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Review Article

Different pulp capping agents and their effect on pulp inflammatory response: A narrative review

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ABSTRACT

Several factors can directly damage dental pulp. Pulp healing requires controlled inflammation, which can be directed through specialized medical materials to eliminate infection and promote pulp repair. This review aimed to categorise these materials and identify their histological and molecular effects on pulp tissue or isolated cells in culture. In addition, we sought to identify which of these materials could trigger a favourable inflammatory pathway that could direct the pulpal response toward healing and regeneration. A single database (PubMed) was used, and the search strategy was based on MeSH terms. The search was conducted for articles published in English between January 2010 and December 2023, including those with histological and molecular findings. Only 33 articles met our inclusion criteria. Several conventional pulp capping agents have been shown to induce pulp healing and repair through dentine bridge formation. These materials show varying degrees of inflammation, ranging from moderate to mild, which may diminish over time. Other experimentally developed materials were also studied, either alone or in combination with conventional products; these materials demonstrated promising potential to reduce inflammation and superficial necrosis associated with conventional products. However, they still do not meet all the criteria for ideal pulp-capping materials and need further development for commercialisation. Several inflammatory pathways were also addressed in this review, along with favourable tissue responses to induce pulp regeneration. The immunomodulatory role of M2 phenotype macrophages is currently the most accepted, though the lack of standardised experimental procedures across studies hinder precise decision-making.

1. Introduction

The dental pulp is a tissue that can be directly damaged by various factors. Short-term stimuli, including cavity preparation, can cause acute damage but often allow for rapid repair. Conversely, long-term irritants such as cracks, dental caries, erosion, and filling leakage can lead to pulp necrosis if left untreated (Samir et al., 2023).

Dental pulp consists of various cells, including odontoblasts, fibroblasts, macrophages, B lymphocytes, T lymphocytes, mast cells, and undifferentiated ectomesenchymal cells (Galler et al., 2021). Odontoblasts are highly specialised cells positioned at the interface with the dentine. This location allows them to serve as a barrier against irritants. They detect damage and respond by initiating an inflammatory response, secreting antibacterial agents, neutralising bacterial toxins, and forming mineralised tissue (Gaje and Ceausu, 2020, Galler et al., 2021).

Inflammation in general is initially characterised by the secretion of pro-inflammatory mediators such as tumour necrosis factor (TNF-α), interleukin (IL)-β, interferon (IFN)-γ, and IL-6 (Al-Ghurabi, 2018, Goldberg et al., 2008). In contrast, the anti-inflammatory mediators, such as nitric oxide, IL-10, and transforming growth factor beta (TGF-β), are released to reduce tissue damage and allow the healing process. The balance between pro-inflammatory and anti-inflammatory signalling can determine the fate of the pulp, as increasing pro-inflammatory mediators over low anti-inflammatory mediators may lead to pulp necrosis (Goldberg et al., 2008, Shah et al., 2020). A favourable pulpal response toward healing is characterised by the formation of tertiary dentine, which protects the pulp from bacteria and other irritants (He et al., 2022).

Several conventional pulp capping agents have been used to induce healing and repair dentine, including calcium hydroxide, mineral trioxide aggregate (MTA), Biodentine, and bioceramic paste (Ali et al., 2022, Dong and Xu, 2023, Hilton et al., 2013). These agents form a calcified dentine bridge to cover the injured region and allow the

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undamaged part of the pulp to heal. However, the formed calcific barrier varies depending on the material used. Calcium hydroxide tends to result in unfavourable tunnel defects and porosities, whereas other materials often produce an atubular (osteoid-like) dentine barrier (Jalan et al., 2017, Muruganandhan et al., 2021).

The literature also illustrates other pulp capping materials which are still under investigation. Most of these newly developed materials are claimed to have an immunomodulatory effect that can alter the inflammation process toward favourable pathways to promote tissue healing over necrosis (Chen et al., 2021, Sousa et al., 2022). However, the immune pathway that controls the pulpal response toward favourable histological and molecular results and its relationship to the capping material used is still ambiguous. Therefore, this review aimed to identify the effects of different pulp-capping materials (conventional or experimental) on the histological and molecular responses of the pulp. Moreover, we sought to identify which of these materials could trigger favourable inflammatory pathways that could direct the pulpal response toward healing and regeneration.

2. Search strategy

Only PubMed database was used, and the search strategy was based on MeSH terms in the following combinations: (**'Pulp Capping Agents' OR 'Pulp Capping Agent' OR 'Pulp Capping') AND ('Immunomodulation' OR 'Immunologic Factors' OR 'Biomodulator' OR 'Biomodulators' OR 'Molecular' OR 'Cell Culture' OR 'histology').** The search was conducted for articles published in English between January 2010 and December 2023. Only studies with histological and molecular findings were included. Case reports, case series, narrative reviews, social media sources, clinical trials, and studies with radiographic findings only were excluded. After an initial search, 126 articles were identified. Of these, 66 were selected for title and abstract screening, and after full text skimming, only 33 met the inclusion criteria.

3. Extracted data

The extracted data included pulp capping materials, study models, and histological and molecular findings, as listed in Table 1.

4. Classification of pulp capping agents

The pulp capping materials identified in the studies included in this review can be classified into three main groups (Fig. 1).

1. Conventional pulp capping agents.
2. Experimental materials developed for pulp capping purpose.
3. Hybrid materials; which includes suggested materials resulted from incorporation of different compounds into conventional capping agents to enhance their properties.

4.1. Conventional pulp capping agents

Calcium hydroxide was first introduced in 1928 and is still successfully used in dental practice (Dammaschke, 2008). It is available in different formulations, including water-based (Calcicur), base-catalyst (Dycal), and light-cured calcium hydroxide (Calcimol LC). These types have varying ingredients, resulting in differences in properties such as pH, biological activity, biocompatibility, and solubility. Water-based calcium hydroxide has a pH of 12.5, while light-cured and Dycal have been reported to have a pH between 10–12 and 9–11, respectively. This, in turn, affects their bioactivity and antibacterial function (Poggio et al., 2014a, Poggio et al., 2015). Calcium hydroxide has the ability to induce pulp healing and dentinal bridge formation after direct pulp exposure (Nangia et al., 2021, Tian et al., 2019). Although the exact mechanism of pulp tissue induction remains unknown, several explanations have been proposed. One suggestion is the effect of high alkaline pH, which could solubilise growth factors sequestered within the remaining dentine

Table 1
Summary of the studies included in this review.

Pulp capping material	Study model	Molecular and histological findings	Reference
Dycal (Dentsply, Sirona, PA, USA), vitrebond, single bond, and ketac molar (GIC) (3 M Espe, St. Paul, USA)	Fibroblast cells (human dental pulp)	Dycal was more cytotoxic and led to cell death. Resinous material increased production of proinflammatory mediators (IL-6, IL-8).	(Modena et al., 2020)
Dycal (Dentsply Caulk Milford, DE, USA), ProRoot MTA (Dentsply Caulk Milford, DE, USA), Adper Single Bond 2 (3 M Espe, St. Paul, USA)	Human premolar teeth (clinical study)	Dycal and single bond showed more inflammation than MTA, quality of dentinal bridge was similar for both MTA and Dycal. In Adper Single Bond group, lower quality of dentinal bridge with more time required for inflammation resolution.	(Nangia et al., 2021)
Calcium hydroxide XR (Dentsply, Montigny-leBretonneux, France), ProRoot MTA (Dentsply Tulsa Dental, Johnson City, TN, USA), and Biodentine (Septodont, Saint-Maur-des-Fosses, France)	Human pulp cells (cell culture)	All of the capping agents increased the level of transforming growth factor beta 1 (TGF −β1), increased expression of dentine sialoprotein (DSP) and nestin which regulate mineralisation.	(Laurent et al., 2012)
ProRoot MTA (Dentsply Tulsa Dental, Tulsa, OK, USA), Biodentine (Septodont, Saint-Maur-des-Fosses, France), Bioaggregate (Innovative BioCeramix Inc., Vancouver, BC, Canada)	Maxillary first molars of Dawley rats (9w age) (animal study)	After 4 weeks of capping, histological sections showed dense and thick reparative (osteodentin) dentine for all capping agents with less density for Bioaggregate, and few inflammatory cells.	(Kim et al., 2016)
ProRoot MTA (Dentsply, Tulsa, OK), calcium enriched matrix (CEM) (BioniqueDent, Tehran, Iran)	Human dental pulp stem cells (cell culture)	Induced differentiation of dental pulp stem cells (DPSC). TGF-β1 was upregulated by MTA, while FGF4 and BMP2 were upregulated by CEM.	(Asgary et al., 2014)
MTA (AWMTA; Angelus, Londrina, PR, Brazil), CEM (Bionique dent, Tehran, Iran)	Maxillary first molars of Wistar rats (age 8–10 w) (animal study)	Both materials induced complete bridge formation, the CEM was associated with higher inflammation when applied in diabetic rats. MTA produced the same level of inflammation between healthy and diabetic rats,	(Madani et al., 2014)

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Table 1 (*continued*)

Pulp capping material	Study model	Molecular and histological findings	Reference
		no correlation was found between the level of inflammation and dentine bridge formation after 4 weeks of procedure.	
Biodentine (Septodont, Saint-Maur-des-Fosses, France)	Human dental pulp stem cells (cell culture)	Upregulation of genes responsible for mineralisation (DSPP, OCN, DMP1, and BSP) through MAPK and CaMKII pathways.	(Luo et al., 2014)
MTA (Angelus, Londrina, PR, Brazil), Biodentine, water-based calcium hydroxide Calcicur (Voco GmbH, Cuxhaven, Germany), light cured calcium hydroxide Calcimol LC (Voco GmbH, Cuxhaven, Germany), TheraCal (Bisco Inc., Schaumburg, IL, USA), Dycal	Rat odontoblast-like cell line (cell culture)	MTA and Biodentine showed the highest cell viability, Dycal showed the lowest cell viability, and the calcium hydroxide-based agents and TheraCal showed intermediate cell viability.	(Poggio et al., 2014b)
TheraCal (Bisco Inc., Schaumburg, IL, USA)	Maxillary 1st molar (6w age) C57BL/6JJmsSlc mice (animal study)	Reparative dentine was formed after 28 days in histological view; mechanism of action related to activation of conical Wnt pathway (Wnt10a, Wnt3a) increasing β catenin in the cytoplasm, leading to differentiation of odontoblasts.	(Hara et al., 2021)
ProRoot MTA (Dentsply, Tulsa, OK), Biodentine (Septodont, Saint-Maur-des-Fosses, France)	Mandibular first molars of Wistar Han rats (animal study)	Both materials showed an intense inflammatory response after 3 days, the inflammation was reduced within time until 21 days. Both showed complete dentinal bridge, but the Biodentine showed pathological intra-pulpal calcification, The Biodentine showed higher expression of DSP gene which is responsible for calcification.	(Paula et al., 2020)
Fast set MTA RetroMTA (BioMTA, Daejeon, Korea)	Human third molar (clinical study)	7 months of pulp capping showed reparative dentine not resembling the genuine dentine. Some specimens showed channels running through the dentinal bridge filled with necrotic debris, irregular	(Dammaschke et al., 2019)

Table 1 (*continued*)

Pulp capping material	Study model	Molecular and histological findings	Reference
		thickness of reparative dentine.	
Neo MTA Plus (NMP; Avalon Biomed Inc., Bradenton, Florida, USA), TotalFill bioceramic sealer (TF; FKG Dentaire, La-Chaux-de-Fronds, Switzerland)	Human premolars (clinical study)	In 3w no difference was found between the two agents regarding dentinal bridge thickness. After 3 months, a complete dentinal bridge was found with higher thickness in the TotalFill group. Both materials showed complete bridge formation with inflammation disappearing after 3 months.	(Al-Saudi et al., 2019)
Bone morrow stem cells (BMSC), ProRoot MTA, hydroxy apatite/Tricalcium phosphate (HA/TCP)	Canines and premolars of dogs (animal study)	Both MTA and BMSC had the ability to produce reparative dentine, while HA/TCP showed superficial necrosis with chronic inflammatory cells and intra-pulpal calcification	(Obeid et al., 2013)
Calcium hydroxide (Sigma Aldrich, St. Louis, MO, USA), self-assembling peptide p11-4 (Curodont™ Repair, Credentis AG, Windisch, SWI), Dentine matrix protein 1 (DMP1) (R&D Systems, Inc. Minneapolis, MN, USA)	Immortalized odontoblast-like cell MDPC-23 (cell culture)	Self-assembling peptide and DMP 1 showed higher cell viability and mineralisation than calcium hydroxide. Increase in the concentration of peptide and DMP1 was associated with an increase in cell viability and mineralisation.	(Araújo et al., 2022)
Concentrated growth factor (CGF), MTA, calcium hydroxide	Pulp cells isolated from molars or premolars (cell culture)	Histologically, after three months, CGF produced a thinner dentinal bridge with a regular arrangement of odontoblast cells. MTA and calcium hydroxide had a thick dentinal bridge with fibrous hyperplasia, congestion, and disappearance of odontoblast cells. CGF Increased the gene expression of mineralisation (DSPP, DMP-1) and alkaline phosphatase (ALP), and increased the dental pulp cells proliferation and migration.	(Tian et al., 2019)
Silver (AG) dopped bioactive glass (BG) with chitosan hydrogel (CS), MTA	Maxillary first molars of Wistar rats with induced pulpitis	In 1st model, the coronal portion of the pulp changed to fibrous while the apical pulp	(Zhu et al., 2019)

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Table 1 (*continued*)

Pulp capping material	Study model	Molecular and histological findings	Reference
(Dentsply Endodontics, USA)	(animal study), human dental pulp stem cells (cell culture)	appeared healthy in AG-BG / CS group. The MTA group showed a thick dentinal bridge, but chronic inflammation was detected in the apical portion. In 2nd model, AG-BG / CS had higher anti-inflammatory properties, reducing (IL-1B, IL-6, TNF-α) by the p38 MAPK pathway, higher DSPP, and BSP gene expression.	
Hyaluronic acid Gengigel (Prof®, Ricerfarma Srl, Italy), calcium hydroxide ApexCal (Ivoclar Vivadent, Liechtenstein), dentine adhesive Excite (Ivoclar Vivadent, Liechtenstein)	Odontoblast and fibroblast cell culture from rats	Hyaluronic acid showed higher odontoblast and fibroblast cells viability, therefore, greater potential for pulpal healing. The calcium hydroxide group showed the lowest cells viability.	(Bogović et al., 2011)
MTA (Angelus, Londrina, PR, Brazil), poly aspartic acid (Alamanda Polymers Inc, Huntsville, AL, USA)	Upper 1st Molars of Wistar rats (animal model)	Both showed similar ability to form reparative dentine after 21 days. Despite MTA producing a thicker dentinal bridge, the poly aspartic acid showed a dentinal bridge with fewer spaces and cellular debris. Both materials showed immunoreactivity to osteopontin (OPN) which is associated with mineralisation. Polyaspartic acid, after 21d, showed immunoreactivity to dentine matrix protein (DMP1) suggesting its role in the healing process.	(dos Santos et al., 2023)
Composites containing polymer and hydroxyapatite (HA) with bone morphogenic protein (BMP-2), ProRoot MTA (Dentsply Sirona, Ballaigues, Switzerland)	Maxillary first molars of Wistar rats (animal study), human dental pulp stem cell (cell culture)	After 4 weeks, both materials induced tubular tertiary dentine, novel composite polymer showed similar cell viability when used in different concentrations and when compared with MTA. Pulp inflammation related to the capping procedure was not evaluated.	(Okamoto et al., 2020)
Composites of collagen scaffold and BMP-2 and/or fibroblast growth factor (FGF-2), ProRoot MTA (Dentsply, USA)	Human third molars (clinical study), Dental pulp stem cells (cell culture),	In the clinical model, at 14 days, the MTA group showed a thin layer of necrosis superficially, while the collagen scaffold group showed no signs of necrosis. In the cell culture model, the composites containing growth factors showed higher cell viability, and proteins related to mineralisation (DMP1, DSPP).	(Chakka et al., 2020)
Lithium and zinc containing bioactive glass, Biodentine	Dental pulp stem cells from exfoliated primary teeth (cell culture)	Lithium and zinc activated the Wnt/β catenin pathway by inhibiting GSK-3 protein, leading to increased AXin-2 expression that is associated with odontoblast differentiation, and also increased DSPP gene expression which is responsible for mineralisation. Release of Ca + ions from bioactive glass induces differentiation of odontoblasts. Biodentine showed the same mechanism by calcium release and activation of Wnt/β catenin	(Tran et al., 2023)
Concanavalin	Dental pulp stem cell isolated from human third molar (cell culture)	Increased proliferation of dental pulp stem cells (DPSC)	(Suardita et al., 2020)
Copaiba, calcium hydroxide, calcium hydroxide + copaiba, MTA, MTA+Copaiba	Dental pulp stem cells from exfoliated deciduous tooth	The addition of Copaiba to calcium hydroxide led to increased cell viability in comparison with the use of pure calcium hydroxide. The copaiba didn't enhance cell viability when used with MTA. Copaiba enhanced the expression of genes associated with biomineralisation when added to either calcium hydroxide or MTA. Also, it increases cell migration.	(Couto et al., 2020)
Simvastatin + Bismuth oxide-Portland cement (BPC), Emdogain +(BPC), Pure (BPC)	Human dental pulp stem cells (cell culture)	The addition of Emdogain or Simvastatin led to increased cell viability, and	(Lee et al., 2012)

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Table 1 (*continued*)

Pulp capping material	Study model	Molecular and histological findings	Reference
		enhanced gene expression of (DMP1, DSPP, ALP, OPN, and OCN) which is associated with mineralisation	
Calcium hydroxide powder (Hydroxido de Calcio P. A, Brazil) with propolis, calcium hydroxide powder	Wistar rats 12-16w old (animal study)	The addition of propolis increased the number of polarised M2 macrophages which have anti-inflammatory properties.	(Setyabudi et al., 2020)
ProRoot MTA (Dentsply Sirona, Charlotte, NC, USA)	Wistar rats 8w old (animal study). The cell line of human monocyte. Dental pulp stem cells clones extracted from human premolar (cell culture)	Dense reparative dentine was formed after 14d. MTA increased polarisation of macrophage M2 from 1-7 days which is identified by CD 163, and CD 206; also, it enhanced odontoblast differentiation with increasing gene expression (DSPP, DMP-1, BMP-2) which is responsible for mineralisation.	(Kadowaki et al., 2022)
ProRoot MTA, GSK −3β inhibitor	Upper 1st molar of 6w old wild mice (animal study)	Activation of Wnt/β −catenin pathway by GSK-3β inhibitor led to polarisation of macrophage to M2 phenotype (indirect way); also, it increased differentiation of odontoblast cells from dental pulp stem (direct way). The superiority of reparative dentinogenesis was found in the GSK-3β inhibitor group when compared with the MTA group	(Neves et al., 2020)
MTA, iRoot SP Innovative Bioceramix, Vancouver, Canada)	Macrophage cell culture	Both of them induced two phenotypes (M1, and M2) of macrophage. Initially, they produced pro-inflammatory mediators IL-1β, TNF-α, and IL-12, then anti-inflammatory (IL-10).	(Zhu et al., 2017)
Biodentine	Dental pulp stem cells from human third molar (cell culture), macrophage cell culture	The pulp capping upregulates anti-inflammatory cytokines (IL-10, TGF-β) and downregulates pro-inflammatory	(Abuarqoub et al., 2022)

Table 1 (*continued*)

Pulp capping material	Study model	Molecular and histological findings	Reference
	differentiated from T-helper 1 cell	cytokines (IL-1β, Il-12p70, and TNF-α) by polarisation of macrophage to M2 phenotype.	
IRoot SP, concentrated growth factors (CGF), a combination of IRoot Sp + CGF	Maxillary molars of rats (animal study), dental pulp stem cells isolated from human third molars (cell culture)	The combination treatment group showed a lower number of macrophage phenotype M1 on day 1 and a higher number of macrophage phenotype M2 on day 7 in comparison with other groups. All of the treatments showed an immune-modulation effect, but the combination treatment had a synergistic effect. The combination treatment showed a higher number of viable dental pulp stem cells on days 4 and 7, downregulation of pro-inflammatory mediators, and upregulation of anti-inflammatory mediators (IL-4, IL-10).	(Zeng et al., 2023)
MicroRNA-enriched extracellular vesicles isolated from DPSCs	Macrophage-conditioned media, DPSCs isolated from human third molar (cell culture)	Macrophage engulfed MicroRNA extravascular vesicles and differentiated into M2 phenotype through inhibition of toll-like receptor (TLR) and NFκB pathway; it upregulated anti-inflammatory mediators (IL-1ra and IL-10) and downregulated proinflammatory (IL-1β, IL-6, and TNF-α). It increased BMP2 secretion, allowing DPSCs differentiation into odontoblasts that can upregulate biomineralisation proteins (DMP-1, DSP)	(Zheng et al., 2020)
Resolvin E1 + collagen sponge, collagen sponge	8w old Sprague-Dawley rats (animal study), dental pulp stem cells isolated from	Resolvin E1 group showed lower bridge porosity in different time intervals (14 days, 21 days, 28 days). Resolvin E1	(Chen et al., 2021)

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Table 1 (*continued*)

Pulp capping material	Study model	Molecular and histological findings	Reference
	human third molars (cell culture)	downregulated the pro-inflammatory mediators (TNF-α, IL-1β, and IL-6), and enhanced alkaline phosphatase activity (ALP). It also upregulated the expression of genes responsible for mineralisation (DMP1, DSPP, BSP)	
Gold nanoclusters	Murine macrophage cell line, dental pulp stem cells from human third molars or premolars (cell culture)	Gold nano reduced proliferation of DPSCs. It induced polarisation of macrophage from M1 to M2 phenotype with reducing inflammatory mediators (IL-6, iNOS, TNF). It increased anti-inflammatory mediators' (BMP2, BMP6, IL-10, Wnt3a, and Wnt5a) activation of the Wnt/β-catenin pathway leading to odontoblast differentiation. Also, it increased the expression of genes related to mineralisation (DSPP, DMP-1, BSP, OPN).	(Yang et al., 2022)

regions, such as TGF-β1 (Huang et al., 2018). This induces the proliferation and differentiation of new odontoblasts or odontoblast-like cells to form a dentinal bridge (Bai et al., 2023). Another proposed mechanism involves the bioactivity of calcium hydroxide that releases calcium ions. These ions may increase bone morphogenic protein 2 (BMP2) expression in human dental pulp cells, which in turn enhances cellular differentiation into odontoblasts. This has been evidenced by the expression of genes associated with mineralisation (Li et al., 2015, Spagnuolo et al., 2023).

One drawback of calcium hydroxide is the induction of dentinal bridges with tunnel defects or incomplete bridge formation (Cox et al., 1996). This could be related to the high alkalinity of calcium hydroxide, which causes an intense release of hydroxyl ions. This alkaline environment reduces the number of viable pulp cells and increases inflammation, which may hinder complete repair (Modena et al., 2020, Nangia et al., 2021, Poggio et al., 2014a). In addition, defects in the dentinal bridge can increase the risk of future infection (Cox et al., 1996).

Calcium silicate-based cements (hydraulic cements) have been developed as pulp capping agents to overcome the aforementioned drawbacks of calcium hydroxide-based materials. MTA was the first commercially available calcium silicate-based cement, first introduced by Mahmoud Torabinejad in 1993 (Torabinejad et al., 1993). This material is composed primarily of Portland cement (di-, tricalcium silicate, and tricalcium aluminate) with the addition of bismuth oxide as an opacifier (Camilleri, 2008). This material shows superior properties to calcium hydroxide by inducing the exposed pulpal tissue to form an adequate dentinal bridge with better healing outcomes (Nangia et al., 2021). However, this cement has a long setting time, reaching approximately 3–4 h, and causes tooth discoloration, which may be related to bismuth oxide (Altan and Tosun, 2016, Lee et al., 2016). Despite the MTA capping material showing a similar calcific bridge quality as calcium hydroxide, it has lower inflammation and cytotoxicity (Nangia et al., 2021). Furthermore, the presence of a calcific bridge, determined clinically or radiographically, may not reflect the entire picture of the capping material because chronic inflammation may be detrimental to pulpal health (Yu and Abbott, 2007).

Another complication is related to the aluminium phase observed within the MTA which is considered a toxic by-product (Camilleri, 2015). This phase is associated with oxidative stress in the brain, kidneys, and liver owing to increased free radical production, which induces tissue damage. It also alters cellular functions, including protein

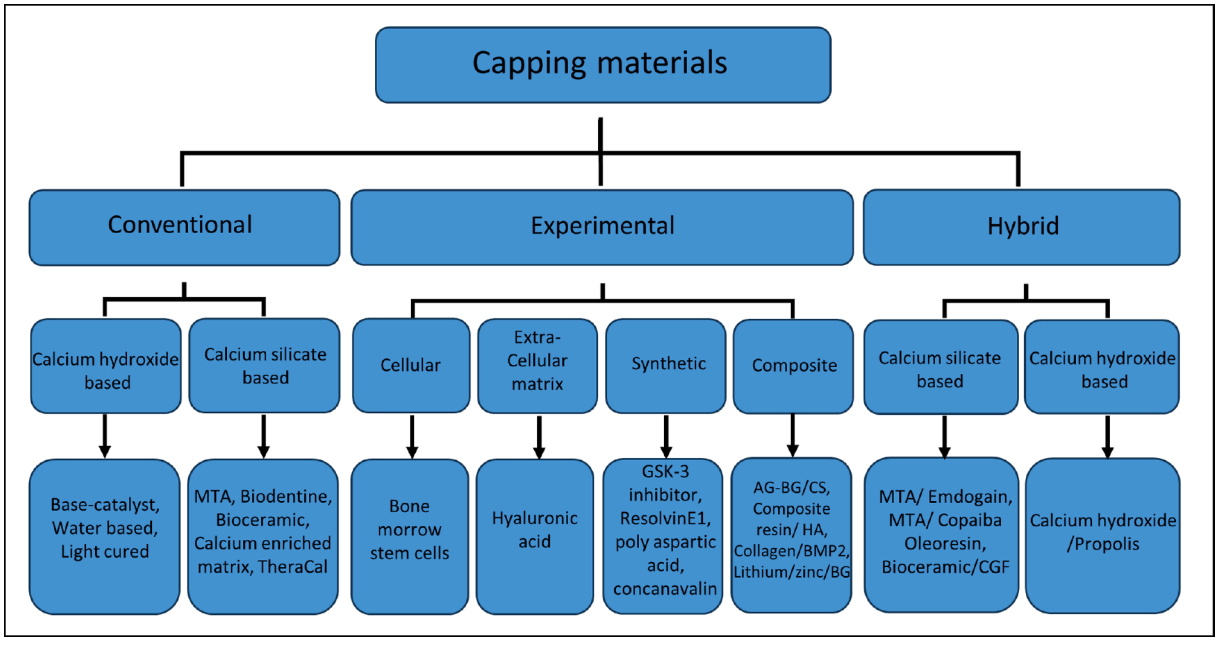

Fig. 1. The three categories of pulp capping materials and their subdivisions.

synthesis, membrane permeability, and enzyme activity (Rahimzadeh et al., 2022). Therefore, to overcome these issues, several modifications have been developed, either by replacing bismuth oxide or eliminating the aluminium phase.

For instance, Biodentine is composed of tricalcium silicate and dicalcium silicate, which act as supporting structures. Additionally, calcium carbonate is incorporated into the powder to enhance its mechanical properties, and calcium chloride in the liquid accelerates the setting time (Demirkaya et al., 2017, Kaup et al., 2015, Lee et al., 2016, Sharifi et al., 2015).

Tricalcium silicate, also known as bioceramic cement, is another pulp-capping material. It is available as a pre-mixed paste (bioaggregate) and has been introduced as a root-end filling material free of the aluminium phase. Another type of bioceramic cement is the IRoot SP, which is packed in a pre-mixed flowable tube. This material was introduced as a root canal sealer and later used successfully as a pulp-capping agent (Camilleri et al., 2015, Kim et al., 2016, Wu et al., 2020, Zhu et al., 2017).

The mechanism controlling the function of calcium silicate cement remains unclear. One of the suggested mechanisms is the release of growth factors by alkaline media, which has been shown to be associated with increasing proteins responsible for mineralisation (DSPP, DSP, OCN, and BSP) (Laurent et al., 2012, Paula et al., 2020). Although different calcium silicate cements share the same bioactivity mechanism, they can induce the formation of mineralisation proteins at different levels (Paula et al., 2020). Biodentine is associated with higher mineralisation proteins, leading to intrapulpal calcification, which can be considered a pathological repair, making future endodontic treatment difficult or even impossible (Paula et al., 2020). This aggressive mineralisation activity could be related to the intense release of calcium ions and high pH compared to other calcium silicate-based cements (Herrera-Trinidad et al., 2023).

Neo MTA Plus is a new-generation MTA with a gel composition that provides putty consistency. This product, in comparison to the bioceramic material (Total Fill bioceramic sealer), demonstrated a similar ability to produce a dentinal bridge after 3 weeks. However, after 3 months, the bioceramic material resulted in a thicker dentinal bridge formation (Al-Saudi et al., 2019). The superiority of the bioceramic material could be related to the higher calcium and hydroxyl ions compared to the MTA capping material (Zamparini et al., 2019). Another possible cause is the inclusion of monobasic calcium phosphate in the bioceramic sealer. The binding of this substance to the CH group creates hydroxyapatite as a byproduct, which can boost the bioactivity of this cement.

A formulation containing resin and Portland cement (TheraCal) has also been introduced. This material sets rapidly and promotes pulpal healing through its incorporated calcium silicate. It has demonstrated the ability to produce reparative dentine after 28 days by activating the Wnt/β catenin pathway. However, this material showed lower pulpal cell viability than other calcium silicate-based cements, which may reduce the success rate of the already inflamed pulp tissue (Hara et al., 2021, Poggio et al., 2014b).

A calcium-enriched matrix (CEM) is a calcium silicate cement composed of calcium phosphate, calcium hydroxide, calcium silicate, calcium carbonate, calcium sulphate, and oxides (Asgary et al., 2008b). This material is alkaline (pH 11) with a setting time of less than 1 h, high flowability, and low film thickness (Kabbinale et al., 2015). CEM differs from other calcium silicate cements in inducing the differentiation of dental pulp stem cells (DPSC). CEM can upregulate BMP2 and fibroblast growth factor 4, while calcium silicate cements upregulate TGF-β1 (Asgary et al., 2014, Laurent et al., 2012).

Histological assessment of both MTA and CEM have showed complete bridge formation for both materials; however, CEM was associated with greater inflammation in diabetic rats. MTA reduced inflammation in both healthy and diabetic rats; however, no correlation was found between the degree of inflammation and dentine bridge formation (Madani et al., 2014). The superiority of MTA in reducing inflammation under hyperglycaemic conditions has not been clarified; this could be related to the difference in composition between the two materials. CEM contains alkaline oxides, which could alter hydroxyl ion release and, in turn, affect bioactivity and immunomodulation (Asgary et al., 2008a).

A recent study focused on the immunomodulatory effects of calcium silicate-based cements. This study examined the function of the macrophage M2 phenotype, identified by the surface proteins CD 163 and CD 206. Both MTA and Biodentine were reported to induce polarisation of M2 macrophages, which could be associated with upregulation of anti-inflammatory mediators (TGF-β, IL-10, C–C motif chemokine ligand family) and downregulation of pro-inflammatory cytokines (IL-1β, Il-12p70). This could help reduce pulpal inflammation and tissue destruction, leading to tissue healing and repair (Abuarqoub et al., 2022, Arabpour et al., 2021, Kadowaki et al., 2022).

The duration of immunomodulation may be crucial for determining the survival of inflamed pulp tissue and the success of the pulp-capping procedure. Zhu et al. compared MTA and IRoot SP (a bioceramic sealer) (Zhu et al., 2017). This study showed that both materials could induce M1 and M2 macrophage phenotypes; however, this process was later proven to be time-dependent (Zhu et al., 2017). Another study showed that MTA can induce the release of pro-inflammatory mediators for up to 3 days, followed by a decline to 7 days, where extensive mineralisation was shown to be indicative of the healing phase (Reyes-Carmona et al., 2010).

Despite the ability of conventional pulp capping materials to produce a favourable pulp response by increasing proteins associated with mineralisation and repair, the results are still far from ideal (see Fig. 2). The calcified bridge formed was dissimilar to that of the original dentine. Additionally, the repair process exhibited varying degrees of inflammation, ranging from moderate to mild, which may diminish over time. Therefore, the development of materials with an ideal pulp response is mandatory.

4.2. Experimental materials

Several experimentally developed pulp-capping materials have been introduced which aim to induce adequate pulpal healing with dentine pulp complex formation. These pulp capping agents can be categorised according to their composition into cellular, extracellular matrix, growth factors, synthetic materials, pharmaceutical drugs, plant-derived compounds, and composites of different materials. Bone morrow stem cells have been used as a cellular capping agent to induce pulpal repair owing to their ability to differentiate into various mesenchymal cells and produce several growth factors (Obeid et al., 2013). Compared to MTA and a composite of hydroxyapatite and tricalcium phosphate (HA/TCP), this material shows no intrapulpal calcification. In contrast, both MTA and HA/TCP produce intrapulpal calcification, with percentages ranging from 15 % to 85 %, respectively (Obeid et al., 2013).

Paracrine signalling between DPSCs and macrophages has also been reported to play a role in immunomodulation and odontogenesis. MicroRNA-enriched extracellular vesicles isolated from DPSCs are engulfed by macrophages in cell culture. This uptake can convert the macrophages into the M2 phenotype by inhibiting the TLR and NFκB pathways. M2 phenotype cells show increased secretion of anti-inflammatory mediators (IL-1ra and IL-10) and decreased secretion of pro-inflammatory mediators (IL-1β, IL-6, and TNF-α) (Zheng et al., 2020). In addition, culturing DPSCs with stimulated M2 macrophages for 14 days can upregulate DMP-1 and DSP proteins, with calcification nodules observed in the culture media, indicating cellular differentiation of DPSCs into odontoblasts by induced M2 macrophages, which is further detected through the BMP1 pathway (Zheng et al., 2020).

Hyaluronic acid is a part of the extracellular matrix that maintains the integrity of the cellular structure. This compound shows higher odontoblast and fibroblast viability in comparison to calcium hydroxide (ApexCal) and dentine adhesives (Excite) (Bogović et al., 2011). The

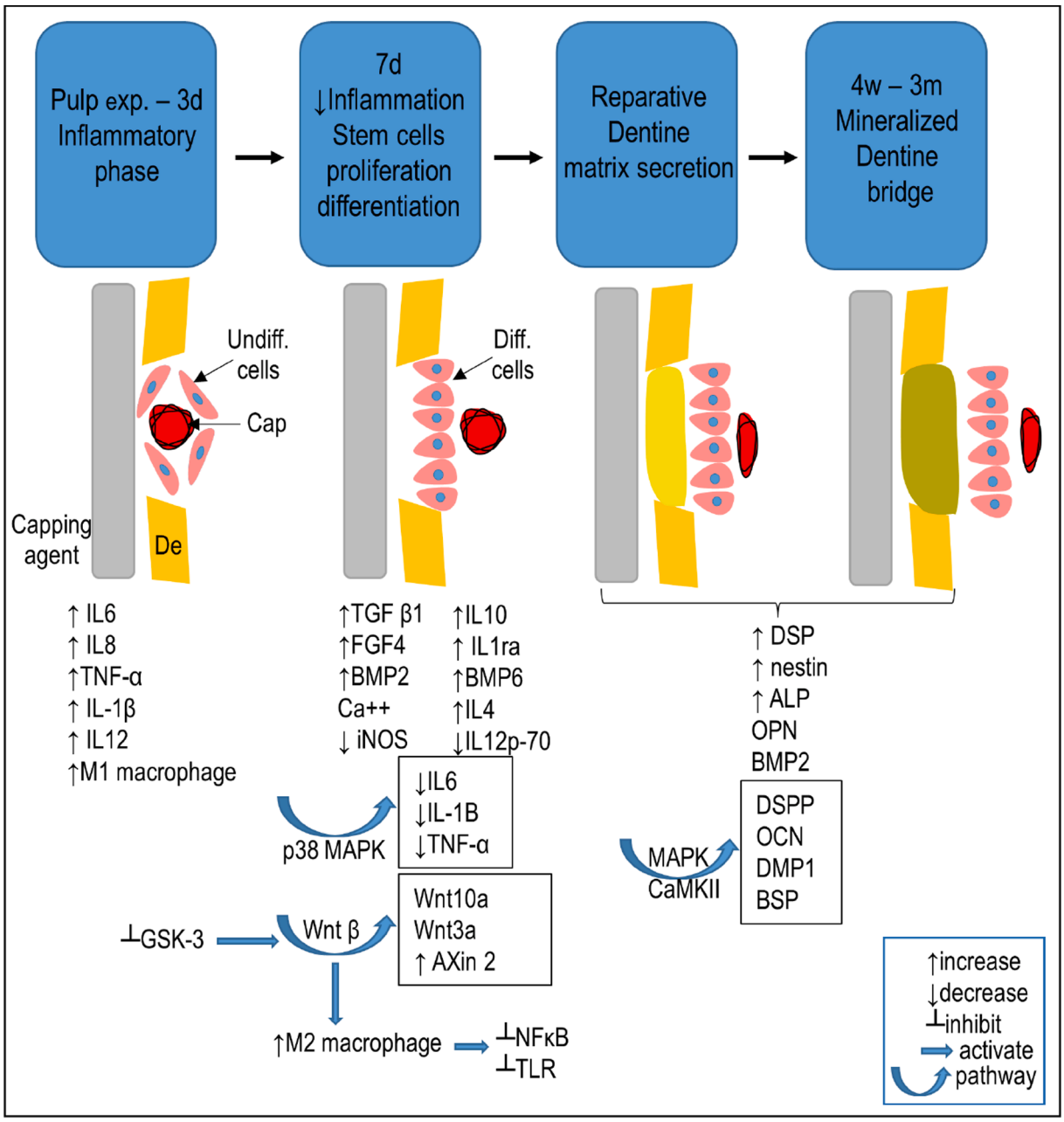

Fig. 2. Schematic illustration summarizing the inflammatory and reparative processes of the pulp cells induced by capping materials. The first stage (pro-inflammatory phase) showed predominance of undifferentiated stem cell (undiff. cells) and increase of interleukins (IL) 1β, IL 6, IL 8, IL 12, Tumor necrosis factor-alpha (TNF-α), macrophage M1. The second phase (anti-inflammatory phase) showed differentiation of pulp cells (Diff. cells) and increase of transforming growth factor betta1 (TGF β1), fibroblast growth factor 4 (FGF 4), bone morphogenic protein (BMP) 2, BMP 6, IL 4, IL 10, IL 12p-70, macrophage M2, and decrease in pro-inflammatory mediators: inducible nitrous oxide synthase (iNOS), IL 6, IL 1β, and TNF-α. The third stage showed reparative dentine matrix formation associated with increase proteins of mineralisation: dentine sialoprotein (DSP), dentine sialophosphoprotein (DSPP), osteocalcin (OCN), dentine matrix protein1 (DMP1), bone sialoprotein (BSP), and nestin. The last stage after 4 weeks showed complete dentinal bridge formation.

ability of this capping material to enhance the expression of genes related to mineralisation has not yet been studied; therefore, further investigation is required to identify the possible mechanisms underlying its function.

Concentrated growth factors (CGF), containing a large number of growth factors within the fibrin mesh, have also been studied as pulp-inducing healing materials. This is considered a third-generation platelet concentrate, showing the ability to induce pulpal cell proliferation in addition to the upregulation of mineralisation proteins (DSPP, DMP-1). Although the dentinal bridge induced by this material is reported to be thinner than conventional cappers, it is lined with a regular odontoblast layer and without vascular congestion, which are indicative signs of ideal pulp healing (Tian et al., 2019).

Concanavalin is a lectin derived from the *Canavalia ensiformis* plant that was introduced as an antitumour drug. Additionally, this type of lectin induces the proliferation and differentiation of animal cells (Shi et al., 2014, Suardita et al., 2020). Later, concanavalin was used as a pulp-capping agent to increase the proliferation of DPSCs (Suardita et al., 2020). However, there is currently no evidence of a signalling pathway for concanavalin function, necessitating further research.

Polyaspartic acid is a biocompatible and biodegradable synthetic polypeptide with high affinity for calcium. It can regulate mineralisation

in a manner similar to that of the non-collagenous proteins of dentine. As a pulp-capping agent, this material stimulates the production of DMP1, a protein typically found in fully developed odontoblasts, indicating its role in the healing process. Furthermore, it has demonstrated the capacity to produce reparative dentine for over 21 days (dos Santos et al., 2023). The ability of this material to guide mineralisation using natural calcium from the tooth itself rather than relying on alkalinity and exogenous calcium release, may facilitate the development of ideal pulp capping materials for optimal pulp response. However, a histological evaluation is required to confirm the efficacy of this material.

Resolvin E1 is a major dietary omega-3 metabolite. It belongs to the resolvin family, which consists of several subtypes, including Resolvin D1, Resolvin E1, and aspirin-triggered Resolvin D1. Resolvins play a role in resolving inflammation in various parts of the body (Ji et al., 2011). As a pulp capping agent, Resolving E1 can perform several functions such as downregulating the pro-inflammatory mediators (TNF-α, IL-1β, and IL-6), enhancing alkaline phosphatase activity (ALP), and increasing expression of genes related to mineralisation (DMP1, DSPP, BSP). Histologically, it shows rapid formation of dentinal bridges within 1 week of application, with lower porosity, when compared with a non-medicated collagen sponge applied directly on the exposure site (Chen et al., 2021).

GSK-3 inhibitors are pharmaceutical drugs initially used to treat Alzheimer's disease and prevent further deterioration through their neuroprotective function (Griebel et al., 2019). Several types of this inhibitor are used for pulp repair and healing, including Tideglusib, BIO (2′Z,3′E)-6-Bromoindirubin-3′-oxime), and CHIR99021(6-[[2-[[4-(2,4-Dichlorophenyl)-5-(5-methyl-1H-imidazol-2-yl)-2 pyrimidinyl] amino] ethyl] amino]-3-pyridinecarbonitrile) (Neves et al., 2017b). The GSK-3 inhibitor has been tested at the molecular level and activates the Wnt/β-catenin pathway, leading to the polarisation of macrophages to the M2 phenotype (indirect way). It also promotes the differentiation of odontoblasts from dental pulp stem cells (direct way) (Neves et al., 2020). Consequently, this can reduce pro-inflammatory mediators and enhance the healing process (Kawashima and Okiji, 2016, Zhou et al., 2022). The GSK-3β inhibitor demonstrated superior reparative dentinogenesis compared to conventional pulp capping materials (Neves et al., 2017a, Neves et al., 2020).

The experimentally developed materials, such as cellular and extracellular matrices, synthetic proteins, and medications, are used individually as pulp-capping agents, each targeting specific functions. Conversely, alternative pulp-capping agents are designed with combinations of compounds that perform multiple roles simultaneously, aiming to enhance pulp repair and regeneration.

Silver-doped bioactive glass with chitosan hydrogel (AG-BG/CS) has been used as a pulp-capping material. The composite components are involved in several functions. The bioactive glass is recognised for its ability to promote hard tissue formation by releasing bioactive ions, specifically calcium (Zhu et al., 2019). Additionally, the presence of silver ions is linked to an increased release of bioactive materials. Another component of this composite is chitosan, which is a biodegradable natural polysaccharide with antibacterial and regenerative capabilities. It can be utilised independently or in conjunction with other elements as a composite material (Sequeira et al., 2024). The AG-BG/CS was compared to MTA and exhibited superior anti-inflammatory characteristics. This was achieved by lowering the levels of IL-1B, IL-6, and TNF-α, possibly through the p38 MAPK pathway (Fig. 2). AG-BG/CS increased DSPP expression, which may be associated with odontoblast differentiation. Although MTA showed a thicker dentinal bridge, it was also associated with an inflammatory response in the apical portion. The ability of this composite material to reduce inflammatory response may enhance treatment outcomes and reduce pulp necrosis (Zhu et al., 2019).

Composite resins containing polymer and HA with BMP-2 exhibit a similar ability to produce dentinal bridges after 4 weeks compared to MTA (Okamoto et al., 2020). In addition, both materials unexpectedly have demonstrated the ability to generate tubular dentine that closely resembles the original dentine, which contradicts earlier research findings. Nevertheless, the study did not address the underlying explanation for this outcome (Okamoto et al., 2020). This may be attributed to the use of different animal models with smaller exposure sizes. This could potentially enable nearby viable primary odontoblasts to contribute to the regeneration of new dentine pulp complexes (Mahdee et al., 2019).

Another composite material containing a collagen scaffold, with either BMP-2 gene activation or fibroblast growth factor 2 gene activation, was also studied and compared to commercially available MTA. This composite material demonstrated a higher capacity for preserving viable cells than MTA. This positive result may be attributed to the growth factors present in the composite, which promote pulpal regeneration without inflammation or necrosis (Chakka et al., 2020).

Lipoic acid (LA) prevents damage caused by harmful molecules In addition to its anti-inflammatory properties, it promotes the production of enzymes that protect against oxidative stress. Supplementing animal models with LA can extend lifespan, provide neuroprotective benefits, and exhibit favourable effects against cancer (Moura et al., 2015). Gold nanoclusters have also been used in drug delivery to address specific tissues. Their usage enhances the availability of drugs, prolongs their therapeutic effect in the target tissue, enables the delivery of drugs through the bloodstream, and enhances the stability of therapeutic agents against degradation. Dihydrolipoic acid-functionalized gold nanoclusters are used as pulp-capping agents. This compound has demonstrated the ability to induce polarisation of macrophages from the M1 to M2 phenotype with downregulation of inflammatory mediators (IL-6, iNOS, and TNF), as well as upregulation of anti-inflammatory mediators (BMP2, BMP6, IL-10, Wnt3a, and Wnt5a). It enhances the differentiation of odontoblast by activating the Wnt/β-catenin pathway. Furthermore, it increases the expression of genes related to mineralisation (DSPP, DMP-1, BSP, and OPN) (Yang et al., 2022). However, further investigations are required to confirm their histological efficacy in dentinal bridge formation.

The presence of lithium and zinc in bioactive glass results in bioactivity associated with the release of calcium from the glass. This release facilitates odontoblast differentiation and dentine repair. Additionally, lithium and zinc ions activate the Wnt/β catenin pathway by inhibiting GSK-3, resulting in an increase in AXin-2 expression and DSPP, which is responsible for mineralisation (Tran et al., 2023).

Despite the ability of experimentally developed pulp-capping materials to reduce inflammation and superficial necrosis associated with conventional products, these materials are still under development and require further research to formalise new products that are acceptable for clinical use.

4.3. Hybrid materials

These pulp-capping agents involve adding experimental materials to conventional agents to enhance properties, including biocompatibility, bioactivity, and immunomodulation. Portland cement with bismuth oxide, commercially known as MTA, was modified to enhance cell viability and increase the proteins associated with mineralisation (DMP1, DSPP, ALP, OPN, and OCN) (Lee et al., 2012). This enhancement was achieved by the addition of Emdogain or Simvastatin. Emdogain is a protein comprising ameloblastin, enamelin, and amelogenin; these natural proteins can trigger biological processes (da Silva et al., 2022). Biological degradation of these proteins can release bioactive peptides that stimulate the production of growth factors such as TGF-β1 and BMP-2 (Lyngstadaas et al., 2009). Clinical and experimental evidence suggests that amelogenins can greatly enhance wound healing, bone formation, and the regeneration of dentine and pulp (Lyngstadaas et al., 2009). When MTA is mixed with emdogain, it provides support, enhances bioactivity, and seals the structure. Emdogain has a gel consistency which allows for the slow release of bioactive material with an enhancement of pulpal cell growth (Lee et al., 2012).

The copaiba oleoresin is extracted by tapping the trunk of members of the genus *Copaifera*. It is composed of various components, including a resinous component that improves its clinical applicability, that are linked to its antibacterial and anti-inflammatory characteristics (Couto et al., 2020). Adding Copaiba to MTA does not improve cell survival. However, an increase in cell migration and the production of proteins linked to mineralisation has been observed (Couto et al., 2020).

Addition of propolis to calcium hydroxide increases the number of polarised M2 macrophages. The main components of propolis are flavonoids and CAPE. It can inhibit the nuclear factor kappa B pathway, responsible for releasing inflammatory mediators, and can reduce neutrophil chemotaxis (Setyabudi et al., 2020). The presence of propolis is associated with decreased cytotoxicity of calcium hydroxide, allowing more viable cells for pulp healing. This could be related to the ability of propolis to reduce hydroxyl ion release from calcium hydroxide, making it less alkaline and more biocompatible (Setyabudi et al., 2020). In addition, the inclusion of Copaiba in calcium hydroxide enhances cell migration, proliferation, and differentiation, as well as increases the production of proteins related to mineralisation (Couto et al., 2020).

IRoot SP (a bioceramic sealer) was compared with CGF and a combination of both IRoot SP and CGF. The addition of CGF led to a lower number of M1 macrophages on day 1 and a higher number of M2 macrophages on day 7; all treatments showed an immunomodulatory effect, but the combination treatment had a synergistic effect (Zeng et al., 2023). The combination treatment also resulted in a higher number of viable dental pulp stem cells on days 4 and 7, the down-regulation of pro-inflammatory mediators, and the upregulation of anti-inflammatory mediators (IL-4 and IL-10) (Zeng et al., 2023). In turn, this may enhance the healing process and survival of the inflamed pulp. Each component of the combination has its own effect: the calcium silicate cement enhances mineralisation, whereas the concentrated growth factor is associated with biocompatibility and enhancement of cell proliferation. Therefore, the combination exhibits synergism associated with the highest anti-inflammatory activity, cell viability, and adequate hard tissue formation (Zeng et al., 2023).

This review identified several inflammatory pathways that may lead to a favourable pulp response (Fig. 2). However, the exact mechanisms that direct the inflammatory process toward healing, dentine matrix secretion, and mineralisation or the time required for each of these events are still unknown. Further research is needed to broaden our knowledge and develop a capping material that offers optimal tissue response with minimum drawbacks.

5. Conclusion

This review classified pulp-capping agents into conventional, experimental, and hybrid materials. Several conventional capping agents have been developed for various products. However, bioceramic-based materials show superior results based on their bioactivity, quality of the formed dentine bridge, and immunomodulatory behaviour. Experimentally developed materials have also shown promising results regarding their bioactivity and immunomodulatory properties; however, these materials are still under investigation. Similarly, the hybridisation of conventional agents with some materials has revealed promising outcomes. Furthermore, several inflammatory pathways were observed, with a new direction toward the stimulation of the M2 macrophage phenotype and related pathways which showed consistent results. However, the lack of standardisation of laboratory experimental procedures with a large variety of sample types, techniques, and measurements hinders our ability identify the most favourable pathway for pulp tissue healing and regeneration.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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