UNIVERSIDADE DE BRASÍLIA
Faculdade de Ciências de Saúde
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Dissertação de Mestrado

Current strategies for biomimetic remineralization of human dentin: a scoping review

Estratégias atuais para remineralização biomimética da dentina humana: uma revisão de escopo

Samantha Jéssica Lopes Sousa

Brasília, 18 de dezembro de 2020

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Dissertação apresentada ao Programa de Pós-Graduação em Odontologia da Faculdade de Ciências da Saúde da Universidade de Brasília, como requisito parcial à obtenção do título de Mestre em Odontologia.

Orientadora: Prof. Dra. Fernanda Cristina Pimentel Garcia

Brasília, 2020

Sa**mantha Jéssica Lopes Sousa**

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Banca examinadora:

_____

Prof. Dra. Fernanda Cristina Pimentel Garcia (Orientadora)

_____

Prof. Dr. Celso de Freitas Pedrosa Filho

_____

Prof. Dra. Liliana Vicente Melo de Lucas Rezende

Brasília, 2020

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“Entrega tudo pra ela que ela vai entregar
tudo a Jesus.”
Acaso não sabeis, Colo de Deus.

RESUMO

Os protocolos que imitam a mineralização natural da dentina, buscam restaurar os minerais perdidos nos tecidos dentais. A remineralização biomimética propõe diferentes formas de substituir o conteúdo mineral do substrato dentinário, utilizando os materiais inorgânicos semelhantes aos minerais naturais, com o objetivo principal de otimizar a longevidade clínica de restaurações e reabilitação dentária. O objetivo deste estudo é apresentar as estratégias bem sucedidas publicadas para a remineralização biomimética da dentina humana. Dois investigadores independentes realizaram a seleção e caracterização dos estudos. Foram incluídos estudos nos quais o objetivo principal era apresentar qualquer estratégia de remineralização biomimética da dentina. Nenhuma restrição de idioma ou de tempo foi estabelecida para as buscas. Estudos foram obtidos através das bases de dados CENTRAL, LILACS, PubMed / MEDLINE, SciELO, SCOPUS e Web of Science. Pesquisas da literatura cinzenta com o Google Scholar e OpenGrey também foram realizadas para encontrar referências adicionais. Com base nos objetivos principais da pesquisa, os artigos foram classificados de acordo com as estratégias de bioremineralização e a metodologia utilizada para a pesquisa. A composição química dos materiais utilizados nos artigos incluídos foi avaliada. Estes foram agrupados de acordo com os principais elementos químicos de sua constituição, e também em ácidos e outros componentes. Cento e quarenta e seis artigos foram incluídos na revisão de escopo final, publicados nos anos de 2003 a 2020. Conclui-se que a remineralização biomimética da dentina é uma área promissora para o desenvolvimento de novos materiais odontológicos. A ação remineralizante pode ser potencializada em materiais com características anti-incrustantes, antibacterianas e biocompatíveis, sem comprometer as propriedades mecânicas e adesivas.

Palavras-chave: Remineralização Dentária; Biomineralização; Dentina; Mimetismo Biológico; Biomimética; Materiais Dentários.

ABSTRACT

Protocols that imitate dentin's natural mineralization seek to restore lost minerals in dental tissues. Biomimetic remineralization proposes different ways to replace demineralized collagen in dentin, using the inorganic materials similar to natural minerals, with the primary purpose of optimizing the clinical longevity of restorations and dental rehabilitation treatments. The purpose of this study is to present the published successful strategies for biomimetic remineralization of human dentin. Two independent investigators performed the selection and characterization of the studies. Studies in which the primary objective was to present any successful dentin's biomimetic remineralization strategy were included. No language or time restrictions were set. Studies retrieved via CENTRAL, LILACS, PubMed/MEDLINE, SciELO, SCOPUS and Web of Science. Gray literature searches with Google Scholar and OpenGrey were also conducted to find additional reference. Based on the main research objectives, articles were classified according to the methodology used for research. The chemical composition of the materials used in the included articles was evaluated. They were grouped according to the main chemical elements of their constitution, and also in acids and other components. One hundred forty-six articles were included in the final scoping review, published from 2003 to 2020. Thus, biomimetic remineralization of dentin is a promising area for the development of new dental materials. The remineralizing action can be enhanced in materials with anti-fouling, antibacterial and biocompatible characteristics, without compromising mechanical and adhesive properties.

Keywords: Tooth Remineralization; Biomineralization; Dentin; Biological Mimicry; Biomimetics; Dental Materials.

LIST OF FRAMES

LIST OF ILLUSTRATIONS

LIST OF TABLES

LIST OF ABBREVIATIONS AND ACRONYMS

4-METCa—Salt calcium salt of 4-methacryloxyethyl trimellitate;

aCa-polyP-MP—Amorphous Ca-polyP microparticles;

ACP— Amorphous calcium phosphate;

AMF—Amine fluoride;

BMC—Bioactive multifunctional composite;

CCMS-HP—Silica mesoporous with phosphoric acid;

CMC/ACP—Carboxymethyl chitosan/amorphous calcium phosphate;

CPP-ACP—Casein phosphopeptide-amorphous calcium phosphate;

CR—Curodont Repair™;

DMADDM—Dimethylaminododecyl methacrylate;

DMP—Dentin matrix protein;

DPP—Dentin phosphophoryn;

EDC-HCl—Carbodiimide hydrochloride;

EDTA—Ethylenediaminetetraacetic acid;

EMD—Enamel matrix derivatives;

L-Glu—L-Glutamic acid;

MP—Mi Paste™;

MTA—Mineral trioxide aggregate;

NaF – Sodium fluoride;

NCPs—Non-collagenous proteins;

NPG—Niobium–phosphate bioactive glass;

PAA—Polyacrylic acid;

PAC—Proanthocyanidin;

PAMAM—Poly(amidoamine) dendrimer;

PA—Phosphoric acid;

pAsp—Poly-aspartic acid;

PBS—Phosphate-buffered saline;

P-chi—Phosphorylated chitosan;

PILP—Polymer-Induced Liquid-Precursor;

PVPA—Polyvinylphosphonic acid;

RMGI—Resin modified glass ionomer;

SBF—Simulated body fluid;

SDF—Silver diamine fluoride;

S-PRG—Surface reaction-type pre-reacted glass-ionomer;

STMP—Sodium trimetaphosphate;

STPP—Sodium tripolyphosphate;

TCS—Tricalcium silicate;

TPP—Tripolyphosphate;

TTCP—Tetracalcium phosphate;

ZrO2—Zirconium oxide.

SUMMARY

1 INTRODUCTION

Consistent with current health science trends to seek regenerative therapies which mimic the body's innate biological processes, several strategies have been developed to recover lost dental tissue. The mineral replacement in type I collagen is critical for recovering the mechanical properties of calcified tissues such as dentin. In dentin, nearly 90% of the organic content is composed of type I collagen, whereas non-collagenous proteins account for 10% of its content (Zurick, Qin & Bernards, 2013). These non-collagenous proteins play a key role in the mineralization process, as their components are highly anionic, phosphorylated and multifunctional (Veis & Dorvee, 2013).

However, the remineralization of dentin appears more challenging than of enamel because of the greater scarcity of apatite particles in dentin (Bertassoni *et al.*, 2009). Different strategies have been applied to the remineralization of dentin, and a recent systematic review has presented some methods used (Cao *et al.*, 2015). Biomineralization is a biological process based on a matrix particle-mediated, non-classical and organic crystallization (Cao *et al.*, 2014a). Extracellular matrix proteins execute an essential function in apatite nucleation growth and control for the process of dentin remineralization (Nudelman *et al.*, 2013). Some materials have been proposed for restoring demineralized dentin by inducing remineralization.

A common classification used for remineralization techniques with biomaterials is called “top-down” or “bottom-up” strategies. The top-down approach involves free particles of biomaterials responsible for incorporating minerals over crystallites in collagen, at nanoscale level (Braga & Fronza, 2020). In this group, the ions involving calcium, phosphate and sodium are incorporated into gels or in recently developed materials. However, for these techniques, there is a need to deposit the non-collagenous protein analogs (NCPs) already mentioned for growth from already existing primers, since there will be no spontaneous nucleation.

The bottom-up approach uses matrix protein biomimetic analogs to stabilize nanoprecursors, starting from organized materials forming a template or scaffold (Cao *et al.*, 2015; Braga & Fronza, 2020). It is considered a “non-classical” pathway technique and is based on the importance of the dentin's intrafibrillary mineral zones

(Cao *et al.*, 2015). The term "biomimetic" usually refers to the use of analogues to guide mineral deposition, therefore, mimicking the biological process. "Top-down" approaches, for instance, are usually not considered biomimetic. These play a fundamental role in biomechanics by making use of the partially or totally dissolved minerals in these areas to create large gaps. Therefore, in these situations, with the presence of NCP analogs, the free calcium and phosphate ions assemble in groups considered pre-enucleation and are added to the ACP nanoprecursors recruited by the NCPs. They then fill the intrafibrillary gaps, stimulating the growth of regular apatites in the mineralization process. Therefore, this strategy includes biomimetic analogs and results in the primordial formation of amorphous ACP nanoprecursors.

Partial caries removal in procedures of minimally intervention are used clinically to save the tooth structure and prevent damage to pulp. The infected dentin is removed and partially demineralized dentin is sealed with materials that enhance remineralization. The glass ionomer cement has been known to be used for this purpose. Furthermore, studies have demonstrated a potential other bioactive cements and adhesives which promote dentin repair through other strategies including ion release Ca-P, biomimetic remineralization tissue-guided, and others (Hernández, Cobb & Swift, 2014).

Techniques that advocates the use of biomimetic analogues to promote remineralization of dentine appears as a promising approach. The objective of this review is to outline an scoping review of current bioactive strategies of remineralization of dentin.

1.1 JUSTIFICATION

Protocols that imitate the natural mineralization of dentin seek to restore minerals in dental tissues that are lost mainly because of caries. Biomimetic remineralization proposes different ways to replace demineralized collagen in dentin by using inorganic materials similar to natural minerals (Cao *et al.*, 2015; Niu *et al.*, 2014). Thus, preventive and operative dentistry researchers have sought to discover methods to induce the remineralization of hypomineralized human dental tissues, especially dentin (Braga & Fronza, 2020).

The last review papers on the similar subject were published between 2014 and 2015 (Niu *et al.*, 2014; Cao *et al.*, 2015). These studies included a smaller number of articles in the discussion and do not have the same study design, being a systematic review (Cao *et al.*, 2015) and a narrative review (Niu *et al.*, 2014), which justifies an update in the discussion about the subject in a scoping review.

1.2 OBJECTIVES

1.2.1 GENERAL OBJECTIVE

The purpose of this scoping review was to present all the published successful strategies for biomimetic remineralization of human dentin.

1.2.2 SPECIFIC OBJECTIVES

Compile all existing strategies that have obtained positive results for dentin remineralization;

Dismember the composition of the materials currently used for this purpose;

Discuss the mechanisms of action based on their chemical formulation, to suggest new materials.

2 MATERIAL AND METHODS

The reporting of this scoping review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) Checklist (Tricco *et al.*, 2018), detailed in Annex 1.

2.1 PROTOCOL AND REGISTRATION

The scoping review protocol was registered at the International Prospective Register of Systematic Reviews (PROSPERO) in association with the systematic review of registration number CRD42016049821. The final protocol was registered prospectively with the Open Science Framework on 21 December 2020 (https://osf.io/5c3vm/).

2.2 ELIGIBILITY CRITERIA

Studies in which the primary objective was to present any successful biomimetic remineralization strategy for dentin were included. No language or time restrictions were set.

Articles were excluded for the following reasons: (1) articles that did not address a remineralizing strategy based on processes that mimic natural biomineralization; (2) articles that were not research studies, including letters, conference abstracts, personal opinions, book chapters, theses, congress proceedings, case reports or case series.

The “PCC” mnemonic (population, concept and context) was used as a guide to construct a clear and meaningful title and strategy search for this review, according to Frame 1.

Frame 1 - . The PCC (population, concept and context) mnemonic of this scoping review.

Mnemonic	**Refers to**
P (population)	Dentin OR Dentine
C (concept)	(Remineralization OR mineralization OR biomineralization OR mineralizing OR remineralisation OR mineralisation OR biomineralisation OR mineralising) AND (biomimetic OR mimetic OR mimetism OR "biological mimetism" OR biomimetism)
C (context)	All published strategies and your mechanical performance

2.3 INFORMATION SOURCES

Electronic searching in databases, namely, CENTRAL, LILACS, PubMed/MEDLINE, SciELO, SCOPUS and Web of Science, identified relevant studies. Non peer-reviewed literature searches with Google Scholar and OpenGrey were also conducted to find additional references. No language, time or other restrictions were set.

After obtaining all references, duplicates were excluded by using an appropriate software program (EndNote Web®, Thomson Reuters, USA and Rayyan®, QCRI, Qatar). All the electronic database searches were conducted for the last time on January 1st, 2020.

2.4 SEARCH

Studies were identified by using a search strategy adapted for each electronic database with the aid of a health sciences librarian. A non peer-reviewed literature search was performed by screening the title and abstracts for the first 150 hits (filtered by “relevance”). In addition, a hand search was performed on the reference lists from the selected articles for any additional references that might have been omitted in the electronic search. Search strategies performed on all databases are described in Frame 2. Non peer-reviewed literature searches strategies performed on GoogleScholar and OpenGrey are described in Frame 3.

Frame 2 - Search strategies performed on databases COCHRANE CENTRAL, LILACS, PUBMED, SCIELO, SCOPUS, and WEB OF SCIENCE (up to January 1st, 2020).

COCHRANE CENTRAL		
Conditions	**Search Strategy**	**Results**
Search All Text	(("bond strength" OR "bond-strength" OR durability OR "mechanical properties" OR "mechanical properties" OR bond OR bonded OR bonding) AND (remineralization OR mineralization OR biomineralization OR mineralizing OR remineralisation OR mineralisation OR biomineralisation OR mineralising) AND (dentine OR dentin)) OR ((biomimetic OR mimetic OR mimetism OR "biological mimetism" OR biomimetism) AND (dentine OR dentin))	81
LILACS		
Conditions	**Search Strategy**	**Results**
Title, abstract, subject	(tw:((tw:((tw:(biomimetic OR mimetic OR mimetism OR "biological mimetism" OR biomimetism)) AND (tw:((dentin OR dentine))))))) OR (tw:((tw:(remineralization OR mineralization OR biomineralization OR mineralizing OR remineralisation OR mineralisation OR biomineralisation OR mineralising)) AND (tw:(dentine OR dentin)) AND (tw:("bond strength" OR "bond-strength" OR durability OR "mechanical properties" OR "mechanical properties" OR bond OR bonded OR bonding))))	610
Title, abstract, subject	(tw:((tw:(biomimetic OR mimetic OR mimetism OR "biological mimetism" OR biomimetism)) AND (tw:((dentin OR dentine)))))	277
Title, abstract, subject	(tw:(remineralization OR mineralization OR biomineralization OR mineralizing OR remineralisation OR mineralisation OR biomineralisation OR mineralising)) AND (tw:(dentine OR dentin)) AND (tw:("bond strength" OR "bond-strength" OR durability OR "mechanical properties" OR "mechanical properties" OR bond OR bonded OR bonding))	386

PUBMED		
Condtions	**Search Strategy**	**Results**
All fields	(((remineralization OR mineralization OR biomineralization OR mineralizing OR remineralisation OR mineralisation OR biomineralisation OR mineralising) AND (dentine OR dentin) AND ("bond strength" OR "bond-strength" OR durability OR "mechanical properties" OR "mechanical properties" OR bond OR bonded OR bonding))) OR ((biomimetic OR mimetic OR mimetism OR "biological mimetism" OR biomimetism) AND (dentin OR dentine))	563
All fields	("bond strength" OR "bond-strength" OR durability OR "mechanical properties" OR "mechanical properties" OR bond OR bonded OR bonding)	357,361
All fields	(biomimetic OR mimetic OR mimetism OR "biological mimetism" OR biomimetism)	40,190
All fields	(dentine OR dentin)	36,524
All fields	(remineralization OR mineralization OR biomineralization OR mineralizing OR remineralisation OR mineralisation OR biomineralisation OR mineralising)	92,092
SCIELO		
Searches	**Search Strategy**	**Results**
#7	#6 OR #5	9
#6	#4 AND #3	4
#5	#4 AND #2 AND #1	7
#4	TS=(dentine OR dentin)	930
#3	TS=(biomimetic OR mimetic OR mimetism OR "biological mimetism" OR biomimetism)	240
#2	TS=("bond strength" OR "bond-strength" OR durability OR "mechanical properties" OR "mechanical properties" OR bond OR bonded OR bonding)	7,678
#1	TS=(remineralization OR mineralization OR biomineralization OR mineralizing OR remineralisation OR mineralisation OR biomineralisation OR mineralising)	1,461

SCOPUS		
	Search Strategy	**Results**
	ALL(remineralization OR mineralization OR biomineralization OR mineralizing OR remineralisation OR mineralisation OR biomineralisation OR mineralising) AND ALL("bond strength" OR "bond-strength" OR durability OR "mechanical properties" OR "mechanical properties" OR bond OR bonded OR bonding) AND ALL(dentine OR dentin) AND ALL(biomimetic OR mimetic OR mimetism OR "biological mimetism" OR biomimetism)	1,844
WEB OF SCIENCE		
Searches	**Search Strategy**	**Results**
#7	#6 OR #5	837
#6	#4 AND #3	314
#5	#4 AND #2 AND #1	612
#4	TS=(dentine OR dentin)	30,729
#3	TS=(biomimetic OR mimetic OR mimetism OR "biological mimetism" OR biomimetism)	53,814
#2	TS=("bond strength" OR "bond-strength" OR durability OR "mechanical properties" OR "mechanical properties" OR bond OR bonded OR bonding)	1,400,795
#1	TS=(remineralization OR mineralization OR biomineralization OR mineralizing OR remineralisation OR mineralisation OR biomineralisation OR mineralising)	124,812

Frame 3 - Search strategies performed on gray literature with GOOGLE SCHOLAR, and OPEN GRAY (up to January 1st, 2020).

GRAY LITERATURE		
GOOGLE SCHOLAR		
Conditions	**Search Strategy**	**Results**
Any time Sort by relevance Include patents Include citations	((remineralization OR mineralization OR biomineralization OR mineralizing OR remineralisation OR mineralisation OR biomineralisation OR mineralising) OR (biomimetic OR mimetic OR mimetism OR "biological mimetism" OR biomimetism)) AND (dentin OR dentine)	44,700
OPEN GREY		
Conditions	**Search Strategy**	**Results**
Any time	(remineralization OR mineralization OR biomineralization OR mineralizing OR remineralisation OR mineralisation OR biomineralisation OR mineralizing) AND dentistry	46

2.5 SELECTION OF SOURCES EVIDENCE

The study selection was conducted in three phases. In phase 1, two investigators (S. J. L. S. and P. F. A.) independently screened the titles of potentially relevant studies and selected articles that appeared to meet the inclusion criteria. In phase 2, the same reviewers independently read the abstracts of all previously selected articles. In phase 3, the two investigators independently read the full text of all selected articles and excluded studies that did not meet the inclusion criteria.

Any disagreements in any of the three phases were resolved by discussion and mutual agreement between the two reviewers. If a consensus could not be reached, a third author (F. S. N.) was involved in making a final decision.

2.6 DATA CHARTING PROCESS AND DATA ITEMS

The first investigator (S. J. L. S.) collected the following data from the selected articles: study characteristics (author(s), year, country and type of study), design (approach or protocol tested) and results characteristics (objectives, main results and conclusions). The second author (P. F. A.) checked all the retrieved information for analysis. If the required data were not complete, attempts were made to contact the authors to retrieve any pertinent missing information.

2.7 SYNTHESIS OF RESULTS

Based on the main research objectives, articles were classified by their strategies according to the methodology used for research. Authors and year of publication were used to categorize the included studies. The methodological characteristics were analyzed and grouped according to similarity. All findings in this review are based on published research, as listed in the references.

3 RESULTS

3.1 SELECTION OF SOURCES OF EVIDENCE

In phase 1 of the study selection, 3,944 citations were identified across six electronic databases. The non peer-reviewed literature results added 196 references; 44,700 citations were identified on Google Scholar, but only 150 citations were considered for analysis (filtered by “relevance”) with 46 results identified by OpenGrey. After the duplicated articles were removed, 3,009 citations remained. In the first phase, 2,728 articles were excluded by the title. A thorough screening of 281 abstracts was conducted, and 146 references were excluded in phase 2. The hand search from the reference lists of the identified studies yielded 10 additional studies. Finally, 145 studies satisfied the inclusion criteria and remained for phase 3 after full-text reading and were selected for this review.

Seven authors were contacted to send some relevant information about their study. Two authors responded with some informations after contact by email and ResearchGate. Another five authors did not respond. Figure 1 details the process of identification, inclusion and exclusion of studies.

A qualitative analysis was performed, in a descriptive manner. A meta-analysis and the risk of bias analysis were not foreseen, as it is a scoping review. The types of studies included were diverse, including *In-vitro*, *Ex-vivo* and *In-vivo* studies. Due to the heterogeneity of the included studies, studies were grouped by material similarity.

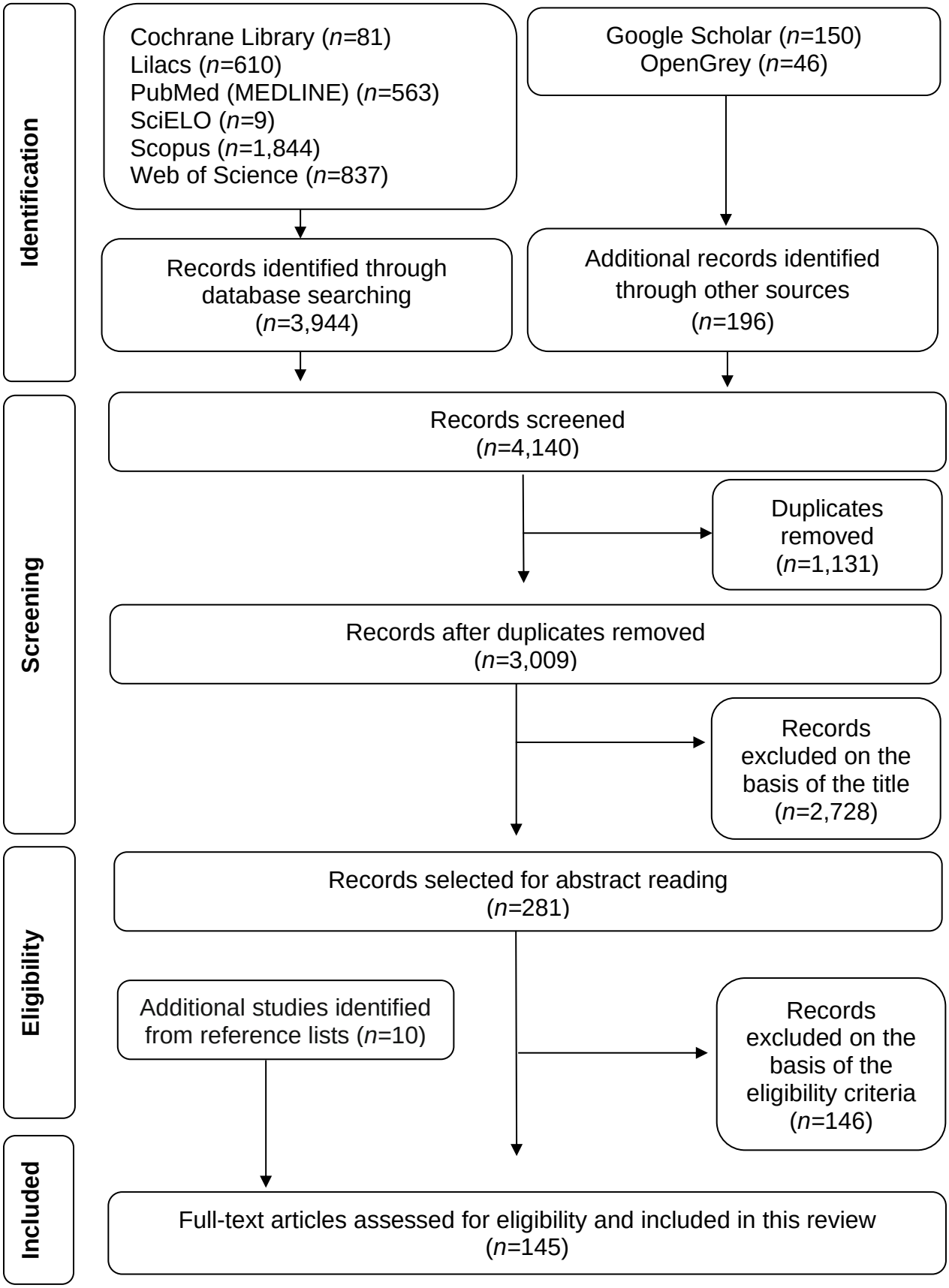

Figure 1 - Flow diagram of literature search and selection criteria according to PRISMA Statement.

3.2 CHARACTERISTICS OF SOURCES OF EVIDENCE

Searches identified studies from 2003 to 2020. Figure 2 shows the global overview of the countries included in this scoping review.

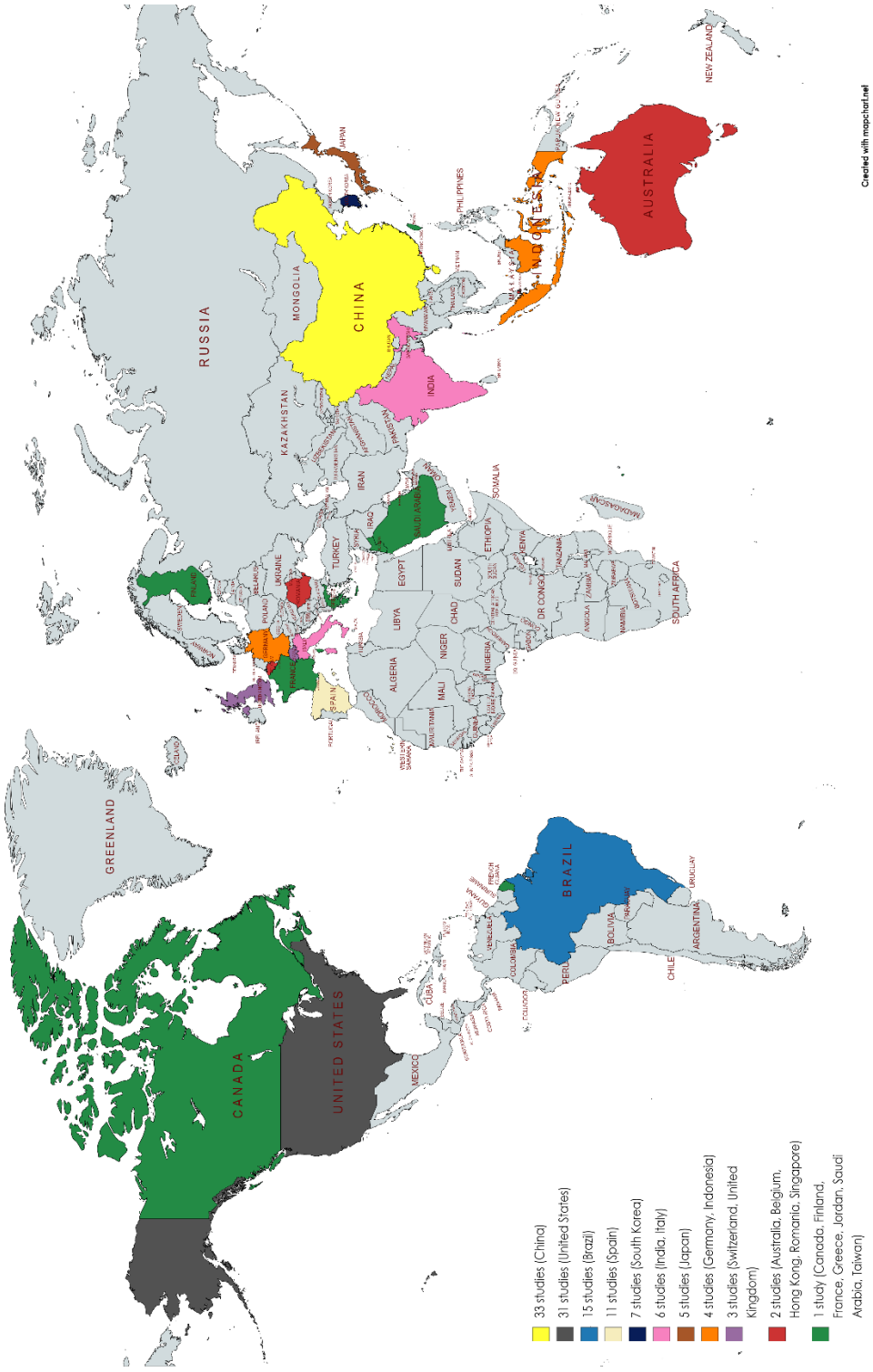

Figure 2 - Countries originating from publications included in this review.

Table 1 summarizes the characteristics of the strategies of the included studies. The data were grouped into products using chemical elements to dentin remineralization (Figure 3), products derived from acids (Figure 4) and other diverse compounds (Figure 5).

Table 1 - Strategic characteristics of all the included studies, grouped by chemical elements, acids and other compounds.

Product	References	
Calcium	1, 5, 7, 9, 17, 18, 19, 33, 35, 36, 39, 41, 44, 48, 49, 50, 52, 53, 59, 61, 68, 69, 70, 71, 74, 76, 77, 81, 82, 86, 90, 91, 92, 93, 95, 97, 98, 100, 101, 102, 103, 107, 110, 111, 115, 116, 118, 119, 123, 130, 131, 139, 141	**Chemical elements**
Silica	5, 9, 17, 18, 29, 35, 39, 41, 65, 68, 69, 74, 76, 77, 81, 82, 92, 93, 97, 98, 100, 101, 102, 103, 107, 110, 111, 115, 116, 118, 119, 139, 141	
Phosphate	1, 14, 17, 18, 19, 26, 33, 36, 44, 46, 47, 48, 49, 50, 52, 53, 59, 61, 70, 71, 81, 86, 90, 92, 93, 95, 98, 100, 107, 109, 122, 123, 130, 132, 139, 142	
Sodium	1, 12, 13, 16, 26, 44, 46, 47, 48, 49, 81, 90, 92, 93, 98, 107, 142	
Hydroxide	7	
Chloride	2, 16, 26, 57	
Tin	16	
Zinc	80, 90, 91, 92, 93, 121, 122, 123	
Zirconium	74, 115	
Aluminum	41	
Fluoride	10, 12, 13, 16, 22, 36, 37, 44, 55, 84, 85, 108	
Carbonate	2, 29, 50	
Niobium	14	
Copper	64	
Amina/Ammonia	2, 10, 16, 22, 50, 84, 85	
Potassium	22	
Iodide	22	
Silver	22, 84, 85	
Nitride	32	
Boron	32	
Lithium	57	
Tantalum	43	

Product	References	
PAA (PolyAcrylic Acid)	1, 41, 48, 49, 50, 68, 76, 77, 81, 82, 83, 98, 109, 114, 118, 119, 126, 128	**Acids**
PVPA (Polyvinylphosphonic Acid)	50, 68, 69, 76, 82, 83, 118, 119	
pAsp (Polyaspartic Acid)	11, 21, 87, 90, 105, 107, 109, 120, 131	
L-Glu (Glutamic Acid)	114	
EDTA (Ethylenediaminetetraacetic Acid)	40, 124	
Citric Acid	40	
Hydroxyapatite (calcium/phosphate)	17, 18, 44, 52, 71, 123	**Other compounds**
Glass Ionomer	7, 9, 11, 56, 88, 110	
Bioactive glass	14, 15, 30, 31, 34, 38, 52, 60, 64, 110, 125, 129, 133, 143, 145	
PILP (polymer-induced liquid-precursor)	21, 87, 105, 108, 109, 120	
Chitosan	8, 16, 54, 106, 137, 138, 140	
Biomimetic analogs and/or synthetic peptides	2, 10, 12, 13, 25, 51, 59, 68, 76, 80, 94, 112, 127	
EMD/DMP (Enamel Matrix Derivates or Dentin Matrix Protein)	10, 25, 80, 94, 127	
CPP/ACP	3, 4, 8, 12, 13, 23, 26, 36, 55, 63, 70, 72, 75, 96, 99, 106, 126, 130, 131, 132	
Chlorhexidine	23, 58, 66, 67, 70, 122	
Natural extract	2, 6, 19, 20, 22, 27, 36, 37, 58, 63, 77, 78, 79, 104, 113, 117, 136	
PAMAM (Polyamidoamine dendrimer)	42, 45, 62, 73, 75, 128, 132, 134, 135, 144, 145	
Agarose	24, 53, 86, 140	
Methacrylate	32, 41, 45, 59, 72	
Glutaraldehyde	28	

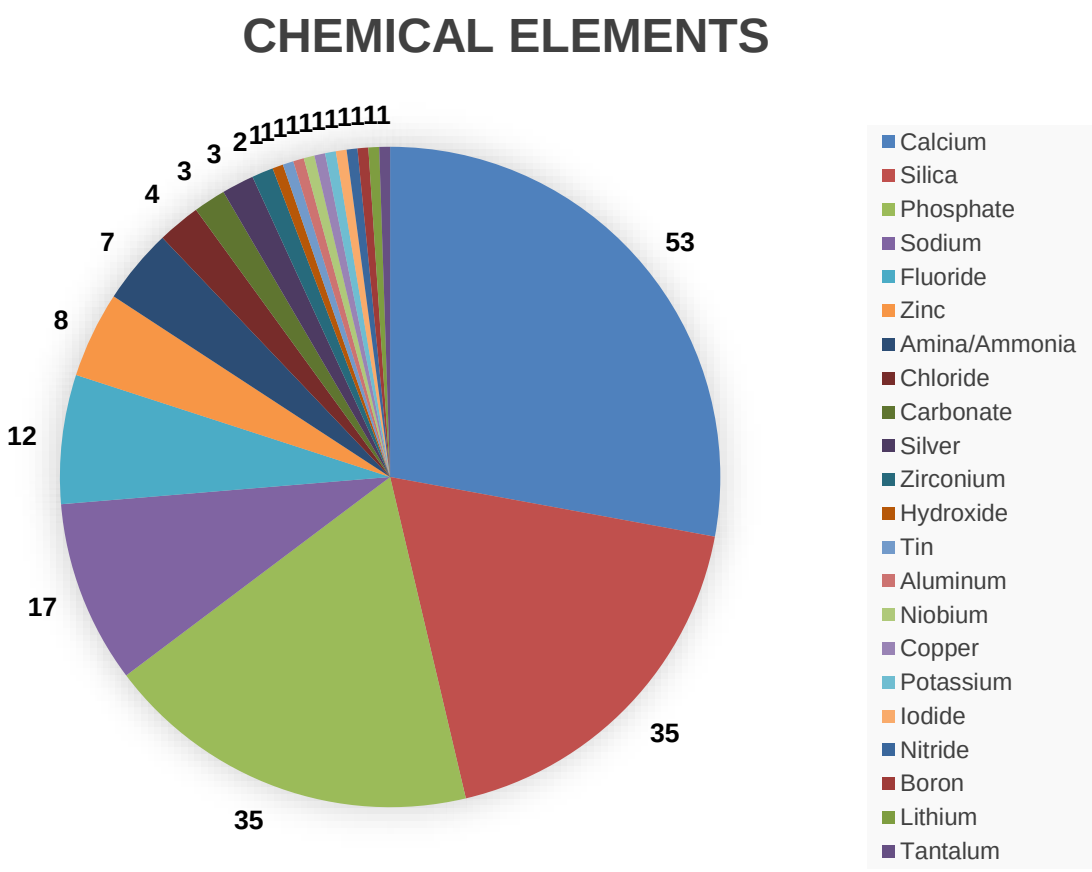

Figure 3 - Categorization graph of the chemical elements or ions used for dentin remineralization, with the number of studies that report strategies using each one.

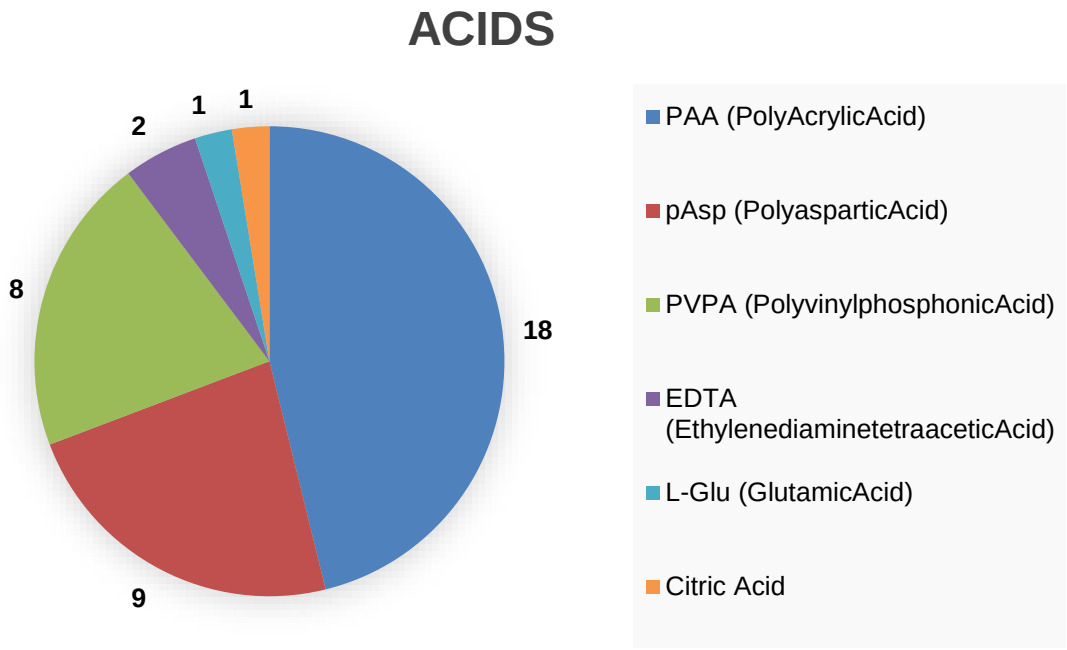

Figure 4 - Categorization graph of the acids used for dentin remineralization, with the number of studies that report strategies using each one.

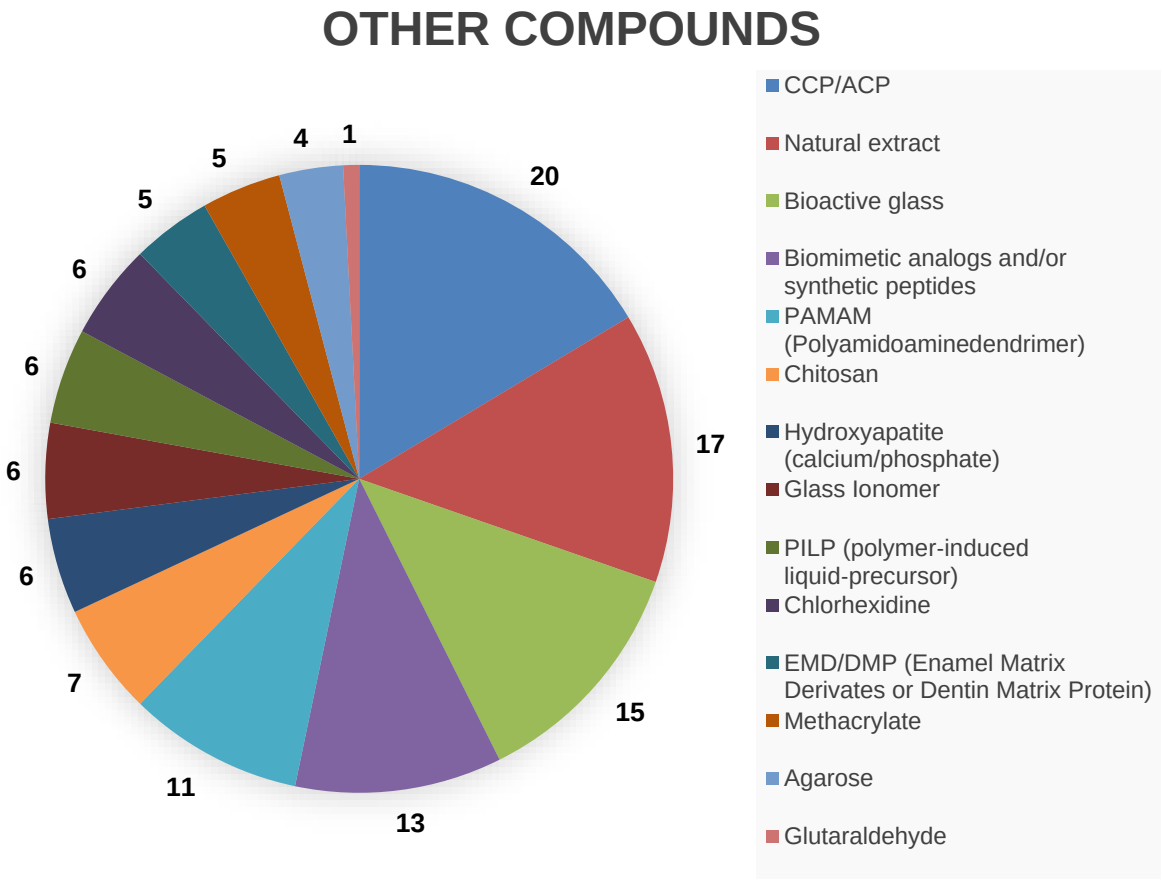

Figure 5 - Categorization graph of the other compounds used for dentin remineralization, with the number of studies that report strategies using each one.

3.3 RESULTS OF INDIVIDUAL SOURCES OF EVIDENCE

Each strategy used with different products and the strategic sources used are described in Table 2.

Table 2 Strategic sources and materials of included articles.

Code	Author	Year	Strategy
1	Abuna *et al.*	2016	Experimental calcium phosphate-based adhesive, PAA, STMP.
2	Abunawareg *et al.*	2017	Natural extract (riboflavin), UV, EDC-HCl
3	Ackermann *et al.*	2019	aCa-polyP-MP-dentifrice

Code	Author	Year	Strategy
4	Adebayo, Burrow & Tyas	2010	CPP-ACP
5	Aggarwal & Bhasin	2018	Calcium silicate materials (CSM) after acid etching
6	Aguiar *et al.*	2014	PAC, Natural extract
7	Al-Abdi, Paris & Schwendicke	2017	Glass Hybrid
8	Annisa *et al.*	2019	p-Chi, CMC/ACP
9	Atmeh *et al.*	2015	Calcium-silicate cement, cement Biodentine(TM) and Glass Ionomer
10	Bachli *et al.*	2019	DMP/EMD, AMF
11	Bacino *et al.*	2019	PILP, pAsp, RMGI
12	Barbosa-Martins *et al.*	2018a	NaF, MP™ e CR™
13	Barbosa-Martins *et al.*	2018b	NaF, CPP-ACP, New peptide
14	Bauer *et al.*	2016	NPG
15	Bauer *et al.*	2019	Bioactive glass
16	Beltrame *et al.*	2018	PBS, AMF/NaF/SnCl2, Chi, p-Chi
17	Besinis, Van Noort & Martin	2014	Silica and hydroxyapatite nanoparticles
18	Besinis, Van Noort & Martin	2012	Silica and hydroxyapatite nanoparticles
19	Bortolotto *et al.*	2017	Riboflavin, Calcium-phosphate based product
20	Boteon *et al.*	2017	PAC, Natural extract
21	Burwell *et al.*	2012	PILP, pAsp
22	Cai *et al.*	2019	PAC, Natural extract, Fluoride based treatment, Silver diamine fluoride
23	Cai *et al.*	2017	Chlorhexidine, ACP
24	Cao & Li	2016	Agarose
25	Cao *et al.*	2014b	DMP1-derived peptides
26	Cao *et al.*	2013	CPP-ACP, STMP

Code	Author	Year	Strategy
27	Castellan *et al.*	2011	PAC, Natural extract
28	Chen *et al.*	2016	Glutaraldehyde
29	Chiang *et al.*	2014	CCMS-HP
30	De Caluwé *et al.*	2017	Bioactive glass
31	De Morais *et al.*	2018	Bioactive glass
32	Degrazia *et al.*	2018	Methacrylate-based adhesive containing boron nitride nanotubes
33	Dickens, Flaim & Takagi	2003	Calcium-phosphate cement
34	D'Onofrio *et al.*	2016	Bioactive glass
35	Dreger *et al.*	2012	MTA, Portland cement
36	Epasinghe, Yiu & Burrow	2016	PAC, Natural extract, Fluoride, CPP-ACP
37	Epasinghe *et al.*	2017	PAC, Natural extract, Fluoride
38	Forsback, Areva & Salonen	2004	Bioactive glass, SBF
39	Gandolfi *et al.*	2009	Calcium-silicate cements
40	Gandolfi *et al.*	2019	EDTA, Citric Acid, SBF
41	Gandolfi *et al.*	2011	Calcium-silicate cement, Portland cement
42	Gao *et al.*	2017	PAMAM
43	Garcia *et al.*	2018	Tantalum oxide
44	Gavrila *et al.*	2016	Artificial saliva, Fluoride, Hydroxiapatite particles
45	Ge *et al.*	2017	PAMAM, DMADDM
46	Gonçalves *et al.*	2018a	STMP
47	Gonçalves *et al.*	2018b	STMP
48	Gu *et al.*	2011a	Portland cement, PAA, STMP
49	Gu *et al.*	2010	Portland cement, PAA, STMP
50	Gu *et al.*	2011b	Portland cement, PVPA, PAA
51	Guentsch *et al.*	2019	Experimental biomimetic mineralization kit (BIMIN)

Code	Author	Year	Strategy
52	Gupta *et al.*	2017	Bioactive glass, Hydroxyapatite nanoparticles
53	Han *et al.*	2017	Agarose gel
54	Huang *et al.*	2019	p-Chi
55	Iafisco *et al.*	2018	Fluoride, ACP
56	Iijima *et al.*	2019	S-PRG
57	Ishimoto *et al.*	2015	Lithium chloride
58	Islam *et al.*	2012	Hesperidin, Chlorhexidine, Natural extract
59	Ito *et al.*	2012	Phosvitin and CEMET (4-METCa salt)
60	Jang *et al.*	2018	Bioactive glass
61	Jayasree *et al.*	2017	Tetracalcium phosphate cement
62	Jia *et al.*	2014	PAMAM
63	Jose, Sanjeev & Sekar	2016	CPP-ACP, Natural extract
64	Jun *et al.*	2018	Bioactive glass, Copper
65	Jung *et al.*	2019	Bioactive glass, Silica nanoparticles
66	Kim *et al.*	2011	Chlorhexidine
67	Kim *et al.*	2012	Chlorhexidine
68	Kim *et al.*	2010a	Portland cement, PAA, PVPA
69	Kim *et al.*	2010b	Portland cement, PVPA
70	Kovtun *et al.*	2012	ACP, Chlorhexidine
71	Kutsch, Chaiyabutr & Milicich	2013	Hydroxyapatite nanoparticles
72	Li *et al.*	2014	DMADDM, ACP
73	Li *et al.*	2013	PAMAM
74	Li *et al.*	2017	Tricalcium silicate, zirconium oxide
75	Liang *et al.*	2019	ACP, PAMAM
76	Lin *et al.*	2016	Portland cement, PVPA, PAA
77	Liu *et al.*	2014	PAC, Natural extract
78	Liu *et al.*	2012	PAC, Natural extract

Code	Author	Year	Strategy
79	Liu *et al.*	2011a	PAC, Natural extract
80	Liu *et al.*	2013	DMP1-derived peptides
81	Liu *et al.*	2011b	PAA, Portland cement, STMP
82	Liu *et al.*	2011c	Portland cement, PAA, PVPA
83	Mai *et al.*	2009	PVPA, PAA
84	Mei *et al.*	2017	SDF
85	Mei *et al.*	2014	SDF
86	Ning *et al.*	2012	Agarose gel, Calcium, Phosphate
87	Nurrohman *et al.*	2016	PILP, pAsp
88	Okuyama *et al.*	2016	S-PRG
89	Osorio *et al.*	2014a	Zinc
90	Osorio *et al.*	2016a	Zinc, Portland cement, pAsp, STMP
91	Osorio *et al.*	2016b	Zinc-loaded nanoparticles, Calcium-loaded nanoparticles
92	Osorio *et al.*	2018	Zinc, Silica, Calcium, Sodium, Phosphate
93	Osorio *et al.*	2014b	Zinc, Calcium-silicate cement
94	Padovano *et al.*	2015	DMP1-derived peptides
95	Peters *et al.*	2010	Calcium-phosphate cement
96	Poggio *et al.*	2013	CPP-ACP
97	Pratiwi, Meidyawati & Djauharie	2017	MTA
98	Qi *et al.*	2012	MTA, PAA, STPP
99	Rahiotis & Vougiouklakis	2007	CPP-ACP
100	Revankar *et al.*	2017	MTA, Calcium phosphate cement
101	Reyes-Carmona, Felippe & Felippe	2009	MTA, Portland cement
102	Reyes-Carmona, Felippe & Felippe	2010	MTA, Portland cement

Code	Author	Year	Strategy
103	Reyes-Carmona *et al.*	2010	MTA
104	Rubel *et al.*	2016	PAC, Natural extract
105	Saeki *et al.*	2017	PILP, p-Asp
106	Santoso *et al.*	2019	ACP, p-Chi
107	Sauro *et al.*	2015	STMP, pAsp, Calcium-silicate cement
108	Saxena *et al.*	2018	Fluoride-dopped PILP
109	Saxena *et al.*	2019	PAA, pAsp, TPP, PILP
110	Schwendicke *et al.*	2019	Bioactive glass, Fluoride, Glass ionomer, MTA, Calcium-silicate cement
111	Seo *et al.*	2013	MTA
112	Sfeir *et al.*	2014	DPP-inspired peptides
113	Shi, Li & Wang	2015	Natural extract
114	Sun *et al.*	2014	PAA, L-Glu
115	Suprastiwi, Putranto & Maharti	2019	Biodentine™, Calcium-silicate cement, Zirconium
116	Taddei, Prati & Gandolfi	2017	Calcium-silicate cement
117	Tang *et al.*	2013	PAC, Natural extract
118	Tay & Pashley	2009	Portland cement, PVPA, PAA
119	Tay & Pashley	2008	Portland cement, PVPA, PAA
120	Thula-Mata *et al.*	2011	PILP, pAsp
121	Toledano *et al.*	2015	Zinc
122	Toledano *et al.*	2020	Chlorhexidine, Phosphate, Zinc
123	Toledano *et al.*	2018	EDTA
124	Toledano *et al.*	2014	Hydroxyapatite, Zinc
125	Vollenweider *et al.*	2007	Bioactive glass
126	Wang *et al.*	2013	CPP-ACP, PAA
127	Wang *et al.*	2011a	DMP1-derived peptides, synthetic peptides
128	Wang *et al.*	2015	PAMAM, PAA

Code	Author	Year	Strategy
129	Wang *et al.*	2011b	Bioactive glass
130	Weir *et al.*	2017	ACP, TTCP
131	Wu *et al.*	2017	ACP, pAsp
132	Xiao *et al.*	2017	BMC, PAMAM, ACP
133	Xie *et al.*	2008	Bioactive glass
134	Xie *et al.*	2015	PAMAM
135	Xie *et al.*	2016	PAMAM
136	Xie, Bedran-Russo & Wu	2008	PAC, Natural extract
137	Xu *et al.*	2011	p-Chi
138	Xun *et al.*	2014	p-Chi
139	Yoo *et al.*	2016	MTA
140	Zaharia *et al.*	2017	Agarose, p-Chi
141	Zanini *et al.*	2012	Biodentine™, Calcium silicate cement
142	Zhang *et al.*	2012	STMP
143	Zhang *et al.*	2019	Bioactive glass, Aminoacids
144	Zhou *et al.*	2014	PAMAM
145	Zhou *et al.*	2012	Polydopamine

Abbreviations: 4-METCa: Salt calcium salt of 4-methacryloxyethyl trimellitate, aCa-polyP-MP: Amorphous Ca-polyP microparticles, ACP: Amorphous calcium phosphate, AMF: Amine fluoride, BMC: Bioactive multifunctional composite, CCMS-HP: Silica mesoporous with phosphoric acid, CMC/ACP: Carboxymethyl chitosan/amorphous calcium phosphate, CPP-ACP: Casein phosphopeptide-amorphous calcium phosphate, CR: Curodont Repair™, DMADDM: Dimethylaminododecyl methacrylate, DMP: Dentin matrix protein, DPP: Dentin phosphophoryn, EDC-HCl: carbodiimide hydrochloride, EDTA: Ethylenediaminetetraacetic acid, EMD: enamel matrix derivatives; L-Glu: L-Glutamic acid, MP: Mi Paste™, MTA: Mineral trioxide aggregate, NaF: Sodium fluoride, NCPs: Non-collagenous proteins, NPG: Niobium–phosphate bioactive glass, PA: Phosphoric acid,PAA: Polyacrylic acid, PAC: Proanthocyanidin, PAMAM: Poly(amidoamine) dendrimer, pAsp: Poly-aspartic acid, PBS: Phosphate-buffered saline, P-chi: Phosphorylated chitosan, PILP: Polymer-Induced Liquid-Precursor, PVPA: Polyvinylphosphonic acid, RMGI: Resin modified glass ionomer, SBF: Simulated body fluid, SDF: Silver diamine fluoride, S-PRG: Surface reaction-type pre-reacted glass-ionomer, STMP: sodium trimetaphosphate, STPP: sodium tripolyphosphate, TCS: Tricalcium silicate, TPP: Tripolyphosphate, TTCP: Tetracalcium phosphate, ZrO_2: Zirconium oxide.

3.4 SYNTHESIS OF RESULTS

All the 145 selected studies were analyzed, and the data extracted. Materials can be classified according to method, activity, or composition. *In-vitro*, *In-vivo* and *Ex-vivo* studies was included. Regarding methods, those with remineralizing or regenerative activity. Which can be by the attraction of chemical modification, the addition of compound or particles or a combination. About activity/bioactives are those with bactericidal or antifouling activity. Also, combinations of these characteristics. Several studies are currently looking at strategies to turn restoratives materials into remineralizing, antimicrobial, and antifouling without compromising mechanical and adhesive properties. Sometimes these strategies even increased adhesive properties in these situations. The detailed strategies used and the results obtained are available in Table 3.

Table 3 Characteristics (type of study, objectives and main results) of included studies.

Code	Author, Year, Country	Type of Study	Objectives	Main results
1	Abuna *et al.*, 2016, Spain	*In-vitro*	The objective of this *In-vitro* study was to evaluate the bonding performance of an experimental remineralizing self-etching adhesive containing micro-fillers of reactive calcium phosphate (Ca/P), and a primer doped with phosphoproteins biomimetic analogs [polyacrylic acid-(PAA): and/or sodium trimetaphosphate-(TMP)].	A Ca/P-doped adhesive with or without dentin pre-treatments with the primer containing both biomimetic analogs (PAA and TMP) promoted stable mutbs over 6 months. Control primer and filler-free adhesive significantly decreased after 6 months. Nanoleakage decreased within the resin-dentin interfaces created using the Ca/P-doped adhesives.
2	Abunawareg *et al.*, 2017, Saudi Arabia	*In-vitro*	The aim of the present study was to investigate the effect of different cross-linking agent protocols (1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (EDC-HCl), UV- or BL-activated riboflavin-5-phosphate on the resin–dentin micro-tensile bond strength (μTBS) and nanoleakage exhibited by a two-step etch-and-rinse adhesive after three storage intervals (24 h, 6 months, and 12 months).	Bond strength significant increases in the groups subjected to dentin pretreatment with either EDC-hcl or light-activated 1% riboflavin. -Dental collagen cross-linking induced by UV- or blue light-activated 1% riboflavin or EDC-hcl enhanced the durability and strength of the resin–dentin bond.
3	Ackermann *et al.*, 2019, Germany	*In-vitro*	In the present study, we investigated the fusion process between amorphous microparticles of the calcium salt of the physiological polymer comprising orthophosphate units, of inorganic polyphosphate (polyP), and enamel.	Reseals tooth defects on enamel, like carious lesions, and dentin, including exposed dentinal tubules, but also has the potential to induce remineralization in the enamel and dentin regions. - aca-polyp-MP was enhanced upon exposure to artificial saliva. -toothpaste enriched with aca-polyp-MP is a promising biomimetic material for accelerating enamel and dentin restoration.
4	Adebayo, Burrow & Tyas, 2010, Australia	*In-vitro*	To evaluate the quality of bonded resin–dentine interfaces produced by two self-etching primer adhesives after casein phosphopeptide–amorphous calcium phosphate (CPP–ACP) treatment, in comparison to untreated dentine.	The quality of the bonded resin–dentine interface produced after CPP–ACP treatment may depend on the adhesive system used.

Code	Author, Year, Country	Type of Study	Objectives	Main results
5	Aggarwal & Bhasin, 2018, India	*In-vitro*	The aim of the present study was to evaluate the effect of the application of calcium silicate materials (CSMs), after acid etching, on the longevity of the hybrid layer and marginal adaptation of composite restorations.	Application of csms improved the marginal adaptation values in both adhesive groups. - Application of csms after acid etching can be a potential avenue in preserving the resin-dentin bonds.
6	Aguiar *et al.*, 2014, United States of America	*In-vitro*	The specific aim of the present study was to assess the total polyphenol content (TPC), perform a high-resolution chemical profiling of the different PAC sources, and correlate these findings with the targeted dentin bioactivities (i.e., mechanical properties and matrix biodegradability).	Extracts with a high polyphenol and PAC content from Vitis vinifera, Theobroma cacao, Camellia sinensis, and Pinus massoniana induced a significant increase in modulus of elasticity and mass. Protective effect against enzymatic degradation was observed for all experimental groups.
7	Al-Abdi, Paris & Schwendicke, 2017, Germany	*In-vitro*	We aimed to compare mineral gains in artificial residual lesions provided by calcium hydroxide and glass hybrid materials in combination with pulpal fluid simulation.	Glass hybrid provided coronal remineralization of residual carious lesions in dentin.
8	Annisa *et al.*, 2019, Indonesia	*In-vitro*	This study analyzed the ability of CMC/ACP to achieve intrafibrillar and extrafibrillar remineralization on demineralized dentin.	CMC/ACP can improve the GTR process. (Guided tissue remineralization- GTR). -control group: directly filled with composite resins CMC/ACP :before being filled with composite resins, the cavity bases were coated with CMC/ACP.
9	Atmeh *et al.*, 2015, Jordan	*In-vitro*	This study evaluated the potential of Biodentine to induce remineralisation of totally demineralised dentine, with GIC as a control material, detected using two-photon fluorescence microscopy with tetracycline labelling, along with Raman spectroscopy and backscattered electron (BSE) SEM imaging.	Biodentine induced calcium phosphate mineral formation within the dentine matrix when stored in phosphate-rich media, which was selectively detectable using the tetracycline labelling.
10	Bachli *et al.*, 2019, Switzerland	*In-vitro*	This study aimed to apply dentin matrix proteins (DMPs) and enamel matrix derivates (EMDs) on artificially induced dentin lesions and to assess their remineralization potential.	This study was able to visually confirm the remineralization potential of demineralized dentin especially after DMP application, which, however, did not outperform AMF.

Code	Author, Year, Country	Type of Study	Objectives	Main results
11	Bacino *et al.*, 2019, United States of America	*In-vitro*	To evaluate the feasibility of applying the PILP method as part of a restorative treatment and test for effectiveness to functionally remineralize artificial lesions in dentin.	In particular the most demineralized outer zone recovered substantially in the elastic modulus, suggesting that functional remineralization has been initiated by pasp delivery upon rehydration of air-dried demineralized dentin. In contrast, the effectiveness of the RMGI on functional remineralization of dentin was minimal when pasp was absent.
12	Barbosa-Martins *et al.*, 2018a, Brazil	*In-vitro*	The aim of this paper was to investigate the influence of Dentin Caries-like Lesions (DCLL)-Producing Model on microtensile bond strength (uTBS) of etch and rinse adhesive systems and investigate the effect of remineralizing agents such as Sodium Fluoride (NaF), MI Paste™ (MP) and Curodont™ Repair (CR) on caries-affected dentin (n = 6).	The highest values were found when demineralized dentin was treated with MP and CR, regardless caries lesion depth. -Additionally MP and CR remineralizing agents could enhance adhesive procedures even at different models of caries lesion.
13	Barbosa-Martins *et al.*, 2018b, Brazil	*In-vitro*	The aim of this study was to determine whether NaF, CPP-ACP and P11-4 pre-treatments, influence the wettability of the demineralized dentin and the micro-tensile bond strengths of composite resin adhesive systems to the surface of demineralized dentin, when using an etch-and-rinse or a self-etch system.	The highest μtbs were found for the demineralized dentin-(DD) treated with CPP-ACP; both adhesives systems . - The results indicated that self-assembling peptide P11-4 associated with SB and CPP-ACP associated with SB or CSE significantly enhanced the bond strength to demineralized dentin.
14	Bauer *et al.*, 2016, Brazil	*In-vitro*	The aim of this study was to evaluate radiopacity, degree of conversion (DC), Knoop hardness (KHN), ultimate tensile strength (UTS) and microtensile bond strength (μTBS) to dentin of an experimental adhesive containing micro-filler of niobium-phosphate bioactive glass (NPG).	Addition of 40% NPG glass may be an alternative to obtain an adhesive system with adequate mechanical and bond strength to dentin properties.
15	Bauer *et al.*, 2019, Brazil	*In-vitro*	The aim of the study was to evaluate the effect of bioactive glass (45S5 and NbG) suspensions on bond strength (μTBS), hardness, modulus of elasticity, pH and antibacterial activity of the resin-dentin interfaces after 3 months.	45S5 and NbG suspensions in concentrations of 20% were shown to be a technique capable of increasing the stability of bond to dentin. Rewetting dentin with the suspension of 20% 45S5 glass prevented the reduction in bond strength; increased hardness; modulus of elasticity of the resin-dentin interface, and demonstrated antibacterial activity against Streptococcus mutans similar as chlorhexidine.

Code	Author, Year, Country	Type of Study	Objectives	Main results
16	Beltrame *et al.*, 2018, United States of America	*In-vitro*	The aim of this study was to evaluate the antierosive effect of phosphorylated chitosan in dentin.	AmF/NaF/SnCl2 presented the most significant reduction in dentin loss upon erosive challenge. The phosphorylated chitosan solutions showed limitations in reducing dentin surface loss after erosive challenge when compared with the fluoride and metal ion solutions.
17	Besinis, Van Noort & Martin, 2012, United Kingdom	*In-vitro*	The aim of this study was to assess the ability of HA and silica nano-particulate solutions to infiltrate demineralized dentin, that retains its collagen structural integrity.	Silica nanoparticles - particle size plays a major role in the degree of dentin infiltration, demonstrating a greater infiltrative capacity. - Collagen infiltrated with HA and silica nanoparticles may provide a suitable scaffold for the remineralization of dentin, whereby the infiltrated particles act as seeds within the collage matrix and given the appropriate remineralizing environment, mineral growth may occur. Silica nanoparticles have the ability to penetrate dentin and remain embedded within the collagen matrix.
18	Besinis, Van Noort & Martin, 2014, United Kingdom	*In-vitro*	The aim of this study is to assess the effectiveness of this strategy as a mechanism for the remineralization of fully demineralized dentin following immersion in artificial saliva.	Infiltration of demineralized dentin with nano-HA restored up to 55% of the P and Ca levels at baseline. Remineralization of demineralized dentin with silica nps by immersion in artificial saliva was the most effective strategy.
19	Bortolotto *et al.*, 2017, Switzerland	*In-vitro*	To evaluate if three dentin treatments improved mechanical properties of demineralized dentin.	A significantly higher E modulus was observed in dentin specimens treated with RF + TM + SBU. In the presence of an adhesive system, crosslinking collagen with RF and TM addition significantly improved mechanical properties of dentin.
20	Boteon *et al.*, 2017, Brazil	*In-vitro*	To analyze the effect of different concentrations and application times of proanthocyanidin gels on dentin befor an erosive challenge in order to evaluate if there is a dose-response or application time response relationship in the use of these gels for erosion prevention.	Grape seed proanthocyanidin gels is considered as a promising therapy to diminish erosive dentin wear because it may interact with the exposed collagen, enhancing the demineralized organic matrix stabilization, which acts as a barrier against the diffusion of the acids from erosion.

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21	Burwell *et al.*, 2012, United States of America	*In-vitro*	It was hypothesized that applying the polymer-induced liquid-precursor (PILP) system to artificial lesions would result in time-dependent functional remineralization of carious dentin lesions that restores the mechanical properties of demineralized dentin matrix.	Functional remineralization of partially demineralized human dentin occurred with recovery of mechanical properties, with progressive intra- and extra-fibrillar mineralization initiated in the depth of the lesion. The degree of remineralization increased with time over the 4 week treatment period.. 28 days of PILP mineralization resulted in 91% improvement of ER compared to the artificial lesion.
22	Cai *et al.*, 2019, Australia	*In-vitro*	In this study, SDF/KI was investigated as a regimen for root caries treatment, and PA was applied as a bio-mediator to protect the dentine organic matrix. An artificial root caries model was used to ensure the consistency of the results.	The combined treatment of PA and SDF/KI achieved a more homogenous mineral distribution throughout the lesions than SDF/KI alone. Application of SDF/KI induced small discrete crystal formation distributed over the dentine surface and PA contributed to the formation of slit-shaped orifices of the dentinal tubules that were partially occluded.
23	Cai *et al.*, 2017, China	*In-vitro*	The current study aimed to synthesis chlorhexidine-loaded ACP nanoparticles, and to explore their performance during the degradation and mineralization of collagen fibrils.	Released chlorhexidine inhibited the degradation of collagen in human dentine powder, and its effect lasted longer than that of pure chlorhexidine of the same concentration. The ACP could induce the mineralization of self-assembled type I collagen fibrils. The chlorhexidine-loaded ACP nanoparticles sustainably released chlorhexidine and ACP, under appropriate conditions.
24	Cao & Li., 2016, China	*In-vitro*	To investigate remineralisation of dentine in the hydrogel microenvironment for the management of hypersensitivity.	The hydrogel acts as the remineralisation microenvironment to initiate occlusion of dentinal tubules and formation of enamel prisms-like tissue on human dentine surface.
25	Cao *et al.*, 2014a, China	*In-vitro*	The objectives were to design and fabricate an oligopeptide that simulates dentine matrix protein 1 (DMP1) to study its ability to bind to dentine collagen fibrils and induce biomimetic mineralization for the management of dentine hypersensitivity.	A novel oligopeptide-simulating DMP1 was developed, that can bind to collagen fibrils, initiate mineralization, and induce biomimetic mineralization of dentine.
26	Cao *et al.*, 2013, China	*In-vitro*	This study aimed to demonstrate *In-vitro* the ability of CPP-ACP to form apatite crystals on phosphorylated dentine collagen fibrils.	CPP-ACP paste was topically applied to the surface of the phosphorylated, immersed in a metastable calcium phosphate remineralising solution and incubated. - No apatite

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				crystal nucleation and growth were observed in either the slices that had no non-phosphorylation or those without CPP-ACP application. CPP-ACP can induce the biomimetic mineralisation of dentine through apatite formation along and between the phosphorylated dentine collagen fibrils.
27	Castellan *et al.*, 2011, Brazil	*In-vitro*	This article aims to analyze the elastic response of dentin that can be achieved by biomodification of the organic matrix with natural agents (grape seed, cocoa, cranberry, açaí berry and cinnamon) at various exposure times (10, 30, 60, 120 and 240 min) and up to 12 months storage in artificial saliva.	Some PA-based extracts were capable of improving and stabilizing collagen matrices through exogenous cross-links induction.
28	Chen *et al.*, 2016, China	*In-vitro*	The purpose of this study was to induce a biomimetic remineralization process by using glutaraldehyde (GA) to reconstruct the mechanical properties and biostability of demineralized collagen.	A significant difference was found in dentin remineralization process between dentin with and without GA pretreating. GA showed a specific affinity to dentin collagen resulting in the formation of a cross-linking superstructure. The results indicated that GA cross-linking of dentin collagen could promote dentin biomimetic remineralization, resulting in an improved mechanical property and biostability.
29	Chiang *et al.*, 2014, Taiwan	*In-vitro*	This paper presents a fast-reacting, more reliable and biocompatible biomaterial that effectively occludes exposed dentinal tubules by forming a biomimetic crystalline dentin barrier.	The developed CCMS-HP holds great promise for treating exposed dentin by growing biomimetic crystals within dentinal tubules. These findings demonstrate that the mesoporous silica biomaterials presented here have great potential for serving as both a catalyst and carrier in the repair or regeneration of dental hard tissue.
30	De Caluwé *et al.*, 2017, Belgium	*In-vitro*	The aim of this study is thus threefold: first, it is investigated if the addition of 2 types of F−containing BAG scan improve the bioactive properties of a conventional GIC. Secondly, the effect of the addition of Al3+to BAG on the compressive strength and bioactive properties of a BAG-GIC is investigated.	The addition of BAG improves the bioactivity of the GIC, which can be observed by the formation of an apatite (Ap) layer, especially in CF9-containing gics. More BAG leads to more bioactivity but decreases strength. The addition of Al3+ to the BAG composition improves strength, but decreases bioactivity.

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31	De Morais *et al.*, 2018, Brazil	*In-vitro*	The objective of this study was to evaluate the effect of a Biosilicate®, associated with dentin adhesive system, on microtensile bond strength (μTBS) to sound and demineralized dentin.	Biosilicate® enhanced bond strength of self-etching and etch-and-rinse adhesives to sound and demineralized dentin. -Bioactive glass ceramic suspension could be recommended to be used to improve the dentin bond strengths of the total-etching and self-etching adhesives after acid-etching and priming.
32	Degrazia *et al.*, 2018, Brazil	*In-vitro*	The aim of this study was to evaluate physicochemical properties, long-term microtensile bond strength and cytotoxicity of methacrylate-based adhesive containing boron nitride nanotubes (BNNTs) as fillers.	Incorporating boron nitride nanotubes up to 0.1 wt% into dental adhesive increased the long-term stability to dentin without decreasing viability of fibroblast cell growth. Thus, the use of BNNTs as filler may decrease failure rate of current dentinal adhesives.
33	Dickens, Flaim & Takagi, 2003, United States of America	*In-vitro*	This study examined strength and bioactive (remineralizing) properties of a powder/liquid formulation (Cement I) and a more practical two-paste formulation (Cement II) of a fluoride-releasing resin-based Ca–PO4 cement.	Concurrently, both cements caused increases of 47% (Cement I) and 38% (Cement II) in the lesion mineral content over that underneath the corresponding controls. The stronger Cement II could serve as a restoration-supporting lining material and could remineralize dentin in areas where complete removal of carious tissue is contra-indicated.
34	D'Onofrio *et al.*, 2016, United Kingdom	*In-vitro*	The aim of this study was to investigate the effect on properties of increasing strontium substitution for calcium in bioactive glasses used as precursors for novel calcium phosphate cements.	These novel injectable bioactive glass cements are promising materials for dental and orthopedic applications. The glass composition has an effect upon cement properties, specifically the setting time, compressive strength and radiopacity.
35	Dreger *et al.*, 2012, Brazil	*In-vivo* (animal testing with rats)	The objective of this study was to evaluate the occurrence of mineral deposition in the dentin-cement interface and in the interior of dentinal tubules after implantation, in rat subcutaneous tissue, of dentin tubes filled with MTA Branco, MTA BIO, and white Portland cement with and without calcium chloride.	All the cements tested were bioactive. MTA BIO and MTA Branco were more effective in promoting the biomineralization process than Portland cements, mainly after 30 and 60 days.
36	Epasinghe, Yiu & Burrow, 2016, China	*In-vitro*	This study compared the effects of three flavonoids, including proanthocyanidin, naringin and quercetin on remineralization of artificial root caries.	Artificial caries lesions treated with CPP-ACFP+PA showed significantly higher microhardness values at 130 μm and 150 μm from the surface -Combined use of PA and CPP-ACFP has a synergistic effect on root caries remineralization by

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				enhancing mineral gain and increasing hardness of artificial root caries.
37	Epasinghe *et al.*, 2017, China	*In-vitro*	To evaluate the effect of proanthocyanidin (PA) in combination with tricalcium phosphate (TCP) and fluoride (F) on resistance to collagen degradation and remineralization of artificial caries lesions.	The addition of PA to TCP + F reduced collagen degradation, inhibited demineralization and enhanced remineralization.
38	Forsback, Areva & Salonen, 2004, Finland	*In-vitro*	To study the use of bioactive glass and the biomimetic method on dentin mineralization.	Pretreatment with BAG decreases the degree of decalcification of dentin during the mineralization process. These findings suggest that bioactive glass S53P4 can be used as a therapeutic material for mineralization of dentin and its tubules in a physiological environment.
39	Gandolfi *et al.*, 2009, Italy	*In-vitro*	The aim of this study was to investigate the effect of ageing of experimental calcium-silicate cements on the chemistry, morphology and *In-vitro* bioactivity of the surface, as well as on osteoblast viability and proliferation.	These materials support osteogenic cells growth and may induce early bone formation, the ageing in DPBS reduced the growth of HMSC, but eliminated the deleterious effect of the bismuth oxide on cell growth. In conclusion, the experimental cements have adequate biological properties to be used as root-end/root repair filling materials or pulp capping materials.
40	Gandolfi *et al.*, 2019, Italy	*In-vitro*	The aim of the study was to investigate the effects of several decalcifying agents used as irrigant solutions in endodontic treatment on collagen and mineral components of dentin.	In conclusion, the highest demineralizing effect was observed for 10% EDTA and 10% citric acid. Collagen rearrangement was found for all the treatments except for 1% EDTA. The highest remineralization capability in SBF values was recorded for 1% EDTA and the lowest for 10% citric acid. A slight collagen rearrangement upon remineralization was still present in 17% EDTA-treated samples. Clinical use as a chelating agent in the endodontic therapy of citric acid and concentrated EDTA solutions should be reconsidered.
41	Gandolfi *et al.*, 2011, Italy	*In-vitro*	The aim of this study was to develop bioactive calcium releasing light-curable hydrophilic composites with tailored remineralizing properties, to be used as restorative base-liner materials in sandwich restorations.	FTC-Ba composite released more fluoride than Vitrebond and formed calcium fluoride (fluorite) precipitates. Polyacrylate calcium complexes formed at high ph. -The ion-leachable experimental composites remineralized the human apatite-depleted dentin. Ion release promotes the formation of a

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				bone-like carbonated-apatite on demineralized dentin within 7 days of immersion in DPBS. The use of bioactive “smart” composites containing reactive calcium-silicate Portland derived mineral powder as tailored filler may be an innovative method for the biomimetic remineralization of apatite-depleted dentin surfaces and to prevent the demineralization of hypomineralized/carious dentin, with potentially great advantage in clinical applications.
42	Gao *et al.*, 2017, China	*In-vitro*	This study aimed to evaluate the *In-vitro* effectiveness and stability of the fourth generation amine-terminated PAMAM on dentinal tubule occlusion, especially on dentine permeability.	PAMAM-induced biomineralization not only on dentine surfaces, but also deeper in dentinal tubules, significantly reduced dentine permeability. Moreover, PAMAM-induced biomineralization elicited excellent stable occlusion effects after acid challenge. In conclusion, PAMAM demonstrated a strong ability to resist acid and showed great potential to be used in the treatment of dentine hypersensitivity in future.
43	Garcia *et al.*, 2018, Brazil	*In-vitro*	The purpose of this study was to formulate and evaluate an adhesive resin with tantalum oxide.	Tantalum oxide is a promising alternative for adhesive formulation and it could be further tested for biomimetic remineralization.
44	Gavrila *et al.*, 2016, Romania	*In-vitro*	The aims of this study research were to investigate the surface topography and to compare the remineralization potential of various commercial remineralizing products on primary and permanent teeth dentine.	The dentin remineralization, both in the temporary teeth and young permanent teeth, was increased, very best quality has been achieved in the study group four.
45	Ge *et al.*, 2017, China	*In-vitro*	The objectives of this study were to incorporate PAMAM and DMADDM into an adhesive and to investigate, for the first time, the biofilm-regulating and remineralization effects of the novel adhesive and dentin bonding properties.	The results showed that incorporating PAMAM and DMADDM into adhesive had no adverse effect on the dentin bond strength. - In conclusion, the adhesive containing PAMAM and DMADDM had strong antimicrobial properties and biological remineralization capabilities, and is promising for anti-caries clinical applications.
46	Gonçalves *et al.*, 2018a, Brazil	*In-vitro*	The purpose of this study was to investigate (1) the STMP antiproteolytic potential against human-	In summary, within the limitations of this *In-vitro* methodology, it may be concluded that 1.5% STMP can

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			purified MMPs-2 and -9, and enzymes extracted from sound dentin; and (2) its capacity to promote caries-like dentin remineralization.	serve as an effective inhibitor of collagen degradation mediated by both human purified MMP-2 and MMP-9, as well as proteases extracted from sound dentin. Furthermore, caries-affected dentin treated with 1.5% STMP supplemented with Ca (OH)2 may induce remineralization.
47	Gonçalves *et al.*, 2018b, Brazil	*In-vitro*	The aim of this *In-vitro* study was to investigate (1) the antiproteolytic potential of STMP against MMPs-2 and -9 and (2) its ability to enhance dentin remineralization.	Concluded that (1) STMP presents an antiproteolytic effect against both MMPs-2 and -9 activities, this inhibition being dose dependent and not observed for concentrations lower than 1.5%, and (2) 1.5% STMP is able to act as a biomimetic agent to promote remineralization of dentin previously submitted to acidic challenge.
48	Gu *et al.*, 2011a, United States of America	*In-vitro*	The first objective of the present study was to determine the optimal concentration for high-affinity binding of Na3P3O9 to collagen within a clinically relevant time frame. The second objective was to test the applicability of those parameters in a single- layer reconstituted collagen mineralization model.	Since there was a significant difference between the 5-minute and one-hour adsorption characteristics of HPA-Na3P3O9 to collagen, the first null hypothesis has to be rejected. The second null hypothesis, that intrafibrillar mineralization does not proceed in an ordered manner when either the ACP-stabilization or matrix phosphoprotein analog is absent, has to be accepted.
49	Gu *et al.*, 2010, United States of America	*In-vitro*	The objective of this study was to test the hypothesis that STMP is capable of binding irreversibly to collagen fibrils, producing the condition that favors homogeneous mineral induction and intrafibrillar remineralization in the presence of PAA-stabilized amorphous calcium phosphate nanophases.	Collectively, STMP functions as an initiator for apatite nucleation *In-vitro* and generates calcium phosphate deposits with a morphology that mimics the crystals found at the mineralization front of bone and dentin. These results provide new insights into basic mechanisms of collagen mineralization, and can lead to the development of a clinically applicable delivery system by incorporating both biomimetic analogs (i.e. STMP and PAA) into the steps involved in the application of the adhesives and filling materials.
50	Gu *et al.*, 2011b, United States of America	*In-vitro*	The objectives of this study were to examine the binding characteristics of PVPA to demineralized dentin collagen, to determine whether immobilization of PVPA to collagen matrices and intrafibrillar	Based on these results, a concentration range for immobilized PVPA to template intrafibrillar apatite deposition was established and validated using a single layer reconstituted type I collagen mineralization model. In the

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			mineralization of the collagen could be achieved by cross-linking collagen using different EDC-mediated strategies.	presence of a polyacrylic acid-containing mineralization medium optimal intrafibrillar mineralization of the EDC-cross-linked collagen was achieved using 500 and 1000 lgml–1 PVPA.
51	Guentsch *et al.*, 2019, United States of America	*In-vitro*	To investigate the effect of an experimental biomimetic mineralization kit (BIMIN) on the chemical composition and crystallinity of caries-free enamel and dentin samples *In-vitro*.	The treatment of enamel and dentin samples resulted in the mineralization of an enamel-like fluoroaptite layer, which evidently seems to be bonded to the underlying tooth structure.
52	Gupta *et al.*, 2017, India	*In-vitro*	The aim of the study was to compare the effect of BG, hydroxyapatite, and diode laser desensitization on the shear bond strength of resin composites to dentin measured at different time intervals.	The groups treated with BG and hydroxyapatite showed increased shear bond strengths, whereas control group and laser group showed a decrease in the bond strength values at all the time intervals.
53	Han *et al.*, 2017, China	*In-vivo* (animal testing with rabbits)	The aim of the present study was to investigate the effectiveness of the agarose hydrogel biomimetic mineralization system in a dentin exposed animal model for its potential clinical translation.	This study reported the use of an agarose hydrogel biomimetic mineralization system loaded with calcium and phosphate to induce dentin remineralization and formation of a oriented densely parallel packed HA layer on dentin surface in a rabbit model *In-vivo*. The results indicated a potential clinical use for repairing dentin-exposed related diseases, such as erosion, wear, and dentin hypersensitivity.
54	Huang *et al.*, 2019, China	*In-vitro*	This study investigated carboxymethyl chitosan (CMC)-induced biomimetic mineralization of collagen fibrils, with the aim of synthesizing experimental resins doped with CMC and calcium phosphate microfillers to remineralize artificial caries-affected dentin (ACAD) and enhance resin–dentin bonding durability.	In conclusion, CMC is efficient in directing the biomimetic mineralization of collagen fibrils. The experimental resins containing CMC can induce dentin biomimetic remineralization and improve the bonding performance of ACAD.
55	Iafisco *et al.*, 2018, Italy	*In-vitro*	The aim of this work is the preparation of new forms of biomimetic ACP nanoparticles as a promising nanomaterial for dental remineralization.	The samples showed good ability to partially occlude the tubules of acid-etched dentin and to restore demineralized enamel into its native structure. Results demonstrate that ACP and FACP are promising biomimetic materials in preventive dentistry to hinder demineralization of dental hard tissues.

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56	Iijima *et al.*, 2019, Japan	*In-vitro*	The purpose of this *In-vitro* study was to investigate the effect of the weekly professional application of pastes containing S-PRG filler on dentin remineralization.	The mechanical properties of specimens polished with S-PRG filler-containing pastes recovered significantly after immersion in remineralization solution for 1 month compared with the other specimens.
57	Ishimoto *et al.*, 2015, Japan	*In-vitro* and animal testing with rats	In this study, we describe a novel pulp capping material that mimics the biological processes of tooth development in nature.	MicroCT and microscopic analyses demonstrated that the topical application of LiCl induced dentin repair, including the formation of a complete dentin bridge.
58	Islam *et al.*, 2012, Japan	*In-vitro*	The aims of this study were to investigate the effects of hesperidin, a citrus flavonoid, on human root dentin demineralization and collagen preservation, and compare it with chlorhexidine and grape seed extract.	In hesperidin and grape seed extract groups, demineralization was reduced when the collagen matrix was preserved. The hesperidin group showed the lowest value in lesion depth and mineral loss, indicating that hesperidin inhibited demineralization and probably enhanced remineralization even under fluoride-free conditions.
59	Ito *et al.*, 2012, Japan	*In-vitro*	The aim of this study is to evaluate the mineralizing potential of acidic monomers and their calcium salts for mineralization, using an *In-vitro* mineral induction model.	Using these data, the interfacial tension for mineral induction of PV and CMET was determined to be 90.1 and 92.7 ergs/cm(2), respectively. Mineral induction time decreased with increasing solution saturation. 4-METCa salt [calcium salt of 4-methacryloxyethyl trimellitate (CMET)] significantly reduced the mineral induction time
60	Jang *et al.*, 2018, South Korea	*In-vitro*	The purpose of this study was to evaluate the effect of bioactive glass (BAG)-containing composite on dentin remineralization.	The BAG-containing composite significantly increased the micro-hardness of the adjacent demineralized dentin. ATR-FTIR revealed calcium phosphate peaks on the surface of the groups which used BAG-containing composite. FE-SEM revealed surface deposits partially occluding the dentin surface. No significant difference was found between SBF and PBS storage.
61	Jayasree *et al.*, 2017, India	*In-vitro*	The objective was to develop novel hydroxyapatite cement from tetracalcium phosphate which gradually releases hydroxyl and strontium ions to exhibit antibacterial activity	The hydroxyl and strontium ions releasing tetracalcium phosphate cement exhibits good antibacterial property, radiopacity and has the potential to encourage dentin remineralization.

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62	Jia *et al.*, 2014, China	*In-vitro*	The aim of this research was the biological mineralization of the generation 4.0 polyamidoamine dendrimer on the demineralized dentinal tubules at different time points.	Generation 4.0 polyamidoamine dendrimer promotes the biomineralization of demineralized dentinal tubules. Moreover, this result also suggests that the 4.0th generation polyamidoamine dendrimer has the potential value for dentine hypersensitivity treatment.
63	Jose, Sanjeev & Sekar, India	*In-vitro*	To assess and compare the remineralization of artificial carious dentin pre treated with white and green tea, before and after application of CPP-ACFP using microhardness test.	Howed that both the tea extracts increased the microharness values when used prior to the application of remineralizing agent. However, 10% white tea showed better microhardness indicating stabilization of collagen in dentine resulting in functional remineralization.
64	Jun *et al.*, 2018, South Korea	*In-vitro*	The aim of this study was to generate and characterize a novel CuBGn and evaluate multifunctionally therapeutic adhesive systems incorporating CuBGn in terms of MMP inhibition from Cu ions and remineralization ability from Ca ions, along with the cytocompatibility and cellular-bioactivity.	These therapeutic adhesives (cubgn-DA) showed enhanced (a) cellular bioactivity, cytocompatibility, microtensile bond strength and MMP deactivation-ability. In conclusion, the incorporation of Cu ions releasing nano-bioactive glass demonstrated multifunctional properties at the resin-dentin interface; MMP deactivation and remineralization, representing a suitable strategy to extend the longevity of adhesive-hard tissue (i.e. Resin-dentin) interfaces.
65	Jung *et al.*, 2019, South Korea	*In-vitro*	To synthesize two different sizes of bioactive glass-coated mesoporous silica nanoparticles (BGN@MSNs) and to investigate their effects on dentinal tubule occlusion and remineralization.	Dentinal tubule remineralization induced by the BGN@MSN biocomposite can be used to stabilize long-term prognosis in dentin hypersensitivity. BGN@MSN biocomposite with its smaller size and larger surface area was more effective for remineralization and dentinal tubule sealing.
66	Kim *et al.*, 2011, South Korea	*In-vitro*	To examine the differences in the amounts of bound chlorhexidine (CHX) on demineralized dentine blocks and to investigate the different aspects of remineralization of demineralized dentine according to different concentrations of CHX.	The application of the 0.2% and 2% CHX seemed to be effective in promoting the remineralization of demineralized dentine. The application of the 0.2% and 2% CHX positively influences on the dentine remineralization.
67	Kim *et al.*, 2012, South Korea	*In-vitro*	The aim of this study was to investigate the mechanical and micromorphological aspects of dentin remineralization according to different	Specifically, with respect to demineralized dentin blocks treated with different concentrations of CHX (0.02–2%) and stored in simulated body fluid, we have observed a

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			concentrations of CHX under the same conditions in which the mineral source is supplied.	significant increase in the elastic modulus of dentin treated with relatively high concentrations of CHX (0.2 and 2%) as storage time increased, whereas the elastic modulus of the non-CHX treated control group decreased.
68	Kim *et al.*, 2010a, United States of America	*In-vitro*	To examine the ultrastructural characteristics of completely demineralized vs. partially demineralized resin-infiltrated dentin collagen matrices (i.e. interdiffusion zones) that had been subjected to biomimetic remineralization.	Biomimetic remineralization via dual biomimetic analogs has the potential to be translated into a functional delivery system for salvaging failing resin-dentin bonds.
69	Kim *et al.*, 2010b, United States of America	*In-vitro*	To examine, with the complementary use of confocal laser scanning microscopy (CLSM) and transmission electron microscopy (TEM), whether hybrid layers created by an aggressive one-step self-etch adhesive in primary dentin can be remineralized at the proof-of-concept level using an open-face model of a dual biomimetic analog-containing remineralization scheme.	Remineralization was predominantly intrafibrillar in nature as interfibrillar spaces were filled with adhesive resin. Biomimetic remineralization of imperfect hybrid layers in primary human dentin is a potential means for preserving bond integrity.
70	Kovtun *et al.*, 2012, Germany	*In-vitro*	We have loaded calcium phosphate nanoparticles with chlorhexidine to combine mineralization ability and antibacterial effect. To achieve an optimal loading with chlorhexidine and to enhance the adhesion properties on the tooth surface, the nanoparticles must be modified by adhesive polymers to make them more sticky.	The nanoparticles may also stick to open dentin tubules at the root surface due to their coating with carboxymethyl cellulose. *In-vitro* studies on teeth show that the paste sticks well to the root surface and closes dentin tubules.
71	Kutsch, Chaiyabutr & Milicich, 2013, United States of America	*In-vitro*	This study documented the deposition of nanoparticle hydroxyapatite on demineralized enamel surfaces after treatment with an experimental remineralization gel.	This finding supports consideration of an additional approach to remineralization that includes pH neutralization strategies and nanoparticle hydroxyapatite crystals.

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72	Li *et al.*, 2014, United States of America	*In-vivo* (animal testing with rats)	The objectives of this study were to investigate novel antibacterial and remineralizing restoratives in a rat tooth model, and examine pulpal inflammation and tertiary dentin formation using nanocomposite and adhesive containing NACP and DMADDM.	Composite and adhesive containing NACP and DMADDM exhibited milder pulpal inflammation and much greater tertiary dentin formation than the control adhesive and composite. Therefore, the novel composite and adhesive containing NACP and DMADDM are promising as a new therapeutic restorative system to not only combat oral pathogens and biofilm acids as shown previously, but also facilitate the healing of the dentin–pulp complex.
73	Li *et al.*, 2013, China	*In-vitro* and *In-vivo* (animal testing with rats)	In this work, we utilize carboxyl-terminated PAMAM dendrimer (PAMAM-COOH) to mimic the functions of NCPs due to its mono-dispersed molecular weight within the size retention range of collagen and the well-defined steric structure. The bioinspired mineralization process induced by PAMAM-COOH on human dentine is characterized and illustrated both *In-vitro* and *In-vivo*.	The design of PAMAM-COOH, especially the 4th generation one (G4-COOH), provides a general strategy to prepare various promising restorative materials for biomineralized hard tissues such as bone and teeth.
74	Li *et al.*, 2017, Belgium	*In-vitro*	To characterize the re-mineralization potential of an experimental zirconium oxide (ZrO2) containing tricalcium silicate (TCS) cement, TCS 50, with the incorporation of biomimetic analogs at demineralized dentin.	The incorporation of biomimetic analogs promoted remineralization upon 6-week SBF storage. However, re-mineralization appeared incomplete, this even for TCS 50 to which biomimetic analogs were added and upon 6-week SBF storage.
75	Liang *et al.*, 2019, United States of America	*In-vitro*	The objective of the present study was to investigate long-term dentin remineralization via the combination of poly(amido amine) (PAMAM) with a novel rechargeable adhesive containing nanoparticles of amorphous calcium phosphate (NACP).	The immersed PAMAM with the recharged NACP adhesive achieved long-term dentin remineralization, and restored dentin hardness to that of healthy dentin. The PAMAM + NACP adhesive completely remineralizes pre-demineralized dentin even after long-term fluid challenges and provides long-term remineralization to protect tooth structures.
76	Lin *et al.*, 2016, China	*In-vitro*	The major aim of the current study was to evaluate the impact of a remineralization medium on collagen matrices of hybrid layers of three different adhesive resins using nanotechnology methods.	After four months, all BRM specimens exhibited a significantly smaller fluorescent area than SBF specimens, indicating a remineralization of the hybrid layer ($P \leq 0.05$).

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77	Liu *et al.*, 2014, China	*In-vitro*	The aims of the present study were to investigate the potential effect of PA on endogenous gelatinolytic activity on demineralized dentin matrices, as well as to determine the capability of PA biomodification to reduce collagen biodegradation in demineralized dentin matrices and adhesive/dentin interfaces on challenge with bacterial collagenases in a clinically relevant manner.	These results suggest that PA biomodification was effective at inhibiting proteolytic activity on demineralized dentin matrix and at stabilizing the adhesive/dentin interface against enzymatic degradation, is a new concept that has the potential to improve bonding durability.
78	Liu *et al.*, 2012, China	*In-vitro*	To investigate the potential effect of proanthocyanidins (PA), a natural cross-linker, on the stability of resin-dentin bonds against thermal cycling.	The application of natural cross-linker PA on demineralized dentin reduced the bond degradation against aging by thermal cycling, and can be helpful to create more durable bonds to dentin.
79	Liu *et al.*, 2011a, China	*In-vitro*	PA-based agents were prepared in different polar solvents, and preconditioning time was reduced to evaluate the effect of PA preconditioning on demineralized dentin matrix, using a more clinical relevant procedure.	The cross-linking degree of the demineralized dentin collagen exhibited concentration- and time- dependent increase after preconditioning treatment, irrespective of the preconditioner and the solvent.
80	Liu *et al.*, 2013, China	*In-vitro*	To design a kind of biomimetic polypeptide of dentin matrix protein-1 (DMP-1), which can bind to dentine collagen fibers and initiate mineralization.	The polypeptide of "DSESSEEDRTKREEVD" can simulate DMP-1 binding collagen and initiate hydroxyapatite nucleation and growth. It may be a potential molecular tool for dentine remineralization.
81	Liu *et al.*, 2011b, United States of America	*In-vitro*	This study examined the use of sodium trimetaphosphate (STMP) as a biomimetic analog of matrix phosphoproteins for remineralization of artificial carious-affected dentin.	Biomimetic remineralization using STMP as an analog of matrix phosphoproteins is a promising method tobremineralize artificial carious lesions from the perspectives of mineral uptake and ultrastructure.
82	Liu *et al.*, 2011c, United States of America	*In-vitro*	The objective in the present study was to examine the difference between the top-down and the bottom-up mineralization approaches in mineralizing thick, partially demineralized collagen scaffolds.	Conversely, the entire partially demineralized scaffold, including apatite-depleted collagen fibrils, was mineralized by the bottom-up approach, with evidence of both intrafibrillar and extrafibrillar mineralization. Understanding the different mechanisms involved in these two mineralization approaches is pivotal in adopting the optimum

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				strategy for fabricating novel nanostructured materials in bioengineering research.
83	Mai *et al.*, 2009, United States of America	*In-vitro*	The objective of this study was to examine whether dentin adhesives containing phosphoric acid esters of methacrylates can replace the use of PVPA for inducing intrafibrillar and interfibrillar remineralization of collagen fibrils within hybrid layers.	The null hypothesis could not be rejected; phosphoric acid esters in dentin adhesives cannot replace PVPA during biomimetic remineralization of adhesive-bonded dentin.
84	Mei *et al.*, 2014, Hong Kong	*Ex-vivo*	This study compared the physico-chemical structural differences between primary carious teeth biannually treated with silver diamine fluoride (SDF) and carious teeth without such treatment.	A highly remineralised zone rich in calcium and phosphate was found on the arrested cavitated dentinal lesion of primary teeth with an SDF application. The collagens were protected from being exposed in the arrested cavitated dentinal lesion
85	Mei *et al.*, 2017, Hong Kong	*In-vitro*	To observe the effect of SDF on hydroxyapatite crystallization occurring *In-vitro*, whereby the observed apatite deposition was described with a simplified chemical model.	The results suggested that SDF reacted with calcium and phosphate ions and produced fluorohydroxyapatite. This preferential precipitation of fluorohydroxyapatite with reduced solubility could be one of the main factors for arrest of caries lesions treated with SDF.
86	Ning *et al.*, 2012, China	*In-vitro*	In this study, a novel biomimetic mineralization system was designed for dentin remineralization induced by agarose gel loaded with calcium phosphate.	The results showed that the deposited hydroxyapatite crystals densely packed to each other, completely covered the dentin surface, and occluded the dentinal tubules after 10 days of biomimetic mineralization *In-vitro*. Therefore, this method may provide the experimental basis for dentin remineralization and for a new method to treat dentin hypersensitivity and dental caries.
87	Nurrohman *et al.*, 2016, United States of America	*In-vitro*	We therefore studied the possibility of mineralization of collagen in the DGI-II mouse model and tested the hypothesis that poly(ASP), as used for PILP mineralization, may restore the mechanical properties of dentin, a critical role attributed to DSPP protein.	Micro-XCT showed mineral recovery similar to wild-type dentin after PILP-treatment. TEM/SAED showed repair of patchy mineralization and complete mineralization of defective dentin. This approach may lead to new strategies for hard tissue repair.

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88	Okuyama *et al.*, 2016, Japan	*In-vitro*	To evaluate a new root coating material containing surface pre-reacted glass-ionomer (S-PRG) filler for remineralization of demineralized dentin.	A new coating material with S-PRG filler can be applied in a thin layer on root dentin, which could be especially useful for hard-to-access lesions. This material remineralized demineralized root dentin and had fluoride diffusion characteristics similar to those of glass-ionomer cement *In-vitro*.
89	Osorio *et al.*, 2014a, Spain	*In-vitro*	The aim of this study was to ascertain whether zinc may improve the repair ability of demineralized dentin.	Zinc and phosphate were important for hydroxylapatite homeostasis. Scholzite formation was encountered in dentin stored in zinc-containing solutions. Zinc might allow to reach the balance between dentin demineralization and remineralization processes.
90	Osorio *et al.*, 2016a, Spain	*In-vitro*	To ascertain whether biomimetic phosphoprotein analogues (polyaspartic acid (PAS) and sodium trimetaphosphate (TMP)) improve bonding efficacy and dentine remineralization ability of a novel zinc-doped Portland-based resinous sealing cement.	Infiltration of polymeric nanoparticles into demineralized dentin increased long-term bond strengths. Zinc-loaded nanoparticles facilitate dentin remineralization within the complete resin–dentin interface. Clinical relevance Resin–dentin bond longevity and dentin remineralization at the hybrid layer were facilitated by zinc-loaded nanoparticles.
91	Osorio *et al.*, 2016b, Spain	*In-vitro*	The aim of the present study was to infiltrate zinc and calcium-loaded polymeric nanoparticles into demineralized dentin to facilitate hybrid layer remineralization.	PAS application onto demineralized dentine produced an inhibition or delay of mineral phase crystallization, enhancing the remineralization potential of the Portland microfillers at the resin–dentine bonded interface.
92	Osorio *et al.*, 2018, Spain	*In-vitro*	Biomaterials for treating dentin hypersensitivity and dentin wear were evaluated to efficiently occlude the dentinal tubules and to increase dentin resistance to abrasion.	Zinc-containing pastes occluded dentinal tubules and improved dentin mechanical properties. Clinical relevance Using zinc as an active component to treat eroded dentin is encouraged.
93	Osorio *et al.*, 2014b, Spain	*In-vitro*	The aim of the present study was to as certain if resin-based endodontic cements containing different bioactive particles may inhibit MMP-mediated collagen degradation of phosphoric acid–etched or EDTA-treated human dentin.	MMP degradation of dentin collagen is strongly reduced after resin infiltration of dentin. Zinc incorporation in βtcs particles exerted an additional protection against MMP-mediated collagen degradation. However, it did not occur in resin containing Bioglass 45S5 particles, probably because of the formation of phosphate-zinc compounds.

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94	Padovano *et al.*, 2015, United States of America	*In-vitro*	In the present study, we developed 2 novel DMP1-derived biomimetic peptides designed to bind collagen and stabilize calcium and phosphate in solution to nucleate HA crystals within human dentin matrix. The hypothesis to be tested in this study was to determine if DMP1-derived biomimetic peptides would promote dentin remineralization.	These findings suggest that DMP1-derived peptides may be useful to modulate mineral deposition and subsequent formation of HA when exposed to physiological concentrations of calcium and phosphate.
95	Peters *et al.*, 2010, United States of America	*In-vitro*	This study evaluated the *In-vivo* remineralization capacity of resin-based calcium-phosphate cement (Ca-P) used for indirect pulp-capping.	After three months, caries-affected dentin underneath the Ca-P base showed significantly increased calcium and phosphorus content to a depth of 30 µm. Mineral content of treated caries-affected dentin was in the range of healthy dentin, revealing the capacity of Ca-P base to promote remineralization of caries-affected dentin.
96	Poggio *et al.*, 2013, Italy	*In-vitro*	The aim was the evaluation of a CPP-ACP paste on preventing dentin/enamel erosion produced by a soft drink.	It can be concluded that the application of a CPP-ACP paste is effective on preventing dentin/enamel erosion produced by a soft drink.
97	Pratiwi, Meidyawati & Djauharie, 2017, Indonesia	*In-vivo*	To compare the remineralization of deep carious lesion-affected dentine with the removal of some and all the infected dentine after the application of MTA.	There was no significant difference in the remineralization level of the affected dentine in both groups I and II four weeks after the MTA application. Remineralization occurred in the affected dentine in both groups, either by removing only some parts or all the infected dentine in the deep carious lesion.
98	Qi *et al.*, 2012, United States of America	*In-vitro*	This study examined the remineralization efficacy of mineral trioxide aggregate (MTA) in phosphate-containing simulated body fluid (SBF) by incorporating polyacrylic acid and sodium tripolyphosphate as biomimetic analogs of matrix proteins for remineralizing caries-like dentin.	It is concluded that the version of MTA employed in this study may be doped with biomimetic analogs for remineralization of unbonded and bonded artificial caries-like lesions in the presence of SBF.
99	Rahiotis & Vougiouklakis, 2007, Greece	*In-vitro*	The effect of a commercial paste based on CPP-ACP complex on the demineralization of sound human dentine and on remineralization potential of artificial caries-like lesions formed on dentine surfaces.	The presence of agent CPP-ACP on dentine surfaces provoked lower demineralization and higher remineralization in comparison with the dentine surfaces without agent.

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100	Revankar *et al.*, 2017, India	*In-vitro*	Evaluate the effect of biomineralization process on the push-out strength of ProRoot MTA, MTA Branco, and CPC after mixing with 0.2% chlorhexidine gluconate solution (0.2% CHX) and 2% lidocaine solution (2% LA) on the bond strength of MTA-dentin.	All samples immersed in experimental group displayed a significantly greater resistance to displacement than that observed for the samples in control group ($P < 0.05$). MTAs displayed a significantly greater resistance to displacement than calcium phosphate cements. The main conclusion of this study was that the push-out bond strength of the cements, mainly the MTA groups, was positively influenced by the biomineralization process.
101	Reyes-Carmona, Felippe & Felippe, 2009, Brazil	*In-vitro*	To analyze the interactions of ProRoot MTA, MTA Branco, MTA BIO, and white Portland cement, with or without calcium chloride, with dentin after immersion in PBS.	All the cements tested were bioactive. The cements release some of their components in PBS, triggering the initial precipitation of amorphous calcium phosphates, which act as precursors during the formation of carbonated apatite. This spontaneous precipitation promotes a biomineralization process that leads to the formation of an interfacial layer with tag-like structures at the cement-dentin interface.
102	Reyes-Carmona, Felippe & Felippe, 2010, Brazil	*In-vitro*	To analyze the influence of the biomineralization process on the push-out bond strength of ProRoot MTA, MTA Branco, MTA BIO (Angelus), or Portland cement with and without calcium chloride.	All samples immersed in PBS displayed a significantly greater resistance to displacement than that observed for the samples in contact with a wet cotton pellet for 72 hours ($p < 0.05$). MTAs displayed a significantly greater resistance to displacement than Portland cements. Conclusion: It was concluded that the biomineralization process positively influenced the push-out bond strength of the cements, particularly the MTA groups.
103	Reyes-Carmona *et al.,* 2010, Brazil	*In-vitro* and *In-vivo* (animal testing with swiss mice)	We evaluated specific signaling molecules related to the inflammatory process and the biomineralization ability of MTA to assess host-biomaterial interactions in vivo.	MTA induced a proinflammatory and pro-wound healing environment. The biomineralization process occurred simultaneously at the biomaterial-dentin-tissue interface, with the acute inflammatory response. This promoted the integration of the biomaterial into the environment.
104	Rubel *et al.,* 2016, India	*In-vitro*	To investigate the effect of grape seed extract (GSE) on artificial enamel caries in human teeth.	GSE is a potential remineralizing agent and can be used to prevent progression of dental caries.

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105	Saeki *et al.,* 2017, United States of America	*In-vitro*	Acetate and lactate are important cariogenic acids produced by oral bacteria. They produced different residual dentin structures in artificial lesions of similar depth. We evaluated if such lesions responded in the same way to a polymer-induced-liquid-precursor (PILP) remineralization.	The PILP process provided significant recovery of both structure and mechanical properties for artificial lesions produced with acetate or lactate.
106	Santoso *et al.,* 2019, Indonesia	*In-vitro*	The aim of this study was to analyze the effects of CMC/ACP in demineralized dentin.	In vitro analysis using micro-CT of dentin remineralization in this study exposed by CMC/ACP demonstrated an increase in the gray level values. It can thus be concluded that CMC/ACP may induce dentin remineralization.
107	Sauro *et al.,* 2015, Spain	*In-vitro*	The study aimed at evaluating the remineralization of acid-etched dentin pre-treated with primers containing biomimetic analogs and bonded using an ion-releasinglight curable resin-based material.	The use of the ion-releasing resin-based system applied to acid-etched dentin pre-treated with biomimetic primers containing analogs of phosphoproteins such as poly-l-aspartic acid and/or sodium trimetaphosphate provides a suitable bonding approach for biomimetic remineralization of resin-dentin interfaces.
108	Saxena *et al.,* 2018, United States of America	*In-vitro*	To examine the effect of fluoride on the PILP system, which we hypothesized would increase mechanical properties of the resultant com-posite by both increasing the amount of interfibrillar mineral relative to intrafibrillar mineral and also by having a stiffer mineral component present within the composite material.	In this study, we were able to successfully incorporate fluorideions into the PILP-mineralization of type I collagen. This work contributes to the development of minimally invasive approaches to caries treatment by determining if collagen can be functionally mineralized.
109	Saxena *et al.,* 2019, United States of America	*In-vitro*	We test the hypothesis that bulk substrates can be effectively mineralized via a dual analog system proposed by others, using a tripolyphosphate (TPP) “templating analog” and a poly(acrylic acid) (PAA) or poly(aspartic acid) (pAsp) “sequestration analog,” the latter of which generates the polymer-induced liquid-precursor (PILP) mineralization process studied in our laboratory.	Poly(acrylic acid) was unable to remineralize demineralized dentin slices under the conditions employed, even when pre-treated with TPP. However, pre-treatment with TPP enhanced overall mineralization of specimens that were PILP-remineralized using pAsp.

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110	Schwendicke *et al.,* 2019, Germany	*In-vitro*	Evaluate the remineralization effects of conventional and experimental ion-releasing materials on different artificial dentin carious lesions.	Biodentine and MTA induced evident mineral precipitation, but intra/inter-fibrillar collagen mineral infiltration was only provided by biomimetic remineralisation via the use of the experimental adhesive. Complete remineralization of caries lesions remains a challenge.
111	Seo *et al.*, 2013, South Korea	*In-vitro*	This study aimed to identify the early genetic changes related to odontogenic differentiation when MTA is applied to DPSCs. This study compared the effect of MTA on gene expression in human odontogenic-differentiated cells and DPSCs by using microarray analysis.	This result shows that MTA stimulates the odontogenic differentiation of dpscs (Odontogenic-differentiated cells), and the effects of MTA are drastically increased in uninduced pulp cells compared with odontogenic-differentiated cells.
112	Sfeir *et al.,* 2014, United States of America	*In-vitro*	The objective of this study was to synthesize composite nanofibrils with highly integrated organic/inorganic phases inspired by the mineralized collagen fibrils of bone and dentin.	Our results demonstrate that using phosphorylated DPP-inspired peptides, we can successfully synthesize biomimetic composite nanofibrils with integrated organic and inorganic phases. These results provide the first step in the development of biomimetic nanostructured materials for mineralized tissue repair and regeneration using phosphopeptides.
113	Shi, Li & Wang, 2015, China	*In-vitro*	To evaluate the effect of grape seed extract (GSE) on remineralization of artificial dentin caries.	GSE positively affects the remineralization processes of artificial dentinal caries lesions, which may be a promising natural agent for remineralization therapy instead of fluoride.
114	Sun *et al.,* 2014, China	*In-vitro*	In this study, the remineralization of dentin collagen was investigated in the presence of polyacrylic acid (PAA) and L-Glu.	In summary, a bio-inspired approach was followed to reconstruct collagen-mineralized tissues with biocompatible functions, morphologies, and characteristics.
115	Suprastiwi, Putranto & Maharti, 2019, Indonesia	*In-vitro*	To analyze the Biodentine™ capability in guided tissue remineralization.	Biodentine™ is able to trigger the process of remineralization by guided tissue remineralization.

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116	Taddei, Prati & Gandolfi, 2017, Italy	*In-vitro*	This study was aimed at evaluating if a poly(HEMA-co-TEGDMA) resin (HEMA: 2-hydroxyethyl methacrylate; TEGDMA: triethyleneglycol dimethacrylate) may increase the in vitro apatite forming ability of a calcium silicate cement (CaSi), in view of developing a hydrophilic light-curable composite bio-remineralizing restorative material (R-CaSi).	The study demonstrated that the novel light-curable composite material is able to induce the remineralization of previously demineralized dentin. The possibility of using such composites as remineralizing agents for caries prevention may be envisaged. The use of poly(HEMA) in dentistry as bonding agent may improve the caries resistance of coronal dentin and root dentin.
117	Tang *et al.,* 2013, China	*In-vitro*	To investigate whether biomodification of caries-like acid-etched demineralized dentine, using proanthocyanidins-rich GSE, would promote its remineralization potential.	Transient GSE biomodification promoted remineralization on the surface of demineralized dentine, and this process was influenced by the concentration and pH value of the preconditioner. GSE preconditioner at a concentration of 15%, without pH adjustment, presented with the best results, and this may be attributed to its high polyphenolic content.
118	Tay & Pashley, 2009, United States of America	*In-vitro*	This study tested the hypothesis that biomimetic remineralization provides a means for remineralizing incompletely infiltrated resin-dentin interfaces created by etch-and-rinse adhesives.	Both interfibrillar and intrafibrillar apatites became readily discernible within the hybrid layers after 2-4 months. In addition, intra-resin apatite clusters were deposited within the porosities of the adhesive resin matrices.
119	Tay & Pashley, 2008, United States of America	*In-vitro*	In this study, hardened white Portland cement was used as the source of slow releasing calcium ions to investigate the feasibility of intrafibrillar and interfibrillar remineralisation of partially demineralised human dentine in the presence of a low molecular weight polyacrylic acid, PVPA and a PCF.	Guided tissue remineralisation is potentially useful in the remineralisation of acid-etched dentine that is incompletely infiltrated by dentine adhesives, as well as partially demineralised caries-affected dentine.
120	Thula-Mata *et al.,* 2011, United States of America	*In-vitro*	To evaluate a remineralization of artificial dentin lesions via the polymer-induced liquid-precursor (PILP) process.	Since no hydroxyapatite (HA) clusters were observed on the surface of the pilp mineralized samples, we could conclude the signal was produced from the mineral embedded within the dentin matrix. TEM and diffraction analyses suggest that both intrafibrillar and interfibrillar remineralization occurred in the demineralized dentin matrix.

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121	Toledano *et al.,* 2015, Spain	*In-vitro*	The aim of this study was to evaluate if mechanical cycling influences bioactivity at the resin–carious dentin interface after bonding with Zn-doped self-etching adhesives.	Zno incorporated in the primer promoted an increase in height of the phosphate and carbonate peaks, crystallinity, relative mineral concentration, and lower collagen crosslinking. Zncl2 included in the bonding attained similar results, but relative mineral concentration decreased, associated to higher crosslinking and restricted collagen maturation. In general, a substantial restoration of the mechanical properties of caries-affected dentin substrata occurred when SEB-Zn doped adhesives were used and load cycled was applied, leading to functional and biochemical remineralization.
122	Toledano *et al.,* 2020, Spain	*In-vitro*	The aim of this study was to evaluate the remineralization ability of three endodontic sealer materials at different root dentin regions.	Oxipatite reinforced the inner root zone at any third of the radicular dentin, by increasing both nanohardness and remineralization. When using calcypatite, the highest nanohardness was found at the apical third of the inner root dentin, but the lowest mechanical performance was obtained at the cervical and the medial thirds of the roots. Therefore, application of oxipatite as sealing cement of root canals is recommended. Oxipatite, when used as an endodontic sealing material, strengthens radicular dentin.
123	Toledano *et al.,* 2018, Spain	*In-vitro*	To evaluate if mechanical and thermal cycling promote remineralization at the resin dentin interface after bonding with three different adhesive approaches.	Thermo+load cycling promoted the highest biomimetic remineralization at the hybrid layer formed with EDTA+SB and Clearfil-SEB, at the 1 month time point.
124	Toledano *et al.,* 2014, Spain	*In-vitro*	The purpose of this study was to evaluate some physical–mechanical and morphological changes of demineralised dentine at early stages of dentine remineralisation.	PDD and TDD preserved some mineral contents. After demineralisation and immersion in all solutions, width of nanomechanical properties and fibrils was increased, and total nanoroughness was decreased. Peritubular and intertubular dentine were remineralised.
125	Vollenweider *et al.,* 2007, Switzerland	*In-vitro*	The present study therefore investigated the use of 20–50 nm bioactive glass for dentin remineralization, and compared this new form of bioactive glass to a micron-sized reference material.	The substantially higher remineralization rate induced by nanometer-sized vs. Micrometric bioactive glass particles corroborated the importance of particle size in clinical bioglass applications.

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126	Wang *et al.,* 2013, China	*In-vitro*	The purpose of this study is to demonstrate the balance between meta-stability and crystallization of ACP precursor phase. Our findings also provide evidence for the role of ACP during biomineralization and reveal a possible approach to repair CMT - collagenous mineralized tissues.	This study provides evidence to understand the role of ACP during biomineralization and a possible approach to repair collagenous mineralized tissues by biomimetic crystal engineering.
127	Wang *et al.,* 2011a, China	*In-vitro* and *In-situ*	To evaluate in situ remineralizaiton of partially demineralized human dentine mediated by a biomimetic non-collagen peptide.	With the presence of our synthetic peptides, these nanoprecursors were transformed into polyelectrolytestabilized apatite nanocrystals that assembled at the ‘‘hole zones’’ (gap remineralization) and along the surface of the dentine collagen fibrils (surface remineralization). It was concluded that deliberately designed peptide (eeeeeeeedspespspeedr) improved in situ remineralization of acid-etched dentine.
128	Wang *et al.,* 2015, China	*In-vitro*	Here we report the use of a modified multifunctional dendrimer, synthesized by the introduction of phosphate groups via a Mannich-type reaction onto poly(amidoamine) (PAMAM) dendrimers, to biomimetically remineralize dentin.	These results showed that demineralized dentinal collagen fibrils were successfully phosphorylated by the treatment of phosphorylated PAMAM dendrimers and embedded with calcium-deficient hydroxyapatite after remineralization. Thus, phosphorylated PAMAM dendrimers could be applied as a minimally invasive method of management of dentin caries, employed to improve the resin–dentin bonding stability and also be used in the treatment of dentin hypersensitivity.
129	Wang *et al.,* 2011b, Canada	*In-vitro*	The present study aimed to evaluate dentine remineralization through a 7-day period of artificial saliva (AS) storage induced by bioactive glass 45S5 (BAG) and by bioactive glass modified with soda-lime spherical glass.	The dentine specimens treated with bioactive glass showed lower roughness, and most of the dentinal tubules appeared completely occluded during the AFM and SEM examination. Although the concentration of bioactive glass in the M-BAG is 60% of that contained in the original version, both formulations have similar potential in dentine remineralization. These bioactive powders developed for air-abrasive use may be considered as innovative bioactive materials for therapeutic remineralization of dental hard tissues.

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130	Weir *et al.,* 2017, China	*In-vitro*	The objective of this study was to investigate the remineralization of human dentin lesions via restorations using nanocomposites containing nanoparticles of amorphous calcium phosphate (NACP) or NACP and tetracalcium phosphate (TTCP) for the first time.	Novel NACP-based nanocomposites were demonstrated to achieve dentin lesion remineralization for the first time. These results, coupled with acid-neutralization and good mechanical properties shown previously, indicate that the NACP-based nanocomposites are promising for restorations to inhibit caries and protect tooth structures.
131	Wu *et al.,* 2017, China	*In-vitro*	This study evaluated self-etch adhesive as a carrier for amorphous calcium phosphate (ACP) nanoprecursors to continuously deliver biomimetic remineralization of self-assembly type I collagen and demineralized dentin.	The intra- and extrafibrillar remineralization of type I collagen and demineralized dentin was confirmed by TEM and selected-area electron diffraction when the adhesives were used as a carrier loaded with Si-ACP particles.Therefore, we propose self-etch adhesive as a novel carrier for ACP nanoprecursors to continuously deliver biomimetic remineralization.
132	Xiao *et al.,* 2017, United States of America	*In-vitro*	To investigate the effects of combined BMC + poly (amido amine) (PAMAM) on remineralization of demineralized root dentin in a cyclic artificial saliva/lactic acid environment for the first time.	The combined BMC + PAMAM induced the greatest root dentin remineralization, *Significance*. The excellent root dentin remineralization effects of BMC + PAMAM were demonstrated for the first time. BMC + PAMAM induced effective and complete root dentin remineralization in an acid challenge environment. The novel BMC + PAMAM method is promising for Class V and other restorations to remineralize and protect tooth structures.
133	Xie *et al.*, 2008, United States of America	*In-vitro*	Development of a novel bioactive resin-modified glass-ionomer cement system with therapeutic function to dentin capping mineralization.	The results show that the system not only provided strengths comparable to original commercial Fuji II LC cement but also allowed the cement to help mineralize the dentin in the presence of SBF. It appears that this bioactive glass-ionomer cement system has direct therapeutic impact on dental restorations that require root surface fillings.
134	Xie *et al.,* 2015, China	*In-vitro*	This study evaluated the biomineralization and dentinal tubules occlusion abilities of the carboxyl-terminated polyamidoamine dendrimer (PAMAM-COOH) on human demineralized dentin in vivo at different time points.	PAMAM+Ca(OH)2 group almost all the dentinal tubules were occluded by the minerals, however this was not found in other groups. There was potential superiority of the carboxyl-modified PAMAM with Ca(OH)2 solution in promoting the remineralization of initial dentin lesions.

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135	Xie *et al.,* 2016, China	*In-vivo* (animal testing with rats)	To evaluate the remineralization effect of Ca(OH)2 pre-treated with carboxylmodified polyamidoamine dendrimer (PAMAM) on demineralized dentin.	The microhardness of PAMAM-COOH-applied specimens had a significantly higher than those without application. These results suggest that the PAMAM-COOH promoted the biomineralization of demineralized dentin and displayed favourable effects on blocking the open dentinal tubules.
136	Xie, Bedran-Russo & Wu, 2008, United States of America	*In-vitro*	We used an in vitro pH-cycling model to evaluate the effect of GSE (grape seed extract) on the remineralization of artificial root caries.	We concluded that grape seed extract positively affects the demineralization and/or remineralization processes of artificial root caries lesions, most likely through a different mechanism than that of Fluoride. Grape seed extract may be a promising natural agent for non-invasive root caries therapy.
137	Xu *et al.,* 2011, Singapore	*In-vitro*	The aim of this study is to remineralize partially demineralized dentine sections using phosphorylated chitosan (P-chi) based on mimicking the nucleating role of the phosphorylated noncollagenous proteins in the biomineralization of dentine.	This biomimetic methodology resulted in favorable surface properties (i.e., highly negative charge and low interfacial free energy between substrate and remineralizing medium) for crystal nucleation. Thus, P-chi can facilitate surface remineralization of dentine and thereby could find application in the minimally invasive management of dentine caries and dentine hypersensitivity.
138	Xun *et al.,* 2014, China	*In-vitro*	To modify biomacromolecules, such as chitosan and collagen, to synthesize a mineralized template that will induce self-growing remineralization of tooth enamel.	The parent hydrogels that were easily obtained and controlled could mimic the template of the enamel mineralization and induce a self-growing hydroxyapatite, which is an important step in the structural bionics of enamel.
139	Yoo *et al.,* 2016, South Korea	*In-vitro*	To investigate and compare the biomineralization ability of this pozzolan-based (Pz-) MTA sealer cement under various root canal obturation conditions.	Pz-MTA cement can be used as a promising bioactive root canal sealer to enhance biomineralization of dentinal tubules under controlled environment.
140	Zaharia *et al.,* 2017, Romania	*In-vitro*	The purpose of this work is to induce biomimetic remineralization of acid etched coronal human dentine in artificial saliva (AS) under agarose (A) hydrogel or chitosan (CS)-A hydrogel action.	Longer exposed (7 days) dentine in the presence of agarose hydrogel shows a higher mineral-to-collagen ratio (A7). Since dentine mineralization increases, the collagen quality factor decreases in succession A-CS4]R]A7. Results show a benefic effect of chitosan on remineralization of etched dentine.

Code	Author, Year, Country	Type of Study	Objectives	Main results
141	Zanini *et al.,* 2012, France	*In-vitro*	To evaluate the biological effect of Biodentine on immortalized murine pulp cells (OD-21).	Our results suggest that Biodentine is bioactive because it increased OD-21 cell proliferation and biomineralization in comparison with controls. Biodentine can be considered as a suitable material for clinical indications of dentin-pulp complex regeneration, such as direct pulp capping.
142	Zhang *et al.,* 2012, Singapore	*In-vitro*	The objective of this study was to develop a biomimetic method to facilitate remineralization of demineralized dentine through phosphorylation of type I collagen in demineralized dentine using sodium trimetaphosphate.	The phosphorylation and Ca(OH)(2) pretreatment enhanced surface remineralization of the partially demineralized dentine. This biomimetic methodology resulted in favorable surface properties (i.e. Highly negative charge and low interfacial free energy between substrate and aqueous medium) for crystal nucleation, and thus could be a promising method to remineralize superficially demineralized dentine lesions.
143	Zhang *et al.,* 2019, China	*In-vitro*	Evaluate the effect of conditioning solutions containing DL-aspartic amino (Asp) on dentine remineralization induced by bioactive glass 45S5 (BAG) in a simulated oral environment.	The study demonstrated that a superior remineralization efficacy of BAG with Asp pretreatment on dentine.
144	Zhou *et al.,* 2014, China	*In-vitro*	To investigate the application of triclosan-loaded PAMAM-COOH dendrimer on the human dentine.	The triclosan-loaded G4-COOH provides a general strategy to cure dental caries and repair damaged dentine at the same time, which forms a potential restorative material.
145	Zhou *et al.,* 2012, China	*In-vitro*	In this study, they coated dopamine on demineralized enamel and dentin surfaces to evaluate the effect of polydopamine coating on dental remineralization.	No significant difference was observed in the remineralization of enamel. However, a significant difference was found in dentin remineralization between dentin with and without polydopamine coating. Thus, coating polydopamine on dental tissue surface may be a simple universal technique to induce enamel and dentin remineralization simultaneously.

Due several classification strategies, for this manuscript we have grouped the main remineralization strategies according to the main chemical compounds of the remineralizing material (Table 1). The group using chemical elements for dentin remineralization includes calcium, silica, phosphate, sodium, fluoride, amina/ammonia, zinc, chloride, carbonate, silver, aluminum, hydroxide, tin, niobium, copper, potassium, iodide, nitride, boron, lithium and tantalum. The acids were divided into polyacrylic acid, polyaspartic acid, polyvinylphosphonic acid, ethylenediaminetetraacetic acid, glutamic acid and citric acid. Moreover, for the group using other compounds, the division was into casein phosphopeptide-amorphous calcium phosphate (CCP/ACP), natural extracts, bioactive glass, biomimetic analogs and/or synthetic peptides, polyamidoamine dendrimer (PAMAM), glass ionomer, chlorhexidine, hydroxyapatite, polymer-induced liquid-precursor (PILP), chitosan, methacrylate, EMD or DMP (enamel matrix derivates or dentin matrix protein), agarose and glutaraldehyde, as shown in Table 2.

4 DISCUSSION

Current techniques for dentin remineralization involve chemical processes based on the original tissue formation (Cao *et al.*, 2015). Therefore, we found that the literature pointed to the development of biomaterials that seek to achieve this objective of mineral replacement through different strategies, and so this review listed the chemical elements involved in each of these biomaterials.

About 90% of the organic matrix of dentin is formed by type I collagen, and caries, acid challenges or other factors can expose this collagen in the oral environment. The action of enzymes, such as endometalloproteinases, can degrade it, after being exposed (Cao *et al.*, 2015). This type of collagen is important for biomineralization, as it attracts amorphous calcium phosphate (ACP) nanoprecursors. This review identified several recent studies that used type I collagen as a framework for attracting ACP mediated by NCPs. This strategy has been exhaustively studied and is explained by the interfibrillar and intrafibrillar remineralization of dentin from the attraction of ACP nanoprecursors and the apatite nucleation of collagen fibrils (Niu *et al.*, 2014). Likewise, casein phosphopeptide - amorphous calcium phosphate (CPP / ACP) has been used and reported as a potential remineralization inducer from the same chemical perspective.

The collagen matrix serves as a deposition of minerals. However, it does not provide clustering mechanisms for hydroxyapatite. There are non-collagenous proteins (NCPs) for this mediation, which correspond to only 10% of the dentin organic composition. NCPs, such as dentin matrix protein (DMP1) and dentin phosphoryn (DPP, DMP2), have an affinity for calcium and collagen and regulate the nucleation and growth of minerals (Nudelman *et al.*, 2013). Different proteins can act as nucleating or mineral inhibitors. Therefore, other strategies involve the study of this part of dentin for the dentin remineralization process. Much research is currently focused on the development of biomimetic analogs of these NCPs, since the purification process of these natural NCPs is difficult and unfeasible on a large scale. Acids such as polyacrylic acid (PAA) and polyvinylphosphonic acid (PVPA) can be used as analogs of these proteins in the biomimetic dentin mineralization process (Cao *et al.*, 2015). Other acids, such as citric acid, polyaspartic acid (pAsp), polycarboxylic acid, glutamic acid (L-Glu) and even ethylenediaminetetraacetic acid (EDTA) have

been proposed as analogs for this same clinical situation in the studies identified in this review.

Using EDTA, dentin's biomimetic remineralization occurs in the preservation of dentin collagen and the maintenance of an exposed layer, free of minerals in dentin. This mechanism has also been proposed in the use of NCP analogs for remineralization. In this same method, strategies using 37% phosphoric acid (PA) for the same methodology have been identified, mainly to mimic the demineralization/remineralization processes of natural physiological imbalance processes, as with dental caries.

The combination of acids with a function analogous to NCPs and other materials containing elements also present in the dentinal matrix, such as phosphorus, calcium and sodium, have also been investigated. Because the current strategies recommend using materials with known remineralizing potential, such as MTA or Portland cement, and other hydraulic cements with different trade names, but based on the same chemical structure containing the phosphate, calcium, and sodium. These cements also include silica, resulting in the formation of a more stable aggregated polymer for the remineralization process (Bertassoni *et al.*, 2009). Therefore, together with materials such as cements containing this composition, these acids more easily stabilize the rescued ACP nanoprecursors. These are small enough to penetrate the intermineralized and damaged collagen interfibrillary and intrafibrillary spaces, imitating the formation of a regularly ordered apatite. However, each acidic chemical attack increases the surface energy and subsequent chemical bonding of ACP nanoprecursors, and some of them are still being elucidated and evaluated in these studies.

The phosphorylated collagenous matrix will serve as a model or niche for attracting the ACP nanoprecursors responsible for the regular apatite nucleation of the remineralization process. This dentin collagen is important because it is phosphorylated so that it can promote remineralization. In addition to the acids already mentioned and the cements that act together, other materials such as chitosan (chi), peptides and oligopeptides with a phosphate group, the PAMAM dendrimer, phosphate solutions and protein analogs have also demonstrated effective results with this same mechanism. Studies included in this review indicated strategies using bioactive glasses, agarose, zinc, chlorhexidine, methacrylate, glutaraldehyde, synthetic peptides and natural extracts (obtained from grapes, green tea and others).

Strategies involving fluoride potential to aid in dentin remineralization have also been extensively studied, and this review identified methods using its free form ions, gels, varnishes, or materials such as the glass ionomer. More recent studies also point to new strategies using several chemical precursors such as tin, aluminum, carbonate, niobium, copper, amine or ammonia, potassium and iodide, silver, nitride, boron, lithium and tantalum, grouped in this review according to their composition by chemical elements of commercially available materials, in Table 1. However, these studies are sparse, and their action mechanisms are still not completely elucidated, despite the positive results obtained for dentin remineralization.

The included articles document the growth of studies in this promising area for the development of new dental materials. However, some limitations are the impossibility of grouping the studies due to the heterogeneity of the articles included, and the impossibility of performing statistical analysis to quantitative synthesis. Even though the biomimetic approaches have demonstrated a potential for promoting dentin remineralization, more studies are required to confirm other desirable properties of remineralizing action, such as materials with antifouling, antibacterial, biocompatibility characteristics for better performance, clinical applicability, and increased dentin-resin bond strength.

For future studies, clinical trials with more extended observation periods and a high degree of scientific evidence would be advisable to confirm the data collected in this scoping review. More research is suggested, mainly with clinical application methodology and *In-vivo* monitoring since most of the included studies have been *In-vitro*. Understanding the dentin remineralization process *in-vivo* allows considering other parameters such as oral hygiene conditions and control of the patient's biofilm, habits, diet, age, and oral microbiota, which may influence the success of restorative treatment depending on strategy. Therefore, despite the scientific challenges in these studies, the main results showed the importance of the biomimetic dentin remineralization for improve the bonding performance of adhesive restorations (Abuna *et al.*, 2016; Abunawareg *et al.*, 2017; Adebayo, Burrow & Tyas, 2010; Aggarwal & Bhasin, 2018; Barbosa-Martins *et al.*, 2018; Barbosa-Martins *et al.*, 2018; Bauer *et al.*, 2016; Bauer *et al.*, 2019; Borlotto *et al.*, 2017; Chen *et al.*, 2016; De Morais *et al.*, 2018; Degrazia *et al.*, 2018; Dickens, Flaim & Takagi, 2003; Ge *et al.*, 2017; Gupta *et al.*, 2017; Huang *et al.*, 2019; Jun *et al.*, 2018; Liu *et al.*, 2014; Osorio *et al.*, 2016a; Reyes-Carmona, Felippe & Felippe, 2010; Sauro *et al.*, 2015; Toledano *et al.*, 2015).

5 CONCLUSION

Biomimetic remineralization of dentin is a promising area for the development of new dental materials. The remineralizing action can be enhanced in materials with anti-fouling, antibacterial and biocompatible characteristics, without compromising mechanical and adhesive properties.

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PRESS RELEASE

Esta dissertação de mestrado visa contribuir com a pesquisa de materiais dentários, apresentando as estratégias disponíveis na literatura científica sobre o assunto de remineralização de um dos tecidos presentes no dente dos seres humanos: a dentina. Estes estudos favorecem o desenvolvimento de novos materiais que substituam o mineral perdido neste tecido perdido de maneira biomimética, ou seja, que imitem o natural. Com os avanços nesta área, espera-se que essas estratégias possam ser incorporadas nos novos materiais odontológicos, de modo que possibilitem a execução de restaurações mais duradouras, bem como a redução de custos de investimento para o dentista e para o paciente e, ainda, possam garantir biocompatibilidade, evitando reações adversas. Assim, é um trabalho de base, que fundamenta e elucida o panorama geral das estratégias de remineralização de dentina, com o objetivo final de melhoria na qualidade de tratamentos oferecidos para o consumidor final, ou seja, os pacientes.

ANNEX

Annex 1 Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) Checklist

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
TITLE			
Title	1	Identify the report as a scoping review.	#1, #2, #3
ABSTRACT			
Structured summary	2	Provide a structured summary that includes (as applicable): background, objectives, eligibility criteria, sources of evidence, charting methods, results, and conclusions that relate to the review questions and objectives.	#17, #18
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known. Explain why the review questions/objectives lend themselves to a scoping review approach.	#29
Objectives	4	Provide an explicit statement of the questions and objectives being addressed with reference to their key elements (e.g., population or participants, concepts, and context) or other relevant key elements used to conceptualize the review questions and/or objectives.	#31
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists; state if and where it can be accessed (e.g., a Web address); and if available, provide registration information, including the registration number.	#32
Eligibility criteria	6	Specify characteristics of the sources of evidence used as eligibility criteria (e.g., years considered, language, and publication status), and provide a rationale.	#32
Information sources*	7	Describe all information sources in the search (e.g., databases with dates of coverage and contact with authors to identify additional sources), as well as the date the most recent search was executed.	#33
Search	8	Present the full electronic search strategy for at least 1 database, including any limits used, such that it could be repeated.	#33
Selection of sources of evidence†	9	State the process for selecting sources of evidence (i.e., screening and eligibility) included in the scoping review.	#37
Data charting process‡	10	Describe the methods of charting data from the included sources of evidence (e.g., calibrated forms or forms that have been tested by the team before their use, and whether data charting was done independently or in duplicate) and any processes for obtaining and confirming data from investigators.	#38
Data items	11	List and define all variables for which data were sought and any assumptions and simplifications made.	#38

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
Critical appraisal of individual sources of evidence§	12	If done, provide a rationale for conducting a critical appraisal of included sources of evidence; describe the methods used and how this information was used in any data synthesis (if appropriate).	Not applicable.
Synthesis of results	13	Describe the methods of handling and summarizing the data that were charted.	#38
RESULTS			
Selection of sources of evidence	14	Give numbers of sources of evidence screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally using a flow diagram.	#39
Characteristics of sources of evidence	15	For each source of evidence, present characteristics for which data were charted and provide the citations.	#41
Critical appraisal within sources of evidence	16	If done, present data on critical appraisal of included sources of evidence (see item 12).	Not applicable.
Results of individual sources of evidence	17	For each included source of evidence, present the relevant data that were charted that relate to the review questions and objectives.	#45
Synthesis of results	18	Summarize and/or present the charting results as they relate to the review questions and objectives.	#51
DISCUSSION			
Summary of evidence	19	Summarize the main results (including an overview of concepts, themes, and types of evidence available), link to the review questions and objectives, and consider the relevance to key groups.	#81
Limitations	20	Discuss the limitations of the scoping review process.	#83
Conclusions	21	Provide a general interpretation of the results with respect to the review questions and objectives, as well as potential implications and/or next steps.	#84
FUNDING			
Funding	22	Describe sources of funding for the included sources of evidence, as well as sources of funding for the scoping review. Describe the role of the funders of the scoping review.	Not applicable.

JBI = Joanna Briggs Institute; PRISMA-ScR = Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews.
* Where *sources of evidence* (see second footnote) are compiled from, such as bibliographic databases, social media platforms, and Web sites.
† A more inclusive/heterogeneous term used to account for the different types of evidence or data sources (e.g., quantitative and/or qualitative research, expert opinion, and policy documents) that may be eligible in a scoping review as opposed to only studies. This is not to be confused with *information sources* (see first footnote).
‡ The frameworks by Arksey and O'Malley (6) and Levac and colleagues (7) and the JBI guidance (4, 5) refer to the process of data extraction in a scoping review as data charting.
§ The process of systematically examining research evidence to assess its validity, results, and relevance before using it to inform a decision. This term is used for items 12 and 19 instead of "risk of bias" (which is more applicable to systematic reviews of interventions) to include and acknowledge the various sources of evidence that may be used in a scoping review (e.g., quantitative and/or qualitative research, expert opinion, and policy document).

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