

Review Article

REMINERALIZATION OF TOOTH: A REVIEW OF LITERATURE

ABSTRACT

The goal of modern dentistry is to manage non-cavitated carious lesions non-invasively through remineralization in an attempt to prevent disease progression, and to improve strength, esthetics, and function of teeth. The emphasis currently is being given to new technologies for enamel remineralization which suggest the changes in the understanding of dental caries, and most of them gave significant positive results when used clinically. The aim of this review article is to put a light on various available remineralizing agents along with some recently introduced agents.

Keywords: Caries, Remineralisation, fluorides, non-fluoridated remineralizing agents

INTRODUCTION

Dental caries is one of the most common oral diseases that affects 60-90% of schoolchildren¹. Dental caries is a multifactorial disease that starts with microbiological shifts within the complex biofilm and is affected by salivary flow and composition, exposure to fluoride, consumption of dietary sugars, and by preventive behaviours (cleaning teeth)². In the face of failure to remove plaque from retentive tooth areas, a diet high in refined carbohydrates, and frequent carbohydrate ingestion, the dynamic equilibrium between demineralization and remineralization will be tipped towards demineralization with the development of clinically detectable white spot lesions³. However, if the pH is higher than 4.5 and F is present, the biofilm fluid is supersaturated with respect to fluorapatite (FA) and there is reprecipitation of minerals in the enamel. As a consequence, the net demineralization is reduced⁴.

The remineralization process is a natural repair mechanism to restore the minerals again, in ionic forms, to the hydroxyapatite (HAP) crystal

lattice. The process of tooth remineralisation has been studied over many decades of research and has led to the development of technologies that can promote enamel remineralisation or reduce enamel demineralisation thus giving potential oral health benefits⁵. Numerous types of remineralizing agents and remineralizing techniques have been researched and many of them are being used clinically, with significantly predictable positive results⁶.

A search of articles from "Pubmed" with the keywords Remineralization-demineralization, Casein derivatives, Fluoridated remineralisation agents, Non-fluoridated remineralizing agents, was conducted, out of which 80 articles that discussed remineralizing agents were read and 33 most relevant articles were included in this paper.

IDEAL REQUIREMENTS OF A REMINERALIZING AGENT:⁴

- Should deliver calcium and phosphate into the subsurface
- Should not deliver any excess of calcium
- Should not favor calculus formation
- Should work at an acidic pH so as to stop demineralization during a carious attack
- Should work in xerostomic patients also, as saliva cannot effectively stop the carious process.
- Should be able to boost the remineralizing properties of saliva
- The novel materials should be able to show some benefits over fluoride.

INDICATIONS:⁴

- An adjunct to preventive therapy for reducing caries in high-risk patients.
- Reduce dental erosion in patients with gastric reflux or other disorders.
- To reduce decalcification in orthodontic patients.
- To repair enamel in cases involving white spot lesions.
- For fluorosis, before and after teeth whitening and to desensitize sensitive teeth.

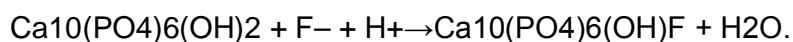
CLASSIFICATION OF REMINERALISING AGENT⁶

Remineralizing agents have been broadly classified into the following:

- Fluorides
- Non-fluoride remineralizing agents
 - ✓ Alpha tricalcium phosphate (TCP) and beta TCP (β -TCP)
 - ✓ Amorphous calcium phosphate
 - ✓ CPP-ACP
 - ✓ Sodium calcium phosphosilicate (bioactive glass)
 - ✓ Xylitol
 - ✓ Dicalcium phosphate dehydrate (DCPD)
 - ✓ Nanoparticles for remineralization
 - Calcium fluoride nanoparticles
 - Calcium phosphate-based nanomaterials.
 - NanoHAP particles
 - ACP nanoparticles
 - Nanobioactive glass materials
 - ✓ Polydopamine
 - ✓ PA
 - ✓ Oligopeptides
 - ✓ Theobromine
 - ✓ Arginine
 - ✓ Self-assembling peptides
 - ✓ Electric field-induced remineralization

FLUORIDATED REMINERALIZING AGENTS

Fluoride enhances enamel remineralisation, increasing the speed of the remineralisation process and the mineral content of early carious lesions⁷. When enamel is exposed to ionic fluoride, it may be taken up with the formation of either fluorhydroxyapatite or calcium fluoride⁸.



The calcium fluoride that is deposited onto a tooth surface after fluoride therapy is not readily soluble and can act as a fluoride reservoir.

Different types and forms of fluoride agents in various concentrations are used in dentistry⁷.

- 1) Topically applied fluoride therapy is classified into self-applied and professionally applied methods.
 - Fluoride mouthrinses and toothpastes are the main forms of self-applied fluoride.
 - Professionally applied products include fluoride gels, fluoride varnish, silver diamine fluoride, and fluoride-containing restorations and sealants, such as glass ionomer cement⁹. The use of professionally applied topical fluoride was extended to remineralise early enamel caries or white spot lesions and arrest dentine caries⁷.
- 2) Systemic fluorides include water fluoridation, salt fluoridation, milk fluoridation and fluoride tablets/drops/lozenges.

SODIUM FLUORIDE:

When sodium fluoride solution is applied on the tooth surface as a topical agent, it reacts with the hydroxyapatite crystals in enamel to form calcium fluoride which is main end product of the reaction. The calcium fluoride formed reacts with the hydroxyapatite crystals to form fluoridated hydroxyapatite. The hydroxyapatite thus formed increases the concentration of fluoride on enamel surface, which in turn makes the tooth surface resistant against caries attack through the action of fluoride. **Gao et al.** showed that the use of a 5% sodium fluoride varnish can remineralize incipient caries lesions, thus making this option an important method to inhibit enamel demineralization¹⁰.

STANNOUS FLUORIDE:

During the decade 1950-1960 and beyond, **Muhler et al. [1950]** produced voluminous literature dealing with the effectiveness of an 8 or 10% solution of stannous fluoride (SnF₂) pH 2.1, as a topical anticaries agent. The basis for the introduction of SnF₂ was the finding that powdered enamel treated with SnF₂ had a greater reduction in rate of dissolution in acids than with other fluorides. Some clinical trials showed a greater caries reduction from one or two annual applications

of 8% SnF₂ than from three or four applications of sodium fluoride; other trials failed to corroborate this conclusion¹¹.

ACIDULATED PHOSPHATE FLUORIDE:

To date, the clinical trials utilizing APF solutions and gels constitute the most impressive evidence in support of its use, over other agents, as a cariostatic reagent¹¹. When APF is applied on the teeth, it initially leads to dehydration and shrinkage in the volume of hydroxyapatite crystals which further on hydrolysis forms an intermediate product called dicalcium phosphate dihydrate (DCPD). Fluoride penetrates into the crystals more deeply through the openings produced by shrinkage and leads to formation of fluorapatite¹⁰. In situ, it could be shown that the single application of a gel containing APF (12,300 ppm F) plus the daily use of a dentifrice (1,100 ppm F) inhibited enamel demineralization as effectively as a highly fluoridated dentifrice containing NaF (5,000 ppm F) [Fernandez et al., 2017]¹².

SILVER DIAMINE FLUORIDE:

Silver diamine fluoride (SDF) is an anti-caries agent that can be used for caries prevention or as a standalone treatment in the control of dental caries, and it is applied until the child is old enough to cooperate during dental treatment¹³. The concentration of the most commonly used SDF was 38%, which contains 44,800 ppm fluoride¹⁴. Chibinski et al., high concentrations of 38% SDF (44,800 ppm F; 253,870 ppm Ag) and 30% SDF (35,400 ppm F; 200,400 ppm Ag) provided greater efficacy in the prevention of dental caries in deciduous teeth than low concentrations¹³. While being used as an alternative treatment to children with special healthcare needs, cavitated lesions treated with SDF are sometimes covered with self-curing glass ionomer cements to mask the staining effect, in which case the technique has been referred to as silver modified atraumatic restorative treatment (SMART)¹⁵.

FLUORIDE CONTAINING SEALANTS AND RESTORATIONS:

The incorporation of fluoride in resin-based FS provides fluoride release and recharge abilities to inhibit demineralization of the adjacent tooth structure but lower compared to glass ionomer sealants (Kus,go'z et al. 2010). By acting as a physical barrier to protect

vulnerable areas FS inhibit not only the formation of occlusal dental caries, but also the progression of the existing carious lesions (Azarpazhooh and Main 2008)¹⁶.

NON-FLUORIDATED REMINERALISING AGENTS

- **TRICALCIUM PHOSPHATE:** Tricalcium phosphate (TCP) has also been considered as one possible means for enhancing the levels of calcium in plaque and saliva¹⁷. Tri-calcium phosphates has remineralization properties with the advantage of the calcium phosphate system, that is stable in aqueous environment and does not affect the fluoride activity when added to dentifrices¹⁸. This material is available in a calcium: phosphate ratio of 1:5 and is available in two forms of α and β (β particles are less soluble than α particles)¹⁹. Products available with TCP include a 5000 ppm sodium fluoride dentifrice and a 5% sodium fluoride varnish⁴. **Rao R et al (2017)** evaluated the remineralization potential of fluoride using Duraphat fluoride varnish, ReminPro paste, ClinPro Tooth Creme and control group (no surface treatment). ClinPro tooth Creme showed the best remineralization potential followed by Duraphat and ReminPro⁸.

AMORPHOUS CALCIUM PHOSPHATE: The Amorphous Calcium Phosphate (ACP) technology is an unstabilized calcium and phosphate system that has been developed and commercialized. It is based on unstabilized amorphous calcium phosphate, where a calcium salt (e.g., calcium sulphate) and a phosphate salt (e.g., potassium phosphate) are delivered separately (e.g., from a dual-chamber device) intra-orally or delivered in a product with a low water activity (Tung and Eichmiller, 2004)²⁰. In 1999, ACP was incorporated into toothpaste called Enamelon and later reintroduced in 2004 in Enamel Care toothpaste by Church and Dwight¹⁷. **Iafisco M. et al (2018)** demonstrated that ACP and FACP are promising biomimetic materials in preventive dentistry to hinder demineralization of dental hard tissues. The samples showed good ability to partially occlude the tubules of acid-etched dentin and to restore demineralized enamel into its native structure²¹.

CASEIN PHOSPHOPEPTIDES – AMORPHOUS CALCIUM

PHOSPHATE: Casein has the ability to stabilize calcium and phosphate ions by releasing small sequences of peptides (CPPs) through partial enzymic digestion that leads to the development of a remineralization technology based on casein phosphopeptide stabilized amorphous calcium phosphate complexes (CPP-ACP) and casein phosphopeptide-stabilized amorphous calcium fluoride phosphate complexes (CPP -ACFP)⁴. In 1998, CPP-ACP (Tooth Mousse, GC India) was introduced by Prof. Reynolds as a remineralizing agent at the school of Dental Sciences at the University of Melbourne in Australia. There is a synergism in remineralising potential when CPP-ACP is combined with fluoride. CPPs enhances efficacy of fluoride as a remineralizing agent by keeping fluoride ions in solution by forming fluoroapatite⁸. It was concluded that significantly more post-orthodontic white-spot lesions regressed with the CPP-ACP cream treatment over a 12-week period (**Bailey et al., 2009**)²⁰.

BIOACTIVE GLASS: Bioglass (BG) is a class of bioactive material which is composed of calcium, sodium, phosphate, and silicate⁶. Bioactive materials induce calcium phosphate formation, and have potential applications in tooth remineralisation. Hench & Anderson bioactive glass in 1969. Bioactive glass formulation contains 45 wt% SiO₂ 4.5 wt% Na₂O and CaO and 6 wt% P₂O₅⁸. Recently, a fluoride-containing bioactive glass (BioMinF; <http://www.biomin.co.uk>) was introduced as a caries remineralising and preventive additive in toothpastes¹⁵. Novamin was developed by Dr. Len and Dr. Hack which is manufactured by Novamin technology and is a trade name for bioactive glass⁸. **TahaAA et al (2017)** extensively studied the Bioglass45S5 regarding the remineralization of white spot lesions. They compared the remineralization potential of bioactive glasses, topical fluoride and CPP-ACP treatment and concluded that enamel remineralization is more effectively and earlier enhanced by bioactive glasses⁸.

XYLITOL: Xylitol is a tooth friendly non-fermentable sugar alcohol which has been shown to have noncariogenic as well as cariostatic effects⁶. The use of chewing gum carrying xylitol increases salivary flow rate and enhances the protective properties of saliva. This is because the concentration of bicarbonate and phosphate is higher in stimulated saliva, and the resultant increase in plaque pH and salivary buffering capacity prevents demineralization of tooth structure. Moreover, the higher concentration of calcium, phosphate, and hydroxyl ions in such saliva also enhances remineralization⁵. **Milburn et al. (2015)** have shown that fluoride varnish, containing xylitol-coated calcium and phosphate, had the greatest initial fluoride release in the first four hours, exceeding 10 times than that of other varnishes such as Enamel Pro®, Duraphat®, or Vanish⁶.

DICALCIUM PHOSPHATE DEHYDRATE : DCPD is a precursor for apatite that readily turns into fluorapatite in the presence of fluoride⁶. Inclusion of dicalcium phosphate dehydrate (DCPD) in a dentifrice increases the levels of free calcium ions in plaque fluid, and these remain elevated for up to 12 hours after brushing, when compared to conventional silica dentifrices (**Walsh LJ, 2009**)¹⁷.

NANOPARTICLES FOR REMINERALISATION: Recently, nanotechnology has attracted a great deal of attention²². **Xu HHK et al.** have shown that the addition of nanoCaF₂ increases the cumulative fluoride release compared to the fluoride release in traditional glass ionomer cements because the CaF₂ nanoparticle (nano-CaF₂) has a 20-fold higher surface area compared with traditional glass ionomer cements⁶. It is possible to prepare β-TCP nanoparticles with improved cariostatic and remineralizing properties on the enamel surface¹⁹. In acidic conditions, nano-HA is capable of significantly increasing the degree of remineralization by aiding more ions diffusion in the center of the demineralized zone²³. ACP nanoparticles, as a source of calcium and phosphate ions, have been added to composite resins, ionomer cements, and adhesives⁶. **Sheng et al. (2016)** have found that nanoBG

particles could promote mineral formation on dentin surfaces and they were shown to make dentin more acid resistant²⁴.

POLYDOPAMINE: Dopamine has been extensively used for biomaterial surface modification regardless of type, size, and shape of hybridized counterpart materials. **Zhou YZ (2012)** have found that Polydopamine coating remarkably promoted demineralized dentin remineralization, and all dentin tubules were occluded by densely packed hydroxyapatite crystals²⁵.

PA: Polyphenols are plant-derived substances which have antioxidant and anti-inflammatory properties. One such polyphenol is proanthocyanidin (PA) which is a bioflavanoid-containing benzene-pyran-phenolic acid molecular nucleus. Proanthocyanidin, a naturally occurring plant metabolite is a natural antioxidant and free radical scavenger. Collagen is considered a proline-rich proteins with extremely high affinity for PA-based components (GSE is a powerful source of PA), forming a proline-PA complex. GSE increase the collagen cross-links by four different mechanisms: ionic, covalent, hydrogen bonding, and hydrophobic interactions. According to these findings, it is expected that exogenous collagen crosslinks involves in the remineralization of enamel defects by GSE. **Nagi SM et al (2019)** evaluated that the specially prepared GSE hydrogels has positive effects on the remineralization process of bleached enamel making it an effective natural agent with remineralizing potential²⁶.

THEOBROMINE: The cariostatic property of theobromine accounts for the presence of two types of substances: one which exhibits anti-glucosyltransferase and the other anti-bacterial activity²⁷. In a comparative evaluation of the remineralizing potential of theobromine and sodium fluoride dentifrice by **Amaechi et al.**, a significantly higher mineral gain was observed with theobromine and fluoride toothpaste relative to artificial saliva⁶.

ARGININE: Arginine bicarbonate is an amino acid with particles of calcium carbonate, which is capable of adhering to the mineral surface.

When the calcium carbonate dissolves, the released calcium is available to remineralize the mineral while the release of carbonate may give a slight local pH rise⁶. Recently, arginine has been incorporated into dentifrice formulations to suppress mineral loss via a buffering effect induced by arginine [Cummins, 2013a]. Clinical studies have suggested a superior effect of arginine-containing FD (AFD) over regular FD in terms of the reversal of white spot lesions [Srisilapanan et al., 2013; Yin et al., 2013; Li et al., 2015a]. However, its clinical significance it is still under debate [Ástvaldsdóttir and Östlund, 2017]²⁸.

SELF-ASSEMBLING PEPTIDES: Because minerals from saliva or minerals supplied by other therapies need nucleation sites for precipitation and remineralization, a biomimetic technology was introduced about a decade ago to promote faster remineralization (Kirkham et al. 2007)²⁹. Rationally designed β -sheet-forming peptides P114 that self-assemble themselves to form three-dimensional scaffolds under defined environmental conditions have been shown to nucleate hydroxyl apatite de novo and to have potential applications in mineralized tissue regeneration, mimicking the action of enamel matrix proteins during tooth development⁴. Nowadays, the self-assembling peptide P11-4 is available in commercial products named Curolox Technology (credentis ag, Windisch, Switzerland)³⁰. The results of this single-blind 6-mo study suggest that P11-4 in combination with F varnish (22,600-ppm F) is superior than F varnish alone on promoting remineralization of early carious lesions (Alkilzy et al. 2017). Others RCTs are currently registered (NCT02101255, NCT02020681, NCT02119507, NCT02913885, NCT02341872)²⁹.

ELECTRIC FIELD-INDUCED REMINERALIZATION: Wu et al. (2015) have introduced this technique to remineralize the completely demineralized dentin collagen matrix and also to shorten the mineralization time, which it achieved in the absence of both calcium phosphates and their analogs with the help of electrophoresis³¹.

REFERENCES

1. Kundu H, Patthi B, Singla A, Jankiram C, Jain S, Singh K. Dental Caries Scenario Among 5, 12 and 15-Year-old Children in India- A Retrospective Analysis. *J Clin Diagn Res.* 2015 Jul;9(7):ZE01-5. doi: 10.7860/JCDR/2015/12439.6150. Epub 2015 Jul 1. PMID: 26393229; PMCID: PMC4573062.
2. Selwitz RH, Ismail AI, Pitts NB. Dental caries. *Lancet.* 2007 Jan 6;369(9555):51-9. doi: 10.1016/S0140-6736(07)60031-2. PMID: 17208642.
3. Hicks J, Garcia-Godoy F, Flaitz C. Biological factors in dental caries enamel structure and the caries process in the dynamic process of demineralization and remineralization (part 2). *J Clin Pediatr Dent.* 2004 Winter;28(2):119-24. doi: 10.17796/jcpd.28.2.617404w302446411. Erratum in: *J Clin Pediatr Dent.* 2004 Spring;38(3):214. PMID: 14969369.
4. Preethi, Naveena. (2014). Remineralizing Agent -Then and Now -An Update. *Dentistry.* 04. 10.4172/2161-1122. 1000256.
5. Li X, Wang J, Joiner A, Chang J. The remineralisation of enamel: a review of the literature. *J Dent.* 2014 Jun;42 Suppl 1:S12-20. doi: 10.1016/S0300-5712(14)50003-6. PMID: 24993850.
6. Arifa MK, Ephraim R, Rajamani T. Recent Advances in Dental Hard Tissue Remineralization: A Review of Literature. *Int J Clin Pediatr Dent.* 2019 Mar-Apr;12(2):139-144. doi: 10.5005/jp-journals-10005-1603. PMID: 31571787; PMCID: PMC6749882.
7. Gao SS, Zhang S, Mei ML, Lo EC, Chu CH. Caries remineralisation and arresting effect in children by professionally applied fluoride treatment - a systematic review. *BMC Oral Health.* 2016 Feb 1;16:12. doi: 10.1186/s12903-016-0171-6. PMID: 26831727; PMCID: PMC4736084.
8. Jindal L, Anukriti NB. Tooth Remineralization: Averting the Dental Decay. *J Res Adv Dent* 2020;10:4:37-45.
9. Nantanee R, Santiwong B, Trairatvorakul C, Hamba H, Tagami J. Silver diamine fluoride and glass ionomer differentially remineralize early caries lesions, in situ. *Clin Oral Investig.* 2016 Jul;20(6):1151-7. doi: 10.1007/s00784-015-1603-4. Epub 2015 Sep 23. PMID: 26395352.

10. Peter S. (2017). Essentials Of Public Health Dentistry (Community Dentistry). 6th Edition.
11. Nikiforuk, G. (1985). Understanding Dental Caries i Etiology and Mechanisms Basic and Clinical Aspects.
12. Erdwey D, Meyer-Lueckel H, Esteves-Oliveira M, Apel C, Wierichs RJ. Demineralization Inhibitory Effects of Highly Concentrated Fluoride Dentifrice and Fluoride Gels/Solutions on Sound Dentin and Artificial Dentin Caries Lesions in vitro. Caries Res. 2021;55(1):41-54. doi: 10.1159/000509931. Epub 2020 Dec 7. PMID: 33285548.
13. Punhagui MF, Jussiani EI, Andrello AC, Favaro JC, Guiraldo RD, Lopes MB, Berger SB. Effect of application time and concentration of silver diamine fluoride on the enamel remineralization. J Clin Exp Dent. 2021 Jul 1;13(7):e653-e658. doi: 10.4317/jced.58318. PMID: 34306528; PMCID: PMC8291156.
14. Yu OY, Mei ML, Zhao IS, Li QL, Lo EC, Chu CH. Remineralisation of enamel with silver diamine fluoride and sodium fluoride. Dent Mater. 2018 Dec;34(12):e344-e352. doi: 10.1016/j.dental.2018.10.007. Epub 2018 Oct 25. PMID: 30482611.
15. Amaechi BT. Remineralisation - the buzzword for early MI caries management. Br Dent J. 2017 Aug 11;223(3):173-182. doi: 10.1038/sj.bdj.2017.663. PMID: 28798421.
16. Dionysopoulos D, Sfeikos T, Tolidis K. Fluoride release and recharging ability of new dental sealants. Eur Arch Paediatr Dent. 2016 Feb;17(1):45-51. doi: 10.1007/s40368-015-0200-1. Epub 2015 Aug 12. PMID: 26264161.
17. Goswami M, Saha S, Chaitra TR. Latest developments in non-fluoridated remineralizing technologies. J Indian Soc Pedod Prev Dent. 2012 Jan-Mar;30(1):2-6. doi: 10.4103/0970-4388.95561. PMID: 22565510.
18. Bajaj M, Poornima P, Praveen S, Nagaveni NB, Roopa KB, Neena IE, Bharath KP. Comparison of CPP-ACP, Tri-Calcium Phosphate and Hydroxyapatite on Remineralization of Artificial Caries Like Lesions on Primary Enamel -An in vitro Study. J Clin Pediatr Dent. 2016;40(5):404-9. doi: 10.17796/1053-4628-40.5.404. PMID: 27617382.
19. Tavassoli-Hojjati S, Atai M, Haghgoo R, Rahimian-Imam S, Kameli S, Ahmaian-Babaki F, Hamzeh F, Ahmadyar M. Comparison of various

- concentrations of tricalcium phosphate nanoparticles on mechanical properties and remineralization of fissure sealants. *J Dent (Tehran)*. 2014 Jul;11(4):379-88. Epub 2014 Jul 31. PMID: 25584048; PMCID: PMC4283738.
20. Cochrane NJ, Cai F, Huq NL, Burrow MF, Reynolds EC. New approaches to enhanced remineralization of tooth enamel. *J Dent Res*. 2010 Nov;89(11):1187-97. doi: 10.1177/0022034510376046. Epub 2010 Aug 25. PMID: 20739698.
21. Iafisco M, Degli Esposti L, Ramírez-Rodríguez GB, Carella F, Gómez-Morales J, Ionescu AC, Brambilla E, Tampieri A, Delgado-López JM. Fluoride-doped amorphous calcium phosphate nanoparticles as a promising biomimetic material for dental remineralization. *Sci Rep*. 2018 Nov 19;8(1):17016. doi: 10.1038/s41598-018-35258-x. PMID: 30451901; PMCID: PMC6242929.
22. Manchery N, John J, Nagappan N, Subbiah GK, Premnath P. Remineralization potential of dentifrice containing nanohydroxyapatite on artificial carious lesions of enamel: A comparative *in vitro* study. *Dent Res J (Isfahan)*. 2019 Sep 5;16(5):310-317. PMID: 31543937; PMCID: PMC6749857.
23. Juntavee A, Juntavee N, Hirunmoon P. Remineralization Potential of Nanohydroxyapatite Toothpaste Compared with Tricalcium Phosphate and Fluoride Toothpaste on Artificial Carious Lesions. *Int J Dent*. 2021 Mar 20;2021:5588832. doi: 10.1155/2021/5588832. PMID: 33824661; PMCID: PMC8007336.
24. Sheng XY, Gong WY, Hu Q, Chen XF, Dong YM. Mineral formation on dentin induced by nano-bioactive glass. *Chinese Chemical Letters*. 2016 Sep 1;27(9):1509-14.
25. Zhou YZ, Cao Y, Liu W, Chu CH, Li QL. Polydopamine-induced tooth remineralization. *ACS Appl Mater Interfaces*. 2012 Dec;4(12):6901-10. doi: 10.1021/am302041b. Epub 2012 Dec 4. PMID: 23176019.
26. Nagi SM, Hassan SN, Abd El-Alim SH, Elmissiry MM. Remineralization potential of grape seed extract hydrogels on bleached enamel compared to fluoride gel: An *in vitro* study. *J Clin Exp Dent*. 2019 May 1;11(5):e401-e407. doi: 10.4317/jced.55556. PMID: 31275511; PMCID: PMC6599700.
27. Premnath P, John J, Manchery N, Subbiah GK, Nagappan N, Subramani P. Effectiveness of Theobromine on Enamel Remineralization: A Comparative

- In-vitro Study. *Cureus*. 2019 Sep 17;11(9):e5686. doi: 10.7759/cureus.5686. PMID: 31720155; PMCID: PMC6823004.
28. Sanchez AY, de Oliveira CL, Negrini TC, Hashizume LN, Hara AT, Maltz M, Arthur RA. In situ Effect of Arginine-Containing Dentifrice on Plaque Composition and on Enamel Demineralization under Distinct Cariogenic Conditions. *Caries Res*. 2018;52(6):588-597. doi: 10.1159/000488212. Epub 2018 May 4. PMID: 29730666.
29. González-Cabezas C, Fernández CE. Recent Advances in Remineralization Therapies for Caries Lesions. *Adv Dent Res*. 2018 Feb;29(1):55-59. doi: 10.1177/0022034517740124. PMID: 29355426.
30. Jablonski-Momeni A, Nothelfer R, Morawietz M, Kiesow A, Korbmacher-Steiner H. Impact of self-assembling peptides in remineralisation of artificial early enamel lesions adjacent to orthodontic brackets. *Sci Rep*. 2020 Sep 15;10(1):15132. doi: 10.1038/s41598-020-72185-2. PMID: 32934335; PMCID: PMC7493957.
31. Wu XT, Mei ML, Li QL, Cao CY, Chen JL, Xia R, Zhang ZH, Chu CH. A Direct Electric Field-Aided Biomimetic Mineralization System for Inducing the Remineralization of Dentin Collagen Matrix. *Materials (Basel)*. 2015 Nov 20;8(11):7889-7899. doi: 10.3390/ma8115433. PMID: 28793685; PMCID: PMC5458896.