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REVIEW ARTICLE

Chemomechanical caries removal methods: A literature review

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KEYWORDS

Brix3000;
Carie-Care;
Caridex;
Carisolv;
Chemomechanical caries removal;
Papacárie

Abstract *Aim:* To provide dental practitioners and researchers with a comprehensive review of the historical development, chemical composition, mechanisms of action, advantages, and drawbacks of different chemomechanical caries removal (CMCR) agents.

Methods: An electronic search was performed for all articles published on CMCR agents in various databases, including the Web of Science, PubMed, Cochrane, Scopus, and Google Scholar bibliographic databases, from January 1, 1975, to July 31, 2022.

Results: Records were identified using the following search terms: Brix3000, Carie-Care, Caridex, Carisolv, chemomechanical caries removal, conventional surgical method, and Papacárie. A total of 171 articles were screened based on the titles and abstracts, of which 126 were deemed eligible for inclusion after duplicates were removed. Following a manual search of the reference list, eight articles were added. Articles were then excluded for other reasons, such as being written before 1975, being written in a language other than English, and the non-availability of the full text. Overall, 120 articles were included in the analysis (literature reviews [n = 27], systematic reviews [n = 8], research articles [n = 82], case reports [n = 3]).

Conclusion: CMCR is a potential method of caries control in the future as an alternative to the conventional surgical approach in standard dentistry applications. It is more widely accepted, less painful, and has comparable efficacy to the conventional surgical method.

Clinical significance: A continuous trend among manufacturers has been observed since 1975 to reduce the drawbacks of CMCR agents. Moreover, evidence-based minimally invasive techniques,

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including CMCR agents that require minimal or no aerosol-generating procedures, are preferred while measures to control the spread of coronavirus disease are in force.

Contents

1. Introduction

Dental caries is managed with different treatment modalities, ranging from removal using the conventional surgical method to minimally invasive dentistry (MID) techniques (Jingarwar et al., 2014). The conventional surgical method tends to over-prepare the cavities by removing healthy dentin, which is caused by a lack of tactile sensation, which can sometimes lead to pulp exposure (Asal et al., 2021). In addition, heat generated during the cutting process can adversely affect the pulp, causing inflammation and pain (Inamdar et al., 2020). Dental anxiety and pain can also be triggered by the noise and vibration of the handpieces (Cardoso et al., 2020). The removal of healthy and decayed dentin compromises the tooth and reduces its long-term durability (Banerjee, 2013).

One of the most common MID modalities over the last 10 years has been the use of CMCR agents (Jingarwar et al., 2014). CMCR involves the decayed dentin being chemically softened and then gently removed using hand instruments (Hamama et al., 2014). It differs from the conventional surgical procedure in that it selectively removes infected dentin while preserving affected dentin that possesses the potential to remineralize; thus, it is considered less destructive (Goomer et al., 2013; Soni et al., 2015).

Several CMCR agents have been developed since 1975. They can be generally categorized as either sodium hypochlorite (NaOCl)-based agents or enzyme-based agents (Abdelaziz et al., 2022).

2. Aim

The aim of this article was to present a comprehensive review of the historical development, chemical composition, mechanisms of action, advantages, and drawbacks of different CMCR agents for dentists and dental researchers.

3. Methods

An electronic search was performed for all articles published on CMCR agents in various databases, including the Web of Science, PubMed, Cochrane, Scopus, and Google Scholar bibliographic databases, from January 1, 1975, to July 31, 2022.

4. Results

Records were identified using the following search terms: Brix3000, Carie-Care, Caridex, Carisolv, chemomechanical caries removal, conventional surgical method, and Papacárie. A total of 171 articles were screened based on the titles and abstracts, of which 126 were deemed eligible for inclusion after duplicates were removed. Following a manual search of the

reference list, eight articles were added. Articles were then excluded for other reasons, such as being written before 1975, being written in a language other than English, and the non-availability of the full text. Overall, 120 articles were included in the analysis (literature reviews [n = 27], systematic reviews [n = 8], research articles [n = 82], case reports [n = 3]). A flow chart of the literature search process is displayed in Fig. 1. A summary of recent articles included in this review is presented in Table 1.

5. Discussion

5.1. The mechanism of action of CMCR agents

Within a carious lesion, two zones of collagen destruction are typically identified: an outer layer that is completely deteriorated and cannot be remineralized, called the infected dentin; and an internal layer that undergoes partial demineralization, called the affected dentin, in which the collagen fibrils are not destroyed. CMCR agents are used to further destruct the permanently damaged collagen fibers in infected dentin, facilitating their removal while avoiding the underlying healthy affected dentin (Soni et al., 2015). This process occurs mainly by chlorination, which involves hydrolysis of the cross-links between the tropocollagen units and/or cleavage of the polypeptide chains inside the triple helix (Chatterjee et al., 2020). However, the chemistry of amino acid chlorination and its consequences are still poorly understood (Hamama et al., 2014).

The chlorination process is the main mechanism of action in NaOCl-based CMCR agents (Maragakis et al., 2001), while it is considered a supplemental mechanism in enzyme-based CMCR agents. It is caused by the addition of chloramine during the manufacturing process. When chloramines chlorinate damaged collagen, oxygen is released, causing the gel to bubble and become bleary (Kumar et al., 2016; Ramamoorthi et al., 2013; Venkataraghavan et al., 2013).

In enzyme-based CMCR agents, the chief mechanism of action relies on papain, which is considered an effective chemical debriding agent, with antibacterial and anti-inflammatory action. It is a cysteine protease derived from the fruits and latex of green papaya (*Carica papaya*). The papain is thought to work by causing the breakdown of partly degraded molecules of collagen and aiding the disintegration and eradication of the mantle of the fibrin generated by the carious process without damaging the unimpaired collagen fibrils. As a result, the infected dentin becomes softer, making it possible to remove it without anesthetic and with non-cutting tools. This specific interaction has been explained by the absence of α-1-antitrypsin, a plasmatic protease inhibitor in infected dentin (Jain et al., 2015).

5.2. NaOCl-Based CMCR agents

The first CMCR agent was a 5 % NaOCl solution, which was tested in 1972. However, it lacked selectivity and was unstable, removing affected, infected, and sound dentin (Schutzbank et al., 1978). To solve this problem, amino acids were included in the versions that followed (Hamama et al., 2014).

5.2.1. Gk-101

To mitigate the difficulty with 5 % NaOCl, the solution was subsequently included in Sorensen's buffer, which consisted of glycine, sodium chloride (NaCl), and sodium hydroxide (NaOH). This included chlorinating glycine to produce *N*-monochloroglycin (NMG). In 1975, the reagent was named GK-101 (Habib et al., 1975) and was produced by combining two solutions: Solution A (25 mL of 2 M NaCl, 2 M NaOH, and 2 M glycine) and Solution B (10 mL of 4–6 % NaOCl) (Goldman and Kronman, 1976).

A specific delivery system was required for GK-101. This consisted of a reservoir (to heat the freshly created solution to 41 °C) and a pump (shaped like a straight handpiece) connected to a 20-gauge needle delivery tip. Minimal pressure had to be exerted when applying the needle tip to the carious lesion, with a motion akin to using a paintbrush to reduce the patient's reaction to pain (Goldman and Kronman, 1976).

5.2.2. GK-101e (Caridex®)

The caries removal was shown to be more effective when glycine was replaced with amino butyric acid, resulting in *N*-monochloroaminobutyrate (NMAB). Therefore, GK-101 was changed to GK-101E (Caridex®). In 1978, the first American application for the NMAB system's patent was known as GK-101E. Later, in 1984, the National Patent Dental Corporation of New York obtained a second patent. The Food and Drug Administration (FDA) approved it for use in the United States, and it was sold as Caridex® (Burke and Lynch, 1995).

The Caridex® system involved the combination of two solutions: Solution A (NaOCl) and Solution B (glycine, aminobutyric acid, NaCl, and NaOH). Prior to use, these solutions were combined to create a functional reagent (pH approx. 11) that retained stability for an hour (Burke and Lynch, 1995).

A delivery system was included, which comprised a solution reservoir, a heater, and a pump that facilitated delivery of the fluid to a handpiece using a variety of application tips through a tube. The applicator used to gently scrape the carious dentin. Thereafter, aspiration was employed to eliminate the debris and any unused solution. The procedure was repeated until the remaining dentin met the standard clinical tactile criteria for sound dentin, which took 5–10 min (Beeley et al., 2000).

Notwithstanding its initial popularity, take-up of the Caridex® system was limited. This is because of the complexity of the equipment used (Burke and Lynch, 1995). Other drawbacks included the high cost due to solution instability, the taste of the liquid, its brief duration, and the large volume of solution needed (200–500 mL). The system also required the product to be heated, resulting in a longer treatment period (10–15 min) (Zinck et al., 1988).

As a result, the popularity of Caridex® in the United States began to wane in the early 1990 s and it was no longer available (Beeley et al., 2000). Neither GK-101 nor GK-101E (Caridex®) significantly improved cariogenic excavation compared with the conventional surgical method (Mithra and Abhishek, 2017).

5.2.3. Carisolv

At the end of 1997, Carisolv was produced by researchers at the Medi Team Dentalutveckling AB company in Göteborg, Sweden. This was the latest available variant of the

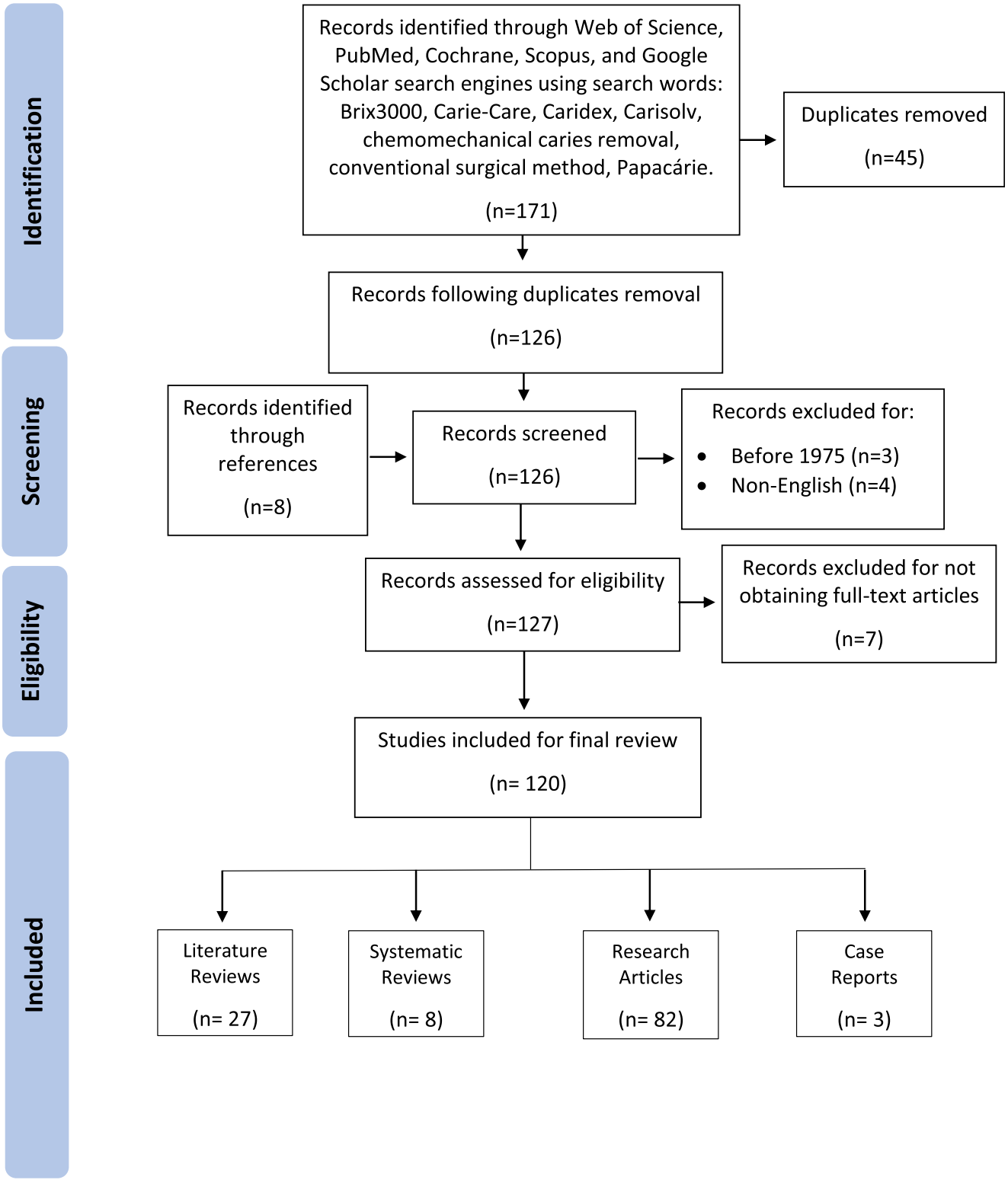

Fig. 1 Flow chart of the literature research process.

NaOCl-based CMCR agents (Kathuria et al., 2013). The crucial difference between this product and previous releases was that it included three amino acids (leucine, lysine, and glutamic acid), as opposed to only one (glycine or amino butyrate), generating a different effect on the infected dentin (Mithra and Abhishek, 2017).

In 1998, the first version of Carisolv® was developed. It comprised two syringes. The first syringe contained carboxymethylcellulose (to provide a viscous consistency), amino acids (leucine, lysine, and glutamic acid), and erythrosine (to increase its visibility in use) (Albrektsson et al., 2001). The second syringe contained 0.25 % NaOCl. The contents of the two

Table 1 Characteristic features of recent included articles.

No.	Year	Authors	Country	Journal	Title	Type of Study	Comparison	Type of Teeth
1	2017	Mithra & Abhishek	India	Adv. Res. Gastroentero. Hepatol.	Chemomechanical caries removal: A conservative and pain-free approach	Literature Review	CMCR agents	–
2	2018	Bottega et al.	Brazil	Sci. Rep.	Costs and benefits of Papacarie in pediatric dentistry: A randomized clinical trial	Clinical Trial	Papacárie® Conventional	Primary and permanent molars
3	2018	Deng et al.	China	Int. J. Paediatr. Dent.	Effects of Papacarie on children with dental caries in primary teeth: A systematic review and *meta*-analysis	Systematic Review and meta-analysis	Papacárie® Conventional	Primary molars
4	2018	Felizardo et al.	Brazil	J. Health Sci.	Use of BRIX-3000 enzymatic gel in mechanical chemical removal of caries: Clinical case report	Case Report	BRIX3000®	Primary molars
5	2018	Prabhakar et al.	India	Int. J. Clin. Pediatr. Dent.	Efficacy of caries removal by Carie-care and erbium-doped yttrium aluminum garnet laser in primary molars: A scanning electron microscope study	In-vitro Study	Carie-Care™ Laser Conventional	Extracted primary molars
6	2018	Yun et al.	Korea	J. Dent. Anesth. Pain Med.	New treatment method for pain and reduction of local anesthesia use in deep caries	Systematic Review	Carie-Care™ Conventional	Primary and permanent teeth
7	2019	Ismail and Al Haidar	Iraq	J. Pharm. Sci. Res.	Evaluation of the efficacy of caries removal using papain gel (Brix 3000) and smart preparation bur (in vivo comparative study)	Clinical Trial	BRIX3000® Cera Bur	Permanent molars
8	2019	Ismail and Al Haidar	Iraq	J. Baghdad Coll. Dent.	Impact of Brix 3000 and conventional restorative treatment on pain reaction during caries removal among group of children in Baghdad city	Clinical Trial	BRIX3000® Cera Bur	Permanent molars
9	2019	Mazumdar et al.	India	J. Indian Dent. Assoc., West Bengal State Branch 2001–2002	Chemomechanical caries removal agents – an overview	Literature Review	CMCR agents	–
10	2019	Nalawade et al.	India	J. Dent. Res. Rev.	Comparative evaluation of efficacy of chemomechanical and conventional methods of caries excavation in young permanent molar teeth: In vivo study	Clinical Trial	Conventional Carie-Care™	First permanent molars
11	2019	Sontakke et al.	India	Dent. Res. J.	A comparative study of the clinical efficiency of chemomechanical caries removal using Carie Care gel for permanent teeth of children of age group of 12–15 years with that of conventional drilling method: A randomized controlled trial	Clinical Trial	Carie-Care™ Conventional	Permanent molars
12	2019	Torresi and Acosta	Argentina	Horiz. Sanitario	Comparative study between the use of brix-3000 and the rotational conventional technique against tooth decay	Clinical Trial	BRIX3000® Conventional	Primary and permanent teeth
13	2020	Alkhouli et al.	Syria	J. Dent.	Comparing the efficacies of two chemo-mechanical caries removal agents (2.25% sodium hypochlorite gel and brix 3000), in	Clinical Trial	BRIX3000® 2.25% NaOCl	Primary maxillary molars

(*continued on next page*)

Table 1 (*continued*)

No.	Year	Authors	Country	Journal	Title	Type of Study	Comparison	Type of Teeth
					caries removal and patient cooperation: A randomized controlled clinical trial		Conventional	
14	2020	Balachandran et al.	India	J. Indian Dent. Assoc.	Evaluation of efficacy of chemo-mechanical method of caries removal using Brix-3000 compared to conventional excavation with burs- a randomized controlled trial	Clinical Trial	BRIX3000® Conventional	Permanent molars
15	2020	Cardoso et al.	Portugal	J. Clin. Med.	Efficacy and patient's acceptance of alternative methods for caries removal—a systematic review	Systematic Review	Carisolv Papacárie® Carie-Care™ BRIX3000® Laser Air and sono-abrasion Conventional	_
16	2020	Chatterjee et al.	India	Int. J. Res. Rev.	Chemomechanical caries removal with respect to COVID-19 in dentistry	Literature Review	CMCR agents	_
17	2020	Inamdar et al.	India	J. Conserv. Dent.	Comparative evaluation of BRIX3000, CARIE CARE, and SMART BURS in caries excavation: An in vivo study	Clinical Trial	BRIX3000® Carie-Care™ Polymer burs	Permanent molars

No.	Year	Authors	Country	Journal	Title	Type of Study	Comparison	Type of Teeth
18	2020	Meyfarth et al.	Brazil	Brazilian J. Dent.	A New efficient agent to chemo-mechanical caries removal	Case Report	BRIX3000®	Permanent molar
19	2020	Santos et al.	Brazil	Sci. Rep.	Comparison between conventional and chemomechanical approaches for the removal of carious dentin: An in vitro study	In-vitro Study	Conventional Papacárie Duo® BRIX3000®	Extracted permanent molars
20	2021	Asal et al.	Egypt	Int. J. Clin. Pediatr. Dent.	Clinical and microbiological assessment of Carisolv and polymer bur for selective caries removal in primary molars	Clinical Trial	Polymer burs Carisolv Conventional	Primary molars
21	2021	Mancini et al.	Italy	Case Rep. Dent.	BRIX3000® papain gel for cavity treatment in the adult patient	Case Report	BRIX3000®	Second premolar
22	2021	Oommen et al.	India	J. Indian Dent. Assoc.	Assessment of pain response during caries removal using conventional tungsten carbide bur and a chemomechanical caries removal agent (brix gel): An in vivo study	Clinical Trial	BRIX3000® Conventional	Permanent molars
23	2022	Abdelaziz et al.	Egypt	Adv. Dent. J.	Chemomechanical caries removal agents and their applications in pediatric dentistry	Literature Review	CMCR agents	_

No.	Year	Authors	Country	Journal	Title	Type of Study	Comparison	Type of Teeth
24	2022	Chakravorty et al.	India	J. Adv. Med. Dent. Sci. Res.	Chemomechanical caries removal: An update	Literature Review	CMCR agents	_
25	2022	Eftimoska et al.	North Macedonia	Serbian Dent. J.	Comparative study of caries removal using BRIX 3000 and classic mechanical method	Clinical Trial	BRIX3000® Conventional	Permanent teeth
26	2022	Souza et al.	Brazil	Eur. Arch. Paediatr. Dent.	Worldwide research trends on the use of chemical–mechanical caries removal products over the years: A critical review	Systematic Review	CMCR agents	_

syringes were mixed in equal amounts at room temperature immediately before use (Beeley et al., 2000).

In 2004, the gel was modified at Sweden's University of Goteborg. A new dual syringe mixing device was released as a modified Carisolv™. To boost its efficacy, the number of free chloramines was increased, which necessitated a greater concentration of NaOCl. Therefore, the color element was removed. The amino acid composition was also reduced by half. The gel was distributed via a mixing tip, which could be used for a maximum of one month under refrigerated storage conditions (Chakravorty et al., 2022).

In 2013, the new Carisolv system was developed by incorporation of both the low-speed Cera-bur and Polymer-bur in the new system to ease the eradication of softened dentinal lesions treated with Carisolv (Mithra and Abhishek, 2017). The new Carisolv system had certain advantages over Caridex®. It is a gel rather than a liquid and the amount needed for each treatment was less (Pathivada et al., 2016). Unlike Caridex®, there was no need for heating or a delivery system (Goomer et al., 2013; Soni et al., 2015).

To improve the efficacy of caries removal and ensure maximum preservation of the residual dentin, the Carisolv company produced a set of non-cutting tip tools that featured a 90° border with a blunt angle (Kathuria et al., 2013).

Numerous studies have found Carisolv to be as effective in caries removal as the conventional surgical method and more comfortable for patients, even though it is a time-consuming procedure (Ammari et al., 2014; Asal et al., 2021; Bohari et al., 2012; Dali and Rao, 2012; Divya et al., 2015; Goomer et al., 2013; Pathivada et al., 2016; Reddy et al., 2015; Soni et al., 2015). Carisolv may have limited use because of its high cost, short shelf life, need for refrigeration, unpleasant taste and odor, and the specialized curettes needed (Ammari et al., 2014; Bohari et al., 2012; Dhamija and Pundir, 2016; Lai et al., 2015).

5.3. Enzyme-Based CMCR agents

The papain enzyme plays the same role in enzyme-based CMCR agents as NaOCl does in NaOCl-based agents. Except for Biosolv™, all enzyme-based CMCR agents are now commercially available (Chakravorty et al., 2022).

5.3.1. Papacárie®

In 2003, papain gel was first released as a CMCR agent named Papacárie® by the Formula and Acao company in Brazil. It contains the enzyme papain (Kulkarni et al., 2016). The gel has various constituents, including chloramine, toluidine blue, salts, preservatives, a thickener, stabilizers, and deionized water (Motta et al., 2014b; Reddy et al., 2015).

In 2011, a modified gel was developed by the manufacturers and was known as Papacárie Due™, which had a higher viscosity and an extended shelf life and did not need to be stored in a refrigerator (Matsumoto et al., 2013; Modimi et al., 2016).

The application of Papacárie® does not require the use of technical devices (Kumar, 2014). During caries excavation, the manufacturer recommends using the reverse side of a blunt spoon. However, the No. 4 Carisolv hand instrument has also proven to be effective (Hamama et al., 2013).

In numerous studies, Papacarie® was found to have similar efficacy to the conventional surgical method in caries removal while causing less pain and discomfort (Almaz et al., 2016; Deng et al., 2018; Hegde et al., 2016; Kulkarni et al., 2016; Motta et al., 2014a, b). However, multiple studies have reported that treatment with Papacárie® took significantly longer than the conventional surgical method (Almaz et al., 2016; Anegundi et al., 2012; Bohari et al., 2012; Hegde et al., 2016). Conversely, Kotb et al. (2009), Matsumoto et al. (2013), and Motta et al. (2014b) found no difference in the duration of caries removal between the conventional surgical method and Papacárie®.

The cost of treatment with Papacárie®, is another limitation that has to be considered. Due to their cost and short shelf life, chemomechanical approaches can prove to be marginally less practical than conventional treatment (Bohari et al., 2012). Nevertheless, a few studies have found that Papacárie® offers a significant cost-benefit analysis for the conservative approach to caries removal in young patients (Ammari et al., 2014; Bottega et al., 2018).

5.3.2. Biosolv™

Biosolv™ (SFC-V/SFC-VIII) was created by the German company 3 M-ESPE AG as an experimental enzyme-based CMCR agent that was not available for sale (Mithra and Abhishek, 2017). Since its development in 2006, information on Biosolv™ has remained scarce and primarily dependent on the claims of the manufacturer (Chakravorty et al., 2022). It was mostly made from pepsin in a phosphoric acid and sodium biophosphate buffer (Clementino-Luedemann et al., 2006). Neves et al. (2011) reported that the phosphoric acid dissolved the inorganic constituents of diseased dentin, while the pepsin was allowed to preferentially break the damaged collagen strands.

Clementino-Luedemann et al. (2006) noted that Biosolv's manufacturers advised that a specific plastic tool (Star V1.3) should be used when employing their system. They found that this tool had a level of hardness that was midway between sound and infected dentin, facilitating easy removal of the softened bulk with no harm to the sound tissue.

Banerjee et al. (2010), Celementino-Luedemann et al. (2006), and Neves et al. (2011) found that the SFC-V solution lacked effectiveness in comparison to Carisolv. They attributed this to the quick buffering action of dentin on the Biosolv™ gel, which impacted the selective activity of pepsin on the denatured collagen fibers.

It is unclear whether this experimental Biosolv™ will be used in a clinical setting (Hamama et al., 2014). To date, no information has been provided as to whether the manufacturer is conducting further studies on its efficacy and biocompatibility compared with other CMCR agents present in the market or has ceased doing so due to the disappointing initial results.

5.3.3. Carie-Care ™

In 2011, Uni-Biotech Pharmaceuticals Private Limited in Chennai, India, in collaboration with Vittal Mallya Scientific Research Foundation, developed a CMCR gel-based preparation named Carie-Care™. This is an Indian invention that was introduced with papain as its main active ingredient, together with chloramines, clove oil, and dye (Rajakumar et al., 2013).

Carie-Care™ has certain advantages over existing CMCR agents. It differs from Carisolv in that no NaOCl or any other powerful chlorinating agents are included due to its reliance on

natural components (Rajakumar et al., 2013). Clove oil is widely used in dentistry. It has anti-inflammatory, mild anesthetic and analgesic, and antibacterial and antioxidant properties (Nisar et al., 2021).

Carie-Care™ is applied directly and generously to the carious dentin with a disposable applicator tip, with periodic gentle mixing for 1–3 min. A sharp spoon excavator is used to scrape the gel and the dissolved caries, which is then washed off with water/suction or gauze/cotton rolls (Rajakumar et al., 2013).

Carie-Care™ comes pre-mixed in a syringe that can be stored in a refrigerator at 4 °C. Carie-Care™ is easy to use as it is directly applied to the carious cavity without the need for special equipment (Venkataraghavan et al., 2013). Carie-Care™ is also less expensive than Papacárie® and has a longer shelf life (Nagaveni et al., 2016).

Several clinical trials and in vitro studies have examined the efficacy of Carie-Care™ in caries removal and found that it was comparable to the standard surgical method (Pathivada et al., 2016; Rajakumar et al., 2013; Yun et al., 2018). This finding is contrary to the studies conducted by Hegde and Chaudhari (2016) and Prabhakar et al. (2018).

The average caries removal time with Carie-Care™ (1.6–18.9 min) was much longer than the conventional surgical method (0.5–11.5 min) (Hegde et al., 2014; Hegde and Chaudhari, 2016; Nagaveni et al., 2016; Nalawade et al., 2019; Pathivada et al., 2016; Rajakumar et al., 2013; Sontakke et al., 2019; Venkataraghavan et al., 2013).

Caries removal with Cari-Care™ was found to be less painful than the conventional surgical method (Hegde et al., 2014; Hegde and Chaudhari, 2016; Nagaveni et al., 2016; Nalawade et al., 2019; Pathivada et al., 2016; Rajakumar et al., 2013; Sontakke et al., 2019; Venkataraghavan et al., 2013; Yun et al., 2018).

5.3.4. Brix3000®

In 2012, the Brix Medical Science company produced a CMCR product called BRIX3000®. Its main mechanism of action is based on papain (Abdelaziz et al., 2022; Mancini et al., 2021; Mazumdar et al., 2019).

As claimed by the manufacturers, the distinction between this product and other enzyme-based CMCR agents is the volume of papain utilized (3,000 U/mg in a 10 % concentration) and that it is bioencapsulated via Encapsulating Buffer Emulsion (EBE) technology (Ismail and Al Haidar, 2019a).

The carious dentin of active lesions has a more acidic environment with a lower mean pH (pH = 4.9), whereas the mean pH of arrested lesions is higher (pH = 5.7) (Goldberg, 2020). Accordingly, this unique bio-encapsulation process permits an appropriate pH, which is neutral (pH = 7), for solidification of the proteolytic enzymes, allowing stability and rapid release when they come into contact with an acidic environment with disrupted collagen strands, thereby enforcing hydrolysis (Felizardo et al., 2018).

BRIX3000® demonstrated greater proteolytic efficacy in removing carious dentin with less disintegration by the fluids of the oral cavity. In addition, the shelf-life of BRIX3000® is 48 months. It can even be stored in critical situations without the need for a refrigerator (4°–36 °C) (Inamdar et al., 2020). Furthermore, the antibacterial, antifungal, and antiseptic properties of BRIX3000® have been greatly increased (Ismail and Al Haidar, 2019a).

Though BRIX3000® was only released in 2012, the number of studies investigating this CMCR agent has increased dramatically in the last five years. When BRIX3000® was compared with conventional surgery, it was found to be just as effective despite taking much longer and being much less painful (Alkhouli et al., 2020; Balachandran et al., 2020; Eftimoska et al., 2022; Felizardo et al., 2018; Ismail and Al Haidar, 2019a, 2019b; Mancini et al., 2021; Meyfarth et al., 2020; Santos et al., 2020). However, Oommen et al. (2021) have been unable to demonstrate any statistically significant difference in the pain response between BRIX3000® and conventional surgical methods. Another notable finding was reported in a study conducted by Torresi and Acosta (2019) that evaluated clinical success in children after 30 days of treatment with BRIX3000® and conventional surgical methods. They discovered that 88.70 % of children treated with BRIX3000® had asymptomatic teeth, compared with 58.10 % of children treated with conventional surgery.

6. Clinical significance

In early 2020, the World Health Organization (WHO) declared the global COVID-19 pandemic. The WHO recommended a quarantine strategy as well as social distancing, handwashing, and contact tracing (WHO, 2020). The COVID-19 virus can be diffused directly or indirectly, mostly via respiratory droplets and spattering of blood and saliva via contact with the mucous membrane and infected fomites (To et al., 2020). Only emergency dental treatment was provided (Al-Halabi et al., 2020). The symptoms of COVID-19 can take a relatively long time to develop (2–14 days) (Huang et al., 2020; Meng et al., 2020). In addition, many dental procedures create aerosols, which have been linked to the spread of acute respiratory infections like COVID-19, and this creates a risk to the health of dental professionals (Tran et al., 2012). Dental and medical organizations therefore, recommended that the use of aerosol-generating procedures during the pandemic be kept to a minimum (Al-Halabi et al., 2020).

Given these recommendations, the use of CMCR agents that require minimal or no aerosol-generating procedures for caries control could be considered more appropriate than the surgical method for children and adults, especially for patients with anxiety and special needs (Chatterjee et al., 2020; Souza et al., 2022).

7. Conclusion

7.1. Implications for practice

Dentistry is increasingly moving toward a patient-centered approach with minimally invasive treatments. The CMCR method is more widely accepted and more comfortable for patients, reducing pain, anxiety, and the requirement for a local anesthetic. Notwithstanding its longer treatment duration and high cost, the CMCR method could be considered as a potential alternative treatment modality in future dental practice.

7.2. Implications for research

CMCR agents warrant further investigation, especially in a clinical setting. Enzyme-based products should be the subject of future research given their increasing popularity. Documented methodology should be encouraged to facilitate proper analysis and conclusions. However, standardizing assessment methods is an issue that is yet to be solved. Further clinical studies are required to assess the cost and long-term survival of restorations.

CRediT authorship contribution statement

Manal S. Maashi: Investigation, Writing – original draft, Project administration. **Heba M. Elkhodary:** Conceptualization, Data curation, Supervision, Writing – review & editing. **Najlaa M. Alamoudi:** Conceptualization, Data curation, Supervision, Writing – review & editing. **Nada O. Bamashmous:** Methodology, Resources, Visualization.

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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