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Remineralizing Agents as a Frontier in the Management of Non-Carious Lesions-A Systematic Review and Meta-Analysis

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Abstract
Aim: To review the effect of recently developed remineralization materials as well as fluorides on enamel and dentin surfaces of non-carious lesions exposed to various erosive agents.
Materials and Methods: This review has been clearly aligned with the preferred reporting items for systematic reviews and meta-analyses (PRISMA). Research on literature has been carried out using online databases such as PubMed/MEDLINE, Scopus, Google Scholar, and Cochrane databases to identify studies published from 2008-2023 (december) by screening titles and abstracts, and making obligatory exclusions after applying eligibility criteria. The QUIN Tool was used to assess potential biases.
Results: The final count of studies included in the review was 23. The average surface roughness and surface microhardness showed substantial variances after the application of remineralizing agents on artificially induced non-carious lesions by erosive agents.
Discussion: It could be concluded that fluorides still pertain to be the most beneficial with titanium and stannous fluoride showing immense protective effects. Casein phosphopeptide-amorphous calcium phosphate combined with fluorides also showed positive effects on enamel, and dentin surfaces and varied in their mode of action on primary teeth.
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Keywords: Casein phosphopeptide-amorphous calcium phosphate, Dental erosion, Fluorides, Non-carious lesions and Remineralising agents.

1. Introduction:

Human teeth plays a remarkable role in mastication, aesthetics and phonetics. Other than dental caries, there are additional oral lesions that can rupture the normal tooth function. With ageing, non-carious lesions, partial or total tooth tissue loss can occur which can negatively impact the quality of life. Subsequent loss of hard tissues, restorative material and root surface because of factors other than caries which results in loss of tooth structure, thus initiates formation of Non carious cervical lesions (NCCLs).[1-3] Dental erosions, abrasions, attrition and abfraction have been attributed to be major sources.[4] Removal of mineral ions from hydroxyapatite crystals of enamel and dentin leads to demineralisation.[5]
The main consequence of demineralisation is erosion and dental caries. Chemical dissolution after acid attack can occur either after consumption of dietary acids (soft drinks) or bacterial attack in oral cavity.[6-8] Saliva can act as intraoral neutralizer due to the presence of ions that inhibits demineralisation by

maintaining a supersaturated state during reduced pH intervals and deliver fluoride ions to enhance remineralisation.[9-10]

Achievement of treatment objective using surgical approach in least invasive manner with minimal reduction of healthy tissues is possible through remineralisation, hence belongs to Minimally Intervention Dentistry (MID).[11,12]

Fluorides act as frontier to inhibit demineralization as it replaces the calcium in hydroxyapatite (HA) by fluorine to form fluoroapatite (FAP) which can act as catalyst and also reduce the weakness in HA to lactic acid due its displacement of fluoride, does not dissolve in the oral cavity.[13-15] Formation of fluoroapatite leads to reduced phosphate and calcium ions. Hence calcium phosphate based agents were developed to overcome this reduction as it leads to formation of clusters of amorphous Calcium Phosphate (ACP) by aggregation, thus prevents demineralization and enhances remineralization through supersaturation of enamel by reduced precipitate formation of calcium phosphate ions.[16] Dental products that are commercially available have also combined Casein phosphopeptide-amorphous calcium phosphate (CPP-ACP) and fluoride to provide more better remineralization.[17-19] Low dose systems of calcium phosphate which includes the addition of functionalized Tricalcium phosphate in single-phase, non-aqueous or aqueous topical fluoride agents also proved to show significant results.[20,21] Bio-mimetic remineralization has the ability to create crystals of apatite within collagen fibers that are demineralized.

1.2 Null hypothesis: - There is no effect of remineralizing agents in non-carious lesions on enamel and dentin exposed to acidic erosions and wear.

1.3 Alternative Hypothesis: - Remineralizing agents provide protection in non-carious lesions on enamel and dentin exposed to acidic erosions and wear.

1.4 Objectives: - The objective is to systematically review the impact of various remineralizing agents on hard tissues of non-carious lesions and their comparison with fluoridated, combination, and non-fluoridated materials on permanent as well as deciduous teeth based on surface microhardness, roughness and mineral loss.

2. Methods:

2.1 Eligibility Criteria: The inclusion and exclusion criteria used in this review is based on the PICOS strategy which included extracted human permanent and deciduous teeth(P) which were subjected to erosive challenges to induce non-carious lesion through carbonated soft drinks and demineralizing solutions followed by application of various remineralizing agents (I) and then compared with fluoridated(Sodium, Tin, Stannous fluorides, Acidulated phosphate fluoride gels and Silver diamine fluoride,), non-fluoridated(Casein phosphopeptide-amorphous calcium phosphate along with Calcium Sodium phosphosilicate) , combined agents(C) in order to observe the changes in enamel microhardness, mineral loss and roughness(O) thus helps in protection of non-carious lesions at an early stage with inclusion of only In-vitro studies(S).

2.2 Literature Search The information was collected from online databases PubMed/MEDLINE, Scopus, Google Scholar, and Cochrane databases to identify studies published until 2023. The MeSH(Medical Subject Headings) terms used were "Remineralizing agent, Enamel, CPP-ACP, dental erosion, Dentin, and extracted human teeth", in various combinations. The reference lists of the studies reviewed for full-text reading were manually screened.

2.4 Study Selection Process: The titles and abstracts of the articles were used to screen them. The complete texts of the articles were retrieved for additional evaluation according to the criteria for inclusion and exclusion. Studies that were in-vitro, which were carried out on extracted human permanent and deciduous teeth were included. In vivo, randomized control trials, ex vivo, and animal studies were excluded.

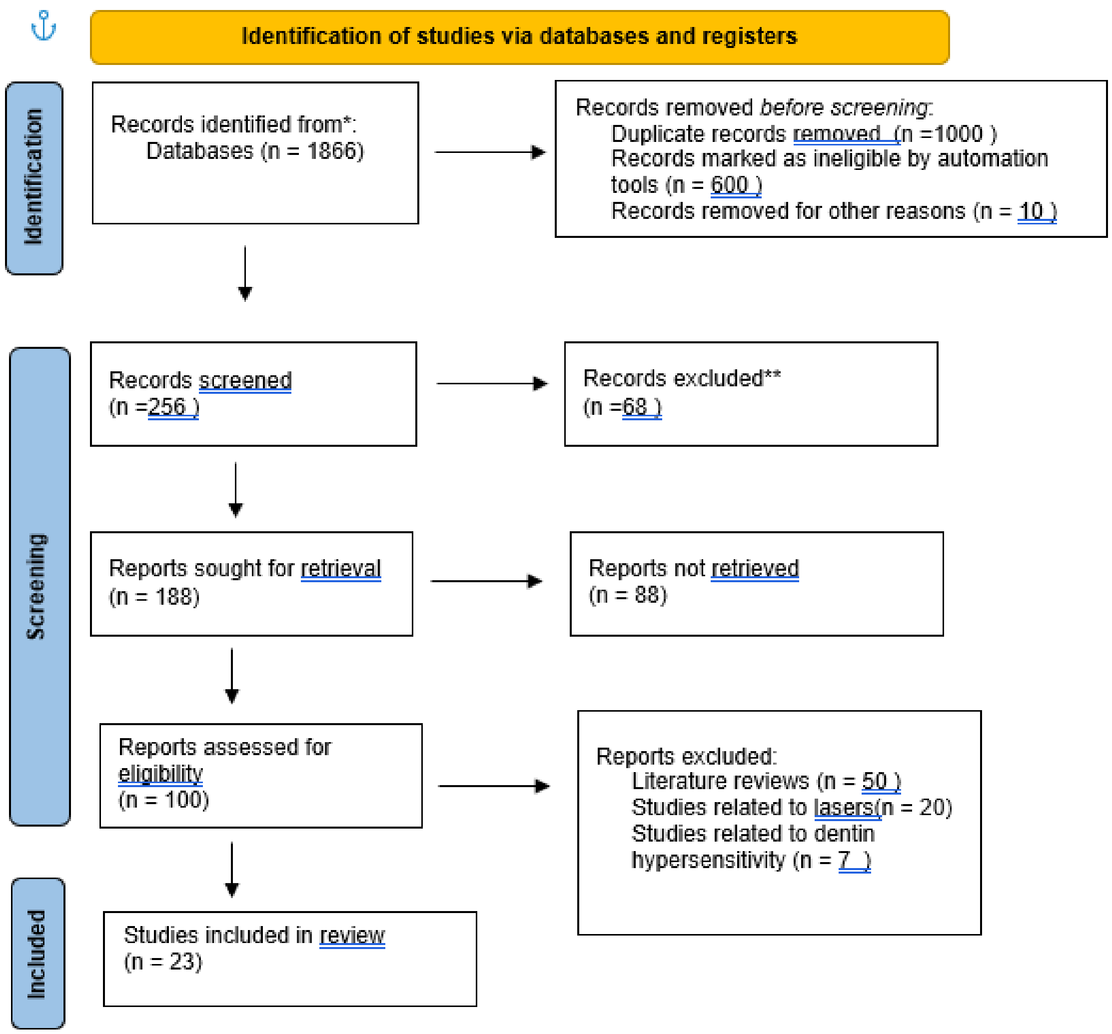
2.5 Data collection process: The main characteristics of the selected studies were evaluated on the basis of descriptive analysis. The data were tabulated under the following headings- Author, year of publication, study type, sample size, the erosive agent used, the remineralizing agent used, method, statistical analysis performed, and their outcome.

2.6 Risk of bias in individual studies: All articles were evaluated for quality using QUIN Tool as either Yes, Unclear, or No.

3. Results

3.1 Study Selection: Initially, 1876 relevant articles were identified from online databases, 1610 duplicates were excluded. 256 articles were further screened.68 articles were excluded based on the inclusion and exclusion criteria. Resulting 188 articles were assessed based on full texts for eligibility after excluding 88 articles due to invalid relevant data. Risk of bias of
23 studies were assessed using the QUIN Tool.

Table 1. 2020 PRISMA flow diagram explaining study selection from various sources



3.2 Study Characteristics: The studies that were included in systematic review were only in-vitro, tested on molars, premolars and incisors of permanent and deciduous teeth in few studies. The sample size of extracted human teeth ranged from 12-240 teeth. The various remineralizing agents used in the study included CPP-ACP, Tricalcium phosphate, CPP-ACP with fluoride, Stannous, Tin and Sodium, Acidulated phosphate fluorides, and silver diamine. The included studies involved exposure to erosive solutions, subjected to remineralizing solutions and then various properties like surface microhardness, roughness, and mineral loss were evaluated.

Table 1.2 Table representing the Author, Sample size, Erosive Agent used, Remineralizing Agent applied, Method of analysis and their outcome

	Author and Year of publication	**Size**	**Erosive agent**	**Remineralizing agent (Comparison group)**	**Method**	**Outcome**
1	S.Ranjitkar et al,2009 [29]	36	HCL	CPP-ACP and fluorides	Reduced enamel volume [profilometer]	Reduced wear in enamel
2	R.Somani et al,2014 [30]	30	Carbonated drink	CPP-ACP and CPP-ACPF	Surface Microhardness [Vickers test]	CPP-ACPF was more effective on erosive tooth wear.
3	M.Panich et al,2009 [31]	40	Coca-cola soft drink	CPP-ACP and fluorides	Enamel hardness [Vickers test]	Hardness increased on eroded surface with CPP-ACP
4	M.Colombo et al,2019 [32]	50	Coca-cola soft drink	CPP-ACP,Remin pro and forte paste	The average percentage of enamel weight reduction	Remin pro and Remin Pro Forte showed positive results
5	S.Eversole et al,2014 [21]	16	Citric Acid	SnF2 and NaF	Depth of eroded surface [Transverse Micro-radiography	SnF2 provided better protection against acidic attacks.
6	S.Ranjitkar et al,2009 [33]	72	Citric Acid	CPP-ACP and fluorides	Tooth wear [Profilometer]	Tooth wear reduced with CPP-ACP
7	C.Piekarz et al,2008 [34]	12	White resling wine	CPP-ACP and fluorides	Erosion depth [Sterio-microscope]	Wine erosion reduced by CPP- ACP
8	X.Wang et al,2011 [35]	90	Orange juice	Novamin, CPP-ACP, CPP-ACPF	Surface nanohardness [Vickers test, SEM analysis]	Novamin did not show significant results.
9	F.Carvalho et al,2013 [36]	40	Coca-cola soft drink	Fluoride varnish,calcium	Surface topography	Calcium nano - phosphate reduced enamel softening.

				nano - phosphate, CPP-ACP	[Atomic force microscopy]	
10	E.Maden et al,2017 [37]	60	Carbonated soft drink	CPP-ACP, APF gel	Surface roughness [Profilometer]	APF gel showed positive results in deciduous teeth.
11	C.Poggio et al,2014 [43]	50	Coco-cola soft drink	Bio repair Plus-sensitive,Total protection, Sensodyne repair and protect	Surface topography [AFM,SEM]	Bio repair Plus- Total Protection and Sensodyne Repair and Protect helps in dentin remineralization.
12	Hegde MN et al,2012 [38]	24	Coco-cola soft drink	CPP-ACPF, β-TCP	Mineral content [SEM,EDAX]	β-TCP provided better results in reducing erosions.
13	J.Rees et al,2007 [39]	30	Citric acid	Pro-enamel, CPP- ACP	Enamel loss [Profilometry]	Both provide protection
14	N.Schluter et al,2009 [22]	240	Citric acid	ZnF2, TiF4, AmF, SnCl2 and NaF	Mineral loss [Profilometry]	Tin and titanium containing fluorides showed better results
15	L.Hove et al,2006 [23]	24	Hydrochloric acid	TiF4, SnF2 and NaF	Etching depth,Roughness [White light interferometry]	Titanium containing fluorides showed better results than stannous fluoride.
16	C.Gans et al,2008 [24]	140	Citric acid	AmF, SnCl2, NaF and SnF2	Mineral loss [SEM]	Amine and stannous fluoride inhibited mineral loss.
17	M.Rallan et al,2013 [40]	40	Coco-cola soft drink	CPP-ACP, CPP-ACPF, fluoride varnish	Surface micro-hardness [Knoop hardness test]	CPP-ACPF provided more potential effect.
18	S.O Toole et al,2016 [25]	60	Citric acid	SnF2 and NaF Varnish	Profilometry and Microhardness change [KHN]	SnF2 inhibited enamel erosion than NaF.
19	N.Schluter et al,2007 [26]	150	Citric acid	TiF4 , NaF varnish	Mineral loss [Micro-radiography]	TiF4 solutions are effective against erosions.
20	C.Zhou et al,2013 [41]	70	Citric acid	CPP-ACP, NaF	Roughness [Atomic force microscopy]	CPP-ACP offers adavantage in remineralization of enamel.

21	C.Murakami et al,2009 [27]	60	Coco-cola soft drink	NaF, APF gels	Surface micro-hardness [Knoop hardness test]	Both inhibited erosive enamel loss in permanent teeth.
22	D.Vinod et al,2020 [28]	30	Demineralizing solution	SDF, CSP, CPP- ACP	Diagnodent readings	SDF was more effective.
23	A. Bakry et al,2014 [42]	100	Orange juice	45S5 Bioglass paste along with CPP-ACP	Surface micro-hardness [Knoop hardness test]	Proved to be effective.

Table- 1.3 QUIN Tool (Quality Assessment for In-Vitro Studies) for risk of bias assessment

	S.Ranjitkar et al,2009	R.Somani et al,2014	M.Panich et al,2009	M.Colombo et al,2019	S.Eversole et al,2014	S.Ranjitkar et al,2009	C.Piekarz et al,2008	X.Wang et al,2011	F.Carvalho et al,2013
1. Clearly stated aims/objectives	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**
2. Detailed explaination of sample size calculation	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
3. Detailed explanation of the sampling technique	**1**	**1**	**1**	**2**	**2**	**2**	**2**	**2**	**2**
4. Details of comparison group	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**
5. Detailed explaination of methodology	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**

6. Operator details	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**
7. Randomization	**1**	**1**	**1**	**2**	**2**	**2**	**2**	**2**	**2**
8. Method of measurement of outcome	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**
9. Outcome assessor details	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**
10. Blinding	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
11. Statistical analysis	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**
12. Presentation of results	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**
13. Overall Score	**16**	**16**	**16**	**18**	**18**	**18**	**18**	**18**	**18**
14. Final Score	**66.66%**	**66.66%**	**66.66%**	**75%**	**75%**	**75%**	**75%**	**75%**	**75%**

E.Maden et al,2017	C.Poggio et al,2014	Hegde MN et al,2012	J.Rees et al,2007 A. Bakry et al,2014	N.Schluter et al,2009 D.Vinod et al,2020	L.Hove et al,2006	C.Gans et al,2008	M.Rallan et al,2013	S.O Toole et al,2016	N.Schluter et al,2007 C.Murakami et al,2009	C.Zhou et al,2013
2	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**
0	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
1	**1**	**1**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**
2	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**
2	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**
1	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**
1	**1**	**1**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**
2	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**
1	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**
0	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
2	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**
2	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**
16	**16**	**16**	**18**	**18**	**18**	**18**	**18**	**18**	**18**	**18**
66.66%	**66.66%**	**66.66%**	**75%**	**75%**	**75%**	**75%**	**75%**	**75%**	**75%**	**75%**

3.3 Risk of Bias Within Studies

Quin Tool for Risk of Bias assessment for in-vitro studies was used. Scoring was done in all the 12 criteria accordingly.

- Adequately specified – 2 points
- Inadequately specified – 1 point
- Not specified – 0 point
- Not applicable – Exclude the criteria from calculation

Total scores were obtained to grade the in -vitro studies.

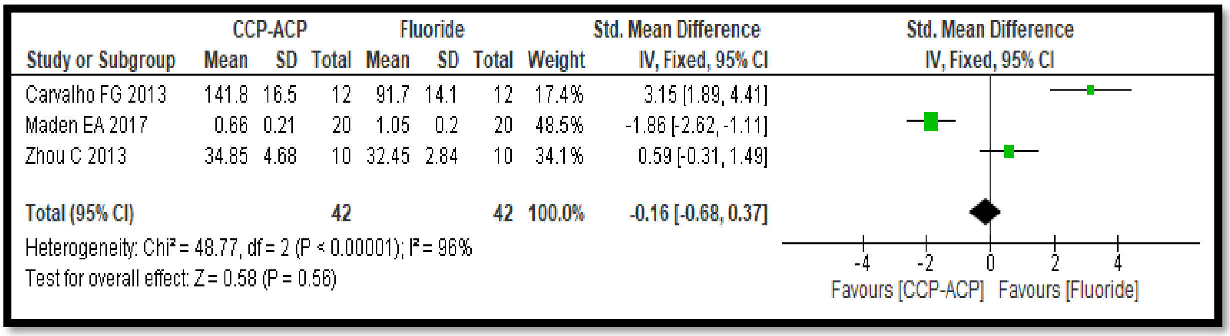
- High- < 50%
- Medium- 50%- 70%
- Low - > 70%

Formulae used- (Total score x 100)/ (2 x Number of criteria available)

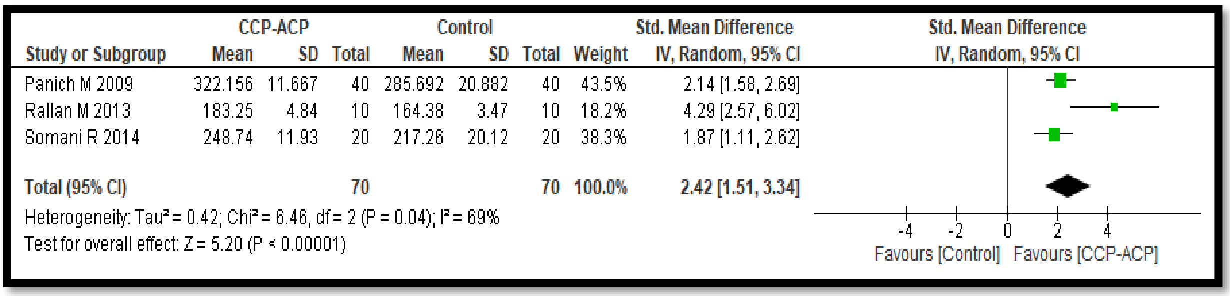
3.4 Meta-Analysis

The Quantitative outcomes were obtained using RevMan 5.3 for Cochrane Reviews. As shown in Figure-2, the pooled data of the included studies showed that the tooth wear reduction was more for CCP-ACP agents when compared to fluorides along with Micro- hardness which increased after remineralization with their use.

Forest Plot 1: Tooth Wear Reduction (Surface Roughness)



Forest Plot 2: Micro-hardness after Remineralization



4. Discussion

4.1 Summary of Evidence: This systematic review includes 23 articles that highlight the effect of fluoridated as well as non-fluoridated remineralizing agents on non-carious lesions exposed to erosive agents. All the articles were subjected to QUIN Tool (Quality Assessment for In-Vitro Studies) for risk of bias assessment. 17 studies had total score of > 70 % and were categorized as low risk and 6 studies had a total score between 50% - 70%, and were categorized as Medium risk as they lacked operator details, fault in the sampling technique and inadequate randomization.

Many unique solutions for preventing erosion through diverse modalities have been developed like strict dietary control and the use of agents that can remineralize the tooth structure. Fluorides are used on a regular base when compared to products containing CPP-ACP.

Various biomimetic remineralizing technologies have been introduced lately. 8 studies evaluated the effect of fluorides.[22-28] 14 studies evaluated the effect of calcium phosphate-based agents alone, combined with fluorides, Beta tricalcium phosphate, and Calcium Sodium phosphosilicate.[29-43] 1 study evaluated the effect of newly formulated tubes of toothpaste on enamel remineralization.[43] Most of the *in-vitro* studies suggested fluorides provide more protection against eroded surfaces. TiF4 was able to provide better protection due to its inhibiting effect [van Rijom et al.,2003]. By prolonged retention time of fluoride, the fluoride-metal complexes can inhibit demineralization [Gron.,1977, McCann.,1969]. Sn- incorporated solutions provided significant results. Enamel embedded with 20% Sn on the extreme layer of 30µm, produced significant changes.

In the case of dentin, the mineral loss was reduced significantly with TiF4 and NaF. Increased thickness of dentine matrix that is demineralized, and organic acts as an important layer for efficient fluoride application [Ganss et al.,2004]. Protein - binding nature of titanium ions is important for stabilization [Gu et al.,1996]. In addition to traditional fluoride-incorporated products, a milk-based protein, casein was introduced to inhibit demineralization.[44] ACP (amorphous calcium phosphate) is the biologically active form, separates at acidic pH from CPP, increases phosphate and calcium ions which get stabilized, and leaves free ions for remineralization. The susceptibility of dentine to erosion is around pH3.0, hence there is rapid removal of enamel at this rate.[46,47] When CPP-ACP was combined with 900ppm fluoride, the degree of remineralization improved as it co-localizes fluoride, calcium, and phosphate ions to form CPP-ACPF nanocomplexes.[48,49]

Calcium sodium phosphosilicate (Novamin) is osteo- regenerative and biocompatible in nature with structure similar to bone, occludes dentinal tubules when deposited on dentin surfaces with limited literature confirming its role in caries, erosion and reducing gingivitis.[50,51]Novamin can bond to dentin surfaces that are exposed in various formulation of kinds of toothpaste to provide prominent results against erosion, as apatite crystals of dentin have a greater concentration of carbonate, smaller sized crystallites and greater susceptibility to acidic erosion when compared to apatite crystals of enamel (Bertassoniet et al.,2010).[43]

The effect of remineralizing agents could vary both in permanent and primary dentition due to different enamel compositions. On primary enamel, CPP-ACPF performed better than CPP-ACP. due to an increase in surface microhardness.[40] APF gel demonstrated significant changes against loss of enamel due to its acidic pH against CPP-ACP.[37] Evolution in science and research has led to the invention of silver diamine fluoride [SDF]and calcium sucrose phosphate [CSP]. Studies reported the formation of a remineralized zone, rich in phosphate and calcium ions, thus inhibits dentin de-mineralization in primary teeth. CSP has a greater solubility in water because it contains more phosphate and calcium ions in the aqueous form, thus contributing to higher remineralizing potential in comparison to CPP-ACP (Kaur et al.,2015).

4.2 Limitations

Due to the difficulty in storage and collection of saliva, it is recommended that artificial saliva be used to simulate situations clinically. Only in-vitro studies have been included in this review, hence the actual process of remineralization taking place in the oral environment (in-vivo) can be different and generate varied results.

5. Conclusions

According to the results obtained from this systematic review, it was concluded that most of the fluoridated agents (gels, varnish, toothpaste) were beneficial in reducing dental erosion and wear, with lower pH and greater concentration, agent protection increased.

Stannous fluoride and Titanium tetrafluoride exhibited immense results in comparison to sodium fluoride, considered a gold standard. Agents containing CPP-ACP inhibited mineral loss but were less efficacious in comparison with CPP-ACPF. Clinical studies are needed to confirm the efficacy of tricalcium phosphate and calcium sodium phosphosilicate. Acidulated phosphate gels and silver diamine fluoride were more effective on primary enamel than CPP- ACP. Permanent teeth mineralize at a significantly faster pace than deciduous ones. Poor acid resistance of enamel of primary teeth leads to its severe demineralization with alteration in microtribological and nanomechanical properties.

6. Registration

The following review has been submitted to the International Prospective Register of Systematic Reviews (PROSPERO): Enrollment number- **CRD42020213374.**

7. Source of funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors

8. Conflict of Interest- The researchers have confirmed that there is no conflict of interest.

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