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Optimizing Pulp Protection : A Systematic Review of Pulp capping agents and their Properties

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Abstract

Pulp capping materials posses a vital role in in maintain structural integrity of tooth. Ca^{++}/OH^{-} release which often play a pivotal role are often ignored. To ensure all the properties are given equal importance, this systematic review was conducted to select the pulp capping agent which fulfils all the properties required for a successful clinical outcome.This review insights common clinician for selecting a material during deep carious management.The aim of this review is to select the best pulp capping material that satisfies all the requirements of physical, chemical and biological properties that are beneficial for pulp therapy.Protocol was formulated in accordance with PRISMA checklist 2020 and registered on PROSPERO (CRD42020160461). Electronic search from databases such as Medline/PubMed, Google Scholar, and Cochrane were performed from the year 2008–2023. In Vitro studies that evaluated chemical, physical, mechanical and biological properties of pulp capping agents were included. A total of 15 studies were included in the systematic review. After assessing the risk of bias using Newcastle-Ottawa Scale, data was compiled of the included studies. A total of 3038 articles were retrieved from selected databases and out of which 15 studies were included in this review. Based on the risk of bias assessment 2 studies were of very good quality, 5 studies of good quality and 8 studies were of satisfactory quality. Among the pulp capping agents, Tech Biosealer capping, MTA Plus gel and Biodentine exhibited high values of Calcium ion release both at short (3 days) and long-time interval (28 days) whereas Lime-Lite released least amount of Calcium ions. Biodentine had the highest compressive strength and is most cytocompatible. This review leads to the conclusion that calcium silicate-based materials demonstrate superior chemical, physico-mechanical and biological properties, closely aligning with the desirable attributes for pulp therapy. Out of the Calcium silicate-based materials Biodentine exhibits properties that are best for pulpal healing.

Keywords: Antimicrobial activity – Biodentine - Calcium Hydroxide - Calcium ion release Cytotoxicity - Direct pulp capping – Mineral Trioxide Aggregate – Properties

INTRODUCTION

Clinical decision-making is central to everyday dental practice. The pulp plays a crucial role in sustaining apexogenesis, which is vital for the long-term retention of a permanent tooth. A root with a favorable crown/root ratio and sufficiently thick dentinal walls is necessary to withstand normal functional stresses. Recent studies have suggested that Vital Pulp Therapy (VPT) could be a broader alternative, even for symptomatic mature permanent teeth with deep caries, aiming to preserve pulp vitality and potentially avoid non-surgical root canal therapy[1]. However, the success of VPT is closely linked to the severity of pulp inflammation and the extent of histopathological involvement in the pulp tissue.

VPT aims to preserve the health of the dental pulp.[1] In cases of deep carious lesions, the inflammation is typically restricted to the superficial coronal pulp, while the tissue deeper inside remains unaffected.[2] This therapy plays a crucial role in stimulating the pulp odontoblasts to produce reparative dentin and promote the remineralization of existing dentin, thereby aiding the healing of the dentin-pulp complex.[3]

Preserving and maintaining pulp vitality is a primary objective in restorative dentistry. Historically, placing a medicament or material directly on a pulpal exposure during caries excavation has been controversial, with conventional endodontic therapy often being recommended instead. This reluctance is due to the unpredictable outcomes of traditional materials and treatment protocols, which lack superior chemical, physico-mechanical, and biological properties.

An ideal pulp capping material(PA) should adhere to tooth substrate, maintain a sufficient seal, be insoluble in tissue fluids, dimensionally stable, nonresorbable, nontoxic, non- carcinogenic and exhibit biocompatibility and bioactivity.[4,5]

Traditionally various materials have been used for pulp capping including calcium hydroxide,[6] hydrophilic resins,[7] resin modified glass ionomer cement,[8] tricalcium phosphate.[9] More recently Calcium silicate-based cements eg. Mineral Trioxide Aggregate (MTA),[10] Biodentine,[11] Calcium enriched mixture,[12] Bioaggregate[13] and Theracal LC [14]have been introduced.

Studies have revealed that properties such as Ca^{++}/OH^{-} ion release, compressive strength,

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solubility, water absorption, depth of cure, and pH are equally important for the success of pulp therapy, alongside their biological properties. However, no conclusive evidence is available to determine "which pulp capping material satisfies all the requirements of physical, chemical, and biological properties beneficial for pulp therapy".

However, to the best of our knowledge, there is limited review on which of these agents possesses the optimal properties for ensuring the selection of an ideal PA for a given clinical scenario. Hence, the purpose of this review was to assess various pulp capping materials and compare their properties for use in pulp therapy.

MATERIALS AND METHODS

Protocol and registration

The PRISMA guidelines 2020[15] was referred for writing the protocol and the systematic review was registered on PROSPERO, reference number CRD42020160461.[16]

Research question

Which among the recent pulp capping materials satisfies all the requirements of physical, chemical and biological properties beneficial for pulp therapy? Literature related to traditional and recent pulp capping agents/materials were selected and their properties such as in terms of Ca^{++}, OH^{-} ion release, solubility, water absorption, pH, compressive strength, setting time, agar overlay cytotoxicity test, gene expression and cytocompatibility were assessed for the purpose of contributing to pulp repair and regeneration.

i. P (Participants/population):- Pulp capping agents.
ii. I (Intervention(s)):- New and improved biocompatible and bioactive agents, with remarkable physicochemical properties, have been recently tested for the purposes of pulp repair and regeneration.
iii. C (Comparison):- Different materials (calcium silicate based) are currently available as alternatives to traditional DPC dressers, such as calcium hydroxide.
iv. O (Outcome):- To know exactly which material exhibits the best properties in terms of Ca^{++}, OH^{-} ion release, solubility, water absorption, pH, compressive strength, setting time, agar overlay cytotoxicity test, gene expression and cytocompatibility (MDPC-2). To review various properties of PA and to determine the suitable pulp capping agents that fulfil the requirements for pulp therapy.

v. S (Study design):- (a) In Vitro studies that evaluated chemical and physicomechanical properties of pulp capping agents,

(b) In Vitro Studies that evaluated the biological properties of pulpcapping agents

SEARCH STRATEGY

From the year 2008-2023, electronic databases such Medline/PubMed, Google Scholar, and Cochrane were searched. The search strategy used were a combination of MeSH terms and keywords. The search terms were divided into three components, i.e.,
" Properties" , "Pulp Capping materials" and finally, the end component "Pulp Capping". The three search components were then combined with the Boolean logic term. The detailed search strategy is mentioned in **Table 1.**

Database Results	No	Search Query	
Date: 08.10.2023	Filters used: 1 .Publication period: 2008-2023		
Pubmed	#1	**(((((Properties[Title/Abstract]) OR (Cytototoxicity[MeSH Terms])) OR (Calcium Ion release[MeSH Terms])) OR (Hydroxyl ion release[MeSH Terms])) OR (Antimicrobial activity[MeSH Terms])) OR (physical properties)**	4,993,418
	#2	**(((((Pulp Capping materials[Title/Abstract]) OR (Tricalcium Silicate[MeSH Terms])) OR (Theracal[MeSH Terms])) OR (Biodentine[MeSH Terms])) OR (MTA[MeSH Terms])) OR (Calcium Hydroxide[MeSH Terms])**	5421
	#3	**Pulp Capping**	3080
	#4	**#1 AND #2 AND #3 AND ((** (2008:2023[pdat]))	145
Google Scholar	#1	**(Properties AND Pulp Capping materials AND Pulp Capping)**	2868
Cochrane	#1	**(Properties[Title/Abstract] AND Pulp Capping materials[Title/Abstract] AND Pulp Capping[Title/Abstract])**	25

Table 1. The adjusted search terms used to extract literature from electronic data base

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Eligibility Inclusion criteria

- In vitro studies that evaluated chemical, physical and mechanical properties of PA
- Experimental studies that evaluated biological properties PA

Exclusion criteria

- Studies that evaluate techniques and not materials
- Studies on patent related dental materials

Data identification and screening

Data screening is mentioned in Figure 1. Total of 15 articles were included in the study.

Data Collection Process

Titles and abstract of studies obtained by using the search strategy along with additional sources were screened by two reviewers to identify whether those studies meet the predetermined inclusion criteria. Each relevant article was then independently and critically evaluated for its research quality. Any discrepancy was then resolved by discussion and consensus with a third reviewer. Only papers that fulfilled all the eligibility criteria were included.

Quantitative assessment

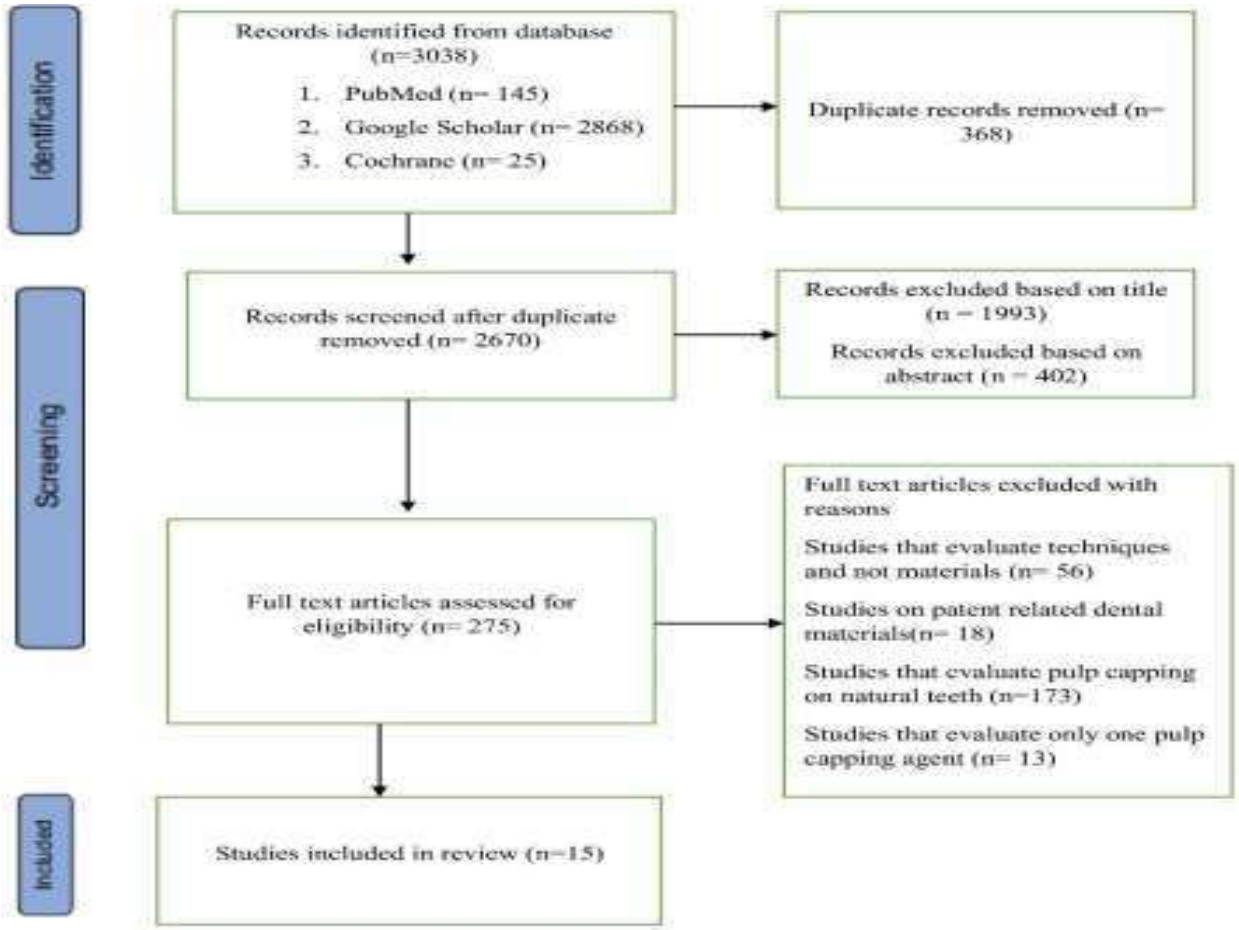
Quantitative data assessment was assimilated in statistical meta-analysis using Review Manager Software (RevMan) 5.3. The outcomes included best properties in terms of Ca^{++}, OH^{-} ion release, solubility, water absorption, pH, compressive strength, setting time, agar overlay cytotoxicity test, gene expression and cytocompatibility(MDPC -2).

Quality assessment

The assessment of each study was done using the Newcastle–Ottawa scale. The quality of studies was done by two independent reviewers (SD and TBD) and disagreements are resolved by consensus with a third reviewer (SN). Newcastle–Ottawa scale has three domains: selection, comparability and outcomes which are used to describe the quality evaluation. Each study was assigned a relevant score which ranged from an unsatisfactory '0' to a very good of '10'. A score between 9-10 is for a very good study, a score between 7–8 is for a good study, a score between 5-6 is for a satisfactory study and a score of ≤ 4 is for an unsatisfactory study and will be rejected.

RESULTS

A total of 3038 articles were retrieved from selected database. After exclusion of duplicates, the title/abstract screening of the remaining articles was done that yielded 275 articles. Of these 275 articles, 260 studies were excluded and the remaining 15 studies were included in this review [Flowchart 1].



Flowchart 1 : PRISMA flowchart. From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, *et al.* The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

Risk of bias

Full-text articles were assessed independently by both the reviewers for the risk of bias of the included studies individually and the overall quality of the included studies are given in Table 2. In this current review, 2 studies were of very good quality, 5 studies of good quality and 8 studies were of satisfactory quality.

Table 2- Quality assessment of included studies

	Selection				**Comparabilility**	**Outcome**		
Author	Representativeness of the sample	Sample Size	Non Response rate	Ascertainment of screening tool	Comparability	Assessment of outcome	Statistical Test	Total
Gandolfi *et al.*[18], 2012	1	0	1	2	0	1	1	6
Gandolfi *et al.*[19], 2015	1	1	1	2	1	2	1	9
Shen *et al.*[20], 2010	0	0	1	2	2	2	1	8
Natale *et al.*[21], 2015	1	0	1	2	2	2	1	9
Farrugia *et al.*[22], 2018	0	0	1	2	0	1	1	5
Poggio C *et al.*[23], 2014	2	0	1	2	1	1	1	8
Jang *et al.*[24], 2014	0	0	1	2	1	1	1	6
Poggio C *et al.*[25], 2014	1	0	1	2	0	1	0	5
Camargo *et al.*[26], 2009	1	0	1	2	0	1	1	6
Camilleri *et al.*[27], 2014	1	0	1	2	0	1	1	6
Kaup *et al.*[28], 2015	0	1	1	2	1	2	1	8
Jun *etal.*[30], 2017	1	0	1	2	1	1	1	7
Torshabi *et al.*[31], 2016	0	0	1	2	0	1	1	5
Lin *et al.*[32],2022	1	1	1	2	1	1	1	8

Key characteristics

The data extraction sheet for this systematic review is described in **Table 3**.[17-31] Comparison of chemical properties of various PA is given in **Table 4**. **Table 5** gives the comparison of physical and mechanical properties of various PA. Comparison of biological properties of various PA is given in **Table 6.**

Table 3: Data Extraction from the included studies

Sl. No.	Authors, Year of publication	Research Focus	Methods and Methodologies used	Research Findings	Conclusions
1.	Gandolfi et al.[20], 2012	To evaluate the chemical–physical properties of TheraCal compared with reference pulp-capping materials (ProRoot MTA and Dycal)	Calcium and hydroxyl ion release over 28 day measured using magnetic stirrer using a multiparameter laboratory meter. (n=10) Solubility and water uptake at 24 h using an analytical balance. (n=10) Cure depth of TheraCal, ProRoot MTA and Dycal were evaluated using ISO 4049. (n=3) Radiopacity of TheraCal, ProRoot MTA and Dycal were evaluated aluminium step wedge. (n=6)	TheraCal released significantly more calcium and alkalinize the surrounding fluid initially to pH 10–11 (3 h–3 days) and subsequently to pH 8–8.5 (7–14 days) than ProRoot MTA and Dycal throughout the test period. Solubility of TheraCal (1.58%) was low and significantly less than that of Dycal (4.58%) and ProRoot MTA (18.34%). TheraCal had a cure depth of 1.7mm. TheraCal had a radiopacity of 1.07 ± 0.06 mm Al.	TheraCal displayed higher calcium releasing ability and lower solubility than either ProRoot MTA or Dycal. The capability of TheraCal to be cured to a depth of 1.7 mm may avoid the risk of untimely dissolution.

Table 3- conti.

2.	Gandolfi et al.[21], 2015	The chemical-physical properties of calcium silicate cements (ProRoot MTA, MTA Angelus, MTA Plus, Biodentine, Tech Biosealer capping, TheraCal) versus conventional pulp capping calcium hydroxide biomaterials were compared	Calcium ion release and pH measured using potentiometric method and compensated electrode. (n=13 for each material) Porosity, water sorption and solubility were assessed (n=13 for each material) Surface analysis was done using ESEM/EDX (n=13 for each material)	Tech Biosealer capping, MTA Plus gel and Biodentine showed the highest values of calcium release, while Lime-Lite the lowest. All the materials showed alkalizing activity except for Life and Lime-Lite. Calcium silicate materials showed high porosity values: Tech Biosealer capping, MTA Plus gel and MTA Angelus showed the highest values of porosity, water sorption and solubility, while TheraCal the lowest. MTA Plus showed the thickest coating, ProRoot MTA showed large.spherulitic deposits, while TheraCal presented very small dense spherulites	The high rate of calcium release and the fast formation of apatite represent epigenetic signals for pulp cells and may explain the role and function of calcium silicate biomaterials as scaffolds to induce the formation of new reparative tissue (dentin bridge) and clinical healing.
3.	Shen et al.[22], 2010	To evaluate the setting time, compressive strength, solubility, pH, calcium release, cytotoxicity, and antimicrobial properties of new calcium phosphate/calcium silicate/bismutite (CPCSBi) materials used for pulp	Ion release measured using Inductively coupled plasma mass spectroscopy (n=3), Setting time using Vicat needle (n=3), Compressive strength using Universal Testing machine (n=3), Solubility using predetermined formula (n=3), pH, cytotoxicity, antibacterial properties and isolation of	Concentrations of Bi3þ, Ca2þ, PO42_, and Si4þ increased with time in deionized water solutions. The setting time of CPCSBi and Dycal was 13 min 50 s and 2 min 25 s, respectively. There were no statistical differences in compressive strength and solubility between CPCSBi and Dycal. The pH of CPCSBi (10.9) was lower than that of CH	CPCSBi has a clinically useful setting time, pH, good compressive strength, excellent antimicrobial properties, minimal cytotoxicity, and acts to stimulate expression of DDSP, OCN, and TGFb1 in human pulp cells.These

		capping.	dissoluble dentin matrix components were assessed (n=3).	(11.6) and Dycal (12.5) after immersion for 24 h. Only slight cytotoxicity appeared for CPCSBi, whereas both CH and Dycal produced moderate discoloration and lysis. Antimicrobial potency of the CPCSBi was approximately 5–10 times greater than that of Dycal and CH groups. CPCSBi demonstrated increased expression of dentin sialo phosphoprotein (DSPP) and osteocalcin (OCN) dramatically in human pulp cells by RT-PCR.	observations suggest that CPCSBi is a promising candidate for use as a pulp-capping Material
4.	Natale et al.[23], 2015	To compare the ion release and mechanical properties of a calcium hydroxide (Dycal) and calcium silicate cements (MTA Angelus & Biodentine)	Calcium and hydroxyl ion release in water from 24-h set cements were calculated from titration with HCl (n=3). Calcium release after 7, 14, 21 and 28 days at pH 5.5 and 7.0 was measured using ICP-OES (n=6). Flexural strength (FS) and modulus (E) were tested after 48-h storage and compressive strength (CS) was tested after 48 h and 7 days (n=10)	Titration curves revealed that Dycal released significantly fewer ions in solution than calcium silicates. Calcium release remained constant at pH 7.0, while at pH 5.5 it dropped significantly by 24% after 21 days. At pH 5.5, MTA Angelus released significantly more calcium than Dycal, while Biodentine had superior ion release than Dycal at pH 7.0 . Biodentine had superior flexural strength, flexural modulus and compressive strength than the other cements, while MTA Angelus had higher modulus than Dycal.	All materials released constant calcium levels over 28 days, but release from Dycal was significantly lower than Biodentine and MTA Angelus depending on pH conditions. Biodentine had substantially higher strength and modulus than MTA Angelus and Dycal.

5.	Farrugia et al.[24], 2018	To characterize new light-curable tricalcium silicate–based pulp capping materials and compare their surface and antimicrobial properties with clinically available Theracal and Biodentine.	The surface characteristics of 3 light-curable pulp capping materials based on a resin and filled with tricalcium silicate and tantalum oxide radiopacifier and Theracal and Biodentine were assessed by scanning electron microscopy, X-ray diffraction, and contact angle measurement (n=3). The antimicrobial activity was determined by the direct contact test and the antibiofilm activity by the adenosine triphosphate assay and the confocal laser scanning Live/Dead assay (n=3).	Biodentine exhibited a hydrophobic surface, significantly higher antimicrobial properties in the direct contact test, but this property was absent in the antibiofilm activity tests. The resins filled with tricalcium silicate and Theracal showed higher antimicrobial activity than Biodentine in the adenosine triphosphate and live/dead assays.	The surface characteristics of a material affect its antimicrobial properties. The experimental resin-modified materials exhibited comparable antimicrobial properties with other light-curable pulp capping agents.
6.	Poggio C et al.[25], 2014	To evaluate and compare the antimicrobial activity and cytocompatibility of six different pulp-capping materials: Dycal, Calcicur, Calcimol LC, TheraCal LC, MTA Angelus and Biodentine.	To evaluate antimicrobial activity, materials were challenged *in vitro* with *S mutans, S salivarius*, and *S sanguis* in the agar disc diffusion test. (n=6). Cytocompatibility of the assayed materials towards ratMDPC-23 cells were evaluated at different times by both MTT and apoptosis assays. (n=6).	MTA-Angelus, TheraCal LC , Dycal , and Calcicur showed a decreasing antibacterial effect on S. mutans only. Dycal was effective against S. salivarius. Calcicur , Dycal , and Calcimol LC , followed by Biodentine , were effective on S. sanguis. Biodentine and MTA-Angelus showed the highest percent of cell cytocompatibility when compared to the other pulp-capping materials.	MTA-based products showed lower cytotoxicity and valuable antibacterial activity, different from calcium hydroxide-based materials, which exhibited not only higher antibacterial activity but also higher cytotoxicity. Dycal was the only pulp-capping

					material showing a discrete antibacterial effect against all the three streptococca l strains.
7.	Jang et al.[26], 2014	To evaluate the cytotoxicity, setting time and compressive strength of MTA and two novel tricalcium silicate-based endodontic materials, Bioaggregate (BA) and Biodentine (BD)	Cytotoxicity was evaluated by (XTT) assay (n=6 for each materials). Measurements of 9 heavy metals (arsenic, cadmium, chromium, copper, iron, lead, manganese, nickel, and zinc) were performed by inductively coupled plasma-mass spectrometry (ICP-MS) of leachates obtained by soaking the materials in distilled water. Setting time measured using Vicat apparatus and compressive strength using UTM (n=10 for each materials).	BA had comparable cell viability to MTA, whereas the cell viability of BD was significantly lower than that of MTA. The ICP-MS analysis revealed that BD released significantly higher amount of 5 heavy metals (arsenic, copper, iron, manganese, and zinc) than MTA and BA. The setting - BD < MTA and BA, and the compressive strength of BA <MTA and BD	BA and BD were biocompatible, and they did not show any cytotoxic effects on human periodontal ligament fibroblasts. BA showed comparable cytotoxicity to MTA but inferior physical properties.

8.	Poggio C et al.[27], 2014	To evaluate the biocompatibility of a new pulp capping material (Biodentine, Septodont) compared with reference pulp capping materials: Dycal (Dentsply), ProRoot MTA (Dentsply) and MTA Angelus(Angelus)	The cytocompatibility of murine odontoblasts cells (MDPC-23) were evaluated at different times using a 24 Transwell culture plate by Alamar blue test and MTT assay.	Results, obtained in 24, 48 and 72 hours show the higher pe rcentage of cell vitality with Biodentine. Histological evaluations carried on samples prepared with Bi odentine demonstrated the ability of the material to induce the differentiation of odontoblasts starting from pulp progenitor cells, forming a mineraliz ing matrix with the characteristics of dentin.	Biodentine & MTA based products show lower cytotoxicity varying from calcium hydroxide-based material which present higher cytotoxicity. Biodentine has shown t o be the material with th e best qualities and char acteristics that are the basis of biocompatibility. Because of the lower cy totoxicity and the highe r bio-inductive ability, Biodentine can be considered an ideal cement for pulp capping
9.	Camargo et al.[28], 2009	To evaluate the cytotoxicity and genotoxicity of the new castor oil bean cement (COB) material in comparison to commonly	Specimens of COB, calcium hydroxide and mineral trioxide aggregate (white and gray MTA) were extracted in culture medium (n=7). Generation of reactive oxygen species (ROS) was determined by	Clear cytotoxic effects were detected only with extracts of Hydro C under the current experimental conditions. The two MTA preparations induced an insignificant reduction in the number of cells. In contrast, the extracts of	The COB and the two MTA preparations did not negatively influence cell survival or ROS production and may thus be further considered for pulp capping studies.

		used pulp capping materials (Calcium hydroxide cement (Hydro C), grey MTA, white MTA).	flow cytometry (FACS) using H2DCF-DA as a dye. Survival of tHPCs was measured photometrically using a crystal violet assay after a 24-h exposure period. Genotoxicity was analysed by FACS.	COB slightly induced cell proliferation. Extracts of Hydro C caused a twofold increase in ROS production, whilst the other tested materials were ineffective. An increase in the number of micronuclei was not detected with any material tested; Hydro C slightly increased the number of cells in G1 and G2.	
10.	Camilleri et al.[29], 2014	To assess the hydration of Biodentine and Theracal LC and a prototype radiopacified tricalcium silicate–based material after their application as pulp-capping materials for 14 days and to compare it with direct hydration for 14 days in an aqueous solution.	The extent of hydration of Biodentine, Theracal LC, and a prototype radiopacified tricalcium silicate–based material with a similar composition to Biodentine but not incorporating the additives was assessed by scanning electron microscopy and energy dispersive spectroscopy (n=6 for each materials). The extent of hydration was compared with material hydration when used as direct pulp capping materials by using a tooth culture model. Material activity was assessed by x-ray	Biodentine hydration resulted in the formation of calcium hydroxide which was present in the material matrix and also on the material surface. Theracal was composed of large cement particles which showed some evidence of reaction rims on hydration. The material matrix included a barium zirconate phase as radiopacifier and also a glass phase composed of strontium, silicon and aluminum. This phase could not be detected in XRD analysis. Formation of a calcium phosphate phase was demonstrated on Theracal. Both materials leached calcium ions in solution.	Presence of a resin matrix modifies the setting mechanism and calcium ion leaching of Theracal.

			diffraction analysis to investigate the deposition of calcium hydroxide by the materials, and calcium ion leaching was assessed by ion chromatography.		
11.	Kaup et al.[30], 2015	To compare solubility, microhardness,radiopacity, and setting time of Biodentine with ProRoot MTA.	Solubility in distilled water (n=72 for each materials) and Phosphate Buffered Saline (PBS) buffer was determined (n=72 for each materials). For microhardness-testing, all samples were loaded with a diamond indenter point with a weight of 100 g for 30s (n=10 for each cement). Radioopacity measured using aluminium step wedge and setting time were evaluated in accordance with International Standard ISO 6876:2001 (n=10 for each cement). .	Both materials showed a solubility of <3% after 24 h. At all exposure times Biodentine was significantly more soluble than ProRoot MTA. After immersion in PBS-buffer a precipitation of hydroxyapatite was visible. The Vickers microhardness for Biodentine was significantly higher (62.35 ± 11.55HV) compared with ProRoot MTA (26.93 ± 4.66HV). ProRoot MTA was significantly more radiopaque (6.40 ± 0.06 mm Al) than Biodentine (1.50 ± 0.10 mm Al). The setting time for Biodentine (85.66 ± 6.03 min) was significantly lower than for ProRoot MTA (228.33 ± 2.88 min)	Both materials can be used in different indications where specific material properties may be favourable. Hence, the here tested material properties are of clinical relevance
12.	Jung et al.[31], 2015	To compare the mineralizatio n inductive capacity of	Viability measured by - 3-[4,5-dimethylthiazol-2-yl]-2,5 diphenyltetrazolium	The effects of MTA, BD, and BA on cell viability were similar. Both enhanced DSPP and	Biodentine and Bioaggregate stimulated odontoblastic differentiation

		Biodentine (BD) and Bioaggregate (BA) with MTA and to investigate possible signalling pathways of mineralizatio n in human dental pulp cells (HDPCs).	bromide. Potential to induce odontoblast differentiation, expression of DSPP and DMP1 - mRNA level evaluated by RTPCR. MAPK signaling inhibition examined by Alizarin red staining.	DMP1 mRNA expression compared to the control group, but to the same extent as MTA.	and mineralization nodule formation by activating the MAPK pathway as did MTA.
13.	Jun et al.[32], 2017	To compare the cytotoxicity and biomineraliza tion of (Bioactive® [BA]) with calcium hydroxide incorporated (Dycal [DC]and a light-curable counterpart (Theracal).	Eluates from set specimens were used for investigating the cytotoxicity and biomineralization ability, determined by alkaline phosphatase (ALP) activity and alizarin red staining (ARS) (n=3). Cations and hydroxide ions in the extracts were measured.	An hDPSC viability of less than 70% was observed with 50% diluted extract in all groups & with 25% diluted extract in the DC. Culturing with 12.5% diluted BA extract statistically lowered ALP activity and biomineralization compared to DC but TC did not. Ca (~110 ppm) and hydroxide ions (pH 11) were only detected in DC and TC. Ionic supplement-added BA,which contained similar ion concentrations as TC, showed similar ARS mineralization compared to TC.	The BA was similar to, yet more cytotoxic to hDPSCs than, its DC and TC. BA was considered to stimulate biomineralizati on similar to DC and TC only when it released a similar amount of Ca and hydroxide ions.
14.	Torshabi et al.[33], 2016	To investigate the cytotoxicity of	Disc shaped specimens of each material (n=3 for each material at each time point) (in 2 set stat: A,	CEM cement demonstrated favorable cell viability values when completely set (24 h set MTA = 24 h set CEM) at	Set CEM and set MTA Angelus exerted similar favourable effects on the mitochon drial activity & viability

		nanohybrid (MTA) in comparison with calcium enriched mixture (CEM) cement & MTA Angelus, using human gingival fibroblasts (HGFs)	set for 24 h; B, set for 30 min; and C, fresh stat) were prepared. HGFs were exposed to tested materials extracts or control media. Cytotoxicity testing was performed using the (4,5dimethylthiazol2yl) 2,5diphenyltetrazoliumbromide assay in 2-time intervals.	both time intervals. After 24hour of incubation, CEM in Groups B and C demonstrated higher cell viability values than MTA. After 72 h of incubation, these groups of CEM and MTA showed equal cell viability. All samples of nanohybrid MTA had slight cytotoxic effects after 24 h of incubation, and moderate cytotoxic effects after 72hrs of incubation.	of fibroblasts. Nanohybrid MTA could not be recommended as a material of choice for cervical root resorption.
15.	Lin et al.[], 2022	To compare the chemical and physical properties of eight contemporary direct pulp capping Materials(Dycal, Lime Lite, Ultrablend Plus, MTA Angelus, Biodentine, Theracal LC,Ceramir, Protect LC, Biocap) .	Specimens were fabricated using silicone molds (10 mm by 1.8 mm). Once the specimens were unmolded, their initial weights were measured with an analytical balance. After their initial weights were obtained, specimens were immersed in plastic test tubes containing 10 mL of deionized water at 36.8 degrees Celsius before the measurement endpoints. pH measured using pH sensor after 24hrs, 7days, 28days and 90 days. (n=10)	Biodentine significantly released more calcium ions followed by Ceramir, Protect LC and Dycal. Lime Lite released least amount of calcium ions. After 90 days Biodentine and MTA Angelus showed significantly higher pH. Lime Lite had limited effects in raising the pH to alkaline. Significantly higher water sorption and solubility was observed with Dycal. More than 10 percent of diamensional expansion after seven days were observed with Ceramir Protect LC and Theracal LC.	Biodentine and MTA Angelus demonstrated more favourable in vitro characteristics for clinical pulp capping purposes.

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			Calcium concentration was measured with a calibrated calcium ion-selective electrode. (n=10) The percentage of water sorption (**Sp**) was calculated using Sp = [(Ws − Wd)/ Wd] × 100, and the following formula was used to determine the water solubility (**So**), So = [(Wi − Wd)/ Wi] × 100]). Ws denotes saturated mass, Wd denotes dry mass. Dimensional change was calculated with the following formula: [(final volume – initial volume)/initial volume] × 100 percent.		

Table 4 : Comparison of chemical properties of various pulp capping materials [19]

	Materials	Ca^{++} release 1 day (ppm)	Ca^{++} release 28 days (ppm)	OH^- release 1 day (ppm)	OH^- release 28 day (ppm)	Solubility%	Water Sorption %
Calcium Hydroxide	Calxyl	515± 17.4	-	12.73± 0.17	-	-	-
	Calxyl RO	530.6± 47.8	-	12.88± 0.05	-	-	-
	Dycal	51.8±1 1.14	122.9± 17.4	10.49± 0.41	9.81±0. 61	4.91±0.2 9	5.06±0.2 8
	Life	31.5±3. 8	109.8± 7.2	7.54±0. 81	7.62±0. 11	3.98±0.5 9	4.41±0.7 5
	Lime-Lite	11.9±4. 0	35.4±7. 8	8.50±0. 39	7.08±0. 07	1.73±0.5 2	8.92±1.9 6
Calcium Silicate	Biodentine	113.4± 11.1	245.8± 17.9	11.63± 0.51	9.26±0. 66	11.83±0. 52	12.60±0. 15
	MTA Plus	68.1±1 2.3	112.6± 16.0	11.48± 0.59	8.24±0. 45	18.55±0. 77	24.87±1. 45
	MTA Plus +gel	165.8± 31.9	230.9± 32.4	12.52± 0.27	7.99±0. 22	14.68±3. 62	26.46±6. 25
	MTA Angelus	84.9±1 2.3	198.1± 21.0	11.22± 0.11	8.94±0. 73	29.55±2. 35	37.02±5. 36
	ProRootM TA	61.0±1 4.1	146.1± 29.7	10.53± 0.59	7.20±0. 12	10.89±0. 48	14.73±0. 52
	Tech Biosealer capping	190.1± 21.0	370.9± 27.5	11.79± 0.25	7.81±0. 49	27.87±1. 13	36.67±2. 74
Resin and Calcium Silicate	TheraCal	52.2±3. 8	137.8± 12.9	7.89± 0.02	8.12±0. 07	2.75±1.0 4	13.96±1. 56

Table 5 :Comparison of physical and mechanical properties of various pulp capping materials[18,21,24,28]

	Materials	Radiopacity (mm of Aluminium)	Setting time(min)	Compressive Strength 48 hours (MPa)	Compressive Strength 7 days (MPa)	Depth of Cure (mm)
Calcium Hydroxide	Calxyl	-	-	-	-	-
	Calxyl RO	-	-	-	-	-
	Dycal	2.30±0.10	2-3	18.2±2.8	16.5±4.7	-
	Life	-	-	-	-	-
	Lime-Lite	-	-	-	-	-
Calcium silicate	Biodentine	2.80±0.48	15±1	45.1±12.5	49.1±2.6	-
	MTA Plus	-	128±8	-	-	-
	MTA Plus +gel	-	-	-	-	-
	MTA Angelus	4.72±0.45	85±2.4 (initial) 130-230(final)	16.1±5.0	18.0±6.5	-
	ProRoot MTA	4.34±0.64	228.33± 2.88	-	-	-
	Tech Biosealer capping	-	55	-	-	-
Resin and Calcium Silicate	TheraCal	1.07±0.06	0.3	-	-	1.69± 0.04

Table 6 : Comparison of biological properties of various pulp capping materials [20,23]

	Materials	Cytotoxicity (Agar Overlay Method)	Gene expression	Cytocompatibility with MDPC -23 cells (Transwell method)
Calcium Hydroxide	Calxyl	(a)Degree of Cytotoxicity Score – 2 (b)Moderate Cytotoxicity	Less expression to DSPP, OCN, TGF-β1 genes	
	Calxyl RO			
	Dycal			Lowest at all 3-time intervals (24hours,48 hours,72 hours)
	Life	-	-	
	Lime-Lite	-	-	
Calcium Silicate	Biodentine	(a)Degree of Cytotoxicity Score – 1 (B) Slight Cytotoxicity	Higher expression to DSPP, OCN, TGF-β1 genes	(a) Similar to MTA at (24hours and 48 hours) - High cytocompatibilty (b) At 72 hours -Highest Cytocompatibility
	MTA Angelus			(a) Similar to Biodentine at (24 hours and 48 hours) - High cytocompatibilty (b) At 72 hours -Slight less cytocompatibility compared to Biodentine
	MTA Plus +gel			
	MTA Plus			
	ProRoot MTA			
	Tech Biosealer capping			
Resin and Calcium Silicate	TheraCal			(a) Low at 24 hours; but high when compared to Dycal (b) Lowest at 48 hours and 72 hours

DISCUSSION

Recent research states that the complete or non-selective carious removal is considered overtreatment.[32] Similarly, in Endodontics a shift has been evident wherein VPT techniques such as PA, partial and complete pulpotomy is slowly replacing complete pulp tissue and root canal treatment. This is based on observations that healing is possible even after carious exposure, provided the inflammation is no more severe than reversible pulpitis.[33]

In this review chemical, physico-mechanical and biological properties of various pulp capping materials are compared. In terms of chemical properties, the goal of using these medicaments is to utilize the calcium ions they release. Calcium ions not only enhance pulp cell proliferation, differentiation but are also essential for hard tissue mineralization in pulp cells.[34,35] It is also crucial that the liner remains non-acidic, as acidity can elevate cytotoxicity.[36] On the other hand, an alkaline material contributes to an antimicrobial effect,[37,38] the desired environment for bridging outcome,[39] releasing growth factors such as TGF- β1.[40]and enhancing the formation of tertiary dentin.[41] An ideal PA material should not dissolve in a water-based solution faster than the deposition of new reparative dentin. Ideal water sorption is essential for ion release,[18] but excessive solubility of materials leads to voids underneath restorations. On the contrary, a significant increase in the volume after water uptake may cause unfavourable stress to the restoration. In terms of physico-mechanical properties, the compressive and flexural strength of pulp capping materials are essential to withstand the forces exerted during placement and function of restorative materials. Additionally, the setting time should be optimized for ease of use by the practitioner. Radiopacity is another important requirement of these materials to observe the radiographic interface between the material and tooth surface as well as for accurate diagnosis and follow-up for treated teeth. With regard to biological properties, it can be said that an ideal pulp-capping material should be bioactive, biocompatible, and exhibit antibacterial activity against microorganisms to facilitate the healing of injured dental pulp.[42,43]

Dental biomaterials have been introduced with the goal of achieving the safest tissue response and optimizing outcomes.[44] Knowledge of the dentin-pulp complex healing mechanism has led to the development of new materials for maintaining pulp vitality [45], and it is often challenging for the clinician to determine which material would work best in

each clinical scenario. The choice of biomaterials should be guided by evidence and should consider patient-centered outcomes, reliable mineralized tissue formation, and the sustained vitality of the pulp.[46]

Calcium hydroxide has been successful for many years for Direct Pulp Capping (DPC) because of its excellent antimicrobial property, induction of mineralization[47] and low cytotoxicity.[48]However, research has highlighted several drawbacks, including high solubility, poor adhesion,[49] and the potential to obliterate the pulp chamber and create tunnel defects. Consequently, there is a need for new materials with improved properties.

One of the materials that has evolved out of this need are the Calcium-silicate based materials. The greatest advantage of these materials is its bioactivity. Bioactive materials are defined as "those that trigger a biological response in the tissue-material interface, resulting in the formation of bonding between material and tissue".[50] This is evident in the favourable responses observed when the material is in contact with soft tissues such as pulp and periodontal tissues, or with hard tissues such as dentin.

Research has also shown that calcium-silicate cements can form a strong bond with dentin through areas of mineral infiltration. This process involves the creation of mineral tags and the diffusion of calcium and silica into the dentin. [51] Furthermore, when these materials come into contact with pulp tissue, they can stimulate the formation of a dentin bridge. [52]

MTA has emerged as a good PA, with less pulpal inflammation, cytocompatibility[45,52] and superior antibacterial properties. The disadvantages include high solubility,[53] longer setting time[54] poor handling characteristics and tooth discoloration.Later, in 2011, a new material appeared in the market: BiodentineTM (Septodont, Saint Maur des Fosses, France), as a replacement for both coronal and root dentin. The quick hardening of this cement, in comparison with previous calcium silicates, and its improved mechanical properties made it suitable for definitive restorations replacing dentin and as a temporary cement to restore enamel.[55] Unlike MTA, Biodentine does not contain calcium aluminate, calcium sulfate, or bismuth oxide. The absence of bismuth oxide in Biodentine is particularly notable, [56] as this component in MTA is known to retard setting, negatively influence biocompatibility and cause discoloration.[57] Consequently, Biodentine demonstrates several advantages over MTA, including better mechanical properties, [20,58] superior color stability,[59] less tooth discoloration, ease of application, and a much shorter initial setting time of 12-16 minutes compared to MTA's 3-4 hours.[54] However, Biodentine's primary drawbacks are its lower radiopacity[60] and the challenge of achieving the desired consistency.[61] These differences

underscore the potential benefits of using Biodentine in specific dental applications where rapid setting and aesthetic outcomes are prioritized.

Material such as TheraCal LC (Bisco Inc., Schamburg, IL, USA), formed by calcium silicates mixed with composite resins, had controllable setting time and exhibited bioactive property. Theracal LC demonstrated higher compressive strength, shear bond strength and superior push out bond strength when compared with other pulp capping materials. A study by Camilleri *et al*.[26]suggested that TheraCal LC restrain moisture diffusion from pulp-dentine complex which leads to incomplete hydration. It was reported that the ability of calcium ion release from TheraCal LC was significantly less than Biodentine.[26]Another study reported[61] that ProRoot MTA released significantly greater amounts of calcium ions than TheraCal LC. In a study by Basel *et al*.[62] where they have compared the effects of Theracal LC and MTA on direct pulp capping based on histological findings it showed that dentin bridge composition in the TheraCal group had 80% effective tubules and 20% defective tubules, while in the MTA group, the proportions were 90% and 10%, respectively. Dentin bridge thickness in the TheraCal group was greater than 0.25 mm in 60%, and 0.1-0.25 mm in 40% of the sample compared to the MTA group, which had 70% greater than 0.25 mm, and 30% between 0.1 and 0.25 mm in dentin bridge thickness. Theracal LC invivo showed inferior results concerning thickness and continuity of the dentine bridge after direct pulp capping in rabbit incisors when compared with Biodentine.[63] Poggio *et al*. studied the antimicrobial activity of different pulp capping materials using agar diffusion tests. They found that TheraCal LC had a significantly lower effect on *S. salivarius* and *S. sanguis* when compared with a calcium hydroxide liner (Dycal).[22]

Till date most of the studies focuses mainly on chemical reactions of various pulp capping agents and the reparative dentine formation by chemical stimulation of these materials, but limited studies are available where bioactive components are being taken into account which will help in dentinogenesis and wound healing the way it occurs naturally in the body. Incorporation of growth factors, Bone Morphogenic Proteins (BMPs), Transforming Growth Factor (TGF) in the currently available pulp capping agents which may help in induction of dental pulp stem cells to odontoblasts has also not been given due consideration .

None of the materials exhibited all the desirable properties that are required for pulp therapy and hence development of a novel biomaterial which will incorporate natural derivatives for predictable dentinogenesisis is the need of the hour.

In this systematic review, all articles concluded that Calcium silicate-based materials exhibited properties which closely resemble ideal properties that are beneficial for pulp therapy. Among the Calcium silicate-based materials, Biodentine exhibited properties that are best for dentinogenenesis and therefore pulpal healing.[64]

Biodentine, a bioactive tricalcium silicate material, is not highly regarded or common among dental professionals. Yet, the literature is usually in favor of Biodentine as a pulp capping material instead of Calcium Hydroxide, MTA, Theracal as well as other PA.

Based on this systematic review it was possible to obtain a scientific overview of the properties of various pulp capping agents. A comprehensive literature search was carried out in this review. This suggests that Biodentine has superior properties for pulp capping. Hence this systematic review will ensure easy selection of best pulp capping agent that fulfils all the requirements for pulp therapy.

LIMITATIONS

One of the important facts to consider in interpretation of the results from the included in vitro studies is that these do not truly represent clinical situations. This is due to the fact that teeth function differently within the oral cavity in harmony with specialized periodontium and in vitro studies fail to reproduce such an environment.

Although Biodentine exhibits superior properties for pulp capping procedures, more clinical trials are required on Biodentine to assess the clinical and radiographical success when compared with other calcium silicate based materials. Because of the diversity of the outcomes of chemical, physico-mechanical and biological properties, meta-analysis was not performed.

CONCLUSION

In this review it can be concluded that Calcium silicate-based materials exhibits best chemical, physico-mechanical and biological properties which closely resembles to ideal properties that are beneficial for pulp therapy. Among the Calcium silicate-based materials Biodentine exhibits properties that are best for pulpal healing. However, more long-term in vivo studies with a larger sample size and controlled clinical settings are required to draw a definitive conclusion on these materials.

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