



Worldwide research trends on the use of chemical–mechanical caries removal products over the years: a critical review

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Abstract

Background Chemical–mechanical caries removal (CMCR) products are in constant evolution and were recommended during the COVID-19 pandemic as substitutes for conventional caries removal.

Aim Characterize the worldwide scientific literature about CMCR products, over the years, by means of a critical review.

Design Electronic search was performed on Medline/PubMed, Scopus, Web of Science, Cochrane Library, Lilacs, and Embase up to November 2020. Year, journal, country of authors, and type of study were the data extracted from the retrieved studies. Additional data of the clinical studies and systematic reviews were investigated.

Results 2221 records were identified, 397 selected. 2011–2020 period concentrates higher number of publications ($n = 169$), in the Journal of Dental Research ($n = 51$), developed in Brazil ($n = 45$) and India ($n = 44$). Most studies were in vitro ($n = 211$) and clinical trials ($n = 101$). Carisolv™ ($n = 48$) and Papacarie Duo Gel™ ($n = 33$) were the most used products, prescript in isolated usage ($n = 101$), and compared with drills ($n = 77$). CMCR were more studied in primary teeth ($n = 78$), receiving glass ionomer cement (GIC) ($n = 51$) as restorative material. The most evaluated outcomes were time spent ($n = 48$) and pain ($n = 41$). Clinical application of CMCR takes more time than other techniques, but can also reduce patient anxiety, pain, and need for anesthesia.

Conclusion In vitro and clinical studies with CMCR products have been increasing, mostly carried out in developing countries, evaluating Carisolv™ and Papacarie Duo Gel™. Clinical studies tend to evaluate the time spent and pain compared to drills for removing caries in primary teeth, posteriorly restored with GIC. CMCR clinical application reduces anxiety, pain, and need for anesthesia, despite increase treatments' time.

Keywords Dental caries · Papain · Sodium hypochlorite

Introduction

The principle of the chemical–mechanical caries removal (CMCR) technique is the promotion of minimally invasive intervention using products of different chemical agents on dentin that causes the softening of the decayed tissue facilitating its removal by hand instruments (Hamama et al. 2015). This technique aims to avoid iatrogenesis and reduce

the need for dental anesthesia and phobias to dental treatment caused by the conventional method of removing dental caries using drills (Sontakke et al. 2019).

Initially described almost 5 decades ago by the observation of action of mixing amino acids with sodium hypochlorite on the softening of carious tissue (Goldman and Kronman 1976), the first generation of CMCR products was developed with sodium hypochlorite-based agents and included GK-101, GK-101E (Caridex™) and Carisolv™ (Hamama et al. 2014). Some of these products were removed from the market, but others were changed to update their usefulness with sodium hypochlorite on the softening of carious tissue (Goldman and Kronman 1976).

The change of paradigms and advances in cariology contributed to reinforce the minimal intervention techniques for the treatment of dental caries (Innes et al. 2019; Li et al. 2018). These changes are considered as advances in the

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research of chemical–mechanical products, including the use of papain as the leading chemical agent. Papain is an enzyme extracted from papaya, which causes the degradation of proteins of the carious tissue and has anti-inflammatory and antibiotic properties (Bussadori et al. 2005). Based on these discoveries, a new generation of enzyme-based CMRC products was released on the market (Hamama et al. 2014), which includes Papacarie Duo Gel™ (Bussadori et al. 2005), Carie-Care™ (Venkataraghavan et al. 2013), and Brix3000™ (Ismail and Al Haidar 2019).

CMCR has a great indication for pediatric dentistry as they could reduce the anxiety and pain experience during caries tissue removal and the need of local anesthesia consequently (Cheng et al. 2018). Besides, those products used for CMCR are in prominence in the current global pandemic scenario by SARS-CoV-2 (COVID-19), since the potential risk of cross-infection during caries removal encourages the avoidance of conventional treatments such as rotatory instruments and, for its replacement by techniques with low aerosol production as CMCR (ALOP 2020). These changes can emphasize the establishment of the minimal intervention philosophy for the treatment of caries lesions that was already occurring in dentistry (Innes et al. 2019).

The constant evolution and improvements of the CMCR products associated with new recommendations for their use make the research field in this area more apparent. Besides, the identification of data about the characteristics of the studies that investigated CMCR products by a critical review analysis can formulate a current state of knowledge that could stimulate and guide future research in the area. Therefore, the present study brings a critical analysis to characterize and discuss the worldwide scientific literature and trends in the use of chemical–mechanical caries removal (CMCR) products.

Materials and methods

Literature search strategy

This study was designed based on the Guideline for Critical Review Form-Quantitative studies (Law et al. 1998). We conducted literature search on the following electronic databases: Medline/PubMed, Scopus, Web of Science, Cochrane Library, Lilacs (via VHL), and Embase to identify articles related to chemical–mechanical caries removal (CMCR).

Two reviewers (TFS and MBM) performed the search strategy up to November 2020 to identify eligible studies. Two experts (MBM and LCM) guided the search strategy. The search used MeSH terms and synonyms related to dental caries, and chemical–mechanical caries removal products, with neither filters nor limits of year or language. Boolean operators “AND” and “OR” were used to

improve the precision of the searches. Search strategies were adapted for each database syntax rules and are listed in Table 1.

Study selection and the eligibility criteria

The retrieved studies were transferred to VantagePoint™ software (Search Technology, Inc., Florida, USA), in which analysis fields were merged and duplicated studies were considered only once.

To a better understanding of the critical review analysis, the authors used the TechMining approach, consisting in the application of text-mining tools to science and technology information through the software VantagePoint™. The authors followed the three phases of TechMining (Porter and Cunningham 2004): I—Intelligence: planning and collecting of data to be extracted; II—Design (generate knowledge from the collected data to solve problems of technology management or innovation); and III—Choice (selecting the innovative opportunities for organization by nominating options via text-mining). Therefore, the nine steps related to these phases, such as: issues identification, selection of information sources, search refinement and data retrieval, data cleaning and grouping, basic analysis, advanced analysis, representation, interpretation, and utilization were also followed in the software (Porter and Cunningham 2004).

The study selection was performed by two independent review authors (TFS and MLM) that included all types of studies, in all languages, published in scientific journals, that evaluated the application of chemical–mechanical techniques to remove caries tissue. Studies that investigated the application of CMCR products for another purpose contrary to caries removal, titles related to book chapters, randomized or non-randomized clinical trials registration protocols, and doctoral or master's thesis were excluded. If there were disagreement and doubts regarding the eligibility of the included studies, an attempt was made to reach a consensus, and when it was not enough, a third author was consulted (LCM).

First, all the titles and abstracts of the studies identified in the electronic databases were read and selected based on the eligibility criteria.

A full-text reading of the manuscript was performed to reach a final decision about studies eligibility when the information provided by the title and abstract was insufficient to certify the eligibility or if discordance or doubts about eligibility were present during title and abstract selection phase.

If access to the full article was restricted, attempts to contact the authors via email, ResearchGate, and social networks were done once a week, up to 3 consecutive weeks. If no answer was reached after this period, the article was excluded.

Table 1 Literature search strategies

Database	Strategy
PubMed	(Dental Caries[MeSH Terms]) OR (Carie*[Title/Abstract]) OR (Cariou*[Title/Abstract]) OR (Decay, Dental[Title/Abstract]) OR (Dental Decay[Title/Abstract]) OR (Decayed tissue[Title/Abstract]) OR (Dentin[MeSH Terms]) OR (Dentin*[Title/Abstract]) AND (caridex[Title/Abstract] OR GK-101E[Title/Abstract] OR GK-101E[Supplementary Concept] OR N-monochloro-DL-2-aminobutyric acid[Title/Abstract] OR GK-101[Supplementary Concept] OR GK-101[Title/Abstract] OR GK 101[Title/Abstract] OR N-monochloroglycine[Title/Abstract] OR glycine chloramine[Supplementary Concept] OR glycine chloramine[Title/Abstract] OR Carisolv[Supplementary Concept] OR Carisolv[Title/Abstract] OR Chemomechanical[Title/Abstract] OR Chemo-mechanical[Title/Abstract] OR removal system[Title/Abstract] OR Enzyme-based[Title/Abstract] OR Papain[MeSH Terms] OR Papain[Title/Abstract] OR Papacárie[Supplementary Concept] OR Papacárie[Title/Abstract] OR papain gel[Title/Abstract] OR removal method[Title/Abstract])
Scopus	(INDEX ({Dental Caries} OR dentin) OR TITILE-ABS-KEY (carie* OR cariou* OR {Decay, Dental} OR {Dental Decay} OR {Decayed tissue} OR dentin*)) AND (INDEX (papain) OR TITILE-ABS-KEY (Caridex™ OR gk-101e OR gk-101e OR {N-monochloro-DL-2-aminobutyric acid} OR GK-101 OR gk-101 OR {GK 101} OR n-monochloroglycine OR {glycine chloramine} OR {glycine chloramine} OR Carisolv™ OR chemomechanical OR chemo-mechanical OR [removal system] OR enzyme-based OR papain OR papacárie OR {papain gel} OR {removal method}))
Web of Science	TS=(Carie* OR Cariou* OR 'Decay, Dental' OR 'Dental Decay' OR 'Decayed tissue' OR Dentin*) AND TS=(Caridex™ OR GK-101E OR GK-101E OR 'N-monochloro-DL-2-aminobutyric acid' OR 'GK-101' OR GK-101 OR 'GK 101' OR N-monochloroglycine OR 'glycine chloramine' OR 'glycine chloramine' OR Carisolv™ OR Chemomechanical OR Chemo-mechanical OR 'removal system' OR Enzyme-based OR Papain OR Papacárie OR 'papain gel' OR 'removal method')
Cochrane Library	#1MeSH descriptor: [Dental Caries] explode all trees 2551 #2MeSH descriptor: [Dentin] explode all trees 1242 #3(Carie* OR Cariou* OR "Decay, Dental" OR "Dental Decay" OR "Decayed tissue" OR Dentin*):ti,ab,kw 9382 #4#1 OR #2 OR #3 9390 #5MeSH descriptor: [Papain] explode all trees50 #6(Caridex™ OR N-monochloroglycine OR "glycine chloramine" OR "glycine chloramine" OR Carisolv™ OR Chemomechanical OR Chemo-mechanical OR "removal system" OR Enzyme-based OR Papain OR Papacárie OR "papain gel" OR "removal method"):ti,ab,kw 361 #7(GK-101E OR GK-101E OR GK-101 OR GK-101 OR "GK 101"):ti,ab,kw2 #8#5 OR #6 OR #7 361 #9#4 AND #8 131
Lilacs (via VHL)	((mh:(Dental Caries)) OR (mh:(Dentin)) OR (Carie*) OR (Cariou*) OR ("Decay, Dental") OR ("Dental Decay") OR ("Decayed tissue") OR (Dentin*)) AND ((mh:(Papain)) OR (caridex) OR (N-monochloroglycine) OR (glycine chloramine) OR (Carisolv) OR (Chemomechanical) OR (Chemo-mechanical) OR (removal system) OR (Enzyme-based) OR (Papain) OR (Papacárie) OR (papain gel) OR (removal method) OR (GK-101E) OR (GK-101E) OR (GK-101) OR (GK-101) OR (GK 101))
Embase	('Dental Caries':mj OR Dentin:mj OR Carie*:ti,ab,kw OR Cariou*:ti,ab,kw OR 'Decay, Dental':ti,ab,kw OR 'Dental Decay':ti,ab,kw OR 'Decayed tissue':ti,ab,kw OR Dentin*:ti,ab,kw) AND (caridex:ti,ab,kw OR GK-101E:ti,ab,kw OR GK-101E:ti,ab,kw OR 'N-monochloro-DL-2-aminobutyric acid':ti,ab,kw OR 'GK-101':ti,ab,kw OR GK-101:ti,ab,kw OR 'GK 101':ti,ab,kw OR N-monochloroglycine:ti,ab,kw OR 'glycine chloramine':ti,ab,kw OR 'glycine chloramine':ti,ab,kw OR Carisolv:ti,ab,kw OR Chemomechanical:ti,ab,kw OR Chemo-mechanical:ti,ab,kw OR 'removal system':ti,ab,kw OR Enzyme-based:ti,ab,kw OR Papain:ti,ab,kw OR Papacárie:ti,ab,kw OR 'papain gel':ti,ab,kw OR 'removal method':ti,ab,kw)

Data extraction

Two review authors performed the data extraction (TFS and MLM), and any disagreements or doubts between them were solved through a consensus meeting. If needed, a third reviewer (MBM) was consulted for a final decision. Quantification of the data of the studies was performed and the results obtained were evaluated.

Authors and journals that presented more than one name format were grouped into a single name for avoiding ambiguity. For all included studies, methodological and some bibliometric data were extracted, recorded, and quantified: authors (five or more publications), year of publication

(divided by decades), journal of publication (five or more publications), country of the authors, and type of study (in vitro, case report/case series, clinical trials, systematic review, other reviews, other types of studies).

Furthermore, clinical methodological features of CMCR techniques and additional data of only the case report/case series and clinical trials were extracted, classified, and quantified, as follows:

1. CMCR Product: GK101, Caridex™/GK101E, Carisolv™, Papacarie Duo Gel™, CarieCare™, Brix 3000™, and others (which included others CMCR products);

2. CMCR method: isolated or combined with other caries removal techniques;
3. Comparison group: atraumatic restorative treatment (ART), drills (high and low speed), other CMCR product, laser, others (when the use of a placebo or different techniques such as the modified ART), and not applicable (for cases report that did not compare techniques);
4. Age group: children (< 10 years), adolescents (from 10 to 19 years), adults/elderly (> 19 years), and unspecified (when the study did not mention the age of the patient);
5. Tooth dentition that was treated: primary, permanent, or uninformed. Primary and permanent dentition could be included at the same clinical study;
6. Material of restoration: glass ionomer cement (GIC), zinc oxide-eugenol (ZOE), resin composite (RC), amalgam, and compomer;
7. Outcomes: behavior or anxiety, time spent, pain (during and after caries removal), acceptability, efficacy of caries removal, restorative success, microbiological evaluations, need for local anesthesia, need for drilling, and others (such as costs, quality of life and pulp sensibility). Case reports/case series that only describes the CMCR techniques were considered as outcome not applicable.

According to their methodology, some studies could be classified into two or more options from the comparison groups. Besides, type of dentition, age group, and outcomes mentioned could receive one or more ratings above at the same clinical study.

The included systematic reviews about the clinical application of CMCR products were classified according to the presence or not of a meta-analysis and considering the following parameters: treatment time, pain, the use of local anesthesia, patient preferences, clinical efficacy, anxiety reducing, quality of life, and reduction in bacteria count.

Data analyses

VantagePoint™ software and Microsoft Office Excel 2010™ were used to analyze some bibliometric data to generate a better understanding about the research field of CMCR in the present critical review. The data were analyzed as follows:

- The “publication year” data were crossed with the “CMCR product” and the “type of study” with the aim to verify the studies profile about these issues through the years.
- The “CMCR method” was correlated with the variable “CMCR product” to understand the association of CMCR products with other methods used to remove caries tissue in clinical studies.
- The mostly dental caries removal techniques that were compared to CMCR product in clinical studies

were checked by correlating “comparison group” with “CMCR product” variables.

- Research trends about “age group”, “type of dentition”, “material of restoration”, and “outcomes” were assessed through their frequency in the clinical studies.

As the same study could contain one or more classification options for some variables (products, comparison group, age group, dentition, and outcomes), such classifications could account with an absolute frequency greater than the number of studies included.

Results

Study selection

A total of 2221 records were identified from databases. After removal of duplicates and applying the eligibility criteria for the titles and abstracts, 517 records were remained. Of these studies, 120 were excluded, since they were classified as book chapters, conference abstracts, and records of clinical trial protocols (Supplementary material). Thus, a total of 397 studies were included and underwent data characterization and final synthesis (Fig. 1).

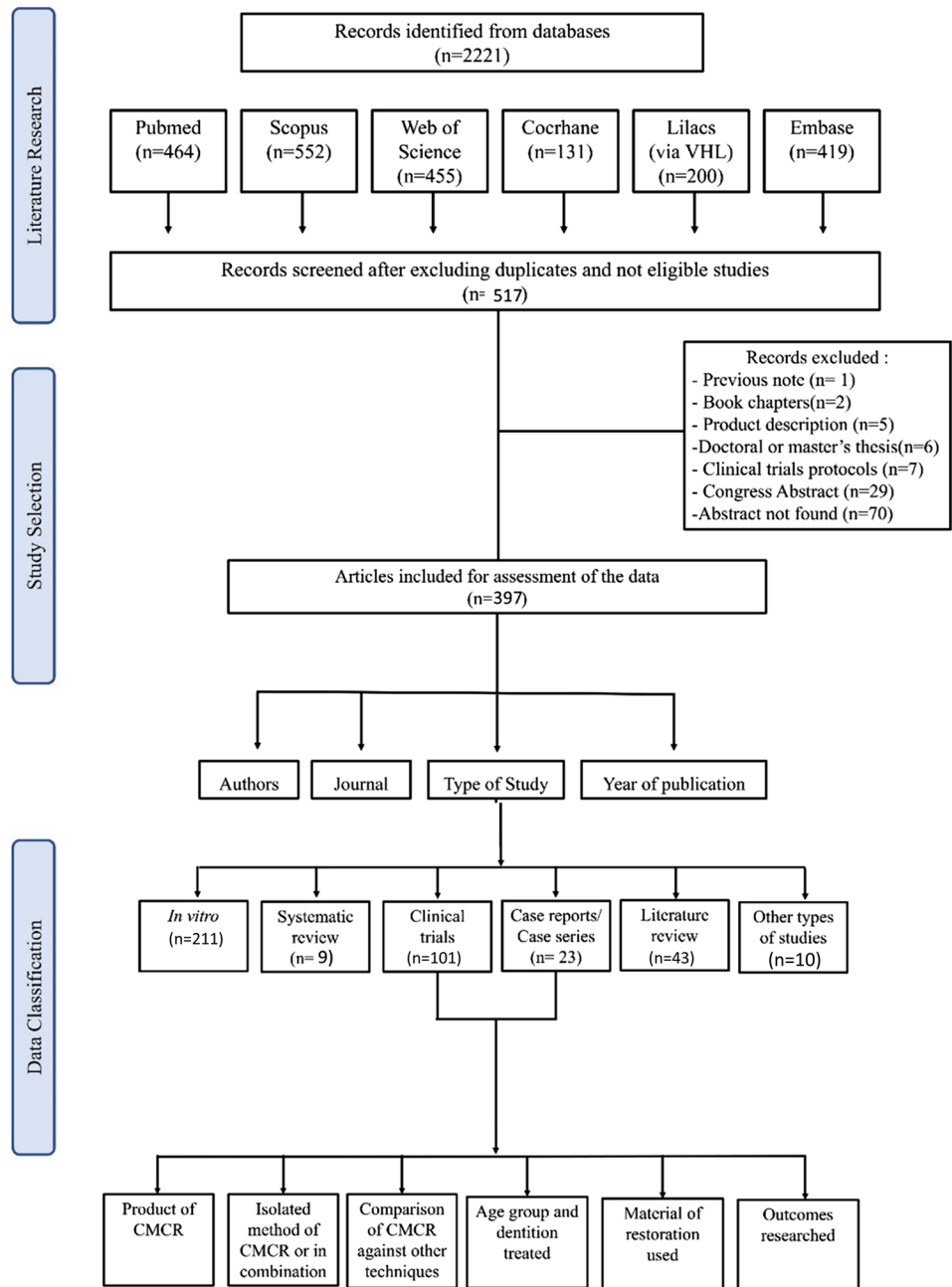
Characteristics of the included studies

Authors, year and journal of publication, and country of the authors

A total of 1327 authors were found with publications about CMCR products. Data from the authors with five or more publications are presented in Fig. 2. Bussadori S.K. was the author with more publications about this subject ($n = 32$), followed by Motta L.J. ($n = 16$) (Fig. 2).

The research about the present issue raised significantly after the 1990s, which moved up from 29 publications in 1991–2000 to 161 in 2001–2010 period, maintaining the same profile during 2011–2020 ($n = 169$). The Journal of Dental Research was the periodic with more publications about the subject ($n = 51$; 12.7%), followed by the Journal of Dentistry ($n = 37$; 9.2%) and Caries Research ($n = 27$; 6.7%).

Studies about CMCR have been conducted in 50 different countries (Fig. 3). Developing nations led the list of publications about this topic, in which Brazil has more publications ($n = 45$), followed by India ($n = 44$). Although developed countries, in general, presented fewer publications on the subject than the developing ones, the United States published a great number of articles in the area ($n = 36$).

Fig. 1 Flowchart of search results in databases

Type of study

Among the 397 studies selected, 211 were *in vitro*, 43 literature review, 9 systematic reviews, 23 case reports/case series, 101 clinical trials, and 10 classified as other type of studies such as *ex vivo* studies ($n=5$), studies with animals ($n=3$) and observational studies with questionnaires ($n=2$). The distribution of the different types of study designs published along the years can be observed in Fig. 4. It is important to highlight that one study classified as other type of study did not informed publication year data. *In vitro* study was the most frequent design since 1975, with the

publication peak in 2001–2010 period ($n=84$). Clinical trials and case report/case series had an expressive growth in publication after 2000s, reaching a peak of 42 and 14 studies, respectively, in this decade.

Use of CMCR products

GK101 was the first CMCR product scientifically published, which its first clinical study published in the year 1975. Few clinical studies were found related to GK 101E (Caridex™) ($n=6$), but a large number related to Carisolv™ ($n=48$), followed by Papacarie Duo Gel™ ($n=33$). Clinical trials

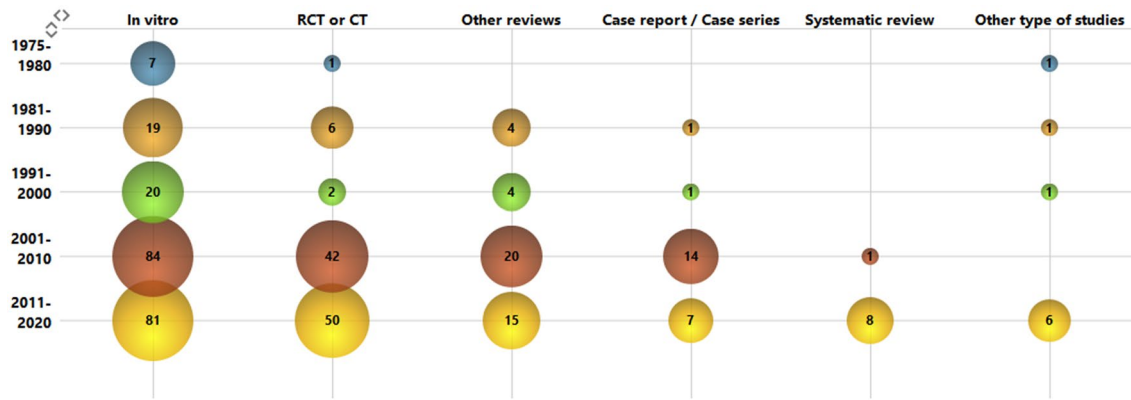


Fig. 4 Type of studies with CMCR products over the years

with Carisolv™ were more published during 2000–2010 ($n = 29$), while Papacarie Duo Gel™ during 2011–2020 ($n = 29$) period. After the year 2010, new papain enzyme-based products (Carie-Care™ and Brix 3000™) emerged in the field of clinical research, and a decrease of Carisolv™ studies was observed (Fig. 5).

Isolated or combined use of CMCR method with other caries removal techniques

The caries removal, in most of the clinical studies, was performed by CMCR products ($n = 101$) in an isolated use form. However, the combined form of use was also described such as CMCR with ART ($n = 4$), drills ($n = 3$), and laser ($n = 3$) (Table 2).

Comparison of CMCR with controls or other techniques

Clinical studies with GK 101 were only compared to placebo, saline solution, or water. All the other clinical studies

about CMCR products mostly compared the action of their products to caries removal with drills ($n = 77$), followed by ART ($n = 23$) and less expressively to other CMCR products ($n = 15$) and laser ($n = 3$) (Table 2).

Age group and type of dentition

Results about age group, dentition, and the used product can be observed in Fig. 6. From the clinical studies, 74 were performed with children, 25 with adolescents, and 19 with adults/elderly. Primary teeth ($n = 78$) were the dentition more treated, mainly in studied with Carisolv™ ($n = 32$) and Papacarie Duo Gel™ ($n = 28$), followed by Carie-care™ ($n = 6$), other CMCR products ($n = 4$), product not specified ($n = 3$), and Brix3000™ ($n = 2$). Forty clinical studies were performed to treat permanent teeth, but in this case, with GK101 ($n = 1$), GK101E (Caridex™) ($n = 7$), and Carisolv ($n = 12$). Some studies did not inform the age or dentition of the population studied ($n = 6$).

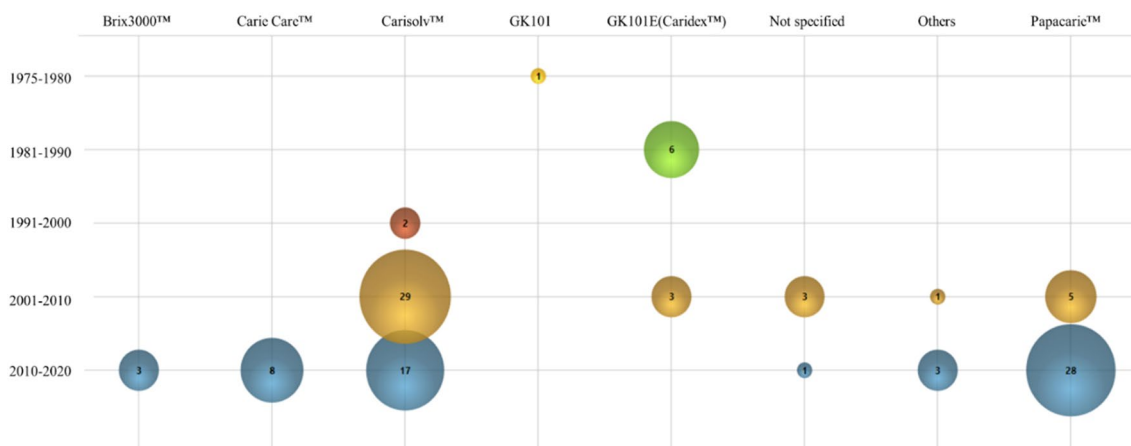


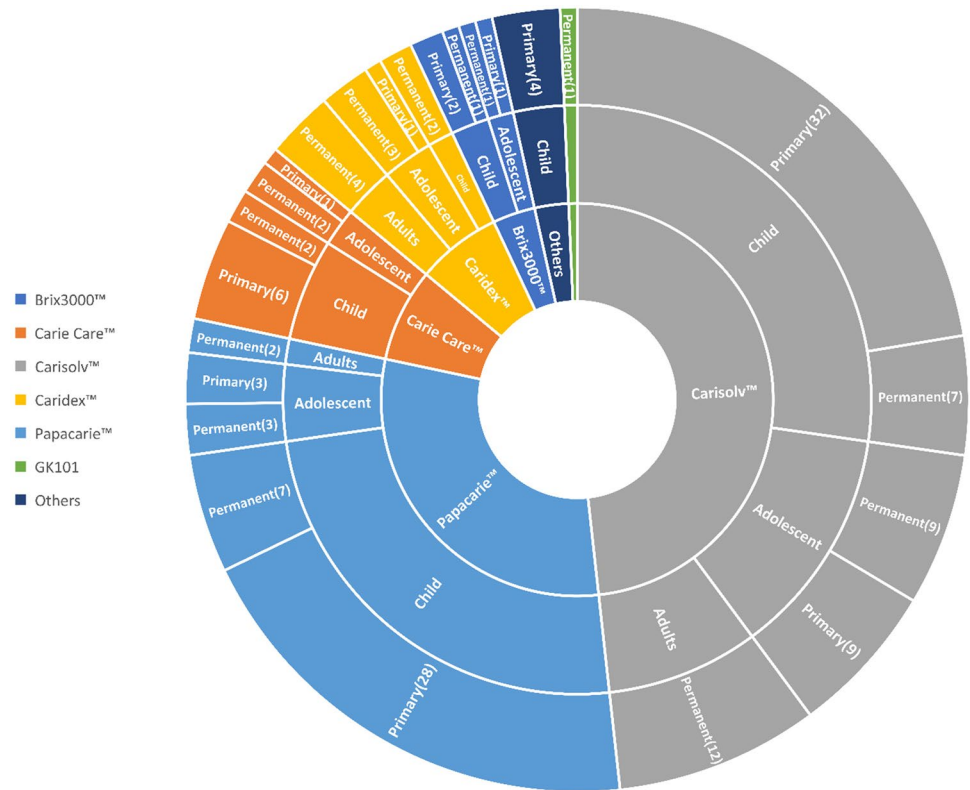
Fig. 5 Buble chart of the CMCR products studies over the years

Table 2 Use of CMCR techniques, CMCR use against other caries removal techniques, and material of restoration used in clinical studies

	GK101	GK101E	Carisolv™	Papacarie™	Carie Care™	Brix3000™	Other	Not specified
<i>Isolated or combined use of CMCR</i>								
Isolated	1	7	44	31	7	3	4	4
Combined	–	2	3	1	1	–	–	–
Not informed	–	–	1	1	–	–	–	–
<i>CMCR against other caries removal techniques</i>								
Drills	–	6	34	20	7	3	3	4
ART	–	1	13	6	1	–	–	2
CMCR	–	–	6	6	–	1	2	–
Laser	–	–	2	1	–	–	–	–
Others	1	1	–	–	1	–	–	–
Not informed	–	3	1	1	–	–	1	–
<i>Material of restoration</i>								
GIC	–	4	16	21	5	2	3	–
Not informed	–	4	23	9	2	1	1	3
RC	–	1	11	4	1	1	1	1
Amalgam	–	3	5	3	1	–	–	–
Compomer	–	–	1	1	–	–	–	–
ZOE	1	–	–	–	–	–	–	–

CMCR chemical caries removal, ART atraumatic restorative treatment, GIC glass ionomer cement, RC resin compomer, ZOE zinc oxide-eugenol, – none

Fig. 6 Age, dentition, and CMCR product used in the studies of clinical application of CMCR products (clinical trials and case report/case series)



Restoration material

Most of the treated teeth were restored with GIC ($n=51$) in the studies that used Papacarie Duo Gel™ ($n=21$), Carisolv™ ($n=16$), Carie-Care™ ($n=5$), GK101E (Caridex™) ($n=4$), and Brix3000™ ($n=2$). Resin composite ($n=20$) was the second most used restoration material, mainly in works with Carisolv™ ($n=11$). Some studies did not report the type of restoration used ($n=33$), and one study was classified as not applicable, because the teeth were extracted after CMCR treatment due to orthodontic recommendations (Table 2).

Outcomes

Time spent ($n=58$) and pain ($n=48$) were the most evaluated outcomes regarding all CMCR products, but they were not assessed by studies with GK 101. Considering “other outcomes”, a few studies evaluated costs ($n=2$), quality of life ($n=2$), pulp sensibility ($n=2$), volume of gel used ($n=2$), volume of removed dentine ($n=2$), and adjacent tooth protection ($n=1$). Papacarie Duo Gel™ and Carisolv™ clinical studies evaluated all the main outcomes researched and some other outcomes (Fig. 7).

Description of the systematic reviews results

Most of the systematic reviews included in this study performed meta-analyses (Hamama et al. 2015; Lai et al. 2015; Li et al. 2014; Ladewig et al. 2018; Schwendicke et al. 2015; Deng et al. 2018). The classification of the data presented in the systematic reviews (Marquezan et al. 2006; Li et al. 2014; Hamama et al. 2015; Lai et al. 2015; Maru et al. 2015; Schwendicke et al. 2015; Deng et al. 2018; Ladewig et al.

2018; Schwendicke 2018) is showed in Table 3. In relation to time spent, Carisolv™ was considered the most time-consuming method of caries removal in all studies in which their performance was evaluated (Marquezan et al. 2006; Li et al. 2014; Hamama et al. 2015; Lai et al. 2015; Maru et al. 2015; Ladewig et al. 2018), despite reducing the need of local anesthesia (Marquezan et al. 2006; Li et al. 2014; Lai et al. 2015; Maru et al. 2015; Ladewig et al. 2018). It was observed that Papacarie Duo gel™ was more time-consuming than ART and the use of drills to remove dental caries (Hamama et al. 2015; Schwendicke et al. 2015; Deng et al. 2018; Ladewig et al. 2018; Schwendicke 2018). The CMCR products showed potential to reduce anxiety and pain than the use of drills (Deng et al. 2018; Ladewig et al. 2018; Schwendicke 2018), and when compared to ART, ultraconservative treatment, and hall technique, CMCR products demonstrated similar results related to the same outcome (Ladewig et al. 2018). No significant difference was found about the clinical efficacy of CMCR products to treat dental caries compared to drills and the improvement in quality of life related to other caries treatment (Lai et al. 2015; Ladewig et al. 2018).

Discussion

The current pandemic state caused by the global dissemination of COVID-19 disease reinforced the spread of the philosophy of minimal intervention for the treatment of caries in dentistry (ALOP 2020). The recommendation of using these techniques by dental guidelines as a caries management alternative for preventing cross-infection can reinforce the concept that less is more, which contraindicates the traditional treatment, which entailed removing large quantities

Fig. 7 Outcomes researching the studies of clinical application of CMCR products (clinical trials and case report/case series)

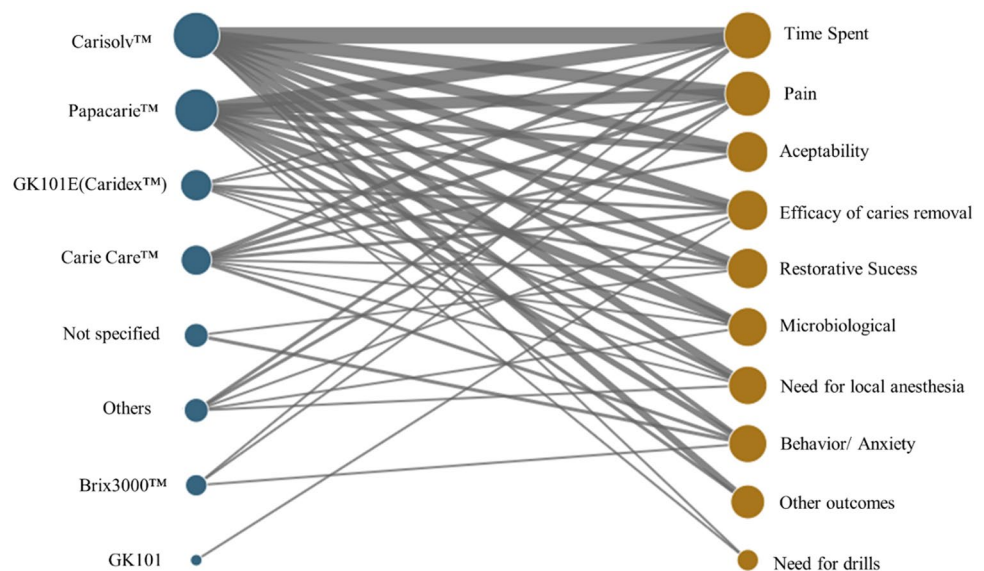


Table 3 Classification of the CMCR products considering the results of the included systematic reviews

Techniques compared	Articles	More time spent	Painless techniques	Reduced the need for anesthesia	Patients preference	Clinical efficacy	Reduced anxiety	Quality of life	Reduced bacteria count
Papacarie Duo Gel™, Carisolv™, ART and drills	Hamama et al. (2015)	Position 1: Carisolv Position 2: Papacarie Position 3: ART Position 4: Drills	-	-	-	-	-	-	-
Carisolv™ and Drills	Maru et al. (2015)	Position 1: Carisolv Position 2: Drills	Position 1: Carisolv Position 2: Drills	Position 1: Carisolv Position 2: Drills	Position 1: Carisolv Position 2: Drills	-	-	-	-
	Lai et al. (2015)	Position 1: Carisolv Position 2: Drills	-	Position 1: Carisolv Position 2: Drills	-	ND#	-	-	-
	Li et al. (2014)	Position 1: Carisolv Position 2: Drills	-	Position 1: Carisolv Position 2: Drills	-	-	-	-	-
	Marquezan et al. (2006)	Position 1: Carisolv™ Position 2: Drills	-	Position 1: Carisolv™ Position 2: Drills	Position 1: Carisolv™ Position 2: Drills	-	-	-	-
CMCR ^a , ART, drills, UCT and HT	Ladewig et al. (2018)	-	Position 1: CMCR Position 2: ART Position 3: UCT Position 4: Drills Position 5: HT	-	-	-	Position 1: CMCR Position 2: ART Position 3: Drills	ND#	-
Papacarie Duo Gel™ and drills	Deng et al. (2018)	Position 1: Papacarie Position 2: Drills	-	-	-	-	Position 1: Papacarie Position 2: Drills	-	Position 1: Papacarie Position 2: Drills
	Schwendicke (2018)	Position 1: Papacarie Position 2: Drills	Position 1: Papacarie Position 2: Drills	-	-	-	-	-	Position 1: Papacarie Position 2: Drills
CMCR ^a lasers and drills	Schwendicke et al. (2015)	Position 1: CMCR Products Position 2: Drills	Position 1: CMCR Products Position 2: Drills	-	-	-	-	-	-

^aChemical–mechanical caries removal products involving especially Carrisolv™ and Papacarie Duo Gel™

#No statistical difference between the evaluated techniques (-) not evaluated in the study

of sound hard dental tissue for treating caries (Frankenberger and Meerbeek 2018). This situation directly opens the field for future research involving the different types of minimum intervention methods, such as the CMCR technique, making fundamental the characterization of this research field, which has not yet been explored, to guide future research.

The present study provided the first review with critical analysis about this CMCR minimal intervention technique, with quantification of the selected studies, reporting their scientific profile and data by means of Tech Mining approach, proposed by Porter and Cunningham (2004). Tech mining is a qualitative different way to use information in science and technology. In the present study, a wide variety of available data in scientific databases was explored through a software (VantagePoint™) (Porter and Cunningham 2004) to assist the organization of data related to CMCR products.

Chemical–mechanical treatment of caries removal has been published in journals with high impact in dentistry, as *Journal of Dental Research* (impact factor = 4.914) and *Journal of Dentistry* (impact factor = 3.242), showing the importance of this minimally invasive technique for dentistry. Developing countries lead publication rank about chemical–mechanical caries removal products. A lower social-economic position has been significantly associated with a greater risk of having caries lesions (Schwendicke et al. 2014), making countries in developing status more affected by caries diseases. Thus, the progress of a less-invasive methods of caries treatment such as CMCR might be necessary for the maintenance of dental health of these populations, explaining the great interest in these research subjects in these countries. Besides, Brazil was the country that developed the most significant number of studies ($n=45$), and Bussadori S.K. and Motta J.L. the authors that lead the rank with more publications. These results possibly are related to Papacarie Duo Gel™, the first papain-based product discovered and produced in Brazil and by these authors (Bussadori et al. 2005). A similar hypothesis can also be given to the second and third countries, India and United States, respectively, in the rank of publication about this subject, since India ($n=44$) is the source country of Carie-Care™ (Venkataraghavan et al. 2013) and the United States ($n=36$) is the pioneer of the CMCR products development (GK 101 and GK 101E (Caridex™) (Habib et al. 1975).

In the health area, for the safe clinical application of treatment methods that use chemical products such as CMCR, researchers must do a sequence of types of research to provide enough scientific evidence (Carroll 1997). Usually, an *in vitro* investigation is performed to assess the properties of the new drugs and materials involved, generating a simulation of its relationship with the human tissue on which it will be applied (Carroll 1997; Mm et al. 2014). Then, if the treatment method demonstrates safety, the next step is to conduct

clinical studies to test similar effects under “real-world” treatment condition (Mm et al. 2014). The distribution of the different types of study designs published through the years about CMCR products is directly affected by these research sequences. Thus, in the present review, we observed that the *in vitro* study design has been the most used type of study from 1975 to 2020 ($n=211$), reflecting the constant emergence of new CMCR products in the market. The expressive growth of clinical studies after the 2000s matches with the launch of two products with different chemical bases on the market, Papacarie Duo Gel™ and Carisolv™. The increase in the last type of study can be based on the development of the knowledge in cariology with studies that scientifically founded that selective caries removal (Li et al. 2018) presents efficacy and might encourage clinical studies with minimally invasive intervention as CMCR.

Besides, the results of systematic review evaluations reinforced the clinical potential of CMCR products to make the caries removal more comfortable (Marquezan et al. 2006), reducing anxiety (Ladewig et al. 2018; Deng et al. 2018; Schwendicke 2018), pain (Marquezan et al. 2006; Li et al. 2014; Schwendicke et al. 2015; Maru et al. 2015; Lai et al. 2015; Deng et al. 2018; Ladewig et al. 2018; Schwendicke 2018), and the need of local anesthesia (Marquezan et al. 2006; Li et al. 2014; Lai et al. 2015; Maru et al. 2015) showing the great importance of this type of technique mainly for child, special care needs, and dental phobic patients. CMCR products, specifically Carisolv™, are more time-consuming (Marquezan et al. 2006; Li et al. 2014; Hamama et al. 2015; Maru et al. 2015; Lai et al. 2015; Ladewig et al. 2018; Schwendicke et al. 2015), although Papacarie Duo Gel™ presented a potential to be faster than ART (Hamama et al. 2015), showing the importance of the development of clinical trials with enzyme-based products. Besides, the systematic reviews’ evaluations indicated limitations of the clinical trials on CMCR that should be overcome by new studies, such as the sample size (Lai et al. 2015), heterogeneity among study designs (Lai et al. 2015; Deng et al. 2018), and high risk of bias (Hamama et al. 2015; Schwendicke et al. 2015).

Clinical trials have considerable importance for developing CMCR products and evaluating their effective use in the treatment of dental caries. Thus, some analyses were done only for these types of studies. The distribution of clinical research about CMCR products through the years is directly influenced by the chronology of the appearance and removal of these products in the market. The pioneer CMCR product was GK 101, composed of NaOCl and 0.05% *N*-monochloroglycine (NMG), prepared by mixing these two solutions (Habib et al. 1975). One study evaluated the GK 101 application, justifying the extremely scarce publications of clinical studies about this product.

GK-101 demonstrated inefficiency in removing carious lesion, so an improvement in the formula of GK-101 was made generating an ethyl derivative, GK-101E, composed by *N*-monochloro-DL-2-aminobutyrate (NMAB), marketed as Caridex™ (Marquezan et al. 2006; Hamama et al. 2015). Nevertheless, the low number of clinical studies on this product has also been observed, which can be explained by the persistence of its unsatisfactory results in cavity excavation compared to conventional methods of caries removal that may have caused its exit of the market (Hamama et al. 2014). In 1998, a Swedish CMCR NaOCl solution called Carisolv™ was introduced to the market¹⁷ and became the last available chemical–mechanical agent based on NaOCl (Ericson et al. 1999). In this product, the monoaminobutyric acid has been replaced by three different amino acids (glutamic, leucine, and lysine) (Ericson et al. 1999), making it more stable and promoting a better selective removal of caries (Hamama et al. 2015).

An expressive change in the number of clinical studies publications about CMCR products is noticed during 2001–2010, which could have been impulse by the introduction of Papacarie Duo Gel™ in 2003. The pioneer's solution with chemical principal agent papain started the new generation of enzyme-based CMCR products (Hamama et al. 2014). The short time between the launch of Carisolv™ and Papacarie Duo Gel™ on the market (Bussadori et al. 2005) and the fact that they are products with different main chemical agents may have caused a tendency to develop clinical studies (Abdelnur et al. 2008; Kochhar et al. 2011; Kumar et al. 2012; Ammari et al. 2014; Chowdhry et al. 2015; Schwendicke et al. 2015; Reddy et al. 2015; Hegde et al. 2016; Moimaz et al. 2019) comparing these products, making them the most CMCR products studied.

Although the Carisolv™ has been the most CMCR product clinically evaluated ($n=48$), it was observed a current reduction of studies about it, contrasting with the growth of clinical studies of Papacarie Duo Gel™, as well as the arisen of other studies with the CMCR products based on papain (Carie-Care™ and Brix3000™) between 2010 and 2020. These found may indicate a reduction of interest in the research field about CMCR solutions based on sodium hypochlorite, since they spend more time when compared to papain-based gel, preserve less sound dentin, and present higher cost because of the customized instruments included (Hamama et al. 2014; Mm et al. 2014; AlHumaid et al. 2018).

As mentioned, after the year 2010, papain enzyme-based products have gained the field of clinical research. The Carie-Care™ released in 2013 by Indians (Venkataraghavan et al. 2013) adds the anti-inflammatory action of essential oils to papain CMCR products formulation and has six clinical studies about it. The last modification made on papain CMCR products was performed with the gel called Brix

3000™, released in the Argentine market in 2016, which explains the few clinical studies about this product ($n=3$). The difference in its formulation is the higher concentration of papain (3000 U/mg in each 10%), and the EBE technology (Encapsulated Buffer Emulsion). This product seems to present an ideal pH needed to immobilize enzymes, which enhances proteolysis of collagen fibrils in decayed tissue and providing better resistance to the product (Ramamoorthi et al. 2013). However, further studies are needed to prove these properties, mainly clinical trials that provide additional information about the vantages and disadvantages brought by the modifications performed in CMCR papain enzyme-based products.

This critical review showed that most clinical studies used CMCR techniques as an isolated method for caries removal ($n=101$). For the few clinical studies that used a combination of different caries removal techniques to the CMCR, the ART technique was the most chosen for association ($n=4$). The association between ART and CMCR products may be easier, because they are performed by similar techniques in removing decayed tissue with the necessary use of manual instruments. The only difference is the addition of a chemical product to facilitate the removal of caries tissue with the aid of a CMCR product (Frencken et al. 1998).

Regarding the comparison groups, drills were the most frequent. The authors believe it happened, since the clinical studies with CMCR products aimed to confirm that the selective removal compared to an invasive technique, as the rotatory drills, showed that sound tissue preservation can hardly be reached (Montedori et al. 2016; Innes et al. 2019). Other method frequently compared to CMCR is the ART, an established minimal intervention technique recommended since 1998 by the World Health Organization (WHO 1998) and with the success of longevity has been proven in the single-surface restoration of permanent and deciduous teeth (Juntavee et al. 2013; Amorim et al. 2018). Most clinical studies about all the CMCR products selected children and studied the clinical application of CMCR in primary teeth. These might be explained by the challenges of caries treatment in this age group. The conventional caries removal method using drills can cause more pain, discomfort, dental phobia, and anxiety in children, making it a challenging step to dental health care considering this age group (Leal et al. 2009). Thus, literature reviews about the CMCR (Hamama et al. 2015) show that this is a minimally invasive technique that can overcome some dental caries removal challenges, making it less traumatic, mainly for pediatric dentistry patients (Alkhouli et al. 2020; Hamama et al. 2015; Leal et al. 2009).

The fact that most studies were performed in primary teeth of children could have directly influenced the results of GIC be the restorative material mostly used. GIC is related to a good clinical performance found after its

application in primary teeth and its easy use may collaborate for restoration in young patients with negative behavior (Turner et al. 2007; Jose et al. 2019), which also require less intervention to be placed in the cavity as eliminates the need of rubber dam (Jose et al. 2019), since it is considered as biocompatible material. The drop in the use of amalgam over the years contrasts with the increased use of adhesive materials reflects the move of the minimal intervention philosophy to the center of oral health care (Innes et al. 2019).

Time spent and pain were the most evaluated outcomes in clinical trials with CMCR studies, as assessed by almost of all CMCR products, except for GK101. This result can be justified due to concern for the CMCR product. Usually, the chemical solution used to facilitate the caries removal needs to be in contact with the decayed tissue during a specific time, and long chair time can contribute to the patient's discomfort (Montedori et al. 2016). A similar explanation can be done to pain outcomes, since negative experiences during dental treatment, mainly in childhood, can cause future dental phobia and avoidance of the treatment (Leal et al. 2009).

The current knowledge indicates that bacteria in the decayed tissue left by selective caries tissue removal did not result in bacterial growth, since the reduction of exogenous nutrients promoted by the restorative materials sealed the dental cavity (Lula et al. 2009). Thus, microbiological evaluation of CMCR products can become an obsolete outcome to be researched.

The findings of this critical review should be taken cautiously as the risk of bias and scientific evidence strength of the included studies were not evaluated. Besides, this study presents limitations as the difficulty of accessing summaries or articles of older titles, mainly carried out between the 1970s and 1980s. In addition, some articles or abstracts did not specify the data surveyed. Despite these limitations, a mapping of data about CMRC techniques was provided by the present critical review such as an useful worldwide panorama of these minimally dental caries removal technique demonstrating their trends of use in children along the years, consequently guiding the researchers to improve studies in this field.

By the evaluations of this study, it was possible to verify the need of improvements in clinical trials to overcome the bias of sample size and to produce more homogenous studies and results, allowing better systematic review evaluations. Besides that, more attention should be paid to vital success after using CMCR products, and further studies in the area are needed to verify the different formulations of CMCR products concerning restorative material survival, an essential pillar to the maintenance of dental health care (Hamama et al. 2015; Ladewig et al. 2018).

Conclusion

- Studies about chemical–mechanical caries removal products have increased over the years, especially in vitro and clinical trials.
- Future clinical studies should focus in the enzyme-based products, since research has so far shown their better performance when compared to the hypochlorite-based products.
- The evaluation of the restorations survival, in addition to time spent and pain perception, in primary teeth is still scarce in the literature when the enzyme-based products (mainly Carisolv™) are compared with the conventional restorations.
- Although the clinical application of chemical–mechanical caries removal products increases the time taken to caries tissue removal, it may have the potential to make the caries removal more comfortable, reducing anxiety, pain, and the need of local anesthesia.

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Author contributions TFS: Performed the search strategy in data bases, studies selection and classification, and data analyses, and wrote the manuscript. MLM: Performed studies selection and classification, data analyses, and critical review of the manuscript. MMB: Performed and guided the search strategy in data bases, responsible for the data management in the program VantagePoint™, and critical review of the manuscript. JMVG: Guided bibliometric analyses and the use of the program VantagePoint™, and critical review of the manuscript. AFG: Critical review of the manuscript. LCM: Supervision and guidance of the search strategy, studies classification, bibliometric analyses, and critical review of the article.

Declarations

Conflict of interest The authors declare no conflict of interest.

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