpotomies followed by ferric sulfate application presented a clinical success rate ranging from 78% to 100%, with similar clinical and radiographic success to formocresol [78].

MTA was also recently indicated for pulpotomy, and showed favorable pulpal responses for both permanent and primary teeth. In permanent teeth, MTA

demonstrated satisfactory treatment outcomes in studies with pulpotomy after caries exposed pulp [31, 81, 82]. However, a study reported that the incidence of unfavourable outcomes up to 2 years tended to be higher in teeth with larger pulp exposure areas [81]. Besides, a systematic review demonstrated that MTA as a pulpotomy agent had a favorable success rate in treating carious exposure of permanent teeth with closed root apices [16]. In primary teeth, MTA presented clinical success superior to formocresol [31, 83-85]. Besides, when comparing all main materials used for pulpotomy of primary teeth, a recent meta-analysis demonstrated that the success rate of MTA (94.6%) was superior than formocresol (87.4%), ferric sulphate (86.6%) and calcium hydroxide (60.5%) [72]. Although MTA presented some drawbacks previously mentioned, it seems to be the best current treatment option for pulpotomy in primary and permanent teeth.

4.2 Recent advances and future perspectives in vital pulp therapy

There is a need to discover a pulp capping material that potentiates the natural pulp healing process, is biocompatible and overcome the benefits of actual biomaterials already available in the market. In an endeavor to develop products that satisfied the ideal pulp capping agent criteria, the composition of materials continues to change as the manufacturers try to improve their efficacy. We also included patent data in our analysis as source of technological information, which demonstrated a divergence between the main countries with studies and patents related to pulp capping materials. The scientific production in this area is not being properly followed by the technological prospecting. Many studies were focused in evaluating already available pulp capping materials than in develop and improve them. The trend observed in technological data suggest that while in the past the focus was in calcium hydroxide based cements, and after in adhesive or resin, in the last years it seems that MTA and bioactive materials has gained attention. Although the high cost is an important disadvantage of MTA, its cost tends to decrease with time. Besides, this material seems to be the currently “gold standard” to vital pulp therapy.

The countries with high numbers of deposited patents were also the United States and Japan, which probably reflects the most important markets for this technology. Considering that the main depositors of patents were companies, the results also suggest the need for an approximate relationship between the university and the industry to improve the integration between scientific and technological

knowledge. There are potential areas to be explored with new innovative pulp capping materials that could disrupt existing business models and provide new better treatment options for patients.

In this context, new MTA derived materials have been suggested in recent years as pulp capping agents, which must change the current scenario of pulp capping agents long dominated by calcium hydroxide. Among them, calcium hydroxide based cements are mainly composed of dicalcium and tricalcium silicates with minor modifications in the MTA formulation [11, 86]. These material have improved properties of MTA, such as good sealing correlated to expansion, the ability to set in the presence of fluids [58, 87, 88], the release of ions as calcium [89] and good biological properties [86, 90-92]. The addition of calcium chloride resulted in a cement with a lower setting time and good biocompatibility [93-95]. Moreover, attempts at replacing the Portland cement component of MTA with tricalcium silicate resulted in a biomaterial with improved physical properties [96]. The most studied calcium silicate based cement was Biodentine (Septodont, France), and due its good physical properties can also be used as a temporary restorative material. Similar outcomes regarding tertiary dentin formation and inflammatory response between Biodentine and MTA were demonstrated in an animal experiment [97], in an *ex-vivo* study with human teeth [98], and in a recent clinical trial when used for pulpotomies of primary molars after 12 months [76]. Moreover, when used for indirect pulp capping, Biodentine showed similar clinical results to a glass ionomer cement (Fuji IX, GC Corporation, USA) after 12 months of follow-up [99].

Another MTA derived material developed was a calcium aluminate based cement, as EndoBinder (Binderware, Brazil), which preserve the properties and clinical applications of MTA without some of its negative characteristics [100, 101]. Its components allows control of impurities such as iron oxide [102], that promotes tooth discoloration, and free magnesium oxide and calcium oxide, which may be responsible for an undesirable expansion of the material in contact with moisture [103]. Animal experiments demonstrated that these cements presented tissue compatibility that allow mineralized tertiary dentin formation after pulpotomy with similar morphology and integrity to those formed with MTA [97, 104-106]. Moreover, EndoBinder was biocompatible when tested in rat subcutaneous tissue [101]. However, further research is needed to evaluate the potential clinical benefits of these new biomaterial in vital pulp therapies.

Calcium phosphate based materials also emerged in recent years: as calcium enriched mixture (CEM) cement. This cement was first introduced by Asgary *et al*. in 2006 [107], and it is similar to MTA, but with better physical properties. When the CEM is mixed with water-based solution, it forms calcium and phosphate enriched mixture [14]. Mixed CEM cement then forms hydroxyapatite not only in simulated body tissue fluid but also in normal saline solution; the latter of which is unlike MTA [108]. The properties of bio-ceramics are very advantageous to material sciences, once CEM cement has antibacterial effect comparable to calcium hydroxide and superior to MTA [109], and sealing ability similar to MTA [110]. The biologic response of the pulpal tissue to MTA and CEM cement has been shown to be similar in animal studies [111]. Besides, its biocompatibility, osseo conductivity property, ability to form hermetic seal, chemical bond to the tooth structure, insolubility in tissue fluids, good radiopacity and easy handling characteristics have led to the widespread use of these materials in recent years [14]. A recent randomized clinical trial showed that vital pulp therapy with CEM was a reliable technique for treatment of permanent molar teeth with pulpitis after 5 years of follow-up [112].

There has been growing optimism about the use of a biologic approach for dental pulp treatments via the stimulation and formation of biological tissue. The knowledge about the repair and regenerative process in dentin-pulp complex is being more exploited by researches, which have demonstrated that repair mechanism may be due to the release of bioactive molecules from dentin matrix, including bone-morphogenetic protein (BMP) and transforming growth factor-Beta-1 (TBF-β1) [25, 28, 29, 113].

Pulp capping agents containing bioactive proteins were evaluated with the available commercially Emdogain (Straumann, Switzerland). The biomaterial is an injectable gel solution comprising enamel matrix proteins (amelogenin), water and a carrier (propylene glycol alginate) [114]. Moreover, enamel matrix proteins acts in cementogenesis and in the development of the periodontal attachment apparatus [115, 116]. These material present multiple applications, and has been mainly indicated in periodontics with favorable results when applied in periodontal defects [114]. Emdogain was suggested as a possible pulp capping material due the presence of amelogenin on its composition, which is involved in the growth and maturation of dental pulp cells during odontogenesis [117]. A more pronounced

tertiary dentin formation was reported in pulps of animals treated with amelogenin when compared with those treated with calcium hydroxide [118-121]. Furthermore, a randomized clinical trial in exposed human pulps reported that postoperative pain symptoms were less frequent after Emdogain application than calcium hydroxide cements [122]. However, Emdogain presented poor sealing qualities and it was ineffective in producing tertiary dentin formation in the trial. To obtain an adequate seal, an animal experiment evaluated MTA application in conjunction with Emdogain, that produced a better quality of tertiary dentin formation when compared with the use of calcium hydroxide [123]. Nevertheless, clinical trials that evaluated Emdogain for direct pulp capping in primary teeth [124] and pulpotomy in permanent teeth [125] failed to demonstrate improvement in tertiary dentin formation. It is not clear if components of Emdogain regulate pulp repair or regenerative process, and probably are dentin matrix proteins more involved in tertiary dentin formation.

On the other hand, many animal experiments with dentin matrix proteins demonstrated their potential benefits in vital pulp therapy, such as direct [126, 127] and indirect pulp capping [128, 129], as well as in pulpotomy [130]. However, the high cost of these biomaterials are yet a imperative drawback that compromises its popularization. Patent data also showed that the protection of materials containg bioactive proteins are growing in recent years, and it was claimed its use in microspheres, hydrogels, delivery systems, scaffolds [131-134]. Novel dental material containing these proteins opens promising treatment options, and both basic and clinical research toward reaching this goal is needed. Hence, the need arises to discover a biomaterial that potentiates the natural pulp healing process and is cost-effective. In the future, it is becoming evident that these novel therapeutic approaches will gain attention in dentistry, being able to promote the repair or regenerative process through a defined interaction between bioactive materials and tooth substrates.

Conclusions

Based on this systematic review it was possible to obtain a scientific and technological overview of pulp capping agents. Although calcium hydroxide was the biomaterial most studied over time with favorable clinical outcomes, the current literature suggests MTA presents superior performance for direct pulp capping and pulpotomy. Meanwhile, recent advances in MTA derived materials (calcium silicate,

calcium phosphate, calcium aluminate based cements) and bioactive materials containing dentin proteins have showed promising results that could improve vital pulp treatments in the near future.

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Tables and Figures

Table 1 – Search strategy used in PubMed (MedLine)

	Search terms
#4	Search #1 AND #2 AND #3
#3	"Pulp Capping and Pulpectomy Agents"[Mesh] OR "Pulp Capping and Pulpectomy Agents" OR "Mineral Trioxide Aggregate" OR "MTA Cement" OR "MTA Aggregate" OR "aggregate ProRoot" OR "Pulp Capping Agent" OR "Pulp Capping Agents" OR "Agent, Pulp Capping" OR "Agents, Pulp Capping" OR "Capping Agent, Pulp" OR "Capping Agents, Pulp" OR "Pulp Capping Agent" OR "Agents, Pulpectomy" OR "Pulpectomy Agent" OR "Calcium Hydroxide" OR "Hydroxide, Calcium" OR "Mineral Trioxide Aggregate" OR "Cavity Linings, Dental" OR "Lining, Dental Cavity" OR "Linings, Dental Cavity" OR "Cavity Lining, Dental" OR "Dental Cavity Linings" OR "Varnish, Cavity" OR "Cavity Varnish" OR "Cavity Varnishes" OR "Varnishes, Cavity" OR "Cavity Lining Varnish" OR "Varnish, Cavity Lining" OR "Cavity Lining Varnishes" OR "Varnishes, Cavity Lining" OR "Cavity Liner, Dental" OR "Cavity Liners, Dental" OR "Liner, Dental Cavity" OR "Dental Cavity Liners" OR "Liners, Dental Cavity" OR "Dental Cavity Liner" OR "Theracal" OR "Biodentine" OR "Emdogain" OR "MTA"
#2	"Dental Pulp Capping" [Mesh] OR "Dental Pulp Capping" OR "Pulp Capping, Dental" OR "Pulp Capping" OR "Capping, Pulp" OR "Cappings, Pulp" OR "Pulp Cappings" OR "Capping, Dental Pulp" OR "Cappings, Dental Pulp" OR "Dental Pulp Cappings" OR "Pulp Cappings, Dental" OR "Pulpotomy" OR "Dental Pulp Exposure" OR "Exposure, Dental Pulp" OR "Pulp Exposure, Dental" OR "Pulp Exposures"
#1	"Dental Materials"[Mesh] OR "Dental Materials" OR "Materials, Dental" OR "Dental Material" OR "Material, Dental" OR "Oral medicine" OR "Medicine, Oral" OR "Dentistry" OR "Odontology" OR "Biomaterials"

Table 2 - Eligibility criteria

Inclusion criteria	Exclusion criteria
▪ Studies that evaluated pulp capping agents to vital pulp therapy ▪ Patents related to dental materials and protection of dentin-pulp complex	▪ Studies that evaluated only techniques and not materials to vital pulp therapy ▪ Review articles, case reports, case series, thesis and dissertations ▪ Studies published in a language other than English, Spanish or Portuguese

Table 3 – Classification of main pulp capping materials identified in the literature

Material	Main indications	General composition	Commercial example
Calcium hydroxide	Direct/indirect pulp capping, pulpotomy	Base paste: titanium dioxide, calcium tungstate 1,3-butylene glycol disalicylate Catalyst paste: calcium hydroxide, zinc oxide, zinc stearate, ethyl toluene sulphonamide	Dycal* (Dentsply, United States), Life (Kerr, United States)
Mineral trioxide aggregate (MTA)	Direct/indirect pulp capping, pulpotomy, root perforation and resorption, retro-end apicoectomy	Powder: tricalcium silicate, dicalcium silicate, tricalcium aluminate. Liquid: distilled water	MTA Angelus* (Angelus, Brazil), MTA ProRoot (Dentsply, United States)
Calcium silicate based	Direct/indirect pulp capping, pulpotomy, root perforation and resorption, retro-end apicoectomy	Powder: tricalcium silicate, dicalcium silicate, calcium carbonate, zirconium dioxide Liquid: water, calcium chloride, modified polycarboxylate (superplasticizing agent)	Biodentine* (Septodont, France), TheraCal LC (Bisco, United States), Tech Biosealer capping (Isasan, Italy)
Calcium phosphate based	Direct/indirect pulp capping, pulpotomy, root perforation and resorption, retro-end apicoectomy	Powder: calcium compounds such as calcium oxide, calcium phosphate, calcium carbonate, calcium silicate, calcium sulfate, calcium hydroxide, calcium chloride Liquid: distilled water	Calcium Enriched Mixture (CEM) Cement* (BioniqueDent, Iran)
Calcium aluminate cement	Direct/indirect pulp capping, pulpotomy, root perforation and resorption, retro-end apicoectomy	Powder: aluminum oxide, calcium oxide, silicon dioxide, magnesium oxide, iron oxid, bismuth oxide Liquid: distilled water	Endobinder* (Binderware, Brazil)
Adhesive systems	Indirect pulp capping	Primer: 10-methacryloyloxydecyl dihydrogen phosphate (MDP), dimetacrylate monomer, hydroxyethyl methacrylate (HEMA), silica, N,N-diethanol-p-toluidine, canforoquinone Bond: Hydroxy ethyl methacrylate (HEMA), dimetacrylate monomer, bisphenol A glycidyl	Clearfil SE Bond* (Kuraray Medical, Japan), Optibond S (Kerr, United States), Prime&Bond 2.1 (Dentsply, United States)

		methacrylate (Bis-GMA), N,N-diethanol-p-toluidine silica, canforoquinone	
Zinc oxide and eugenol	Indirect pulp capping	Powder: zinc oxide, poly-methyl methacrylate (PMMA) pigment. Liquid: eugenol, acetic acid	IRM* (Dentsply, United States), Temp Bond (Kerr, United States), Relix Tempo (3M ESPE, United States)
Formocresol	Pulpotomy	Formaldehyde, ortho-cresol, gliceryn, ethyl alcohol	Buckley's Formocresol* (Sultan Healthcare, United States)
Ferric sulphate	Pulpotomy	Ferric sulphate, silica, aqueous vehicle	ViscoStat* (Ultradent, United States), Astringedent (Ultradent, United States)
Bioactive materials (containg bioactive proteins)	Direct/indirect pulp capping, pulpotomy	Enamel matrix proteins, water, propylene glycol alginate.	Emdogain* (Straumann, Switzerland)

* Material with general composition informed

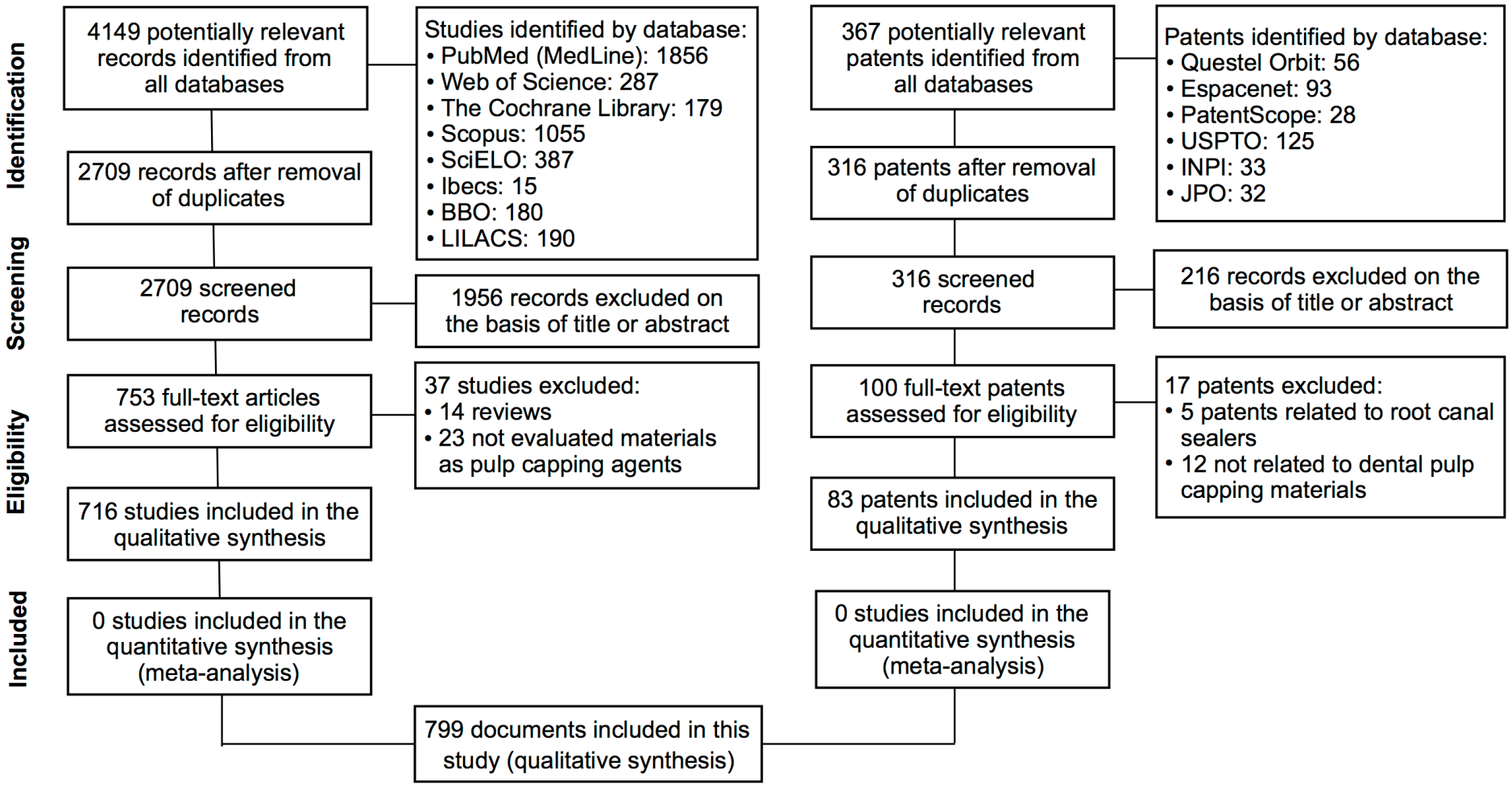

FIGURE 1 - Search flow (adapted from the PRISMA statement) [17]

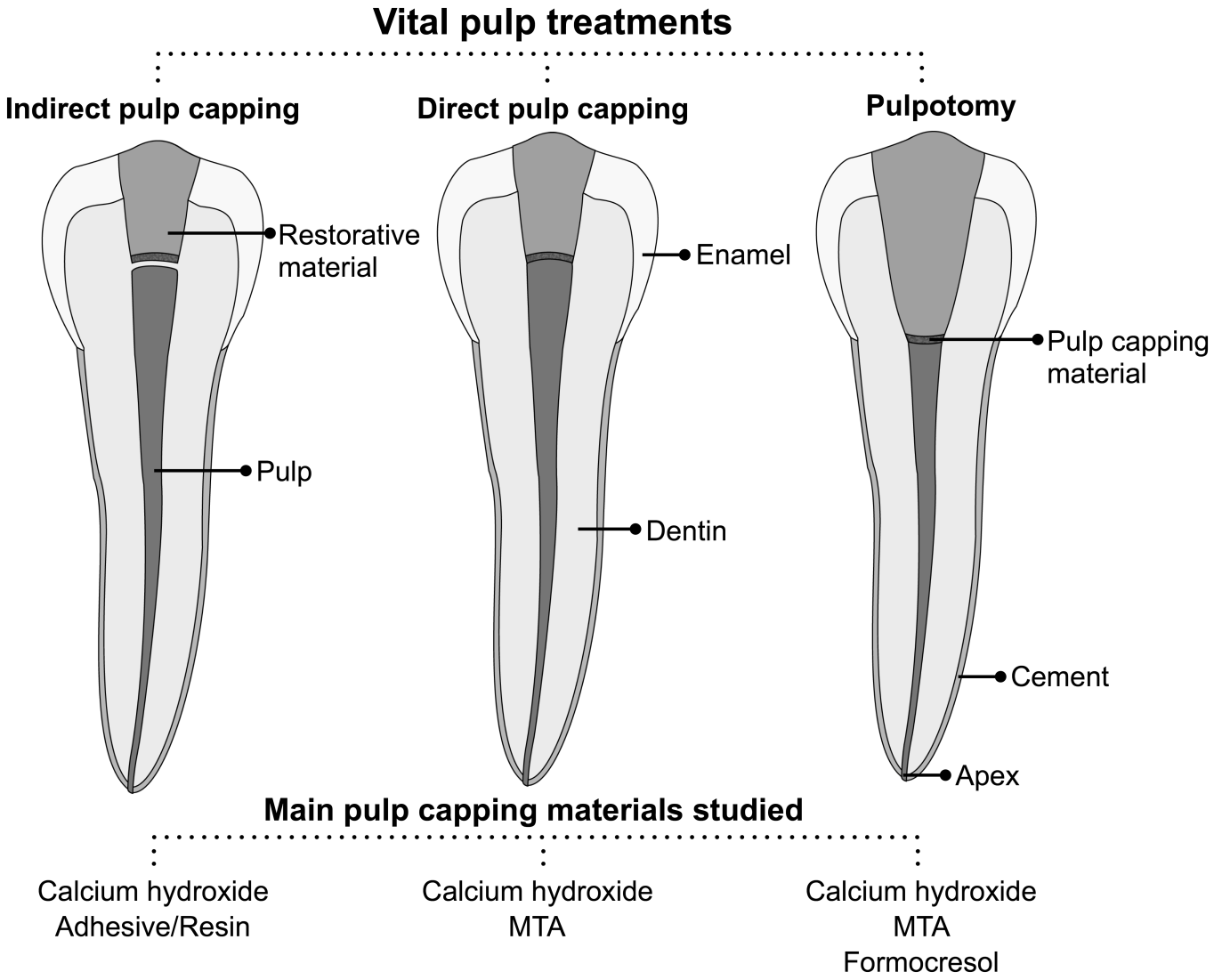

FIGURE 2 – Vital pulp treatments and main pulp capping materials studied for each therapy

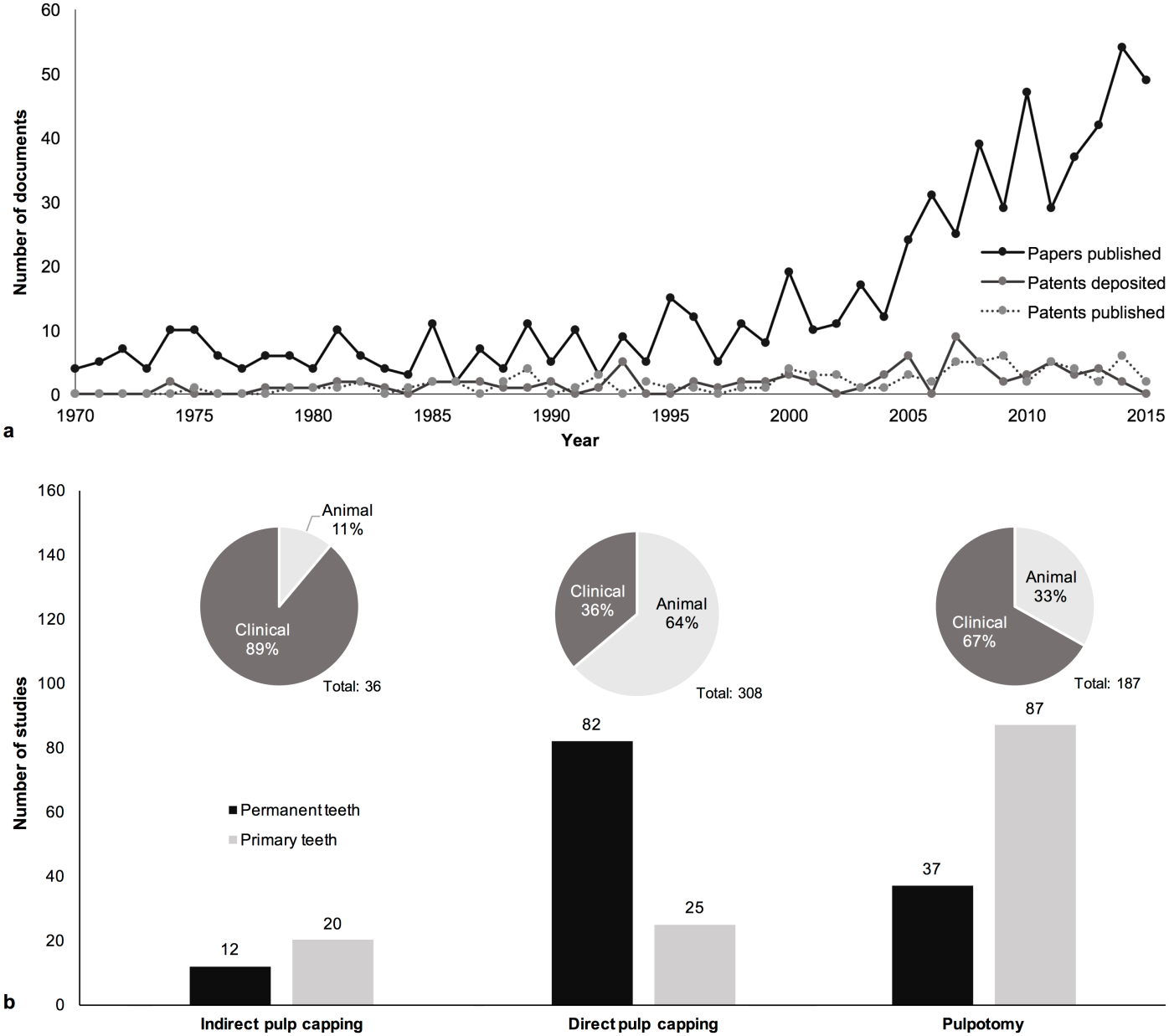

FIGURE 3 – Studies and patents related to pulp capping materials (a) annual evolution of the scientific (papers published) and technological production (patents deposited and later published) (1970-2015); (b) number of studies related to type of study (clinical or animal study), pulp treatment (indirect or direct pulp capping, pulpotomy) and type of teeth (permanent or primary)

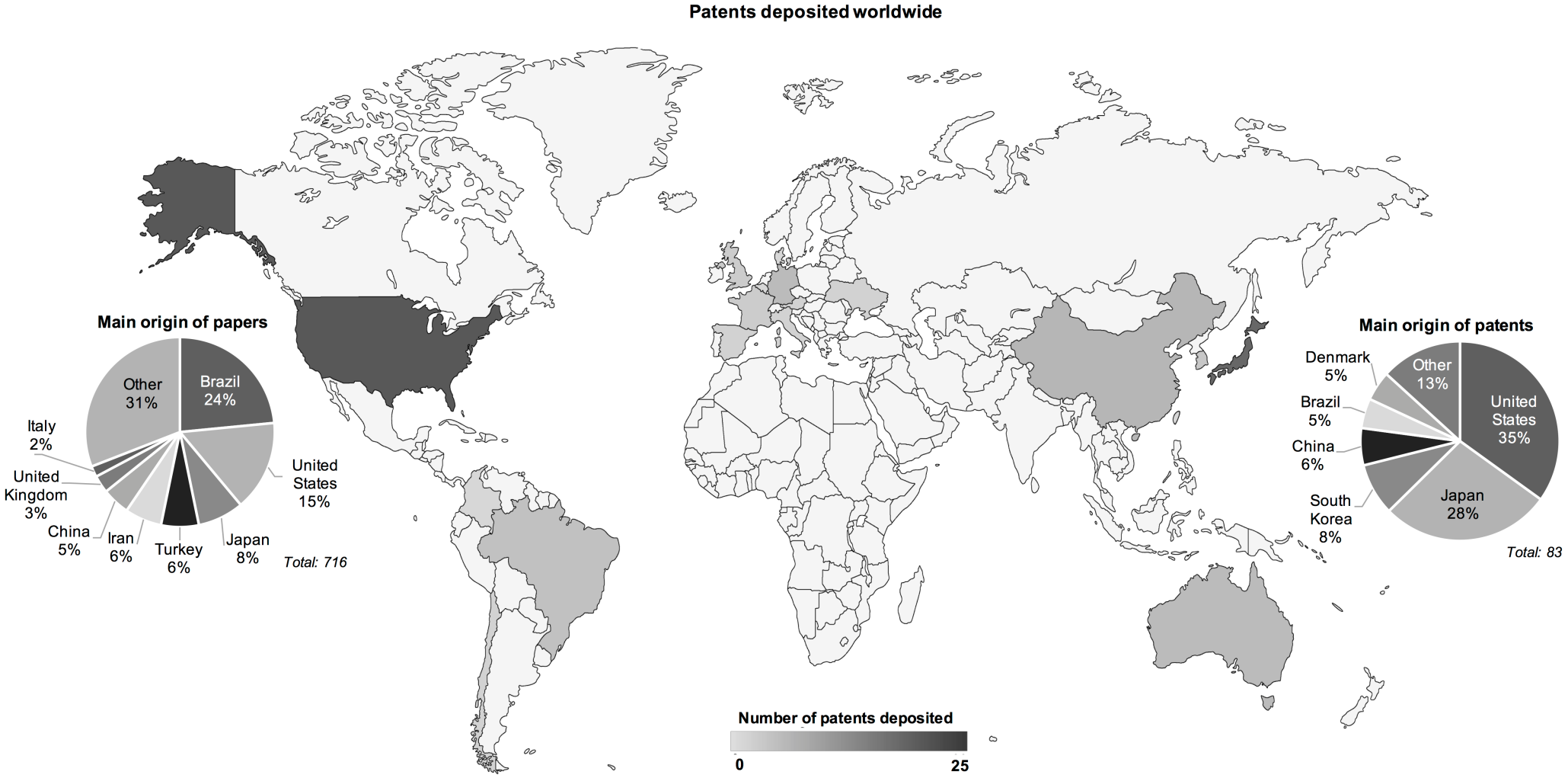

FIGURE 4 – Scientific and technological production of pulp capping materials in the world. Main countries with patents deposited: United States (25 patents), Japan (22 patents), China (7 patents), Australia (6 patents) and Germany (6 patents); and main origin of papers (according to corresponding authors) and patents (priority countries)

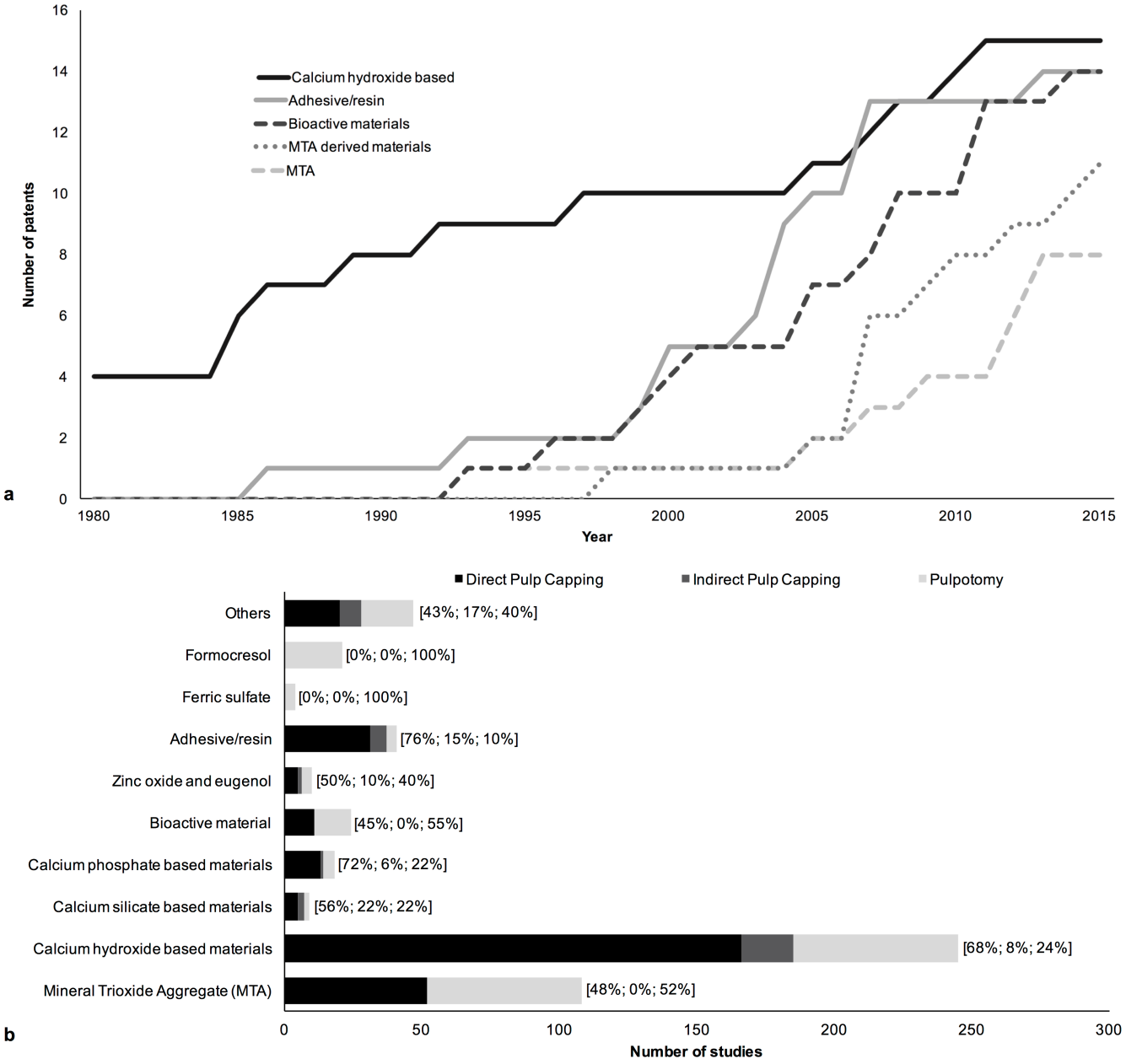

FIGURE 5 – Scientific and technological production of pulp capping materials: (a) annual production (cumulative) of main type of pulp capping materials patented (1980-2015); and (b) type of material evaluated according to pulp treatments

3 Capítulo 2

Strategical approaches with bioactive materials for vital pulp treatments: a systematic review[2]

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Abstract

Objectives: Systematically review the literature of animal studies to evaluate the efficacy to deliver bioactive dentin proteins for vital pulp therapy strategies. **Methods:** This study is reported in accordance with the PRISMA Statement. Two reviewers independently conducted a literature search in eight databases: PubMed (MedLine), Lilacs, IBECS, BBO, Web of Science, Scopus, SciELO and The Cochrane Library. It was included animal experiments in which bioactive dentin proteins were applied directly or indirectly to the pulp tissue. Data regarding the characteristics of proteins evaluated, the delivery systems used and the main findings from each study were tabulated in order to assess the outcomes of interest (tertiary dentin formation, inflammatory response, intratubular mineralization). **Results:** A total of 3019 studies were initially identified. After screening, 32 papers fulfilled selection criteria and were included in the qualitative analysis. Direct pulp capping was the most evaluated therapy with bioactive dentin proteins. Besides, the most studied proteins were BMP-7, TGF-β1 and soluble dentin matrix proteins extracted. In general, bioactive proteins enhanced tertiary dentin formation in direct and indirect pulp capping, and promoted a initial lower inflammatory response. However, for pulpotomy the bioactive materials did not demonstrated diferences from control in the outcomes evaluated. **Significance:** There are potential areas to be explored for novel therapeutic approaches to dental tissue repair and regeneration with bioactive materials. There is evidence in the literature that suggest bioactive dentin molecules could be able to improve tertiary dentin formation with less initial inflammatory response in direct and indirect pulp therapy.

Keywords: Dental pulp capping, transforming growth factors, bone morphogenetic protein, review.

1. Introduction

The dentin–pulp complex is able to respond to injuries (e.g. caries, traumatic injury, cavity preparation, restorative procedures) by hard tissue deposition in teeth [1, 2]. The mechanism involves dentin matrix constituents, which can induce odontoblast-like cell differentiation and tertiary dentin formation [3, 4]. Broadly speaking, dentin extracellular matrix (ECM) contains a reservoir of bioactive proteins sequestered within dentin and predentin, including growth factors, cytokines, chemokines, and matrix molecules, which regulate signal transduction between cells and function as stimulators and/or inhibitors of proliferation and differentiation [5, 6]. The knowledge that dentin is not an inert and passive tissue, as previously believed, but a reservoir of bioactive molecules that can be recruited on demand enabled a major discovery in the field of dental pulp tissue repair and regeneration [7].

In this context, repair and regeneration process of dentin-pulp complex comprise a cascade of cellular and molecular events with matrigenic, angiogenic, and neurogenic outcomes [6]. The non-collagenous proteins (NCPs) presented in ECM includes bioactive molecules such as family members of transforming growth factor-β (TGF-β) superfamily: TGF-β (isoforms TGF-β1, -β2, -β3), bone morphogenetic protein (BMP-2, BMP-3, BMP-4, BMP-5, BMP-6, BMP-7/OP-1), insulin-like growth factor-1 and 2 (IGF-1 and -2), fibroblast growth factor-2 (FGF-2), adrenomedullin, dentin sialoprotein (DSP), derntin phosphoprotein (DPP), bone sialoprotein (BSP), dentin matrix protein-1 (DMP-1), matrix extracellular phosphoglycoprotein (MEPE), platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF) [5-8]. This diverse group of molecules reflects the complexity of the cellular signaling events capable of induce tooth repair and regeneration [6].

Thus, advances to understand the applicability of bioactive dentin proteins are emerging side by side with the development of new drug delivery systems and biologically based therapies with bioactive materials. The paradigm of dentin as a bioactive matrix allows us to exploit a new concept in pulp therapy based on stimulation and upregulation of teeth substrates [5, 9, 10]. In this context, more biocompatible dental materials can be developed, which could perform a desirable function without eliciting any undesirable local or systemic effects, and generating the most appropriate tissue response, optimizing the clinically relevant performance of the therapy [11]. It has been reported that dental materials such as calcium hydroxide

cements and mineral trioxide aggregate (MTA), which are commonly used in vital pulp therapy (e.g. indirect pulp capping, direct pulp capping, partial or full pulpotomy) [12, 13], could be able to solubilize bioactive components sequestered within dentin and, consequently, induce dentin bridge formation [14, 15]. Better treatment strategies to many dental diseases could be benefit with using bioactive proteins in dental materials, such as caries disease, traumatic lesions of dental tissues, pulp exposures, pulpitis, apexogenesis, dentin sensitivity, being its full implications in pulp biology to be yet determined. In the near future, novel therapeutic approaches can enable to promote biological treatments through a defined and targeted interaction between dental tissue and bioactive molecules.

Thereby, the aim of this study was systematically review the literature of animal experiments to evaluate the efficacy of using bioactive proteins in therapeutic approaches to dental tissue repair and regeneration. Additionally, we aimed to analyze the cellular and molecular mechanisms involved in the cascade of biological events of dentin-pulp complex for novel biologically based therapies. The hypothesis tested was that these molecules would potentiate the tertiary dentin formation and the intratubular mineralization, as well as to decrease the inflammatory response.

2. Materials and methods

This systematic review is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA Statement) [16]. To formulate the question in evidence-based practice, it was used the following PICO: Population: animals submitted to biologically based therapies; Intervention: use of bioactive dentin proteins; Comparison: treatment without bioactive molecules; Outcome: tertiary dentin bridge formation, inflammatory process, intratubular mineralization. The research question was: Does the use of bioactive dentin proteins improve morphological outcomes on vital pulp treatments?

2.1. Search strategies

The literature search was carried out by two independent reviewers (WLOR and TMS) until October of 2015. Eight databases were screened: Pubmed (MedLine), Lilacs, Ibecs, Web of Science, BBO, Scopus, SciELO and The Cochrane Library - using the search strategy initially developed for PubMed (MedLine) and adapted for use in other databases (Table 1). Terms related to bioactive dentin

proteins and vital pulp treatments were crossed in order to optimize the retrieval of relevant documents. The references cited in the included papers were also handsearched to identify other potentially relevant articles. After the identification of studies in databases, they were imported into Endnote X7.4 software (Thompson Reuters, USA) to remove duplicates.

2.2. Study selection

Two review authors independently assessed the titles and abstracts of all documents. The studies were analyzed according to the selection criteria (Fig. 1). It was performed a pilot search in clinical trials using bioactive dentin proteins, however no record was retrieved. Thus, our review included only animal experiments in which bioactive proteins were applied directly or indirectly at the pulp. Full copies of all of the potentially relevant studies were identified. Those appearing to meet the inclusion criteria or for which there were insufficient data in the title and abstract to make a clear decision were selected for full analysis. The full-text papers were assessed independently and in duplicate by two reviewers. Any disagreement regarding the inclusion of studies was resolved through discussion and consensus or by a third reviewer (AFS). Only papers that fulfilled all of the eligibility criteria were admitted.

2.3. Data extraction

The data were extracted using a standardized form in Microsoft Office Excel 2016 software (Microsoft Corporation, USA). If there was some information missing, the authors of the included papers were contacted via e-mail to retrieve any missing data. The reviewers tabulated the following data of all included studies: type and number of animals, number of teeth evaluated, type of vital pulp therapy, follow-up period (Table 2). The characteristics of the included studies, such as bioactive molecules evaluated, protein dilution, carriers and delivery systems used were also analyzed (Table 3). Besides, evaluation methods and main findings from each included study were tabulated in order to assess the outcomes of interest: tertiary dentin formation, inflammatory response, and intratubular mineralization.

2.4. Quality assessment

The methodological quality of each included study was independently assessed by the two reviewers based on the SYRCLE's risk of bias tool for animal studies [17]. The studies were evaluated to provide a framework for judging the

studies methodological quality according to the description of the following information: random sequence generation (selection bias), baseline characteristics (selection bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias) and other bias. Each component was graded at low, unclear or high risk of bias in the software RevMan 5.2 (The Cochrane Collaboration, Denmark).

3. Results

3.1. Search strategy

Fig. 2 is a flowchart that summarizes the article selection process according to the PRISMA Statement [16]. A total of 3019 potentially relevant records were identified from all databases. After the title and abstract examination, 1990 studies were excluded once they did not meet the eligibility criteria. Of the 42 documents retained for detailed review, 10 studies could not be able to be included: in 4 studies the treatment was implanted intrapulpally [2, 18-20]; 4 were review articles [10, 21-23]; 2 studies not evaluated proteins effects after vital pulp capping treatment [24, 25]. A total of 32 studies fulfilled all of the selection criteria and were included in the qualitative analysis.

3.2. Descriptive analysis

Thirty-two animal studies evaluating the effects of bioactive proteins in vital pulp teeth were published between 1990 and 2015 (Table 2). Six different animals were used in the studies design: most of them evaluated rats (12 studies), followed by dogs (9), ferrets (5), monkeys (4), goats (1) and mini pigs (1). Regarding vital pulp therapies, direct pulp capping was the most evaluated (24 studies), and 4 studies were with indirect pulp capping. The other 4 animal experiments evaluated pulpotomy. Follow-ups varied from 14 days to 6 months. Besides, the majority of pulp exposures were performed with sterile burs, and some studies the procedure was followed by tip of a steel probe or dental explorer. Moreover, different materials were used to cover the cavities, and the most common were glass ionomer cements and zinc-oxide-eugenol cement.

Regarding the bioactive proteins evaluated (Table 3), BMP-7 (bone morphogenetic protein-7), TGF-β1 (transforming growth factor-β1) and soluble dentin matrix proteins extracted from rabbit's teeth were the most studied, respectively, by

16, 6 and 4 animal experiments. Other proteins investigated were DMP-1 (dentin matrix protein-1), BSP (bone sialoprotein), EGF (epidermal growth factor), FGF-2 (fibroblast growth factor-2), IGF-1 (insulin-like growth factor-1), IGF-2 (insulin-like growth factor-2), PDGF-BB (pratelet-derived growth factor BB), BMP-2 (bone morphogenetic protein-2) and DPP (dentin phosphophoryn). Commonly, bioactive molecules were dissolved in reagents such as phosphate-buffered saline (PBS) [26-28], pyrogen-free water [29], sodium acetate [30], serum albumin [31, 32], acetic acid [33]. Although some proteins were applied in vivo in lyophilized form [1, 34-36], a lot of studies used carriers to the proteins, such as collagen [28-30, 37-47], gelatin [27, 48, 49], agarose [26], sodium alginate [33], chitosan [50]. The use of microspheres of gelatin hydrogel [27, 28], chitosan [50] and polylactic-co-glycolic acid (PLGA) [32] were also investigated to the controlled release of these molecules. Moreover, calcium hydroxide was the most common commercial control used. Fig. 3 represents the main principal carriers identified in the literature and main outcomes observed after their application in vital pulp therapy.

The main methods used to analyze the effects of biologically based therapies were qualitative (morphological) and quantitative (histomorphometric) evaluations. Some studies used radiographic analysis or immunohistochemical evaluation for DSP (dentin sialoprotein) [26, 28, 33, 51] and DMP-1 (dentin matrix protein-1) [26, 27, 37]. In general, BMP-7, TGF-β1 and soluble dentin matrix proteins extracted enhanced tertiary dentin formation in direct pulp capping, and promoted a lower inflammatory response (Table 4). For indirect pulp capping (Table 5), a higher deposition of tertiary dentin matrix was observed after application of TGF-β1 [31] and soluble dentin matrix proteins extracted [34, 35], and to a lesser extent, BMP-7 [31]. Intratubular mineralization was also evaluated by only one study [31] that demonstrated TGF-β1 was able to induced mineralization with indirect pulp therapy. Moreover, after pulpotomy (Table 6), BMP-7 and BMP-2 was not able to induce tertiary dentin formation [29, 52], especially in studies with reversible pulpits induced [43, 44].

3.3. Risk of bias

Regarding the assessment of risk of bias, Fig. 4 summarizes the information used to assess methodological quality of the studies. The studies scored particularly poorly on the following items: random sequence generation (selection bias), blinding

of outcome assessment (detection bias) and other bias. A low risk of bias was related to baseline characteristics (selection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias).

4. Discussion

Through this review it was possible to demonstrate that bioactive dentin matrix proteins could be able to potentiate the tertiary dentin formation with less initial inflammatory response in direct and indirect pulp capping. In dentin–pulp complex, repair and regeneration process reflects the natural wound healing responses seen in many of the body's tissues [5]. In this context, dentin matrix components are involved in the cascade of biological events that may stimulate pulpal progenitor/stem cells proliferation to expand their cell population prior to differentiation into odontoblast-like cells, as well as providing chemotactic attraction of these cells to sites of injury in order to promote deposition of tertiary dentin [1, 3, 5]. Although animal experiments with bioactive dentin proteins presented heterogeneity, there is evidence in the literature that suggests the use of bioactive molecules in biologically based therapies can be effective in direct and indirect pulp capping, with potential to be exploited for novel therapeutic approaches to dental tissue repair and regeneration.

However, the hypothesis was partially accepted, once for pulpotomy bioactive dentin proteins failed to induce dentin bridge formation. Only four studies are available in the literature with pulpotomy, and further research should be conducted with other bioactive molecules, once only BMP-7 and BMP-2 was evaluated. Besides, in two studies [43, 44] dental pulps inflammation was induced by direct injection of a solution with *Salmonella typhimurium lipopolysaccharide* (LPS; Sigma Chemical, USA). However, this microorganism is not related to dental caries progression, and a model that stimulate dental caries in vivo (as the widely accepted proposed by Bowen [53, 54]) could be important to assess the biological effects of these bioactive materials in inflamed pulps due to caries. Besides, it could be necessary that the immune response precedes reparative or regenerative events, and the removal of invading cariogenic bacteria and ensuing inflammatory processes could be deleterious to the dentin-pulp complex, which in turn compromise tissue repair [5].

Although our complete understanding of dental tissues interactions is limited,

dental pulp contains stem cells within niches, which provide a microenvironment responsible for maintaining these cells in their undifferentiated state, and could be stimulated by many bioactive proteins [6]. The literature demonstrated that bone morphogenetic proteins (BMP-2, -4 and -7) induce tertiary dentin formation in vivo in direct pulp capping. Only one study reported that MTA showed significantly more complete dentin bridge formation compared with BMP-7, however the follow-up was of just 2 weeks [51]. These proteins are a family of signaling molecules involved in the formation of many tissues and organs including bones and teeth [43, 55, 56]. Furthermore, it was previously demonstrated that pulp fibroblasts express the BMP receptors BMPR-IA, -IB, ActR-1 and BMPR-II mRNA transcripts [57], and dentin, like bone, contains BMP activity [43]. Other studies also reported that BMP-7 can mediate epithelial-mesenchymal interactions during the initiation phase of odontogenesis and morphogenesis [58], which demonstrated that this protein can maximize results from biollogicaly based therapies. These molecules stimulate a broad range of different outcomes in dental tissues, and the knowledge of this complex mechanism is fundamental to scientists optimize new therapeutic approaches.

Another important bioactive dentin protein extensively studied was transforming growth factor-β1 (TGF-β1), which is a complex molecule with multiple effects in dental tissues [59]. Other studies reported that the protein can induce up-regulation of dentin matrix by odontoblasts and the odontoblast-like cell differentiation in vitro [60]. Besides, TGF-β1 is able to induce the dental pulp stem-cell mediated mineralization [61], the dentin intratubular mineralization in vivo and it is a physiological regulator of osteoblast differentiation [62]. Other proteins that also induced deposition of mineralized tissue in teeth from animal studies were epidermal growth factor (EGF), insulin-like growth factor-1 and -2 (IGF-1 and-2), pratelet-derived growth factor BB (PDGF-BB), bone sialoprotein (BSP), fibroblast growth factor-2 (FGF-2), dentin phosphophoryn (DPP) and dentin matrix protein-1 (DMP-1). DMP-1 plays an essential role in dentin mineralization [63], and it is reported to be involved in the inflammatory process activating the synthesis of interleukin-6 and -8 (IL-6 and -8) from pulp fibroblasts [64]. Besides, in vitro studies showed that fibroblast growth factor-2 (FGF-2) also up-regulates chemokines [65], and induced cellularization and revascularization of human teeth implanted into the dorsum of rats [66]. Further research is needed to evaluate the efficacy of using these different

dentin matrix molecules, and the interactions between them in bioactive materials.

Although studies usually evaluated the effects of a single bioactive protein, it may not be the action of only one growth factor responsible for induction of odontoblast-like cell differentiation, once the process involves the interaction of many proteins that are likely to be key to dentin-pulp complex repair and regeneration[5]. Four studies [1, 34-36] evaluated soluble dentin matrix proteins extracted from rabbits teeth, which probably better represents the pool of bioactive molecules necessary to create the adequate microenvironment to repair or regenerative events in teeth. The detailed process employed to the extraction of non-collagenous proteins was first described by Smith et al. [36]. It has been reported that this lyophilized pool should be directly used to induce tertiary dentinogenesis as the chemotactic and other factors necessary for morphogenic activity are lost when this preparation is submitted to further purification [36]. All studies showed a significant deposition of tertiary dentin matrix in direct [36] or indirect pulp capping [1, 34, 35] after application of these protein pool, which it was also higher than the commercially available pulp capping agent calcium hydroxide [1]. It was also reported that some specimens presented dentin deposition with similar appearance to sound dentin [34]. However, the understanding of protein pool present in dentin-pulp complex is still very limited; and could provide a powerful means to extract the complex cocktail of bioactive proteins able to stimulate natural repair or regenerative processes [6]. Besides, the extraction of bioactive dentin proteins can be a low cost method when compared to using recombinant growth factors, which can be exploited by novel therapies and dental materials focused on hard tissue engineering approaches, especially regenerative dentistry.

In this context, regenerative dentistry has increase in the last decades through tissue engineering, which involves the use of progenitor cells capable of tissue regeneration when seeded in biodegradable scaffolds and exposed to bioactive molecules [7, 67, 68]. Although none included studies used progenitor cells in experimental pulp capping agents, the main goal of the proposed treatments involves a strategy of recruitment and stimulation of progenitor pulp cells, which is similar to tissue engineering goal. Furthermore, the translation of biologically based therapies into routine clinical use faces significant challenges. For example, bioactive materials need to release its molecules in the active form, and some proteins are susceptible to degradation at high temperature or pH of setting reaction. Besides, the

interaction between dental materials in contact with tooth tissue is influenced by many factors, including the composition of the material, the acidity or alkalinity, the chemistry and concentration of its components or degradation products, the presence of microorganisms, as well as the ability of the tissue to respond to bioactive materials [69]. Thus, the preservation of biological activity of these materials in clinical applications is still a challenge considering storage and molecule delivery at desired release kinetics and active form (bioactivity). Moreover different clinical treatments require the optimization of ideal release rate capable of providing a spatial and temporal control of these proteins over repair and regeneration.

There are many ways to control release kinetics of bioactive molecules, and the carriers used by animal studies included collagen [28-30, 37-47], gelatin [27, 48, 49], agarose [26], sodium alginate [33] and chitosan [50]. The optimization of how much proteins is ideal goes hand in hand with the definition of how quickly it should be released and for how long [7]. Although few studies are currently available in the literature, the combination of these molecules and drug delivery systems has attracted attention because of the potential benefits of controlled release of proteins. The use of material with multiple layers has recently been reported for direct pulp capping [50], which tested in vivo a chitosan membrane loaded with microspheres containing TGF-β1. Additionally, there are other reports in the literature of gelatin hydrogel [28] and polylactic-co-glycolic acid (PLGA) microspheres [32] with encapsulation of biactive molecules, and all studies demonstrated an improvement in protein release in pulp capping treatments. The development of new strategies for controlled release of these proteins can be critical to maximize their effects at shorter and longer time periods [7]. Some recent studies have also show other potentially drug delivery systems to these bioactive materials, such as poly-2-hydroxyethyl methacrylate (polyHEMA)-based hydrogel [70], tricalcium phosphate microsphere–hydrogel composite [71], porous silk fibroin scaffolds [72] and biodegradable polymer matrix of lactide and glycolide [73]. Further research could also aim to use bioactive proteins combined with other agents (e.g., antibiotics, inhibitors of inflammation), which could improve the action of bioactive dental materials.

The formation, quality, and thickness of tertiary dentin brigde, as well as the presence of inflammatory cells and preservation of the pulp are commonly used as evaluation criteria after vital pulp therapy in many investigations on animal teeth [74-79]. The included studies also presented heterogeneity regarding these different

evaluation methods to assess the efficacy of bioactive materials, such as morphological, histomorphometric, immunohistochemical and radiographic evaluation. Besides, it was observed variation regarding different follow-up periods and commercial controls. Only two studies [51, 52] used mineral trioxide aggregate (MTA) as commercial control compared to bioactive materials in direct pulp capping, while the majority used calcium hydroxide. Besides, one study presented the shorter follow-up period among included animal experiments, of up to 2 weeks, and demonstrated that MTA capped pulps presented more complete dentin bridge formation compared with BMP-7 group in pulpotomy [51]. Although calcium hydroxide remains the gold standard in vital pulp therapy, further research should be conducted to compare the bioactive proteins with different commercial controls, as MTA, which recently has been reported to present better long-term results after direct pulp capping compared with calcium hydroxide [12, 13], and it is the commercial reference recommended by normatives ISO 7450 (2008) or ANSI/ADA no. 41 [80, 81].

Although there is no consensus about the most adequate follow-up to analyze morphological outcomes in teeth, it is important to assess their short and long-term effects, which can differ regarding the outcomes of interest. For example, while it is important to analyze inflammatory response at short-term, for tertiary dentin formation a higher follow-up is necessary. In general, the deposition of tertiary dentin was assessed by the majority of animal studies, and only 5 studies [26, 28, 33, 37, 51] performed immunohistochemical analysis with the antibodies for DSP (dentin sialoprotein) and DMP-1 (dentin matrix protein-1). However, primary odontoblasts express a profile of molecular markers that is not unique to these cells, as nestin, dentin sialophosphoprotein (DSPP), DMP-1, and matrix extracellular phosphoglycoprotein, among other markers [6]. DSP is a cleaved product from dentin sialophosphoprotein (DSPP) and are mainly expressed by odontoblasts [5], while DMP-1 is expressed in differentiating odontoblasts [82] and is essential for mineralization and maturation of predentin to dentin during dentinogenesis [83, 84]. The expression of these two proteins are strongly linked with the biological effects expected after using bioactive materials in vital pulp therapy, which makes them an important histological marker for research in this area. However, other identification criteria such as cellular morphology and matrix morphology can increase confidence of identifying the odontoblast phenotype. The morphology of these cells varies

through its life cycle [85, 86], and a simple molecular characterization is not necessarily a robust means of identifying its phenotype [6].

In support of the inducer potential of the dentin matrix components, it is interesting to note that molecules previously shown to be key of tertiary dentin formation were also able to control the inflammatory process [5, 87, 88]. It is reported that some dentin matrix proteins promote the migration and pro-inflammatory activation of immune system cells when they are released from their matrix-immobilized state. Molecules such as TGF-β1 and adrenomedullin (ADM) have well-know anti-inflammatory properties, and the modulation and resolution of the immune and inflammatory response within the dentin–pulp complex may favour repair [5]. Furthermore, intratubular mineralization was assesses by scanning electron microscopy (SEM) for only one study [31], which evaluated the effects of 4 different growth factors (TGF-β1, IGF-1, FGF-2, BMP-7) indirectly applied over dental pulp. It was demonstrated that TGF-β1 significantly improved intratubular mineralization after 8 weeks, and it could be one of the main factors involved in dentin sclerosis. The upregulation of odontoblasts can lead to focal secretion of new matrix at the dentin-pulp interface and possibly, intratubularly. This can contribute to the histological appearance of dentin sclerosis at the injury site with a decrease in dentin permeability [1, 89]. The understanding of the physiological mechanism involved in obliteration of dentin tubules can allow exploiting new opportunities for biologically based therapies in dentistry, e.g. for dentin hypersensitivity, which occurs after dentin receive stimuli that lead to the movement of fluid within dentin tubules [90].

Although this is the best currently available evidence that demonstrates a benefit in using bioactive dentin proteins in vital pulp therapy, only animal studies are nowadays available in the literature and the strength of clinical inference is not strong. One limitation of this review was the degree of scientific evidence obtained and the quality level of the studies found. The included studies also showed heterogeneity regarding the type of bioactive molecule used and the treatment protocol, which precluded a direct comparison. Besides, the quality of the included studies emphasized the need for further well-designed, randomized and controlled animal studies to highlight the benefits of using bioactive materials in vital pulp therapy. Factors such as random sequence generation, sample size calculation, blinding the outcome assessment, and use of different evaluation methods could improve the quality of studies in this research field. Besides, it is important to follow

adequate normative in animal experiments for pulp capping evaluations, as ISO 7450 (2008) or ANSI/ADA no. 41) [80, 81], which it was not reported by any included study. In general, it is recommended that the study design have at least 10 teeth containing test material and 5 control teeth for each time period, to use a minimum of two non-rodent mammals of one species, to use MTA as reference control, and to evaluate the results at the time point of 25±5 and 70±5 days. Furthermore, although only two studies included were published after the publication of ARRIVE guidelines (Animal Research: Reporting of In Vivo Experiments) [91], following the standard in report of animal studies may improve studies quality and facilitate the comparison between different treatments in future systematic reviews.

Finally, biologically based therapies have long been important in dentistry and offer significant promise for future advances in materials and technological innovations. Bioactive dentin proteins act upon numerous cell types through cell surface receptors, and some factors must be taken into consideration that could influence treatments to vital pulp with these molecules. Their effects vary depending on their dose, state of activation, differentiation stage of target cells, and interplay with other bioactive molecules and extracellular matrix [3, 31]. Moreover, the high cost of biomaterials containing dentin matrix proteins may be a market entry barrier for bioactive materials. Dentin protein extraction at low cost may be an important alternative source of molecules in the future. Furthermore, this research field is inherently interdisciplinary, in particular relating to biomaterials, tissue engineering, and molecular and cellular biology. The understanding of the molecular mechanisms to control tooth repair and regeneration offers exciting opportunities to develop dental materials focused on novel biological treatment strategies [7]. Although these are rather substantial challenges, it is becoming evident that the successful development of bioactive materials has long-lasting benefits that surpass potential risks.

5. Conclusions

There is evidence in the literature that suggest dentin bioactive molecules could be able to improve tertiary dentin formation with initial less inflammatory response in vital pulp treatments. Furthermore, these molecules are of potential use for novel therapeutic approaches with bioactive materials not only in tissue repair but also in regeneration.

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Tables

Table 1 – Search strategy used in PubMed (MEDLINE)

	Search terms
#3	Search #1 AND #2
#2	“Dentin matrix protein” OR “protein, dentin matrix” OR "Transforming Growth Factors"[Mesh] OR "Transforming Growth Factors” OR “Bioactive protein” OR “proteins, bioactive” OR “bioactive proteins” OR “Bone Morphogenetic Protein 7” OR “Osteogenic Protein-1” OR “Osteogenic Protein 1” OR “BMP-7” OR “Bone Morphogenetic Proteins” OR “Morphogenetic Proteins, Bone” OR “Bone Morphogenetic Protein” OR “Morphogenetic Protein, Bone” OR “Factors, Transforming Growth” OR “Growth Factors, Transforming” OR “Transforming Growth Factor” OR “Factor, Transforming Growth” OR “Growth Factor, Transforming” OR “Transforming Growth Factor beta1” OR “Transforming Growth Factor beta I” OR “TGF-beta1” OR “TGF-beta-1” OR “TGF beta 1” OR “Transforming Growth Factor beta 1 Latency Associated Peptide” OR “TGF-beta1 Latency-Associated Protein” OR “Latency-Associated Protein, TGF-beta1” OR “TGF beta1 Latency Associated Protein” OR “TGF-beta1LAP” OR “TGF beta1LAP” OR “Transforming Growth Factor beta2” OR “TGF-beta2” OR “TGF-beta-2” OR “Transforming Growth Factor beta 2 Latency Associated Peptide” OR “TGF-beta2LAP” OR “TGF beta2LAP” OR “TGF-beta2 Latency-Associated Protein” OR “Latency-Associated Protein, TGF-beta2” OR “TGF beta2 Latency Associated Protein” OR “Insulin-Like Growth Factor I” OR “Insulin-Like Somatomedin Peptide I” OR “Insulin Like Somatomedin Peptide” OR “Somatomedin C” OR “IGF-I-smc” OR “IGF-1” OR “IGF-I” OR “Insulin Like Growth Factor I” OR “dentin sialophosphoprotein” OR “dentin phosphoprotein, human” OR “dentin matrix protein” OR “dentin sialoprotein, human” OR “DSPP protein, human” OR “dentin sialophosphoprotein, human” OR “dentin matrix protein 3, human” OR “dentin phosphophoryn protein, human” OR “dentin phosphoprotein” OR “dentin phosphophoryn” OR “dentin sialoprotein” OR “Osteopontin” OR “Sialoprotein 1” OR “Secreted Phosphoprotein 1” OR “Bone Sialoprotein 1” OR “Sialoprotein 1, Bone” OR “Bone Sialoprotein I” OR “Sialoprotein I, Bone” OR “Uropontin” OR “Fibroblast Growth Factor 2” OR “Basic Fibroblast Growth Factor” OR “FGF-2” OR “FGF 2” OR “FGF2” OR “Fibroblast Growth Factor, Basic” OR “Fibroblast Growth Factor-2” OR “EGF Family of Proteins” OR “Proteins EGF Family” OR “Epidermal Growth Factors” OR “EGF Receptor Ligands” OR “Ligands, EGF Receptor” OR “Receptor Ligands, EGF” OR “Epidermal Growth Factor-Like Proteins” OR “Epidermal Growth Factor Like Proteins”
#1	"Dental Pulp"[Mesh] OR “Dental Pulp” OR “Pulp, Dental” OR “Pulps, Dental” OR “Dental Pulps” OR “Dental Pulp Diseases” OR “Pulp Diseases, Dental” OR “Diseases, Dental Pulp” OR “Pulp Disease, Dental” OR “Dental Pulp Disease” OR “Disease, Dental Pulp” OR “Dental Pulp Exposure” OR “Exposure, Dental Pulp” OR “Pulp Exposure, Dental” OR “Pulpitis” OR “Inflammation, Endodontic” OR “Endodontic Inflammation” OR “Endodontic Inflammations” OR “Inflammations, Endodontic” OR “Apexogenesis” OR “Apexogeneses” OR “Dental Pulp Capping” OR “Pulp Capping, Dental” OR “Pulp Capping” OR “Capping, Pulp” OR “Cappings, Pulp” OR “Pulp Cappings” OR “Capping, Dental Pulp” OR “Cappings, Dental Pulp” OR “Dental Pulp Cappings” OR “Pulp Cappings, Dental” OR “Pulp Capping Agents” OR “Pulp Capping Agents” OR “Agent, Pulp Capping” OR “Agents, Pulp Capping” OR “Capping Agent, Pulp” OR “Capping Agents, Pulp” OR “Pulp Capping Agent”

Table 2 - Demographic and main study design data of included studies

Author	Year	Country	Animal	Number of animals	Number of teeth (total per protein group)	Treatment evaluated	Pulp exposure	Restoration	Follow-up
Almushayt [37]	2006	United States	Rats	24	30 (10)	Direct Pulp Capping	Induced with sterile burs followed by tip of a sterile dental explorer	-	14 and 28 days
Andelin [51]	2003	United States	Rats	-	35 (10)*	Direct Pulp Capping	Induced with sterile burs	MTA (ProRoot MTA, Dentsply, USA)	14 days
Bezerra da Silva [29]	2008	Brazil	Dogs	6	60	Pulpotomy	Induced with sterile burs	Resin-modified glass ionomer cement (Vitremer, 3M ESPE, USA)	7 and 70 days
Chaussain [26]	2009	France	Rats	16	- (-)	Direct Pulp Capping	Induced with round bur and tip of a steel probe	Glass ionomer cement (GC Fuji II, GC Corportion, Japan)	7, 15 and 30 days
Duque [1]	2006	Brazil	Monkeys	4	18 (6)	Indirect Pulp Capping	No exposure	Dental amalgam***	180 days
Gao [92]	1995	China	Dogs	2	40 (-)	Direct Pulp Capping	Induced with sterile burs	Zinc phosphate cement followed by composite resin***	14 and 28 days
Goldberg [48]	2001	France	Rats	-	- (-)	Direct Pulp Capping	Induced with sterile burs followed by tip of a steel probe	Glass ionomer cement (Fuji IX, GC Corporation, Japan)	8, 14, and 28 days
Hu [30]	1998	United States	Rats	>50	95 (-)	Direct Pulp Capping	Induced with sterile burs followed by tip of a sterile dental explorer	Dental amalgam***	14 and 21 days
Ishimatsu [27]	2009	Japan	Rats	30	60 (6)	Direct Pulp Capping	Induced with sterile burs	Alfa-TCP Cement (New apatite liner, Dentsply, Japan)	7 and 21 days
Jepsen [38]	1997	Germany	Miniature pigs	4	16 (8)*	Direct Pulp Capping	Induced with sterile burs	Zinc-oxide-eugenol cement***	35 days
Kalyva [31]	2010	Greece	Dogs	8	- (-)	Indirect Pulp Capping	No exposure	Dental amalgam***	21 and 60 days

Kikuch [28]	2007	Greece	Dogs	8	- (-)	Direct Pulp Capping	Induced with sterile burs	Alfa-TCP Cement (New apatite liner, Dentsply, Japan) and adhesive resin (Super-Bond C&B, Sun Medical Co, Japan)	1, 3, 5, 14 and 21 days
Ko [52]	2010	Korea	Rats	32	64 (16)	Pulpotomy	Induced with sterile burs	Glass ionomer cement (Fuji II LC, GC Corporation, Japan)	14 and 50 days
Koike [39]	2014	Japan	Rats	-	63 (21)	Direct Pulp Capping	Induced with sterile burs	Glass ionomer cement (Hy-bond Glasionomer CX, Shofu, Japan) and composite resin (Unifilflow, GC, Japan)	7, 14 and 21 days
Li [50]	2014	China	Dogs	6	48 (10)*	Direct Pulp Capping	Induced with sterile burs	Resin-modified glass ionomer cement (GC Fuji, Japan)	10 and 60 days
Li Zhimei [40]	2007	Singapore	Monkeys	9	36 (15)*	Direct Pulp Capping	Induced with sterile burs	Intermediate Restorative Material (IRM, Dentsply, USA)	42 and 90 days
Lovschall [93]	2001	Denmark	Rats	68	71 (9)*	Direct Pulp Capping	Induced with sterile burs	Intermediate Restorative Material (IRM, Dentsply, USA)	3, 7 and 28 days
Nakashima [94]	1990	Japan	Dogs	5	- (-)	Direct Pulp Capping	Induced with sterile burs	Zinc phosphate cement (Elite cement, GC Dental, Japan)	7, 15, 30 and 60 days
Nakashima [42]	1994	Japan	Dogs	3	18 (6)	Direct Pulp Capping	Induced with sterile burs	Zinc phosphate and a composite resin***	70 days
Nakashima [41]	1994	Japan	Dogs	2	12 (4)	Direct Pulp Capping	Induced with sterile burs	Zinc phosphate cement (Elite cement, GC Dental, Japan)	60 days
Oliva-Rodriguez [33]	2011	Mexico	Rats	48	96 (12)	Direct Pulp Capping	Induced with sterile burs followed by tip of a steel probe	Glass ionomer cement (Vitrebond, 3M Espe, USA)	14 and 28 days
Rutherford [46]	1993	United States	Monkeys	4	30 (15)*	Direct Pulp Capping	Induced with sterile burs	Temp-Bond NE (Kerr, USA)	42 days
Rutherford [45]	1994	United States	Monkeys	4	58 (50)*	Direct Pulp Capping	Induced with sterile burs	Ketac Silver (3M ESPE, USA) and dental amalgam (Kerr, USA)	30, 60, 120 and 180 days

Rutherford [44]	2000	United States	Ferrets	15	60 (8)	Pulpotomy with pulpitis induced	-	Glass ionomer cement (3M ESPE, USA)	30 days
Rutherford [43]	2001	United States	Ferrets	3	12 (4)	Pulpotomy with pulpitis induced	-	-	30 days
Six [49]	2002	France	Rats	48	96 (12;18)**	Direct Pulp Capping	Induced with sterile burs followed by tip of a steel probe	Glass ionomer cement (Fuji IX, GC Corporation, Japan)	8, 15 and 30 days
Six [47]	2002	France	Rats	29	58 (34)*	Direct Pulp Capping	Induced with sterile burs followed by tip of a steel probe	Glass ionomer cement (GC Fuji II, GC Corporation, Japan)	8 and 28 days
Smith [36]	1990	United Kingdom	Ferrets	10	40 (15)*	Direct Pulp Capping	Induced with sterile burs followed by tip of a steel probe	Zinc-oxide-eugenol cement (Kalzinol, Dentsply, USA)	14 and 28 days
Smith [34]	1994	United Kingdom	Ferrets	15	45 (35)*	Indirect Pulp Capping	No exposure	Zinc-oxide-eugenol cement (Kalzinol, Dentsply, USA)	2, 5, 14, 28 and 90 days
Smith [35]	2001	United Kingdom	Ferrets	15	45 (35)*	Indirect Pulp Capping	No exposure	Zinc-oxide-eugenol cement (Kalzinol, Dentsply, USA)	2, 5, 14, 28 and 90 days
Suwa [95]	1993	Japan	Dogs	4	- (-)	Direct Pulp Capping	Induced with sterile burs	-	14, 21, 30 and 60 days
Zhang [32]	2008	Netherlands	Goats	24	24 (6)	Direct Pulp Capping	Induced with sterile burs	Glass ionomer cement***	90 days

*Control group with number of teeth different of intervention groups; ** Number of teeth respectively for BMP-7 (bone morphogenetic protein-7) and BSP (bone sialoprotein) group; *** Commercial manufacture non-informed; - Data not reported

Table 3 – Dentin matrix proteins, dilution, carrier and controls used

Author	Proteins	Protein dilution	Carrier	Controls
Almushayt [37]	DMP-1 (recombinant dentin matrix protein-1)*	-	Collagen membrane	NC: collagen membrane; CC: calcium hydroxide (Dycal, Dentsply, USA)
Andelin [51]	BMP-7 (recombinant bone morphogenetic protein-7, Creative Biomolecules, USA)	BMP-7 placed directly on exposed pulps	-	NC: pulp exposure without treatment; CC: MTA (Pro Root MTA, Dentsply, USA)
Bezerra da Silva [29]	BMP-7 (recombinant human bone morphogenetic protein-7, ProSpec Tany TechnoGene Ltd, Israel)	BMP-7 and collagen solubilized in pyrogen-free water (Milli-Q Ultrapure Water Purification, Millipore, Billerica, Mass)	BMP-7 and recombinant human-like collagen (rhCollagen) in pyrogen-free water and lyophilized	NC: collagen; CC: calcium hydroxide powder (Calcium Hydroxide zur Analyse, Merck, Darmstadt, Germany) and zinc oxide and Eugenol Cement (IRM, Dentsply, USA)
Chaussain [26]	DMP-1 (dentin matrix protein-1)*	DMP-1 dissolved in phosphate-buffered saline (PBS) solution	Affi-gel agarose beads (Bio-Rad, USA) soaked in a solution of DMP-1	NC: buffer soaked beads without proteins
Duque [1]	Soluble dentin matrix proteins extracted from rabbits teeth	Lyophilized aliquots of proteins (Not dissolved)	Proteins introduced as lyophilized aliquots	NC: no proteins applied followed by resin-modified glass-ionomer cement (Vitrebond, 3M ESPE, USA); CC: calcium hydroxide (Dycal, Dentsply, USA)
Gao [92]	BMP (bone morphogenetic protein) extracted from young bovine bones	BMP mixed in guanidinium chloride (GuHCl) and adding ceramic dentin (CD)	Ceramic dentin (CD)	NC: Ceramic dentin (CD) without BMP;
Goldberg [48]	BSP (bone sialoprotein) and BMP-7 (bone morphogenetic protein-7)*	BMP-7 mixed with collagen	Gelatin	NC: Carrier without bioactive substance; CC: calcium hydroxide*
Hu [30]	EGF (mouse epidermal growth factor, Sigma-Aldrich, USA); FGF (human recombinant fibroblast growth factor, Sigma-Aldrich, USA); IGF-2 (human recombinant insulin-like growth factor-2, Boehringer, Germany); PDGF-BB (human recombinant platelet-derived growth factor BB, Upstate Biotechnology, USA); TGF-β1 (human recombinant transforming growth factor-β1, Upstate Biotechnology, USA)	Proteins dissolved in sterile water or sodium acetate	Sterile absorbable collagen membrane BioMend (Calcitek, USA)	NC: collagen control; CC: calcium hydroxide (Dycal, Dentsply, USA)
Ishimatsu [27]	FGF-2 (human recombinant fibroblast growth factor-2, Kaken Pharmaceutical Co, Japan)	FGF-2 dissolved in PBS (phosphate buffered saline)	Gelatin hydrogel microspheres incorporating FGF-2 in	NC: gelatin hydrogel without proteins

			phosphate-buffered saline (PBS)	
Jepsen [38]	BMP-7 (human recombinant bone morphogenetic protein-7)*	BMP-7 mixed with collagen carrier matrix	Collagen carrier matrix moistened with saline	NC: collagen matrix moistened with saline at 3 mg/tooth; CC: calcium hydroxide (Calxyl,OCO-Präparat GMBH, Germany)
Kalyva [31]	TGF-β1 (recombinant human transforming growth factor-β1, Sigma Aldrich, USA); IGF-1 (recombinant human insulin-like growth factor-1, R&D systems, Germany); FGF-2 (recombinant human fibroblast growth factor, R&D Systems, Germany); BMP-7 (recombinant human bone morphogenetic protein-7, R&D Systems, Germany)	Proteins dissolved in solutions containing dog serum albumin (DSA) in PBS (phosphate buffered saline)	Dog serum albumin (DSA) and phosphate-buffered saline (PBS)	NC: anti-TGF-β1 and TGFβ1 + Anti-TGFβ1
Kikuch [28]	FGF-2 (human fibroblast growth factor-2 , Kaken Pharmaceutical Co., Japan)	FGF-2 dissolved in PBS (phosphate buffered saline) and dropped onto freeze-dried gelatin hydrogel microspheres	Gelatin hydrogel microspheres with FGF-2 were mixed with small pieces of collagen sponge	NC: mixture of collagen sponge without FGF-2 gelatin hydrogel microspheres;
Ko [52]	BMP-2 (recombinant human bone morphogenetic protein-2, R&D Systems, USA)	BMP-2 placed directly on exposed pulps and covered with MTA	-	CC: MTA (ProRoot, Dentsply, USA)
Koike [39]	DPP (dentin phosphophoryn) extracted from molar teeth from young porcine	DPP was cross-linked to porcine-derived type I atelocollagen brils with divinylsulfone (Sigma Chemical, St. Louis, MO, USA)	Type I atelocollagen fibrils (Collagen sponge, Nitta Gelatin, Japan)	NC: Type I Atelocollagen without proteins; CC: calcium hydroxide (Multi-Cal, Pulpdent, USA)
Li [50]	TGF-β1 (transforming growth factor-β1)*	Dry microspheres were placed into acetic buffer solution containing TGF-β1	A chitosan bilayer membrane consisting of dense film on one side and a macroporous spong on the other side loaded with chitosan microspheres containing TGF-β1	NC: membrane without proteins; CC: calcium hydroxide (Dycal, Dentsply, USA)
Li Zhimei [40]	aFGF (acidic fibroblast growth factor, Biosource, USA)	aFGF carried on the collagen membrane	Sterile bioabsorbable type-I collagen membrane (Biomend, Calcitek, Carlsbad, USA)	NC: membrane without proteins; CC: calcium hydroxide (Calasept; Nordiska Dental, Angelholm, Sweden)

Lovschall [93]	IGF-1 (recombinant human insulin-like growth factor-1, Pharmacia AB, Sweden)	IGF-1 in solution (Pharmacia AB, Sweden)	Fresh gel with proteins or saline prepared by means of a methylcellulose (Sigma Aldrich, USA)	NC: gel with physiological sterile saline; CC: calcium hydroxide (Dycal, Dentsply, USA)
Nakashima [94]	BMP extracted from canine bone matrix	Crude BMP (Not dissolved)	Proteins introduced as crude BMP	NC: canine serum albumin (Sigma, St Louis, USA)
Nakashima [42]	TGF-β1 (transforming growth factor-β1), BMP-2 and 4 (recombinant human bone morphogenetic protein-2 and 4)*	Proteins mixed with acid-soluble type I collagen (Cellmatrix Type LA, Nitta Gelatin Corp., Japan)	Collagen matrix (Cellmatrix Type LA, Nitta Gelatin Corp., Japan).	NC: collagen carrier without proteins
Nakashima [41]	BMP-2 and 4 (recombinant human bone morphogenetic protein-2 and 4)*	BMP-2 and BMP-4 added to the carriers	Inactivated dentin matrix powder, chondroitin 6-sulfate sodium salt (Seikagaku Kogyo Co., Japan) and acid-soluble type 1 rat tail tendon collagen	NC: collagen carrier without proteins
Oliva-Rodriguez [33]	TGF-β1 (transforming growth factor-β1) and lyophilized BMP-7 (bone morphogenetic protein-7)*	Proteins mixed with sodium alginate (Sigma-Aldrich, USA). TGF-β1 solution contained Tris–acetate, EDTA and glycerol, and lyophilized BMP-7 was reconstituted in acetic acid	Biopolymers of sodium alginate that include BMP-7 and TGF-β1	NC: Pulp exposure without treatment; CC: calcium hydroxide*
Rutherford [46]	BMP-7 (bone morphogenetic protein-7, Creative BioMolecules, USA)	BMP-7 combined with the collagen carrier matrix and drying under vacuum	Collagen matrix	NC: collagen carrier without proteins; CC: calcium hydroxide (Dycal, Dentsply, USA)
Rutherford [45]	BMP-7 (bone morphogenetic protein-7, Creative BioMolecules, USA)	BMP-7 combined with the collagen carrier matrix and drying under vacuum	Collagen matrix	NC: collagen carrier without proteins
Rutherford [44]	BMP-7 (bone morphogenetic protein-7)*	BMP-7 combined with the collagen carrier (Creative BioMolecules, Hopkinton, USA)	Collagen matrix (Creative BioMolecules, Hopkinton, USA)	NC: collagen carrier without proteins
Rutherford [43]	BMP-7 (bone morphogenetic protein-7)*	BMP- 7 suspended in a type I collagen thermoset hydrogel (RD Bioscience, USA)	Collagen thermoset hydrogel (RD Bioscience, USA)	NC: carrier with virus-free
Six [49]	BSP (bone sialoprotein) and BMP-7 (bone morphogenetic protein-7)*	BSP covalently crosslinked to gelatin; and BMP-7 in polyglycol	Gelatin for BSP and polyglycol for BMP-7	NC: gelatin or polyglycol without proteins; CC: calcium hydroxide*

Six [47]	BMP-7 (recombinant human bone morphogenetic protein-7)*	BMP-7 combined with the collagen carrier	Collagen matrix	NC: collagen carrier without proteins; CC: calcium hydroxide powder (Sigma–Aldrich, L'Isle d'Abeau Chesnes, St Quentin Fallavier, France)
Smith [36]	Soluble dentin matrix proteins extracted from rabbits teeth	Lyophilized aliquots of proteins (Not dissolved)	Proteins introduced as lyophilized aliquots	NC: Rabbit albumin (Sigma Aldrich, USA) with omission of proteins
Smith [34]	Soluble dentin matrix proteins extracted from rabbits teeth	Lyophilized aliquots of proteins (Not dissolved)	Proteins introduced as lyophilized aliquots	NC: Rabbit albumin (Sigma Aldrich, USA) or omission of proteins
Smith [35]	Soluble dentin matrix proteins extracted from rabbits teeth	Lyophilized aliquots of proteins (Not dissolved)	Proteins introduced as lyophilized aliquots	NC: omission of proteins
Suwa [95]	BMP (partially purified bone morphogenetic protein) extracted from bovine bone	BMP redissolved in guanidinium chloride (GuHCl), to which porous HAP was added. Complex HAP/BMP was lyophilized	Porous HAP (Hydroxyapatite) combined with BMP	NC: hydroxiapatite alone
Zhang [32]	TGF-β1 (transforming growth factor-β1)*	PLGA microparticles submerged in BSA/PBS solutions (bovine serum albumin/phosphate-buffered saline solution) with TGF-β1. The complex was lyophilized.	Polylactic-co-glycolic acid (PLGA) microspheres	NC: PLGA microspheres without proteins and none capping material

* Commercial manufacture non-informed; - Data not reported; NC: negative control; PC: positive control; CC: commercial control

Table 4 – Evaluation methods and main findings from included studies with direct pulp capping

Study	Evaluation methods	Main findings
Almushayt [37]	Morphological and immunohistochemical evaluation (antibodies for DMP-1), confocal scanning laser microscopy	DMP-1 was able to induce dentin brigde formation after 4 weeks and could act as a morphogen on undifferentiated mesenchymal cells present in the dentin-pulp complex. Besides, inflamation was also reduced after DMP-1 application.
Andelin [51]	Morphological and immunohistochemical evaluation (antibodies for DSP)	Pulps capped with MTA formed hard tissue that demonstrated significantly more immunostaining for DSP compared with BMP-7 and also showed significantly more complete bridge formation. Besides, MTA demonstrated a hard tissue that was bone-like in appearance and devoid of DSP staining.
Chaussain [26]	Morphological and immunohistochemical evaluation (antibodies for DSP and DMP-1)	At day 15, a continuous tertiary dentin bridge was observed after DMP-1 treatment, and a poorly organized reparative structure was observed in the control group without proteins. In the DMP-1 group, the cells associated with the bridge and located at the opposite side of the injury, presented a polarized morphology and were organized as a palisade, with a basal location of the nucleus, probably representing odontoblasts. These polarized cells were positively labeled for DSP and DMP-1. The corresponding cells in the control group were not polarized and showed a faint immunostaining for either DSP or DMP-1.
Gao [92]	Morphological evaluation	Some osteodentinal matrix was formed after 2 weeks in BMP and ceramic dentin group. At 4 weeks, the dentinal bridge was complete. When ceramic dentin without BMP was used, there was minimal bone-like matrix formed.
Goldberg [48]	Morphological and histomorphometric evaluation	BSP induced homogeneous and well-mineralized tertiary dentin at 28 days, while BMP-7 gave tertiary dentin of the osteodentin type in the coronal part of the pulp at the same period. Both proteins were superior to CH in their mineralization-inducing properties, and displayed larger areas of mineralization containing fewer pulp tissue inclusions.
Hu [30]	Morphological evaluation	At 21 days groups with TGF-β1 showed significantly improved soft and hard tissue healing compared with the procedure control. Tertiary dentin bridges contained abundant short reparative dentinal tubules that were not observed in any of the other treatment groups.
Ishimatsu [27]	Morphological and immunohistochemical evaluation (antibodies for DMP-1)	The dosage of released FGF-2 presented an influence on the structure of mineralized tissue regenerated in dentin defects. The controlled release of high doses of FGF-2 from gelatin hydrogels induced DMP-1 positive calcified particles in the proliferating pulp, while a moderate dose of FGF-2 induced DMP-1 positive dentinal bridge on the surface of the proliferating pulp.
Jepsen [38]	Morphological and histomorphometric evaluation	Teeth treated with BMP-7 presented substantial amounts of hard tissue formation (osteodentin and tubular dentin) after 35 days, which led to a complete bridging of the defects. Control with collagen matrix alone failed to form complete dentin bridges, and less dentin formation was seen at CH group.
Kikuch [28]	Morphological and immunohistochemical evaluation (antibody for DSP)	Induction of dentin formation was distinctly different between the two types of FGF-2 release. The noncontrolled release of free FGF-2 from collagen sponge induced excessive tertiary dentin formation; and its controlled release from gelatin hydrogels induced the formation of dentin-like particles with dentin defects above exposed pulp. The group with gelatin hydrogel microspheres incorporating FGF-2 showed intense DSP signals in pulp

		cells and calcified particles.
Koike [39]	Morphological and histomorphometric evaluation	The tertiary dentin formation induced by DPP with collagen composite was more rapid than by CH, and the compactness of tertiary dentin formed was much superior to CH. DPP showed high covering ability of exposed pulp, and led to slight pulp inflammation at the beginning whereas CH formed necrotic layer and induced severe inflammation in pulp tissue at 1 week.
Li [50]	Morphological evaluation	After 10 days, mild to moderate pulp inflamation was observed in all groups, with no dentin bridge formation. At 60 days, pulp inflammation disappeared, but there was no tertiary dentin bridge in the group with no pulp-capping material. Chitosan membranes with TGF in microspheres generated tertiray dentin 3-6 times thicker than that with CH or membrane without proteins.
Li Zhimei [40]	Morphological evaluation	After 13 weeks, both aFGF with collagen carrier group and the collagen carrier group produced significantly better hard tissue barrier than earlier timing at 6 weeks. However, these two groups did not induce significantly these tissue barrier cmpared to that produced by CH paste.
Lovschall [93]	Morphological evaluation	On day 3, identical inflammatory responses in the upper pulp were observed in molars with IGF-1 gel or control gel. After 28 days, complete dentin bridging and tubular dentin formation were observed more frequently and closer to the test substance containing IGF-I. The tertiary dentin response to capping with IGF-1 was similar to that after the use of CH.
Nakashima [94]	Morphological evaluation	The remaining pulp showed little sign of inflammation after 1 week of BMP implantation. Besides, after 8 weeks tertiary dentin filled more than half of the cavity. In control, a little osteodentin and no tubular dentin were seen after 8 weeks.
Nakashima [42]	Morphological evaluation	BMP-2 and -4 induced tertiaty dentin formation when combined with collagen matrix. In teeth implanted with TGF-β1, little pulp tissue proliferation was demonstranting, suggesting a possible inhibitory effect of TGF-β1 in pulp regeneration.
Nakashima [41]	Morphological evaluation	BMP-2 and -4 induced a large amount of dentin. After 2 months, pulp was filed with tubular dentin in the lower part and osteodentin in the upper part. Besides, BMP-2 and -4 induced differentiation of adult pulp cells into odontoblasts.
Oliva-Rodriguez [33]	Morphological and immunohistochemical evaluation (antibody for DSP)	The group with encapsulated BMP-7 showed an increased DSP immunostaining after 14 days and did not find any significant difference with the immunostaining observed for CH treatment. Groups with TGF-β1 did not show significant difference with CH. Besides, treatment with both factors BMP-7 and TGF-β1 showed higher DSP immunostaining in comparison with CH.
Rutherford [46]	Morphological and histomorphometric evaluation	Substantially more new dentin was present in teeth treated with BMP-7/collagen than in those treated with CH, and the amount of tertiary dentin formed was proportional to the amount of BMP-7/collagen. No tertiary dentin was formed in collagen carrier or untreated teeth.
Rutherford [45]	Morphological and histomorphometric evaluation	It was showed that the use of BMP-7 maintained radicular pulp vitality, the tertiary dentin was formed, and mineralization was nearly 75% complete after 1 month and more than 95% after 4 months.

Six [49]	Morphological evaluation	BSP stimulated the recruitment of cells which produced an homogeneous atubular dentin-like structure after 1 month, as well as BMP-7 that induced the formation of osteodentin in the coronal pulp and the radicular part of the pulp was totally filled by a mineralized material.
Six [47]	Morphological evaluation	After 8 days, all groups showed varying inflammation, from mild of severe. At 28 days the collagen carrier group displayed irregular osteodentin formation. In most BMP-7 treated specimens, the initial inflammation has resolved at 8 days and at 28 days heterogeneous mineralization or osteodentin filled the mesial coronal pulp.
Smith [36]	Morphological evaluation	A strong tertiary response was observed after implantion of pool from dentin matrix proteins extracted, characterized by the presence of newly formed dentin after 28 days. The reparative response was characterized by its intensity within a comparatively short time period and also by the low grade or complete absence of any localized inflammatory response. Minimal or absent tissue response was observe in controls.
Suwa [95]	Morphological evaluation	A thin and necrotic layer was found on the surface of the exposed pulp after 2 weeks of capping with hidroxyapatite and BMP complex. After 3 weeks, regular dentin was induced in the pulp, and many dentin tubules in the shape of normal dentin were observed. After 4 weeks, the rate of dentin formation increased, and a dentin bridge composed of osteodentin without any dentin tubules was formed. By 8 weeks, the osteodentin bridge had calcified. In the control group with HA alone, a dentin bridge was not found by 8 weeks.
Zhang [32]	Morphological evaluation	New dentin formation was seen in all specimens with TGF-β1, except the negative controls. The composite with 400ng of TGF-β1 was able to trigger resident stem cells in the pulp to differentiate into odontoblast-like cells and to induce the formation of tertiary dentin.

CH: calcium hydroxide; MTA: mineral trioxide aggregate; BMP-2: bone morphogenetic protein-2; BMP-4: bone morphogenetic protein-4; BMP-7: bone morphogenetic protein-7; BSP: bone sialoprotein; DMP-1: dentin matrix protein-1; DSP: dentin sialoprotein; DPP: dentin phosphophoryn; FGF-2: fibroblast growth factor-2; TGF: transforming growth factor-β1

Table 5 – Evaluation methods and main findings from included studies with indirect pulp capping

Study	Evaluation methods	Main findings
Duque [1]	Morphological evaluation	Soluble dentin matrix proteins extracted stimulated higher deposition of tertiary dentin matrix than CH. No inflammatory pulpal response was observed for all experimental and control groups.
Kalyva [31]	Morphological and histomorphometric evaluation, and scanning electron microscopy (SEM) examination	The group treated with TGF-β1 and, to a lesser extent, the one treated with BMP-7 showed significantly greater tertiary dentin formation and intratubular mineralization over 8-week period when compared with the control and the other experimental groups. No significant differences was observed between groups in reduction in dentin permeability after treatment.
Smith [34]	Morphological evaluation	After 14 days there was significant deposition of tertiary dentin by the odontoblasts beneath the cavity in all teeth without pulp exposure, and this response increased in a non-linear manner with time of implantation. Controls cavities showed no evidence of tertiary dentin deposition. In some specimens tertiary dentin had a similar appearance to that of the sound dentin after 90 days.
Smith [35]	Morphological and histomorphometric evaluation	Restored cavities without pulp exposures with two lyophilized preparations of dentin matrix components increased the mean area of tertiary dentin secreted by 433 and 578%, and the numbers of odontoblasts remained stable. Minimal tertiary dentin area was observed after 2 and 7 days post-surgery, and maximal dentin brigde formation was observed after 90 days.

CH: calcium hydroxide; BMP-2: bone morphogenetic protein-2; TGF: transforming growth factor-β1

Table 6 – Evaluation methods and main findings from included studies pulpotomy

Study	Evaluation methods	Main findings
Bezerra da Silva [29]	Radiographic evaluation	BMP-7 with collagen after pulpotomy did not induce mineralized tissue deposition, leading to the formation of radiographically visible periapical lesions. CH group showed dentin bridge formation, intact lamina dura and no periapical bone rarefaction.
Ko [52]	Morphological evaluation	At 2 weeks, no complete dentin bridge was formed in any group. After 7 weeks, inflammation was reduced and dentin bridge formation was nearly complete after MTA or BMP-2 use. The pulp reaction to BMP-2 was not significantly better than use of MTA alone.
Rutherford [44]	Morphological evaluation	A single application of a therapeutic dressing comprising BMP-7 and a bovine bone-derived collagen carrier failed to induce tertiary dentin formation in an animal model of reversible pulpitis after one month.
Rutherford [43]	Morphological evaluation	BMP-7 failed to produce tertiary dentin after one month in inflamed dental pulps

CH: calcium hydroxide; BMP-2: bone morphogenetic protein-2**;** BMP-7: bone morphogenetic protein-7

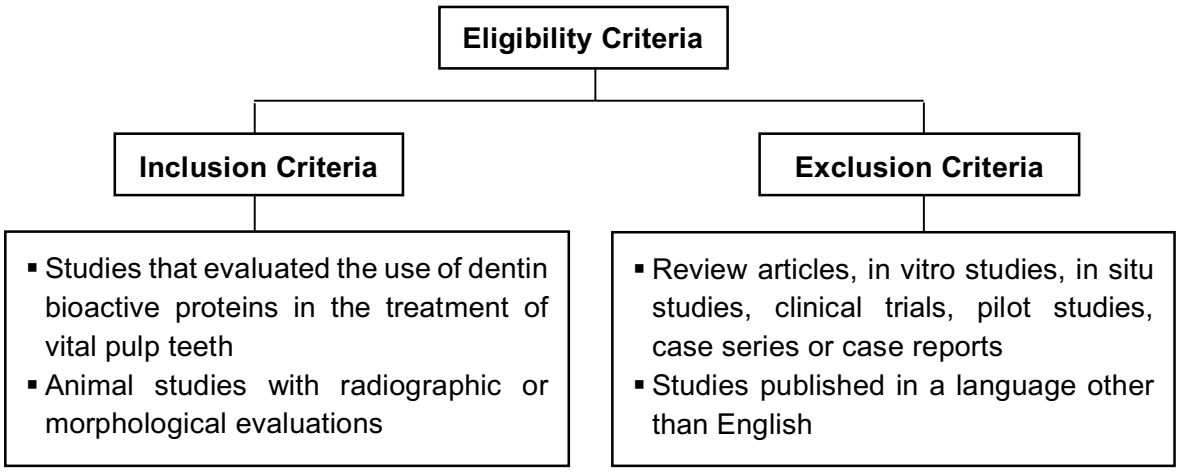

Fig. 1 – Eligibility criteria

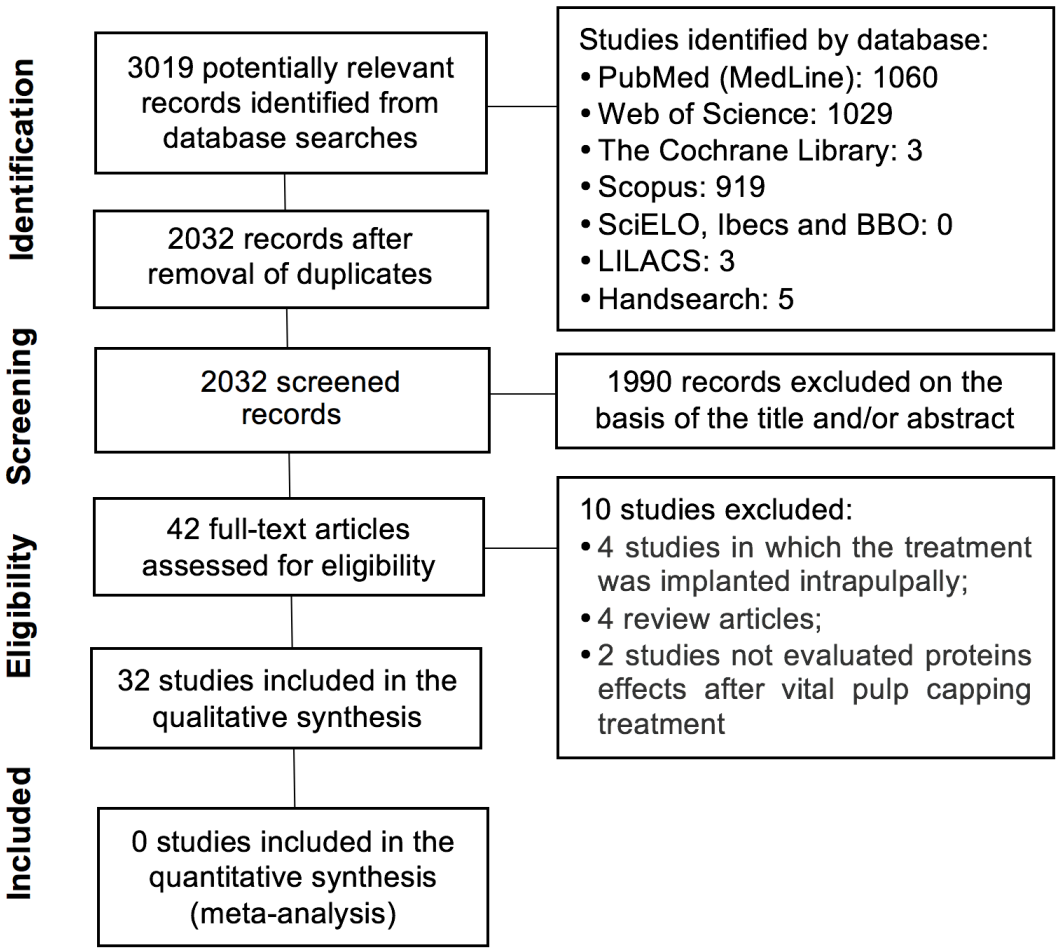

Fig. 2 - Search flow (as described in the PRISMA statement) [16]

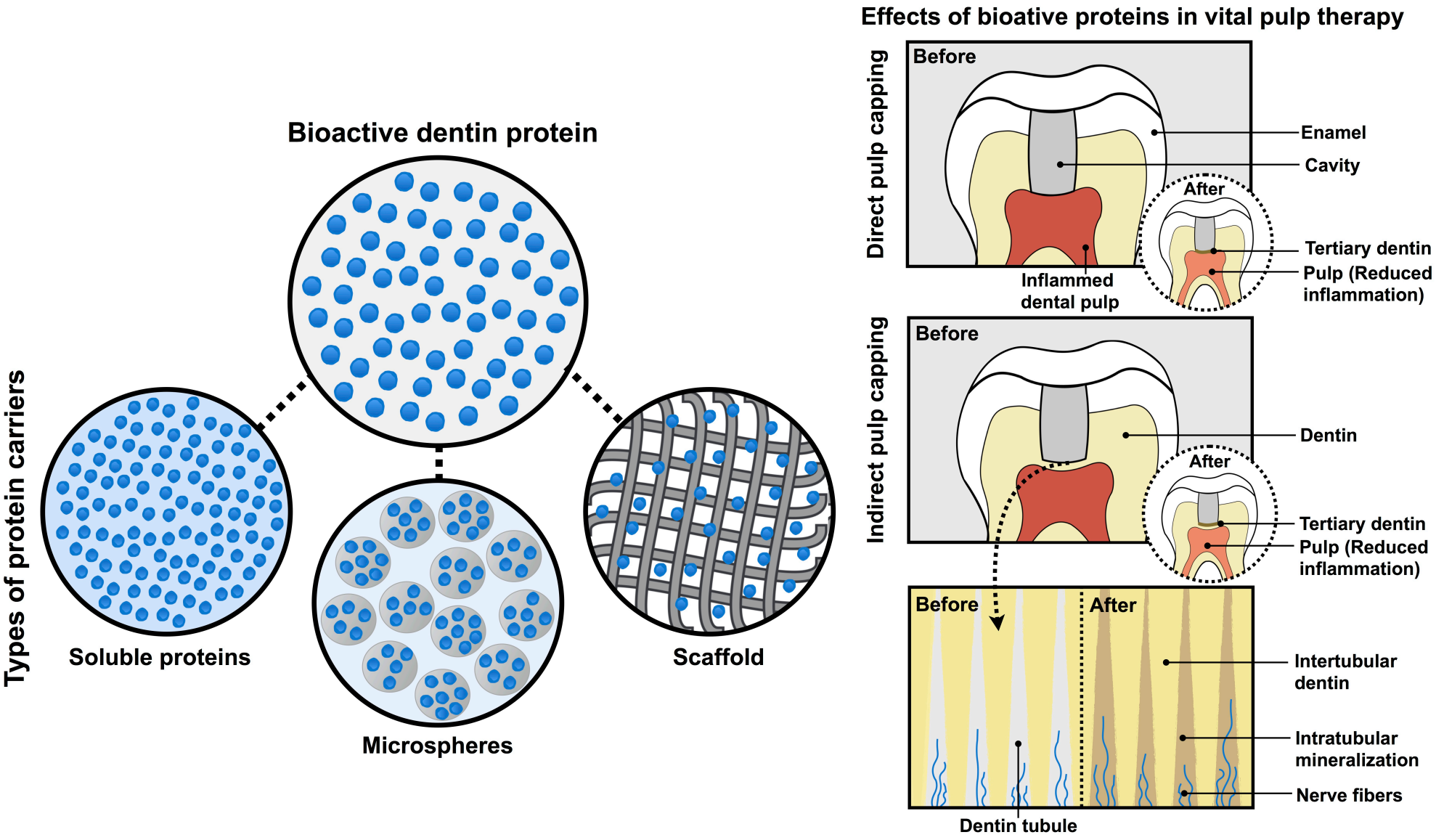

Fig. 3 - Representation of main carriers identified in the literature for bioactive dentin proteins and the main outcomes observed after their application in vital pulp therapy

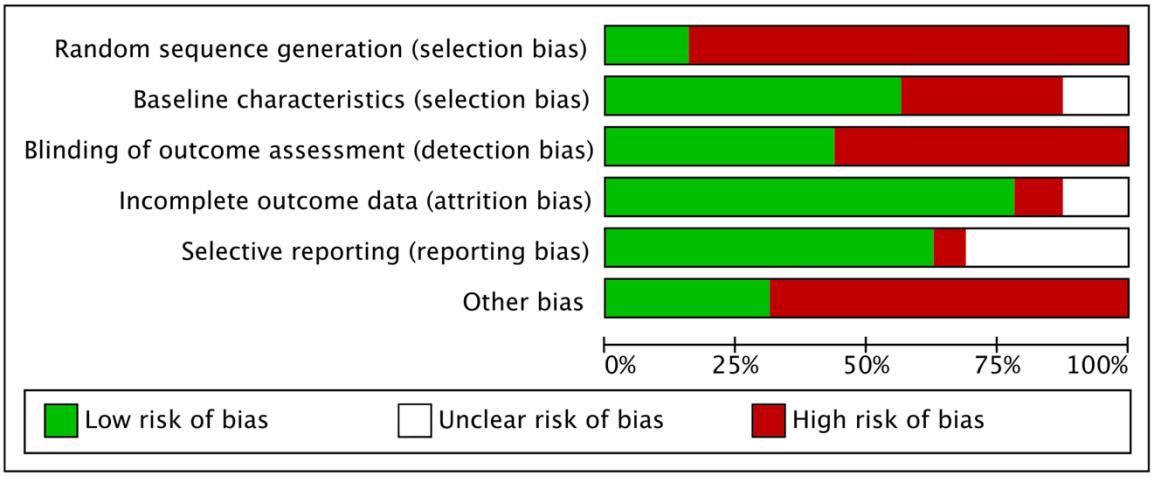

Fig. 4 - Review authors' judgements about each risk of bias item presented as percentages across all included studies

5 Considerações finais

Uma alteração na tendência do desenvolvimento de materiais para proteção pulpar foi observada nos últimos anos a partir da análise científico-tecnológica inicial. Anteriormente, essa área era dominada pelo cimento de hidróxido de cálcio e, mais recentemente, pelo mineral trióxido agregago (MTA). Contudo, os materiais derivados do MTA, como cimento de silicato de cálcio, aluminato de cálcio, fosfato de cálcio; bem como os materiais bioativos, têm ganhado atenção com a proposta de superar as desvantagens dos materiais tradicionais. Adicionalmente, foi demonstrado que o uso de moléculas bioativas poderia potencializar o efeito de formação de dentina terciária e mineralização intratubular. Contudo, os desafios de encontrar um biomaterial que potencialize os efeitos de reparo e regeneração tecidual, seja biocompatível e apresente custo-benefício ainda persistem. Além disso, os efeitos dessas proteínas variaram de acordo com diversos fatores, entre eles a dose de aplicação, o estágio de ativação, a taxa de liberação e o controle da temperatura. Tais dificuldades ainda precisam ser superadas para que seja possível explorar novas abordagens terapêuticas para variadas patologias orais, como cárie, reabsorção radicular, sensibilidade dentinária, entre outros. Dessa maneira, o uso de materiais bioativos poderá permitir promover uma resposta fisiológica induzida e programada em tratamentos para odontologia reparativa ou regenerativa.

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Apêndices

Apêndice A – Nota da Dissertação

Materiais dentários com propriedades bioativas

Dental materials with bioactive properties

A presente dissertação de mestrado visou analisar materiais para odontologia que estimulam processos de reparo ou regeneração dos dentes, bem como desenvolver novos materiais bioativos. A partir da análise de revisões sistemáticas foi possível obter um panorama do atual estado da arte e da técnica em tratamentos para polpa vital. Além disso, foi avaliado a eficácia do uso de proteínas dentinárias no processo de reparo dentinário, bem como os efeitos morfológicos da aplicação dessas moléculas para proteção do complexo dentino-pulpar de animais. A utilização de materiais bioativos pode permitir explorar tratamentos mais biológicos na odontologia com foco nos processos de reparo e regeneração do órgão dental.

Campo da pesquisa: Clínica Odontológica, Materiais Odontológicos.

Candidato: Wellington Luiz de Oliveira da Rosa, Cirurgião-dentista pela Universidade Federal de Pelotas (2014)

Data da defesa e horário: 29/02/2015 as 19h.

Local: Auditório do Programa de Pós-graduação em Odontologia da Universidade Federal de Pelotas. 5º andar da Faculdade de Odontologia de Pelotas. Rua Gonçalves Chaves, 457.

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Apêndice B – Súmula do currículo do candidato

Súmula do currículo

Wellington Luiz de Oliveira da Rosa nasceu em 19 de julho de 1989, em Tubarão, Santa Catarina, Brasil. Ingressou na Faculdade de Odontologia da Universidade Federal de Pelotas (UFPel) em 2009, tendo sido graduado cirugião-dentista em 2014. No mesmo ano ingressou no Mestrado do Programa de Pós-graduação em Odontologia da Universidade Federal de Pelotas (UFPel), área de concentração Dentística, sob orientação do Prof. Dr. Evandro Piva. Durante o período de graduação atuou como aluno de iniciação científica sob orientação do mesmo professor e da Prof[a]. Dr[a]. Adriana Fernades da Silva. Durante o período de mestrado foi bolsista do Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq) e trabalhou nas áreas de biologia celular e molecular, dentística restauradora e materiais dentários.

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Anexos

Anexo A – Carta de aprovação do Comitê de Ética em Pesquisa

MINISTÉRIO DA EDUCAÇÃO
UNIVERSIDADE FEDERAL DE PELOTAS
FACULDADE DE ODONTOLOGIA
COMITÊ DE ÉTICA EM PESQUISA

PELOTAS, 26 de maio de 2011.

PARECER Nº 203/2011

O projeto de pesquisa intitulado "**Avaliação da presença de TGF-β1 na dentina de dentes humanos permanentes hígidos**" está constituído de forma adequada, cumprindo, na suas plenitudes preceitos éticos estabelecidos por este Comitê e pela legislação vigente, recebendo, portanto, **PARECER FAVORÁVEL** à sua execução.

Prof.ª Marcos Antonio Torriani
Coordenador do CEP/FO/UFPel

Prof. Marcos A. Torriani
Coordenador
Comitê de Ética e Pesquisa